Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35, Salem, Oregon 97301-1079
Phone 503-947-5220 | **Fax** 503-947-1119

Abbreviated Drug Evaluation: Omega-3 Fatty Acids

Month/Year of Review: November 2013
Generic Name: Omega-3 Fatty Acid
Dossier Received: NA
PDL CLASS: Other Lipid Lowering Agents

End date of literature search: September 30, 2013
Brand Name (Manufacturer): Varies

Research Questions:

- Are omega-3 fatty acids effective in reducing cardiovascular mortality or stroke, cancer prevention, decreasing cognitive decline or as adjunctive therapy for mood disorders such as depression and bipolar?
- Are omega-3 fatty acids safe?
- Are there subpopulations that will benefit from omega-3 fatty acids in terms of effectiveness or harms compared to other therapies for the treatment of cardiovascular conditions, cancer, dementia or mood disorders.
- Is there evidence of improved efficacy or safety of one product over another?

Conclusions:

- There is moderate level evidence from 4 of 5 meta-analyses that omega-3 fatty acids do not reduce cardiovascular events (mostly myocardial infarction, stroke and cardiovascular death) in primary or secondary prevention.[1–5]
- There is moderate level evidence from 3 meta-analyses that omega-3 fatty acids have no significant beneficial effect in controlling atrial fibrillation.[6-8]
- There is low level evidence from 1 meta-analysis[9] omega-3 fatty acids improve cardiac function in patients with chronic heart failure and low level evidence they lower blood pressure.[10]
- There is moderate level evidence from 3 systematic reviews including observational studies that omega-3 fatty acids are of no benefit for cancer prevention.
- There is low level evidence from a Cochrane review that omega-3 fatty acids when used for 6-40 months do not prevent dementia in healthy participants over the age of 60 years who were cognitively healthy.[11]
- There is moderate level evidence of no benefit of omega-3 fatty acids on cognitive function in cognitively healthy older people and patients with Alzheimer's disease but there was a small benefit for immediate recall and attention and processing speed in subjects with cognitive impairment no dementia.[12]
- There is low level evidence that omega-3 fatty acids have mixed results for the treatment of bipolar symptoms[70,71] and depression.[13–15]
- There is moderate level of evidence that omega-3 fatty acids are safe and well tolerated.[2,11,12,16]
- There are numerous dietary fish oil supplements available and the amount of EPA and DHA per serving is highly variable. There are not strong recommendations on which supplements are preferred. Adherence, pill burden, and cost should be considered when choosing appropriate supplements.

Recommendations

- Retain legend omega-3 acid ethyl esters (Lovaza®) as non-preferred.
- Pull all over-the-counter FO/O3 products on the "Excluded Drug List". Drugs on this list used for funded diagnoses will be approved through the administrative appeals process.
- Publish an Oregon State Drug Review on FO/O3 detailing the lack of evidence and announcing the policy prior to implementation.
- Bring back Lovaza as old business to evaluate PA, as we may see a shift in use

Reason for Review:

Omega-3 fatty acids (i.e. fish oil) have been postulated to have a number of beneficial effects in patients at risk for vascular disease, including: 1)the treatment of hypertriglyceridemia, prevention of stroke, sudden cardiac death and heart failure, 2) used as adjunctive therapy for the treatment mood disorders such as major depression and bipolar disorders, 3) prevention of cognitive decline and dementia in Alzheimer's patient and 4) its possible role in cancer prevention. This review will exam the effectiveness and safety of fish oil in above settings by reviewing the high quality meta-analyses, systematic reviews and relevant treatment guidelines.

Background/Current landscape

Omega-3 and omega-6 fatty acids are considered essential fatty acids. They are not endogenously synthesized and must be obtained from the diet. Omega-6 fatty acids include linoleic, gamma-linolenic, and arachidonic acids. The typical Western diet is rich in omega-6 fatty acids due to the abundance of linoleic acid in corn, sunflower, and sunflower oils.[17] Omega-3 fatty acids typically include the long chain eicosapentaenoic (EPA), dicisapentanoic (DPA) and docosahexanoic (DHA), and the plant oil derived alpha linolenic acid (ALA). Omega-3 fatty acids account for only a small percentage of the dietary sources – plants and fish.[18] EPA and DHA are absorbed from the gastrointestinal tract. Consumption of fish oil increases the concentration of EPA and DHA in plasma lipids and membrane phospholipids within days, with maximal incorporation at about two weeks. Increases are dose-dependent but nonlinear, with a larger increase at lower doses and then smaller increments with increasing dose.[19]

The physiologic effects of fish oil occur within weeks of habitual consumption and may result from altered cell membrane fluidity and receptor responses following incorporation of omega-3 fatty acids into cell membranes and direct binding of omega-3 fatty acids to cytosolic receptors that regulate gene transcription. Consequently, this affects metabolic or signaling pathways associated with coronary heart disease, depression, and bipolar disorder.[20–22]

The interest in the therapeutic use of omega-3 fatty acids to prevent and treat cardiovascular disease began after a report showed that high consumption of fish oil in people living in Greenland was associated with a decreased risk of cardiovascular disease.[23] The protective component was suggested to be the long chain n-3 fatty acids consumed in very high amounts as a result of the regular intake of seal meat and whale blubber.[23] Additional epidemiological work has found similar patterns of low cardiovascular disease in populations that consume a diet rich in seafood, in Japan, Norway, Holland, and India.[24–27] However, not all epidemiological studies agree and a meta-analysis of cohort data has found no clear effect of long-chain and shorter-chain n-3 fats (from both fish and vegetable oils) on cardiovascular events.[28] The Gruppo Italiano per lo Studio della Sopravvivenza mell'Infarto (GISSI) – Prevenzion trial of 11,324 patients randomized into a mixture of omega-3 fatty acids EPA and DHA or placebo showed a significant reduction in all cause mortality and death from cardiovascular causes over 3.5 years of follow- ups. However, results from other clinical trials showed conflicting results.[29–31] The most recent large scale randomized controlled trial Rischio and

Prevenzione (R & P) Study showed daily treatment with n-3 fatty acids did not reduce cardiovascular mortality and morbidity.[32] Of the 12,513 patients enrolled, 6244 were randomly assigned to n-3 fatty acids and 6269 to placebo. With a median of 5 years of follow-up, the primary end point occurred in 1478 of 12,505 patients included in the analysis (11.8%), of whom 733 of 6239 (11.7%) had received n-3 fatty acids and 745 of 6266 (11.9%) had received placebo (adjusted hazard ratio with n-3 fatty acids, 0.97; 95% confidence interval, 0.88 to 1.08; P=0.58).[32] Experimental and epidemiological studies indicated that fish oil could improve cardiac function and functional capacity in patients with CHF[33,34] and in prevention of atrial fibrillation (AF).[35,36] However, clinical trials have shown inconsistent results in CHF[37–43] and in preventing postoperative AF.[44–48]

It was observed in migrant studies that changes in food patterns are more often associated with an increased incidence of cancers.[49] Several epidemiological studies have shown a risk reduction of some cancers associated with long chain omega-3 fatty acids or fish intake.[50] A role of fish intake and prostate cancer has been studied in several settings. Populations with a high consumption of fish, such as in populations in Japan and in Alaskan Eskimos, have lower rates of prostate cancer than populations with Western diets, in which fish intake is generally lower.[51,52]

The Epidemiological and animal studies suggested that omega-3 fatty acid could be protective against cognitive decline and dementia. Omega-3 fatty acids constitute 60% of the membrane fatty acids in neurons.[53] An ecological study of diet and Alzheimer's disease[54], and a study in Japanese with Japanese lifestyle had lower rates of cognitive decline[55] suggested that consumption of fish might be protective. While the literature suggests promise, findings have not shown consistent beneficial effects in population examined.

Evidence from ecological, cross-sectional and case-control studies suggest that fish consumption and omega-3 fatty acids intake may affect the prevalence of major depressive disorder (MDD). There is a strong negative correlation between fish consumption and national rates of MDD.[56] Cross-sectional studies have demonstrated higher rates of MDD in individuals who rarely consume fish.[57] Although some randomized clinical studies found positive effects associated with the supplementation, others did not find this benefit. [58–60]

EPA and DHA Products on the Market

There are numerous dietary fish oil supplements available. However they are not regulated by the Food and Drug Administration (FDA). The concentrations of EPA and DHA in omega-3 fatty acid supplements range from a modest level of less than 20% to more than of 80%.[61] Reports regarding the accuracy of the stated amount of EPA and DHA in supplement labels have been inconsistent. There are two FDA approved prescription agents Lovaza® and Vescepa®. Lovaza® contains high-purity omega-3 acid ethyl esters and is FDA approved as adjunctive therapy to diet to reduce very high triglyceride levels (500mg/dL or higher) in adults. Vescepa® is a high-purity form of EPA ethyl ester, like Lovaza® it is indicated as an adjunct to diet to reduce triglyceride levels in adults with severe hyperglyceridemia (500mg/dL or higher). Both of these agents are non-preferred under the Oregon Health Plan and require non-PDL prior authorization criteria due to their use as an alternative to a fibric acid derivative and niacin for hypertriglyceridemia.

Some preliminary evidence suggested that EPA and DHA affects the serum fatty acids and hemodynamics, such as heart rate differently.[62–64] A meta-analysis of randomized placebo-controlled trials of monotherapy with EPA (n=10), DHA (n=17), or EPA versus DHA (n=6) in 2011 examined the effects of EPA versus DHA on serum lipids.[65] The results showed that compared with placebo, DHA raised LDL 7.23 mg/dL (95% CI, 3.98–10.5) whereas EPA non-significantly reduced LDL. In direct comparison studies, DHA raised LDL 4.63 mg/dL (95% CI, 2.15–7.10) more than EPA. Both EPA and DHA reduced triglycerides, with a greater reduction by DHA in direct comparison studies. DHA also raised high-density lipoprotein (4.49 mg/dL; 95% CI, 3.50–5.48) compared with placebo, whereas EPA did not. A

More recent exploratory, hypothesis-generating literature review evaluated potentially differential effects of EPA and DHA on LDL, HDL and triglycerides, and non-HDL-C in published studies of omega-3 fatty acid supplementation or prescription omega-3 fatty acid ethyl esters. Placebo-adjusted changes in mean lipid parameters were compared in randomized, controlled trials in subjects treated for ≥ 4 weeks with DHA or EPA. Of 22 studies identified, 6 compared DHA with EPA directly, 12 studied DHA alone (including 14 DHA-treated groups), and 4 examined EPA alone. In studies directly comparing EPA with DHA, a net increase in LDL-C of 3.3% was observed with DHA (DHA: +2.6%; EPA: -0.7%). In such head-to-head comparative studies, DHA treatment was associated with a net decrease in TG by 6.8% (DHA: -22.4%; EPA: -15.6%); a net increase in non-HDL-C by 1.7% (DHA: -1.2%; EPA -2.9%); and a net increase in HDL-C by 5.9% (DHA: +7.3%; EPA: +1.4%). Increases in LDL-C were also observed in 71% of DHA-alone groups [with demonstrated statistical significance ($P < .05$) in 67% (8 of 12) DHA-alone studies] but not in any EPA-alone studies. Changes in LDL-C significantly correlated with baseline TG for DHA-treated groups. The range of HDL-C increases documented in DHA-alone vs. EPA-alone studies further supports the fact that HDL-C is increased more substantially by DHA than EPA. In total, these findings suggest that DHA-containing supplements or therapies were associated with more significant increases in LDL-C and HDL-C than were EPA-containing supplements or therapies. The authors concluded future prospective, randomized trials are warranted to confirm these preliminary findings, determine the potential effects of these fatty acids on other clinical outcomes, and evaluate the generalizability of the data to larger and more heterogeneous patient populations.[66]

Methods:
A MEDLINE Ovid search was conducted using key words: omega-3 fatty acids, EPA, DHA, cancers, cardiovascular disease, prevention, stroke, hypertension, cardiac outcomes, hyperlipidemia, hypertriglyceridemia, dementia, cognitive function, Alzheimer's disease, depression, bipolar disorder, and psychiatric disorders. The search was limited to meta-analysis, systematic reviews in English language, and to studies conducted in humans in the last ten years. The Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, Oregon Evidence-based Practice Center, National Institute for Health and Clinical Excellence (NICE), and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were searched for high quality and relevant systematic reviews. The AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines.

Systematic Reviews: (See Appendix A for Abstract)

<u>Cardiovascular Disease</u>
The effect of omega-3 fatty acids was most studied in cardiovascular (CV) disease. Below is the summary of the most recent systematic review and meta-analyses on its effect on the overall CV outcomes and selected CV events related to heart failure, arrhythmias including atrial fibrillation, stroke and hypertension.

Overall Cardiovascular Disease (CVD) Outcomes
Kotwal et al.[2]published a meta-analysis in 2012 that examined the effects of omega-3 fatty acids on cardiovascular and other important outcomes. The authors reviewed the randomized controlled trials using dietary supplements, dietary interventions or both. The primary outcome was a composite of cardiovascular events (mostly myocardial infarction, stroke, and cardiovascular death). Secondary outcomes were arrhythmia, cerebrovascular events, hemorrhagic stroke, ischemic stroke, coronary revascularization, heart failure, total mortality, nonvascular mortality, and end-stage kidney disease. Twenty studies including 63,030 participants were included. There was no overall effect of Omega-3 fatty acids on composite cardiovascular events (relative risk [RR]=0.96; 95% confidence interval [CI], 0.90-1.03; P=0.24) or on total mortality (RR=0.95; 95% CI, 0.86-1.04; P=0.28). Omega-3 fatty acids did protect against vascular death (RR=0.86; 95%

CI, 0.75-0.99; P=0.03), but not coronary events (RR=0.86; 95% CI, 0.67-1.11; P=0.24). There was no effect on arrhythmia (RR=0.99; 95% CI, 0.85-1.16; P=0.92) or cerebrovascular events (RR=1.03; 95% CI, 0.92-1.16; P=0.59). Adverse events were more common in the treatment group than the placebo group (RR=1.18, 95% CI, 1.02-1.37; P=0.03), predominantly because of an excess of gastrointestinal side effects. A key strength of this overview is the attempt to extract data on all commonly reported vascular outcomes from all trials and to systematically report the summary estimates of effect in each case. However, the reporting of outcomes across studies is inconsistent and in part because there is significant heterogeneity between the trials' results for several of the outcomes studied. The authors acknowledge the heterogeneity may also contribute to the absence of positive findings in this meta-analysis. They concluded that the beneficial effects of omega 3 fatty acids are not as large as previously implied and recommendations for widespread use should be tempered.

Kwak SM et al.[4] conducted a meta-analysis on the effects of omega-fatty acids in the secondary prevention of CV disease. The analysis included 14 randomized, double-blind, placebo-controlled trials involving 20,485 patients with a history of CVD. Supplementation with omega-3 fatty acids did not reduce the risk of overall cardiovascular events (relative risk, 0.99; 95% CI, 0.89-1.09; I^2 = 27.1%), all-cause mortality, sudden cardiac death, myocardial infarction, congestive heart failure, or transient ischemic attack and stroke. There was a small reduction in cardiovascular death (relative risk, 0.91; 95% CI, 0.84-0.99), which disappeared when a study with major methodological problems was excluded. Furthermore, no significant preventive effect was observed in subgroup analyses by the following: country location, inland or coastal geographic area, history of CVD, concomitant medication use, type of placebo material in the trial, methodological quality of the trial, duration of treatment, dosage of eicosapentaenoic acid or docosahexaenoic acid, or use of fish oil supplementation only as treatment. This analysis showed moderate evidence of no secondary preventive effect of omega-3 fatty acid supplements against overall CV events among patients with a history of CV disease.

Similar results were observed by another recent meta-analysis conducted by Rizois EC et al.[5] The analysis included 20 randomized clinical trials with total of 68,680 patients. There were 7,044 reported deaths in these trials, 3,993 cardiac deaths, 1,150 sudden deaths, 1,837 myocardial infarctions, and 1,490 strokes. No statistically significant association was observed with all-cause mortality (RR, 0.96; 95% CI, 0.91 to 1.02; p = 0.17;I^2 = 12%; risk reduction [RD] -0.004, 95% CI, -0.01 to 0.02; p = 0.19; I^2 = 38%), cardiac death (RR, 0.91; 95% CI, 0.85 to 0.98; p = 0.01; I^2 = 6%) and a non-significant absolute risk reduction of -0.01(95% CI, -0.02 to 0.00; p = 0.09; I^2 = 78%), sudden death (RR, 0.87; 95% CI, 0.75 to 1.01; RD, -0.003; 95% CI, -0.012 to 0.006), myocardial infarction (RR, 0.89; 95% CI, 0.76 to 1.04; RD, -0.002; 95% CI, -0.007 to 0.002), and stroke (RR, 1.05; 95% CI, 0.93 to 1.18; RD, 0.001; 95% CI, -0.002 to 0.004) when all supplement studies were considered. Omega-3 fatty acids are not statistically significantly associated with major cardiovascular outcomes across various patient populations. The authors concluded the findings from this analysis do not justify the use of omega-3 fatty acids as a structured intervention in everyday clinical practice or guidelines supporting dietary omega-3 fatty acids administration.

Unlike three meta-analyses mentioned above, another recent meta-analysis by Delgado-Lista J et al.[3] showed different findings on several endpoints compared with the above analyses. This meta-analysis included clinical trials and randomized controlled trials of omega-3 fatty acids either in capsules or in dietary intake, compared to placebo or usual diet, equal to or longer than 6 months, and written in English. Most of the studies analyzed included persons with high cardiovascular risk. The primary outcome was a cardiovascular event of any kind and secondary outcomes were all-cause mortality, cardiac death and coronary events. The analysis included 21 of the 452 pre-selected studies. The results showed an overall decrease of risk of suffering a cardiovascular event (N = 45,285) of any kind of 10 % (OR 0·90; [0·85-0·96], p = 0·001; I^2 = 53%), a 9 % decrease of risk of cardiac death (OR 0·91; [0·83-0·99]; p = 0·03; I^2 = 32%), a decrease of coronary events (fatal and non-fatal) of 18 % (OR 0·82; [0·75-0·90]; $p < 1 \times 10^{-4}$;I^2 0%), and a trend to lower total mortality (5 % reduction of risk; OR 0·95; [0·89-

1·02]; p = 0·15. Based on these findings, the authors concluded marine omega-3 fatty acids are effective in preventing cardiovascular events, cardiac death and coronary events, especially in persons with high cardiovascular risk. However, the trials included for various endpoints with exception of coronary events all showed heterogeneity. Results should be interpreted with caution.

Arrhythmias

Leon H et al.[6] conducted a meta-analysis focusing on the effects of fish oil (DHA and EPA) on mortality and arrhythmias and explore dose response and formulation effects. The primary outcomes of interest were the arrhythmic end points of appropriate implantable cardiac defibrillator intervention and sudden cardiac death. The secondary outcomes were all cause mortality and death from cardiac causes. Subgroup analyses included the effect of formulations of EPA and DHA on death from cardiac causes and effects of fish oil in patients with coronary artery disease or myocardial infarction. 12 studies totaling 32,779 patients met the inclusion criteria. A neutral effect was reported in three studies (n=1,148) for appropriate implantable cardiac defibrillator intervention (odds ratio (OR) 0.90, 95% confidence interval (CI) 0.55 to 1.46) and in six studies (n=31,111) for sudden cardiac death (0.81, 0.52 to 1.25). 11 studies (n=32,439 and n=32,519) provided data on the effects of fish oil on all cause mortality (OR: 0.92; CI: 0.82 to 1.03) and a reduction in deaths from cardiac causes (OR: 0.80; CI: 0.69 to 0.92). The dose-response relation for DHA and EPA on reduction in deaths from cardiac causes was not significant. The conclusions from the analysis were that fish oil supplementation was associated with a significant reduction in deaths from cardiac causes but had no effect on arrhythmias or all cause mortality. Evidence to recommend an optimal formulation of EPA or DHA to reduce these outcomes is insufficient. Fish oils are a heterogeneous product, and the optimal formulations for DHA and EPA remain unclear.

Liu T et al[7] reviewed the role of omega-3 fatty acids in AF prevention. This meta-analysis included 10 randomized clinical trials with total of 1,955 patients. The results showed omega-3 fatty acids had no significant effect on the prevention of AF (OR 0.81, 95% CI 0.57 to 1.15; p=0.24). There was significant heterogeneity among the studies (p=0.002, I^2=65.0%). Subgroup analysis showed no significant beneficial effect of fish oils in any subset of population.

Armaganijan L et al.[8] conducted meta-analysis to examine the role of omega-3 fatty acids preventing AF after open heart surgery. Four randomized studies (3 double blind, one open-label) that enrolled 538 patients were identified. The use of omega-3 fatty acids was not associated with a reduction in the occurrence of postoperative AF in the patients undergoing cardiac surgery compared to the untreated patients (odds ratio, 0.79; 95% confidence interval, 0.56 - 1.13; p = 0.195). Similar results were observed when the open-label study was excluded from the analyses (odds ratio, 0.99; 95% confidence interval, 0.65 - 1.49; p = 0.963).

Chronic Heart Failure (CHF)

Xin W et al.[9] published a meta-analysis to evaluate effects fish oil on cardiac function and related parameters in CHF patients. Randomised controlled trials of fish oil supplementation on cardiac function in patients with CHF were identified. Seven trials with 825 participants were included. Meta-analysis results showed that left ventricular ejection fraction was significantly increased (weighted mean difference (WMD) = 2.25%, 95% CI 0.66 to 3.83, p = 0.005) and left ventricular end-systolic volume was significantly decreased (WMD = 7.85 ml, 95% CI -15.57 to -0.12, p = 0.05) in the fish oil group compared with the placebo group, although left ventricular end-diastolic volume was not significantly affected. Meta-regression and subgroup analysis indicated that the improvement in left ventricular systolic function was more remarkable in patients with non-ischemic heart failure. Fish oil supplementation also improved the New York Heart Association functional classification and peak oxygen consumption in patients with non-ischemic heart failure. Although this analysis suggested that improvements in cardiac function, remodeling and functional capacity may be important mechanisms underlying the potential therapeutic role of fish oil for

patients with CHF and these effects might be more remarkable in patients with non-ischemic heart failure, it was noted that the number of studies and patients included in this analysis was small, the results of estimations should be interpreted with caution.

Hypertension

Campell F et al.[10] in 2012 published a meta-analysis that reviewed the randomized controlled trials and crossover trials that evaluated the effectiveness of fish oil supplements in lowering blood pressure. The analysis included trials enrolling adults who were given fish oil supplements with at least 8 weeks' follow-up. There were 17 studies with a total of 1,524 participants were included in the analysis. The analysis examined the effects of fish oil supplements in both normotensive and hypertensive participants with blood pressure of 140/85 mmHg at least. Meta-analysis was performed using the inverse-variance method. Data from eight studies in hypertensive participants found a statistically significant reduction in systolic and diastolic BP; 2.56 mmHg (95% CI 0.58 to 4.53) and 1.47 mmHg (95% CI 0.41 to 2.53), respectively. Nine studies in normotensive participants showed a non-significant reduction in both systolic and diastolic BP. Meta-regression showed no significant relationship between dose of fish oil and the effect on blood pressure. The analysis concluded the small but statistically significant effects of fish-oil supplements in hypertensive participants in this review have important implications for population health and lowering the risk of stroke and ischemic heart disease. Their modest effects, however, mean that they should not be recommended as an alternative to BP-lowering drugs where guidelines recommend treatment.

Stroke

Larsson SC et al.[1] conducted a meta-analysis of prospective studies to summarize available evidence regarding the relation between long-chain omega-3 fatty acids intake and stroke. Prospective studies that provided relative risks (RRs) with 95 % confidence intervals (CIs) for the association between dietary long-chain omega-3 fatty acids intake and stroke were eligible. A random-effects model was used to combine study-specific results. Eight prospective studies, with 5,238 stroke events among 242,076 participants, were included in the meta-analysis. The combined RR of total stroke was 0.90 (95 % CI, 0.81-1.01) for the highest versus lowest category of long-chain omega-3 fatty acids intake, without heterogeneity among studies (P = 0.32). Results were similar for ischemic (RR, 0.82; 95 % CI, 0.71-0.94) and hemorrhagic stroke (RR, 0.80; 95 % CI, 0.55-1.15). A statistically significant reduction in total stroke risk was observed in women (RR, 0.80; 95 % CI, 0.65-0.99). This meta-analysis showed no overall association between omega-3 fatty acids intake and stroke, but suggests that women might benefit from a higher intake of these PUFAs.

<u>Cancer</u>

Gerber M[67] published an updated systematic review in 2012 on omega-3 fatty acids and cancers. The review included all prospective and case-control observational studies since the ones reported in the Food and Agriculture Organization (FAO) and the World Health Organization (WHO) expert consultation. Studies included in this review were prospective and case-control observational studies, intervention studies and randomised controlled trials were also considered. The specific validity criteria and evaluation of the level of evidence were defined in the review. The author concluded a probable level of evidence that fish oil is neither a risk factor nor a beneficial factor with regards to cancers. Observational studies on colorectal, prostate and breast cancers only provided limited evidence suggesting a possible role of fish oil in cancer prevention due to insufficient homogeneity of the observations.

Additionally Szmanski KM et. al.[68] performed a meta-analysis on fish intake and prostate cancer by focusing on the incidence of prostate cancer and prostate cancer-specific mortality and included subgroup analyses based on race, fish type, method of fish preparation, and high-grade and high stage cancer. Case-control and cohort studies were included in the analysis. The results showed no association between fish consumption and a significant reduction in prostate cancer incidence based on 12 case-control studies (n = 5,777cases and 9,805 control subjects), odds ratio: 0.85; 95% CI: 0.90, 1.14). The meta-analysis was not performed on high-grade disease, locally advanced disease and metastatic disease due to only one case-control study available for each subgroup. However, there was an association between fish consumption and a significant 63% reduction in prostate cancer-specific mortality based on 4 cohort studies (n= 49,661, RR: 0.37; 95 CI: 0.18, 0.74). The authors concluded that there was no strong evidence of protective association of fish consumption with prostate cancer incidence but there is a significant 63% reduction on prostate cancer-specific mortality. The analysis was based on cohort case-control studies not randomized control clinical trials.

Ries A et al[16] also examines the role of fish oil in patients with cachexia due to advanced cancer. The analysis included only clinical studies and systematic reviews evaluating clinical studies. There were three systematic reviews included, 10 controlled trials, 11 uncontrolled/case series included in the review. Two out three systematic reviews found no clear advantage of treatment with fish oil; four of the six-high-quality randomized controlled trials found no significant benefit from fish oil supplementation. The authors concluded insufficient evidence to support a net benefit of fish oil in cachexic patients with advanced cancer. However, adverse effects were infrequent with no severe adverse effects.

Cognitive Function and Dementia

Cochrane Review[11] *(2012)*

The authors of this review included studies where healthy participants over the age of 60 years who were cognitively healthy at the start of the study were randomly assigned to receive extra omega-3 fatty acids in their diet or a placebo (such as olive oil).Three randomized clinical trials were included in the analysis. Information on cognitive function at the start of a study was available on 4,080 participants randomised in three trials. Cognitive function data were available on 3,536 participants at final follow-up. In two studies participants received gel capsules containing either omega-3 fatty acids (the intervention) or olive or sunflower oil (placebo) for six or 24 months. In one study, participants received margarine spread for 40 months; the margarine for the intervention group contained omega-3 fatty acids. Two studies had cognitive health as their primary outcome; one study of cardiovascular disease included cognitive health as an additional outcome. None of the studies examined the effect of omega-3 fatty acids on incident dementia. In two studies involving 3,221 participants there was no difference between the omega-3 and placebo group in mini-mental state examination score at final follow-up (following 24 or 40 months of intervention); MD-0.07 (95%CI -0.25 to 0.10). In two studies involving 1043 participants, other tests of cognitive function such as word learning, digit span and verbal fluency showed no beneficial effect of omega-3 fatty acids supplementation. Participants in both the intervention and control groups experienced either small or no cognitive declines during the studies.

The main reported side-effect of omega-3 fatty acids supplementation was mild gastrointestinal problems. Overall, minor adverse events were reported by fewer than 15%of participants, and reports were balanced between intervention groups. Adherence to the intervention was on average over 90% among people who completed the trials. All three studies included in this review are of high methodological quality. The review concluded evidence on the effect of omega-3 fatty acids on incident dementia is lacking. The available trials showed no benefit of omega-3 fatty acids supplementation on cognitive function in cognitively healthy older people. Omega-3 fatty acids supplementation is generally well tolerated with the most commonly reported side-effect being mild gastrointestinal problems.

The authors suggested further studies of longer duration are required. Longer-term studies may identify greater change in cognitive function in study participants which may enhance the ability to detect the possible effects of omega-3 fatty acids supplementation in preventing cognitive decline in older people.

The above Cochrane review only included the healthy elderly patients. Alternatively Mazereeuw G et al.[12] conducted a meta-analysis examined the neuropsychological benefit of omega-3 fatty acids in randomized double-blinded placebo-controlled studies including healthy, cognitive impairment no dementia (CIND), or Alzheimer's Disease (AD) subjects. Ten randomized clinical trials were combined quantitatively. Treatment effects were summarized across cognitive sub-domains, and effect sizes were estimated using Hedge's g and random effects modeling. All of the included studies scored above the suggested cutoff for high quality (5 points) according to the PEDro scale. Scores ranged from 6 to 10 with a mean of 8.85. Hedge's g was used to represent effect sizes between treatment and placebo groups for continuous neuropsychological outcomes in each study. The results suggested no effect of omega-3 fatty acids on composite memory (g = 0.04 [95% CI: -0.06 – 0.14], N = 934/812, *p* = 0.452). When examined by domain, no overall benefit for immediate recall (0.04 [-0.05 – 0.13], N = 934/812, *p* = 0.358) was detected; however, an effect in CIND subjects (0.16 [0.01 – 0.31], N= 349/327, *p* = 0.034) was found. A benefit for attention and processing speed was also detected in CIND (0.30 [0.02 – 0.57], N = 107/86, *p* = 0.035), but not healthy subjects. Benefits for delayed recall, recognition memory, or working memory and executive function were not observed. Treatment did not benefit AD patients as measured by the Mini-Mental State Examination (MMSE) or Alzheimer's Disease Assessment Scale–Cognitive Subscale (ADAS–cog). No differences in adverse events (AE), dropout, or dropout due to AE between groups were observed. The authors concluded omega-3 fatty acid treatment was associated with a small, but significant benefit for immediate recall and attention and processing speed in subjects with CIND but not in healthy subjects or those with AD. There was high degree of safety and tolerability observed in these RTCs. However the findings suggest the effects of omega-3 fatty acids on cognitive decline are not uniform, and that there is a need to identify potentially responsive populations.

Psychiatric Disorders

In 2012 Ortega RM et al[69] conducted a systematic review of effects of omega-3 fatty acids supplementation in behavior and non-neurodegenerative neuropsychiatric disorders. The review included 38 published randomized, controlled clinical trials up to April 2011. There were 23 studies examined the influence of omega-3 fatty acid supplementation on the prevention /treatment of depression, 6 on perinatal depression and 9 were on attention deficit hyperactivity disorder (ADHD). Great heterogeneity was noticed in terms of study design, sample size, the doses of omega-3 fatty acids and study duration. Some benefit was noted with respect to the treatment of hyperactivity and depression in over half the examined studies, although the evidence was not conclusive. For any firm conclusions to be drawn, further studies will be needed that take into account the initial omega-3 fatty acids status of the subjects.

Bipolar Disorder

Sarris J et al.[70] published a review article in 2011 that examined the clinical trials using nutrient-based nutraceuticals, such as omega-3 fatty acids, N-acetyl cysteine, inositol, and vitamins and minerals in combination with standard pharmacotherapies to treat bipolar disorder (BD). Specifically for omega-3 fatty acids, the review included 9 clinical trials. Seven were randomized, double blinded and placebo controlled design with total 341 patients. Study duration ranges between 4 to 16 weeks. Only three out of seven RCTs showed omega-3 fatty acids statistically positive results on depression. No omega-3 study revealed a statistically significant finding on the outcome of mania. The meta-analytic comparison between DHA and EPA found that DHA monotherapy was not significant, whereas in studies using supplements containing greater than 50% EPA, a significant effect occurred in favor of omega-3 [standardized mean difference = 0.446; 95%confidence interval (CI): 0.753 to 0.138; z =2.843; p = 0.005]. The authors acknowledge that limitation specific to this review is that a meta-analysis could not

be conducted as the varied types of nutraceuticals covered in this review provide too much heterogeneity. Caution should be extended in interpreting the large effects of several isolated studies, as they have not yet been replicated in larger trials.

In 2006 Turnbull et al.[71] reviewed the level of evidence regarding the efficacy of omega-3 fatty acid supplementation in improving bipolar disorder symptoms. Of 99 articles meeting initial search criteria, 5 randomized control trials and 2 quasi-experimental studies were selected for review. Omega-3 fatty acid supplementation was effective in 4 of 7 studies. Those using an omega-3 combination of eicosapentaenoic acid and docosahexanoic acid demonstrated a statistically significant improvement in bipolar symptoms, whereas those using a single constituent did not. Dosage variations did not demonstrate statistically significant differences. The authors concluded due to its benign side effect profile and some evidence supporting its usefulness in bipolar illness, omega-3 may be a helpful adjunct in treatment of selected patients. Future studies are needed to conclusively confirm the efficacy of omega-3 fatty acids in bipolar disorder, uncovering a new well-tolerated treatment option. It was noted five studies had a sample size less than 45. In two of the seven studies, nearly 50% of the participants failed to complete the trial, thereby diminishing confidence in study outcomes. Of these two studies, only one performed an ITT analysis; neither found a significant reduction in symptoms. Due to major concern of internal validity of the review studies, specifically small sample size and high level of attrition rate, the conclusion should be interpreted with caution.

Depression

There are several meta-analyses were published in the past decade.[13–15] The most recent one was conducted by Bloch MH et. al[13] in 2012. This review included randomized, placebo-controlled trials of omega-3 fatty acid treatment of major depressive disorder. Review's primary outcome measure was standardized mean difference in a clinical measure of depression severity. In stratified meta-analysis, the review examined the effects of trial duration, trial methodological quality, baseline depression severity, diagnostic indication, dose of eicosapentaenoic acid (EPA) and docosahexanoic acid (DHA) in omega-3 preparations, and whether omega-3 fatty acids was given as monotherapy or augmentation. In 13 randomized, placebo-controlled trials examining the efficacy of omega-3 fatty acids involving 731 participants, meta-analysis demonstrated no significant benefit of omega-3 fatty acids treatment compared with placebo (standard mean difference (SMD) = 0.11, 95% confidence interval (CI): 0.04, 0.26). Meta-analysis demonstrated significant heterogeneity and publication bias. Nearly all evidence of omega-3 benefit was removed after adjusting for publication bias using the trim-and-fill method (SMD = 0.01, 95% CI: 0.13, 0.15). Secondary analyses suggested a trend toward increased efficacy of omega-3 fatty acids in trials of lower methodological quality, trials of shorter duration, trials which utilized completers rather than intention-to-treat analysis, and trials in which study participants had greater baseline depression severity. Current published trials suggest a small, non-significant benefit of omega-3 fatty acids for major depression. Nearly all of the treatment efficacy observed in the published literature may be attributable to publication bias. The authors concluded that although there is still strong evidence based on the epidemiological and cellular literature that omega-3/omega-6 fatty acids balance may have an important role in the pathogenesis of depression, there is limited evidence for omega-3 fatty acids supplementation being an effective acute treatment for it.

Earlier meta-analysis by Sublette ME et al.[14] in 2011 on omega-3 fatty acids in treatment of depression reviewed 15 randomized clinical trials involving 916 participants. The results indicated that supplements with EPA ≥ 60% showed benefit on standardized mean depression scores (effect size = 0.532; 95% CI, 0.277–0.733; t = 4.195; P < .001) versus supplements with EPA < 60% (effect size = −0.026; 95% CI, −0.200 to 0.148; t = −0.316; P = .756), with negligible contribution of random effects or heteroscedasticity and with no effects of treatment duration or age. Supplements with EPA < 60% were ineffective. Exploratory analyses supported a nonlinear model, with improvement determined by the dose of EPA in excess of DHA, within the range of 200 to 2,200 mg/d of EPA. The authors concluded supplements containing EPA ≥ 60% of total EPA + DHA, in a dose range of 200 to 2,200 mg/d of EPA in excess of DHA, were effective against primary

depression. Translational studies are needed to determine the mechanisms of EPA's therapeutic benefit. Several limitations were noted by the authors: 1) the number of potential moderators examined was limited by considerations of statistical power and inconsistent information in the source articles; 2) unexamined covariates that might be relevant include baseline level of depression, presence of stabilizing antioxidant in the supplement, response by sex or ethnicity, baseline plasma PUFA levels, and dietary intakes; 3) the selection of a diagnostic phenotype for study was limited by the relatively small number of clinical trials primarily focusing on depression, and by a lack of diagnostic clarity in some of the studies. Thus no inferences can be made about depressive episodes occurring within Major Depressive Disorder as opposed to Bipolar Disorder.

Similarly Appleton KM et al.[15] conducted a systematic review and meta-analysis on effects of omega-3 fatty acids in treatment of depressed mood. Thirty-five randomized controlled trials were identified, and twenty-nine were included in the meta-analyses. The pooled standardized difference in mean outcome of the 29 trials that provided data to allow pooling (fixed-effects model) was 0.10 SD (95% CI: 0.02, 0.17) in those who received omega-3 fatty acids compared with placebo, with strong evidence of heterogeneity (I^2 = 65%, P < 0.01). The presence of funnel plot asymmetry suggested that publication bias was a likely source of this heterogeneity. Depressive symptom severity and participant diagnosis also explained some of the observed heterogeneity. Greater effects of omega-3 fatty acids were found in individuals with more-severe depressive symptoms. In trials that enrolled individuals with a diagnosed depressive disorder, the combined mean difference was 0.41 (95% CI: 0.26, 0.55), although evidence of heterogeneity was also found (I^2= 71%). In trials that enrolled individuals without a depressive diagnosis, no beneficial effects of omega-3 fatty acids were found (largest combined mean difference: 0.22; 95% CI: -0.01, 0.44; I^2= 0%). In summary, although trial evidence of the effects of omega-3 fatty acids on depressed mood has increased but remains difficult to summarize because of considerable heterogeneity. The evidence available provides some support of a benefit of omega-3 fatty acids in individuals with diagnosed depressive illness but no evidence of any benefit in individuals without a diagnosis of depressive illness.

Treatment Guidelines

The European Society of Cardiology (ESC) Guidelines for the diagnosis and treatment of Acute and Chronic Heart Failure 2012 listed omega-3 fatty acids as one of the recommended treatments for potentially all patients with systolic heart failure.[72] The guidelines did recognize evidence of omega-3 fatty acids after myocardial infarction is uncertain. The small treatment effect of omega-3 fatty acids was based on the Gruppo Italiano per lo Studio della Sopravvivenza mell'Infarto micocardico-heart failure (GISSI-HF)[73] trial was only detected after covariate adjustment in the statistical analysis and there was no effect on HF hospitalization. In addition, the guidelines for specialized nutritional and metabolic support in the critically – ill patients in Spain also recommended administer at least 1gm/day EPA plus DHC (level C) in patients with acute coronary syndrome who require enteral nutrition.[74]

American Heart Association (AHA) published a scientific statement on Triglyceride and Cardiovascular disease in May 2011.[75] The statement stated "As monotherapy, fibrates offer the most TG reduction, followed by immediate-release niacin, omega-3 methyl esters, extended-release niacin, statins, and ezetimibe". It recommends 2 to 4 grams of eicosapentaenoic acid (EPA) plus docosahexanoic acid (DHA) per day for patients who need to lower their TG level.

Canadian Network for Mood and Anxiety Treatment (CANMAT) Clinical guidelines for the management of major depressive disorder in adults under section "Complementary and alternative medicine treatments"[76] has Level 1 recommendation of using omega-3 fatty acids as second line monotherapy and adjunctive therapy in patients with mild to moderate severity of major depressive disorder in 2009.

In November of 2013, the American Heart Association (AHA) and the American College of Cardiology (ACC) released four clinical practice guidelines for the prevention of CV disease.[77] . The objective of the second guideline was to update the clinical practice recommendations for the treatment of blood cholesterol levels to reduce atherosclerotic cardiovascular disease (ASCVD) risk using data from RCTs and systematic reviews. The panel could find no data supporting the routine use of nonstatin drugs combined with statin therapy to reduce further coronary events. There were no RCTs that assessed clinical outcomes in statin-intolerant patients. It was recommended based on expert opinion only that: Clinicians treating high-risk patients who have a less than anticipated response to statins, who are unable to tolerate a recommended intensity of a statin, or who are completely statin intolerant may consider the addition of a nonstatin cholesterol-lowering therapy. The panel also recommends (C recommendation; weak evidence) that if EPA and/or DHA are used for the management of severe hypertriglyceridemia, it is reasonable to evaluate the patient for gastrointestinal disturbances, skin changes, and bleeding.

On-going Randomized Clinical Trials Scan

The above reviews further the uncertainty of the effects of omega-3 fatty acids' role in the treatment of hypertriglyceridemia, prevention of stroke, sudden cardiac death and heart failure; being used in as adjunctive therapy for the treatment mood disorders such as major depression and bipolar disorders; and the prevention of cognitive decline and dementia in Alzheimer's patient and its possible role in cancer prevention. The following table summarizes the current on-going randomized clinical trials that might bring more evidence to current practice.

RCTs	Study Population	Number of Participants/Estimated Completion Date	Primary Endpoints
A *S*tudy of **C**ardiovascular **E**vents i**N** **D**iabetes (ASCEND)[78]	Type I or II diabetic subjects with no known vascular disease allocated to take either 100mg aspirin daily or placebo and 1 gram capsules containing naturally occurring omega-3 fatty acids or placebo capsules containing olive oil.	15,480/2017	"Log rank" analyses of serious vascular events during the scheduled treatment period (5-7 years) among all those allocated omega-3 fatty acid capsules versus all those allocated placebo capsules.
Reduction of Cardiovascular Events With EPA - Intervention Trial (REDUCE-IT)[79]	High risk patients with hypertriglyceridemia and on statin.	8,000/2016	Evaluate whether EPA, combined with a statin therapy, will be superior to the statin therapy alone, when used as a prevention in reducing long-term cardiovascular events measured as composite endpoint of CV death, MI, stroke, coronary revascularization, and hospitalization for unstable angina, in high-risk patients with mixed dyslipidemia.
Inositol and Omega-3 Fatty Acids in Pediatric Mania[80]	Children ages 6-12 years old with bipolar spectrum disorders.	60/2014	Improvement in mania symptoms by change in Young Mania Rating Scale (YMRS)
Omega 3 FA Supplements as Augmentation in the Treatment of Depression[81]	Adult patients with select medical conditions (cancer, cardiovascular diseases and diabetes). Patients were randomized to receive Omega 3 Fatty acid augmentation of desvenlafaxine (DVS) or placebo augmentation of DVS.	90/2015	Hospital Anxiety and Depression Scale

References

1. Larsson SC, Orsini N, Wolk A. Long-chain omega-3 polyunsaturated fatty acids and risk of stroke: a meta-analysis. *European Journal of Epidemiology*. 2012;27(12):895–901. doi:10.1007/s10654-012-9748-9.

2. Kotwal S, Jun M, Sullivan D, Perkovic V, Neal B. Omega 3 Fatty Acids and Cardiovascular Outcomes Systematic Review and Meta-Analysis. *Circ Cardiovasc Qual Outcomes*. 2012;5(6):808–818. doi:10.1161/CIRCOUTCOMES.112.966168.

3. Delgado-Lista J, Perez-Martinez P, Lopez-Miranda J, Perez-Jimenez F. Long chain omega-3 fatty acids and cardiovascular disease: a systematic review. *British Journal of Nutrition*. 2012;107(Supplement S2):S201–S213. doi:10.1017/S0007114512001596.

4. Kwak S, Myung S, Lee Y, Seo H, Korean Meta-analysis Study Group f. Efficacy of omega-3 fatty acid supplements (eicosapentaenoic acid and docosahexaenoic acid) in the secondary prevention of cardiovascular disease: A meta-analysis of randomized, double-blind, placebo-controlled trials. *Arch Intern Med*. 2012;172(9):686–694. doi:10.1001/archinternmed.2012.262.

5. Rizos EC, Ntzani EE, Bika E, Kostapanos MS, Elisaf MS. Association between omega-3 fatty acid supplementation and risk of major cardiovascular disease events: A systematic review and meta-analysis. *JAMA*. 2012;308(10):1024–1033. doi:10.1001/2012.jama.11374.

6. Leon H, Shibata MC, Sivakumaran S, Dorgan M, Chatterley T, Tsuyuki RT. Effect of fish oil on arrhythmias and mortality: systematic review. *BMJ*. 2008;337(dec23 2):a2931–a2931. doi:10.1136/bmj.a2931.

7. Liu T, Korantzopoulos P, Shehata M, Li G, Wang X, Kaul S. Prevention of atrial fibrillation with omega-3 fatty acids: a meta-analysis of randomised clinical trials. *Heart*. 2011;97(13):1034–1040. doi:10.1136/hrt.2010.215350.

8. Armaganijan L, Lopes RD, Healey JS, Piccini JP, Nair GM, Morillo CA. Do Omega-3 fatty acids prevent atrial fibrillation after open heart surgery? A meta-analysis of randomized controlled trials. *Clinics*. 2011;66(11):1923–1928. doi:10.1590/S1807-59322011001100012.

9. Xin W, Wei W, Li X. Effects of fish oil supplementation on cardiac function in chronic heart failure: a meta-analysis of randomised controlled trials. *Heart*. 2012;98(22):1620–1625. doi:10.1136/heartjnl-2012-302119.

10. Campbell F, Dickinson HO, Critchley JA, Ford GA, Bradburn M. A systematic review of fish-oil supplements for the prevention and treatment of hypertension. *European Journal of Preventive Cardiology*. 2013;20(1):107–120. doi:10.1177/2047487312437056.

11. Sydenham E, Dangour AD, Lim W-S. Omega 3 fatty acid for the prevention of cognitive decline and dementia. In: *Cochrane Database of Systematic Reviews*. John Wiley & Sons, Ltd; 1996. Available at: http://onlinelibrary.wiley.com.liboff.ohsu.edu/doi/10.1002/14651858.CD005379.pub3/abstract. Accessed September 9, 2013.

12. Mazereeuw G, Lanctôt KL, Chau SA, Swardfager W, Herrmann N. Effects of omega-3 fatty acids on cognitive performance: a meta-analysis. *Neurobiology of Aging*. 2012;33(7):1482.e17–1482.e29. doi:10.1016/j.neurobiolaging.2011.12.014.

13. Bloch MH, Hannestad J. Omega-3 fatty acids for the treatment of depression: systematic review and meta-analysis. *Mol Psychiatry*. 2012;17(12):1272–1282. doi:10.1038/mp.2011.100.

14. Sublette ME, Ellis SP, Geant AL, Mann JJ. Meta-Analysis of the Effects of Eicosapentaenoic Acid (EPA) in Clinical Trials in Depression. *The Journal of Clinical Psychiatry*. 2011;72(12):1577–1584. doi:10.4088/JCP.10m06634.

15. Appleton KM, Rogers PJ, Ness AR. Updated systematic review and meta-analysis of the effects of n−3 long-chain polyunsaturated fatty acids on depressed mood. *Am J Clin Nutr*. 2010;91(3):757–770. doi:10.3945/ajcn.2009.28313.

16. Ries A, Trottenberg P, Elsner F, et al. A systematic review on the role of fish oil for the treatment of cachexia in advanced cancer: An EPCRC cachexia guidelines project. *Palliat Med*. 2012;26(4):294–304. doi:10.1177/0269216311418709.

17. James MJ, Gibson RA, Cleland LG. Dietary polyunsaturated fatty acids and inflammatory mediator production. *Am J Clin Nutr*. 2000;71(1 Suppl):343S–8S.

18. Nettleton JA. Omega-3 fatty acids: comparison of plant and seafood sources in human nutrition. *J Am Diet Assoc*. 1991;91(3):331–337.

19. Masson S, Latini R, Tacconi M, Bernasconi R. Incorporation and washout of n-3 polyunsaturated fatty acids after diet supplementation in clinical studies. *J Cardiovasc Med (Hagerstown)*. 2007;8 Suppl 1:S4–10. doi:10.2459/01.JCM.0000289269.98105.65.

20. Vanden Heuvel JP. Diet, fatty acids, and regulation of genes important for heart disease. *Curr Atheroscler Rep*. 2004;6(6):432–440.

21. Clandinin MT, Cheema S, Field CJ, Garg ML, Venkatraman J, Clandinin TR. Dietary fat: exogenous determination of membrane structure and cell function. *FASEB J*. 1991;5(13):2761–2769.

22. Chang C-Y, Ke D-S, Chen J-Y. Essential fatty acids and human brain. *Acta Neurol Taiwan*. 2009;18(4):231–241.

23. Bang HO, Dyerberg J, Hjøorne N. The composition of food consumed by Greenland Eskimos. *Acta Med Scand*. 1976;200(1-2):69–73.

24. Bulliyya G. Fish intake and blood lipids in fish eating vs non-fish eating communities of coastal south India. *Clin Nutr*. 2000;19(3):165–170. doi:10.1054/clnu.1999.0092.

25. Kromhout D, Bosschieter EB, de Lezenne Coulander C. The inverse relation between fish consumption and 20-year mortality from coronary heart disease. *N Engl J Med*. 1985;312(19):1205–1209. doi:10.1056/NEJM198505093121901.

26. Engler MB. Vascular effects of omega-3 fatty acids: possible therapeutic mechanisms in cardiovascular disease. *J Cardiovasc Nurs*. 1994;8(3):53–67.

27. Yano K, MacLean CJ, Reed DM, et al. A comparison of the 12-year mortality and predictive factors of coronary heart disease among Japanese men in Japan and Hawaii. *Am J Epidemiol*. 1988;127(3):476–487.

28. Hooper L, Thompson RL, Harrison RA, et al. Risks and benefits of omega 3 fats for mortality, cardiovascular disease, and cancer: systematic review. *BMJ*. 2006;332(7544):752–760. doi:10.1136/bmj.38755.366331.2F.

29. Kromhout D, Giltay EJ, Geleijnse JM, Alpha Omega Trial Group. n-3 fatty acids and cardiovascular events after myocardial infarction. *N Engl J Med*. 2010;363(21):2015–2026. doi:10.1056/NEJMoa1003603.

30. Brouwer IA, Katan MB, Zock PL. Effects of n-3 fatty acids on arrhythmic events and mortality in the SOFA implantable cardioverter defibrillator trial. *Am J Clin Nutr*. 2006;84(6):1554; author reply 1554–1555.

31. Leaf A, Albert CM, Josephson M, et al. Prevention of fatal arrhythmias in high-risk subjects by fish oil n-3 fatty acid intake. *Circulation*. 2005;112(18):2762–2768. doi:10.1161/CIRCULATIONAHA.105.549527.

32. Risk and Prevention Study Collaborative Group, Roncaglioni MC, Tombesi M, et al. n-3 fatty acids in patients with multiple cardiovascular risk factors. *N Engl J Med*. 2013;368(19):1800–1808. doi:10.1056/NEJMoa1205409.

33. Duda MK, O'Shea KM, Stanley WC. omega-3 polyunsaturated fatty acid supplementation for the treatment of heart failure: mechanisms and clinical potential. *Cardiovasc Res*. 2009;84(1):33–41. doi:10.1093/cvr/cvp169.

34. Marchioli R, Silletta MG, Levantesi G, Pioggiarella R, Tognoni G. N-3 polyunsaturated fatty acids in heart failure: mechanisms and recent clinical evidence. *Cell Mol Biol (Noisy-le-grand)*. 2010;56(1):110–130.

35. Kang JX, Leaf A. Protective effects of free polyunsaturated fatty acids on arrhythmias induced by lysophosphatidylcholine or palmitoylcarnitine in neonatal rat cardiac myocytes. *Eur J Pharmacol*. 1996;297(1-2):97–106.

36. Kang JX, Leaf A. Antiarrhythmic effects of polyunsaturated fatty acids. Recent studies. *Circulation*. 1996;94(7):1774–1780.

37. Zhao YT, Shao L, Teng LL, et al. Effects of n-3 polyunsaturated fatty acid therapy on plasma inflammatory markers and N-terminal pro-brain natriuretic peptide in elderly patients with chronic heart failure. *J Int Med Res*. 2009;37(6):1831–1841.

38. Nodari S, Triggiani M, Campia U, et al. Effects of n-3 polyunsaturated fatty acids on left ventricular function and functional capacity in patients with dilated cardiomyopathy. *J Am Coll Cardiol*. 2011;57(7):870–879. doi:10.1016/j.jacc.2010.11.017.

39. Skou HA, Toft E, Christensen JH, Hansen JB, Dyerberg J, Schmidt EB. N-3 fatty acids and cardiac function after myocardial infarction in Denmark. *Int J Circumpolar Health*. 2001;60(3):360–365.

40. Radaelli A, Cazzaniga M, Viola A, et al. Enhanced baroreceptor control of the cardiovascular system by polyunsaturated Fatty acids in heart failure patients. *J Am Coll Cardiol*. 2006;48(8):1600–1606. doi:10.1016/j.jacc.2006.05.073.

41. Ghio S, Scelsi L, Latini R, et al. Effects of n-3 polyunsaturated fatty acids and of rosuvastatin on left ventricular function in chronic heart failure: a substudy of GISSI-HF trial. *Eur J Heart Fail*. 2010;12(12):1345–1353. doi:10.1093/eurjhf/hfq172.

42. Moertl D, Hammer A, Steiner S, Hutuleac R, Vonbank K, Berger R. Dose-dependent effects of omega-3-polyunsaturated fatty acids on systolic left ventricular function, endothelial function, and markers of inflammation in chronic heart failure of nonischemic origin: a double-blind, placebo-controlled, 3-arm study. *Am Heart J*. 2011;161(5):915.e1–9. doi:10.1016/j.ahj.2011.02.011.

43. Nodari S, Metra M, Milesi G, et al. The role of n-3 PUFAs in preventing the arrhythmic risk in patients with idiopathic dilated cardiomyopathy. *Cardiovasc Drugs Ther*. 2009;23(1):5–15. doi:10.1007/s10557-008-6142-7.

44. Calò L, Bianconi L, Colivicchi F, et al. N-3 Fatty acids for the prevention of atrial fibrillation after coronary artery bypass surgery: a randomized, controlled trial. *J Am Coll Cardiol*. 2005;45(10):1723–1728. doi:10.1016/j.jacc.2005.02.079.

45. Saravanan P, Bridgewater B, West AL, O'Neill SC, Calder PC, Davidson NC. Omega-3 fatty acid supplementation does not reduce risk of atrial fibrillation after coronary artery bypass surgery: a randomized, double-blind, placebo-controlled clinical trial. *Circ Arrhythm Electrophysiol*. 2010;3(1):46–53. doi:10.1161/CIRCEP.109.899633.

46. Mariscalco G, Sarzi Braga S, Banach M, et al. Preoperative n-3 polyunsatured fatty acids are associated with a decrease in the incidence of early atrial fibrillation following cardiac surgery. *Angiology*. 2010;61(7):643–650. doi:10.1177/0003319710370962.

47. Heidt MC, Vician M, Stracke SKH, et al. Beneficial effects of intravenously administered N-3 fatty acids for the prevention of atrial fibrillation after coronary artery bypass surgery: a prospective randomized study. *Thorac Cardiovasc Surg*. 2009;57(5):276–280. doi:10.1055/s-0029-1185301.

48. Heidarsdottir R, Arnar DO, Skuladottir GV, et al. Does treatment with n-3 polyunsaturated fatty acids prevent atrial fibrillation after open heart surgery? *Europace*. 2010;12(3):356–363. doi:10.1093/europace/eup429.

49. Nelson NJ. Migrant studies aid the search for factors linked to breast cancer risk. *J Natl Cancer Inst*. 2006;98(7):436–438. doi:10.1093/jnci/djj147.

50. Gerber M. Background Review Paper on Total Fat, Fatty Acid Intake and Cancers. *Annals of Nutrition and Metabolism*. 2009;55(1-3):140–161. doi:10.1159/000229000.

51. Dewailly E, Mulvad G, Sloth Pedersen H, Hansen JC, Behrendt N, Hart Hansen JP. Inuit are protected against prostate cancer. *Cancer Epidemiol Biomarkers Prev*. 2003;12(9):926–927.

52. Nutting PA, Freeman WL, Risser DR, et al. Cancer incidence among American Indians and Alaska Natives, 1980 through 1987. *Am J Public Health*. 1993;83(11):1589–1598.

53. Lukiw WJ, Bazan NG. Docosahexaenoic Acid and the Aging Brain. *J Nutr*. 2008;138(12):2510–2514. doi:10.3945/jn.108.096016.

54. Grant WB. Dietary Links to Alzheimer's Disease: 1999 Update. *Journal of Alzheimer's Disease*. 1999;1(4):197–201.

55. Graves AB, Rajaram L, Bowen JD, McCormick WC, McCurry SM, Larson EB. Cognitive decline and Japanese culture in a cohort of older Japanese Americans in King County, WA: the Kame Project. *J Gerontol B Psychol Sci Soc Sci*. 1999;54(3):S154–161.

56. Hibbeln JR. Fish consumption and major depression. *Lancet*. 1998;351(9110):1213. doi:10.1016/S0140-6736(05)79168-6.

57. Tanskanen A, Hibbeln JR, Hintikka J, Haatainen K, Honkalampi K, Viinamäki H. Fish consumption, depression, and suicidality in a general population. *Arch Gen Psychiatry*. 2001;58(5):512–513.

58. Marangell LB, Martinez JM, Zboyan HA, Kertz B, Kim HFS, Puryear LJ. A double-blind, placebo-controlled study of the omega-3 fatty acid docosahexaenoic acid in the treatment of major depression. *Am J Psychiatry*. 2003;160(5):996–998.

59. Grenyer BFS, Crowe T, Meyer B, et al. Fish oil supplementation in the treatment of major depression: a randomised double-blind placebo-controlled trial. *Prog Neuropsychopharmacol Biol Psychiatry*. 2007;31(7):1393–1396. doi:10.1016/j.pnpbp.2007.06.004.

60. Silvers KM, Woolley CC, Hamilton FC, Watts PM, Watson RA. Randomised double-blind placebo-controlled trial of fish oil in the treatment of depression. *Prostaglandins Leukot Essent Fatty Acids*. 2005;72(3):211–218. doi:10.1016/j.plefa.2004.11.004.

61. Zargar A, Ito MK. Long chain omega-3 dietary supplements: a review of the National Library of Medicine Herbal Supplement Database. *Metab Syndr Relat Disord*. 2011;9(4):255–271. doi:10.1089/met.2011.0004.

62. Grimsgaard S, Bonaa KH, Hansen JB, Nordøy A. Highly purified eicosapentaenoic acid and docosahexaenoic acid in humans have similar triacylglycerol-lowering effects but divergent effects on serum fatty acids. *Am J Clin Nutr*. 1997;66(3):649–659.

63. Grimsgaard S, Bønaa KH, Hansen JB, Myhre ES. Effects of highly purified eicosapentaenoic acid and docosahexaenoic acid on hemodynamics in humans. *Am J Clin Nutr*. 1998;68(1):52–59.

64. Woodman RJ, Mori TA, Burke V, Puddey IB, Watts GF, Beilin LJ. Effects of purified eicosapentaenoic and docosahexaenoic acids on glycemic control, blood pressure, and serum lipids in type 2 diabetic patients with treated hypertension. *Am J Clin Nutr*. 2002;76(5):1007–1015.

65. Wei MY, Jacobson TA. Effects of eicosapentaenoic acid versus docosahexaenoic acid on serum lipids: a systematic review and meta-analysis. *Curr Atheroscler Rep*. 2011;13(6):474–483. doi:10.1007/s11883-011-0210-3.

66. Jacobson TA, Glickstein SB, Rowe JD, Soni PN. Effects of eicosapentaenoic acid and docosahexaenoic acid on low-density lipoprotein cholesterol and other lipids: a review. *J Clin Lipidol*. 2012;6(1):5–18. doi:10.1016/j.jacl.2011.10.018.

67. Gerber M. Omega-3 fatty acids and cancers: a systematic update review of epidemiological studies. *British Journal of Nutrition*. 2012;107(Supplement S2):S228–S239. doi:10.1017/S0007114512001614.

68. Szymanski KM, Wheeler DC, Mucci LA. Fish consumption and prostate cancer risk: a review and meta-analysis. *Am J Clin Nutr*. 2010;92(5):1223–1233. doi:10.3945/ajcn.2010.29530.

69. Ortega RM, Rodríguez-Rodríguez E, López-Sobaler AM. Effects of omega 3 fatty acids supplementation in behavior and non-neurodegenerative neuropsychiatric disorders. *British Journal of Nutrition*. 2012;107(Supplement S2):S261–S270. doi:10.1017/S000711451200164X.

70. Sarris J, Mischoulon D, Schweitzer I. Adjunctive nutraceuticals with standard pharmacotherapies in bipolar disorder: a systematic review of clinical trials. *Bipolar Disorders*. 2011;13(5-6):454–465. doi:10.1111/j.1399-5618.2011.00945.x.

71. Turnbull T, Cullen-Drill M, Smaldone A. Efficacy of Omega-3 Fatty Acid Supplementation on Improvement of Bipolar Symptoms: A Systematic Review. *Archives of Psychiatric Nursing*. 2008;22(5):305–311. doi:10.1016/j.apnu.2008.02.011.

72. McMurray JJV, Adamopoulos S, Anker SD, et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012 The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. *Eur Heart J*. 2012;33(14):1787–1847. doi:10.1093/eurheartj/ehs104.

73. GISSI-HF investigators. Effect of n-3 polyunsaturated fatty acids in patients with chronic heart failure (the GISSI-HF trial): a randomised, double-blind, placebo-controlled trial. *The Lancet*. 4;372(9645):1223–1230. doi:10.1016/S0140-6736(08)61239-8.

74. Jiménez Jiménez FJ, Cervera Montes M, Blesa Malpica AL. Guidelines for specialized nutritional and metabolic support in the critically-ill patient: Update. Consensus SEMICYUC-SENPE: Cardiac patient. *Nutrición Hospitalaria*. 2011;26:76–80.

75. Miller M, Stone NJ, Ballantyne C, et al. Triglycerides and Cardiovascular Disease: A Scientific Statement From the American Heart Association. *Circulation*. 2011;123(20):2292–2333. doi:10.1161/CIR.0b013e3182160726.

76. Ravindran AV, Lam RW, Filteau MJ, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) Clinical guidelines for the management of major depressive disorder in adults.: V. Complementary and alternative medicine treatments. *Journal of Affective Disorders*. 2009;117, Supplement 1:S54–S64. doi:10.1016/j.jad.2009.06.040.

77. Stone NJ, Robinson J, Lichtenstein AH, et al. 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2013. doi:10.1161/01.cir.0000437738.63853.7a.

78. ASCEND. A Study of Cardiovascular Events in Diabetes. Available at: http://www.ctsu.ox.ac.uk/ascend/. Accessed November 25, 2013.

79. A Study of AMR101 to Evaluate Its Ability to Reduce Cardiovascular Events in High Risk Patients With Hypertriglyceridemia and on Statin. The Primary Objective is to Evaluate the Effect of 4 g/Day AMR101 for Preventing the Occurrence of a First Major Cardiovascular Event. - Full Text View - ClinicalTrials.gov. Available at: http://clinicaltrials.gov/ct2/show/NCT01492361?term=REDUCE-IT&rank=1. Accessed December 5, 2013.

80. ClinicalTrials.Gov. Inositol and Omega-3 Fatty Acids in Pediatric Mania - Full Text View - ClinicalTrials.gov. Available at: http://clinicaltrials.gov/ct2/show/study/NCT01396486?term=fish+oil+randomized+control+trials&no_unk=Y&type=Intr&rank=40. Accessed November 25, 2013.

81. ClinicalTrials.Gov. Omega 3 FA Supplements as Augmentation in the Treatment of Depression - Full Text View - ClinicalTrials.gov. Available at: http://clinicaltrials.gov/ct2/show/NCT01803711?term=fish+oil+randomized+control+trials&no_unk=Y&type=Intr&rank=64. Accessed November 25, 2013.

Appendix A: Abstract of Systematic Reviews

1. **Omega 3 Fatty acids and cardiovascular outcomes: systematic review and meta-analysis.** Kotwal S, Jun M, Sullivan D, Perkovic V, Neal B. *Circ Cardiovasc Qual Outcomes*. 2012;5(6):808–818. doi:10.1161/CIRCOUTCOMES.112.966168.

   Abstract

   BACKGROUND: Early trials evaluating the effect of omega 3 fatty acids (ω-3 FA) reported benefits for mortality and cardiovascular events but recent larger studies trials have variable findings. We assessed the effects of ω-3 FA on cardiovascular and other important clinical outcomes.

   METHODS AND RESULTS: We searched MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials for all randomized studies using dietary supplements, dietary interventions, or both. The primary outcome was a composite of cardiovascular events (mostly myocardial infarction, stroke, and cardiovascular death). Secondary outcomes were arrhythmia, cerebrovascular events, hemorrhagic stroke, ischemic stroke, coronary revascularization, heart failure, total mortality, nonvascular mortality, and end-stage kidney disease. Twenty studies including 63030 participants were included. There was no overall effect of ω-3 FA on composite cardiovascular events (relative risk [RR]=0.96; 95% confidence interval [CI], 0.90-1.03; P=0.24) or on total mortality (RR=0.95; 95% CI, 0.86-1.04; P=0.28). ω-3 FA did protect against vascular death (RR=0.86; 95% CI, 0.75-0.99; P=0.03) but not coronary events (RR=0.86; 95% CI, 0.67-1.11; P=0.24). There was no effect on arrhythmia (RR=0.99; 95% CI, 0.85-1.16; P=0.92) or cerebrovascular events (RR=1.03; 95% CI, 0.92-1.16; P=0.59). Adverse events were more common in the treatment group than the placebo group (RR=1.18, 95% CI, 1.02-1.37; P=0.03), predominantly because of an excess of gastrointestinal side effects.

   CONCLUSIONS: ω-3 FA may protect against vascular disease, but the evidence is not clear-cut, and any benefits are almost certainly not as great as previously believed.

2. **Efficacy of omega-3 fatty acid supplements (eicosapentaenoic acid and docosahexaenoic acid) in the secondary prevention of cardiovascular disease: a meta-analysis of randomized, double-blind, placebo-controlled trials**. Kwak SM, Myung SK, Lee YJ, Seo HG; Korean Meta-analysis Study Group**.** *Arch Intern Med*. 2012;172(9):686–694. doi:10.1001/archinternmed.2012.262.

   Abstract

   BACKGROUND: Although previous randomized, double-blind, placebo-controlled trials reported the efficacy of omega-3 fatty acid supplements in the secondary prevention of cardiovascular disease (CVD), the evidence remains inconclusive. Using a meta-analysis, we investigated the efficacy of eicosapentaenoic acid and docosahexaenoic acid in the secondary prevention of CVD.

   METHODS: We searched PubMed, EMBASE, and the Cochrane Library in April 2011. Two of us independently reviewed and selected eligible randomized controlled trials.

   RESULTS: Of 1007 articles retrieved, 14 randomized, double-blind, placebo-controlled trials (involving 20 485 patients with a history of CVD) were included in the final analyses. Supplementation with omega-3 fatty acids did not reduce the risk of overall cardiovascular events (relative risk, 0.99; 95% CI, 0.89-1.09), all-cause mortality, sudden cardiac death, myocardial infarction, congestive heart failure, or transient ischemic attack and stroke. There was a small reduction in cardiovascular death (relative risk, 0.91; 95% CI, 0.84-0.99), which disappeared when we excluded a study with major methodological problems. Furthermore, no significant preventive effect

was observed in subgroup analyses by the following: country location, inland or coastal geographic area, history of CVD, concomitant medication use, type of placebo material in the trial, methodological quality of the trial, duration of treatment, dosage of eicosapentaenoic acid or docosahexaenoic acid, or use of fish oil supplementation only as treatment.

CONCLUSION: Our meta-analysis showed insufficient evidence of a secondary preventive effect of omega-3 fatty acid supplements against overall cardiovascular events among patients with a history of cardiovascular disease.

3. **Association between omega-3 fatty acid supplementation and risk of major cardiovascular disease events: a systematic review and meta-analysis.** Rizos EC, Ntzani EE, Bika E, Kostapanos MS, Elisaf MS. *JAMA*. 2012;308(10):1024–1033. doi:10.1001/2012.jama.11374.

Abstract

CONTEXT: Considerable controversy exists regarding the association of omega-3 polyunsaturated fatty acids (PUFAs) and major cardiovascular end points.

OBJECTIVE: To assess the role of omega-3 supplementation on major cardiovascular outcomes.

DATA SOURCES: MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials through August 2012.

STUDY SELECTION: Randomized clinical trials evaluating the effect of omega-3 on all-cause mortality, cardiac death, sudden death, myocardial infarction, and stroke.

DATA EXTRACTION: Descriptive and quantitative information was extracted; absolute and relative risk (RR) estimates were synthesized under a random-effects model. Heterogeneity was assessed using the Q statistic and I2. Subgroup analyses were performed for the presence of blinding, the prevention settings, and patients with implantable cardioverter-defibrillators, and meta-regression analyses were performed for the omega-3 dose. A statistical significance threshold of .0063 was assumed after adjustment for multiple comparisons.

DATA SYNTHESIS: Of the 3635 citations retrieved, 20 studies of 68,680 patients were included, reporting 7044 deaths, 3993 cardiac deaths, 1150 sudden deaths, 1837 myocardial infarctions, and 1490 strokes. No statistically significant association was observed with all-cause mortality (RR, 0.96; 95% CI, 0.91 to 1.02; risk reduction [RD] -0.004, 95% CI, -0.01 to 0.02), cardiac death (RR, 0.91; 95% CI, 0.85 to 0.98; RD, -0.01; 95% CI, -0.02 to 0.00), sudden death (RR, 0.87; 95% CI, 0.75 to 1.01; RD, -0.003; 95% CI, -0.012 to 0.006), myocardial infarction (RR, 0.89; 95% CI, 0.76 to 1.04; RD, -0.002; 95% CI, -0.007 to 0.002), and stroke (RR, 1.05; 95% CI, 0.93 to 1.18; RD, 0.001; 95% CI, -0.002 to 0.004) when all supplement studies were considered.

CONCLUSION: Overall, omega-3 PUFA supplementation was not associated with a lower risk of all-cause mortality, cardiac death, sudden death, myocardial infarction, or stroke based on relative and absolute measures of association.

4. **Long chain omega-3 fatty acids and cardiovascular disease: a systematic review.** Delgado-Lista J, Perez-Martinez P, Lopez-Miranda J, Perez-Jimenez F. *British Journal of Nutrition*. 2012;107(Supplement S2):S201–S213. doi:10.1017/S0007114512001596.

Abstract

Introduction: Cardiovascular disease remains the commonest health problem in developed countries, and residual risk after implementing all current therapies is still high. The use of marine omega-3 fatty acids (DHA and EPA) has been recommended to reduce cardiovascular risk by multiple mechanisms.

Objectives: To update the current evidence on the influence of omega-3 on the rate of cardiovascular events.

Review Methods: We used the MEDLINE and EMBASE databases to identify clinical trials and randomized controlled trials of omega-3 fatty acids (with quantified quantities) either in capsules or in dietary intake, compared to placebo or usual diet, equal to or longer than 6 months, and written in English. The primary outcome was a cardiovascular event of any kind and secondary outcomes were all-cause mortality, cardiac death and coronary events. We used RevMan 5·1 (Mantel-Haenszel method). Heterogeneity was assessed by the I2 and Chi2 tests. We included 21 of the 452 pre-selected studies.

Results: We found an overall decrease of risk of suffering a cardiovascular event of any kind of 10 % (OR 0·90; [0·85-0·96], p = 0·001), a 9 % decrease of risk of cardiac death (OR 0·91; [0·83-0·99]; p = 0·03), a decrease of coronary events (fatal and non-fatal) of 18 % (OR 0·82; [0·75-0·90]; $p < 1 \times 10^{-4}$), and a trend to lower total mortality (5 % reduction of risk; OR 0·95; [0·89-1·02]; p = 0·15. Most of the studies analyzed included persons with high cardiovascular risk.

Conclusions: marine omega-3 fatty acids are effective in preventing cardiovascular events, cardiac death and coronary events, especially in persons with high cardiovascular risk.

5. **Effect of fish oil on arrhythmias and mortality: systematic review.** León H, Shibata MC, Sivakumaran S, Dorgan M, Chatterley T, Tsuyuki RT. *BMJ*. 2008;337(dec23 2):a2931–a2931. doi:10.1136/bmj.a2931.

Abstract

OBJECTIVE: To synthesise the literature on the effects of fish oil-docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA)-on mortality and arrhythmias and to explore dose response and formulation effects.

DESIGN: Systematic review and meta-analysis.

DATA SOURCES: Medline, Embase, the Cochrane Library, PubMed, CINAHL, IPA, Web of Science, Scopus, Pascal, Allied and Complementary Medicine, Academic OneFile, ProQuest Dissertations and Theses, Evidence-Based Complementary Medicine, and LILACS. Studies reviewed Randomised controlled trials of fish oil as dietary supplements in humans.

DATA EXTRACTION: The primary outcomes of interest were the arrhythmic end points of appropriate implantable cardiac defibrillator intervention and sudden cardiac death. The secondary outcomes were all cause mortality and death from cardiac causes. Subgroup analyses included the effect of formulations of EPA and DHA on death from cardiac causes and effects of fish oil in patients with coronary artery disease or myocardial infarction.

DATA SYNTHESIS: 12 studies totalling 32 779 patients met the inclusion criteria. A neutral effect was reported in three studies (n=1148) for appropriate implantable cardiac defibrillator intervention (odds ratio 0.90, 95% confidence interval 0.55 to 1.46) and in six studies (n=31 111) for sudden cardiac death (0.81, 0.52 to 1.25). 11 studies (n=32 439 and n=32 519) provided data on the effects of fish oil on all cause mortality (0.92, 0.82 to 1.03) and a reduction in deaths from cardiac causes (0.80, 0.69 to 0.92). The dose-response relation for DHA and EPA on reduction in deaths from cardiac causes was not significant.

CONCLUSIONS: Fish oil supplementation was associated with a significant reduction in deaths from cardiac causes but had no effect on arrhythmias or all cause mortality. Evidence to recommend an optimal formulation of EPA or DHA to reduce these outcomes is insufficient. Fish oils are a heterogeneous product, and the optimal formulations for DHA and EPA remain unclear.

6. **Prevention of atrial fibrillation with omega-3 fatty acids: a meta-analysis of randomised clinical trials**. Liu T, Korantzopoulos P, Shehata M, Li G, Wang X, Kaul S. *Heart*. 2011;97(13):1034–1040. doi:10.1136/hrt.2010.215350.

Abstract

CONTEXT: Previous randomised controlled trials (RCT) regarding n-3 PUFA supplementation for atrial fibrillation (AF) prevention have yielded conflicting results.

OBJECTIVE: A systematic review and meta-analysis of RCT was conducted to examine the role of n-3 PUFA in AF prevention.

DATA SOURCES: MEDLINE, Web of Science and Cochrane clinical trials database were searched until November 2010.

STUDY SELECTION: Of 127 initially identified studies, 10 RCT with 1955 patients were finally analysed.

DATA EXTRACTION: Two blinded reviewers extracted data independently to a predefined form. Disagreements were resolved through discussion and consensus.

RESULTS: n-3 PUFA had no significant effect on the prevention of AF (OR 0.81, 95% CI 0.57 to 1.15; p=0.24). There was significant heterogeneity among the studies (p=0.002, I(2)=65.0%). Subgroup analysis showed no significant beneficial effect of fish oils in any subset of population.

CONCLUSIONS: No significant effects of n-3 PUFA supplementation on AF prevention were observed in this meta-analysis. A large-scale trial with higher doses and longer follow-up might be required to rule out the possibility of any treatment benefit.

7. **Do omega-3 fatty acids prevent atrial fibrillation after open heart surgery? A meta-analysis of randomized controlled trials.** Armaganijan L, Lopes RD, Healey JS, Piccini JP, Nair GM, Morillo CA. *Clinics*. 2011;66(11):1923–1928. doi:10.1590/S1807-59322011001100012.

Abstract

OBJECTIVES: N-3 polyunsaturated fatty acids have been proposed as a novel treatment for preventing postoperative atrial fibrillation due to their potential anti-inflammatory and anti-arrhythmic effects. However, randomized studies have yielded conflicting results. The objective of this study is to review randomized trials of N-3 polyunsaturated fatty acid use for postoperative atrial fibrillation.

METHODS: Using the CENTRAL, PUBMED, EMBASE, and LILACS databases, a literature search was conducted to identify all of the studies in human subjects that reported the effects of N-3 polyunsaturated fatty acids on the prevention of postoperative atrial fibrillation in cardiac surgery patients. The final search was performed on January 30, 2011. There was no language restriction, and the search strategy only involved terms for N-3 polyunsaturated fatty acids (or fish oil), atrial fibrillation, and cardiac surgery. To be included, the studies had to be randomized (open or blinded), and the enrolled patients had to be ≥18 years of age.

RESULTS: Four randomized studies (three double-blind, one open-label) that enrolled 538 patients were identified. The patients were predominantly male, the mean age was 62.3 years, and most of the patients exhibited a normal left atrial size and ejection fraction. N-3 polyunsaturated fatty acid use was not associated with a reduction in postoperative atrial fibrillation. Similar results were observed when the open-label study was excluded.

CONCLUSIONS: There is insufficient evidence to suggest that treatment with N-3 polyunsaturated fatty acids reduces postoperative atrial fibrillation. Therefore, their routine use in patients undergoing cardiac surgery is not recommended.

8. **Effects of fish oil supplementation on cardiac function in chronic heart failure: a meta-analysis of randomised controlled trials.** Xin W, Wei W, Li X. *Heart*. 2012;98(22):1620–1625. doi:10.1136/heartjnl-2012-302119.

Abstract

CONTEXT: The effects of fish oil on cardiac function, ventricular remodelling and functional capacity in patients with chronic heart failure (CHF) remain controversial.

OBJECTIVE: The aim of this meta-analysis was to evaluate effects of fish oil on cardiac function and related parameters in CHF patients.

DATA SOURCES: Medline, Embase, the Cochrane Library and references cited in related reviews and studies.

STUDY SELECTION: Randomised controlled trials of fish oil supplementation on cardiac function in patients with CHF were identified.

DATA EXTRACTION: Two investigators read all papers and extracted all relevant information. A fixed effect or, in the presence of heterogeneity, a random effect model, was used to estimate the combined effects.

RESULTS: 7 trials with 825 participants were included. Meta-analysis results showed that left ventricular ejection fraction was significantly increased (weighted mean difference (WMD) = 2.25%, 95% CI 0.66 to 3.83, p = 0.005) and left ventricular end-systolic volume was significantly decreased (WMD = 7.85 ml, 95% CI -15.57 to -0.12, p = 0.05) in the fish oil group compared with the placebo group, although left ventricular end-diastolic volume was not significantly affected. Meta-regression and subgroup analysis indicated that the improvement in left ventricular systolic function was more remarkable in patients with nonischaemic heart failure. Fish oil supplementation also improved the New York Heart Association functional classification and peak oxygen consumption in patients with non-ischaemic heart failure.

CONCLUSIONS: Improvement in cardiac function, remodelling and functional capacity may be important mechanisms underlying the potential therapeutic role of fish oil for patients with CHF. These effects might be more remarkable in patients with non-ischaemic heart failure.

9. **A systematic review of fish-oil supplements for the prevention and treatment of hypertension.** Campbell F, Dickinson HO, Critchley JA, Ford GA, Bradburn M. *European Journal of Preventive Cardiology*. 2013;20(1):107–120. doi:10.1177/2047487312437056.

Abstract

AIMS: Fish oils are widely believed to promote cardiovascular health by lowering blood pressure (BP) but the evidence supporting this is not conclusive. We aimed to systematically review existing evidence.

METHOD: We undertook a systematic review of randomized controlled trials and crossover trials that evaluated the effectiveness of fish-oil supplements. We included trials enrolling adults who were given fish-oil supplements with at least 8 weeks' follow up. Effects on systolic and diastolic BP were assessed using meta-analysis. Meta-regression was undertaken to explore the relationship between dose of fish oil and BP outcomes.

RESULTS: We included 17 studies, with a total of 1524 participants. We explored the effects of fish-oil supplements in both normotensive and hypertensive participants with BP 140/85 mmHg at least. Meta-analyses were performed using the inverse-variance method. Data from eight studies in hypertensive participants found a statistically significant reduction in systolic and diastolic BP; 2.56 mmHg (95% CI 0.58 to 4.53) and 1.47 mmHg (95% CI 0.41 to 2.53), respectively. Nine studies in normotensive participants showed a non-significant reduction in both systolic and diastolic BP. Meta-regression showed no significant relationship between dose of fish oil and the effect on BP.

CONCLUSION: The small but statistically significant effects of fish-oil supplements in hypertensive participants in this review have important implications for population health and lowering the risk of stroke and ischaemic heart disease. Their modest effects, however, mean that they should not be recommended as an alternative to BP-lowering drugs where guidelines recommend treatment.

10. **Long-chain omega-3 polyunsaturated fatty acids and risk of stroke: a meta-analysis**. Larsson SC, Orsini N, Wolk A. *European Journal of Epidemiology*. 2012;27(12):895–901. doi:10.1007/s10654-012-9748-9.

Abstract

Prospective studies of long-chain omega-3 polyunsaturated fatty acids (PUFA) in relation to stroke have yielded inconsistent results. The authors conducted a meta-analysis of prospective studies to summarize available evidence regarding the relation between long-chain omega-3 PUFA intake and stroke. Pertinent studies were identified by searching PubMed and Embase databases to November 1, 2012 and by reviewing the reference lists of relevant publications. Prospective studies that provided relative risks (RRs) with 95 % confidence intervals (CIs) for the association between dietary long-chain omega-3 PUFA intake and stroke were eligible. A random-effects model was used to combine study-specific results. Eight prospective studies, with 5238 stroke events among 242,076 participants, were included in the meta-analysis. The combined RR of total stroke was 0.90 (95 % CI, 0.81-1.01) for the highest versus lowest category of long-chain omega-3 PUFA intake, without heterogeneity among studies (P = 0.32). Results were similar for ischemic (RR, 0.82; 95 % CI, 0.71-0.94) and hemorrhagic stroke (RR, 0.80; 95 % CI, 0.55-1.15). A statistically significant reduction in total stroke risk was observed in women (RR, 0.80; 95 % CI, 0.65-0.99). This meta-analysis showed no overall association between omega-3 PUFA intake and stroke, but suggests that women might benefit from a higher intake of these PUFAs.

11. **Adjunctive nutraceuticals with standard pharmacotherapies in bipolar disorder: a systematic review of clinical trials**
Sarris, J., Mischoulon, D. and Schweitzer, I. (2011), Adjunctive nutraceuticals with standard pharmacotherapies in bipolar disorder: a systematic review of clinical trials. Bipolar Disorders, 13: 454–465. doi: 10.1111/j.1399-5618.2011.00945.x

Objective: Studies using augmentation of pharmacotherapies with nutraceuticals in bipolar disorder (BD) have been conducted and preliminary evidence in many cases appears positive. To date, however, no specialized systematic review of this area has been conducted. We present the first systematic review of clinical trials using nutrient-based nutraceuticals in combination with standard pharmacotherapies to treat BD. A subsequent aim of this report was to discuss posited underlying mechanisms of action.

Methods: PubMed, CINAHL, Web of Science, and Cochrane Library databases, and grey literature were searched during mid-2010 for human clinical trials in English using nutraceuticals such as omega-3, N-acetyl cysteine (NAC), inositol, and vitamins and minerals, in combination with pharmacotherapies to treat bipolar mania and bipolar depression. A review of the results including an effect size analysis (Cohen's *d*) was subsequently conducted.

Results: In treating bipolar depression, positive evidence with large effect sizes were found for NAC (*d* = 1.04) and a chelated mineral and vitamin formula (*d* = 1.70). On the outcome of bipolar mania, several nutraceuticals reduced mania with strong clinical effects: a chelated mineral formula (*d* = 0.83), L-tryptophan (*d* = 1.47), magnesium (*d* = 1.44), folic acid (*d* = 0.40), and branched-chain amino acids (*d* = 1.60). Mixed, but mainly positive, evidence was found for omega-3 for bipolar depression, while no evidentiary support was found for use in mania. No significant effect on BD outcome scales was found for inositol (possibly due to small samples).

Conclusions: BD treatment outcomes may potentially be improved by additional use of certain nutraceuticals with conventional pharmacotherapies. However, caution should be extended in interpreting the large effects of several isolated studies, as they have not yet been replicated in larger trials.

12. **Efficacy of Omega-3 Fatty Acid Supplementation on Improvement of Bipolar Symptoms: A Systematic Review.**
Teresa Turnbull, Mary Cullen-Drill, and Arlene Smaldone; *Archives of Psychiatric Nursing*. 2008;22(5):305–311. doi:10.1016/j.apnu.2008.02.011.

Abstract

The purpose of this review was to examine the current level of evidence regarding the efficacy of omega-3 fatty acid supplementation in improving bipolar disorder symptoms. Of 99 articles meeting initial search criteria, 5 randomized control trials and 2 quasi-experimental studies were selected for review. Omega-3 fatty acid supplementation was effective in 4 of 7 studies. Those using an omega-3 combination of eicosapentaenoic acid and docosahexanoic acid demonstrated a statistically significant improvement in bipolar symptoms, whereas those using a single constituent did not. Dosage variations did not demonstrate statistically significant differences. Due to its benign side effect profile and some evidence supporting its usefulness in bipolar illness, omega-3 may be a helpful adjunct in treatment of selected patients. Future studies are needed to conclusively confirmthe efficacy of omega-3s in bipolar disorder, uncovering a newwell-tolerated treatment option.

13. **Effects of omega 3 fatty acids supplementation in behavior and non-neurodegenerative neuropsychiatric disorders.** R. M. Ortega[a1a2] [c1], E. Rodríguez-Rodríguez[a2a3] and A. M. López-Sobaler; British Journal of Nutrition / Volume 107 / Supplement S2 / June 2012, pp S261-S270; Published online: 17 May 2012

Abstract

This work provides a systematic review of all published randomised, controlled clinical trials (RCT) investigating the effects of *n*-3 PUFA intake on the prevention and treatment of non-neurodegenerative neuropsychiatric disorders. Five databases (PubMed, EMBASE, LILACS, CINAHL and The Cochrane Database) were searched for RCT in this area published up to April 2011. The selected studies all involved human participants and included a comparison group. Thirty eight studies were identified, which examined the influence of *n*-3 PUFA supplementation on the prevention/treatment of depression (non-perinatal) (*n* 23), perinatal depression (*n* 6) and attention deficit hyperactivity disorder (ADHD) (*n* 9). Great heterogeneity was noticed in terms of study design, the doses of *n*-3 PUFA administered, and study duration. Some benefit was noted with respect to the treatment of hyperactivity and depression in over half the examined studies, although the evidence was not conclusive. For any firm conclusions to be drawn, further studies will be needed that take into account the initial *n*-3 PUFA status of the subjects. Excessive *n*-3 PUFA intakes might be associated with a greater risk of peroxidation events and therefore neuropsychiatric deterioration. Indeed, some studies only recorded benefits when lower doses were administered. It is therefore important that the dose required to achieve any potential benefit be determined.

14. **Omega-3 fatty acids for the treatment of depression: systematic review and meta-analysis.** Bloch MH, Hannestad J. Omega-3 fatty acids for the treatment of depression: systematic review and meta-analysis. *Mol Psychiatry*. 2012;17(12):1272–1282. doi:10.1038/mp.2011.100.

Abstract

We conducted a meta-analysis of randomized, placebo-controlled trials of omega-3 fatty acid (FA) treatment of major depressive disorder (MDD) in order to determine efficacy and to examine sources of heterogeneity between trials. PubMed (1965-May 2010) was searched for randomized, placebo-controlled trials of omega-3 FAs for MDD. Our primary outcome measure was standardized mean difference in a clinical measure of depression severity. In stratified meta-analysis, we examined the effects of trial duration, trial methodological quality, baseline depression severity, diagnostic indication, dose of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) in omega-3 preparations, and whether omega-3 FA was given as monotherapy or augmentation. In 13 randomized, placebo-controlled trials examining the efficacy of omega-3 FAs involving 731 participants, meta-analysis demonstrated no significant benefit of omega-3 FA treatment compared with placebo (standard mean difference (SMD) = 0.11, 95% confidence interval (CI): _0.04, 0.26). Meta-analysis demonstrated significant heterogeneity and publication bias. Nearly all evidence of omega-3 benefit was removed after adjusting for publication bias using the trim-and-fill method (SMD = 0.01, 95% CI: _0.13, 0.15). Secondary analyses suggested a trend toward increased efficacy of omega-3 FAs in trials of
lower methodological quality, trials of shorter duration, trials which utilized completers rather than intention-to-treat analysis, and trials in which study participants had greater baseline depression severity. Current published trials suggest a small, non-significant benefit of omega-3 FAs for major depression. Nearly all of the treatment efficacy observed in the published literature may be attributable to publication bias.

15. **Meta-Analysis of the Effects of Eicosapentaenoic Acid (EPA) in Clinical Trials in Depression.** Sublette ME, Ellis SP, Geant AL, Mann JJ. Meta-Analysis of the Effects of Eicosapentaenoic Acid (EPA) in Clinical Trials in Depression. *The Journal of Clinical Psychiatry*. 2011;72(12):1577–1584. doi:10.4088/JCP.10m06634.

Abstract

Objective: Randomized trials of omega-3 polyunsaturated fatty acid (PUFA) treatment for depression have differed in outcome. Recent meta-analyses ascribe discrepancies to differential effects of eicosapentaenoic acid (EPA) versus docosahexaenoic acid (DHA) and to diagnostic heterogeneity. This meta-analysis tests the hypothesis that EPA is the effective component in PUFA treatment of major depressive episodes.

Data Sources: PubMed/MeSH was searched for studies published in English from 1960 through June 2010 using the terms fish oils (MeSH) AND (depressive disorder [MeSH] OR bipolar depression) AND randomized controlled trial (publication type). The search was supplemented by manual bibliography review and examination of relevant review articles.

Study Selection: The search yielded 15 trials involving 916 participants. Studies were included if they had a prospective, randomized, double-blinded, placebo-controlled study design; if depressive episode was the primary complaint (with or without comorbid medical conditions); if omega-3 PUFA supplements were administered; and if appropriate outcome measures were used to assess depressed mood.

Data Extraction: Extracted data included study design, sample sizes, doses and percentages of EPA and DHA, mean ages, baseline and endpoint depression ratings and standard deviations for PUFA and placebo groups, and P values. The clinical outcome of interest was the standardized mean difference in the change from baseline to endpoint scores on a depression rating scale in subjects taking PUFA supplements versus subjects taking placebo.

Data Synthesis: In a mixed-effect model, percentage of EPA in the supplements was the fixed-effect predictor, dichotomized into 2 groups: EPA < 60% or EPA ≥ 60% of the total EPA + DHA. Secondary analyses explored the relevance of treatment duration, age, and EPA dose.

Results: Supplements with EPA ≥ 60% showed benefit on standardized mean depression scores (effect size = 0.532; 95% CI, 0.277–0.733; t = 4.195; P < .001) versus supplements with EPA < 60% (effect size = −0.026; 95% CI, −0.200 to 0.148; t = −0.316; P = .756), with negligible contribution of random effects or heteroscedasticity and with no effects of treatment duration or age. Supplements with EPA < 60% were ineffective. Exploratory analyses supported a nonlinear model, with improvement determined by the dose of EPA in excess of DHA, within the range of 200 to 2,200 mg/d of EPA.

Conclusions: Supplements containing EPA ≥ 60% of total EPA + DHA, in a dose range of 200 to 2,200 mg/d of EPA in excess of DHA, were effective against primary depression. Translational studies are needed to determine the mechanisms of EPA's therapeutic benefit.

16. **Updated systematic review and meta-analysis of the effects of n-3 long-chain polyunsaturated fatty acids on depressed mood.** Appleton KM, Rogers PJ, Ness AR. Am J Clin Nutr. 2010 Mar;91(3):757-70. doi: 10.3945/ajcn.2009.28313. Epub 2010 Feb 3.

Abstract

BACKGROUND: The debate over a role for n-3 long-chain polyunsaturated fatty acids (n-3 PUFAs) in depressed mood continues.

OBJECTIVE: The objective was to update a previous systematic review and meta-analysis of published randomized controlled trials investigating the effects of n-3 PUFAs on depressed mood and to explore potential sources of heterogeneity.

DESIGN: Eight databases were searched for trials that randomly assigned participants to receive n-3 PUFAs/fish, measured depressed mood, used human participants, and included a comparison group up to April 2009.

RESULTS: Thirty-five randomized controlled trials were identified; 17 were not included in the previous review. The pooled standardized difference in mean outcome of the 29 trials that provided data to allow pooling (fixed-effects model) was 0.10 SD (95% CI: 0.02, 0.17) in those who received n-3 PUFAs compared with placebo, with strong evidence of heterogeneity ($I(2) = 65\%$, $P < 0.01$). The presence of funnel plot asymmetry suggested that publication bias was a likely source of this heterogeneity. Depressive symptom severity and participant diagnosis also explained some of the observed heterogeneity. Greater effects of n-3 PUFAs were found in individuals with more-severe depressive symptoms. In trials that enrolled individuals with a diagnosed depressive disorder, the combined mean difference was 0.41 (95% CI: 0.26, 0.55), although evidence of heterogeneity was also found ($I(2) = 71\%$). In trials that enrolled individuals without a depressive diagnosis, no beneficial effects of n-3 PUFAs were found (largest combined mean difference: 0.22; 95% CI: -0.01, 0.44; $I(2) = 0\%$).

CONCLUSIONS: Trial evidence of the effects of n-3 PUFAs on depressed mood has increased but remains difficult to summarize because of considerable heterogeneity. The evidence available provides some support of a benefit of n-3 PUFAs in individuals with diagnosed depressive illness but no evidence of any benefit in individuals without a diagnosis of depressive illness.