



## THE IMPORTANCE OF OMEGA-3



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## What are Omega-3 Fatty Acids and Where Can I Find Them?

Omega-3 fatty acids are polyunsaturated fatty acids and consist of *eicosapentaenoic acid* (EPA), *docosahexaenoic acid* (DHA), and *alpha-linolenic acid*.<sup>[1]</sup> Omega-3 is an essential fatty acid (EFA) that must be provided in the diet, and cannot be made within the human body.<sup>[2]</sup> Fatty fish, such as salmon, are the primary source of both EPA and DHA currently

in the human diet. However, the EPA and DHA that fish store in their fat comes from ingestion of microalgae, such as zooplankton and phytoplankton. *Microalgae Oil*, thus, is an alternative to fish oil which is more sustainable, and is also high in EPA and DHA, and already available on the market.<sup>[3]</sup> *Microalgae Oil* has the added benefit of being more appropriate for some vegetarian diets. Flax seed, walnuts and soybeans are the primary sources of ALA.<sup>[1]</sup>

Another class of polyunsaturated fatty acids are the omega-6 fatty acids. The first member of the omega-6 fatty acids is *linoleic acid* (LA) and the major dietary source consist of most vegetable oils including corn, peanut, sunflower, safflower, and olive oil.<sup>[2]</sup> The ideal dietary ratio of omega-6 to omega-3 fatty acids is approximately 1:1. However, the ratio of omega-6 to omega-3 fatty acids in the average American diet is about 20:1.

<sup>[4]</sup>What we lack in omega-3 in our diet, our bodies must instead, use omega 6 as a substitute. The consequences of excess omega-6 fatty acids are detrimental and promote many diseases including cardiovascular disease, cancer, diabetes, inflammatory, and autoimmune diseases.<sup>[5][6][7][8][9]</sup> It is important to note that omega-3 and omega-6 fatty acids compete for the same desaturase enzyme, delta-6 desaturase.<sup>[10]</sup> Both alpha-linolenic acid (omega-3) and linoleic acid (omega-6) bind to delta-6 desaturase, however, alpha-linolenic acid (ALA) has a higher affinity for the enzyme. Upon binding to delta-6 desaturase, alpha-linolenic acid (ALA) can be converted into eicosapentaenoic acid (EPA) and, subsequently, docosahexaenoic acid (DHA), whereas, linoleic acid (LA) is converted into arachidonic acid, a very potent pro-inflammatory molecule.<sup>[10]</sup> An additional study found that linoleic acid (omega-6) inhibits eicosapentaenoic acid (EPA) incorporation from dietary fish oil supplements.<sup>[11]</sup> These data suggest that in order to obtain maximum benefits from omega-3 fatty acids it is important to decrease omega-6 fatty acid intake. It is also very important to note that although ALA can be converted into EPA and DHA, this conversion is very inefficient. In one study, only 5% of ALA was converted into EPA and only 0.5% was converted into DHA.<sup>[12]</sup> (ALA).

## Recommended Doses of Omega-3 Supplementation

In 2002, the U.S. Institute of Medicine established a daily adequate intake of omega-3 fatty acids (see table below).<sup>[13]</sup> However, these recommended values are contested by studies that suggest higher levels of omega-3 may be necessary for the general population.<sup>[14]</sup>

Age/Sex	Amount
Infants (0-12 months)	0.5 grams
Children (1-3 years)	0.7 grams
Children (4-8 years old)	0.9 grams
Children (9-13 years old)	1.0 grams
Female Adolescents and Adults (14+ years)	1.1 grams
Male Adolescents and Adults (14+ years)	1.6 grams
Female (Pregnant)	1.4 grams

The American Heart Association recommends 2-4 grams daily of EPA + DHA omega-3 fatty acids for patients that need to lower their serum triglyceride levels.<sup>[15]</sup>

## Vitamin E

Omega-3 fatty acids are easily oxidized and highly susceptible to lipid peroxidation, which is oxidative damage of lipids. <sup>[16]</sup> Vitamin E plays a critical role in the prevention of oxidation of omega-3 fatty acids. Data from both animal and human studies indicates that as omega-3 fatty acid intake is increased, higher levels of vitamin E are required to prevent lipid peroxidation. The recommended ratio of vitamin E to omega-3 intake is 0.6 mg of vitamin E or every gram of omega-3 fatty acid. <sup>[16]</sup>

## Omega-3 Safety, Side Effects, and Toxicity

The National Institute of Medicine has not established a tolerable upper level of intake for omega-3 fatty acids. <sup>[13]</sup> Omega-3 fatty acids are well-tolerated and serious adverse side effects have not been reported. The most common adverse side effect is a fishy aftertaste. It has been reported that excessive doses of omega-3 fatty acids may prolong bleeding time. <sup>[17]</sup>

## The Anti-Inflammatory Properties of Omega-3

Inflammation is responsible for an plethora of diseases including rheumatoid arthritis, atherosclerosis, asthma, inflammatory bowel disease, depression, Crohn's disease, ulcerative colitis, psoriasis, lupus erythematosus, multiple sclerosis, migraine headaches, and diabetes. <sup>[18][19][20]</sup> Omega 6 fatty acids produce arachidonic acid and subsequently generate pro-inflammatory eicosanoids such as prostaglandin (PG)E<sub>2</sub>, leukotriene B<sub>4</sub>, and thromboxane A<sub>2</sub>, which all mediate the inflammatory response. <sup>[21]</sup> Fish Oil, as well as other omega-3 fatty acids, inhibit the conversion of arachidonic acid to prostaglandins and leukotrienes, decreasing the inflammatory response. <sup>[22]</sup> Supplementation with omega-3 also reduces serum levels of tumor necrosis factor alpha (TNF-alpha) and interleukin 1 (IL-1), both markers of inflammation. <sup>[23][24]</sup> Additionally, DHA supplementation reduces inflammation as measured by decreased levels of C-reactive protein (CRP) and IL-6, both markers of inflammation. <sup>[25]</sup> These data suggest that omega-3 fatty acids are potent anti-inflammatory molecules.

## Rheumatoid Arthritis



The pro-inflammatory cytokines TNF-alpha and IL-1 are both implicated in the cause of chronic arthritis. <sup>[26][27]</sup> The synthesis of both TNF-alpha and IL-1 beta are dramatically reduced in humans supplementing with omega-3 fatty acids from fish oil. <sup>[28]</sup>

In another study, humans supplementing 9 grams of fish oil daily for four weeks displayed a **74% reduction in TNF-alpha and 80% decrease in IL-1 beta synthesis**. <sup>[29]</sup> Patients with rheumatoid arthritis ameliorated their clinical symptoms and decreased their TNF-alpha and IL-1 beta levels when supplementing with high doses of fish oil daily. <sup>[30]</sup> In a mouse model

## Eczema



Severe Eczema

There is increasing evidence that consumption of omega-3 fatty acids are beneficial in the treatment of eczema. In a double-blind, randomized, controlled study patients suffering from eczema supplementing with 5.4 grams of DHA omega-3 daily showed significant clinical improvement of eczema compared to controls. <sup>[32]</sup> Another study found that fish intake during early infancy decreased the incidence of developing eczema in childhood. <sup>[33]</sup>

## Diabetes

### Type 1 Diabetes

Several studies have shown that inflammation is a causative factor in the pathogenesis of *type 1 diabetes*. <sup>[34][35]</sup> An 8 year study involving 1,770 children with an increased risk for type 1 diabetes, concluded that those children with a high omega-3 intake were **55% less likely to develop type 1 diabetes**. <sup>[36]</sup>

### Type 2 Diabetes

Inflammation has also been implicated in the cause of *type 2 diabetes*, the pro-inflammatory cytokine, TNF-alpha, induces insulin resistance, a hallmark of type 2 diabetes. <sup>[37][38]</sup> Several studies have demonstrated that omega-3 fatty acids can reduce TNF-alpha levels <sup>[23][29][30]</sup>, therefore, can play a preventative role in the etiology of type 2 diabetes. Patients with type 2 diabetes supplementing with fish oil have improved insulin resistance and lower triglyceride levels. <sup>[39]</sup> In another study, people supplementing with 6g of fish oil daily reduced their insulin response to glucose by 40%, which means they are significantly less likely to become insulin resistant and/or diabetic. <sup>[40]</sup>

### Type 2 Diabetes and Cardiovascular Disease

People with type 2 diabetes have an increased risk for cardiovascular disease (CVD). <sup>[41]</sup> A meta-analysis of 18 randomized, controlled studies examining the effect of fish oil supplementation on patients with type 2 diabetes, found that fish oil **lowered triglyceride levels by 31mg/dl**, thus, decreased their risk for CVD. <sup>[42]</sup> In another meta-analysis of 18 randomized controlled studies, patients supplementing with fish oil had **25% lower triglyceride levels, 36% lower VLDL-cholesterol levels, and 39.7% lower VLDL-triacylglycerol levels**. <sup>[43]</sup> A 16 year long study including approximately 5,000 women with type 2 diabetes, found that those with a high consumption of fish oil had a significantly lower incidence of coronary heart disease (CHD) and a significantly lower total mortality.

[44]Therefore, people that are insulin resistant or have type 2 diabetes should include consumption of fish oil as a part of their daily regimen as a means of cardioprotection. [45] Additionally, fish oil supplementation prevents insulin resistance from a high fat diet in a rat model for diabetes. [46]

## Obesity

Fish oil promotes weight loss. In young, obese males, the addition of fish oil to their caloric-restricted diet, resulted in 1 kg more weight loss after 4 weeks, compared to those on a caloric-restricted diet without fish oil. [47]Omega-3 fatty acids have anti-obesity effects by inhibiting lipid uptake into adipocytes, decreasing fatty acid synthesis, and increasing lipid oxidation. [48]The omega-3 fatty acids EPA and DHA drastically reduce triglycerol and free fatty acid levels, which have tremendous benefits for people that are overweight and those with metabolic syndrome. [49][50]

Omega-3 fatty acids has been shown to positively affect muscle mass in steers. [51] Fish oil given to steers resulted in an increase in protein metabolism when compared to controls. The steers were able to use twice the amount of amino acids to synthesize new proteins. This is hypothesized to result from an increase in insulin sensitivity by the ingestion of fish oil in the steers. The ability to convert nutrients into muscle decreases with age, a consequence of increased insulin resistance of aging muscle cells. [51] Consequently, physical strength itself has previously been found to have a strong correlation to an individuals overall mortality risks. Low muscle mass is associated with an increased mortality risk. [52]

## Atherosclerosis



atherosclerotic aorta

Chronic inflammation can lead to *atherosclerosis*, the primary cause of heart disease. [53] The anti-inflammatory effects of omega-3 fatty acids are thought to protect against atherosclerosis. [23][24][25] Several epidemiological studies have shown that daily supplementation with as little as 1 gram of EPA and DHA can significantly decrease the risk of developing atherosclerosis. [54] In addition to reducing the risk of developing

atherosclerosis, omega-3 fatty acids, particularly DHA, also slow the progression of the disease. [55]

## Multiple Sclerosis

Patients with *multiple sclerosis* (MS) supplementing 1 gram of fish oil daily for 2 years significantly reduced clinical symptoms of MS. [56]

## Inflammatory Bowel Disease

Omega-3 fatty acids may have positive benefits for patients with inflammatory bowel disease. Inflammatory bowel disease is often characterized by high levels of pro-inflammatory molecules such as arachidonic acid and leukotrienes. [57] Since the conversion of arachidonic acid to leukotrienes is inhibited by omega-3 fatty acids, [22] clinical trials have investigated the role of omega-3 supplementation on inflammatory bowel disease. Studies have demonstrated that supplementation with at least 3 grams of EPA omega-3 significantly reduces leukotriene levels and patients show some improvements with disease activity. [58]

## Endometriosis



Peritoneal Endometriotic Lesion

Endometriosis is one of the most common gynecological diseases that affect women of reproductive age. Endometriosis causes pelvic pain that is hypothesized to result from the production of prostaglandins and leukotrienes. [59] Prostaglandins are the most potent stimulators of aromatases, which convert steroids into estrogens, in endometriosis. [60] In endometriotic lesions, the pro-inflammatory cytokine, IL-1 beta, increases prostaglandin synthesis through the production of cyclooxygenase-2 (COX2). [61] It is well known that omega-3 fatty acids decrease prostaglandin and leukotriene synthesis, thus, inhibit chronic inflammation in both humans and animal models. [62][22][58][63] Several studies in rabbits found that supplementation with fish oil and EPA inhibit the production of prostaglandins, decrease IL-1 beta levels, and reduce the growth of endometriotic cysts. [64][65] An additional study found that omega-3 supplementation reduced prostaglandin synthesis in cows with low progesterone levels. [66]

More compelling evidence for the omega-3 fatty acid, EPA, as a possible therapy for endometriosis comes from histological and gene expression studies in rats. Histological data from the endometriotic tissue of EPA fed rats reveals a massive decrease in the thickening of the interstitium compared with the control group. [67] This is important because mast cells play an important role in interstitium thickness and is correlated with the development and progression of endometriosis. [68] The microarray analysis of endometriotic tissue from EPA

fed rats reveal downregulation of 19 genes, most of which are immunomodulators and pro-inflammatory cytokines, including IL-1 beta <sup>[67]</sup> as well as matrix metalloproteinases, which are also implicated in the progression of endometriosis. <sup>[69]</sup> These results strongly suggest

that the omega-3 fatty acid, EPA, may be very effective for the treatment of endometriosis. Of note, in most of these studies, very high quantities of EPA were used.

## Cardiovascular Benefits of Omega-3

### Cardiovascular Disease

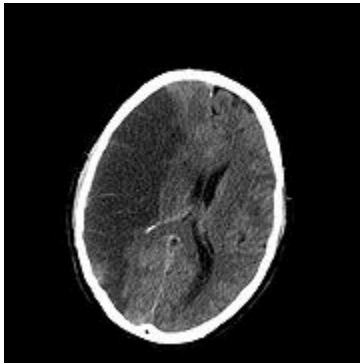
*Cardiovascular Disease* (CVD) is one of the major causes of death in the world. <sup>[70]</sup> Numerous epidemiological studies have shown that omega-3 consumption can significantly reduce the incidence of CVD. For example, epidemiological studies have demonstrated that patients with *hypertriglyceridemia* supplementing between 2 to 4 grams of EPA +DHA daily, **lowered their plasma triglyceride levels by 25% to 30%**. <sup>[71]</sup> In another randomized, double-blind study patients with hypertriglyceridemia supplementing 1 gram daily of either DHA or both EPA +DHA for 8 weeks lowered their triglyceride levels by 21.8% and 18.3%, respectively. <sup>[72]</sup> Additionally, patients with mild *hyperlipidemia* reduced their triglyceride levels by 23% when supplementing 4g of EPA per day <sup>[73]</sup> whereas healthy patients decreased triglyceride levels by 12% <sup>[74]</sup> One of the mechanisms by which omega-3 fatty acids reduces triglyceride levels is through increased expression of lipoprotein lipase (LPL), an enzyme that hydrolyzes lipids, therefore reducing lipid levels. <sup>[75]</sup> Supplementation with 3 grams of omega-3 fatty acids daily for 6 weeks increased the gene expression of lipoprotein lipase and **reduced tryglyceride levels by 35%**. <sup>[75]</sup>

The reduction in triglyceride levels by omega-3 fatty acids is also attributed to a decrease in the production of very-low-density lipoproteins (VLDL), which are responsible for the transport of triglycerides, phospholipids, and cholesterol. <sup>[76][77]</sup> One study found that daily supplementation with 10-14 grams of fish oil resulted in a **66% reduction in triglyceride levels** and a **78% reduction in VLDL levels**. <sup>[76]</sup> Patients with metabolic syndrome supplemented with 1 gram of fish oil daily had decreased body weight, systolic blood pressure, low density lipoprotein cholesterol, cholesterol, triglycerides, and C-reactive protein. <sup>[78]</sup>

### Hypertension (High Blood Pressure)

Daily supplementation with 3 grams or more of fish oil decreases both systolic and diastolic blood pressure. <sup>[79]</sup> A systematic analysis of 90 randomized studies concluded that supplementation with approximately 3.7 grams of fish oil daily results in a reduction of systolic blood pressure by 2.1 mmHg and diastolic blood pressure by 1.6 mmHg. <sup>[80]</sup> Another meta-analysis of 17 controlled trials reveals that patients with normal blood pressure could further reduce their systolic blood pressure by 1.0 mmHg and diastolic blood pressure by 5.0 mmHg when supplementing approximately 3 grams of fish oil daily. In the same meta-analysis, patients with high blood pressure **reduced their systolic blood pressure by 5.5 mmHg and diastolic blood pressure by 3.5 mmHg**. <sup>[81]</sup>

## Stroke



left side:ischemic stroke

A stroke can either be caused by a blood clot, which prevents blood flow to the brain, called an ischemic stroke or from a ruptured blood vessel, also preventing blood flow to the brain, called a hemorrhagic stroke. Approximately 795,000 Americans suffer from a new or recurrent stroke each year and more than 143,000 of those result in death. <sup>[82]</sup> In the United States, 85% of all strokes are ischemic strokes. <sup>[82]</sup> It is well documented that increased fish consumption is correlated with a reduced risk in ischemic stroke and stroke mortality. <sup>[83][84]</sup> Both women and men that consume omega-3 fatty acids significantly reduce their risk of ischemic stroke. <sup>[85][86]</sup> The protective effect of omega-3 fatty acids are due, in part, to its ability to inhibit platelet aggregation <sup>[87]</sup> as well as a reduce whole blood viscosity. <sup>[88]</sup>

## Fish Oil and Cancer

Epidemiological studies have revealed that consumption of fish oil decreases cancer incidence. An epidemiological study involving 14,500 Norwegian women showed that women who consumed poached fish (such as salmon) at least 5 times per week were **30% less likely to develop breast cancer** <sup>[89]</sup> Even more so, another study demonstrated that Norwegian women with breast cancer and a high intake of fish, had a **30% reduction in mortality** compared to women with a low intake of fish. <sup>[90]</sup> Another case-control study found that women who consumed fish oil were **70% less likely to develop breast cancer**. <sup>[91]</sup> Additionally, women that consume large quantities of omega-3 fatty acids have a significantly reduced risk of developing endometrial cancer. <sup>[92]</sup> Women with a diet high in omega-3 fatty acids have a **40% lower risk of ovarian cancer**. <sup>[93]</sup> In a case-controlled study involving 14,916 men indicated that supplementation with omega-3 fatty acids from fish oil resulted in a decreased risk for prostate cancer. <sup>[94]</sup> compared to those who consumed fish only 2 times per week.

## Animal Models for Cancer

Several animal studies also support a preventive role of fish oil on cancer. In a mouse model for prostate cancer, mice that were supplemented with omega-3 fatty acids had a



**in breast cancer incidence** and a **60% increase in BRCA1**, a major tumor suppressor gene. <sup>[96][97]</sup> The reduction in tumorigenesis is attributed to the ability of fish oil to decrease

cyclooxygenase (COX), an enzyme responsible for the production of prostaglandins, which is upregulated in tumors of the colon. <sup>[97]</sup> In a mouse model for colon cancer, mice fed a high-

fat-fish oil diet had a decreased tumor incidence compared to controls.

## **Fish Oil and the Nervous System**

Approximately 50-60% of the adult brain is composed of lipids. The primary omega-3 fatty acid found in the brain is DHA, consisting of 10-20% of total lipid composition. <sup>[98]</sup> DHA promotes the formation of synaptic membranes as well as increases the levels of pre- and post-synaptic membrane proteins. <sup>[99]</sup> Both DHA and EPA increase the number of dendritic spines and synapses in the hippocampus, the area of the brain involved in memory. <sup>[100]</sup> DHA increases neurotransmission as a result of increasing the number of synapses in certain areas of the brain. Omega-3 fatty acids influence dopaminergic, noradrenergic, serotonergic and GABAergic neurotransmission in particular areas of the brain. Dietary **omega-3 fatty acids can increase dopamine levels in the frontal cortex by 40%**. <sup>[101]</sup>

Omega-3 fatty acids also protect neuronal cells from the inflammatory effects of TNF- alpha. <sup>[102]</sup> TNF-alpha inhibits acetylcholine, the primary vagal neuro-transmitter, <sup>[103]</sup>

therefore, omega-3 fatty acids increase acetylcholine, which in turn increase nitric oxide synthesis in the brain <sup>[102]</sup> and thus, prevent neuronal apoptosis <sup>[104][105]</sup> and promote memory enhancement and consolidation. <sup>[106][107]</sup>

## **Brain Development**

The omega-3 fatty acid, DHA, is the most abundant fatty acid in the brain. The levels of DHA are exceedingly high during development <sup>[108]</sup> and decrease with age. <sup>[109]</sup> Omega-3 fatty acids are essential during development and must be obtained from the mother's circulation. <sup>[110]</sup> Reduced intake of DHA omega-3 fatty acids during development results in decreased metabolism of both dopamine and serotonin neurotransmitters, and a decrease in neurogenesis, dendritic arborization, synaptogenesis, selective pruning, and myelination. <sup>[111][112]</sup> Studies have also shown that omega-3 deficiency during development reduces the size of neurons in the hippocampus, hypothalamus and parietal cortex. <sup>[113]</sup>

## **Fish Oil and IQ**

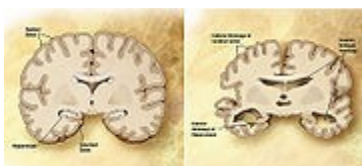
Several studies have shown that higher omega-3 consumption during pregnancy results in children showing better neurological function than those who do not. Fish Oil given to pregnant mothers later boosted the hand-eye coordination of their children. One study showed that pregnant women given 1.1g of EPA per day, and 2.2g of DHA per day significantly increased hand-eye coordination compared to controls when later re-assessed at 2.5 years of age. The improvements in hand-eye coordination were correlated to an increase in omega-3 fatty acids found in the umbilical cord blood sampled. <sup>[114]</sup>


Another study found that maternal consumption of less than 380mg of fish per week later resulted in their children scoring in the lowest quartile of verbal IQ, compared to those who consumed greater than 380mg per week. Additionally, low maternal fish consumption later resulted in poor outcomes for their children in fine motor, communication, and social development scores. <sup>[115]</sup> Another study including 2,000 healthy 15-year old males, found that those who ate fish frequently had higher stanine scores in combined intelligence, verbal performance, and in visuospatial performance. <sup>[116]</sup>

## Neurodegenerative Diseases

Fish Oil shows promise in preventing cognitive decline in the elderly. In a study of 210 elderly men between the ages of 70 and 89 it was shown that the omega-3 fatty acid intake from consumption of fish had a significant effect on cognitive decline over a period of five years. Those of whom ate more fish showed subsequent less cognitive decline than nonconsumers of fish.<sup>[117]</sup>

### Alzheimer's Disease



 normal aged brain (left) and an Alzheimer's patient's brain (right)

Alzheimer's Disease (AD) is the most common neurodegenerative disease among the elder. Omega-3 offers a likely means for preventing Alzheimer's disease. Studies have shown that DHA, and omega-3 fatty acids, reduce the secretion of amyloid-beta plaques, the hallmark of Alzheimer's disease. It also induces the expression of anti-apoptotic and neuroprotective genes. Basically, it helps you keep your brain cells intact.<sup>[118]</sup> A 9 year epidemiological study including 899 men and women found **people with the highest percentage of plasma DHA omega-3 were 47% less likely to develop Alzheimer's disease.**<sup>[119]</sup>

In order to investigate the role of omega-3 fatty acids on the pathogenesis of Alzheimer's disease (AD), a transgenic mouse model for AD, in which mice were genetically engineered to over-express amyloid-beta 42, was used. This study found that **mice fed a diet high in DHA omega-3 had greater than 70% reduction in total amyloid-beta plaques compared to mice fed a regular diet.**<sup>[120]</sup> Moreover, transgenic mice fed a diet lacking DHA resulted in 80%-90% loss of post-synaptic proteins and displayed exacerbated symptoms of AD including impaired cognitive function. Whereas, transgenic mice fed a diet high in omega-3 fatty acids had improved cognitive function spatial memory.<sup>[121][122]</sup> Therefore, low dietary intake of omega-3 fatty acids are an environmental risk factor for Alzheimer's disease. On the other hand, high dietary consumption of omega-3 exerts a neuroprotective effect and aids in the prevention of Alzheimer's disease.

### Parkinson's Disease

The most common treatment for Parkinson's disease is dopamine replacement therapy using L-dopa. Unfortunately one of the major side effects of levodopa is the development of dyskinesias, which are involuntary movements.<sup>[123]</sup> Studies have shown that administration of DHA omega-3 (100mg/kg) in a non-human primate model for Parkinson's disease, reduce the incidence of dyskinesias induced by levodopa.<sup>[124]</sup> Another study found that levodopa administered to non-human primates decreased DHA levels in the cortex by 15% compared to controls.<sup>[125]</sup> These data suggest that the most common treatment for PD, levodopa, reduces the levels of DHA in the brain of patients resulting in dyskinesias which could potentially be prevented with supplementation of DHA.

Additionally, omega-3 prevented neuronal damage in an animal model for Parkinson's disease. In an animal model of Parkinson's, a neurotoxin, MPTP, was used to induce damage to dopamine neurons in mice. Damage normally caused by this neurotoxin was completely prevented by consumption of a diet high in omega-3 fatty acids when compared to controls.<sup>[126]</sup>

## Visual Acuity

A study found that fish oil plays a protective role in blinding eye diseases such as retinitis pigmentosa and age-related macular degeneration. The major cause of blindness in these diseases are loss of photoreceptor cells (rods and cones). The omega-3 fatty acid, DHA, prevents the degeneration and death of photoreceptor cells and could drastically halt progression and prevent the blinding eye diseases.<sup>[127]</sup> In addition, omega-3 fatty acids also play a beneficial role during development. Several studies report that infants supplemented with omega-3 fatty acids during their first year of life have significantly better visual acuity compared to those who were not administered omega-3.<sup>[128][129]</sup>

## Attention-deficit/hyperactivity disorder (ADHD)

Attention-deficit hyperactivity disorder (ADHD) affects approximately 8-12% of children worldwide.<sup>[130]</sup> ADHD is characterized by a wide range of attentional deficits including difficulty listening, paying attention, and finishing tasks.<sup>[131]</sup> Additionally, some children with ADHD may also have difficulty with reading and writing.<sup>[132]</sup> Greater than 80% of children diagnosed with ADHD in the US are treated with stimulants such as Ritalin. Although Ritalin has shown efficacy in the treatment of symptoms in some children, it has considerable side effects including decreased appetite, insomnia, impaired growth and irritability.<sup>[133]</sup>

It has been postulated that the lack of omega-3 fatty acids influences the brain in such a way that may cause and/or worsen symptoms of ADHD.<sup>[134]</sup> Both children and adults with ADHD have lower plasma concentrations of DHA omega-3 compared to age- and sex-matched controls.<sup>[135][136][137][138]</sup> Several clinical trials have demonstrated the efficacy of both EPA and DHA omega-3 fatty acids in reducing ADHD-related symptoms.<sup>[139][140]</sup> In addition, children (5-12 years of age) with developmental coordination disorder, which is also associated with difficulties in learning and behavior, showed improvements in reading, spelling, and behavior after 3 months treatment with omega-3 fatty acids.<sup>[141]</sup>

## Schizophrenia

Schizophrenia is characterized by a very diverse range of symptoms including but not limited to, distortion in thinking and perception, abnormalities in motor function, lack of initiative and apathy, difficulty in communication, and affective expression.<sup>[142]</sup> Schizophrenia is associated with either positive or negative symptoms. Positive symptoms include hallucinations, delusions, and other distortions of reality. Whereas, negative symptoms include apathy, lack of communication, and depression.<sup>[142]</sup> The dopaminergic neurons of the prefrontal cortex are significantly reduced in schizophrenics, and is associated with negative symptoms of schizophrenia. In contrast, the dopaminergic neurons of the limbic system are enhanced and is associated with positive symptoms of schizophrenia.<sup>[143]</sup> Normally, the dopamine system of the prefrontal cortex inhibits the limbic dopamine system.<sup>[144]</sup> However, people with schizophrenia have very little dopamine in the prefrontal cortex and therefore lack this type of negative regulation. It has previously been shown that dietary omega-3 fatty acids can increase dopamine levels in the prefrontal

cortex by 40%.<sup>[145]</sup> This means that omega-3 fatty acids could potentially provide therapeutic benefits to patients with schizophrenia by raising the dopamine levels in the prefrontal cortex, thereby, lowering dopamine levels in the limbic system.

Several studies have reported that patients with schizophrenia have significantly lower EPA and DHA plasma levels.<sup>[146][147][148]</sup> Interestingly, one study found that patients with primarily negative symptoms had significantly lower omega-3 plasma levels compared to patients with positive symptoms and controls.<sup>[149]</sup> In a double-blind, placebo controlled study, EPA was found to be more effective than DHA in the treatment of schizophrenia. By the end of the study all 12 of the placebo controls were taking antipsychotic drugs, whereas 8 out of 14 patients on EPA were no longer on antipsychotic drugs.<sup>[150]</sup> In another study involving 20 schizophrenic patients, daily supplementation with 10 grams of concentrated fish oil (maximum EPA) resulted in amelioration of schizophrenic symptoms and tardive dyskinesia,<sup>[151]</sup> which is associated with the use of certain anti-psychotics such as Haloperidol.

### **Effects on Depression**

Several studies have reported a strong negative correlation between depression and fish consumption.<sup>[152][153][154]</sup> In addition, omega-3 levels are significantly lower in individuals afflicted with depression compared to healthy individuals.<sup>[155][156][157][158]</sup> There is compelling evidence fish oil may be a natural treatment for depression. Patients with bipolar depression supplementing 2g of fish oil daily for 6 months, had a 50% or greater reduction in Hamilton Rating Scale for Depression scores.<sup>[159]</sup> In a double-blind, placebo-controlled study, individuals with bipolar depression supplementing 9.6g of omega-3 daily showed significant improvement in mood stabilization.<sup>[160]</sup>

### **Fish oil and the Autistic Spectrum**

Several studies have demonstrated that both children and adults with autism have significantly lower levels of omega-3 fatty acids compared to controls.<sup>[161][162][163]</sup> Fish oil shows potential behavioral benefits for autistic children, including, aggression, tantrums, and self-injurious behavior.<sup>[164]</sup> An additional study involving children (4-7 years old) supplementing with 1 gram of omega-3 daily, showed a 33% improvement on the Autism Treatment Evaluation Checklist (ATEC).<sup>[165]</sup> This suggests that fish oil may show promise in the treatment of autistic spectra disorders.

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