

# Science Review: Clinical Applications of EPA and DHA Consumption

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Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are long-chain omega-3 polyunsaturated fatty acids (PUFA). Biosynthesis of EPA and DHA from other fatty acids is poor, and as a result EPA and DHA are considered “conditionally essential” nutrients required in the diet for optimal health.<sup>1</sup>

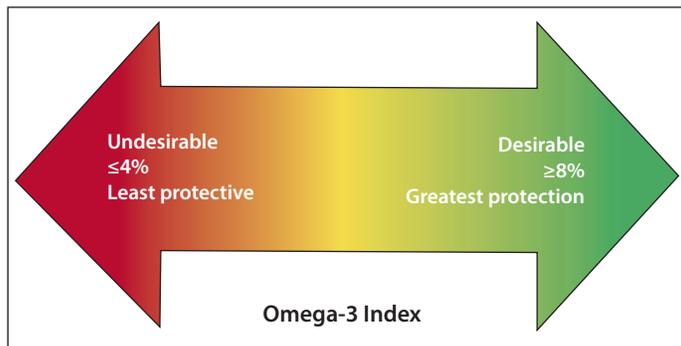
## EPA and DHA nutrient gap

On average, the daily intake of EPA and DHA, plus estimated EPA equivalents (endogenous biosynthesis from other fatty acids) from food and supplements, among American adults is 170 mg per day.<sup>2</sup> Ninety-percent of people consumed less than the minimally recommended 500 mg per day,<sup>3</sup> and reported consumption is markedly below amounts that promote therapeutic benefits (see Table 1). This nutrient gap is presumably not being met through the intake of fish oil supplements, as only 6.2% of US adults report taking fish oil supplements within the past 30 days.<sup>2</sup>

## How do I measure EPA and DHA status?

Omega-3 Index is a test that can give an indication of EPA and DHA status. Lower results on the Omega-3 Index test have been associated with increased risk of cardiovascular disease and cardiovascular risk markers and have also been linked with depression.<sup>4,5</sup> Consumption of EPA and DHA has been shown to increase the Omega-3 Index in a dose-dependent manner.<sup>6</sup>

**Figure 1.** Higher Omega-3 Index has been associated with protective health benefits<sup>7</sup>



## What is the difference between ethyl ester (EE) and triglyceride (TG) forms?

The question of whether TG or EE supplements lead to better outcomes has been the subject of controversy and has received a lot of research and clinical attention. However, a consensus has not been reached in the literature regarding which form is preferable.

In fish, fatty acids are found in a TG form, meaning that three fatty acids are attached to a glycerol backbone. To concentrate EPA and DHA in fish oil, these natural TG molecules are broken apart, and the resulting EPA and DHA free fatty acids are esterified to an alcohol backbone to form an EE. Of note, these EE molecules can be broken down, and the released EPA and DHA free fatty acids can be then reesterified back to a TG (reesterified TG form), facilitating the development of more concentrated EPA and DHA TG oil.

Pharmacokinetic studies that have examined EPA and DHA increases in plasma generally show that these fatty acids are higher in the hours following supplementation in the TG compared to EE form.<sup>8-10</sup> However, both EE and TG forms of EPA and DHA supplements have been shown to drive improvements in clinical outcomes (see Table 1).

## What do studies show about dosing of EPA and DHA supplements?

Consuming higher amounts of EPA and DHA, not unexpectedly, leads to greater increases in EPA and DHA status.<sup>11</sup> Studies that have examined the difference in status after daily supplementation or delivering as a bolus dose twice weekly (with both delivery options providing the same amount of EPA and DHA) showed that daily intake led to faster improvement in EPA and DHA status and higher status after one year,<sup>12</sup> suggesting that consuming EPA and DHA daily is advisable. Numerous clinical research studies have also shown that EPA and DHA supplementation can promote a variety of specific therapeutic outcomes and benefits (Table 1).

Table 1

Condition or Application	Outcomes of EPA and DHA Supplementation†
Cardiovascular events and mortality <sup>13,14</sup>	<ul style="list-style-type: none"> <li>Consumption of fish (1-2 servings/week of oily fish), or ≥250 mg/d of EPA+DHA have been shown to reduce the risk of coronary heart disease (CHD) mortality and sudden cardiac death (SCD).</li> <li>A 2017 American Heart Association Science Advisory recommends omega-3 PUFA supplements for secondary prevention of 1) CHD and SCD among patients with prevalent CHD and 2) hospitalization or death in patients with heart failure.</li> </ul>
Vascular function <sup>15</sup>	<ul style="list-style-type: none"> <li>EPA and DHA have each been shown to increase systemic arterial compliance, a measure of arterial elasticity, in human subjects.</li> <li>DHA has been shown in some studies to improve vascular function at doses of ~3.7 g/day.</li> </ul>
Heart rate <sup>16</sup>	<ul style="list-style-type: none"> <li>A meta-analysis of 51 randomized controlled trials (RCTs), demonstrated that compared to placebo, omega-3 PUFA supplementation mildly but significantly reduced heart rate (2.2 bpm). The heart rate lowering effect was most attributable to DHA content.</li> </ul>
Triglyceride lowering <sup>15,17</sup>	<ul style="list-style-type: none"> <li>EPA and DHA have each been shown clinically to lower triglycerides in a dose-dependent manner, with doses of 2-4 g per day considered effective. Reductions as high as 26% have been reported.</li> <li>In studies comparing EPA and DHA, DHA is seen to effectively lower triglycerides and also increase HDL-C and apoB.</li> </ul>
Non-alcoholic fatty liver disease (NAFLD) <sup>18-21</sup>	<ul style="list-style-type: none"> <li>A reduction in liver fat, as assessed by ultrasonography, and improvements in liver function tests (AST, ALT, and GGT) have been reported with doses of EPA and DHA of &gt;800 mg per day, with the majority of studies supplementing over 2 g EPA+DHA per day.</li> </ul>
Arthritis <sup>22-24</sup>	<ul style="list-style-type: none"> <li>Reduction in arthritis pain, tender joint count, morning stiffness, pain, and use of NSAIDs seen with doses of ~3 g per day and higher.</li> <li>Clinical studies support a higher EPA combination formula (ratio of ~1.5:1 EPA:DHA).</li> </ul>
Strength and muscle function in aging individuals <sup>25-29</sup>	<ul style="list-style-type: none"> <li>Increased muscle volume and strength as well as a greater increase in muscle quality in response to resistance training have been shown in older individuals, suggesting that EPA and DHA counteract the anabolic resistance associated with aging. Studies support a combination of EPA+DHA in doses of ~3 g per day.</li> </ul>
Dry eye <sup>30-32</sup>	<ul style="list-style-type: none"> <li>Reduction in markers of dry eye including improvement in the Schirmer Test and tear break-up time (TBUT). Clinical data supports a combination of EPA+DHA at a doses range of 1-2 g per day.</li> </ul>
Age-related macular degeneration <sup>33-35</sup>	<ul style="list-style-type: none"> <li>DHA is highly concentrated in the retina, the most metabolically active tissue in the body. Preclinical data shows that DHA can modulate oxidative stress, inflammation, and vascularization as well as membrane function in this tissue.</li> <li>Epidemiologic studies have shown benefit of EPA and DHA prophylaxis of AMD and reduced risk of neovascular AMD. Intervention studies did not show benefit, although intervention length and baseline EPA/DHA status have been suggested to drive this lack of support from large RCTs.</li> </ul>
Depression <sup>36,37</sup>	<ul style="list-style-type: none"> <li>Reduced depression scores have been demonstrated at doses of ~1.8 g/day. A meta-analysis concluded that higher EPA (EPA ≥ 60%) formulations were effective against primary depression.</li> </ul>
Cognitive function <sup>38-40</sup>	<ul style="list-style-type: none"> <li>Improved episodic memory in adults with mild cognitive impairment [has been reported], an effect largely driven by studies providing DHA between 501–999 mg daily.</li> <li>In observational studies, EPA and DHA status are related to memory function, including episodic, working, and semantic memory.</li> </ul>

†Clinical data summarized in the table above include studies of both EE and TG forms of EPA and DHA

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