Omega-3 fatty acids Suggest an improvement to this article

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Introduction

Omega-3 fatty acids are polyunsaturated fats that play critical roles in human health, participating in a wide range of biochemical pathways and processes and modulating the expression of genes throughout the lifespan. Omega-3 fatty acids include plant-derived **alpha-linolenic acid (ALA)** and marine-derived **eicosapentaenoic acid (EPA)** and **docosahexaenoic acid (DHA)**, among others. A growing body of evidence indicates that omega-3 fatty acids may prevent or ameliorate symptoms associated with chronic health conditions such as cardiovascular disease,[1] neurodegenerative disease,[2] and rheumatoid arthritis[3] and may be beneficial in combating aging-related diseases.

Although ALA plays important roles in human health,[4] this article focuses primarily on the beneficial effects of the marine-derived omega-3 fatty acids, EPA and DHA.

Effects at a glance

Research demonstrates that omega-3 fatty acids exert a multitude of effects on health and aging, including:

- Reducing ischemic events, including cardiovascular death by as much as 25 percent[5]
- Preventing age-related macular degeneration[6] and improving night vision[7]
- Reducing DNA damage, oxidative stress, and influencing various biomarkers of aging[8]
- Reducing muscle loss in older adults[9]
- Influencing infant brain development[10]
- Protecting against damage from fine particulate air pollution exposure[11]
- Increasing hypothalamic neurogenesis in animal models[12]
- Ameliorating or reducing olfactory losses[13]
- Increasing verbal IQ in children[14]
- Reducing preterm birth[15]
- Improving clinical outcomes in COVID-19,[16] [17] possibly via induction of interferons.[18]

Supplemental forms of omega-3 EPA and DHA

Omega-3 fatty acids that are found as over-the-counter supplements and prescription medications come in a variety of forms.

The most common among these include:

- **Triglyceride** – naturally occurring and produced by re-esterification of ethyl ester in some commercial products to enhance bioavailability
- **Phospholipid** – thought to have the highest bioavailability; however, commercial sources appear to be generally of reduced concentration or less economical
- **Ethyl ester** – a product of molecular distillation and thought to be somewhat *less bioavailable* than triglyceride or phospholipid[19]; the formulation found in major pharmaceutical preparations, such as *Lovaza* and *Vascepa*

For intestinal absorption, triglyceride and phospholipid forms must be digested by pancreatic lipase, while ethyl esters require an additional digestive enzyme called carboxyl ester lipase. Consequently, the latter of these formulations must be taken with a high-fat meal to stimulate the activity of these enzymes. In contrast, free fatty acid formulations do not require enzymatic digestion and can be taken without regard to food intake.[20]

Supplemental and prescription omega-3s are available as fish oil and algal oil products.[19] Algal sources of EPA and DHA are suitable for people following a vegan (non-gelatin capsules only) or vegetarian diet or for those who do not eat fish.[21] However, these products generally provide lower concentrations of omega-3s than similarly priced fish oil products.

Triglyceride form

The omega-3 fatty acids EPA and DHA in fish are mostly in triglyceride form, composed of three omega-3 fatty acids bound to a glycerol backbone. The molecular distillation process removes the glycerol backbone and replaces it with an ethanol backbone, creating the ethyl ester form. At this stage, it can be converted back into a triglyceride form by a process called re-esterification by adding the glycerol backbone back onto EPA or DHA.[22]

Phospholipid form

Some of the omega-3s present in fatty fish are in the form of phospholipids, facilitating the fatty acids' uptake into red blood cell membranes and subsequent delivery to the body's tissues.[23] However, phospholipid formulations often provide substantially lower concentrations or less economic dosages of this form, potentially negating some of their enhanced bioavailability.

- *Dietary intake of salmon roe is a unique, highly concentrated source of this particular form of omega-3.*

Ethyl ester form

Ethyl esters are produced via molecular distillation of natural triglycerides.[24] They have been used in some of the most successful intervention trials but may have lower bioavailability than some of the other forms, especially in the absence of a fatty meal.[25] This can be problematic for some people with cardiovascular disease, who are often counseled to follow low-fat diets.[26] Ethyl ester formulations are used in some supplements as well as prescription omega-3s *Lovaza* (EPA and DHA) and *Vascepa* (EPA only).[27]

Determining omega-3 status in clinical trials

A possible confounding variable of certain omega-3 clinical trials and their results may be the use of potentially unreliable biomarkers, a factor that may produce hard-to-interpret results.

Long-term measure of omega-3 intake

"[The Omega-3 Index] really is just a risk factor like cholesterol, except this is one that you can modify easily...you can just eat more fish or take supplements and you can raise your omega-3 levels and reduce risk." - William Harris, Ph.D. Click To Tweet

Omega-3 concentrations can be measured in plasma, serum, or red blood cells; however, red blood cell concentrations are more stable and more representative of long-term intake than plasma concentrations, which fluctuate daily.[28] [29]

The **Omega-3 Index**, developed by Harris and von Schacky, measures the quantity of EPA + DHA as a percentage of total fatty acids in the red blood cell membrane and may serve as a measurable biomarker of sudden cardiac death risk.[30] **Robust evidence suggests that an omega-3 index target range of 8 to 11 percent provides the greatest health benefits**.[30] Although the Omega-3 Index reflects the omega-3 concentrations of most organs, plasma brain-derived neurotrophic factor levels may better reflect concentrations in the brain.[31]

There is a need for standardized methodologies that can produce equivalent measures, allowing researchers to compare different studies and assess clinical trial outcomes.[32]

- *Learn more about the **Omega-3 Index** in this short clip featuring Dr. Bill Harris.*

Why the recommended intake is too low

Emerging research suggests that optimal human health – especially in populations with low intake – may require substantially higher intake than current standards of adequacy.[33] The Food and Nutrition Board of the National Academies of Medicine focuses on an adequate intake of ALA because it can be converted to EPA and DHA. However, the recommended amounts are conservative at only 1.6 and 1.1 grams per day for men and women, respectively. While these amounts are presumed to represent approximately 500 milligrams of EPA and DHA,[34] the conversion process is inefficient and varies greatly in humans (perhaps as low as 10 percent converted).[35]

How a person's omega-3 blood concentration responds to intake depends on multiple factors, including individual baseline concentration, body weight, quantity consumed, genetic differences in fatty acid metabolism, sex, age, and in the case of supplements, dose and formulation.[36] [33] In one study, triglyceride formulations increased the Omega-3 Index 1 percent more than ethyl ester formulations of the same dose.[33] This may be partly explained by the presumably increased bioavailability of triglyceride forms over ethyl esters (shown by some studies but not others).[22][37] In addition, supplemental omega-3s are subject to oxidation, so product quality and/or oxidation status may factor in as well.[38]

Optimal omega-3 intake for most adults

To predict how much supplemental EPA and DHA are required to raise the Omega-3 Index from 4 to 8 percent, researchers analyzed data from more than 1,400 participants across 14 intervention studies. The mean duration of supplementation was 13.6 weeks, and the mean dose was 1,983 milligrams of either a dietary supplement or a prescription product. *The researchers estimated that the dosage required to increase the Omega-3 Index into the recommended range of 8 percent or greater ranged from* ***1,750 to 2,500 milligrams (1.75 to 2.5 grams) per day***.[33]

Omega-3 fatty acid tissue incorporation varies

A person's omega-3 status varies depending on several factors, including genetics, diet, gender, and age and **may not be reflective of intake**.

A global survey of blood omega-3 fatty acid levels.

A global survey indicated that while citizens of most countries have low omega-3 concentrations, a few countries, including Japan, South Korea, Denmark, and Greenland, have higher levels, likely due to differences in dietary intake and the presence of **single nucleotide polymorphisms** (SNPs, genetic variations) that influence fatty acid metabolism.[39] [40] The primary SNPs that influence omega-3 metabolism in humans are those found in genes that encode the fatty acid desaturase (called *FADS*) and fatty acid elongase (called *ELOVL*) enzymes.[41]

Dietary factors can also influence omega-3 concentrations. For example, people following vegan and vegetarian diets are susceptible to having lower concentrations.[42] [43] In addition, the fat content of foods consumed along with supplemental omega-3s can influence absorption.[20]

Omega-3 fatty acids: An overview

Gender and age also influence human polyunsaturated fatty acid concentrations. A meta-analysis of 51 studies found lower levels of arachidonic acid (an omega-6 fatty acid) and DHA as a percentage of plasma lipid in men compared to women,[44] suggesting that gender-specific differences occur in long-chain fatty acids, possibly modulated by sex hormones. Similarly, young women tend to have higher DHA and lower EPA levels than older women, suggesting that younger women have an **enhanced ability to convert EPA to DHA**, likely due to DHA's important role in reproduction and development.[45] Furthermore, fatty acid levels tend to shift with age such that the Omega-3 Index is higher and linoleic acid levels are lower.[45] [46]

Health effects of omega-3 fatty acids

More than five decades of research have revealed that omega-3 fatty acids are involved in nearly every aspect of human physiology, exerting a wide range of effects on multiple organ systems and influencing cardiovascular, neurocognitive, musculoskeletal, immunological, and respiratory health, among others.

Resolution of inflammation

"It is actually a bewildering array of molecules... made from EPA and DHA that operate on different cell types and receptors through different mechanisms [...] that suppress an inflammatory response and keep it from getting out of control." - William Harris, Ph.D. Click To Tweet

Inflammation, a critical element of the body's immune response, is a protective response that involves an array of immune cells, cell-signaling proteins, and pro-inflammatory factors. Although preventing or reducing inflammation may seem prudent, emerging evidence indicates that *resolving* inflammation may be equally important for maintaining good health.

The resolution of inflammation is a coordinated response involving byproducts of omega-3 fatty acid metabolism, called **specialized pro-resolving mediators** (SPMs).[47] [48] Four families of SPMs have been identified and include the resolvins, lipoxins, protectins, and maresins. These SPMs promote apoptosis, regulate leukocyte (white blood cell) activity, and reduce the production of proinflammatory mediators.

Findings from a clinical trial suggest that omega-3 fatty acid supplementation increases blood levels of SPMs up to 24 hours after ingestion. The double-blinded, placebo-controlled, crossover study involved 22 healthy volunteers between the ages of 19 and 37 who took a fish oil supplement enriched in omega-3 fatty acids. At two, four, six, and 24 hours after taking the supplement, participants provided blood samples for analysis, which revealed a time- and dose-dependent increase in blood SPM levels that persisted for up to 24 hours.[49]

Reduced biomarkers of inflammation in aging

Chronic low-grade inflammation promotes the hallmarks associated with many diseases of aging, a phenomenon termed **inflammaging**. This form of inflammation is often referred to as "sterile" because it involves minor immune cell infiltration in the absence of a pathogen.[50] The processes that drive inflammaging and the pathological conditions that arise because of it are bidirectional and involve multiple physiological processes and pathways, many of which intersect with the hallmarks of aging, such as the oxidative stress that drives telomere shortening.

Supplementing with omega-3 fatty acids may counteract telomere shortening and slow aging. A double-blind randomized controlled trial involving 106 adults between the ages of 40 and 85 years who were sedentary and had overweight investigated the effects of supplemental omega-3 fatty acids versus a placebo daily. To evaluate the influence of the omega-3 fatty acids versus a placebo, the investigators measured telomere length, telomerase activity, and markers of oxidative stress. They found that supplementation lowered the omega-6-to-omega-3 fatty acid ratio in the blood, a finding that was associated with longer telomere length. They also observed that omega-3 fatty acid supplementation decreased markers of oxidative stress by 15 percent.[8]

A separate study tested the effects of omega-3 supplementation on inflammation and telomere length in response to stress. The randomized, controlled intervention trial included 138 sedentary adults with overweight who were between 40 and 85 years old. The participants received daily omega-3 supplements or a placebo for four months. Before and after the intervention, the participants took a test to gauge social stress. Participants also provided blood and saliva samples as a means to measure cortisol (a stress hormone), telomerase; anti-inflammatory cytokines, including interleukin (IL)-10 (IL-10); and proinflammatory cytokines, including IL-6, IL-12, and tumor necrosis factor-alpha (TNF-alpha).

Following the stress test, participants in the placebo group experienced a 24 percent reduction in telomerase activity and a 26 reduction in IL-10; however, both omega-3 groups were protected from this response, even after accounting for baseline stress reactivity, age, waist circumference, and sex. Participants who received 2.5 grams of omega-3s had a 19 percent reduction in cortisol levels and a 33 percent reduction in IL-6 compared to the placebo group. The authors concluded that by reducing inflammation and stress hormone levels, omega-3 supplementation may boost cellular repair and slow aging. This decrease in stress response may also translate to a reduced risk of depression, making these findings relevant to mental health as well.[51]

- *Learn more about inflammaging and the hallmarks of aging in our overview article.*

Omega-3 fatty acids may reduce inflammation via epigenetic effects.

Higher omega-3 fatty acid consumption may mitigate chronic inflammation by altering the methylation pattern of the interleukin-6 (IL-6) promoter, reducing the activity of this pro-inflammatory cytokine. Interleukin-6 participates in the immune response by mediating the acute phase response and fostering beneficial outcomes [such as insulin sensitization after exercise.[52] However, when chronically elevated, IL-6 can also contribute to age-related chronic diseases.

A 2015 study found that people with higher concentrations of omega-3s, particularly DHA derived from fatty fish, **exhibited lower IL-6 levels and reduced methylation of the IL-6 promoter at a CpG site called cg01770232.** This association between lower methylation levels of the IL-6 promoter and reduced circulating IL-6 emphasizes the significance of omega-3s in mitigating chronic inflammation through DNA epigenetics, which may have a profound cumulative impact on human health over time and possibly even longevity.[53]

This epigenetic mechanism highlights omega-3s' capacity to govern gene expression and shape the genetic landscape, transcending its contributions to cell membrane dynamics or mediator production and positioning its effects at the molecular blueprint level rather than merely fine-tuning cellular responses. However, it is worth noting that some individuals carrying a specific genetic variant of IL-6 did not experience the same methylation changes from omega-3 consumption, suggesting that their genetic makeup may influence the degree of beneficial physiological response to omega-3 fatty acids within certain biological domains.

Improving longevity and reducing early death

"People that had the highest omega-3 levels compared to the lowest were 15 percent or so less likely to die [...] and it was very dose-dependent: the higher the omega-3, the lower the risk." - William Harris, Ph.D. Click To Tweet

Epidemiological data have identified robust links between omega-3 intake and reduced risk of premature death.

In a study involving more than 42,000 people across 17 prospective cohorts, blood omega-3 concentrations were inversely associated with the risk of death from all causes. All-cause mortality was 15 to 18 percent lower in those with the highest versus the lowest levels of long-chain omega-3s EPA, DHA, and docosapentaenoic acid, but no association was observed with ALA. These data suggest that omega-3 fatty acids – primarily marine-derived – are responsible for the reduced risk of premature death.[54]

A community-based population study tracked 2,240 people in their mid-60s without cardiovascular disease for 11 years. The investigators found that red blood cell fatty acid concentrations predicted the risk of death from all causes of premature death as accurately as standard risk factors for cardiovascular disease such as age, blood pressure, smoking, and diabetes status. The 11-year survival rate was 85 percent for non-smokers with high omega-3 concentrations, compared to 47 percent for smokers with low omega-3 levels. Interestingly, smokers with high omega-3s and non-smokers with low omega-3s had the same survival rate of 71 percent, suggesting that low omega-3 status is as detrimental as smoking.[55]

In a study of 2,500 participants between the ages of 66 and 73 years who were followed for approximately seven years, a higher Omega-3 Index was associated with a reduced risk of dying from all causes of premature death. Those in the highest quintile of omega-3 fatty acids intake had a 35 percent lower risk of death than those in the lowest quintile.[56]

- *Learn more in our YouTube episode, **"Omega-3 may reduce risk of premature death."***
- *Learn more in this clip featuring Dr. Bill Harris discussing whether omega-3 is a longevity compound.*

Reduced risk of death from cardiovascular disease

Cardiovascular disease is a major cause of death and disability, and its incidence increases with age. Many factors influence the risk for cardiovascular disease, including behavioral factors, such as diet, physical activity, and smoking status. Health parameters, including cholesterol, blood pressure, glucose control, weight, genetics, and age, also help stratify risk. Some of these factors, such as diet, are modifiable, while others, such as age and genetics, are not.[57] Some research indicates that the Omega-3 Index is a good predictor of heart disease, similar to other well-known risk factors.[30]

Observational data suggest that omega-3 fatty acids help reduce the risk of cardiovascular events, including death. For example, a prospective study involving more than 20,000 male physicians between the ages of 40 and 84 years found that men who ate one to two servings of fish twice a week had a lower risk of sudden cardiac death than those who ate fish less than once a month over the 11-year study period.[58] This association was likely attributable to the omega-3s found in fish.[59]

Clinical trials evaluating whether supplemental omega-3s can achieve the same cardiovascular benefits as fish intake have yielded mixed results, possibly due to trial design variations.[60]

Two landmark randomized controlled trials, GISSI-Prevenzione and JELIS, evaluated omega-3 fatty acids' ability to prevent cardiovascular disease and death in people with existing cardiovascular disease or abnormal blood lipids, respectively. The GISSI-Prevenzione study, which involved more than 5,600 participants with existing cardiovascular disease who received either 900 milligrams of EPA+DHA or a placebo daily, demonstrated a reduction in sudden cardiac death over the 3.5-year follow-up period.[61] In the JELIS trial, which involved more than 18,000 participants who were taking statins and either 1.8 grams of purified EPA or a placebo daily for five years, participants who received the EPA supplement experienced a 19 percent reduction in cardiovascular events. However, those with higher triglyceride levels (greater than 150 mg/dL) and lower HDL-C (high-density lipoprotein-cholesterol) levels (less than 40 mg/dL) experienced a 53 percent reduction in cardiovascular events with EPA treatment.[62]

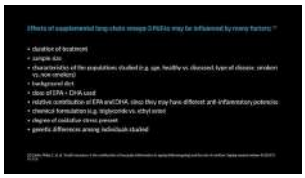
Summary of REDUCE-IT, STRENGTH, and VITAL omega-3 intervention trials.

In the VITAL trial, investigators randomized more than 25,000 healthy participants to receive either 840 milligrams of EPA and DHA (via the drug Omacor) or a placebo for approximately five years. The primary composite outcome – a reduction in cardiovascular death or major cardiovascular events – did not differ between the groups. However, secondary outcomes revealed that heart attack risk decreased by 28 percent and total coronary heart disease decreased by 17 percent in the omega-3 group, particularly in participants with low fish intake.[63]

The randomized controlled trial REDUCE-IT, which involved more than 8,000 participants who were taking statins and had high cardiovascular risk, found that supplementation with 4 grams of EPA (a prescription EPA-only formulation called icosapent ethyl) per day for approximately five years was associated with a 25 percent reduction in the rate of ischemic events, including cardiovascular death.[5]

Surprisingly, another large trial, STRENGTH, was stopped early due to the unlikelihood of producing a favorable outcome. The trial involved more than 13,000 people who were taking statins and had high cardiovascular risk who received 4 grams of EPA and DHA (via the drug Epanova, a free fatty acid form) or a placebo (corn oil) daily. Some researchers suggest that the addition of DHA may have negated the effects of EPA, or the high dose and pure formulation of EPA was the determining factor in the success of REDUCE-IT and the failure of STRENGTH.[64] Curiously, lower adverse outcomes occurred in both the treatment and placebo groups in the STRENGTH trial, compared to the treatment group in REDUCE-IT. These differing effects reflect how a trial design that involves a composite endpoint may alter the interpretation of the findings.

A comprehensive analysis of the data from 40 clinical trials found that supplementation with fish oil was associated with a 35 percent reduced risk of fatal heart attacks, a 13 percent reduced risk of heart attacks, and a 9 percent reduced risk of fatal coronary heart disease. The analysis revealed that the effects of omega-3s were dose-dependent, with cardiovascular benefits increasing as the dosage increased. For example, adding an extra 1,000 milligrams of EPA and DHA per day reduced the risk of cardiovascular disease events by an additional 5.8 percent and reduced the risk of heart attack by an additional 9 percent.[65]



A multitude of factors may influence omega-3 trial outcomes.

The formulations, doses, and full clinical contexts in which omega-3 fatty acids are optimally cardioprotective are yet to be fully settled. Even so, omega-3 fatty acids influence many biological mechanisms that benefit the cardiovascular system, such as anti-inflammatory, anti-platelet aggregation, plasma triglyceride-lowering, and blood pressure-lowering effects. Moreover, several intervention trials support their use in preventing cardiovascular disease. Future clinical trials controlling for individual genetics and measuring pre- and post-intervention omega-3 blood levels may answer some of the outstanding questions.

Research has not fully elucidated the mechanisms that drive the cardioprotective effects of omega-3s. However, the fatty acids' participation in the maintenance of cell membrane fluidity, regulation of cell membrane ion channels (to promote healthy heart rhythms), prevention of proinflammatory processes, and resolution of inflammation are likely candidates.[66]

Anti-catabolic effects of omega-3

"The women on the omega-3 supplement saw a really mild disuse atrophy response and then returned to normal much quicker than the other group who saw a much greater atrophic response and didn't get back to normal after two weeks of what we call passive remobilization. [...] It's anti-catabolic for sure." - Stuart Phillips, Ph.D. Click To Tweet

The musculoskeletal system plays important roles in structure, movement, and metabolic function. Sarcopenia, a progressive, age-related musculoskeletal condition characterized by the loss of skeletal muscle mass and strength, is one of the leading causes of functional decline and loss of independence in older adults. Contributing factors for sarcopenia include poor nutrition, low physical activity, and inflammation, among others. Some evidence demonstrates that omega-3 fatty acids play roles in maintaining muscle mass synthesis and function.

A meta-analysis of ten randomized controlled trials involving more than 550 adults aged 60 years or older explored the effects of omega-3 fatty acids on muscle mass, strength, and performance. The trials spanned 10 to 24 weeks in duration and provided omega-3 fatty acids from various sources, with doses ranging from 0.16 to 2.6 grams per day of EPA and from 0 to 1.8 grams per day of DHA. One study provided 14.0 grams per day of ALA. The participants experienced increases in muscle mass of about 0.33 kilograms (~11 ounces), and their Timed Up & Go Test (a test of functional mobility and fall risk) times decreased by 30 seconds. Participants who consumed more than 2 grams of omega-3s per day saw greater improvements, with average increases in muscle mass of 0.67 kilograms (~1.8 pounds). Among those enrolled in interventions lasting six months or longer, walking times improved by nearly 2 meters per second.[67]

Another meta-analysis revealed that supplementation with omega-3 fatty acids increased lean body mass, skeletal muscle mass, and strength of the quadricep muscles, which are vital for mobility. With one exception, all studies used EPA and DHA supplements (one used only alpha-linolenic acid), with doses ranging from 102 milligrams to more than 4,000 milligrams. While the investigators did not find a relationship between dose and effectiveness, the data revealed that even low-dose omega-3 supplementation was sufficient to increase lean body mass.[9]

A study involving 60 healthy adults aged 60 to 85 years who took either fish oil-derived omega-3 fatty acids (1.86 grams EPA and 1.50 grams DHA per day) or a placebo for six months demonstrated that those who took omega-3s had increased muscle mass, handgrip, upper- and lower-body strength and leg power than the placebo group.[68]

Taken together, the current literature suggests that many factors, such as a person's age and metabolic status as well as supplement dose and duration, can affect the outcome of omega-3 supplementation on musculoskeletal health.

- Learn more about the anti-catabolic effects of omega-3 in this clip featuring Dr. Stuart Phillips

Aging

Cognitive decline

Dementia and the subsequent loss of cognitive function are common features of aging. Alzheimer's disease is the predominant form of dementia, affecting as many as 55 million people worldwide.

MFSD2A is essential for blood-brain barrier integrity and DHA transport

A randomized, controlled trial examined the effects of long-term, high-dose omega-3s (EPA and DHA) on cognitive function. The study involved 285 cognitively healthy participants who had stable coronary artery disease and were on statin treatment. The investigators randomly assigned participants to receive either 3.36 grams of EPA and DHA combined or none daily for 30 months and assessed the participants' cognitive function at baseline and at 12 and 30 months into the intervention. They found that participants who took the EPA and DHA performed better on tests of verbal fluency, language, memory, and visual-motor coordination, regardless of age, sex, or diabetes status than those who took none.[69]

However, a systematic review of seven studies assessing the effects of supplemental or dietary omega-3 fatty acids on cognitive performance found that most of the findings failed to achieve statistical significance. Although some studies demonstrated some benefits from omega-3s, the effects were limited to a few cognitive assessment scales, with the greatest benefits observed in participants with very mild Alzheimer's disease.[2] Authors of another review involving 14 randomized controlled trials concluded that omega-3 supplementation might have beneficial effects on cognitive function and could be useful as a preventive or therapeutic tool in older adults.[70] As described above, some of the variability in findings may be related to differences in dose, duration, and outcome measures.

One mechanism that drives the beneficial effects of omega-3s on cognitive function may be the fatty acids' capacity to promote hypothalamic neurogenesis, which is impaired in the setting of Alzheimer's disease.[12] In a rodent study in which researchers provided mice DHA via diet or injection, the treated animals showed increased levels of hypothalamic neurogenesis.[71]

Similarly, a prospective interventional trial investigated the effects of omega-3s on cognition. They provided 65 older adults with 2.2 grams of omega-3s or a placebo per day for 26 weeks. The investigators found that omega-3s improved the microstructural integrity of white and gray matter in multiple brain areas and enhanced executive function. These changes were associated with increases in the Omega-3 Index and peripheral brain-derived neurotrophic factor.[72]

APOE-4 and Alzheimer's disease

The major genetic risk factor for Alzheimer's disease is a variant in the apolipoprotein E (*APOE*) gene called *APOE4*.[73]

Interestingly, people who carry the *APOE4* gene respond well to the DHA in fish but not as well to the DHA provided in most dietary supplements. Although scientists do not fully understand the mechanisms that drive this varied response, a few mechanisms have been proposed. First, many of the studies examining supplementation used low omega-3 doses below 2 grams per day, suggesting that APOE-4 carriers may need omega-3 doses greater than 2 grams per day. Second, preliminary evidence suggests that the difference lies in the form of DHA found in the two sources. That is, fish contain DHA in phospholipid form, whereas many fish oil supplements do not. This determines whether DHA is metabolized to nonesterified DHA (free DHA) or a phospholipid form called lysophosphatidylcholine DHA (DHA-lysoPC), ultimately influencing how the DHA is transported into the brain.

Some evidence suggests that *APOE4* carriers have impaired brain transport of free DHA but not of DHA-lysoPC, increasing their risk of Alzheimer's disease. Dietary sources that provide DHA in phospholipid form may increase plasma levels of DHA-lysoPC, suggesting that this form of DHA may play a special role in the prevention of Alzheimer's disease.[74]

Behavioral effects of omega-3

Depression

Omega-3 fatty acids play important roles in neuronal cell function, neurotransmission, and immune reactions involved in neuropsychiatric disease states, ultimately influencing mood and behavior. Multiple studies have investigated the effects of omega-3s on depression, the most common mood disorder worldwide.[75]

Because people who have depression are at greater risk for cardiovascular disease, researchers conducted a case-control study involving 86 inpatients with depression but without cardiovascular disease and 80 age- and sex-matched healthy outpatients. They assessed the patients' depressive symptoms, cardiovascular disease risk factors, Omega-3 Indices, and interleukin-6 levels. They found that patients with depression were more likely to have increased cardiovascular disease risk factors, lower Omega-3 indices, and higher IL-6 concentrations than healthy patients.[76]

One double-blind, randomized, controlled trial involved more than 430 outpatients enrolled in treatment programs at eight academic and psychiatric clinics in Canada. Patients took either a supplement containing omega-3 fatty acids (1,050 milligrams of eicosapentaenoic acid and 150 milligrams of docosahexaenoic acid) or a placebo daily for eight weeks. They provided self-reports about their depressive symptoms and underwent clinical psychiatric assessments. Patients who took the omega-3 supplement showed improvements in self-reported and clinical assessments of their symptoms, particularly among those with no accompanying anxiety disorders. These improvements were comparable to those observed with common antidepressant drugs.[77]

Another study investigated the effects of omega-3s on brain inflammation, which impairs neurogenesis and is often high among people with depression. The investigators pre-treated human hippocampal cells with either EPA or DHA and then exposed the cells to interleukin (IL)-1 beta, IL-6, and interferon-alpha. They found that EPA and DHA maintained neurogenesis and prevented programmed cell death via the effects of specialized pro-resolving mediators. Then they gave people diagnosed with depression either 3 grams of EPA or 1.4 grams of DHA for 12 weeks. They measured lipid mediators in the participants' blood and assessed their depression symptoms. They found that the anti-inflammatory lipid mediators increased in the participants' blood, and the participants' depressive symptoms decreased by approximately 64 percent with EPA and 71 percent with DHA.[78]

However, some evidence suggests that EPA alone is responsible for the anti-depressive effects of omega-3s. Researchers randomized 81 mild-to-moderately depressed outpatients to receive either 1 gram of EPA or DHA or a placebo daily for 12 weeks and assessed their depressive symptoms before and after the intervention. There was no difference between the two groups before the intervention, but patients who received EPA exhibited fewer depressive symptoms than those who received DHA or a placebo.[79]

A meta-analysis of 20 studies involving more than 5,800 participants indicated that omega-3s reduce depressive symptoms, especially in studies of longer treatment duration involving participants with mild-to-moderate depression. Evidence pointed to low-dose EPA as having the greatest benefit.[80]

The mechanisms that drive the anti-depressive effects of omega-3s are likely related to their anti-inflammatory properties as well as their capacity to influence neuroendocrine function.[81]

- *Learn more about how the immune system interacts with the brain in depression here.*

Antisocial and aggressive behavior in children

Evidence suggests that early-life omega-3 exposure exerts long-term effects on children, ultimately reducing antisocial and aggressive behavior problems. A trial involving 200 school-aged children (8 to 16 years old) provided children with 1 gram of mixed omega-3 fatty acids or a placebo every day for six months. The children underwent personality assessments, and their parents provided reports about the children's behavior, especially externalizing behavior (such as fighting or lying) and internalizing behavior (such as depression, anxiety, and withdrawal). The children who took the omega-3 fatty acids showed marked reductions in negative behaviors that persisted to the 12-month follow-up point, with externalizing behaviors reduced by nearly 42 percent, and internalizing behaviors reduced by nearly 69 percent. These effects were attributed to omega-3 fatty acids' role in neuronal health and neurotransmitter production and function.[82]

Amelioration of the effects of exposure to air pollution

An estimated 4.2 million deaths each year are associated with exposure to air pollution. The mechanisms that drive this association include systemic inflammation, endothelial dysfunction, oxidative stress, hypertension, and metabolic dysfunction. Evidence suggests that omega-3s protect the heart and brain from the deleterious effects of air pollution.

In one study, participants living in an area of high particulate matter (a component of air pollution) received either a 2.5-gram EPA- and DHA-rich fish oil supplement or a placebo daily for four months. Biomarker profiles among participants that took the fish oil were

cardioprotective. In particular, participants exhibited higher levels of glutathione peroxidase, an enzyme that protects against oxidative stress.[11] However, biomarkers among participants who took the placebo were associated with inflammation and cardiovascular disease.

In an observational study involving more than 1,300 women between the ages of 65 and 80 years who were dementia-free at the time of enrollment, investigators measured omega-3 fatty acid concentrations in the women's red blood cells and white matter volumes in the women's brains. The imaging studies revealed that exposure to particulate matter was associated with white matter and hippocampal volume loss. These losses were particularly noticeable among women with the lowest levels of omega-3s in their red blood cells.

- *Learn more about air pollution's damaging effects on brain health in our overview article.*

Respiratory health

Asthma is a chronic inflammatory disorder of the airways. Evidence suggests that omega-3s reduce symptoms of asthma.

A randomized placebo-controlled trial investigated the effects of omega-3s on multiple respiratory disorders, including asthma. The trial involved 736 pregnant women who received either 2 grams of EPA and DHA per day or a placebo, starting at 24 weeks of gestation and continuing until one week after delivery. The women's children were monitored for the first three years of life and assessed for signs of asthma and persistent wheezing. The study revealed that EPA and DHA reduced asthma or persistent wheezing risk in the children by half, particularly among those of women with low EPA and DHA status at baseline.[83]

An observational study found that dietary intake of omega-3 fatty acids among children who carry a common variant in the fatty acid desaturase gene reduces the risk of developing asthma. Impairments in the expression and activity of this gene drive many pathological conditions, including asthma.[84] The study revealed that among children who carried the variant, high intake of omega-3 fatty acids from fish reduced the risk of developing asthma by 51 percent.[85]

Investigators conducted a systematic review and meta-analysis of 11 studies involving more than 99,000 people that investigated associations between fish and omega-3 intake and asthma. They found that fish consumption reduced the risk of asthma in children by 24 percent, and omega-3 intake reduced the risk by 29 percent. Similarly, an intervention trial involving 64 children with asthma found that increasing the dietary intake of fatty fish for six months markedly reduced the children's bronchial inflammation.[86]

Migraine

Migraine is a neurological disorder that affects approximately 15 percent of people worldwide. Evidence suggests that oxylipins, byproducts of omega-3 metabolism, reduce headache pain among people with migraine.

Investigators conducted a randomized controlled trial to examine the effects of dietary omega-3s versus omega-6s in 182 adults who regularly experienced migraine headaches. They found that a high omega-3 or a high omega-3/low omega-6 diet decreased the number of headache hours participants experienced per day as well as the number of headache days experienced per month. A high omega-3/low omega-6 diet was nearly twice as effective at reducing the number of headache days per month than a high omega-3 diet, suggesting that lowering linoleic acid provided an additional beneficial effect. Both diets increased concentrations of 17-hydroxydocosahexaenoic acid, a type of pain-reducing oxylipin, in the participants' blood.[87]

Eye health

Evidence suggests that omega-3s improve aspects of vision, including night vision and age-related changes in macular health.

Night vision

An intervention study assessed the effects of omega-3 supplementation on night vision. The study involved 20 adults who took approximately 3 grams of EPA and 1 gram of DHA daily for four weeks. Six weeks after the last supplementation, the investigators measured the participants' blood concentrations of omega-3 fatty acids and their eyes' ability to adjust to low light. Participants who received the fish oil supplements demonstrated a 25 percent improvement in their ability to identify numbers in low light, compared to those who took a placebo. These changes in visual acuity were attributed to increased levels of omega-3 fatty acids in the participants' blood.[7]

Age-related macular degeneration

Age-related macular degeneration (ARMD) is a vision disorder characterized by impaired or loss of vision in the center of the visual field. It is the leading cause of irreversible vision loss in adults over the age of 60 years. Genetics and environmental factors that drive oxidative stress likely play a role in the pathogenesis of macular degeneration.

Investigators conducted a meta-analysis of 21 studies that examined associations between dietary omega-3s and/or fish intake and the risk of age-related macular degeneration incidence and progression. They found that higher dietary intakes of omega-3s or fish reduced the risk of ARMD by as much as 29 percent. They also conducted a dose-response analysis that revealed that for each additional gram of omega-3 intake, the risk of ARMD decreased by as much as 22 percent.[6]

Enhanced immunological function

Omega-3 fatty acids play important roles in immune function. Evidence suggests they dampen the proinflammatory state associated with autoimmune disorders and may decrease the risk and severity of viral diseases such as COVID-19.

Autoimmune disease

Rheumatoid arthritis

A systematic review of 23 randomized controlled trials found that marine-derived omega-3 fatty acids shortened the duration of morning stiffness, reduced joint swelling and pain, and decreased the use of non-steroidal anti-inflammatory drugs associated with rheumatoid arthritis, a chronic inflammatory autoimmune disease of the joints and bones. The authors of the review posited that EPA and DHA counter the pro-inflammatory effects of omega-6 fatty acids via the production of molecules that exert anti-inflammatory and pro-resolving effects. EPA and DHA may influence other aspects of immunity and inflammation, including dendritic cell and T cell function and the production of reactive oxygen species.[3]

Multiple sclerosis

A systematic review of seven studies that examined the effects of omega-3 fatty acids on quality of life among people with multiple sclerosis, an autoimmune disorder characterized by the progressive destruction of myelin, found that omega-3s reduced the rate of relapse, decreased markers of inflammation, and improved quality of life.[88]

Viral disease

Evidence suggests that omega-3 fatty acids enhance the body's antiviral response by inducing the release of interferons, a class of proteins that inhibit viral replication.[18] For this reason, omega-3s may be beneficial against COVID-19.

COVID-19

COVID-19 is an infectious disease caused by the SARS-CoV-2 virus. Omega-3 fatty acids may reduce symptom severity and risk of death associated with COVID-19.

A pilot trial involving 100 hospitalized COVID-19 patients found that patients with the highest Omega-3 Index scores (5.7 percent or higher) were 75 percent less likely to die from the disease than those with the lowest scores.[16] These data were preliminary and did not meet the classical criteria for statistical significance. A double-blind, randomized clinical trial involving 101 critically ill hospitalized patients (average age, 65 years) diagnosed with COVID-19 found that omega-3 fatty acids markedly reduced symptom severity. Twenty-eight patients received 1,000 milligrams of supplemental omega-3 fatty acids (400 milligrams of EPA and 200 milligrams of DHA) via enteral feeding daily for two weeks, commencing 24 hours after admission the intensive care unit. The remainder of the participants received enteral feeding without supplemental omega-3 fatty acids. The one-month survival rate was 21 percent among the patients who received the supplemental omega-3 fatty acids, versus 3 percent among those who did not. The supplemented group also had improved respiratory and renal function markers, including higher arterial pH, bicarbonate, and urinary output levels, and lower blood urea nitrogen, creatinine, and potassium levels.[17]

In silico (computer modeling) experiments demonstrate that the mechanism driving the fatty acids' protective effects in the setting of COVID-19 may be related to their effects on the spike protein, the primary antigenic component of SARS-CoV-2. The spike protein can assume two different spatial arrangements: a closed, or "pre-fusion" arrangement, or an open, "post-fusion" arrangement. When the spike protein binds to the ACE2 receptor on cells, it changes from its pre-fusion structure to its post-fusion one. The computer models demonstrated that DHA keeps the spike protein closed, potentially reducing viral entry into cells.[89] Due to omega-3 fatty acids' neuroprotective effects and their capacity to promote synaptic plasticity and neurotransmitter function,[90] they are currently under investigation as a therapeutic strategy to ameliorate olfactory losses in COVID-19.[13]

- Learn about the plausibility of this effect from this clip featuring Dr. Bill Harris: "Omega-3 DHA may influence COVID-19 severity"

Improved neurocognitive health

Brain tissue is abundant in omega-3 fatty acids, with DHA comprising approximately 30 percent of the brain's lipids.[74] The importance of omega-3 fatty acids in neurocognitive health begins *in utero* and continues throughout the lifespan.

Pregnancy and development

Maternal omega-3 status is an important factor for fetal and infant neurodevelopment. Investigators conducted a clinical trial involving 92 full-term infants (fully or mostly breastfed) to identify nutrients involved in early-life brain development. Imaging studies conducted at one month of age revealed that infants whose mothers had higher omega-3 intakes exhibited larger volumes in the frontal cortex and corpus callosum, areas of the brain involved in consciousness, communication, memory, attention, and integration of motor, sensory, and cognitive function between the brain's hemispheres.[10]

DHA, in particular, influences mental and psychomotor development. The quantity of DHA present in breast milk is strongly influenced by the mother's diet and lifestyle. For example, when lactating women took a dietary supplement containing 400 milligrams of DHA, their breast milk contained 123 percent more DHA than the breast milk of women who took a placebo. Furthermore, infants whose mothers took the DHA supplement exhibited significantly lower plasma omega-6 to omega-3 ratios compared to infants whose mothers took a placebo.[91]

Maternal dietary intake of omega-6 and omega-3 fatty acids influences aspects of child psychomotor development. A study involving mother-child pairs, when the children were six months old (more than 82,000 pairs) and 12 months old (more than 77,000 pairs), found that the children whose mothers consumed fish or omega-3 fatty acids during pregnancy were less likely to experience delays in problem-solving at six months of age and in fine motor skills and problem-solving at 12 months of age. The researchers found that dietary intake of omega-6 fatty acids was associated with a lower risk of delays in communication and fine motor skill development at six months of age and in gross motor skills, fine motor skills, and problem-solving at 12 months. However, the children whose mothers had a high dietary omega-6 to omega-3 ratio were more likely to experience delays in problem-solving skills at the age of 12 months.[92]

A randomized, double-blinded study investigated the effects of omega-3s (in cod liver oil) or corn oil during pregnancy when taken from 18 weeks gestation until three months after delivery. Children whose mothers took cod liver oil during pregnancy and lactation performed better on mental processing tests than children whose mothers took corn oil. A higher test score correlated with a larger head circumference at birth.[93]

- *Learn more about breast milk and breastfeeding in our overview article.*
- *Learn more in our YouTube clip on this topic, **"Omega-3s in breast milk may improve brain function in infants."***

Improved pregnancy outcomes

Epidemiological data indicate that most pregnant women or women of childbearing age do not consume sufficient dietary sources of omega-3 fatty acids, placing them at risk for maternal undernutrition, impaired fetal growth, and poor pregnancy outcomes.[94] [95] Omega-3 intake from dietary or supplemental forms may ameliorate this risk, however. Evidence suggests that consuming up to 5 grams per day of EPA and DHA (combined) is likely safe for pregnant and lactating women.[96]

Preterm birth

"They said at this point, no more research should be done on this. So the question is settled. [...] If you're down at 3%, that's the high risk group for preterm birth, over 5% is not a problem." - William Harris, Ph.D. Click To Tweet

Maternal nutrition is crucial during pregnancy for both the mother and the infant. Public health experts recommend that pregnant women consume approximately 500 milligrams of DHA per day via intake of low-mercury fish. DHA levels can be measured as a percentage of total fatty acids in red blood cell membranes, and some researchers recommend that pregnant women aim for a DHA target of at least 5 percent, as this is the point below which the risk of early preterm birth increases. Approximately 70 percent of women of childbearing age in the United States are likely below this level.[97]

Preterm birth (less than 37 weeks gestational age) and early preterm birth (less than 34 weeks gestational age) are the primary causes of neonatal death. Findings from the ADORE randomized controlled trial, which involved more than 1,100 pregnant women, indicated that supplementation with 1,000 milligrams of DHA (supplied in algal oil) daily was superior to 200 milligrams in reducing early preterm birth, particularly in women with low baseline DHA status. The higher dose of DHA was also associated with fewer maternal and neonatal serious adverse outcomes.[15] Therefore, DHA supplementation may represent an effective, high-yield, low-risk strategy to decrease early preterm birth.

A Cochrane review of studies involving nearly 20,000 women across 70 randomized controlled trials explored the effects of omega-3 fatty acids, as supplements or food, during pregnancy on maternal and neonatal outcomes. The meta-analysis revealed that women

receiving omega-3 fatty acids were 11 percent less likely to experience preterm birth and 42 percent less likely to experience early preterm birth when compared to women who received no omega-3s. The evidence from these studies was so compelling that the authors declared that no more studies comparing omega-3s to placebo during pregnancy are needed at this time.[98]

In contrast, a randomized placebo-controlled trial completed shortly after the Cochrane review was published did not support these findings. The ORIP trial involving more than 5,500 women explored whether supplementation with omega-3s from early pregnancy would reduce the risk of preterm birth. Women were randomized to receive either 900 milligrams of omega-3 fatty acids or a placebo from 20 to 34 weeks gestation or delivery, whichever occurred first. The trial did not find an association between early-pregnancy supplementation with omega-3s and reduced risk for early preterm birth. However, the adherence to the supplement regimen for women in mid-to-late pregnancy was lower than that reported in similar trials.[99]

- Learn more about the effect of omega-3 on preterm birth in this clip featuring Dr. Bill Harris

Gestational diabetes

Gestational diabetes is a condition of dysregulated glucose metabolism and insulin resistance during pregnancy. It sometimes resolves after delivery but can have serious outcomes for the pregnancy and adverse effects for the mother and child. A meta-analysis of seven randomized controlled trials involving 478 women with gestational diabetes analyzed the effectiveness of EPA and DHA supplementation in glycemic control. The analysis determined that compared to women who took a placebo, those who supplemented with EPA and DHA had dramatically reduced fasting blood sugar and insulin resistance.[100]

Childhood

Attention deficit hyperactivity disorder (ADHD) is a neurobehavioral condition characterized by inattention, impulsive behavior, and emotional dysregulation. An analysis of studies that investigated the effects of dietary interventions on the symptoms associated with ADHD found that elimination diets (diets that exclude foods that trigger symptoms) and fish oil supplementation showed the most promise. The authors of the analysis questioned the quality of the studies, however, and recommended future research.[101]

Findings from a randomized controlled study indicate that blood levels of DHA predict how well children concentrate and learn. The study involved 362 children between the ages of seven and nine years who had below-average reading skills, with most of the children reading at levels about 18 months younger than their chronological ages. Each of the children took either 600 milligrams of supplemental DHA per day or a placebo for 16 weeks. The investigators didn't observe improvements in reading scores in the supplemented group as a whole, but they did see small improvements among those who were reading at the lowest levels, with children reading at the 20th percentile gaining nearly a month in terms of reading age level and those reading at the 10th percentile gaining nearly two months – roughly a 50 percent improvement above what would normally be expected. The parents reported improvements in behavior, but the teachers did not. Supplementation did not affect the children's working memory.[102]

Another study found that children (aged two to six years) with the highest levels of total omega-3 fatty acids (especially DHA) performed better on tests of cognitive function.[103]

Red blood cell structure and function

Red blood cell distribution width

"Maybe they're really changing the way red cells carry oxygen, pick up CO2, squeeze through capillaries because, you know, red cells have got to squeeze through half its diameter as it goes through a capillary." - William Harris, Ph.D. Click To Tweet

Red blood cell distribution width (RDW) is a numerical measure of the variability in the size of circulating red blood cells. It is typically included in a complete blood count in the differential diagnosis of anemia. A high RDW may indicate a nutrient deficiency or disease. In fact, RDW is a robust and independent predictor of adverse health outcomes and is closely associated with the risk of cardiovascular disease and death among people who have had a myocardial infarction (heart attack).[104] [105] Evidence suggests that omega-3s influence RDW.

Researchers investigated possible links between the Omega-3 Index and RDW in healthy adults. They found that a lower Omega-3 Index was correlated with higher RDW, even after taking sex, age, body mass index, and inflammatory status into consideration, suggesting that higher blood concentrations of omega-3s may help maintain normal red blood cell structural and functional integrity.[106]

- *Learn more about the unique effects of omega-3 on red blood cell biology in this clip featuring Dr. Bill Harris.*

Sickle cell disease

Sickle cell disease encompasses a broad class of inherited blood disorders in which red blood cells assume a crescent shape due to hemoglobin abnormalities. Globally, 300,000 infants are born each year with sickle cell disease, many of which will die before the age of 5 years.[107]

People with sickle cell disease often experience vaso-occlusive events – a condition that occurs when sickled red blood cells block blood flow, depriving nearby tissues of oxygen. Because blood cell aggregation and inflammation play key roles in vaso-occlusive events, researchers investigated the effects of omega-3 fatty acids in 120 children and adults with sickle cell disease. Participants received EPA and DHA or a placebo every day for one year, at doses that varied according to age. At the end of the year of treatment, the median rate of vaso-occlusive events among participants that received omega-3s was zero, compared to one per year for those that received the placebo. Those who received the omega-3s were also considerably less likely to experience anemia or require a transfusion, suggesting that the fatty acids improved red blood cell structure and function.[108]

Cancer risk

"We then looked at cardiovascular mortality, cancer mortality, and then everything else, kitchen sink, you know, if it's not cancer, not cardiovascular, it's group three. And we saw the same thing in all groups... It wasn't as strong in cancer. It wasn't as stair-steppy like it was in cardiovascular. But the highest group in omega-3s did have a significantly lower risk of death from cancer." - William Harris, Ph.D. Click To Tweet

Identification of the precise role omega-3s play in cancer risk was complicated somewhat by a 2020 systematic review and meta-analysis that cast some doubt on the anti-cancer effects of omega-3s. This review, which involved more than 100,000 participants across 47 randomized controlled trials, found that long-chain omega-3s have little or no effect on cancer risk.[109] However, many of the studies reviewed in this analysis were too brief to fully capture cancer risk, which is influenced by age and time.

In contrast, a 2021 study involving more than 42,000 people enrolled in 17 prospective (long-term) cohorts found that higher blood omega-3 concentrations were associated with a **7 to 13 percent lower risk of death from cancer**.[54]

In support of the idea that omega-3s likely exert some anti-cancer effects, many discrete biological mechanisms are known to exist that may contribute to such an effect, including their capacity to:

- Suppress cancer-promoting inflammatory molecules called **eicosanoids**[110] [111]
- Regulate transcription factors and genes involved in cell proliferation and apoptosis[112] [113]
- Repress growth factors that influence the formation of new blood vessels, a process required for tumors to grow[114] [114] and is involved in metastasis[114]
- Inhibit free radical and reactive oxygen species production
- Influence insulin sensitivity[115]
- Alter estrogen synthesis[112]

Interestingly, the Selenium and Vitamin E Cancer Prevention Trial (SELECT) reported that higher plasma omega-3 fatty concentrations were associated with an increased risk of developing prostate cancer.[116] However, these findings have been disputed by other researchers, who posit that the investigators in the SELECT trial failed to consider other factors that might increase cancer risk including high dose supplementation with alpha-tocopherol, ignored compelling epidemiological data that contradicted their findings, and extrapolated conclusions that extended beyond their data.[117]

- *Drs. Bill Harris and Rhonda Patrick dissect the SELECT trial's prostate cancer link.*

Prostate cancer

"They were given 400 IUs of alpha-tocopherol or selenium. My mentor Bruce Ames and one of his post-docs had shown that when you give a high dose of alpha-tocopherol that you basically deplete another tocopherol, gamma-tocopherol, which is anti-inflammatory." - Rhonda Patrick, Ph.D. Click To Tweet

One particular trial that received a lot of media coverage, the Selenium and Vitamin E Cancer Prevention Trial (SELECT) reported that higher plasma omega-3 fatty concentrations were associated with an increased risk of developing prostate cancer.[116] However, these findings have been disputed by other researchers, who posit that the investigators in the SELECT trial failed to consider other factors that might increase cancer risk, ignored compelling epidemiological data that contradicted their findings, and extrapolated conclusions that extended beyond their data.[117]

Safety concerns associated with omega-3 intake

Omega-3s are generally considered to be safe, eliciting few adverse effects. However, some evidence suggests that they may carry moderate risks for some groups.

Extended bleeding time

"Even if you give people...10 grams of omega-3 a day before surgery, [...] there was actually less post-op bleeding with...the omega-3 than the placebo. Less need for transfusion, which was kind of cool." - William Harris, Ph.D. Click To Tweet

Early omega-3 research demonstrated that omega-3s extended bleeding time, in turn slowing clot formation, an effect often referred to as "blood thinning."[118] However, concerns over the blood-thinning effect of omega-3s haven't materialized, and data indicate that the effect of omega-3s on bleeding time is similar to that achieved with aspirin.[118] Some evidence even suggests that preoperative omega-3 loading reduces blood losses during surgery, and findings from a large clinical trial revealed that preoperative omega-3s had no effect on bleeding time during or after surgery.[119] [120]

Atrial fibrillation

"If you're giving that high a dose to people, you might want to be a little more attentive to AFib. But there was no increased risk for stroke. There's actually decreased risk for stroke, which would be the clinical outcome of AFib." - William Harris, Ph.D. Click To Tweet

The findings from several recent large-scale trials investigating the effects of omega-3 supplementation on cardiovascular outcomes in people with pre-existing heart conditions suggest that omega-3 supplementation may be associated with a statistically significant increased risk of atrial fibrillation in some populations.

The primary clinical outcome of atrial fibrillation is ischemic stroke, the risk of which increases four to fivefold in the presence of atrial fibrillation.[121] In most circumstances, stroke risk is markedly exacerbated by the presence of atrial fibrillation; however, an abundance of data indicates that omega-3s generally *reduce the risk of stroke*, underscoring some of the complexity in interpreting the clinical significant of this particular association.[122].

Nevertheless, a meta-analysis of seven studies involving more than 81,000 participants found that long-term intake of omega-3s increased the risk of atrial fibrillation by 25 percent overall. Doses less than 1 gram per day increased the risk of atrial fibrillation by 12 percent; doses greater than 1 gram increased the risk by 49 percent.[123] A more recent meta-analysis including many of these same studies found that the association with an increased risk of atrial fibrillation appears to be among people who have elevated triglycerides and other cardiovascular disease risks, **suggesting that atrial fibrillation risk is population-specific**.[124]

Another trial, the Omega-3 Fatty Acids for Prevention of Post-operative Atrial Fibrillation (OPERA) study, investigated the effects of short-term preoperative omega-3 supplementation on outcomes for cardiac surgical patients, who are at greater risk for atrial fibrillation after surgery. Investigators randomized patients to receive omega-3s or a placebo, with preoperative loading of 10 grams of omega-3s spread over three to five days (or 8 grams over two days), followed postoperatively by 2 grams per day until discharge day or postoperative day 10, whichever came first. The results of the trial indicated that omega-3 supplementation had no effect on postoperative atrial fibrillation risk.[120]

More research is necessary to provide insights into the link between omega-3 supplementation and A-fib and its overall clinical significance in light of broader cardiovascular benefits demonstrated in trials like REDUCE-IT.

- *Watch this clip in which omega-3 expert Dr. Bill Harris discusses the controversy surrounding omega-3 intake and increased risk of atrial fibrillation.*

Effects of handling, storage, and cooking on omega-3 content of foods

Generally, the omega-3 content of most foods remains stable during cooking, but some cooking techniques do induce greater losses.

A study measured the omega-3 content of salmon after preparing the fish using several cooking techniques, including poaching, steaming, microwaving, pan frying (no added oil), oven baking (no added oil), and deep frying (in sunflower oil). They observed only minor differences in content with the various cooking methods, but the fish fried in sunflower oil showed a slight increase in polyunsaturated fat content (due to uptake from the oil in which it was fried) and had the lowest omega-3 content of all the fish.[125]

Another study investigated the effects of handling, cold storage, and cooking techniques (steaming versus grilling) on omega-3 content. They found that six hours after fish death, omega-3 content decreased by an average of approximately 20 percent, indicating that fish should be stored in very cold temperatures as soon after death as possible. They also found that grilling increased omega-3 content compared to steaming.[126]

The history – and future – of omega-3 research

"We treated them and that's where we got huge, you know, 80% drops in triglycerides. When the triglycerides are very high, you get a big drop." - William Harris, Ph.D. Click To Tweet

The omega-3 story unfolded with a series of surprising discoveries half a century ago when Drs. Hans Olaf Bang and Jørn Dyerberg set out to learn why the Greenlandic Inuit had the world's lowest incidence of cardiovascular disease-related deaths – despite their high-fat diet, which was rich in seal meat and fatty fish. Their research revealed that the average Inuit had lower triglyceride and lipid concentrations than the average Dane. But the Inuit's concentrations were also lower than their Inuit peers living in Denmark, suggesting that environmental factors, rather than genetic ones, were at play. Subsequent research revealed that the Inuit living in Greenland had high blood concentrations of EPA and DHA. Bang and Dyerberg posited that these fatty acids, now commonly known as omega-3s, were critical to the Inuit's health.[127] [128] [129] [130]

Around the same time, Drs. Bill Connor and Bill Harris were investigating how salmon oil – an animal fat that is uncharacteristically liquid at room temperature – influenced cholesterol levels. They fed volunteers large quantities (almost 30 grams per day) of omega-3 fatty acids in the form of salmon oil and salmon steaks, roughly equivalent to 20 times the recommended intake for males. Surprisingly, they found that this mega-dose of omega-3s lowered triglycerides by an impressive 25 percent.[131] Ten years later, three papers published simultaneously in the *New England Journal of Medicine* put omega-3 fatty acids on the map. They are now one of the most researched molecules in medicine.[130]

Those early findings provided a catalyst for an extensive field of research that continues today. Conducting that research has posed challenges, however, and the findings from five decades of study have been remarkably inconsistent, with some studies showing benefits, and others not. Some of these inconsistencies have arisen from differences in study designs, which have varied markedly. The use of the Omega-3 Index as a quantifiable biomarker and the recognition that multiple factors (including dose, formulation, product oxidation, genetics, and characteristics of the population under study) influence omega-3 status and clinical response has reduced much of that confusion.

- Learn more about the early history of research and the overall safety profile of omega-3 fatty acids in this clip featuring Dr. Bill Harris: "The Highest Omega-3 Dose Ever Studied (25 grams per day)."

Conclusion

Omega-3 fatty acids play critical roles in human health, participating in a wide range of biochemical pathways, modulating the expression of hundreds of genes, and affecting multiple organ systems throughout the lifespan, from *in utero* development through old age. These essential nutrients are available in both food and supplemental forms and vary considerably in their bioavailability due to both characteristics of the forms as well as interindividual differences in age, overall health, disease status, genetics, and other factors.

A growing body of evidence suggests that omega-3 fatty acids influence learning, enhance immune function, improve pregnancy outcomes, prevent or ameliorate symptoms associated with a wide range of chronic health conditions, and markedly reduce the risk of premature death. The principal mechanism by which omega-3s exert their beneficial effects is via the resolution of inflammation, a coordinated response that involves byproducts of omega-3 metabolism, called specialized pro-resolving mediators, or SPMs. Omega-3s may have particular importance in maintaining neurocognitive function in aging, especially among people who carry the *APOE4* gene, which predisposes individuals to Alzheimer's disease.

Omega-3s are well-tolerated and generally considered safe. Although omega-3s do exert blood-thinning effects, data indicate that the effect of omega-3s on bleeding time is comparable to that achieved with aspirin. Some recent data suggest that high-dose omega-3s increase the risk of atrial fibrillation; however, the incidence of stroke (the expected clinical outcome of atrial fibrillation) is reduced among people taking omega-3s.

Variations in study designs have led to some confusion and a wide array of inconsistencies in the data surrounding the effects of omega-3s. Recent, well-designed trials that provide sufficient doses, carefully consider aspects of the population under study, and rely on quantifiable biomarkers, such as the Omega-3 Index have delivered robust, consistent results.

Omega-3 FAQs

Q: What are the best dietary sources of omega-3?

A: Dietary fish and roe contain omega-3s in phospholipid and triglyceride forms. Fatty fish such as salmon, anchovies, mackerel, herring, and sardines are excellent dietary sources of EPA and DHA.[132] However, environmental toxicants, such as mercury, dioxins, dioxin-like polychlorinated biphenyls, polybrominated diphenyl ethers, and organochlorine pesticides, readily bioaccumulate in fatty fish, so consumption of younger, smaller fish is recommended to avoid or limit exposure.[133]

Q: What are the best plant sources of marine omega-3 fatty acids?

A: There are a variety of products already available that are derived from algae rather than fish; however, a trial investigating the uptake of omega-3s from genetically engineered *Camelina sativa* (an oilseed plant from the Brassica family) in healthy men and women revealed that the engineered fatty acids were safe and well tolerated, and their uptake and incorporation into blood and plasma lipids were comparable to that achieved with fish oil.[134] In other words, genetic engineering of plants that produce high-yield and high-quality EPA and DHA may offer yet another strategy to meet the growing needs of people that prefer to avoid animal-based products or are concerned about sustainability.[135]

Q: Are free fatty acid formulations more bioavailable?

"So they're unesterified EPA and DHA, which they had previously shown are more readily absorbed. You don't have to hydrolyze them, they're already free fatty acids. But the trouble with those is they're also pretty irritating. [...] And that may induce some kind of chronic inflammatory response that's going on systemically from taking these detergents." - William Harris, Ph.D. Click To Tweet

Free fatty acid or carboxylic acid formulations do not require enzymatic digestion and can be taken without regard to food intake, a quality that differs from common ethyl ester formulations, for example. [20] However, clinical trials for these formulations have not been universally positive. [64] Possibly as a contributing consequence of this, the major pharmaceutical preparation for a "free fatty acid form" of omega-3 *Epanova* was ultimately discontinued.

- *Learn more in this clip featuring Dr. Bill Harris discussing potential shortcomings of the STRENGTH trial.*

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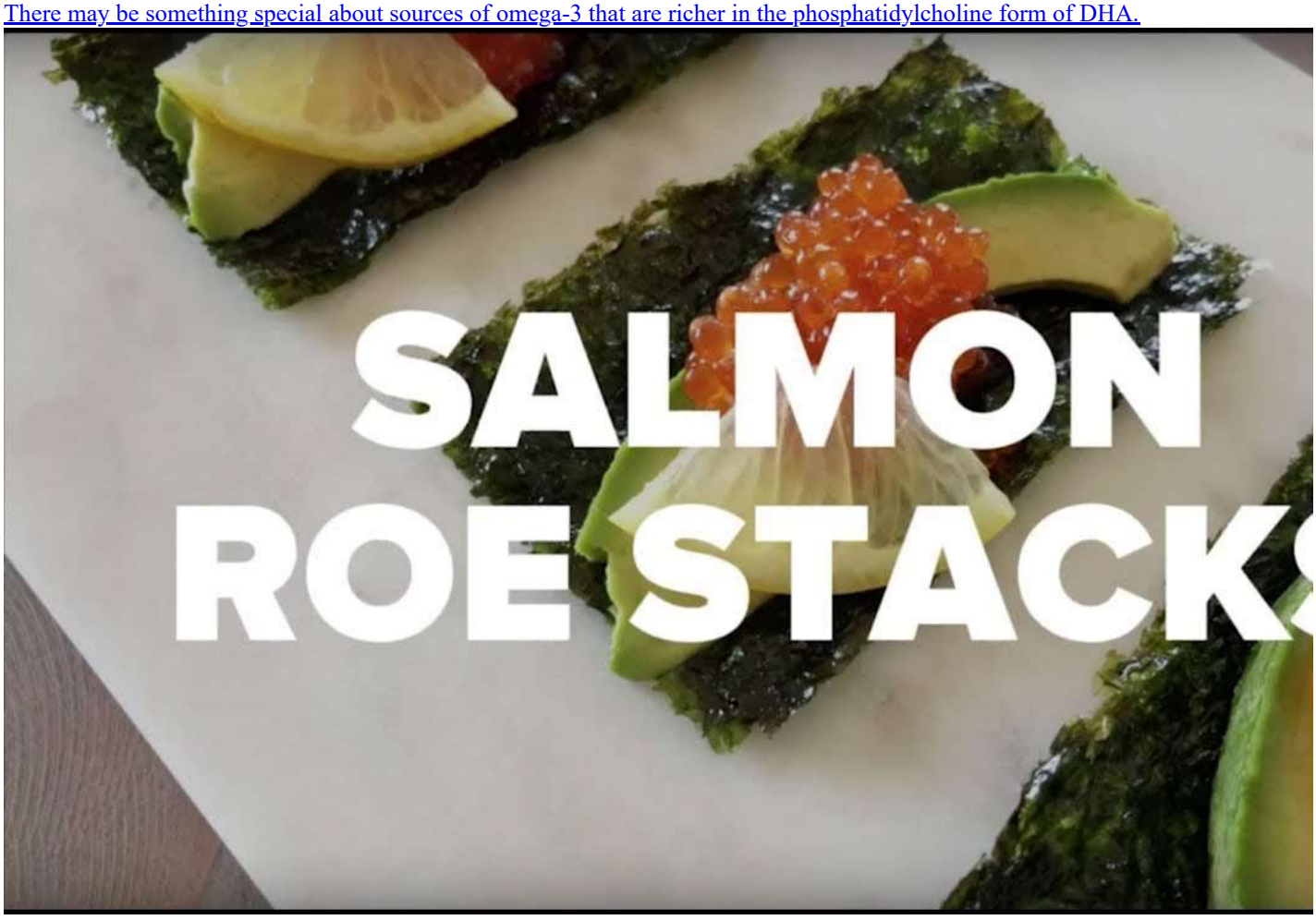
The Phospholipid Brain-DHA Advantage

There may be something special about sources of omega-3 that are richer in the phosphatidylcholine form of DHA.



Salmon Roe Stacks Recipe

This short recipe video shows a fun, tasty way to eat salmon roe. Salmon roe is rich in the omega-3 fatty acid, docosahexaenoic acid,

Topics related to Omega-3view all

- FOXO
  FOXO proteins are transcriptional regulators that play an important role in healthy aging. Some FOXO genes may increase lifespan.

- Quercetin
  Quercetin is a plant-based bioactive compound that exerts antioxidant, anti-inflammatory, and anti-aging properties across multiple organ systems.
- Breast milk and breastfeeding
  Breast milk is a complex, dynamic fluid that contains nutritional and non-nutritional components that positively influence an infant's development. Breastfeeding benefits both infants and mothers.
- Brain-derived neurotrophic factor (BDNF)
  BDNF is a growth factor known for its influence on neuronal health and for its role in mediating the beneficial cognitive effects associated with exercise.
- Sirtuins
  Sirtuins play a key role in healthspan and longevity by regulating a variety of metabolic processes implicated in aging.
- Hallmarks of aging
  The hallmarks of aging are observable biological patterns of dysfunction that accrue in a biological organism over time.

Omega-3 Newsview all

- **Study shows people with a high omega-3 DHA level in their blood are at 49% lower risk of Alzheimer's**

  Submitted 12 months by Teresa
  alzheimer's
  omega-3

- **High-dose 2.4g EPA/DHA omega-3 in third trimester of pregnancy decreased the risk of wheeze & asthma during first 5 years of child's life by 54%**

  Submitted over 1 year by dan
  omega-3
  pregnancy
  development
  asthma

- **Eating fish rich in omega-3 fatty acids reduces risk of asthma in some children.**

  Submitted over 2 years by rhonda
  omega-3
  asthma

- **Neonatal brain damage decreased by ~50% when a triglyceride lipid emulsion containing omega-3 DHA was injected within two hours of ischemic stroke**

  Submitted almost 3 years by dan
  brain
  omega-3
  stroke

- **Low levels of omega-3 fatty acids are associated with early-onset coronary atherosclerosis.**

  Submitted over 3 years by rhonda
  heart disease
  omega-3

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Our Mission

Promoting strategies to increase healthspan, well-being, cognitive and physical performance through deeper understandings of biology. Learn more about Dr. Rhonda Patrick.

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