

Evidence Based Review of Fish Oil: Going Beyond the Headlines

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Omega-3 fatty acids are postulated to have beneficial effects in patients at risk for vascular disease, including the prevention of stroke, sudden cardiac death and heart failure; adjunctive therapy for the treatment mood disorders such as major depression and bipolar disorders; prevention of cognitive decline and dementia in Alzheimer's patients and in cancer prevention. Over the years, headlines of fish oil have been covered widely in the media with conflicting claims of its benefit or harm.¹⁻⁴ This review will summarize the evidence reviewed and conclusions drawn from the high quality meta-analyses and systematic reviews evaluating the therapeutic effects of fish oil supplementation on the previous identified outcomes.

Summary of the Evidence

The high quality meta-analysis and systematic reviews published in the past 10 years were examined. These reviews had high confidence that the evidence reflects the true effect; and further research is very unlikely to change our confidence in the estimate of effect. See Table 1 for the grading definitions and Table 2 for the summary of these reviews.

Cardiovascular Disease (CVD)

- Omega -3 fatty acids do not reduce cardiovascular (CV) events (primary and secondary prevention of myocardial infarction, stroke and cardiovascular death).⁵⁻⁹ (Level of Evidence: Moderate)
- Fish oil supplements have no significant beneficial effect in controlling atrial fibrillation (AF).¹⁰⁻¹² (Level of Evidence: Moderate)
- Omega – 3 fatty acids improve cardiac function in patients with chronic heart failure (CHF)¹³ and lower blood pressure¹⁴, but the changes are too small to make a clinical difference. (Level of Evidence: Low)

Cancer

- Fish oil supplements are of no benefit for cancer prevention based on 3 systematic reviews including observational studies.¹⁵⁻¹⁷ (Level of Evidence: Moderate)

Cognitive Function and Dementia

- Omega – 3 fatty acids show no benefit on cognitive function in cognitively healthy older people and patients with Alzheimer's disease (AD) but there was a small benefit for immediate recall and attention, and processing speed in subjects with cognitive impairment without dementia.¹⁸ (Level of Evidence: Moderate)
- When used for 6-40 months, Omega-3 fatty acids did not prevent dementia in healthy participants over the age of 60 years who were cognitively healthy.¹⁹ (Level of Evidence: Low)

Psychiatric Disorders

- Evidence on effectiveness of omega-3 fatty acids for the treatment of bipolar symptoms and depression is inconclusive.²⁰⁻²³ (Level of Evidence: Low)

Safety

- A consistent theme throughout multiple trials was that Omega-3 fatty acids/fish oil supplements are safe and well tolerated.^{6,15,18,19} (Level of Evidence: Moderate)

Conclusion

The currently available evidence does not support claims of beneficial outcomes from the use of omega-3 fatty acids for any of the following indications: prevention of stroke, sudden cardiac death and heart failure, adjunctive therapy for the treatment of mood disorders such as major depression and bipolar disorders, prevention of cognitive decline and dementia in Alzheimer's patient, and cancer prevention. Ongoing randomized clinical trials are still investigating the benefits in cardiovascular disease and mood disorders.²⁴⁻²⁷

Policy Changes in Response to the Evidence – Implementation 5/1/14

- Retain legend omega-3 acid ethyl ester (i.e. LovazaTM) as non-preferred on Preferred Drug List (PDL) for treatment of hypertriglyceridemia.
- Put all over-the-counter omega-3 fatty acids/fish oil products on the "Excluded Drug List". Products on this list used for funded diagnoses will be approved through the administrative appeals process.

Table 1. Strength of Evidence Grades and Definitions

Grade	Definition
High	High confidence that the evidence reflects the true effect. Further research is very unlikely to change our confidence in the estimate of effect.
Moderate	Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of effect and may change the estimate.
Low	Low confidence that the evidence reflects the true effect. Further research is likely to change our confidence in the estimate of effect and is likely to change the estimate.
Insufficient	Evidence either is unavailable or does not permit the estimation of an effect.

Table 2: Summary of Meta-analyses and Systematic Reviews

Disease	Significant Findings
CV Events	Delgado-Lista J et al: ⁵ Marine omega-3 fatty acids are effective in preventing cardiovascular events, cardiac death and coronary events, especially in persons with high cardiovascular risk.
	Kotwal S et al: ⁶ There was no overall effect of Omega-3 fatty acids on composite cardiovascular events or on total mortality. Adverse events were more common in the treatment group than the placebo group, predominantly because of an excess of gastrointestinal side effects.
	Kwak SM et al: ⁷ Supplementation with omega-3 fatty acids did not reduce the risk of overall cardiovascular events, all-cause mortality, sudden cardiac death, myocardial infarction, congestive heart failure, or transient ischemic attack and stroke.
	Larsson SC et al: ⁸ No association between omega-3 fatty acids intake and stroke, but suggests that women might benefit from a higher intake of omega-3 fatty acids.
	Rizois EC et al: ⁹ Omega-3 fatty acids are not statistically significantly associated with major cardiovascular outcomes across various patient populations.
Arrhythmias	Armaganjian L et al: ¹⁰ 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.
	Leon H et al: ¹¹ 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 eicosapentaenoic acid (EPA) or docosahexanoic acid (DHA) to reduce these outcomes is insufficient.

	Liu T et al: ¹² Omega-3 fatty acids had no significant effect on the prevention of AF.
CHF	Xin W et al: ¹³ Left ventricular ejection fraction was significantly increased and left ventricular end-systolic volume was significantly decreased in the fish oil group compared with the placebo group, although left ventricular end-diastolic volume was not significantly affected.
Blood Pressure	Campbell F et al: ¹⁴ There was a statistically significant reduction in systolic and diastolic BP; 2.56 mmHg and 1.47 mmHg respectively in hypertensive participants; non-significant reduction in both systolic and diastolic BP in normotensive participants.
Cancer	Ries A et al: ¹⁵ Insufficient evidence to support a net benefit of fish oil in cachexic patients with advanced cancer. Adverse effects were rare with no severe adverse effects.
	Gerber, et al: ¹⁶ A probable level of evidence that fish oil is neither a risk factor nor a beneficial factor with regards to cancers.
Cognition/ Dementia	Szmanski KM et al: ¹⁷ 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.
	Mazereeuw G et al: ¹⁸ Omega-3 fatty acid treatment was associated with a small, but significant benefit for immediate recall and attention and processing speed in subjects with cognitive impairment and no dementia, but not in healthy subjects or those with AD.
Bipolar Disorder	Sydenham E et al: ¹⁹ Omega-3 fatty acids when used for 6-40 months did not prevent dementia in healthy participants over the age of 60 years who were cognitively healthy. Minor adverse events were reported by fewer than 15% of participants.
	Tumbull T et al: ²⁰ Studies using an omega-3 combination of EPA and DHA demonstrated a statistically significant improvement in bipolar symptoms, whereas those using a single agent did not. Side effect profile is benign.
Depression	Bloch MH et al: ²¹ There is limited evidence for omega-3 fatty acids supplementation being an effective acute treatment for depression.
	Sublette ME et al: ²² Supplements with EPA ≥ 60% showed benefit on standardized mean depression scores.
	Appleton KM et al: ²³ There were increased effects of omega-3 fatty acids on improvements in depressed mood, but it remains difficult to summarize because of considerable heterogeneity.

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