Polyunsaturated Fatty Acids: Impact on Health and Disease Status
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ABSTRACT
Over the last decades, the polyunsaturated fatty acids (PUFAs) have been largely explored not only for their nutritional value but also for the numerous biological functions and therapeutic effects. The serum and erythrocyte levels of PUFAs depend on the genetic control of metabolism as well as the dietary intake and are considered to reflect the health and disease status of an individual. Two families of PUFAs, omega-3 (n-3) and omega-6 (n-6), have gained much attention because of their involvement in the production of bioactive lipid mediators and therefore, a balanced omega-6/omega-3 ratio is crucial in maintaining the overall health of an individual. Omega-3 PUFAs, notably eicosapentaenoic acid (EPA, 20:5n-3) and docosahexaenoic acid (DHA, 22:6n-3) have been shown to exert beneficial effects, possibly due to their lipid-lowering, anti-inflammatory, anti-hypertensive and cardioprotective effects, whereas omega-6 fatty acids such as arachidonic acid (ARA, 20:4n-6) exhibit the opposite properties. Even though, numerous epidemiological studies and clinical interventions have clearly established the effectiveness of omega-3 PUFAs in various pathological conditions including dyslipidemia, obesity, diabetes, cancer, cardiovascular and neurodegenerative diseases, some controversies do exist about the beneficial effects of omega-3 PUFAs and need to be clarified. Larger clinical trials with extended follow-up periods are required along with a careful dose selection, in order to confirm the clinical significance and efficacy of omega-3 PUFAs as therapeutic agents.

Key Words: Cardiovascular Diseases, Docosahexaenoic Acid, Disease, Polyunsaturated Fatty Acids, Health.

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Introduction
Lipids are small non-polar biological molecules which perform diverse functions in a cell. Lipids serve as the main source of energy (9 kcal/mol), compared to proteins and carbohydrates (4.5 kcal/mol) and form a major structural constituent of biological membranes. The simplest lipids are the fatty acids that contain a carboxyl group (COOH) attached to a hydrocarbon chain with a terminal methyl group. Most of the naturally occurring fatty acids have an even number of carbon atoms and linear hydrocarbon chains, except for some exceptions in bacteria which have branched or cyclic structures.1 Moreover, fatty acids are further classified based on the absence or presence of one or more double bonds into saturated or mono-/poly-unsaturated fatty acids respectively. Polyunsaturated fatty acids (PUFAs) of interest include omega-3 (n-3) and omega-6 (n-6), depending on the position of the first double bond at third or sixth carbon atom from the methyl end of the fatty acids. The long-chain polyunsaturated fatty acids (LC-PUFAs) from the omega-3 and omega-6 families are derived from their respective precursors, namely, α-linolenic acid (ALA; C18:3n-3) and linoleic acid (LA; C18:2n-6). ALA and LA are essential fatty acids that mammals have very limited capacity to synthesize and therefore can only be obtained from the diet.

Dietary sources of PUFAs
Studies have shown that human populations around the world may have different capacities to synthesize LC-PUFAs from plant-based medium chain PUFAs, due to the variations in the fatty acid desaturase (FADS) gene cluster.7 In humans, ALA is converted into eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) at the approximate rates of 8-20% and 0.5-9%, respectively.7 Furthermore, diet is considered as one of the
important factors to modify the human capacity to synthesize LC-PUFAs from their respective precursors. Therefore, a continuous supply in the diet is very important to ensure whole-body LC-PUFAs content.

Omega-3 PUFAs can be obtained from fish (e.g., salmon, mackerel, sardines, pollock, bluefish, and black cod), walnuts, flax seeds, linseeds and green leafy vegetables such as purslane and spinach, while omega-6 fatty acids are mainly obtained from vegetable oils such as soybean, safflower, sunflower and corn.

Although fish is the primary source for health-promoting omega-3 PUFAs, the biggest challenge is to achieve their sustainable production due to decreasing global fish stocks as well as the safety issues related to environmental pollutants. Therefore, there has been considerable interest in the last few decades to produce omega-3 PUFAs from alternative sources such as marine bacteria and microalgae. However, in order to overcome the low productivity of PUFAs using these organisms, various metabolic engineering strategies have been employed to optimize the biosynthetic pathways of PUFAs with the ultimate objective to achieve a successful industrial-scale production.

**Biosynthesis of long-chain omega-3 and omega-6 fatty acids**

The biosynthesis of LC-PUFAs is a process that takes place primarily in liver. However, the efficiency of these processes is low (less than 0.5%) in humans and is influenced by ALA and LA intake and various pathological conditions.

In liver, dietary precursors ALA and LA are converted into EPA or arachidonic acid (ARA) respectively via different steps involving desaturation by Δ6 FADS (encoded by FADS2 gene), chain elongation by very long chain fatty acids (ELOVL) protein 5, further desaturation by Δ5 desaturase (encoded by FADS1 gene) (Figure 1). Two successive elongations of EPA by ELOVL5 & 2 and a desaturation by Δ6-desaturase produces tetracosahexaenoic acid (24:6n-3) in endoplasmic reticulum (ER).

In mammals, DHA production from 24:6n-3 involves the peroxisomal β-oxidation through the successive actions of acyl-coenzyme A oxidases, D-bifunctional protein and peroxisomal thiases, referred to as ‘Sprecher’s shunt’. DHA is then transported back to ER to be incorporated into membrane phospholipids by esterification or the deacylation-reacylation reaction. These translocations between ER and peroxisomes are supposed to be responsible in part for the low efficiency of DHA biosynthesis in mammals.

In addition, omega-3 and omega-6 PUFAs can be further metabolized into eicosanoids by the action of cyclooxygenases and lipoxygenases to produce different series of biologically-active molecules such as prostaglandins, thromboxanes, leukotrienes, 5-hydroxy-eicosatetraenoic acids and lipoxins (Figure 1). Interestingly, the omega-6 PUFAs-derived eicosanoids are important mediators of inflammation and atherogenesis, whereas the eicosanoids produced from omega-3 PUFAs (prostanoids, docosanoids and neuroprotectins) possess anti-inflammatory, anti-oxidative, immunoregulatory, vasodilatory and neuroprotective properties. Therefore, an imbalance in the production of these eicosanoids may lead to the development of various pathophysiological conditions.

**The omega-6/omega-3 ratio and dietary recommendations**

The omega-6/omega-3 ratio in the diet is of crucial importance in predicting and maintaining the overall health of an individual. Our ancestral diets were found to be enriched with omega-3 fatty acids and therefore a balanced omega-6/omega-3 ratio. However, the shift from omega-3 fatty acids towards high amounts of saturated fatty acids and omega-6 fatty acids has perturbed the omega-6/omega-3 balance from 1:1 to 10-20:1 in modern Western diets. This has consequently led to an increased prevalence of various inflammation-related chronic diseases such as cancer, inflammatory bowel disease, rheumatoid arthritis and cardiovascular and neurodegenerative diseases. The recommended dose of EPA+DHA in the diet ranges from 40 to 250 mg per day for infants older than six months as well as for children and adolescents, however, 250 to 1000 mg per day has been recommended for adults.

**PUFAs as predictors of health and diseased status**

The implication of omega-3 and omega-6 fatty acids
Implications of Fatty Acids in Maintaining Health

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Fig 1: Biosynthesis of long-chain omega-3 and omega-6 fatty acids in mammals

Biosynthesis of long-chain omega-3 and omega-6 fatty acids involves a cascade of desaturation-elongation reactions in endoplasmic reticulum to produce arachidonic acid (ARA; C20:4n-6) from linoleic acid (LA; C18:2n-6). The conversion of α-linolenic acid (ALA; C18:3n-3) into eicosapentaenoic acid (EPA; C20:5n-3) and docosahexaenoic acid (DHA; C22:6n-3) occurs in endoplasmic reticulum and/or peroxisomes. The LC-PUFAs thus produced, are further metabolized to produce signaling molecules which are implicated in various anti-inflammatory or pro-inflammatory processes.

in human health and disease has been increasingly reported in the last few decades. Unlike omega-6 PUFAs, a large body of evidence has supported the beneficial roles of omega-3 PUFAs in various pathophysiological conditions including metabolic syndrome, cardiovascular diseases, cancer, depression, and neurodegenerative illnesses (Figure 2). Omega-3 PUFAs have also been shown to function against inflammation and oxidative stress, which are underlying causes of different disorders. Several mechanisms may be involved in mediating the effects of fatty acids, including modifications in the physicochemical properties and functions of biological membrane, control in expression of genes, receptors and associated proteins, or the production of metabolites. Moreover, the erythrocyte levels of PUFAs (omega-3 index) have been shown to be strongly correlated with the PUFAs enrichment in different organs, thereby reflecting an individual's health condition. Nevertheless, the findings that illustrate the opposite or no effects of these PUFAs in different groups of patients with various pathologies should also be taken into consideration, in order to devise meaningful therapeutic strategies to improve health and prevent diseases.

Metabolic syndrome

Metabolic syndrome (MetS) is a complex disorder which refers to a clustering of three or more interrelated conditions including hypertension, dyslipidemia (high triglycerides and low HDL levels), abdominal obesity and impaired glucose tolerance. A large body of evidence has revealed the patients with MetS as predictors of diabetes and
A meta-analysis comprising of 20 cross-sectional and seven case-control studies showed that higher levels of plasma/serum omega-3 PUFAs were related with a reduced MetS risk. Owing to their anti-inflammatory and lipid-lowering properties, omega-3 PUFAs supplementation has been found to improve the individual features of MetS, thus conferring protection from cardiometabolic disorders. Several studies have shown that fish and fish oil-derived omega-3 PUFAs could decrease plasma lipid levels, insulin resistance, and blood pressure, remediating the effects of MetS. The consumption of EPA and DHA reduced serum triglycerides in type 2 diabetes mellitus. However, the longitudinal cohort study indicated an inverse relationship of the serum omega-6 PUFAs levels with the incidence of MetS. Nevertheless, the studies based on meta-analyses of randomized controlled trials (RCTs) did not show any effectiveness of omega-3 and omega-6 PUFAs in the prevention or treatment of type 2 diabetes or insulin sensitivity, suggesting further clinical investigation in order to attain a conclusive evidence.

Obesity is a multifactorial chronic disease caused by the accumulation of excessive/abnormal fat associated with dyslipidemia, insulin resistance, hypertension and MetS. Studies have shown that the fish oil supplementation leads to elevated plasma adiponectin and leptin levels with an improved plasma lipid profile in comparison with a sucrose-fed diet in insulin-resistant rats. In addition, fish-based dietary supplementation of non-obese healthy Japanese volunteers showed higher serum omega-3 PUFAs and adiponectin levels, indicating the significance of the consumption of the diet rich in omega-3 fatty acids for the maintenance of body weight. Since few intervention trials have been conducted regarding omega-3 supplementation in obesity, there is limited suggestive evidence about the anti-obesity effects of omega-3 PUFAs, emphasizing upon the need for more clinical trials.

Cardiovascular diseases (CVDs) are considered to be the leading cause of worldwide mortality, with 32% of the 56 million deaths in 2015. Globally, the individuals have been recommended to replace saturated fatty acids with polyunsaturated fatty acids in the diet for coronary heart disease risk reduction, owing to the cardioprotective effects of omega-3 fatty acids including lowering of blood pressure and cholesterol levels. Omega-3 PUFAs such as EPA and DHA mainly contribute in preventing cardiac arrhythmias, decreasing platelets aggregation, reducing inflammation, lowering plasma triglycerides and reducing blood pressure. They have also been found effective in enhancing the arterial endothelial function and reducing the expression of vascular adhesion molecules. In addition, early RCTs showed a reduced risk of mortality from CVDs with a higher intake of fatty fish or omega-3 PUFAs dietary supplements. The mechanisms of these PUFAs have been found to be similar to the pleiotropic effects of statins by improving endothelial functions and exerting antioxidant and anti-thrombotic effects. These results are further supported by animal studies, as rats fed with 12% fish oil (12% DHA, 18% EPA) exhibited significantly smaller infarct size as...
compared to control group. In addition, dietary supplementation of 12% fish oil in rats (13% DHA, 19% EPA) exerted cardioprotective effects against ischemia and reperfusion in isolated rat hearts. Additionally, a significant reduction in myocardial infarct size was observed in rabbits supplemented with EPA (600 mg/kg/day) and in pigs treated with DHA (45 mg), as compared to their respective controls. In addition, protective effects of omega-3 PUFAs from fish have been of special interest in coronary artery disease (CAD). High intakes of EPA and DHA were found to be associated with decreased CAD mortality in ecologic population prospective cohort studies and dietary intervention studies. Interestingly, DHA was found to be consistently reduced in patients with coronary heart disease as compared with controls, further highlighting the cardioprotective functions of this fatty acid. In middle-aged men from the ERA-JUMP study, high serum levels of LA and ARA were found to be linked with decreased concentrations of large very low density lipoprotein (VLDL) and increased levels of high density lipoprotein (HDL) particles, which have been found to be associated with increased risk for CAD.

Though a large body of evidence has supported the beneficial effects of omega-3 fatty acids, some recent clinical trials have shown conflicting results on the association of PUFAs in patients with prior CAD, stroke or major vascular outcomes. The randomized placebo-controlled trials including A Study of Cardiovascular Events in Diabetes (ASCEND) and Vitamin D and Omega-3 Trial (VITAL) have revealed that the supplementation with omega-3 PUFAs (1 g/day) has no effects on major cardiovascular events. Furthermore, the studies based on meta-analysis of large RCTs showed little or no association of omega-3 fatty acids with the risk of fatal and nonfatal coronary heart disease and major vascular events. Further investigation is required to develop a better understanding of the effects of omega-3 PUFAs on various CVD outcomes as well as to identify the optimal dose and risk-benefit balance for each individual receiving the therapy.

**Inflammation**

Inflammation is a body defense mechanism against pathogens and infections attacking the host along with tissue repair and hemostasis restoration. It is a self-regulatory process that involves secretion of anti-inflammatory mediators and activation of regulatory cells with the inhibition of signaling cascades that are pro-inflammatory. Fatty acids regulate inflammatory processes through different mechanisms involving membrane fluidity, surface/intracellular receptor binding, and cell signaling control, ultimately leading to the alterations in gene expression. Studies have shown that a high-fat diet alters the distribution of gut microbes and metabolic processes, activates inflammatory signaling pathways, resulting in an elevated number of inflammatory biomarkers such as TNF-α, IL-1 and IL-6. The enrichment with omega-3 PUFAs has been shown to reduce the levels of ARA and hence the production of ARA-derived pro-inflammatory eicosanoids e.g., leukotrienes, prostaglandins and thromboxanes. It has also been identified previously that the anti-inflammatory actions of EPA and DHA are largely responsible for their therapeutic efficacy in inflammation-related conditions including rheumatoid arthritis, dyslipidemia, diabetes, obesity, atherosclerosis, plaque rupture, cardiovascular and neurodegenerative diseases. Feeding fish oil results in the replacement of ARA by EPA in cell membranes, leading to the reduced expression of cyclooxygenases and lipoxygenases, thereby decreased activation of pro-inflammatory cascade. Studies have clearly shown that the protective effects of omega-3 fatty acids against various pathological conditions are largely mediated by their shifts in gut microbial populations, individual sensitivity and anti-inflammatory properties. However, some clinical studies and meta-analyses have shown inconsistent findings regarding the effects of PUFAs on the inflammatory status caused by various pathological conditions. Keeping in view these inconsistent findings, further investigation is needed to explore the mechanism of action of PUFAs as well as their therapeutic doses for the treatment of patients with different underlying conditions.

**Oxidative Stress**

Elevated oxidative stress is linked with increased risks of various inflammatory and heart diseases. The intake of omega-3 PUFAs particularly EPA and DHA has been considered as an effective preventive
strategy for the possible rise in lipid peroxidation, cytotoxicity and antioxidant modulation. Omega-3 PUFAs are sensitive to oxidative stress due to the presence of multiple double bonds in their polyene chain and therefore also contribute to the development of various pathologies related to the production of excessive free radicals, especially reactive oxygen species. Oxidative stress also leads to unsaturated lipid peroxidation which enhances the disbalanced redox homeostasis. An important example in this regard is, retinal lipofuscin, which is formed by the accumulation of pigments in epithelial cells of retina leading to an excessive oxidative stress and as a result an increased cellular toxicity. Omega-3 PUFAs have also shown antioxidant effects not only in retinal lipofuscin but also in CAD and related pathologies. There are some studies that have examined the baseline relationship between biomarkers of oxidative stress and omega-3 PUFAs and have also shown successful association of inflammation and depression with omega-3 PUFAs treatment. In particular, DHA and EPA are known to exhibit antioxidant effects by reducing the production of hydroxyl and superoxide radicals. However, treatment doses of PUFAs and individual responses of patients to treatment lead to variability in results.

Depression
Depression is one of the leading causes of mental disorders that results in productivity loss among individuals and increases the ratio of accidents and suicidal deaths. It also creates economy burden due to costly and long-term treatment of patients. Omega-3 PUFAs play important roles in brain functions and mood disorders, as EPA and DHA have been found in low levels in the patients’ blood samples. These PUFAs can be absorbed through neuronal cell membranes and affect mood swings, therefore, the consumption of fish oil and certain marine algae is highly recommended for patients with depression. This has also been studied in postpartum depression, manic depression, schizophrenia, attention seeking personality disorders and obsessive-compulsive disorders. The anti-inflammatory effects of these fatty acids may also be useful in depression and improving memory. Clinical trials with nonsteroidal and anti-inflammatory drugs have shown the beneficial effects of omega-3 PUFAs in managing depression in randomized placebo-controlled trials. However, due to the limited research and contradictory conclusions about the role of PUFAs in depression, further research is needed to reveal the benefits and risks associated with PUFAs treatment for the control of depression.

Cancer
The alterations in lipid composition have been reported in various cancer cell lines. Though the cancer patients show an impaired nutritional status, few studies have been performed to determine their fatty acid composition. A large body of evidence has revealed the importance of omega-3 PUFAs in the prevention of cancer, whereas, omega-6 PUFAs have been reported to promote cancer development. Therefore, the ratio 2-4:1 of omega-6/omega-3 is considered ideal to decrease the risk of cancer. Hence the diets containing disproportionately high omega-6/omega-3 PUFA ratios are supposed to contribute to the development of cancer. Epidemiological studies have shown that the consumption of a diet rich in omega-3 PUFAs exerts protective effects in suppressing the progression of different types of cancers including prostate, colon, breast and kidney cancer. Interestingly, reduced levels of plasma omega-3 PUFAs were found in patients with pancreatic cancer and non-small cell lung cancer. Bladder cancer cells showed high levels of stearic acid (18:0) and oleic acid (18:1n-9), whereas a significant reduction in ARA was detected in bladder cancer tissue, indicating changes in lipid metabolism during human bladder tumorgenesis. In addition, patients with multiple myeloma showed significant increase in plasma levels of omega-6 PUFAs and decreased levels of omega-3 PUFAs compared with healthy controls. Furthermore, the roles of an FDA-approved fish oil emulsion (Omegaven®) have been appreciated in the last years, as parenteral nutrition for postoperative recovery and as adjuvant in reducing chemotherapy-related toxicity in different cancers.

In contrast, however, some recent clinical studies (VITAL research group) and meta-analysis of RCTs (PUFAH group) have shown conflicting results regarding the role of these PUFAs in various cancer types, suggesting that the omega-3 PUFAs supplementation did not lower the risk or incidence
of cancer. The variability in the results can be attributed to the omega-3 PUFAs dose, omega-6/omega-3 PUFA ratios as well the genetic variability among individuals and requires further investigation.

**Neurodegenerative Disorders**

LC-PUFAs, notably DHA and ARA comprise about 15-30% of the brain’s dry weight where they play key roles in enhancing brain functions and development at various stages in life, from perinatal period, child- and adult-hood to aging. They mainly influence the architecture and functions of central nervous system, thereby regulating the blood-brain barrier functions, neurotransmission, and neuronal membrane fluidity. Studies have shown that low plasma DHA levels are associated with cognitive or behavioral impairments during early development or aging. Interestingly, an inadequate intake of maternal omega-3 PUFAs leads to a poor child’s neural development and vice versa. Furthermore, the deficiencies of these PUFAs in adults result in serious deficits in cognitive functions, leading to the onset of various age-related neurodegenerative disorders.

Alzheimer’s disease (AD) is the most common form of dementia, causing more than 70% of dementia cases worldwide in individuals older than 65 years. AD is characterized by multiple cognitive impairments, memory loss and altered behaviors, including delusion and paranoia. The pathology and symptoms of AD are poorly understood. Previous studies have linked AD to the respective neuroprotective and pathogenic effects of omega-3 and omega-6 PUFAs. However, how the imbalance in the ratio omega-3/omega-6 affects different stages of AD pathology is currently not fully understood.

The accumulation and aggregation of A has been found to be a central event in the pathogenesis of AD. DHA and EPA have been found to increase Aβ42 elimination, thereby enhancing the neurotrophin levels and reducing the pro-inflammatory cytokine production.

Epidemiological studies have suggested the higher intake of omega-3 PUFAs to be linked with reduced risk of AD. Innumerable prospective studies have shown that an increased intake of omega-3 or fish oil is inversely associated with dementia and AD risks.

The protective role of DHA is mainly due to its presence in large amounts in neuronal membrane phospholipids, where it is involved in the maintenance of nervous system functions. Furthermore, altered fatty acid profiles and low DHA levels were reported in different regions of brain in AD patients.

In 2006, the first placebo-controlled RCT (OmegAD Study) treated patients from mild to moderate AD with omega-3 PUFAs (1.7 g DHA + 0.6 g EPA). The study did not show any reduction in decline rate of the cognitive dysfunction except for a subgroup of patients (n=32) with very mild cognitive impairment. Furthermore, the data obtained from a systematic meta-analysis did not reveal any beneficial effects of omega-3 PUFAs in the treatment of mild to moderate AD, instigating the need to conduct highly controlled RTCs with longer treatment durations and optimal dose selection for each individual.

On the other hand, elevated levels of omega-6 PUFAs, particularly ARA were observed with PET scan in AD patients compared to healthy controls. Furthermore, an ARA-enriched diet has been shown to increase brain sensitivity towards the amyloid oligomer toxicity in mice.

Moreover, higher intake of omega-6 PUFAs causes a large production of the ARA derived pro-inflammatory cytokines (i.e. TNF-α, IL-1, and IFN-γ) which results in brain damage. Hence, the balance in the ratio of omega-6/omega-3 plays a significant role in the onset of AD, as lower ratios have been shown to decrease the possibility of developing dementia especially in depression patients.

Together, it can be suggested that patients having characteristics of cognitive impairments and dementia can be improved with an increased intake of omega-3 PUFAs or a balanced omega-6/omega-3 PUFAs ratio in the early stages of the disease.

Another neurodegenerative condition includes Parkinson’s disease (PD), which was described in 1817 by James Parkinson as a complex age-related neurological syndrome, with common features including dementia, tremor, rigidity and depression in the later stage of the disease. High intake of omega-3 PUFAs was found to be neuroprotective, in an animal model of Parkinsonism, against a neurotoxin-induced decrease in dopamine in the striatum. Furthermore, DHA has been shown to
induce the recovery of the dopaminergic system after an extensive Parkinson’s injury in mice, suggesting that the role of DHA in neuro-recovery can be potentially exploited after PD diagnosis. There are insufficient clinical trials studying the role of PUFAs in PD, however in vitro and in vivo studies have shown EPA as potential adjunctive therapy for PD. A recent clinical trial explored the functions of DHA in decreasing dyskinesia in PD (ClinicalTrials.gov; identifier: NCT01563913). Moreover, another study showed the correlation of DHA supplementation with a lower risk of PD-associated depression. A six-months treatment with fish oil (800 mg/d DHA and 290 mg/d EPA) showed 50% reduction in the Hamilton Rating Scale for Depression score in DHA-treated patients, suggesting that DHA supplementation reduced depression symptoms. Furthermore, a randomized double-blind placebo-controlled clinical trial on 60 patients supplemented with 1000 mg of omega-3 with vitamin E supplements for three months showed beneficial effects in improving clinical symptoms associated with PD. However, a case-control study has reported the lack of association between omega-3 PUFAs and PD development risk. Further large randomized controlled clinical trials need to be conducted with relatively longer treatment durations to explore the role of PUFAs in PD.

Huntington’s disease is an inherited neurodegenerative disorder caused due to dominant polyglutamine expansion located close to the N-terminus of the Huntingtin protein. A pilot study on the advanced (stage III) Huntington’s disease showed that the patients treated with ethyl-ester of EPA (ethyl-EPA) had a beneficial effect on the orofacial abnormalities associated with this disease. Recently, in order to cope with the oxidative damage caused by lipid peroxidation in HD, the diet enriched with deuterium-reinforced PUFAs (D-PUFAs) was fed to a knock in mouse model of HD (Q140), which represents motor deficits and cognitive decline. Interestingly, the mice showed significant reduction in F₂-isoprostanes in the striatum (80%), suggesting that D-PUFAs may represent a promising new strategy in improving the HD core deficits in humans. Moreover, some clinical studies have also observed the promising efficacy of omega-3 PUFAs in the prevention or onset delay of other neurological disease such as multiple sclerosis, amyotrophic lateral sclerosis, and epilepsy. The neuroprotective effects of omega-3 PUFAs have shown potential as adjunctive therapies for neurodegenerative diseases. However, these compounds may also have the potential to worsen the condition and essential measures should be taken while considering their roles in neurodegenerative disorders and targeted therapeutic interventions.

Conclusion
A growing body of evidence from experimental and epidemiological studies invigorated the investigation of the effectiveness of omega-3 PUFAs supplementation in clinical trials. Most of these trials have suggested that omega-3 PUFAs contribute significantly to the prevention, treatment and/or management of various pathophysiological conditions and do not raise serious safety concerns. PUFAs have gained considerable significance for the identification of risk factors associated with a wide number of pathological conditions, thus stratifying the individuals based on their health and disease status. However, some research findings have also shown conflicting results regarding the beneficial properties of omega-3 PUFAs in different diseases including CVDs, diabetes, cancer, and neurodegenerative disorders. Several reasons may explain these controversies and emphasize upon the careful consideration of different treatment parameters, such as the natural sources containing different amounts of PUFAs, the chemical form and the quality of PUFAs formulations affecting their bioavailability, the omega-6/omega-3 ratio as well as the omega-3 index indicating the PUFAs enrichment in different organs. This may lead to variable effects in different clinical trials as well as in the studies based on meta-analyses of these trials. Therefore, there is an evident need to conduct highly controlled RCTs with larger sample sizes and longer duration of supplementation in order to assess the therapeutic potential of these PUFAs for different age groups, and also taking into consideration the ethnicity as well as individuals’ genetic backgrounds.

REFERENCES
1. Zarate R, El Jaber-Vazdeks N, Tejera N, Perez JA, Rodriguez...
C. Significance of long chain polyunsaturated fatty acids in human health. Clin Transl Med. 2017; 6: 25.
2. Mathias RA, Fu W, Akey JM, Ainsworth HC, Torgerson DG, Ruczinski I, et al. Adaptive evolution of the FADS gene cluster within Africa. PLoS One. 2012; 7: e44926.
3. Stark AH, Crawford MA, Reifen R. Update on alpha-linolenic acid. Nutr Rev. 2008; 66: 326-32.
4. Hussein N, Ah-Sing E, Wilkinson P, Leach C, Griffin BA, Millward DJ. Long-chain conversion of [13C]linoleic acid and alpha-linolenic acid in response to marked changes in their dietary intake in men. J Lipid Res. 2005; 46: 269-80.
5. Benatti P, Peluso G, Nicolai R, Calvani M. Polyunsaturated fatty acids: biochemical, nutritional and epigenetic properties. J Am Coll Nutr. 2004; 23: 281-302.
6. Jonasdottir SH. Fatty Acid Profiles and Production in Marine Phytoplankton. Mar Drugs. 2019; 17: 151.
7. Peltoamaa E, Johnson MD, Taipale SJ. Marine Cryptophytes Are Great Sources of EPA and DHA. Mar Drugs. 2017; 16: 3.
8. Moi IM, Leow ATC, Ali MSM, Rahman R, Salleh AB, Sabri S. Polysaturated fatty acids in marine bacteria and strategies to enhance their production. Appl Microbiol Biotechnol. 2018; 102: 5811-26.
9. Ghiffary MR, Kim HU, Chang YK. Metabolic Engineering Strategies for the Enhanced Microalgal Production of Long-Chain Polysaturated Fatty Acids (LC-PUFAs). Biotechnol J. 2019; 14: e1900043.
10. Wang Y, Botolin D, Xu J, Christian B, Mitchell E, Jayaprakasam B, et al. Regulation of hepatic fatty acid elongase and desaturation expression in diabetes and obesity. J Lipid Res. 2006; 47: 2028-41.
11. Burke PA, Ling PR, Forse RA, Lewis DW, Jenkins R, Bistrian BR. Sites of conditional essential fatty acid deficiency in end stage liver disease. JPEN J Parenter Enteral Nutr. 2001; 25: 188-93.
12. Moore SA, Hurt E, Yoder E, Sprecher H, Spector AA. Docosahexaenoic acid synthesis in human skin fibroblasts involves peroxisomal retroconversion of tetracosahexaenoic acid. J Lipid Res. 1995; 36: 2433-43.
13. Su HM, Moser AB, Moser HW, Watkins PA. Peroxisomal straight-chain Acyl-CoA oxidase and D-bifunctional protein are essential for the retroconversion step in docosahexaenoic acid synthesis. J Biol Chem. 2001; 276: 38115-20.
14. Sprecher H, Chen Q. Polysaturated fatty acid biosynthesis: a microsomal-peroxisomal process. Prostaglandins, Leukotrienes and Essential Fatty Acids. 1999; 60: 317-21.
15. Sprecher H. Metabolism of highly unsaturated n-3 and n-6 fatty acids. Biochimica et Biophysica Acta (BBA) - Molecular and Cell Biology of Lipids. 2000; 1486: 219-31.
16. Saini RK, Keum YS. Omega-3 and omega-6 polyunsaturated fatty acids: Dietary sources, metabolism, and significance - A review. Life Sci. 2018; 203: 255-67.
17. Schmitz G, Ecker J. The opposing effects of n-3 and n-6 fatty acids. Prog Lipid Res. 2008; 47: 147-55.
18. Simopoulos AP. Importance of the omega-6/omega-3 balance in health and disease: evolutionary aspects of diet. World Rev Nutr Diet. 2011; 102: 10-21.
19. Wall R, Ross RP, Fitzgerald GF, Stanton C. Fatty acids from fish: the anti-inflammatory potential of long-chain omega-3 fatty acids. Nutr Rev. 2010; 68: 280-9.
20. Weylandt KH, Serini S, Chen YQ, Su HM, Lim K, Cittadini A, et al. Omega-3 Polyunsaturated Fatty Acids: The Way Forward in Times of Mixed Evidence. Biomed Res Int. 2015; 2015: 143109.
21. Amjad KW, Chun-Mei H, Khan N, Iqbal A, Lyu SW, Shah F. Bioengineered Plants Can Be a Useful Source of Omega-3 Fatty Acids. Biomed Res Int. 2017; 2017: 7348919.
22. Shahidi F, Ambigaipalan P. Omega-3 Polyunsaturated Fatty Acids and Their Health Benefits. Annu Rev Food Sci Technol. 2018; 9: 345-81.
23. Expert Panel on Detection Evaluation Treatment of High Blood Cholesterol in Adults. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). 2001 May 16. Report No. 0098-7484 (Print) 0098-7484 (Linking) Contract No. 19.
24. Wilson PW, D’Agostino RB, Parise H, Sullivan L, Meigs JB. Metabolic syndrome as a precursor of cardiovascular disease and type 2 diabetes mellitus. Circulation. 2005; 112: 3066-72.
25. Guo XF, Li X, Shi M, Li D. n-3 Polyunsaturated Fatty Acids and Metabolic Syndrome Risk: A Meta-Analysis. Nutrients. 2017; 9: 703.
26. Lorente-Cebrian S, Costa AG, Navas-Carretero S, Zubala M, Martinez JA, Moreno-Aliaga MJ. Role of omega-3 fatty acids in obesity, metabolic syndrome, and cardiovascular diseases: a review of the evidence. J Physiol Biochem. 2013; 69: 633-51.
27. Carpenter YL, Portois L, Malaisse WJ. n-3 fatty acids and the metabolic syndrome. Am J Clin Nutr. 2006; 83: 1499S-504S.
28. Chen C, Xu Y, 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.
29. Vanhala M, Saltevo J, Soininen P, Kautiainen H, Kangas AJ, Ala-Korpela M, et al. Serum omega-6 polyunsaturated fatty acids and the metabolic syndrome: a longitudinal population-based cohort study. Am J Epidemiol. 2012; 176: 253-60.
30. Brown TJ, Brainard J, Song F, Wang X, Abdelhamid A, Hooper L, et al. Omega-3, omega-6, and total dietary polyunsaturated fat for prevention and treatment of type 2 diabetes mellitus: systematic review and meta-analysis of randomised controlled trials. BMJ. 2019; 366: l4697.
31. Akinkuolie AO, Ngwa JS, Meigs JB, D’Agostino RB, Wilson PW, D’Agostino RB, Parise H, Sullivan L, Meigs JB. Report No. 0098-7484 (Print) 0098-7484 (Linking) Contract No. 19.
32. Rossi AS, Lombardo YB, Lacorte JM, Chicco AG, Rouault C, Slama G, et al. Dietary fish oil positively regulates plasma leptin and adiponectin levels in sucrose-fed, insulin-resistant rats. Am J Physiol Regul Integr Comp Physiol. 2005; 289: R486-R94.
33. Kondo K, Morino K, Nishio Y, Kondo M, Fuke T, Ugi S, et al. Effects of a fish-based diet on the serum adiponectin concentration in young, non-obese, healthy Japanese
subjects. J Atheroscler Thromb. 2010; 17: 628-37.
34. Du S, Jin J, Fang W, Su Q. Does Fish Oil Have an Anti-Obesity Effect in Overweight/Obesen Adults? A Meta-Analysis of Randomized Controlled Trials. PLoS One. 2015; 10: e0142652.
35. Howe P, Buckley J. Metabolic health benefits of long-chain omega-3 polyunsaturated fatty acids. Mil Med. 2014; 179: 138-43.
36. Mortality GBD, Causes of Death C. Global, regional, and national life expectancy, all-cause mortality, and cause-specific mortality for 249 causes of death, 1980-2015: a systematic analysis for the Global Burden of Disease Study 2015. Elsevier; 2016 Oct 8. Report No. 1474-547X (Electronic)0140-6736 (Linking) Contract No. 10053.
37. Ramsden CE, Zamora D, Leelarthaepin B, Majchrzak-Hong SF, Faurot KR, Suchindran CM, et al. Use of dietary linoleic acid for secondary prevention of coronary heart disease and death: evaluation of recovered data from the Sydney Diet Heart Study and updated meta-analysis. BMJ. 2013; 346:e8707.
38. Bird JK, Calder PC, Eggersdorfer M. The Role of n-3 Long Chain Polyunsaturated Fatty Acids in Cardiovascular Disease Prevention, and Interactions with Statins. Nutrients. 2018; 10: 775.
39. Goodfellow J, Bellamy MF, Ramsey MJ, Lewis MJ. Dietary supplementation with marine omega-3 fatty acids improve systemic large artery endothelial function in subjects with hypercholesterolemia. Journal of the American College of Cardiology. 2000; 35: 265-70.
40. Hu Y, Hu FB, Manson JE. Marine Omega-3 Supplementation and Cardiovascular Disease: An Updated Meta-Analysis of 13 Randomized Controlled Trials Involving 127 477 Participants. J Am Heart Assoc. 2019; 8: e013543.
41. Sethi A, Bajaj A, Khosla S, Arora RR. Statin Use Mitigate the Implications of Fatty Acids in Maintaining Health
42. Omen CM, Feskens EJ, Rasanen L, Fidanza F, Nissinen AM, Menotti A, et al. Fish consumption and coronary heart disease mortality in Finland, Italy, and The Netherlands. Am J Epidemiol. 2000; 151: 999-1006.
43. Bucher HC, Hengstler P, Schindler C, Meier G. N-3 polyunsaturated fatty acids in coronary heart disease: a meta-analysis of randomized controlled trials. The American Journal of Medicine. 2002; 112: 298-304.
44. Harris WS, Poston WC, Haddox CK. Tissue n-3 and n-6 fatty acids and risk for coronary heart disease events. Atherosclerosis. 2007; 193: 1-10.
45. Choo J, Ueshima H, Curb JD, Shin C, Evans RW, El-Saied A, et al. Serum n-6 fatty acids and lipoprotein subclasses in middle-aged men: the population-based cross-sectional ERA-JUMP study. Am J Clin Nutr. 2010; 91: 1195-203.
46. Tummala R, Ghosh RK, Jain V, Devanabanda AR, Bandypadhyay D, Deedwania P, et al. Fish Oil and Cardiometabolic Diseases: Recent Updates and Controversies. The American Journal of Medicine. 2019; 132: 1153-9.
47. Bowman L, Mafham M, Stevens W, Haynes R, Aung T, Chen F, et al. ASCEND: A Study of Cardiovascular Events in Diabetes: Characteristics of a randomized trial of aspirin and of omega-3 fatty acid supplementation in 15,480 people with diabetes. Am Heart J. 2018; 198: 135-44.
48. Manson JE, Cook NR, Lee IM, Christen W, Wassell SS, Mora S, et al. Marine n-3 Fatty Acids and Prevention of Cardiovascular Disease and Cancer. N Engl J Med. 2019; 380: 23-32.
49. Aung T, Halsey J, Kromhout D, Gerstein HC, Marchioli R, Tavazzi L, et al. Associations of Omega-3 Fatty Acid Supplement Use With Cardiovascular Disease Risks: Meta-analysis of 10 Trials Involving 77917 Individuals. JAMA Cardiol. 2018; 3: 225-34.
50. Abdelhamid A, Martin N, Bridges C, Song F, Deane KHO, Hooper L. Polyunsaturated fat intake for prevention of cardiovascular disease. Cochrane Database of Systematic Reviews. 2016.
51. Calder PC. Marine omega-3 fatty acids and inflammatory processes: Effects, mechanisms and clinical relevance. Biochim Biophys Acta. 2015; 1851: 469-84.
52. Mantzoros E, Cleland LG, Gibson RA, Neumann MA, Demasi M, James MJ. Biochemical effects of a diet containing foods enriched with n-3 fatty acids. Am J Clin Nutr. 2000; 72: 42-8.
53. Fritsche KL. The science of fatty acids and inflammation. Adv Nutr. 2015; 6: 2935-3015.
54. Endres S, Meydani SN, Ghorbani R, Schindler R, Dinarello CA. Dietary supplementation with n-3 fatty acids suppresses interleukin-2 production and mononuclear cell proliferation. Journal of Leukocyte Biology. 1993; 54: 599-603.
55. Miles EA, Calder PC. Influence of marine n-3 polyunsaturated fatty acids on immune function and a systematic review of their effects on clinical outcomes in rheumatoid arthritis. Br J Nutr. 2012; 107: S171-84.
56. Ferrucci L, Cherubini A, Bandinelli S, Bartali B, Corsi A, Lauretani F, et al. Relationship of plasma polyunsaturated fatty acids to circulating inflammatory markers. J Clin Endocrinol Metab. 2006; 91: 439-46.
57. Sabour H, Larijani B, Vafa MR, Hadian MR, Heshmat R, Meybodi HA, et al. The effects of n-3 fatty acids on inflammatory cytokines in osteoporotic spinal cord injured patients: A randomized clinical trial. J Res Med Sci. 2012; 17:
72. Su H, Liu R, Chang M, Huang J, Jin Q, Wang X. Effect of dietary alpha-linolenic acid on blood inflammatory markers: a systematic review and meta-analysis of randomized controlled trials. Eur J Nutr. 2018;57:877-91.

73. Johnson GH, Fritsche K. Effect of dietary linoleic acid on markers of inflammation in healthy persons: a systematic review of randomized controlled trials. J Acad Nutr Diet. 2012;112:1029-41.

74. Paszkow FJ. Oxidative Stress and Inflammation in Heart Disease: Do Antioxidants Have a Role in Treatment and/or Prevention? Int J Inflamm. 2011;2011:514623.

75. Mazereeuw G, Lanctot KL, Chau SA, Swardfager W, Herrmann N. Effects of omega-3 fatty acids on cognitive performance: a meta-analysis. Neurobiol Aging. 2012;33:e17-29.

76. Nowak JZ. Oxidative stress, polyunsaturated fatty acids-derived oxidation products and bis retinoids as potential inducers of CNS diseases: focus on age-related macular degeneration. PharmacoRes. 2013;65:288-304.

77. Markesbery WR, Kryscio RJ, Lovell MA, Morrow JD. Lipid peroxidation is an early event in the brain in amnestic mild cognitive impairment. Ann Neurol. 2005;58:730-5.

78. Azizi-Soleiman F, Jazayeri S, Eghtesad S, Rajab A, Heidari I, Vafa MR, et al. Effects of pure eicosapentaenoic and docosahexaenoic acids on oxidative stress, inflammation and body fat mass in patients with type 2 diabetes. International journal of preventive medicine. 2013;4:922-8.

79. Mazereeuw G, Herrmann N, Andreazza AC, Scola G, Ma DWL, Oh PI, et al. Oxidative stress predicts depressive symptom changes with omega-3 fatty acid treatment in coronary artery disease patients. Brain Behav Immun. 2017;60:136-41.

80. Abdukeyum GG, Owen AJ, Larkin TA, McLennan PL. Up-Regulation of Mitochondrial Antioxidant Superoxide Dismutase Underpins Persistent Cardiac Nutritional-Preconditioning by Long Chain n-3 Polyunsaturated Fatty Acids in the Rat. Journal of clinical medicine. 2016;5:32.

81. Mazereeuw G, Herrmann N, Oh PI, Ma DW, Wang CT, Kiss A, et al. Omega-3 Fatty Acids, Depressive Symptoms, and Cognitive Performance in Patients With Coronary Artery Disease: Analyses From a Randomized, Double-Blind, Placebo-Controlled Trial. J Clin Psychopharmacol. 2016;36:436-44.

82. Okereke OI, Reynolds CF, 3rd, Mischoulon D, Chang G, Cook NR, Copeland T, et al. The ViTamin D and OmegA-3 TriA-L DepresSion Endpoint Prevention (VITAL-DEP): Rationale and design of a large-scale ancillary study evaluating vitamin D and marine omega-3 fatty acid supplements for prevention of late-life depression. Contemp Clin Trials. 2018;68:133-45.

83. Baumgart M, Snyder HM, Carrillo MC, Fazio S, Kim H, Johns H. Summary of the evidence on modifiable risk factors for cognitive decline and dementia: A population-based perspective. Alzheimers Dement. 2015;11:718-26.

84. Zanoaga O, Jurj A, Ruduly L, Cojocneanu-Petric R, Fuentes-Mattei E, Wu O, et al. Implications of dietary omega-3 and omega-6 polyunsaturated fatty acids in breast cancer. Exp Ther Med. 2018;15:1167-76.

85. Zamaria N. Alteration of polyunsaturated fatty acid status and metabolism in health and disease. Reproduction Nutrition Development. 2004;44:273-82.

86. Simopoulos AP. The omega-6/omega-3 fatty acid ratio: health implications. Oléagineux, Corps gras, Lipides. 2010;17:267-75.

87. Fradet V, Cheng I, Casey G, Witte JS. Dietary omega-3 fatty acids, cyclooxygenase-2 genetic variation, and aggressive prostate cancer risk. Clin Cancer Res. 2009;15:2559-66.

88. Courtney ED, Matthews S, Finlayson C, Di Pierro D, Belluzzi A, Roda E, et al. Eicosapentaenoic acid (EPA) reduces crypt cell proliferation and increases apoptosis in normal colonic mucosa in subjects with a history of colorectal adenomas. Int J Colorectal Dis. 2007;22:765-76.

89. Wolk A, Larsson SC, Johansson JE, Ekman P. Long-term fatty fish consumption and renal cell carcinoma incidence in women. JAMA. 2006;296:1371-6.

90. Zheng JS, Hu XJ, Zhao YM, Yang J, Li D. Intake of fish and marine n-3 polyunsaturated fatty acids and risk of breast cancer: meta-analysis of data from 21 independent prospective cohort studies. BJM. 2013;346:f3706.

91. Zuijdegeest-van Leeuwen SD, van der Heijden MS, Rietveld T, van den Berg JW, Tilanus HW, Burgers JA, et al. Fatty acid composition of plasma lipids in patients with pancreatic, lung and oesophageal cancer in comparison with healthy subjects. Clin Nutr. 2002;21:225-30.

92. Miryaghoubzadeh J, Darabi M, Madaen K, Shaaker M, Meh dizadeh A, Hajjhosseini R. Tissue fatty acid composition in human urothelial carcinoma. Br J Biomed Sci 2013;70:1-5.

93. Jurczyzyn A, Czepli J, Gdula-Argasinska J, Pasko P, Czap kiewicz A, Librowski T, et al. Plasma fatty acid profile in multiple myeloma patients. Leuk Res. 2015;39:400-5.

94. Zhang B, Wei G, Li R, Wang Y, Yu J, Wang R, et al. n-3 fatty acid-based parenteral nutrition improves postoperative recovery for cirrhotic patients with liver cancer: A randomized controlled clinical trial. Clin Nutr. 2017;36:1239-44.

95. Eltweri AM, Thomas AL, Chung WY, Morgan B, Thompson J, Dennison AR, et al. The Effect of Supplementary Omega-3(R) on the Clinical Outcome of Patients With Advanced Esophagogastroduodenal Adenocarcinoma Receiving Palliative Epirubicin, Oxaliplatin, and Capecitabine Chemotherapy: A Phase II clinical trial. Anticancer Res. 2019;39:853-61.

96. Hanson S, Thorpe G, Winstanley L, Abdelhamid AS, Hooper L, group P. Omega-3, omega-6 and total dietary polyunsaturated fat on cancer incidence: systematic review and meta-analysis of randomised trials. Br J Cancer. 2020;122:1260-70.

97. Conquer JA, Tierney MC, Zecevic J, Bettger WJ, Fisher RH. Fatty acid analysis of blood plasma of patients with Alzheimer’s disease, other types of dementia, and cognitive impairment. Lipids. 2000;35:1305-12.

98. Innis SM. Dietary omega 3 fatty acids and the developing brain. Brain Res. 2008;1237:35-43.

99. Cederholm T, Salem N, Palmblad J. Omega-3 fatty acids in the prevention of cognitive decline in humans. Adv Nutr.
103. Samieri C, Feart C, Letenneur L, Dartigues JF, Peres K, Auriacombe S, et al. Low plasma eicosapentaenoic acid and depressive symptomatology are independent predictors of dementia risk. Am J Clin Nutr. 2008; 88: 714-21.

104. Goetz CG. The history of Parkinson's disease: early clinical descriptions and neurological therapies. Cold Spring Harb Perspect Med. 2011; 1: a008862.

105. Bousquet M, Saint-Pierre M, Julien C, Salem N, Cicchetti F, Calon F. Beneficial effects of dietary omega-3 polyunsaturated fatty acid on toxin-induced neuronal degeneration in an animal model of Parkinson's disease. FASEB J. 2008; 22: 1213-25.

106. Coulombe K, Saint-Pierre M, Cisbani G, St-Amour I, Gibrat C, Gigueré-Rancourt A, et al. Partial neurorescue effects of DHA following a 6-OHDA lesion of the mouse dopaminergic system. The Journal of Nutritional Biochemistry. 2016; 30: 133-42.

107. da Silva TM, Munhoz RP, Alvarez C, Naliwaiko K, Kiss A, Andreatti R, et al. Depression in Parkinson's disease: a double-blind, randomized, placebo-controlled pilot study of omega-3 fatty acid supplementation. J Affect Disord. 2008; 111: 351-9.

108. Pomponi M, Loria G, Salvati S, Di Biase A, Conte G, Villella C, et al. DHA effects in Parkinson disease depression. Basal Ganglia. 2014; 4: 61-6.

109. Taghizadeh M, Tamtaji OR, Dadgostar E, Daneshvar Kakhki R, Bahmani F, Abolhassani J, 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: 183-9.

110. Miyake Y, Sasaki S, Tanaka K, Fukushima W, Kiyohara C, Tsuboi Y, et al. Dietary fat intake and risk of Parkinson's disease: a case-control study in Japan. J Neurol Sci. 2010; 288: 117-22.

111. Puri BK, Bydder GM, Counsell SJ, Corridan BJ, Richardson AJ, Hajnal JV, et al. MRI and neuropsychological improvement in Huntington disease following ethyl-EPA treatment. Neuroreport. 2002; 13: 123-6.

112. Hatami A, Zhu C, Relano-Gines A, Elias C, Galstyan A, Jun M, et al. Deuterium-reinforced linoleic acid lowers lipid peroxidation and mitigates cognitive impairment in the Q140 knock in mouse model of Huntington's disease. FEBS J. 2018; 285: 3002-12.

113. Fitzgerald KC, O'Reilly EJ, Falcone GJ, McCullough ML, Park Y, Kolonen LN, et al. Dietary omega-3 polyunsaturated fatty acid intake and risk for amyotrophic lateral sclerosis. JAMA Neurol. 2014; 71: 1102-10.

114. Schlanger S, Shinitzky M, Yam D. Diet enriched with omega-3 fatty acids alleviates convulsion symptoms in epilepsy patients. Epilepsia. 2002; 43: 103-4.