Review

Effects of omega-3 fatty acids on serum markers of cardiovascular disease risk: A systematic review

Ethan M. Balk a,∗, Alice H. Lichtenstein b, Mei Chung a, Bruce Kupelnick a, Priscilla Chew a, Joseph Lau a

a Tufts-New England Medical Center Evidence-based Practice Center, Institute for Clinical Research and Health Policy Studies, Tufts-New England Medical Center, NEMC #63, 750 Washington Street, Boston, MA 02111, United States
b Cardiovascular Nutrition Laboratory, Jean Mayer USDA Human Nutrition Research Center on Aging, Tufts University, 711 Washington Street, Boston, MA 02111, United States

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Abstract

Greater fish oil consumption has been associated with reduced CVD risk, although the mechanisms are unclear. Plant-source oil omega-3 fatty acids (ALA) have also been studied regarding their cardiovascular effect. We conducted a systematic review of randomized controlled trials that evaluated the effect of consumption of fish oil and ALA on commonly measured serum CVD risk factors, performing meta-analyses when appropriate. Combining 21 trials evaluating lipid outcomes, fish oil consumption resulted in a summary net change in triglycerides of −27 (95% CI −33, −20) mg/dL, in HDL cholesterol of +1.6 (95% CI +0.8, +2.3) mg/dL, and in LDL cholesterol of +6 (95% CI +3, +8) mg/dL. There was no effect of fish oil on total cholesterol. Across studies, higher fish oil dose and higher baseline levels were associated with greater reductions in serum triglycerides. Overall, the 27 fish oil trials evaluating Hgb A1c or FBS found small non-significant net increases compared to control oils. Five studies of ALA were inconsistent in their effects on lipids, Hgb A1c, or FBS. Four studies investigating the effects of omega-3 fatty acids on hs-CRP were also inconsistent and non-significant. The evidence supports a dose-dependent beneficial effect of fish oil on serum triglycerides, particularly among people with more elevated levels. Fish oil consumption also modestly improves HDL cholesterol, increases LDL cholesterol levels, but does not appear to adversely affect glucose homeostasis. The evidence regarding the effects of omega-3 fatty acids on hs-CRP is inconclusive, as are data on ALA.

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Keywords: Omega-3 fatty acid; Cardiovascular disease; Fish oil; Systematic review; Meta-analysis

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Abbreviations: ALA, alpha linolenic acid (18:3 n-3); CI, confidence interval; CVD, cardiovascular disease; DHA, docosahexaenoic acid (22:6 n-3); EPA, eicosapentaenoic acid (20:5 n-3); FBS, fasting blood sugar; HDL, high density lipoprotein; Hgb A1c, hemoglobin A1c; hs-CRP, highly sensitive C-reactive protein; LDL, low density lipoprotein; VLDL, very low density lipoprotein
∗ Corresponding author at: Tufts-New England Medical Center, Box 63, 750 Washington Street, Boston, MA 02111, United States. Tel.: +1 617 636 3282; fax: +1 617 636 8628.
E-mail address: ebalk@tufts-nemc.org (E.M. Balk).

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1. Background

The relationship between dietary omega-3 fatty acids and risk of developing CVD began to emerge in the late 1970s [1–3]. Thereafter, a limited number of intervention trials reported lower rates of CVD mortality and sudden death, but not stroke, after supplementation with the long-chain omega-3 fatty acids EPA or DHA; however, the data on the shorter-chain omega-3 fatty acid ALA are far less certain [4]. Potential mechanisms for the cardioprotective effect of omega-3 fatty acids include anti-arrhythmic effects, anti-thrombotic effects, anti-inflammatory effects, lowered blood pressure, improved endothelial function, hypotriglyceridemic effects in hypertriglyceridemic individuals and retarded growth of atherosclerotic plaque [5,6].

EPA and DHA are commonly referred to as very long chain omega-3 fatty acids. The primary sources in the diet of humans are fish, especially dark fleshed fish, and, if consumed, fish oil supplements. ALA is a plant form of omega-3 fatty acid. The major dietary sources in the human diet are soybean and canola oils. In addition, the amounts in flaxseeds and walnuts and their respective oils are high and when consumed can provide relatively high levels of intake. The rate of conversion by humans of ALA to EPA is low, with estimates ranging from 0.2% to 15%, as is the conversion of EPA to DHA [7]. However, high intakes of ALA have been reported to result in significant increases in very long chain omega-3 fatty acids in various body compartments [8,9].

To better understand how both fish oil (and dietary fish) and ALA consumption exert their effects on clinical CVD, we systematically reviewed the literature on various cardiovascular disease risk factors and intermediate markers [10]. We have previously reported on coronary restenosis, intima-media thickness, and exercise tolerance [11]. Here we report on serum markers of CVD risk, including blood lipid and lipoprotein levels (total cholesterol, LDL cholesterol, HDL cholesterol, triglyceride), a measure of inflammation (CRP) and measures of glucose homeostasis (FBS and Hgb A1c).

2. Methods

2.1. Literature search and eligibility criteria

Details of the systematic review and statistical methods have been reported [11]. Briefly, we conducted a systematic review of the English-language literature on omega-3 fatty acids and cardiovascular disease in Medline, Embase, Cochrane Central Register of Controlled Trials, Biological Abstracts, and Commonwealth Agricultural Bureau databases through April 2003. Search terms included the specific omega-3 fatty acids, fish and other marine oils, and omega-3 fatty acid-rich plant oils. We also reviewed additional publications found by domain experts.

We evaluated randomized controlled trials of omega-3 fatty acid interventions, as either supplements or dietary components. The omega-3 fatty acids of particular interest with respect to cardiovascular disease include EPA, DHA, and ALA. To qualify, studies could include only subjects who were either generally healthy; had diabetes, hypertension, or dyslipidemia; or had cardiovascular disease. We excluded studies of omega-3 fatty acid supplementation of >6 g/day or of <4 weeks’ duration, and studies that did not quantify fatty acid supplementation or fish amounts.

A large number of studies met the minimum eligibility criteria for the various CVD outcomes we investigated (327 articles), we therefore limited eligibility of studies of lipids, FBS and Hgb A1c to the larger randomized trials, as summarized in Table 1. We determined minimum study size based on a goal of approximately 20 studies per outcome analyzed. We accepted all studies of CRP.

2.2. Quantitative analysis

For analysis, we evaluated the relative change of the outcome compared to placebo – the net difference between the within-treatment effect and the within-placebo effect. For fish oil studies (including dietary fish) of lipids and glucose homeostasis we performed meta-analysis with the DerSimonian and Laird random effects model, which assigns a weight to each study that is based on both the within study
Table 1

Numbers and eligibility criteria for studies of omega-3 fatty acids and cardiovascular risk factors

<table>
<thead>
<tr>
<th>CVD risk factor</th>
<th>Total studies meeting minimum eligibility criteria</th>
<th>Total randomized studies</th>
<th>Minimum number of subjects consuming omega-3 fatty acidsa</th>
<th>Analyzed studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lipid profile</td>
<td>182b</td>
<td>108</td>
<td>≥60</td>
<td>≥40 25</td>
</tr>
<tr>
<td>Hemoglobin A1c</td>
<td>32</td>
<td>22</td>
<td>≥10</td>
<td>≥10 18</td>
</tr>
<tr>
<td>Blood sugar, fasting</td>
<td>57</td>
<td>34</td>
<td>≥25</td>
<td>≥15 17</td>
</tr>
<tr>
<td>C reactive protein</td>
<td>5</td>
<td>4</td>
<td>All</td>
<td>All 5</td>
</tr>
</tbody>
</table>

a Minimum number of subjects refers to all subjects in study consuming omega-3 fatty acids. Specific groups (such as men vs. women, or different doses of fatty acids) may have smaller numbers of subjects.
b ≥20 subjects consuming omega-3 fatty acids.

variance and the between-study heterogeneity [12]. When necessary, we estimated the standard error of the net change from reported variance data. We contacted authors for additional data when variance data were missing. For two studies, we made conservative estimates of variance data from other sources, as described in the legend to Fig. 1. Studies of fish oil (or dietary fish) and of ALA were analyzed separately.

We also performed multivariate linear regression analyses (meta-regression) to evaluate the effect of fish oil. In meta-regression, each data point represents the mean effect from each study, instead of data from an individual as in traditional regression. We used the random-effects regression model described by Berkey et al. and Morris [13,14]. We evaluated the effects of fish oil dose, baseline value, study duration, change of outcome value in the control group, and study quality (using dummy variables) on net change levels.

2.3. Quality and applicability assessment

All randomized trials were assessed for both study quality and applicability. Methodological quality refers to the design, conduct, and reporting of the clinical study. Because studies with a variety of design types were evaluated, a three-level classification of study quality and applicability was used as described previously [15]. The quality and applicability classifications, along with the target populations, are described in Table 2.

3. Results

The literature search for all studies of omega-3 fatty acids and cardiovascular disease related conditions yielded 7464 citations. We retrieved and reviewed 807 articles to analyze cardiovascular events, risk factors or intermediate markers. Of these we analyzed 123 articles that reported about 23 different cardiovascular disease risk factors and intermediate markers. Here, we discuss the 52 randomized controlled trials that reported data on the effect of omega-3 fatty acid consumption on the predetermined serum markers of CVD risk.

3.1. Characteristics of all evaluated studies

Fish or other marine oils (EPA and DHA as supplements, dietary fish, or oil spreads) were evaluated by 47 of 52 studies; whereas, six evaluated plant oils (ALA as supplements, vegetable oils, nuts or oil spreads), one of which also evaluated fish oil. EPA + DHA doses ranged from 0.045 to 5.9 g/day, fish diets ranged from 0.9 to 3.8 servings per week, ALA doses ranged from 1.8 g to about 5 g/day. No study examined possible correlations between the effect of omega-3 fatty acid consumption on serum markers and the effect on clinical or cardiovascular disease.

3.2. Lipid profile

We reviewed the 25 largest randomized trials that contained data on omega-3 fatty acid intake and plasma lipids (Table 2) [16–40]. Nineteen studies evaluated fish oil, three fish (or Mediterranean) diets, one various combinations of fish oil and diet, and three plant oils. These studies represented about 8000 subjects. Approximately, two-thirds of the subjects were included in the GISSI study of fish oil supplements [34]. The studies were generally of fair quality, with moderate to broad applicability.

3.2.1. Fish and fish oil

Twenty-one studies included 37 individual study arms of fish oil or fish diet that evaluated any of the lipid profile components (Fig. 1 and Table 2) [16–36]. For all four-lipid profile components, studies were heterogeneous in their results (P < 0.0001) with wide ranges of net effects—from 6% to 60% net improvements to 6–14% net worsening. However, in the majority of studies, the net effects on total, LDL, and HDL cholesterol levels were small (<5%). In contrast, most studies of triglycerides found at least a 15% net reduction with fish oil consumption.

Across the studies, random effects model meta-analyses found a significant net improvement of triglycerides with fish oil consumption of −27 (95% CI −33, −20) mg/dL, and of HDL cholesterol of +1.6 (95% CI +0.8, +2.3) mg/dL, and a significant net worsening of LDL cholesterol of +6 (95% CI +3, +8) mg/dL. There was no effect on total cholesterol. The
Table 2
Summary of evaluated evidence for the effect of omega-3 fatty acids on serum markers of CVD risk

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Omega-3 fatty</th>
<th>Dose range (g/day)</th>
<th>No. of randomized studies</th>
<th>No. of subjects&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Quality&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Applicability&lt;sup&gt;c&lt;/sup&gt;</th>
<th>Range of net effects (net % change)</th>
<th>Summary estimate of net effect (95% CI)</th>
<th>Explanation for heterogeneity (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol (mg/dL)</td>
<td>Fish oils</td>
<td>0.045–5.4</td>
<td>19</td>
<td>7853</td>
<td>3 11 5 8 10 1</td>
<td>–19, +21 (&lt;–6%, +9%)</td>
<td>0 (–1, +2) NS</td>
<td>+6 (+3, +8) P = 0.0006</td>
<td>Meta-regression: baseline –0.08&lt;sup&gt;d&lt;/sup&gt; (–0.15, –0.02)</td>
</tr>
<tr>
<td></td>
<td>ALA</td>
<td>~1.8 to ~5</td>
<td>5&lt;sup&gt;e&lt;/sup&gt;</td>
<td>1089</td>
<td>1 0 4 1 1 3</td>
<td>–1, +13 (&lt;–0.4%, +4%)</td>
<td>None found</td>
<td>None found</td>
<td>None found</td>
</tr>
<tr>
<td>LDL (mg/dL)</td>
<td>Fish oils</td>
<td>0.045–5.4</td>
<td>13</td>
<td>6969</td>
<td>3 8 2 4 9 0</td>
<td>–5, +21 (&lt;–3%, +14%)</td>
<td>None found</td>
<td>None found</td>
<td>None found</td>
</tr>
<tr>
<td></td>
<td>ALA</td>
<td>~1.8–4.5</td>
<td>3&lt;sup&gt;e&lt;/sup&gt;</td>
<td>700</td>
<td>1 0 2 1 1 1</td>
<td>–2, +3 (&lt;–1%, +2%)</td>
<td>None found</td>
<td>None found</td>
<td>None found</td>
</tr>
<tr>
<td>HDL (mg/dL)</td>
<td>Fish oils</td>
<td>0.045–5.4</td>
<td>17</td>
<td>7353</td>
<td>3 10 4 7 10 0</td>
<td>–3.5, +5.4 (&lt;–7%, +12%)</td>
<td>None found</td>
<td>None found</td>
<td>None found</td>
</tr>
<tr>
<td></td>
<td>ALA</td>
<td>~1.8–4.5</td>
<td>3&lt;sup&gt;e&lt;/sup&gt;</td>
<td>700</td>
<td>1 0 2 1 1 1</td>
<td>–1, +1 (&lt;–2%, +2%)</td>
<td>None found</td>
<td>None found</td>
<td>None found</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>Fish oils</td>
<td>~0.1–5.4</td>
<td>17</td>
<td>7803</td>
<td>3 13 1 6 10 1</td>
<td>–80, +6 (&lt;–60%, +6%)</td>
<td>None found</td>
<td>None found</td>
<td>None found</td>
</tr>
<tr>
<td></td>
<td>ALA</td>
<td>~1.8 to 4.5</td>
<td>3&lt;sup&gt;e&lt;/sup&gt;</td>
<td>700</td>
<td>1 0 2 1 1 1</td>
<td>–19, +23 (&lt;–10%, +16%)</td>
<td>None found</td>
<td>None found</td>
<td>None found</td>
</tr>
<tr>
<td>Fasting blood sugar (mg/dL)</td>
<td>Fish oils</td>
<td>0.6–5.2</td>
<td>17</td>
<td>1427</td>
<td>4 10 3 6 10 1</td>
<td>–29, +25 (&lt;–16%, +19%)</td>
<td>None found</td>
<td>None found</td>
<td>None found</td>
</tr>
<tr>
<td></td>
<td>ALA</td>
<td>4.5–5.9</td>
<td>2</td>
<td>52</td>
<td>1 0 1 1 0 1</td>
<td>–5 (&lt;–5%)</td>
<td>None found</td>
<td>None found</td>
<td>None found</td>
</tr>
<tr>
<td>Hemoglobin A&lt;sub&gt;1c&lt;/sub&gt; (%)</td>
<td>Fish oils</td>
<td>0.6–4.6</td>
<td>18</td>
<td>578</td>
<td>5 11 2 3 14 1</td>
<td>–0.8, +1.0 (&lt;–9%, +13%)</td>
<td>None found</td>
<td>None found</td>
<td>None found</td>
</tr>
<tr>
<td></td>
<td>ALA</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Homogeneous</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C-reactive protein (mg/L)</td>
<td>Fish oils</td>
<td>1.6–5.9</td>
<td>3&lt;sup&gt;i&lt;/sup&gt;</td>
<td>73</td>
<td>0 2 1 1 1 1</td>
<td>–0.2&lt;sup&gt;k&lt;/sup&gt;, +1.7 (&lt;–14%, +35%)</td>
<td>None found</td>
<td>None found</td>
<td>None found</td>
</tr>
<tr>
<td></td>
<td>ALA</td>
<td>2.5% kcal</td>
<td>1</td>
<td>18</td>
<td>0 0 1 1 0 0</td>
<td>+0.1 (&lt;+22%)</td>
<td>None found</td>
<td>None found</td>
<td>None found</td>
</tr>
</tbody>
</table>

<sup>a</sup> Receiving omega-3 fatty acids.
<sup>b</sup> A = Least bias; study mostly adheres to the commonly held concepts of good quality, including: formal randomized study; clear description of the population, setting, interventions and comparison groups; appropriate measurement of outcomes; appropriate statistical and analytic methods and reporting; no reporting errors; <20% dropout; clear reporting of dropouts; and no obvious bias. B = Susceptible to some bias; study has some deficiencies but none likely to cause major bias or may be missing information making assessment of the limitations and potential problems difficult. C = Significant bias; study has serious errors in design, analysis, or reporting or may have large amount of missing information or discrepancies in reporting.
<sup>c</sup> I = Sample is representative of the population of interest; sufficiently large to cover both sexes, a wide age range, and other important features of the target population including baseline dietary intake broadly similar to that of the US population. II = Sample is representative of a relevant sub-group of the target population, but not the entire population. III = Sample is representative of a narrow subgroup of subjects only, and not well applicable to other subgroups.
<sup>d</sup> Change in net change (mg/dL) per baseline value (mg/dL). See text for interpretation.
<sup>e</sup> One study of an Indo-Mediterranean diet reported total omega-3 fatty acids.
<sup>f</sup> Change in net change (mg/dL) per change in lipid level (mg/dL) in the control group. See text for interpretation.
<sup>g</sup> 0.9 fish servings per week.
<sup>h</sup> Based on median values.

95% CI = 95% confidence interval.

<sup>90</sup> Change in net change (mg/dL) per baseline value (mg/dL). See text for interpretation.
effects of fish oil on triglycerides, HDL and LDL cholesterol were all highly significant ($P<0.001$). Despite the heterogeneity across studies, the meta-analysis results did not substantially (or significantly) change either with removal of the GISSI study – which contributed both the majority of subjects and the majority of weight in the meta-analyses – or with removal of outlier studies.

To further examine the study heterogeneity, meta-regression was performed (Table 2). Across studies, there were significant, independent associations between the effect of fish oil consumption on triglyceride levels and both the dose of fish oil used and the baseline triglyceride levels. Across studies, each increase in fish oil dose of 1 g/day was associated with a decrease in triglycerides of approximately 8 mg/dL. Likewise, each 10 mg/dL increase in the mean baseline triglyceride level was associated with an additional 1.6 mg/dL decrease in triglycerides after fish oil consumption. However, fish oil dose and baseline triglyceride levels interacted with each other, such that in studies with low baseline triglycerides (e.g., 60 mg/dL) higher fish oil dose was predicted to have a small effect (e.g., $-2$ mg/dL per additional g fish oil), while in studies with high baseline triglycerides (e.g., 294 mg/dL) higher fish oil dose was predicted to have a much larger effect (e.g., $-19$ mg/dL per additional g fish oil). Study duration was not associated with treatment effect between 4 weeks and 2 years suggesting that once the maximal effect was achieved it was maintained throughout the intervention period. The control rate – the change in triglyceride levels in the control group – and study quality were also not associated with treatment effect.

The four studies that compared different fish oil doses [17,26,33,35] similarly found that the greatest net decreases in triglycerides occurred among subjects consuming the highest doses of fish oil; although no study reported on the statistical significance of this effect. One study likewise found larger effects of fish oil among subjects in successively higher...
quartiles of baseline triglyceride levels; although, again no statistical analysis was reported [20]. The effect of duration of fish oil consumption was inconsistent among four studies that reported outcomes at different time points [21,30,33,35]. Evaluation of the studies that reported HDL cholesterol suggested that interventions in which the subjects in the control arms had a greater (positive) change in their HDL levels from baseline reported a smaller net increase in HDL in the experimental group after fish oil consumption. This possibly implies that fish oil may be most effective at raising (or stabilizing) HDL levels in people whose HDL levels would otherwise decrease with time. Of note, in the GISSI study, the mean HDL level in the control arms rose by 6 mg/dL and the net effect on HDL was smaller than the meta-analysis average across studies (see Fig. 1).

Although across studies fish oil consumption had no significant effect on total cholesterol, baseline total cholesterol was associated with treatment effect, such that each 10 mg/dL increase in the mean baseline total cholesterol was associated with an additional 0.8 mg/dL decrease after fish oil consumption. None of the tested outcomes were associated with the effect of fish oil consumption on LDL cholesterol levels. Individual studies generally confirmed that lack of association of either fish oil dose or duration of fish oil consumption and HDL cholesterol effect [17,21,24,26,29,33,36], LDL effect [17,33,36], or total cholesterol [17,21,24,26,29,30,33,35,36].

Further subgroup analyses and meta-regressions failed to elicit other sources of heterogeneity among the studies. Qualitative review of the studies, which also included specific evaluations of age and sex also failed to uncover an explanation for the large range of net effects seen across studies.

An additional set of meta-analyses were performed to investigate at what point the published randomized trial data were sufficient to yield the same results as were found by the current complete analyses. These cumulative meta-analyses sequentially add studies based on year of publication [41]. Regarding the effect of fish oil on triglycerides, by 1992, after the publication of three studies, meta-analysis revealed a statistically significant improvement ($P < 0.05$). The estimate of the effect size stabilized at $-28$ mg/dL in 1994 with six studies. Also by 1994, with the publication of six studies, the effect of fish oil on HDL cholesterol was both statistically significant and stable. The effect on LDL cholesterol was statistically significant after publication of the earliest two studies we reviewed in 1992; however, the estimate of the effect size was larger at that time (a net increase of 10 mg/dL) and did not stabilize until the publication of eight studies by 1997. Notably, all cumulative meta-analyses were statistically significant and stable prior to the publication of the GISSI study, with over 5000 subjects consuming fish oil, in 1999.

### 3.2.2. ALA

Five studies reported on the effect of ALA consumption on lipids (Table 3) [33,37–40]. The studies were mostly of poor quality, but broad applicability. Three studies used plant...
oil supplements or margarine with 4.5 to about 5 g ALA; two studies used variations on the “Mediterranean diet” with approximately 2 g/day of omega-3 fatty acids. The only study to find significant improvements in all lipids, by Singh et al., was a problematic study [39]. Issues related to this study’s reliability have been examined by several bodies [42,43]. The remaining studies generally found small effects (≤2 mg/dL net change) on total cholesterol, LDL, and HDL. An older study reported a 13 mg/dL (4%) net increase in total cholesterol, but no statistical analysis was performed. The remaining two studies that reported triglyceride effects both found non-significant changes of at least 10%, but in opposite directions.

3.3. Glucose homeostasis

We reviewed the 28 largest randomized trials that contained data on omega-3 fatty acid intake and either Hgb A1c or FBS (Table 2) [23,27,30,33,39,44–66]. Of these, 24 evaluated fish oil, three fish (or “Mediterranean”) diets, and two plant oils (one evaluated both fish oil and plant oil). These studies represented about 1700 subjects. The studies were generally of fair to good quality, with moderate applicability.

3.3.1. Fish and fish oil

Twenty-seven studies included 35 individual study arms of fish oil or fish diet that evaluated either Hgb A1c or FBS (Fig. 2 and Table 2). Among the studies of FBS there was a wide range of net effects found with fish oil consumption, from 29 mg/dL net reduction to 25 mg/dL net increase. However, in the majority of studies, the net effects were small (<5%). With the exception of two outlier studies [60,65], the net effect of fish oil on Hgb A1c was small (<5%, between −0.4% and 0.4%).

Across the studies, random effects model meta-analyses found a non-significant net increase in FBS with fish oil consumption of +3 (95% CI −0.2, +6) mg/dL and a similarly non-significant net increase in Hgb A1c of +0.1% (95% CI −0.01%, +0.2%). Removal of outlier studies from meta-analysis did not substantially affect the results.

Meta-regression (Table 2) found significant associations across studies between both baseline FBS and fish oil dose and the net effect of fish oil on FBS. Across studies, each increase in fish oil dose of 1 g/day was associated with an increase in FBS of approximately 3 mg/dL. Likewise, each 10 mg/dL increase in the mean baseline FBS level was associated with an additional 3 mg/dL increase in FBS after fish

![Fig. 2. Meta-analysis of randomized controlled trials of the effect of fish oil on Hgb A1c and FBS (see Fig. 1). (*) Initial dose given for 2 months, followed by lower dose for remainder of study.](image-url)
Table 4
The effect of omega-3 fatty acids on hs-CRP in individual studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Omega-3 fatty acid</th>
<th>Dose (g/day)</th>
<th>No. of subjects</th>
<th>Duration (weeks)</th>
<th>Qualityb</th>
<th>Applicabilityb</th>
<th>Base (mg/L)</th>
<th>Net change (mg/L)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Madsen et al. [67]</td>
<td>Fish oils</td>
<td>5.9</td>
<td>20</td>
<td>12</td>
<td>B</td>
<td>I</td>
<td>[1.07]c</td>
<td>[−0.15]d</td>
<td>NS</td>
</tr>
<tr>
<td>Chan et al. [68]</td>
<td>Fish oils</td>
<td>3.4</td>
<td>12</td>
<td>6</td>
<td>B</td>
<td>II</td>
<td>[2.11]c</td>
<td>+0.05f</td>
<td>NS</td>
</tr>
<tr>
<td>Mezzano et al. [69]</td>
<td>Totalg</td>
<td>1.6</td>
<td>21</td>
<td>13</td>
<td>C</td>
<td>III</td>
<td>4.9</td>
<td>+1.7</td>
<td>NS</td>
</tr>
<tr>
<td>Junker et al. [70]</td>
<td>ALA</td>
<td>2.5% kcal</td>
<td>18</td>
<td>4</td>
<td>C</td>
<td>I</td>
<td>[0.5]d</td>
<td>[+0.11]f</td>
<td>NS</td>
</tr>
</tbody>
</table>

95% CI = 95% confidence interval.

a Receiving omega-3 fatty acids.
b See Table 2.
c Median.
d Calculated value from median values.
e Geometric mean.
f Calculated value from geometric means.
g Mediterranean diet. Total omega-3 fatty acids reported.

Although the relationship between dietary fish and fish oil and CVD risk has been known for some time, the relationship between omega-3 fatty acids and surrogate circulating markers of CVD risk has been less clear. This area is of interest in light of our previous observations that in randomized studies, compared to placebo, the summary risk ratio of coronary artery restenosis was in favor of fish oil is (0.87 [95% CI 0.73, 1.05]) [11]. However, the data from prospective and cross-sectional studies on carotid IMT were inconsistent. Furthermore, small non-significant improvements in exercise capacity have been reported after fish oil supplementation. There were insufficient data on which to draw conclusions about the effect of ALA on these outcomes. A previous systematic review with meta-regression concluded that increased consumption of fish oil resulted in, on average, a 2 mmHg reduction in both systolic and diastolic blood pressure [5]. Numerous other factors related to CVD, including markers of thrombosis and endothelial function have been evaluated by a small number of studies, but these remain inconclusive [6,10].

The most direct effect of increased intake of omega-3 fatty acids is an increase in the relative proportion of these fatty acids throughout the body, most thoroughly documented in serum, platelet and red blood cell phospholipids, which are the most accessible tissues for testing [10,17,20,32]. How-ever, whether this change in phospholipids is a mediator of CVD is unknown.

The results of this review support the conclusion that the major and most consistent effect of relatively high doses of dietary omega-3 fatty acids on plasma markers of CVD risk was that fish oil consumption decreases triglyceride levels. This outcome was dose dependent and influenced by the baseline plasma triglyceride level of the study subjects. Prior work has suggested that this effect is in part attributable to a decrease in the hepatic production of triglyceride rich particles (VLDL, the lipoprotein responsible for transporting
triglycerides for subsequent delipidation by lipoprotein and hepatic lipases by peripheral tissue and the liver, respectively) and to an increase in fractional clearance rates [71–73]. Additionally, there is some evidence that omega-3 fatty acids increase the conversion rate of VLDL to LDL, similar to fibrate drugs [74].

In both cases, modest decreases in the levels of triglycerides are frequently accompanied by increases in the level of LDL cholesterol. The summary estimate of the change in triglyceride levels with increased fish oil consumption was 27 mg/dL. On an individual basis it is difficult to predict the effect of this change on clinical outcomes. However, triglyceride levels \(\geq 150\) mg/dL is one of the components when classifying individuals with metabolic syndrome. Therefore, a change in triglyceride levels as observed with increased fish oil intake could potentially result in a reclassification with regard to metabolic syndrome. Concomitant with lower triglyceride levels, increased fish oils resulted in modestly higher LDL cholesterol (6 mg/dL) and HDL cholesterol levels (1.6 mg/dL), an effect that is consistent with other interventions that reduced triglyceride levels [75]. Since the magnitude of the effect of raising HDL cholesterol levels on CVD is still unclear, and there are no data on the effect of raising both LDL and HDL cholesterol levels, the clinical significance of these changes remains unclear [76]. However, given their modest magnitude, they are unlikely to have a large independent effect on CHD risk.

Concern has been raised that fish oils may worsen glycemic control in diabetic subjects [77,78], although this concern is by no means universal [79,80]. The results of our assessment indicate that within the doses of fish oil provided to the subjects, there was little effect on FBS or Hgb A1c levels. Although there was a certain level of variability among studies there was not an indication of adverse effects of fish oil on glucose homeostasis.

Omega-3 fatty acids have well-established anti-inflammatory effects [81]. Observational data suggests that dietary fish oil and ALA are inversely associated with CRP level, whereas, the intervention data are less consistent [67,82–88]. Intervention studies have also reported an anti-inflammatory effect of fish and fish oil supplements on other inflammatory markers [89,90]. Regardless of vehicle, our analysis indicates that among the few randomized trials there was no significant effect of either ALA, EPA or DHA on hs-CRP levels. The lack of consistency between the observational and some of the intervention studies may be attributable to unidentified factors that co-varied with reported intakes of fish oil that were the responsible agent and difficulties with measuring inflammatory markers other than CRP in large scale observational studies.

The effects of ALA on serum lipids were, for the most part, not consistent with that reported for the very long chain omega-3 fatty acids, EPA and DHA. It is likely that the limited capacity of humans to elongate and desaturate ALA to EPA, even when ALA is fed at high levels, accounts for this inconsistency [8,91,92]. Similarly, it has recently been reported that not only do humans have a limited capacity to convert ALA to EPA, but likewise EPA to DHA [8,9]. However, this latter restriction is unlikely to alter the effect of fish oil or very long chain omega-3 fatty acid supplementation on CVD risk [7].

Overall, while data on the effect of ALA on serum lipids, Hgb A1c, and FBS are sparse, as are data regarding the effect of either fish oil or ALA on CRP, sufficient data have been reported to conclude that fish oil consumption lowers triglyceride levels and has a small beneficial effect on HDL cholesterol, while raising LDL cholesterol levels by a similarly small amount. While questions remain regarding the optimal dose and type of omega-3 fatty acids, the clinical significance of these changes, and possibly which groups of people would best be served by increasing fish oil consumption, it is unlikely that additional studies would change our conclusions regarding overall treatment effect of fish oil. In fact, the publication of the large GISSI study in 1999 did not alter conclusions available in the literature regarding the effect of fish oil on lipid values had meta-analyses been performed at that time. Similarly, future studies would be unlikely to alter the conclusion that fish oil consumption has no substantial effect on glucose homeostasis.

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