MONOGRAPH

The Omega-3 Index

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ODX RESEARCH

Abstract

The omega-3 index (O3I) is emerging as a valuable biomarker for assessing long-term omega-3 status in the body.

Omega-3 fatty acids are polyunsaturated fatty acids (PUFAs) that are vital to the maintenance of cardiovascular, pulmonary, immune, endocrine, and nervous systems. Research validates low omega-3 index as a cardiovascular risk factor that significantly increases risk of sudden cardiac death. A low O3I is also associated with increased inflammatory, metabolic, and neurological disorders.

Alpha-linolenic acid (ALA) is the essential omega-3 PUFA that must be consumed in the diet as it can't be synthesized by humans. It serves as a precursor to long-chain omega-3s eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) which are further metabolized into prostaglandins, thromboxanes, leukotrienes, resolvins, protectins, and neuroprotectins, many of which are anti-inflammatory.

Conversion of ALA to EPA and DHA may be limited or compromised in some individuals, which can lead to disruption of downstream metabolic processes.

The O3I measures the percentage of long-chain omega-3 EPA and DHA in red blood cell membranes, where they contribute to cell membrane fluidity and function. Cell membranes maintain a reserve of EPA and DHA that can be released and used throughout the body.

Adequate intake of omega-3s is important to health and metabolism. However, evaluation of intake alone is not a good reflection of omega-3 status. Instead, research supports the omega-3 index as the preferred measurement of omega-3 status. While an omega-3 index of greater than 4% had been considered ideal in the past, current research suggests that an optimal omega-3 index should be greater than 8%.

Introduction

Chronic inflammation underlies most chronic diseases yet often gets overlooked or underappreciated as a significant factor. A major factor in the risk of chronic inflammation and chronic disease is suboptimal omega-3 status.

This review will summarize:

- The characteristics and functions of omega-3s, especially EPA and DHA and their metabolites
- The role of omega-3 status in cardiovascular disease, inflammatory disorders, metabolic dysfunction, neurological dysfunction, and pregnancy
- The merits of assessing omega-3 status using the omega-3 index
- The optimal omega-3 index goal and relevant research supporting that goal
- The omega-3 index as a biomarker of cardiovascular disease and risk of sudden cardiac death
- Nutrition intervention, food sources, and supplementation
- Omega-3, omega-6 balance
- Optimal takeaways for the clinician

The omega-3 index

The omega-3 index (O3I) was first introduced as a biomarker of coronary artery disease mortality risk in 2004. Subsequent research confirmed its utility as a gauge of CVD risk, as well as its clinical application in inflammatory disorders, including major depressive disorders.[1]

The long-chain omega-3s EPA and DHA and their metabolites reduce oxidative stress biomarkers[2] and beneficially regulate blood pressure, blood clotting, cell membrane fluidity, heart rate, inflammation, immune activity, muscle metabolism, and neurological function. [3 4 5 6 7 8]

Adequate intake of omega-3s and efficient incorporation into cell membranes is crucial to maintaining balance in each of these metabolic processes.

Unfortunately, omega-3 intake is suboptimal in many regions. The all-too-common Western-style diet is low in omega-3s and high in processed foods and omega-6s. This creates an imbalance that favors production of inflammatory prostaglandins and cytokines, contributing to the characteristic pathology of many Western diseases.[9]

The O3I can be used to assess omega-3 nutrition status as well as compliance with omega-3 recommendations over time.[10]

Using RBC membrane measurement is preferred as it best reflects long-term omega-3 intake. It is the most efficient technical method and has less EPA and DHA variability than plasma phospholipid or whole blood measurements.[11] The standardized, preferred methodology is known as the HS-Omega-3 Index®.

Since the O3I corresponds to tissue levels of EPA and DHA, especially cardiac, gastrointestinal, and brain tissue, it can be used to evaluate risk of cardiovascular disease, inflammation, neurological dysfunction, etc.[12 13 14] The O3I maintains an inverse correlation with inflammatory biomarkers, major depressive disorder, and non-alcoholic fatty liver disease.[15] Therefore, the O3I should be assessed and monitored in individuals at risk for these disorders.

Cardiovascular disease risk

The omega-3 index correlates with EPA and DHA content of cardiac tissue. A decreased value is associated with increased risk of cardiovascular mortality.[16]

Researchers conclude that “a low omega-3 index fulfills the current criteria for a novel cardiovascular risk factor.”[17] It can be especially useful as a risk factor for sudden cardiac death,[18 19 20] and maintains an inverse association with death from coronary heart disease.[21]

This isn’t new news.

A prospective, double-blind, dose-response study published in 2004 determined that an O3I of 4% or less increased risk of sudden cardiac death by 10-fold compared to an O3I greater than 8%.[22] The 20-week, randomized study demonstrated an increase in the O3I with omega-3 supplementation. The O3I increased from 4.7% to 7.9% with 500 mg/day EPA+ DHA; to 9.9% with 1000 mg/day; and to 11.6% with 2000 mg/day. The O3I decreased in the placebo group. In this early study, the correlation coefficient between the O3I, whole blood omega-3 PUFAs, and plasma phospholipid EPA + DHA was greater than 0.9, allowing researchers to compare results to past studies.[23]

Review of 10-cohort studies evaluating the association between O3I and coronary heart disease estimates a 30% reduction of risk for fatal disease when O3I was increased from 4% to 8%.[24]

Randomized trials report significant reductions in myocardial infarction, vascular death, and major CVD events with omega-3 supplementation. One major trial used high doses of 4 grams/day in statin treated patients and found a 25% reduction of risk for CVD events. Supplementation will have a dose-related effect on the O3I as it is considered a “stable biomarker of dietary intake.” [25]

Omega-3s help reduce triglycerides by increasing fatty oxidation in the liver as well as inhibiting lipogenesis. Their effects on lowering cholesterol come from an inhibition of hepatic cholesterol synthesizing enzymes.[26]

Heart arrhythmias may have an association with suboptimal O3I:[27]

- ✓ A significantly lower level of RBC membrane omega-3s was found in subjects with atrial fibrillation (AF), 2.8% versus 5.3%.
- ✓ The median O3I in ventricular fibrillation (VF) subjects was found to be 4.88%. Low levels of omega-3s in cardiac tissue can increase VF during acute MI. A 1% increase in O3I translated into a 48% reduction in VF risk.
- ✓ A low O3I of 4.24% was predictive of ventricular arrhythmias, versus higher values of 5.12%. However, one study in Italy suggests that while an increase in O3I from 4.8% to 6.7% was associated with cardiovascular benefits, the level was not high enough to reduce malignant arrhythmias.
- ✓ A goal of 1-2 grams of omega-3 PUFAs per day was recommended to minimize ventricular dilatation, a risk factor for malignant arrhythmias.
- ✓ Research suggests that treatment with 3.6 grams of EPA + DHA over a six-month period significantly reduced ventricular tachycardia in implantable cardioverter defibrillator subjects with ischemic cardiomyopathy.
- ✓ Researchers attribute the benefits of omega-3 PUFAs to their positive effects on blood pressure, endothelial function, reduced inflammation, modulation of blood lipid profiles, attenuation of oxidative stress and calcium overload, reduced fibrosis, and favorable modulation of mitochondrial processes.
- ✓ DHA and its metabolic byproducts resolvins, protectins, neuroprostanes, etc., have potent anti-arrhythmic effects.
- ✓ No significant changes in mild or moderate bleeding risk were seen with increasing O3I.
- ✓ Researchers emphasize the importance of preventing AF because invasive treatments and drugs used after the fact do not reduce adverse outcomes related to this disorder.

Meta-analyses demonstrate that omega-3 fatty acids EPA and DHA directly reduce cardiovascular risk by:[28]

Reducing

- ✓ Blood pressure (systolic and diastolic)
- ✓ C-reactive protein
- ✓ Heart rate
- ✓ Platelet aggregation
- ✓ Pro-inflammatory cytokines, TNF, IL-6
- ✓ Pro-inflammatory eicosanoids, thromboxane B2, leukotriene B4
- ✓ Triglycerides

Increasing

- ✓ Arterial compliance
- ✓ Flow-mediated dilatation
- ✓ HDL-cholesterol
- ✓ Heart rate variability

Inflammation

Polyunsaturated fatty acids and their metabolites regulate gene expression associated with inflammatory pathways as well as lipid metabolism. These pathways involve EPA, DHA, and arachidonic acid (AA).[29]

Researchers note that many placebo-controlled trials support the use of fish oil supplementation (rich in EPA and DHA) in chronic inflammatory states such as rheumatoid arthritis, inflammatory bowel disease, lupus, multiple sclerosis, psoriasis, and migraine headaches. Past research reveals a correlation between increased cell membrane omega-3 EPA and substantial inhibition of pro-inflammatory compounds, leading to decreased use of NSAIDs. Increasing dietary omega-3s and reducing omega-6s may help reduce inflammation in susceptible individuals.[30] An increase in dietary EPA and DHA will be reflected in the O3I over time.

Omega-3 PUFAs exert immunomodulatory and anti-inflammatory effects as they promote a decrease in TNF-alpha, NF-kappaB, IL-6, IL-12, IL-13, IL17A, and macrophage inflammatory protein. Anti-inflammatory effects of EPA and DHA also extend to inhibition of free radical formation and reduction of oxidative stress.[31]

Review of data from the Framingham Offspring and minority Omni cohorts revealed that the O3I had significant negative correlations with 10 inflammatory biomarkers including CRP, IL-6, LpPLA2 activity and mass, p-selectin, and tumor necrosis factor receptor 2.[32]

Researchers have proposed optimal intake levels of EPA + DHA categorized by specific inflammatory conditions:[33]

Multiple sclerosis	0.4 g/day EPA + 0.5 g/day DHA
Rheumatoid arthritis	2.7 g/day EPA + 1.8 g/day DHA
Sjogren's Syndrome	0.42 g/day EPA + 0.28 g/day DHA
Systemic Lupus Erythematosus	0.18 g/day EPA + 0.12 g/day DHA
Type 1 Diabetes Mellitus	0.4 g/day EPA + 0.6 g/day DHA

Asthma

Systemic inflammation is a hallmark characteristic of asthma. Research indicates that a higher O3I is significantly associated with better asthma control (6% versus 5.6%). An O3I of 8% or above was associated with significantly reduced dose of inhaled corticosteroids for maintenance.[34]

A three-week randomized double-blind crossover study of 16 asthmatics found that fish oil supplementation containing 3.2 grams of EPA + 2 grams of DHA reduced exercise-induced bronchoconstriction below diagnostic threshold values and significantly reduced markers of inflammation including TNF-alpha and IL-1B. Bronchodilator use was significantly reduced in the treatment group.[35]

COVID-19

Rapid progression of inflammation and a "cytokine storm" are associated with increased mortality from coronavirus disease 2019 (COVID-19). Researchers suggest that omega-3s may be able to decrease inflammatory markers and the cytokine storm, reduce cardiovascular complications, and reduce severity of acute respiratory distress syndrome (ARDS).[36]

A small pilot study of 100 hospitalized COVID-19 patients found that those with an O3I of 5.7% or above were 75% less likely to die than those with an O3I of less than 5.7%.[37]

Metabolic dysfunction

Epidemiological research reveals that many symptoms of metabolic syndrome, cardiovascular disease, and depression cluster together. These include abdominal adiposity, hyperglycemia, hypertension, hyperlipidemia, and insulin resistance. Meta-analysis reveals a 37% increased risk of diabetes in adults with depression.[38]

Mounting evidence confirms that suboptimal omega-3 intake is associated with cardiometabolic disease and mortality.[39]

- ✓ Data support the use of supplementation for improving risk factors including hyperglycemia, hypertriglyceridemia, insulin metabolism, increased waist circumference, and endothelial dysfunction.
- ✓ The O3I was found to be negatively associated with metabolic dysfunction indices including HOMA-IR calculations, cholesterol levels, and intima-media thickness.
- ✓ Researchers considered the O3I a predictor for both metabolic syndrome and non-alcoholic fatty liver disease (NAFLD).

The largest to date meta-analysis and meta-regression reviewed the results of omega-3 supplementation in 45 trials with 2674 adults with type 2 diabetes. Results demonstrated significant reduction in LDL, VLDL, triglycerides, hemoglobin A1C, IL-6, and TNF-alpha. A range of omega-3 dosing was administered from 0.4 – 18 grams/day, for a duration of between 2 and 104 weeks.[40]

Meta-analysis of 23 randomized controlled trials investigating NAFLD demonstrated that supplementation with omega-3 PUFAs significantly improved liver fat content as well as serum triglycerides, total cholesterol, HDL, and BMI. Dosage and duration of supplementation varied.[41]

Neurological dysfunction

Lipid signaling and metabolism are vital to neurological processes and brain function, and omega-3s are vital to lipid metabolism. Depletion or deficiency of omega-3s can lead to:[42]

Anxiety disorders	Neurodegeneration	Mood disorders
Dementia	Neuroinflammation	Poor cognition
Depression	Neurotransmission disruption	
Eye disorders		

Omega-3s are crucial to cell membrane fluidity and cell membrane fluidity is crucial to nerve function. For example, serotonin and dopamine depend on this fluidity for neurotransmission.[43]

Omega-3 DHA is especially important as it is the most abundant lipid in the central nervous system (CNS).[44] Its significance lies in its structural and functional roles in blood brain barrier integrity, cerebral phospholipids, neurotransmission, synthesis of dopamine and serotonin, membrane fluidity, and neuroprotection.[45] [46]

Researchers suggests that doses of 600 mg or more of DHA may be needed to promote improvements in executive function, memory, and learning. However, despite increased intake, uptake of DHA into circulation and into the brain can be impaired in carriers of the ApoE4 variant, a major risk factor for Alzheimer's disease.[47]

Omega-3 EPA is vital as well, as it regulates neurotransmission, neuroinflammation, and even cell survival.[48] Both DHA and EPA are essential to controlling CNS inflammation and supporting endothelial function, benefits that translate into reduced cardiovascular risk as well.[49]

Omega-3s are also metabolized into endocannabinoids, compounds with a profound impact on physiology, especially due to their anti-inflammatory effects. Omega-3 endocannabinoids complex with neurotransmitters dopamine and serotonin, enhancing their effects on mood and cognitive function.[50]

Omega-3 neurological research

A subset of memory-impaired subjects in the Multidomain Alzheimer Preventive Trial (MAPT) with a suboptimal O3I of 4.83% or less were supplemented with DHA (800 mg) and EPA (up to 225 mg). Results indicated that supplementation had some benefit on executive function though not of statistical significance. The study did not investigate higher doses of omega-3s for comparison.[51]

Individuals with ultra-high risk of psychosis, a group known to be deficient in long-chain omega-3s, were found to have an O3I 26.9% lower than healthy controls.[52] Six months of supplementation with fish oil (840 mg EPA, 560 mg DHA) in the high-risk group increased O3I from 3% to 4.12%.[53]

Systemic review and meta-analysis indicate that EPA and DHA supplementation in children with attention-deficit/hyperactivity disorder resulted in a "small but significant" improvement in attention, hyperactivity, and even parental ratings of behavior. Higher doses of EPA were especially beneficial and significantly increased supplement efficacy.[54] Optimal dosing was not determined or recommended in the analysis.

Supplementation with 4 grams of omega-3 fatty acids (2520 mg DHA, 840 mg EPA) in patients with age-related macular degeneration significantly increased their omega-3 index. Mean baseline O3I was 5% and levels rose by an average of 7.6% during the six-month study. Researchers considered the trial too short to see significant changes in eye function.[55]

Signs and symptoms of occupational burnout were found to decrease with omega-3 PUFA supplementation. A 52-week study found improvement with 1200 mg EPA + 600 mg DHA for 52 weeks. Another study revealed that even lower doses of 180 mg EPA + 120 mg DHA for 8 weeks had a positive effect [56]

A review of baseline data from 14 subjects with schizophrenia and 116 subjects with depression revealed that all subjects had suboptimal O3I with an average value of 3.95%. Both groups had risk factors for cardiovascular disease and metabolic syndrome.[57]

However, omega-3 supplementation in those with schizophrenia comes with a few caveats. While supplementation was effective in early prodromal and first- episode schizophrenia, results were mixed in chronic schizophrenia. Although some subjects benefited, supplementation was associated with a worsening of symptoms during acute exacerbations and in those who had discontinued anti-psychotic medication.[58]

Evidence-based guidelines have been developed for youth with the following neuropsych disorders. Supplementation was especially effective in those with inflammation or a low O3I: [59]

- ✓ Attention deficit hyperactivity disorder
    - A combination of eicosapentaenoic acid (EPA) + docosahexaenoic acid (DHA) ≥ 750 mg/d, and a higher dose of EPA (1,200 mg/d) for those with inflammation or allergic diseases for duration of 16–24 weeks.
- ✓ Major depressive disorder (MDD)
    - A combination of EPA + DHA of 1,000–2,000 mg/d, with EPA:DHA ratio of 2 to 1, for 12–16 weeks.
- ✓ Autism spectrum disorder
    - A combination of EPA + DHA of 1,300–1,500 mg/d for 16–24 weeks as add-on therapy to target lethargy and hyperactivity symptoms.
    - The current review also suggested that O3I and inflammation may be potential treatment response markers for youth, especially in ADHD and MDD, receiving omega-3 PUFA.

Depression

Omega-3 index was significantly lower in subjects with major depressive disorder (O3I 3.8%) and bipolar disorder (O3I 3.3%) versus subjects without these mood disorders (O3I 4.8%). Both depressed and bipolar subjects had significantly lower RBC membrane DHA than controls.[60]

Systemic review and meta-analysis revealed that a mean dose of 1.3 grams of EPA + DHA was efficacious for treating mild to moderate depression in subjects over 65 years of age.[61]

Severity of depression symptoms was reduced when the O3I increased. One study indicated that risk of depression decreased for every 1% increase in O3-I.[62]

An inverse association between depressive symptoms and O3I was observed in subjects who had both depression and acute coronary syndrome. The study confirmed a 1 point decline in depressive symptoms for every 4.54% increase in O3I.[63]

A case-control study of 166 adults (86 with MDD but no CVD, and 80 controls) found a low O3I in depressed subjects along with increased risk factors for metabolic syndrome and cardiovascular disease, i.e.,[64]

- ✓ 3.9% mean O3I
- ✓ 152 mg/dL mean serum triglycerides
- ✓ 96 mg/dL mean fasting glucose
- ✓ 97 cm mean waist circumference
- ✓ Elevated IL-6

Pregnancy

Omega-3 fatty acids are important to human health from the very beginning:[65]

- Pregnant women are advised to increase their intake of long-chain omega-3s because low levels of EPA and DHA are associated with complications including premature birth.
- Intake of DHA is especially important. In general, an additional 200 mg per day is recommended during pregnancy.
- An inverse correlation is observed between pre-term birth and maternal levels of EPA and DHA in RBCs, plasma, and whole blood.
- The longer the pregnancy, the higher the level of DHA found in the child's erythrocytes.
- A large, randomized intervention trial of 2399 pregnant women (DOMINO) observed an increase in EPA and DHA in cord blood when supplements of 800 mg of DHA and 100 mg of EPA were consumed.
    - Cord blood increases corresponded to higher erythrocyte O3I.
    - Premature births prior to week 34 were reduced by 51%.
    - Mean birth weight was increased
    - Intensive care admissions were decreased.
    - Only 3 newborns perished in the treatment group versus 12 in the placebo group.
- Better EPA and DHA status at birth was associated with improved cognitive development.
- Meta-analysis of 7 studies found that EPA and DHA effectively reduced fasting blood glucose and HOMA-IR in gestational diabetics.
- Increased intake and supplementation should be guided by O3I levels as excess omega-3 intake may have consequences as well.

- According to the European Food Safety Authority, an intake of up to 5 grams per day of EPA and DHA is considered safe for the general public, as well as pregnant and lactating women. However, researchers suggest a limit of 2.7 grams per day total and a maximum O3I below 16% during pregnancy.
- Researchers recommend monitoring O3I and maintaining a level of 8-11% during pregnancy and into lactation.

Nutrition intervention

Nutrition intervention that improves omega-3 status can make a significant difference in clinical outcomes including reduction of cardiovascular disease, cancer, and other inflammatory pathologies.[66]

Omega-3 intake sufficient to raise the O3I above 8% is thought to help protect the heart and brain from the negative effects of a high omega-6 Western-type diet.[67] Preformed EPA and DHA may be the preferred form of omega-3s in the diet, especially for individuals unable to adequately convert the plant-based omega-3 ALA into long-chain omega-3s. This conversion may be reduced due to gender, metabolic, or genetic factors.[68]

A world-wide survey indicates very low blood levels of 4% or less EPA + DHA were found in North, Central, and South America, South-East Asia, Middle East, Africa, and Europe.[69]

Bioavailability of dietary EPA and DHA can vary depending on foods and compounds eaten at the same meal. Presence of fat at a meal can increase bioavailability by a factor of 13.[70]

Additional factors that may influence individual response to omega-3 intake include:[71]

- ✓ Age
- ✓ Baseline O3I
- ✓ Body weight
- ✓ Chemical formulation of EPA and DHA
- ✓ Gender
- ✓ Genetic factors
- ✓ Smoking

Omega-3s and Omega-6s

The balance of omega-3s and omega-6s in the diet and in the body can affect omega-3 status. For example, excess intake of omega-6s can interfere with the anti-inflammatory effects of omega-3s.[72]

In the body, omega-3s and omega-6s compete for the same desaturation and elongation enzymes. Their balance in the diet can determine whether pro- or anti-inflammatory compounds will be produced downstream.[73] [74] [75]

Within cell membranes, an excess of omega-6 to omega-3 compounds will negatively affect fluidity and thickness of the membrane and disrupt the position and function of embedded proteins.[76]

Dietary omega-3 ALA is converted to EPA and then DHA, compounds which in turn are converted to anti-inflammatory prostaglandins, leukotrienes, resolvins, and protectins.[77] [78] The precursor ALA is found in plant-based foods, while EPA and DHA can be consumed preformed in non-plant-based foods, especially oily fish such as salmon, tuna, mackerel, and sardines. Less oily fish and seafood will have less EPA and DHA, including bass, tilapia, cod, and shellfish.[79]

Omega-6 LA, which is essential in the diet, can be converted to both anti-inflammatory and inflammatory compounds. It can be converted to omega-6 gamma-linolenic acid (GLA) and dihomo-gamma-linolenic acid (DGLA) which produce anti-inflammatory prostaglandins. Research suggests that a combination of GLA and omega-3s may be most effective for addressing inflammatory skin disorders such as psoriasis, acne, and atopic dermatitis.[80]

However, the primary byproduct of omega-6 LA metabolism is arachidonic acid (AA) which can be converted to pro-inflammatory eicosanoid compounds. The resulting prostaglandins, thromboxanes, and leukotrienes contribute to inflammation, platelet aggregation, and vasoconstriction, all risk factors for CVD.[81]

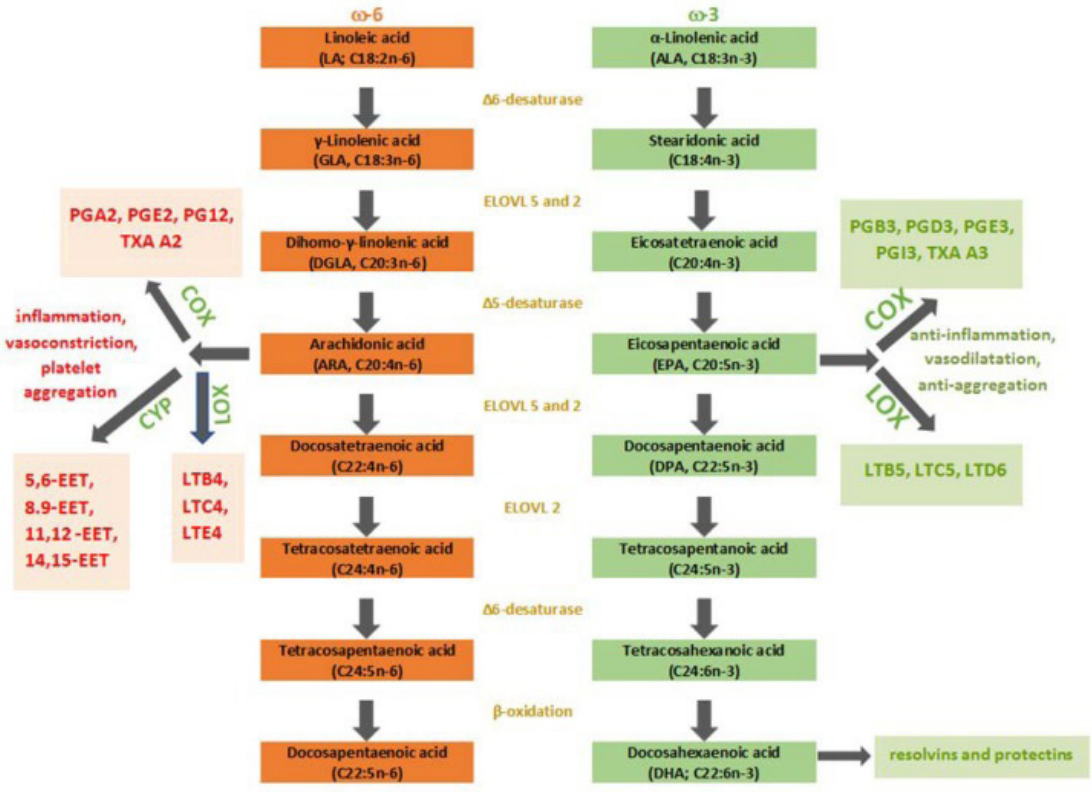
Interestingly, the picture is not completely clear with regard to total omega-6 status and cardiovascular disease risk. Omega-6s LA and GLA were found to be inversely correlated with CVD and all-cause mortality.[82] Multi-country observational studies found that tissue and blood levels of LA were inversely correlated with CVD, CVD mortality, and ischemic stroke.[83] Further research into these observances is warranted.

AA/EPA ratio

The ratio of arachidonic acid to EPA can also provide clues to risk of inflammation and CVD using the compounds that are ultimately converted to bioactive compounds. With an AA/EPA ratio of 1/1 to 5-10/1, both omega-3s and omega-6s will be incorporated into cell membranes. However, if the AA/EPA ratio increases above 10/1, AA will preferentially be incorporated into membranes, increasing the likelihood of inflammation and increased platelet aggregation.[84]

Ultimately, adequate omega-3 intake is important to omega-3/omega-6 balance as well as the balance of their metabolites.

Schematic presentation of the PUFAs pathway



ω-3, omega-3 fatty acids; ω-6, omega-6 fatty acids; COX, cyclooxygenase; CYP, cytochrome P450; EET, epoxyeicosatrienoic acid; ELOVL, elongase; LOX, lipoxygenase; LT, leukotriene; PG, prostaglandin; TXA, thromboxane. Source: Balić, Anamaria et al. "Omega-3 Versus Omega-6 Polyunsaturated Fatty Acids in the Prevention and Treatment of Inflammatory Skin Diseases." International journal of molecular sciences vol. 21,3 741. 23 Jan. 2020, doi:10.3390/ijms21030741 [R] Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license ([R]).

Food sources

A high intake of omega-3s is independently associated with low cardiometabolic risk and reduced risk of cardiometabolic mortality.[85] Essential omega-3 ALA as well as EPA and DHA can be found in food. Alpha-linolenic acid, the precursor to EPA/DHA is primarily found in plant-based foods while EPA and DHA are primarily found in oily fish and foods from animals fed omega-3s (e.g., those fed grass versus grains, or supplemented with flax).

Consumption of preformed EPA and DHA is prudent, as the conversion of ALA to EPA/DHA is generally inefficient.[86] Also, conversion may be limited in some people, altered by genetic factors, or disrupted by overconsumption of omega-6 PUFAs.

Vegetarians are at high risk for low O3I if preformed EPA and DHA consumption is restricted.[87] Vegans, who consume no animal-based products at all, had significantly lower omega-3s in RBC membranes and in plasma. This pattern was associated with lower heart rate variability which, in turn, increases risk of sudden cardiac death.[88]

Seafood is the most concentrated source of EPA and DHA, particularly fatty fish such as salmon, mackerel, trout, sardines, and herring. These will provide 1-3.6 grams of EPA/DHA per adult serving. [89]

Multivariant relative risk of sudden death was found to be 0.48 in men who ate fish at least once per week compared to men who men who ate it less than once per month. [90]

Higher intake of fish, as well as higher levels of preformed EPA and DHA, are directly related to reduced risk of MI, CVD, and CVD mortality. Researchers attribute these benefits to the positive effects they have on blood pressure, blood lipids, heart rate, endothelial function, clotting, and inflammation:[91]

- ✓ Randomized controlled studies and meta-analyses confirm the use of EPA, and EPA + DHA for secondary prevention in CVD patients.
- ✓ The Physician's Health Study revealed subjects with the highest levels of whole blood EPA and DHA had an 80% lower risk of sudden death than those with the lowest levels.
- ✓ A 16-year follow up of 420,000 subjects in the National Institutes of Health AARP Diet and Health Study found a significant inverse relationship between fish consumption, EPA DHA intake, and mortality. Intake of EPA and DHA correlated with 15% and 18% reduced CVD mortality in men and women, respectively.

Choose your source of preformed EPA +DHA carefully.

Although larger predatory fish may contain an abundance of EPA and DHA, consumption is not recommended due to increased accumulation of toxins, especially mercury. Smaller omega-3 sources are preferred and include sardines, mackerel, and salmon. Purified fish oil and krill can also provide EPA and DHA in supplement form.[92]

Primary food sources[93] [94] [95]

Omega-3s

- Alpha-linolenic acid (ALA)
  - Dark leafy greens, flaxseeds and oil, chia seeds, English walnuts, canola oil, soybean oil, mustard oil, black walnuts, firm tofu
- EPA, DHA
  - Cold water fish, salmon, sardines, anchovies, herring, oysters, rainbow trout, tuna, Dungeness crab, Antarctic krill, omega-3 eggs, grass-fed beef

Omega-6s

- Linoleic acid (LA)
  - Safflower, sunflower, corn, soybean, grapeseed, hemp, palm, poppy seed, and sesame oils
  - pine nuts, pecans, Brazil nuts, wheat germ
- Arachidonic acid (AA)
  - Meat, poultry, eggs, organ meats,
- GLA
  - Borage, black currant, and evening primrose oils

ALA, EPA, and DHA Content of Selected Foods[96]

Food	Grams per serving		
	ALA	DHA	EPA
Flaxseed oil, 1 tbsp	7.26		
Chia seeds, 1 ounce	5.06		
English walnuts, 1 ounce	2.57		
Flaxseed, whole, 1 tbsp	2.35		
Salmon, Atlantic, farmed cooked, 3 ounces		1.24	0.59
Salmon, Atlantic, wild, cooked, 3 ounces		1.22	0.35
Herring, Atlantic, cooked, 3 ounces*		0.94	0.77
Canola oil, 1 tbsp	1.28		
Sardines, canned in tomato sauce, drained, 3 ounces*		0.74	0.45
Mackerel, Atlantic, cooked, 3 ounces*		0.59	0.43
Salmon, pink, canned, drained, 3 ounces*	0.04	0.63	0.28
Soybean oil, 1 tbsp	0.92		
Trout, rainbow, wild, cooked, 3 ounces		0.44	0.40
Black walnuts, 1 ounce	0.76		
Mayonnaise, 1 tbsp	0.74		
Oysters, eastern, wild, cooked, 3 ounces	0.14	0.23	0.30
Sea bass, cooked, 3 ounces*		0.47	0.18
Edamame, frozen, prepared, ½ cup	0.28		
Shrimp, cooked, 3 ounces*		0.12	0.12
Lobster, cooked, 3 ounces*	0.04	0.07	0.10
Tuna, light, canned in water, drained, 3 ounces*		0.17	0.02
Tilapia, cooked, 3 ounces*	0.04	0.11	
Scallops, cooked, 3 ounces*		0.09	0.06
Cod, Pacific, cooked, 3 ounces*		0.10	0.04
Tuna, yellowfin, cooked 3 ounces*		0.09	0.01
Ground beef, 85% lean, cooked, 3 ounces**	0.04		
Egg, cooked, 1 egg		0.03	
Chicken, breast, roasted, 3 ounces		0.02	0.01

**Except as noted, the USDA database does not specify whether fish are farmed or wild caught.*

***The USDA database does not specify whether beef is grass fed or grain fed.*

Conclusions from 26 randomized controlled trials determined an association between dietary omega-3s and lower plasma biomarkers of inflammation and endothelial activation. Researchers note that DHA can have specific anti-inflammatory effects as it reduces production of inflammatory eicosanoids from arachidonic acid. Additional research that increased omega-3 intake, and/or reduced the omega-6/omega-3 ratio revealed that:[97]

- ✓ Increased intake of ~25 ounces of fatty fish/week along with 1 tablespoon of sardine oil/day reduced CRP and IL-6, and improved insulin resistance in subjects who were older than 60.
- ✓ Long-term consumption of a margarine rich in ALA (~6-8 grams ALA/day) significantly reduced CRP compared to LA-rich margarine.
- ✓ Flaxseed flour (containing ~5 grams of ALA) administered to morbidly obese subjects was effective in significantly reducing CRP as well as fibronectin, serum amyloid A, and white blood cell count.
- ✓ Researchers recommend fish oil supplementation in peripheral artery disease upon observing:
    - An inverse association between O3I and inflammatory markers CRP and IL-6.
    - Those with mean O3I of 6.8% had lowest CRP value of 0.6 mg/L
    - Those with O3I of 3.7% and 4.5% had CRP values of 1.4 mg/L

An imbalance of fatty acids in the diet will lead to an imbalance in the body

Excess intake of linoleic and arachidonic acid promotes or exacerbates a number of disorders including myocardial infarction, atherosclerosis, bone loss, arthritis, asthma, malignancy, hospital stay, depression, suicide, disruptive behavior, and reduced work productivity.[98]

Research suggests that intake of omega-6s 10 times greater than the recommended level of 0.5% of total energy has negative health consequences. This level of intake contributes to cardiovascular and inflammatory disorders including thrombosis, myocardial infarction, stroke, arrhythmias, atherosclerosis, arthritis, asthma, osteoporosis, and even tumor metastases. Ultimately, omega-6 content of tissues in the body mimic cardiovascular mortality rates. The production of omega-6 pro-inflammatory compounds can be reduced by increasing intake of omega-3s.[99]

The typical Western diet, high in processed foods, sugars, additives, and meat, has a high omega-6 to omega-3 ratio of 15 to 1. International agencies recommend an omega-6/omega-3 ratio of no greater than 5 to 1. However, prospective cohort studies and randomized trials suggest that a ratio of 1 to 1 is preferred and associated with decreased incidence of common chronic diseases seen by those consuming a Western diet. A lower ratio of omega-6s to omega-3s correlates with reduction in several types of cancer.[100]

In general, reducing omega-6s from processed foods and vegetable/grain-based oils, and increasing omega-3s from seafood or supplementation, should help bring omegas back into balance.[101] Even increasing dietary ALA can help shift the ratio of omega-3 to omega-6 intake.

Supplementation

Research demonstrates that supplementation with EPA and DHA can significantly increase their levels in cells and tissues, with a significant increase in red blood cells, plasma, cheek, and cardiac tissue.[102]

Increasing omega-3 intake has been found to reduce blood pressure, heart rate, and systemic vascular resistance; enhance vagal activity; improve myocardial metabolic efficiency; control inflammation and blood clotting; and may reduce atrial fibrillation.[103] If clients aren't amenable to consuming high EPA and DHA food sources, supplementation is indicated.

The "OMEICOS study" of 20 healthy volunteers demonstrated a dose- and time-dependent increase in O3I using fish oil. Supplementation with 460 mg EPA/380 mg DHA for four weeks, with an increase to 980 mg EPA/760 mg DHA for the next four weeks, resulted in an increase in mean baseline O3I from 4.9% to 8.4%. Individual peak values increased to a level between 6.7% and 10.7%. Maximal effects occurred at eight weeks.

Researchers also observed a significant decrease in omega-6 metabolites (arachidonic acid, linoleic acid, and oleic acid), diastolic blood pressure, and triglycerides. The omega-3 index did decline once supplementation was discontinued but remained significantly elevated above baseline at 6.6% for the following eight weeks.[104]

Bioavailability of supplemental EPA and DHA may vary depending on source and composition. A small double-blind crossover trial indicated that a 1680 mg dose of EPA and DHA from phospholipid-bound krill oil promoted the highest level of incorporation of EPA and DHA into plasma phospholipids compared to the same total dose of EPA and DHA from fish oil (re-esterified triacylglycerides/rTAG), and ethyl-esters. The rTAG supplements promoted the second highest incorporation of EPA and DHA while ethyl-esters (the form found in pharmaceuticals) had the lowest.[105]

An analysis of 14 studies comprising 1422 subjects revealed that supplementation with 1983 mg of EPA + DHA (mean) for a mean of 13.6 weeks (mean) significantly increased O3I values from a mean of 4.9% to 8.1%. The review confirmed the efficacy of the naturally occurring triglyceride form of EPA + DHA over the ethyl ester form.[106]

A study of healthy subjects found that 7-week supplementation with both krill oil (3 grams) and fish oil (1.8 grams) significantly increased plasma EPA and DHA. Plasma levels were comparable even though the daily EPA+DHA dose in the krill group (543 mg) was lower than that of the fish oil group (864 mg). However, there was a significant increase in plasma arachidonic acid in the krill group while AA decreased in the fish oil group. [107]

Another potential drawback of krill supplementation is the concern over sustainability as krill is a major source of food for marine life and birds. Algae is another source of EPA and DHA. It is a source for fish and potentially a direct source for humans.

Omega-3 PUFAs are prone to oxidation from excess heat or light. Therefore, careful production and storage methods are important for maintaining supplement quality and efficacy.[108]

Fish oil supplements should be purified to remove common toxins such as mercury, PCBs, and dioxins and be produced with FDA Current Good Manufacturing Practices (CGMPs) which "requires persons who manufacture, package, label, or hold a dietary supplement to establish and follow current good manufacturing practice to ensure the quality of the dietary supplement and to ensure that the dietary supplement is packaged and labeled as specified in the master manufacturing record."[109]

Recommended intake

It is estimated that less than 10% of the population of the United States consume the recommended 0.5 grams/day of EPA + DHA, with an average intake of only 0.11 to 0.17 grams per day.[110]

A daily Adequate Intake (AI) level has been set for consumption of alpha-linolenic acid at 1.6 grams for men and 1.2 grams for women. However, this may not take into account inefficient conversion of ALA to EPA and DHA, which can be as low as 15%.[111]

Traditional guidelines do provide specific recommendations for fish intake, though these may still fall short. The basic 2015-2020 Dietary Guidelines recommend 8 ounces of seafood per week while the American Heart Association (AHA) recommends 1-2 seafood meals per week.[112]

Researchers estimate that this level of intake may raise an O3I from 4% to ~6%.

However, only an estimated 20% of Americans meet a goal of 250 mg/d of EPA + DHA and only 10% meet a goal of 500 mg/day.

Instead, higher doses of ~2000 mg/day EPA + DHA may be needed to achieve an O3I of 8% from a baseline of 4% (1750 mg/day of TG form or 2500 mg/day of ethyl ester form).

Maintenance doses may then be reduced depending on O3I values over time.

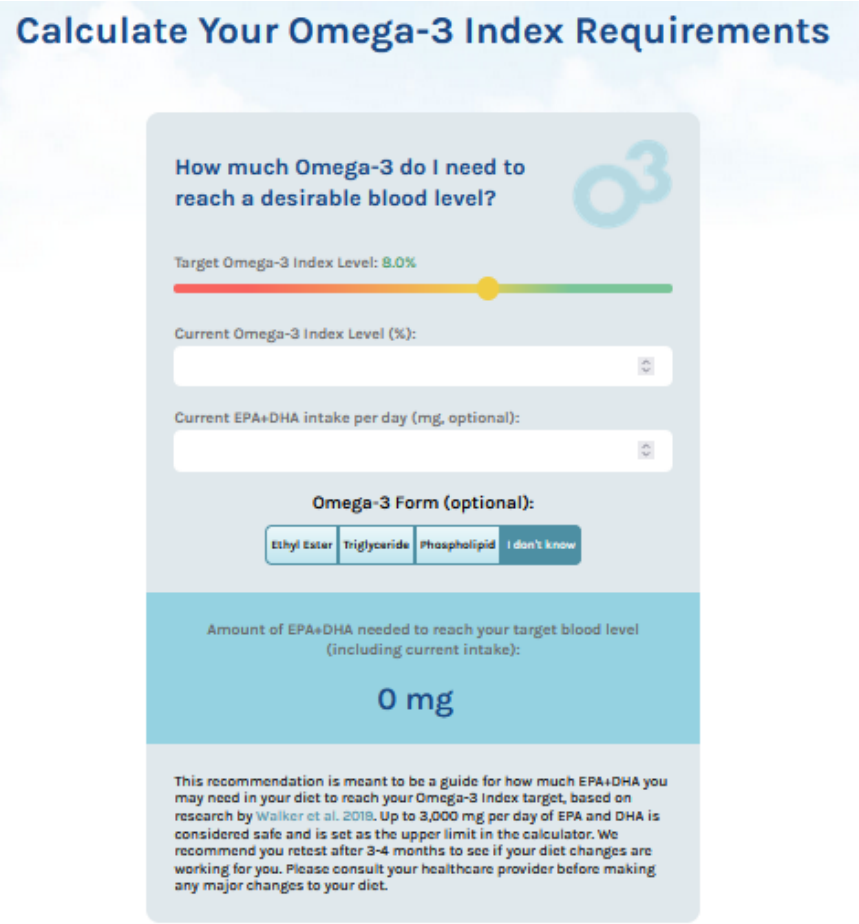
For example, intake of 800-1000 mg/day maintains an average O3I of 8% in the Japanese.

Therapeutic doses of omega-3 EPA + DHA range from 1-4 grams per day and can be consumed in food and supplement form. A 3-ounce serving of Atlantic salmon can provide 2 grams of EPA + DHA per day.[113]

Two cross-sectional studies confirm that AHA recommendations fall short in attempts to achieve an optimal O3I of 8% or greater. Researchers advocate for the consumption of at least 3 servings of fish per week along with EPA + DHA supplementation.[114]

- ✓ They also note that the 2018 revision of the AHA guidelines from "a variety of (preferably oily) fish at least twice a week" to "1 to 2 seafood meals per week" may contribute to inadequate intake of omega-3 EPA and DHA.
- ✓ It is important to emphasize oily fish such as sardines, wild coho salmon, and bluefin or Albacore tuna which provide ~1250 mg EPA + DHA in a 4 ounce serving.

Calculators can help guide omega-3 intake based on baseline O3I



Source: https://omegaquant.com/omega-3-index-calculator/

Omega-3 Index reference ranges

Quest Diagnostics Reference Range(s) using plasma phospholipids[115]

Omega-3 (EPA+DHA) Index	1.4-4.9 %
Risk	
Optimal	>3.2 %
Moderate	2.2-3.2 %
High	<2.2 %
Omega-6/Omega-3 Ratio	5.7-21.3
EPA/AA Ratio	≤0.2
Arachidonic Acid	5.2-12.9 %
EPA	0.2-1.5 %
DHA	1.2-3.9 %

Optimal Omega-3 Index greater than 8%

As demonstrated, contemporary research confirms that a suboptimal O3I below 8% correlates with myocardial infarction, sudden cardiac death, cardiovascular disease, cognitive impairment, dementia progression, major depression, ischemic stroke, premature birth, psychiatric disorders, and even reduced brain volume.[116] [117]

A suboptimal O3I between 0 and 4% is associated with an increased risk of sudden cardiac death, acute coronary syndrome, cognitive impairment, dementia, non-alcoholic fatty liver disease, depression, eye disease, and death from all causes.[118]

A 2014 literature review found that a mean O3I below 8% correlated with:[119]

- Increased risk of CVD (O3I 7.1%)
- Myocardial infarction (O3I 4.88-6.08%)
- Major depression (O3I 2.9%)
- Severe sleep apnea (O3I 4%)
- Diabetes (O3I 3.47%)
- Unexpectedly, Korean subjects with myocardial and brain infarction had an observed O3I between 8.19-10.55%. Researchers suggest the presence of additional underlying factors.

A 2017 meta-analysis of 10 cohort studies revealed that risk of fatal coronary heart disease was significantly reduced by 15% for every standard deviation increase in the O3I.[120]

- Dose-response research suggests that increasing EPA and DHA intake by 1.5 grams per day will increase the index by 4%.
- Researchers confirm that an index below 4% is high risk, while an index above 8% is desirable with ranges from 8-12% observed in clinical research.

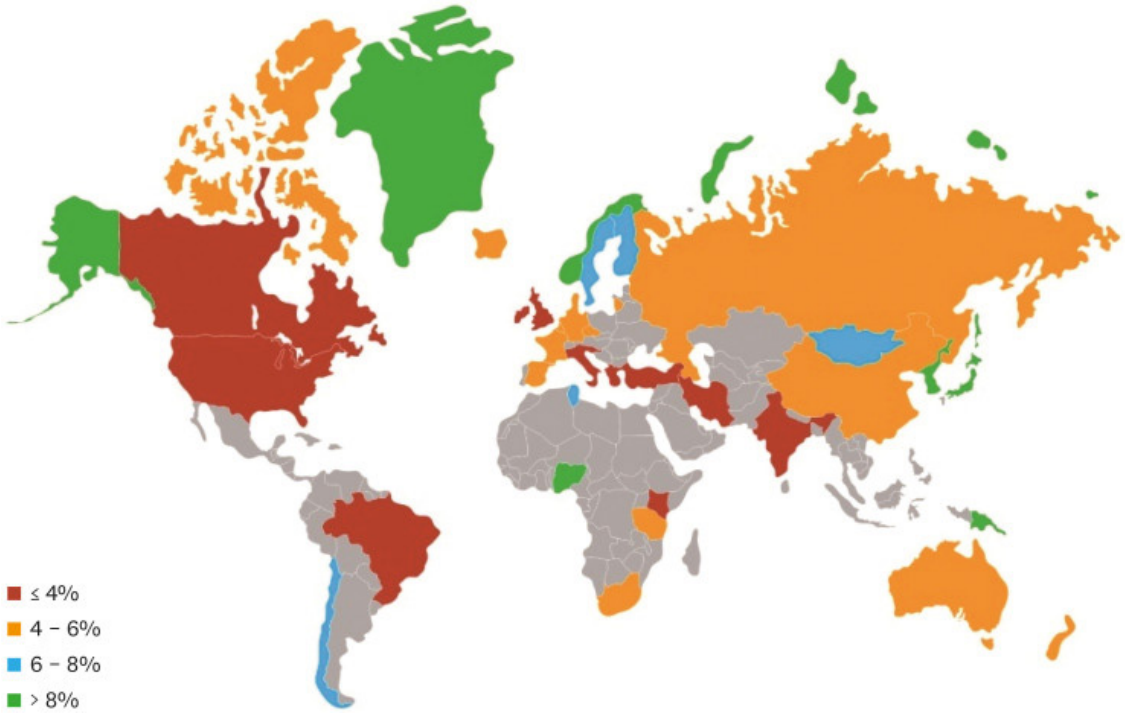
Results from the Physician Healthy Study categorized the association of O3I with sudden death from cardiac causes as follows:[121] [122]

High risk	less than 3.45%
45% reduced risk	3.46-4.16%
72% reduced risk	4.17-4.98%
81% reduced risk	Greater than 4.98%

An O3I greater than 8% is considered an optimal therapeutic target to reduce risk of cardiovascular and inflammatory disorders. An index of 4-8% may be considered intermediate risk and below 4% may be considered high risk for these conditions.[123]

The preferred standardized method of measuring the O3I is the HS-Omega-3 Index®.[124] [125]

The global view of omega-3 index level



The omega-3 index risk zones are as follows:

- High Risk ≤ 4%.
- Intermediate risk = 4 - 8%.
- Low risk > 8%

Source: Hathaway, Donald et al. "Omega 3 Fatty Acids and COVID-19: A Comprehensive Review." Infection & chemotherapy vol. 52,4 (2020): 478-495. doi:10.3947/ic.2020.52.4.478

Optimal Takeaways

- ✓ The omega-3 index (O3I) is a biomarker that reflects risk of cardiovascular disease and provides valuable information regarding risk of inflammation, depression, neurological dysfunction, pregnancy complications, fatty liver disease, and metabolic syndrome.
- ✓ The O3I correlates with cardiac, brain, and other tissue levels of EPA and DHA.
- ✓ Red blood cell membrane O3I is the best way to evaluate omega-3 status in the body, preferably measured with the standardized HS-Omega-3 Index® method.
- ✓ Maintaining an O3I above 8% may reduce risk of
    - Arrhythmias
    - Asthmatic exercise-induced bronchoconstriction and inflammation
    - Cardiovascular disease
    - Depression
    - Hypertriglyceridemia
    - Inflammatory disorders
    - Metabolic disorders, diabetes
    - Mood disorders
    - Neurological dysfunction
    - Sudden cardiac death
- ✓ Optimal brain function depends on an optimal supply of EPA and DHA. A deficiency, especially an O3I of 3.2% or less, may manifest as a psychological or psychiatric disorder.[126]
- ✓ Increased intake of omega-3s, especially EPA and DHA, can increase O3I over time and improve the balance between omega-6s and omega-3s.
- ✓ Researchers suggest returning to an intake of omega-6 to omega-3 closer to pre-industrialization, i.e., an omega-6/omega-3 ratio of 1-4 to1 instead of the 16-20 to 1 ratio characteristic of current Western diets.
- ✓ Consumption of three ounces of a high omega-3 oily fish such as Atlantic salmon (providing ~2 grams of EPA + DHA per serving) consumed three times per week comes close to meeting the daily recommendation of 1 to 4 grams of EPA + DHA daily.
- ✓ Addition of plant-based ALA will help balance omega-3s and omega-6s, and promote endogenous production of EPA + DHA.
- ✓ Supplements can help fill the gap between actual dietary intake and recommended intakes.
- ✓ Fish oil supplements should be purified to remove toxins and be produced and stored carefully to avoid oxidative damage from heat and light.

Additional references[127]

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