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Fish Oil: Prominent Clinical Trial Research of Oral Doses

Key Points at a Glance

Results from Meta-Analysis & Systematic Review

hyperlipidaemia
- significant reduction of 14% in triglycerides
- no effect on total cholesterol or HDL-cholesterol
- slight rise in LDL-cholesterol may occur
- dosage required: corresponding to 3.25 g/day EPA + DHA
- effect may be dose-dependent
- baseline level is a factor in triglyceride-lowering effect; effect may still be clinically relevant for those with normal baseline levels if dosage is sufficient (> 2 g/day EPA + DHA)

lipid profile in dialysis and kidney transplant patients
- dialysis: significant decrease in triglycerides and total cholesterol; significant increase in HDL-cholesterol
- kidney transplant: modest increase in HDL-cholesterol (included some high doses)

hypertension
- small significant reductions in systolic and diastolic blood pressure
- effect thought to be achievable at relatively low doses
- kidney transplant recipients: reduced diastolic blood pressure (included some high doses)

endothelial function
- significant improvement in endothelial function particularly in those without diabetes or high blood pressure but results were not rigorous

chronic heart failure
- significant improvement in left ventricular ejection fraction and left ventricular end-systolic volume (i.e. cardiac function), particularly in non-ischaemic heart failure

atrial fibrillation
- did not reduce risk of recurrence, and may increase the risk in those in normal sinus rhythm; outcome might be improved if taken for at least 4 weeks prior to cardioversion
- did not reduce postoperative incidence; reduced length of hospital stay for > 1 g/day DHA

ventricular fibrillation:
- no overall effect on the relative risk of implantable cardioverter defibrillator discharge

heart rate and heart rate variability
- modest reduction of heart rate; increased reductions for those with baseline heart rate of ≥ 69 bpm and those treated ≥ 12 weeks
- enhanced vagal tone, particularly when dose > 1.2 g/day EPA + DHA

arterial stiffness
- improved pulse wave velocity and arterial compliance

platelet aggregation and thrombosis
- decreased platelet aggregation in cardiovascular diseases, diabetes, those taking antiplatelet medications, but not in healthy volunteers
- reduced graft thrombosis in maintenance haemodialysis

secondary prevention of cardiovascular events
- patients with existing cardiovascular disease
  - no protective effect for all-cause mortality or stroke
  - reduced risk of cardiac death, sudden death and myocardial infarction
  - dose: 0.8-4.8 g/day EPA + DHA for more than 1 year
  - effect on mortality may be reduced in those on statins
- maintenance haemodialysis patients
  - significantly reduced cardiovascular events

homocysteine levels
- modest lowering, which is greater if combined with folate and B-vitamins

diabetes
- reduces triglyceride levels; effect may be greater if dose >2 g/day EPA + DHA, and in those with poor glycaemic control
- no effect on blood glucose, Hb1Ac or cardiovascular mortality

cognition
- generally no effect found
- may help short-term memory in omega-3 fatty acid-deficient children, but results not robust
- results conflicting in the elderly

ADHD
- small effect on reducing emotional lability and possibly on reducing oppositional behaviour (included treatment with phosphatidylserine)
- small effect on reducing aggression

depression
- effective for DSM-defined diagnosis of major depressive disorder and for patients with symptoms of depression without this diagnosis
- EPA dosage influenced the efficacy
- no benefit in healthy volunteers (e.g. pregnancy or for prevention); inconclusive where depression was not the primary disorder; may benefit depressive symptoms in bipolar disorder (limited evidence)

rheumatoid arthritis
- reduced consumption of NSAIDs (> 2.9 g/day EPA + DHA)

nonalcoholic fatty liver disease
- beneficial effects on liver fat, some liver enzymes and some blood lipids

obesity and weight management
- no effect on body weight or BMI; may reduce waist circumference and waist hip ratio particularly if combined with diet and/or exercise
- reduced serum leptin levels in the nonobese

IgA nephropathy
- may reduce proteinuria (results conflicting); no effect on renal function

during pregnancy
- decreased the incidence of perinatal death if intake begun at or before 20 weeks' gestation
- may support higher infant birth weight
- produced a small increase in the mean length of gestation but did not reduce risk of preterm birth
- inconsistent effect generally on childhood allergies, but may reduce the incidence of sensitisation

Results from Multiple Trials

cancer
- may reduce weight loss or stabilise weight (but most studies evaluated omega-3 fatty acids in combination with other nutrients)

cystic fibrosis
- improved lung function, but larger, better-designed trials need to be conducted

other conditions
- may decrease pain in dysmenorrhoea
- may improve or maintain muscle function in older, healthy adults, especially in women and if combined with resistance training
- improved symptoms of dry eye
- decreased symptoms of recurrent mouth ulcers
- improved motor skills and information processing in children with phenylketonuria

Safety

- adults 60 years or older without CVD
  - no severe adverse effects, including stroke and bleeding
  - belching can occur
- adults 60 years or older with CVD
  - severe adverse effects are unlikely
  - major bleeding in surgical and non-surgical patients were infrequent
  - one study found no increase in stroke in surgical patients, but number of total bleeds increased (high dose and high baseline levels)
  - non-severe adverse effects are infrequent
- no effect on major bleeding during heart and other surgeries
- risk of bleeding generally is very low
- not advisable during acute bleeding episodes such as haemorrhagic stroke
- unlikely to have adverse effect or cause interaction in those taking antiplatelet or anthrombotic medications
  - may assist patients with aspirin insensitivity when combined with low-dose aspirin
- unlikely to have an adverse effect on glucose homoeostasis or lipid peroxidation
- interactions with ibrutinib and sirolimus noted; conflicting information for dexamethasone
- caution in known hypersensitivity to fish or shellfish

Meta-analyses and systematic reviews are a convenient way to provide an overview of the large body of clinical research featuring fish oil and the important long-chain omega-3 fatty acid constituents, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA).

Conclusions on the efficacy however, are sometimes elusive. Many pooled analyses combine results from trials that have administered a variety of formulations: marine and plant-based oils, isolated long-chain omega-3 fatty acids, ester derivatives of these fatty acids, fatty acid combinations including the shorter-chain omega-3, and other, fatty acids. For example, the hyperlipidaemia meta-analysis outlined below is described as analysing 43 studies of fish oil, however probably only 27 trials used fish oil, at least eleven evaluated esters of EPA/DHA, one investigated both fish oil and esters and the remainder used isolated omega-3 fatty acids. A meta-analysis of trials said to be reporting the effect of omega-3 fatty acids on dry eye syndrome included 7 trials: only 2 trials used fish oil or a preparation containing predominantly EPA and DHA, two evaluated fish oil plus linseed oil, one investigated linseed oil alone, one used the omega-6 fatty acids linolenic acid (LA; present in linseed oil) plus GLA (gamma-linolenic acid) and the other combined vitamins, minerals, amino acids and glutathione with EPA and DHA. Often too, the evaluated products are not well defined.

Despite these limitations, a survey of this overview invites the conclusion that fish oil and relevant EPA and DHA preparations provide therapeutic activity for many aspects of cardiovascular health in particular.

The information summarised here provides a general review of the potential actions and indications that might be achieved from the therapeutic use of fish oil. Generally, data has not been included, for the sake of brevity, where pooled analysis found that the fish oil/omega-3 fatty acid

formulations had no effect (e.g. inflammatory bowel disease, asthma).

EVIDENCE FROM META-ANALYSIS & SYSTEMATIC REVIEWS

Cardiovascular Disease

Hyperlipidaemia

To detect a potential effect on hyperlipidaemia, a comprehensive meta-analysis evaluated 43 randomised controlled trials that had been published by March 2008.[1] Lipids were measured in patients with hyperlipidaemia (12 trials), coronary heart disease (14 trials), other cardiovascular disorders (8 trials), diabetes (4 trials) and in other patients as well as postmenopausal women and the obese. In several studies patients were taking statins or fish oil/omega-3 fatty acid formulations in combination with a statin drug. The average trial length was 24 weeks (median: 16 weeks; range: 4 to 260 weeks). In 72% of studies the participants were men with a mean age of 49 years.

- Compared with placebo, fish oil and omega-3 fatty acid formulations produced a **significant reduction of fasting blood triglycerides** of 0.34 mmol/L from a mean baseline triglyceride level of 2.44 mmol/L. In other words, in those with mild hypertriglyceridaemia, fish oil/omega-3 fatty acid formulations reduced triglycerides by an average of 14%.
- These formulations did not produce significant improvement for fasting total cholesterol or HDL-cholesterol. There was a slight, nonsignificant rise in LDL cholesterol.
- The authors estimated that clinically-significant triglyceride lowering occurred when an average daily dose corresponded to 3.25 g of omega-3 fatty acids, consisting of 1.9 g of EPA and 1.35 g of DHA.
- Meta-regression analysis indicated that the proportional reduction of triglyceride was significantly related to both the baseline triglyceride level ($p < 0.001$) and intake of EPA + DHA ($p = 0.01$).

Another way of looking at the data was presented in a review that investigated if there was a dose-dependent response.[2] To avoid duplication of previous review findings, randomised placebo-controlled trials published between 2002 and August 2007 were assessed, and included 15 trials, two of which were evaluated in the above meta-analysis. The trials included a range of participants, including healthy volunteers, with varying baseline triglyceride levels: normal triglyceride levels (5 trials), borderline-high triglyceride levels (3), combinations of either normal, borderline-high or high triglyceride levels (7). Study durations ranged from 4 to 24 weeks (7 studies had a duration of 6 weeks, 4 studies lasted 12 weeks). The amounts of EPA and/or DHA administered ranged from 209 mg/day to 5.6 g/day, with an average intake across the 15 studies of 2.3 g/day. Fish oil was administered in at least 6 trials. Other trials used omega-3 fatty acid-enriched foods (4 trials; at least 2 may have been prepared using fish oil), DHA-rich algal oil (3), isolated omega-3 fatty acids (1) or EPA/DHA-rich oils (possibly of fish oil origin; 1).

- **Triglyceride levels were dose-dependently reduced** by fish oil and omega-3 fatty acid formulations.
- The data was adjusted for the change in triglyceride level from baseline in the placebo group and weighting factors that took into account each study's sample size and quality score were applied. The resulting mathematical model predicated that an intake of omega-3 fatty acids corresponding to 200-500 mg/day of EPA and/or DHA reduces fasting serum triglyceride levels by 3.1 to 7.2%.
- Of the 5 trials conducted with volunteers having normal baseline triglyceride levels, 1 trial, administering 460 mg/day of EPA + DHA, showed no improvement, although the results of this trial have been questioned. In the other 4 studies, fasting triglyceride levels were reduced by 19.1 to 35.7% following consumption of preparations providing 2.1-5.6 g/day of EPA and/or DHA for 4 to 12 weeks.

It has been suggested that at least 2 g/day of EPA + DHA is required for an effective triglyceride-lowering effect,[3] but for controlled trials published after these reviews where this dosage or lower was administered the results vary.[4-11] The baseline level of triglycerides/lipids may partially explain these results.

- Triglyceride-lowering effect was observed in mild hyperlipidaemia (1.9 g/day EPA + DHA),[4] and hypertriglyceridaemia (0.8 and 1.7 g/day of EPA + DHA),[5] but in another study of mildly hypertriglyceridaemic patients the effect, although dose-dependent, was not significant (0.5-2 g/day of EPA + DHA).[6]
- No effect was found on blood lipids in stroke patients with normal/good baseline levels of triglycerides and other lipids, 80% of whom were taking lipid-lowering medications including statins (1.2 g/day EPA + DHA);[6] and in moderate hypertriglyceridaemia (0.85 g/day EPA + DHA).[8]
- No effect was found on blood lipids in healthy volunteers (0.8-1.6 g/day of EPA + DHA).[9-11]

Although not specifically designed to assess the effects in dyslipidaemic patients, fish oil/omega-3 fatty acid formulations were found to reduce serum triglycerides and total cholesterol in patients undergoing dialysis. HDL-cholesterol levels were increased. The meta-analysis included 13 randomised controlled trials to October 2013, seven of which administered fish oil. Subgroup analysis found no difference in the effects on lipid profile when comparing trials administering formulations providing less than 2 g/day of EPA + DHA with trials using 2 g/day or more – so a high dose might not be needed.[12] A meta-

analysis reviewed controlled trials involving kidney transplant recipients on immunosuppressive regimen (such as cyclosporin A or tacrolimus) published by March 2016. Patients receiving fish oil/omega-3 fatty acid formulations for more than 6 months had a modest increase in HDL-cholesterol (0.12 mmol/L; p = 0.01) compared to placebo. Formulations provided doses of EPA + DHA in the range of 1.8-5.4 g/day. Effects on lipids were not significantly different from the effect demonstrated by low-dose statins.[13]

Four controlled trials published to January 2011 that assessed the effect of fish oil/omega-3 fatty acid formulations in lowering triglyceride levels of HIV patients who were receiving antiretroviral treatment were analysed.[14]

- Overall, after 8 to 16 weeks of treatment with formulations providing 0.9 to 3.36 g/day of EPA + DHA, triglycerides were significantly reduced by 0.91 mmol/L.
- The pooled result of 2 studies that enrolled patients with mean baseline triglycerides of 3.38 mmol/L or greater (i.e. hypertriglyceridaemia) and administered 1.8-2.9 g/day EPA + DHA, was a reduction of 1.46 mmol/L. At the same baseline level, with doses of 0.9-2.9 g/day (3 trials), the reduction was 1.17 mmol/L.

Hypertension

Meta-analysis of 8 studies in hypertensive participants found a statistically **significant reduction in systolic and diastolic blood pressure**: 2.56 mm Hg and 1.47 mm Hg, respectively. The review was restricted to trials of at least 8 weeks' duration published by January 2011, and involved mainly middle-aged patients who had moderately elevated hypertension (141.3/90.4 mm Hg). In some trials participants were taking antihypertensive medications, although trials were excluded if the medications changed during the course of a trial. Meta-regression analysis found no evidence of a dose-response relationship, however quite a range of doses was used: formulations providing 13-13330 mg/day of EPA + DHA, with 5 trials in the range of 2 to 4.5 g/day.[15]

A more recent meta-analysis of randomised controlled trials published by February 2013 has been conducted. Trials involving patients treated with antihypertensive medications were excluded. Sixteen trials were analysed, ranging in duration from 28 to 120 days. Fish oil was said to be administered in all but one trial, which instead provided DHA-enriched bread. At least 4 trials used ethyl ester-enriched fish oil or ethyl esters. In one trial, fish meals were tested alongside of fish oil. Four of the trials were included in the above, January 2011 meta-analysis. The dose of EPA + DHA ranged from 0.3 to 15 g/day, with 9 trials in the range of 1.9 to 4 g/day. Significant reductions in systolic blood pressure of 4.51 mm Hg and diastolic blood pressure of 3.05 mm Hg were found.[16]

Treatment with fish oil/omega-3 fatty acid formulations in kidney transplant recipients was associated with a lower diastolic blood pressure (-4.53 mm Hg; p = 0.004) compared to placebo, as assessed by meta-analysis. Formulations provided doses of EPA + DHA in the range of 1.92-5.4 g/day, taken for 3 to 12 months.[13]

Endothelial Function

A meta-analysis investigated the effect of fish oil/omega-3 fatty acid formulations on endothelial function, as measured by fasting flow-mediated dilation in the brachial artery. The results of 16 randomised controlled trials published by February 2012 were analysed. Treatment ranged from 2 to 52 weeks and formulations provided 450-4530 mg/day of EPA + DHA. Six studies consisted of healthy volunteers; 2 studies involved overweight adults and the remainder included patients with at least one chronic condition (such as dyslipidaemia, type 2 diabetes, other cardiovascular disorders (3 trials each)). Some patients were taking medications.[17]

- Omega-3 fatty acid formulations significantly **improved flow-mediated dilation** (weighed mean difference: 1.49%; p = 0.004), but meta-regression and subgroup analysis suggested that the quality of included studies were inversely related to the overall effect, and the significance of the effect appeared to mainly depend on the studies of relatively poor quality.
- Diabetes and baseline diastolic blood pressure may also influence the effects. Normoglycaemic participants showed significant improvements in flow-mediated dilation compared to studies that treated only diabetic patients. Those with diastolic blood pressure lower than 75 mm Hg had greater improvements than those with higher baseline levels.

Chronic Heart Failure

The results from 7 randomised, placebo-controlled trials involving patients with chronic heart failure were pooled in meta-analysis, from research published by November 2011. Omega-3 fatty acid formulations provided a dose of EPA + DHA that ranged from 600 to 4300 mg/day, and the duration of treatment varied from 3 to 12 months. The results suggest **improvements in cardiac function, remodelling** and functional capacity.[18]

- Left ventricular ejection fraction was significantly increased (weighted mean difference: 2.25%; p = 0.005) and left ventricular end-systolic volume was significantly decreased (weighted mean difference: 7.85 mL; p = 0.05) compared with the placebo group. Meta-regression and subgroup analysis indicated that the improvement in left ventricular

ejection fraction was more remarkable in patients with non-ischaemic heart failure.
- Treatment with omega-3 fatty acid formulations also improved the New York Heart Association functional classification and peak oxygen consumption in patients with non-ischaemic heart failure (results were obtained from a subset of trials).

Fibrillation

Of randomised controlled trials published by May 2013 that investigated the role of "fish oil" in the prevention of atrial fibrillation, 2 studies found a significant reduction in recurrence, and five found neutral results (no significant difference compared with controls). The meta-analysis included these 7 studies and another that administered the short-chain omega-3 fatty acid, alpha-linolenic acid (ALA), so the pooled results are not relevant to the longer chain omega-3 fatty acids and fish oil.[19] When 3 of the 8 trials were excluded (one that did not provide a dose, the ALA trial, and one that administered a low dose of about 0.5 g/day of EPA + DHA), leaving 5 trials that prescribed ongoing doses of fish oil or ethyl esters providing 0.85-3.4 g/day of EPA + DHA, the risk of recurrent atrial fibrillation was not significantly different from placebo. (In 2 trials, the initial/loading dose differed from the ongoing dosage.)[20-24] Subgroup analysis suggests that taking the supplement at least 4 weeks before cardioversion might improve the outcome. Analysis of the results for patients in normal sinus rhythm suggests omega-3 fatty acids increased the risk of recurrent atrial fibrillation (those receiving control/placebo experienced decreased risk of recurrence).[19]

Evidence from 7 randomised controlled trials (to November 2012) found that fish oil/omega-3 fatty acid formulations did not reduce the incidence of postoperative atrial fibrillation. Subgroup analysis suggested that length of **hospital stay after cardiac surgery was significantly reduced** in patients who took doses of DHA greater than 1 g/day.[25]

Meta-analysis of 3 randomised controlled trials published by May 2007 found considerable variation in the response to intake of omega-3 fatty acid formulations (0.8-2.6 g/day of EPA + DHA) among patients with implantable cardioverter defibrillators, leading to the conclusion that some patients may benefit, others may not benefit and some may be adversely affected. The patients in each trial had received an implantable cardioverter defibrillator because of ventricular tachycardia or ventricular fibrillation. The primary outcome was implantable cardioverter defibrillator discharge at a follow-up period of at least 1 year.[26]

Heart Rate

In a 2005 meta-analysis of 30 randomised, double-blind, placebo-controlled clinical trials, administration of omega-3 fatty acid formulations reduced heart rate by a modest, but significant, 1.6 beats per minute (bpm) compared with placebo ($p = 0.002$). The heart rate reduction was greater in patients with a mean baseline heart rate of 69 bpm or greater: omega-3 fatty acids reduced heart rate by 2.5 bpm. Trials in which the formulations were administered for 12 or more weeks also produced a reduction of 2.5 bpm. A dose-dependent response was not evident. Trials included those who were generally healthy as well as those with chronic conditions. The median EPA + DHA dose was 3.5 g/day (range: 0.8-15 g/day), and was prescribed for 4 to 52 weeks.[27]

A 2013 meta-analysis investigated the effect of fish oil/omega-3 fatty acid formulations on heart rate variability indexes. Fifteen trials were included. High-frequency power (an indicator of vagal function) was significantly increased by taking these formulations. Other parameters were not significantly affected, although when results obtained from lower doses were excluded (leaving comparisons where doses of EPA + DHA of 1.28-3.36 g/day were provided) there was a significant reduction in the ratio of low-frequency to high-frequency power. These results suggests **an enhanced vagal tone**. The median EPA + DHA dose was 1.68 g/day (range: 0.64-5.9 g/day). The preparations were taken for 6 to 24 weeks.[28]

Arterial Stiffness

A review of randomised, controlled trials published by September 2010 included for meta-analysis 10 trials that investigated the effects of fish oil/omega-3 fatty acid formulations on arterial stiffness in adults. Four trials used pulse wave velocity and six used arterial compliance to measure arterial stiffness. Participants were overweight, diabetic, hypertensive, dyslipidaemic or hyperlipidaemic and one trial involved healthy volunteers. The daily doses provided 640 to 3000 mg of EPA + DHA, and treatment lasted from 6 to 105 weeks. Omega-3 fatty acid formulations significantly improved both pulse wave velocity ($p < 0.01$) and arterial compliance ($p < 0.001$). Results were not influenced by changes in blood pressure, heart rate or body mass index.[29]

Effect on Platelet Aggregation & Thrombosis

Meta-analysis of the results of randomised controlled trials published by July 2011 found that supplementation with fish oil/omega-3 fatty acid formulations was associated with a significant **reduction in platelet aggregation in patients with cardiovascular diseases**, but not in healthy volunteers. Seven randomised trials included the healthy, and 8 trials examined the effect on patients with dyslipidaemia, coronary artery disease, peripheral arterial

disease, type 2 diabetes or end-stage renal disease. In 3 trials, patients were treated with aspirin or aspirin and clopidogrel. Subgroup analysis indicated that the addition of omega-3 fatty acid formulations to antiplatelet therapy was associated with decreased platelet aggregation induced by adenosine diphosphate when compared with placebo.[30]

Meta-analysis of the results of 4 randomised controlled trials found fish oil/omega-3 fatty acid formulations significantly reduced arteriovenous graft thrombosis in maintenance haemodialysis patients.[31]

Secondary Prevention of Cardiovascular Events

A 2013 meta-analysis investigated the protective effect of fish oil/omega-3 fatty acid formulations in patients with existing cardiovascular disease, where doses were sufficiently high ("at least 1 g/day") and for sufficiently long periods (at least 1 year). Eleven randomised, double-blind, placebo controlled trials were included for analysis. Previous cardiovascular events in the patients included coronary heart disease, myocardial infarction, atrial fibrillation, coronary angioplasty and those with implantable cardioverter defibrillators. Duration of treatment ranged from one to five years. In one trial the placebo group received statin drugs and in another trial the effect of omega-3 fatty acids was compared to a control group who received no treatment.[32]

- No statistically significant association was observed for all-cause mortality or stroke. (The 9 trials that evaluated all-cause mortality were also analysed in the following meta-analysis for the effect of statins.)
- Compared to patients who received placebo or no treatment, those who were administered omega-3 fatty acids had **risk reductions for cardiac death** (-32%; 8 trials; 0.9-4.8 g/day EPA + DHA), sudden death (-33%; 5 trials; 0.8-4.8 g/day EPA + DHA) and myocardial infarction (-25%; 9 trials; 0.9-4.8 g/day EPA + DHA).

The use of statins in more recent years is thought to possibly reduce the benefits of taking fish oil/omega-3 fatty acid formulations. Another analysis reviewed the results of trials that assessed the cardioprotective effect of these supplements by considering concomitant statin treatment. Of 22 trials that investigated total mortality, 17 reported use of lipid-lowering medications in the control group (5 trials did not specifically identify them as statin drugs).[33]

- Meta-regression of randomised controlled trials found that higher use of statin or lipid-lowering drugs in the control group was associated with lower reduction in total mortality in those treated with omega-3 fatty acids.

Meta-analysis of 5 trials indicated a significant reduction in cardiovascular events, but not in mortality, in those taking fish oil/omega-3 fatty acid formulations compared to controls in maintenance haemodialysis patients.[31]

Homocysteine-Lowering Activity

A meta-analysis of 11 randomised controlled trials published by September 2010, found that supplementation with fish oil/omega-3 fatty acid formulations was associated with a significant decrease in plasma homocysteine level (weighted mean difference: -1.59 μmol/L) compared with those who received a control. Most trial participants had cardiovascular disease or type 2 diabetes or related complications. In one study, all participants were healthy normolipidaemic volunteers. Of the included studies, four did not show a significant decrease in plasma homocysteine, and for 2 trials an increase was observed. Excluding the study in which use of fish oil produced an increase in plasms homocysteine level in healthy volunteers, the mean difference of plasma homocysteine was -1.81 μmol/L. The authors suggested that the conflicting results may be due to different durations of treatment (6 weeks to 12 months) and non-comparable participants.[34]

A meta-analysis published in 2015 also found that omega-3 fatty acid supplementation was associated with a significant reduction in homocysteine (-1.09 μmol/L; 13 trials), although combining these fatty acids with folic acid, and sometimes also with vitamins B6 and B12, produced a larger effect (-1.37 μmol/L; 8 trials). Ten of the 13 omega-3 fatty acid trials reported the median daily dose of EPA + DHA as 1.63 g/day (range: 0.25-3 g/day). Eight trials that administered omega-3 fatty acids with folic acid reported the EPA + DHA median daily dose as 0.33 g (range: 0.19-3 g). The median folic acid dose was 150 μg/day (range: 150-2500 μg/day). Of these 8 trials, also prescribed was vitamin B6 (one trial), vitamin B12 (one trial) or both (4 trials). The effect on homocysteine was inconsistent: the effect differed between the 2 trials with healthy participants; was inconsistent between the three trials with vascular disease patients; was lowered (not always significantly) for trials selecting patients with metabolic or renal diseases.[35]

Diabetes

The most recent meta-analysis that investigated the potential effect of fish oil/omega-3 formulations in type 2 diabetes included randomised controlled trials of more than 2 weeks' duration published by January 2015.[36]

- **Triglyceride levels were decreased** by 0.24 mmol/L, which was significant compared to placebo ($p < 0.01$). The results of 14 trials were pooled. The formulations provided EPA or EPA + DHA ranging from 1.68 to 4 g/day and patients were treated for 3-48 weeks.

- Total cholesterol, Hb1Ac, fasting plasma glucose and postprandial glucose did not change significantly. The pooled results for Hb1Ac and fasting plasma glucose included 2 trials where the dose of EPA + DHA exceeded 5 g/day. Subgroup analysis found fasting plasma glucose levels were increased by 0.42 mmol/L in Asians (p = 0.023), whilst there was no significant change in US and European participants.

Another meta-analysis reviewed randomised controlled trials involving adults with impaired glucose metabolism, which included patients with impaired fasting glucose, impaired glucose tolerance as well as type 2 diabetics.[37]

- Fish oil/omega-3 fatty acid formulations significantly reduced triglyceride levels. The effect was greater in patients who received preparations providing doses of EPA and/or DHA greater than or equal to 2 g/day, and where mean baseline Hb1Ac level was greater than or equal to 7%.
- There was no effect on total cholesterol, LDL-cholesterol or HDL-cholesterol, although subgroup analysis found significant reduction of total cholesterol levels in the trials providing doses of more than 2 g/day.
- No effect was found on fasting blood glucose or HbA1c.
- Supplementation with fish oil/omega-3 fatty acid formulations did not reduce risk of cardiovascular mortality, major cardiovascular events or all-cause mortality.

No effect was also found on insulin sensitivity,[38] blood pressure,[39] or body weight.[36,40]

The effect of omega-3 fatty acids on circulating adiponectin was examined in 14 randomised controlled trials published by June 2012. Trials enrolled a range of patients and healthy volunteers, many were overweight or hyperlipidaemic and 1 trial evaluated type 2 diabetics. Fish oil/omega-3 fatty acid formulations provided a dose of EPA + DHA that ranged from 710 to 4200 mg/day – in 1 trial, gamma-linolenic acid (GLA) was included with EPA and DHA, and 1 trial also assessed 2 fish diets providing 260 mg and 2100 mg per day of EPA + DHA. The duration of treatment varied from 3 to 156 weeks. The overall effect was a modest, 0.37 µg/mL increase in adiponectin, which would correspond to about 3% lower incidence of diabetes.[41]

See also aspirin insensitivity in the Safety section.

Cognitive Function

Several meta-analyses, analysing results of trials as recent as September 2011 and September 2014, have found no effect for fish oil/omega-3 fatty acid formulations on cognition or memory function specifically, in children, the healthy or patients. Generally this holds true for pooled results of diverse study populations (e.g. typically developing and children with ADHD; cognitively normal and dementia patients; those with mental illness, the healthy and cognitively impaired) as well as for the subgroups when analysed separately.[42-44] There were a range of fatty acid formulations administered, which makes the results difficult to interpret. Of the 34 trials analysed in 2 meta-analyses,[42,44] EPA and/or DHA was combined with some or many of the following fatty acids: ALA, GLA, linoleic acid (LA), arachidonic acid (AA) in 7 trials; and with carnosine, phosphatidylserine or vitamins A, C and D in 1 trial each.

- Subgroup analysis found a small effect for short-term memory in those who probably were deficient in omega-3 fatty acids. The 4 trials included typically developing children, those with ADHD and healthy young adults. In 1 trial, children were supplemented with a fish flour bread spread containing both omega-3 and omega-6 fatty acids. No effect was found in 4 other cognitive performance domains (working memory, reading, reaction time, inhibition). The study that supplemented with vitamins was excluded from this analysis.[42]
- An effect on immediate recall as well as attention and processing speed was observed in those with a mild form of cognitive impairment known as cognitive impairment no dementia (CIND), but not in the healthy or Alzheimer's disease patients. In the 4 trials that investigated those with CIND only, two used preparations containing DHA or DHA + EPA. In the others, AA or phosphatidylserine was combined with one or both of these omega-3 fatty acids.[44] In a trial published after this review, no effect on cognition was found in those with CIND administered omega-3 fatty acids for 4 months.[45]

A meta-analysis reviewed only trials that used the Mini-Mental State Examination (MMSE) test to assess cognitive function in the elderly. Six randomised controlled trials published by December 2014 were analysed, and included patients with mild cognitive impairment, mild to moderate Alzheimer's disease, age-related cognitive decline and patients with a history of heart attack.[46]

- Formulations of omega-3 fatty acids significantly **decreased the rate of cognitive decline**.
- In subgroup analyses, omega-3 fatty acids had a protective effect against cognitive decline in the trials where participants had a low baseline MMSE score (MMSE score less than or equal to 27), were of older age (greater than 70 years), or received long-term supplementation (more than 6 months). (A MMSE score of 24 is regarded as abnormal, with increased odds of dementia for scores less than 21.)
- The trials ranged in duration from 3 to 40 months, with the dosage of formulations providing 400 to 1800 mg/day of DHA or DHA + EPA (although 1 trial administered an oil emulsion containing

phospholipids, tryptophan and melatonin as well as DHA and EPA).

Two Cochrane reviews have also analysed the data. Assessing the data available up to April 2012, no benefit to cognitive function was found from 3 high-quality randomised controlled trials for omega-3 fatty acid supplementation in cognitively healthy people over 60 years of age.[47] Taking omega-3 fatty acid supplements (1.0-2.3 g/day of DHA + EPA) was not beneficial for people with mild to moderate Alzheimer's disease. When measured at 6 months, there was no effect on cognition, everyday functioning, quality of life or mental health. Three high-quality trials were included from literature published by December 2015. One of the studies, with very small numbers of participants, found that fish oil (providing 1.65 g/day of EPA + DHA) improved cognitively complex daily activities, such as shopping, after 12 months of treatment.[48]

Attention Deficit/Hyperactivity Disorder (ADHD) & Aggression

Meta-analysis of randomised controlled trials published by September 2013 found no significant effects on emotional lability, oppositional behaviour, conduct problems or aggression in children with ADHD or a related neurodevelopmental disorder prescribed omega-3 fatty acid formulations. Ten studies were included in this analysis. Five of the trials prescribed, DHA or EPA + DHA. In the other trials, these fatty acids were combined with phosphatidylserine or other fatty acids including GLA, AA, LA or ALA. There were no studies that evaluated adolescents or adults. Children were unmedicated (8 studies), medicated (1 study) and in one study this was not specified. Three of the 10 trials involved those with a developmental disorder known to overlap with ADHD (developmental coordination disorder, disruptive behaviour disorder and reading difficulties).[49]

- In the subgroup analysis (which excluded a trial that administered omega-3 fatty acids with phosphatidylserine) a small but significant effect was found for **parent-rated emotional lability**.
- In the subgroup analysis of high quality studies (which included the phosphatidylserine trial), a small but significant effect was found for parent-rated oppositional behaviour.
- There was a trend for treatment with omega-3 fatty acid formulations to improve parent-rated oppositional behaviour after exclusion of the study that supplemented with phosphatidylserine; and a trend to improve teacher-rated oppositional behaviour in 3 studies that provided doses greater than 100 mg/day of EPA (500-600 mg/day of EPA plus small amounts of ALA and/or DHA).

A meta-analysis conducted in December 2015 examined the relationship between supplementation of fish oil/omega-3 fatty acid formulations and aggression across various populations and patient groups. Forty-three research studies (intervention and observational studies) were analysed, involving 7405 participants most of whom were children and adolescents with and without neurodevelopmental/behavioural disorders (e.g. ADHD, developmental coordination disorder and autism spectrum disorder). The analysis revealed overall support, although the effect was small, for the relationship between omega-3 fatty acid consumption and **reduced aggression**.[50]

Depression

Several meta-analyses have recently been conducted and report conflicting conclusions for the treatment of depression.[51-53] The variability of results may depend on clinical and methodological issues such as baseline severity, methods of diagnosis and assessment, diagnosis and the pooling of all studies with little distinction among patient groups.[52]

A meta-analysis pooled results for randomised controlled trials published by August 2013. Among them, 11 trials were conducted in patients with a DSM-defined diagnosis of major depressive disorder (MDD) and 8 involved patients with an assessment of depression but not rigorously diagnosed according to the DSM criteria (for example, those with depression despite ongoing treatment, borderline personality disorder, recurrent self-harm, postmenopausal women). Eight studies were performed with adults, and 3 with elderly patients. Four trials administered fish oil, at least 6 used the ethyl esters and the remainder supplemented with isolated omega-3 fatty acids or these acids provided within otherwise undefined preparations.[52]

- A beneficial effect of omega-3 fatty acid formulations was found on depressed mood compared with placebo in patients with diagnosis of MDD. The dosage of EPA provided was in the range of 0.6-2 g/day, and DHA was 0.15-2 g/day for periods ranging from 4 to 16 weeks.
- A similar result was found for the non-MDD group. The dosage of EPA provided was in the range of 0.18-4 g/day, and for DHA was 0.12-2.4 g/day for periods ranging from 4 to 24 weeks.
- Meta-regression analysis found no association between baseline depression scores and efficacy for all studies, as well as for MDD patients and non-MDD patients separately.
- The use of mainly EPA within the preparation, rather than DHA, appeared to influence efficacy. When the analysis was split into pure EPA, mainly EPA (greater than 50% EPA), mainly DHA (greater than 50% DHA) and pure DHA supplementation, both EPA preparations were significant. The total dose of DHA was not

related to efficacy. The dose of EPA was related to efficacy for all trials (MDD + non-MDD) but when the analyses were repeated separately for each group, the association remained significant only for MDD patients.
- Considering trials that investigated perinatal depression, 3 studies enrolled pregnant women with MDD and three involved apparently healthy women (hence evaluated prevention). Both analyses revealed inconclusive results. Only 1 study concluded that omega-3 fatty acids might be beneficial in depression during pregnancy. (This trial used the highest daily dose (2.2 g of EPA + 1.2 g of DHA) and ran for 8 weeks.)
- For trials conducted in patients with primary disease other than depression, specifically Alzheimer's disease or mild cognitive impairment and cardiovascular disease, inconclusive results were reported. Trials performed with healthy volunteers found omega-3 fatty acid formulations had no effect in improving mood.

A Cochrane review conducted in February 2008 considered 5 randomised controlled trials that assessed the effect of omega-3 fatty acid formulations for the treatment of bipolar disorder. Fish oil, ethyl ester of EPA or algal DHA were used alone or in addition to patient's usual drug regimens. There was insufficient data to draw conclusions but omega-3 fatty acids appeared to reduce at least some symptoms of bipolar disorder in at least some patients. Use of omega-3 fatty acids may reduce depression symptoms and broader everyday symptomatology but no trials have shown any benefits for manic symptoms. It was also noted that the duration of trials ranged from 1 month, which may be too short given the slow absorption of fatty acids into neuronal membranes, to 1 year, which is probably too long for good compliance.[54]

Schizophrenia

A literature search conducted in March 2011 uncovered 7 studies suitable for meta-analysis, that had evaluated EPA as an add-on treatment in schizophrenia. Two of the trials assessed first-episode schizophrenia, the other trials were for chronic schizophrenia. Overall, 167 patients were treated with placebo and matched with 168 participants treated with EPA (2-3 g/day, for 12-16 weeks). No consistent, significant effect for the EPA supplementation on psychotic symptoms was found.[55] A later meta-analysis that pooled data from 10 studies found that in patients with first-episode schizophrenia, omega-3 fatty acids decreased nonpsychotic symptoms, required lower antipsychotic medication dosages and improved early treatment response rates. Omega-3 fatty acids had mixed results in patients with stable chronic schizophrenia, with only some patients experiencing significant benefits.[56]

Rheumatoid Arthritis

Randomised controlled trials published by December 2011 that featured "omega-3 polyunsaturated fatty acid intake of more than 2.7 g/day" for a minimum duration of 3 months to patients with rheumatoid arthritis were pooled for analysis. Ten trials with 370 patients were included. The dose ranged from 2.9-5.2 g/day of EPA + DHA for 9 trials with follow up period of 12 weeks to 15 months (8 trials: 12-24 weeks) and 1 trial administered 9.6 g/day of ALA (via linseed oil) for 3 months.[57]

- Treatment with omega-3 fatty acids did not significantly improve physical function, tender joint count, swollen joint count, pain or morning stiffness.
- Two of the 10 studies analysed consumption of non-steroidal anti-inflammatory drugs (NSAIDs). Meta-analysis found that omega-3 fatty acids in the fish oil preparations significantly **reduced NSAID consumption**. In these trials, 2.85 and 3 g/day of EPA + DHA were administered for 12 and 6 months, respectively.

Nonalcoholic Fatty Liver Disease

A review of the literature to May 2015 selected 10 randomised controlled trials with data on 577 patients with nonalcoholic fatty liver disease or nonalcoholic steatohepatitis for meta-analysis. One trial included diabetic patients with nonalcoholic steatohepatitis. Fish or seal oils, isolated omega-3 fatty acids and ethyl esters of EPA or EPA + DHA were administered. The dose ranged from 0.71 to 6.8 g/day of EPA + DHA. The preparations were taken for 12 months (range: 2-18 months). Diagnosis was confirmed by ultrasonography, magnetic resonance spectroscopy or liver biopsy.[58]

- Omega-3 fatty acid formulations improved liver fat (as measured by ultrasound), GGT (gamma-glutamyltransferase), triglycerides and HDL-cholesterol.
- No significant effect was observed on ALT (alanine aminotransferase), AST (aspartate aminotransferase), total cholesterol or LDL-cholesterol.

Obesity & Weight Management

The influence of fish oil/omega-3 fatty acid formulations on body composition in overweight or obese adults was investigated in a meta-analysis. Results from 21 randomised controlled trials published as recently as 2013 were analysed. Ten studies involved healthy participants; 5 assessed those with type 2 diabetes, metabolic syndrome or hyperinsulinaemia; there were 3 trials of women with polycystic ovary syndrome and the remainder enrolled those with cardiovascular risk, hypertension or severe obesity (one study each). Body mass index (BMI) ranged from 29 to 35 kg/m^2 in the 20 studies that did not include the severely obese (BMI: 46). In 12 studies, the only treatment was the fish oil/omega-3 fatty acid formulation

(one study used different forms of fish) and in the other 9 studies participants additionally received or undertook calorie restriction (7), physical exercise or both. The omega-3 fatty acid dose was quoted as ranging from 0.54 to 11.3 g/day, with a median dose of 1.92 g/day. (The actual dose range of EPA, EPA + DHA or long-chain omega-3 fatty acids was 0.54 to 4.2 g/day, with the other trial administering 11.3 g/day of fish oil.) Treatment lasted for 4 to 24 weeks (median: 12 weeks).[59]

- Waist circumference was significantly reduced in those with omega-3 fatty acid supplementation combined with diet and/or exercise.
- **Waist-hip ratio was significantly reduced** in those who received fish oil/omega-3 fatty acids with or without diet modifications.
- There was no effect on body weight or body mass index.

A review of 14 randomised controlled trials found that in 4 studies, omega-3 fatty acid supplementation significantly reduced circulatory leptin levels, while the other studies did not show a significant effect. Meta-analysis was conducted with the results of 13 of the trials. The dose of EPA or EPA + DHA provided by fish oil or omega-3 fatty acid preparations including ethyl esters, ranged between 138 mg/day and 4.2 g/day. One trial evaluated linseed (milled and oil), providing 7.7 g/day of ALA, and 1 trial compared fish oil (providing 3.6 g/day of EPA + DHA) with linseed oil (providing 3.7 g/day of ALA) with a control oil.[60]

- Subgroup analysis based on BMI status showed that omega-3 fatty acids reduce leptin when used for nonobese volunteers. This did not occur for obese participants.
- Subgroup analysis also showed that omega-3 from fish sources may significantly reduce leptin levels, but plant sources do not significantly affect serum leptin levels.

Nephropathy

Two 2012 meta-analyses have reviewed the effect of fish oil/omega-3 fatty acid preparations on IgA nephropathy, and concluded there is no beneficial effect on renal function. However, their conclusions differ in regard to proteinuria. The same 5 randomised controlled trials were assessed in each meta-analysis, and generally involved small numbers of patients. One meta-analysis found that omega-3 fatty acids significantly reduced proteinuria, the other found no effect. Dose-dependent effects, in which the results were separated into trials that administered less than or equal to 3 g/day of EPA + DHA and those administering greater than 3 g/day, were not found.[61,62] This may be due to how the data from one early trial was assessed – results for patients with renal dysfunction were separated from patients with normal serum creatinine at baseline.

Mother & Baby Health

Several meta-analyses have investigated the effect of supplementation with fish oil/omega-3 fatty acid formulations during pregnancy, and in some cases, lactation.

- Although there was no significant difference in the incidence of perinatal death found when all trials were considered, pooled results from 2 trials in which supplementation (3 g/day of EPA; fish oil providing 900 mg/day of EPA + DHA) started at or before 20 weeks' gestation showed a 73% decrease. Perinatal death was defined as the sum of still births and neonatal death.[63,64]
- Although supplementation during pregnancy was not associated with prevention of small-for-gestational age (i.e. birth weight less than the 10th percentile for gestational age) or with prevention of low birth weight, it was associated with statistically significant **higher birth weight** (mean difference 47.2 g).[63]

These formulations have been found to have no significant effect on pre-eclampsia,[65] intrauterine growth restriction,[63] gestational diabetes, pregnancy-induced hypertension,[66] infant vision after birth; language development, intelligence or problem-solving ability beyond 24 months; or child adiposity.[63,67-69] Although a small increase of 2.6 days in the mean length of gestation was observed,[65] these preparations did not reduce the risk of preterm birth.[64,65] The effect of intake of fish oil/omega-3 fatty acid formulations during pregnancy on childhood allergies is inconsistent. The most significant and consistent finding, determined by meta-analysis of 3 randomised controlled trials, was a reduction in the incidence of sensitisation (positive skin prick test) of infants tested within the first 12 months of life, in those whose mothers took fish oil (1.5-4.5 g/day, providing 0.9-3.3 g/day of EPA + DHA).[70]

OTHER EFFECTS FROM MULTIPLE CLINICAL TRIALS

Cancer

Oral nutritional supplements containing omega-3 fatty acids may **reduce weight loss or stabilise weight** in patients with advanced cancer, specifically those with tumours of the upper digestive tract and pancreas. This assessment is based on clinical trials or prospective studies published up to and including 2004, in patients not undergoing chemotherapy or radiotherapy at the time. Patients with potentially hormone-sensitive or emetogenic brain, breast, ovarian, prostate or endometrial cancer that would prevent proper oral intake were excluded. The effect on weight was observed in 10 studies (five of which were controlled), many of which involved low patients numbers. In 6 studies a nutritional supplement was evaluated and the remainder used fish oil (2) or ethyl

esters of EPA + DHA (2). Four of the six trials administered a nutritional supplement containing nutritional ingredients such as protein, fat, vitamins, minerals and trace elements in addition to EPA and DHA. Of the other 2 trials, one controlled for the nutritional content and the other did partially (addressing the macronutrient content but not taking into consideration the vitamins A, E, C and selenium). The latter trial found that the dose of omega-3 fatty acids (in addition to presence of the antioxidants) needed to be greater than 1.5 g/day of EPA and 0.96 g/day of DHA for a net gain of weight to occur. No effect on weight was demonstrated in 2 studies, and these controlled trials evaluated fish oil. In 2 studies, but not a third, the weight gain occurred at the expense of lean body mass.[71]

In additional studies:

- 70% of patients with head or neck cancer who consumed a nutritional supplement containing EPA + DHA, macronutrients and vitamins, minerals and trace elements, maintained or gained weight before surgery, and had increased lean body mass at discharge (uncontrolled trial);[72]
- a positive trend for weight gain occurred in cancer patients taking 2 g/day of EPA, but not those taking the higher dose of 4 g/day (placebo-controlled trial);[73]
- there was no beneficial effect on weight in postsurgical head and neck cancer patients that compared 2 nutritional supplements with differing omega-3 and omega-6 fatty acid ratios but similar contents of EPA + DHA.[74]

Fish oil/omega-3 fatty acid formulations promote weight maintenance or weight gain during chemotherapy: 6 of 7 randomised controlled trials found a beneficial effect. Additionally, no effect was found in patients undergoing radiotherapy, but better weight maintenance and lower decrease in lean body mass was observed in lung cancer patients undergoing chemoradiotherapy. The 9 trials were published between 2007 and 2014. In other results, quality of life, specifically physical function and global health status, was improved, although results were affected by maintenance of weight and lean body mass and lower inflammation (4 trials: only two of which controlled for the nutritional content of the supplement and hence discerned an effect for EPA and DHA).[75]

Cystic Fibrosis

A meta-analysis published in January 2016 analysed 4 small randomised trials that compared omega-3 fatty acid formulations with placebo in people with cystic fibrosis. An additional study which was unavailable for assessment at the time has been subsequently published (May 2016, *results follow*). There were insufficient results to pool for analysis. Unfortunately the trials to date have not assessed the most clinically-meaningful outcomes. One trial reported that FEV1 and FVC (parameters of lung function) as well as Shwachman score (a clinical parameter) improved when adolescents and adults took 2.7 g/day of EPA for 6 weeks. This study also found an improvement in sputum volumes in those treated with EPA, although the treatment group had a higher sputum volume at baseline and therefore had more scope for improvement. Other trials reported on the effect on biochemical markers of fatty acid status and adverse effects.[76] The more recent study found that compared to placebo, omega-3 fatty acids significantly decreased the number of pulmonary exacerbations at 12 months and the duration of antibiotic therapy. This pilot study had a total of 15 patients complete the treatment (placebo or omega-3 fatty acids, 60 mg/kg/day (consisting of 50% EPA and 33% DHA)) for 1 year.[77] (One of the studies reviewed for the meta-analysis, reported no difference in antibiotic use compared with a similar time period in the previous year.)

Other Conditions

In 3 crossover trials, fish oil/omega-3 fatty acid formulations have significantly decreased pain and reduced the use of rescue medication (ibuprofen) compared with placebo in young women with **dysmenorrhoea**. The supplements were taken for 2 to 3 months, with the daily dose of EPA + DHA ranging from 300 mg to 1800 mg.[78-80] The effect was not as strong in those with severe dysmenorrhoea.[80] In an earlier, double-blind, placebo controlled trial, although fish oil (providing 1.6 g/day of EPA + DHA; taken for 3 to 4 months) decreased the number of menstrual symptoms from baseline, the results were not significant compared to placebo.[81] A controlled trial also found that taking fish oil every day reduced the frequency of, and alleviated pain during menstruation to a significantly greater extent than using ibuprofen at the start of pain and up to 8 hours thereafter.[82]

Fish oil/omega-3 fatty acid formulations may improve or decrease the normal decline in **muscle function in older, healthy adults**. This has been demonstrated in 4 controlled trials, with participants aged 64 to 70 years.[83-86] Treatment with omega-3 fatty acids was not successful in older people with low muscle mass.[87]

- Combined with resistance training, a significant increase in muscle function, measured by maximal isometric torque of knee-extensor muscles, compared to placebo was observed in women but not men. There was no change in the chair-rise time. An increase in muscle quality (defined as strength per unit muscle area) was also demonstrated in women but not men. Fish oil (3 g/day), providing 2.7 g/day of EPA + DHA was taken for 18 weeks.[83]
- Fish oil (5 g/day, providing 3 g/day of EPA + DHA) taken for 12 weeks significantly improved results for the Timed Get Up and Go test. No change in the placebo group was observed.[84]

- There were significant beneficial effects on handgrip strength, and upper- and lower-body one-repetition maximum (1-RM) muscle strength found in those taking ethyl esters (providing 3.4 g/day of EPA + DHA) for 6 months, compared to the placebo group. The omega-3 fatty acid treatment also tended to increase the average isokinetic leg muscle power.[85]
- Strength training for 90 days increased muscle strength in women, but taking fish oil (2 g/day, providing about 700 mg/day of EPA + DHA) produced significantly greater improvements (peak torque, rate of torque development for all muscles, chair-raising performance).[86]

Symptoms of **dry eye syndrome** were significantly relieved by oral use of fish oil (providing 1.8 g/day of EPA + DHA for 12 weeks) or an omega-3 fatty acid formulation (providing 600 mg/day of EPA + DHA for 30 days) in patients participating in randomised, placebo-controlled trials.[88]

Two randomised, double-blind, placebo-controlled trials found that use of omega-3 fatty acid formulations for 6 months **decreased the symptoms of recurrent mouth ulcers**.[89,90]

Infants with phenylketonuria usually receive dietary treatment consisting of amino acid mixtures (excluding phenylalanine) but enriched with omega-3 fatty acids. The omega-3 fatty acids are not routinely provided after infancy. Two clinical trials found that fish oil given for 3 months to children aged 1-11 years with **phenylketonuria** improved motor function and coordination and improved the speed of processing information.[91] Children received 2-10 capsules of fish oil per day (providing 300-1500 mg/day of EPA + DHA), in order to achieve a dose of more than 15 mg/kg body weight of DHA.[91,92] The optimal dosage needs further investigation.[91,93]

Safety

A systematic review of randomised controlled trials published by September 2011 investigated the reported adverse effects arising from administration of fish oil/omega-3 fatty acid formulations in adults aged 60 years or older. Trials were excluded from the review if they included participants with known cardiovascular or metabolic disease, malignancy, kidney or liver disease or known cardiovascular disease risk factors (such as diabetes, hypertension, hyperlipidaemia) at study entry. Ten randomised controlled trials involving 994 participants were included. The dose of EPA + DHA ranged from 180 mg/day to 3.36 g/day, for 6 to 52 weeks. The authors defined severe adverse events as death, stroke, bleeding or major bruising. Four of the 10 studies reviewed excluded participants medicated with oral anticoagulants.[94]

- **No severe adverse events** were reported and there were no significant differences in the total adverse events rate between the omega-3 fatty acid and placebo groups (9.8% vs 6.2%, respectively; p = 0.07).
- Gastrointestinal disturbances (vomiting, halitosis, indigestion, pain, flatulence, diarrhoea, nausea or belching) were the most commonly reported non-severe adverse events however, there was no significant increase in the proportion of these disturbances reported in participants treated with omega-3 fatty acids compared to the placebo group (7.8% vs 5.3%, respectively; p = 0.18). One trial found significantly more cases of belching in fish oil-treated participants than the controls who consumed soy oil (42.3% vs 15.4%, respectively; p = 0.04).

Another systematic review of randomised controlled trials involving adults aged at least 60 years has been conducted. In this case, trial participants had diagnosed cardiovascular disease (CVD) or CVD risk factors. Both surgical and non-surgical settings were considered. Severe adverse events were defined as mortality, stroke, cardiovascular-related adverse events, bleeding or major bruising. Twenty-seven studies (1985-2011) with 26679 participants were included in the final review. Of these trials, eight included patients awaiting elective cardiac surgery. The lowest dose provided was 180 mg/day of EPA (+ 1120 mg/day of GLA) for 2 weeks, increasing if tolerated to 270 mg/day of EPA (+ 1680 mg/day of GLA) for a total of 2 years. The highest dose was 15 g/day of fish oil (omega-3 fatty acids not defined) taken for 8 weeks. Twelve trials used preparations providing constant doses ranging between 1.8 and 4.7 g/day of EPA and/or DHA. The main results are summarised in Table 1.[95]

Although fish oil/omega-3 fatty acid formulations may not increase the risk of haemorrhagic stroke, they probably should be discontinued during acute bleeding episodes, including haemorrhagic stroke,[96] and in those with bleeding disorders e.g. von Willebrand disease.

Pooling of the results of 5 randomised controlled trials (prior to November 2012) for patients undergoing cardiac surgery, found no significant influence of fish oil/omega-3 fatty acid formulations on the incidence of major bleeding.[25] (Included in this analysis was one trial also evaluated in the review of randomised trials involving older adults with diagnosed cardiovascular disease discussed above.[95])

Adverse Event	Occurrence
all-cause mortality	• reported in 5 studies involving surgical participants and 6 studies involving non-surgical participants • causes of death were unrelated to omega-3 fatty acid treatment
stroke	• reported in 2 studies involving surgical participants • infrequent and unrelated to omega-3 fatty acid treatment
	• reported in 2 studies involving non-surgical participants • no significant difference in the frequency of ischaemic and haemorrhagic stroke between groups (1.6% vs 1.5%, for omega-3 fatty acids and control groups, respectively) • one study observed an increased number of total bleeds (cerebral, fundal, epistaxis and subcutaneous bleeds) among those randomised to treatment with 1.8 g/day of EPA as ethyl esters (1.1% vs 0.6% in controls; p = 0.0006) – the difference in the incidence of total bleeds was not due to the contribution of cerebral bleeds alone, and these patients had high plasma EPA levels at baseline
major bleeding complications	• serious bleeds in surgical participants was seen equally in the omega-3 fatty acid groups and control groups (1.3% in both groups; reported in 2 studies) • considering surgical and non-surgical studies, major bleeding incidents were infrequent, affecting less than 1% of the entire study population
blood loss or bleeding time	• reported in 4 studies (surgical participants) • one study observed significant prolongation in bleeding time after 3 weeks of treatment with 1.8 g/day of EPA (4.5 minutes vs 4 minutes for controls; p = 0.02), the difference was no longer significant after 6 weeks of treatment • another study found there was a requirement for anticoagulant therapy in 12 of 610 (total) participants due to thromboembolic episodes, atrial fibrillation and left ventricular thrombus (2.5% of those treated with about 3.4 g/day of EPA + DHA vs 1.4% of the control group); in addition, 2 participants of the omega-3 fatty acid group developed contraindications to the antithrombotic drug treatment
gastrointestinal disturbances	• significant increase in the proportion of surgical participants who received omega-3 fatty acids reporting GI adverse events (1.9% vs 0.9% in controls; p = 0.002; reported in 2 studies) • significant increase in the proportion of non-surgical participants who received omega-3 fatty acids reporting GI adverse events (4.0% vs 2.0% in controls; p < 0.0001) • considering surgical and non-surgical studies, overall symptoms attributable to omega-3 fatty acids were infrequent with GI disturbances affecting only about 3.5% of participants
non-fatal coronary events	• subgroup analysis (among participants of non-surgical studies): significantly lower proportion of these events among participants who received omega-3 fatty acid treatment (4.0% vs 4.7% for controls; p = 0.01)

Table 1. Summary of adverse events reported from randomised controlled trials of omega-3 fatty acid formulations in adults over 60 years with diagnosed cardiovascular disease (CVD) or CVD risk factors.[95]

A 2007 review came to the conclusion that the risk for **clinically-significant bleeding** caused by intake of omega-3 fatty acids prior to surgery **was almost nonexistent**. The evidence was derived from observations of adverse events, specifically bleeding complications, from 19 clinical studies of patients who underwent major vascular surgery (coronary artery bypass grafting or endarterectomy) or femoral artery puncture for either diagnostic cardiac catheterisation or percutaneous transluminal coronary angioplasty from 1988 to 2003. In 3 trials patients took the formulations until surgery or through surgery. In the remaining studies, patients took the formulations for 4 to 28 months. The administered preparations provided doses ranging from 1.4 to 21 g/day apparently of EPA + DHA (or "omega-3 fatty acids", not further undefined) – in 14 trials the dose was in the range of 3-5.4 g/day. Concomitant medications were aspirin with or without heparin (15 trials), aspirin or warfarin, heparin and in 2 trials patients were not taking other medications.[97] (Included in this analysis were 2 trials also evaluated in the review of randomised trials involving older adults with diagnosed cardiovascular disease discussed above.[95])

A 2012 review by the European Food Safety Authority of the primary data (some of which was analysed in the above reviews) drew the following conclusions.[98]

- Long-term intake of EPA + DHA of up to about 5 g/day for up to 2 years and up to about 7 g/day for up to 6 months **does not increase the risk of spontaneous bleeding** episodes or bleeding complications even in those at high risk of bleeding (e.g. those taking aspirin or anticoagulants).
- Intake of EPA + DHA of up to about 6 g/day **does not enhance the effects of antiplatelet or antithrombotic medications** on bleeding time. The changes in bleeding times within the normal range which have been observed in some intervention studies, are not considered to be adverse as they were not associated with an increased risk of clinical complications (e.g. spontaneous bleeding). (This assessment was based on clinical studies published by 1998.)
- Changes to platelet function which are observed at intake of EPA and DHA (either alone or in combination) up to about 4 g/day are not considered to be adverse as they are not associated with an increased risk of clinical complications (e.g.

spontaneous bleeding). (This assessment was based on clinical studies published by 2008.)
- Intake of EPA + DHA of up to 5 g/day consumed for up to 12 weeks does not have significant adverse effects on glucose homoeostasis in healthy volunteers or diabetics.
- Intake of EPA and DHA consumed either alone or in combination at doses up to about 5 g/day for up to 16 weeks do not induce adverse changes in lipid peroxidation as long as the oxidative stability of these fatty acids is guaranteed.

Two retrospective, case-control studies that investigated the relationship between omega-3 fatty acid pre-treatment and bleeding in patients undergoing lumbar decompression surgery were published in 2012. The authors concluded that pre-operative use of omega-3 fatty acids did not increase bleeding complications during this surgery. In both studies, patients were asked to discontinue the omega-3 fatty acid formulations 2 to 5 days before surgery. Although the same outcomes would have been expected had they not stopped taking them before surgery, because of the very long half-life of omega-3 fatty acids in tissues: cessation for this short duration would have had virtually no effect on tissue omega-3 fatty acid levels.[99]

A review of the literature published between 2000 and 2015 describing an interaction between fish oil/omega-3 fatty acid formulations and warfarin uncovered only 3 case reports. The results obtained from these clinical reports were very conflicting. A retrospective analysis was conducted utilising patient information from a large private Queensland pathology clinic in an attempt to quantify the effect of omega-3 fatty acid supplementation on warfarin control. Patients with atrial fibrillation and deep vein thrombosis taking warfarin for more than 30 days and who had consumed fish oil or krill oil were included. Four hundred and twenty-eight patients were allocated to the control group, and 145 patients were allocated to the supplement group. It was found that fish and krill oils **did not significantly alter warfarin** TTR (time in therapeutic range) or bleeding incidence.[100]

EPA ethyl ester (4 g/day) did not affect the pharmacokinetics (such as extent of absorption) or the anticoagulation pharmacodynamics (specifically, international normalised ratio) of warfarin in healthy volunteers.[101]

Treatment with low-dose aspirin (100 mg/day) plus omega-3 fatty acid formulation (1985 mg/day of EPA + DHA) for 2 months improved uterine blood flow and did not increase menstrual bleeding in women with recurrent miscarriage.[102] No significant changes in bleeding on probing was found in adults with periodontitis participating in a double-blind, placebo-controlled parallel trial lasting 3 months. They were randomised to receive an algal oil (providing 2 g/day of DHA) plus low-dose aspirin (81 mg/day) or a placebo oil plus the same dose of aspirin.[103]

Aspirin insensitivity is associated with an increased risk of cardiovascular disease-related events, and is more common in diabetics than healthy individuals. Patients with aspirin insensitivity do not benefit from other antiplatelet drugs and the combination with other antiplatelet drugs, such as clopidogrel, is associated with a significantly higher risk of major bleeding than with aspirin alone. The effects of low-dose aspirin (81 mg/day, for 7 days) alone or together with fish oil (4 g/day, providing 2.4 g/day of EPA + DHA, for 28 days) on platelet aggregation in 30 adults with type 2 diabetes was evaluated. Overall, aspirin alone had generally similar effects as aspirin plus fish oil on platelet aggregation measures after both 4 hours and 7 days of aspirin ingestion. Five of 7 participants classified as aspirin insensitive 1 week after ingesting aspirin alone became sensitive after taking the combination.[104] By adding omega-3 fatty acids, 80% of aspirin-resistant patients were no longer resistant after treatment. The patients with stable coronary artery disease took low-dose aspirin plus omega-3 fatty acids (2.4 g/day of EPA + DHA) for 30 days.[105]

A retrospective study reviewed the medical records for bleeding complications in 182 patients, most with coronary artery disease and being treated with fish oil/omega-3 fatty acid formulations, aspirin (mean dose: 161 mg/day) and clopidogrel (mean dose: 75 mg/day) and in 182 age- and gender-matched controls treated with aspirin and clopidogrel alone. The mean follow-up period was 33 months.[106] Ninety-five percent of patients were taking a known brand of EPA and DHA ethyl esters, with a mean dosage of omega-3 fatty acid preparation of 3 g/day (approximately 2.5 g/day of EPA + DHA).
- One major bleeding episode occurred in the treatment group and none occurred in the control group.
- Four minor bleeding episodes (2.2%) occurred in the treatment group and 7 (3.9%) in the control group.
- More patients had minor bleeding complications in the control group than in the treatment group, although the difference was not statistically significant.
- The authors concluded that a substantial dose of EPA and DHA is safe in combination with aspirin and clopidogrel and does not increase the risk of bleeding compared with that observed with aspirin and clopidogrel alone.

Fish oil supplements were associated with 2 nose bleeds in a clinical trial that evaluated the drug ibrutinib in 63 previously treated patients with Waldenström's macroglobulinaemia (a malignant B-cell lymphoma), and these events resolved when the fish oil products were discontinued.[107]

EPA ethyl ester (4 g/day) did not adversely affect the pharmacokinetics of the following drugs in healthy volunteers: statins (rosuvastatin,[108] atorvastatin,[109,110] simvastatin[111]), omeprazole,[112] rosiglitazone.[113]

Retrospective analysis of pharmacokinetic data observed that fish oil/omega-3 fatty acid formulations increased exposure to the immunosuppressive drug sirolimus in kidney transplant patients on calcineurin inhibitor-free treatment. These patients required a 25% reduction of their sirolimus dose.[114]

Addition of fish oil (1.5 g/day, providing 530 mg/day of EPA + DHA) to the glucocorticoid dexamethasone had a detrimental effect on insulin resistance in healthy volunteers.[115] The same research team found a partial prevention of insulin resistance induced by the drug in an earlier study that used a higher dose of fish oil (6 g/day, providing 1.8 g/day of EPA + DHA).[116] Fish oil had a beneficial effect on fat oxidation and adipose tissue lipolysis, which may protect against increasing adiposity. Further studies are required to understand the risks and benefits in patients taking fish oil and treated chronically with synthetic glucocorticoids.[115]

On the basis that a long-chain omega-3 fatty acid (not EPA or DHA), known to be present in several species of fish and some fish oils, has caused resistance to chemotherapy (specifically, cisplatin) in mouse models, it has been recommended that fish oil (and possibly fish) be avoided on the days during and surrounding chemotherapy,[117] however, this research is regarded as preliminary at best and not convincing enough to require this caution.[118,119]

Fish oil should be used with caution in patients with known hypersensitivity to fish and/or shellfish.

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