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## Fish oil for kidney transplant recipients (Review)

Lim AKH, Manley KJ, Roberts MA, Fraenkel MB

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Fish oil for kidney transplant recipients.

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**Fish oil for kidney transplant recipients (Review)**

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[Intervention Review]

# Fish oil for kidney transplant recipients

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## ABSTRACT

### Background

Calcineurin inhibitors used in kidney transplantation for immunosuppression have adverse effects that may contribute to nephrotoxicity and increased cardiovascular risk profile. Fish oils are rich in very long chain omega-3 fatty acids, which may reduce nephrotoxicity by improving endothelial function and reduce rejection rates through their immuno-modulatory effects. They may also modify the cardiovascular risk profile. Hence, fish oils may potentially prolong graft survival and reduce cardiovascular mortality.

### Objectives

This review aimed to look at the benefits and harms of fish oil treatment in ameliorating the kidney and cardiovascular adverse effects of CNI-based immunosuppressive therapy in kidney transplant recipients.

### Search methods

We searched the Cochrane Kidney and Transplant Specialised Register (up to 17 March 2016) through contact with the Information Specialist using search terms relevant to this review.

### Selection criteria

All randomised controlled trials (RCTs) and quasi-RCTs of fish oils in kidney transplant recipients on a calcineurin inhibitor-based immunosuppressive regimen. RCTs of fish oil versus statins were included.

### Data collection and analysis

Data was extracted and the quality of studies assessed by two authors, with differences resolved by discussion with a third independent author. Dichotomous outcomes were reported as risk ratio (RR) and continuous outcome measures were reported as the mean difference (MD) with 95% confidence intervals using the random effects model. Heterogeneity was assessed using a Chi<sup>2</sup> test on n-1 degrees of freedom and the I<sup>2</sup> statistic. Data not suitable for pooling were tabulated and described.

### Main results

Fifteen studies (733 patients) were suitable for analysis. All studies were small and had variable methodology. Fish oil did not significantly affect patient or graft survival, acute rejection rates, or calcineurin inhibitor toxicity when compared to placebo. Overall SCr was significantly lower in the fish oil group compared to placebo (5 studies, 237 participants: MD -30.63 µmol/L, 95% CI -59.74 to -1.53; I<sup>2</sup> = 88%). In the subgroup analysis, this was only significant in the long-course (six months or more) group (4 studies, 157 participants: MD -37.41 µmol/L, 95% CI -69.89 to -4.94; I<sup>2</sup> = 82%). Fish oil treatment was associated with a lower diastolic blood pressure (4 studies, 200 participants: MD -4.53 mm Hg, 95% CI -7.60 to -1.45) compared to placebo. Patients receiving fish oil for more than six months had a modest

increase in HDL (5 studies, 178 participants: MD 0.12 mmol/L, 95% CI 0.03 to 0.21;  $I^2 = 47%$ ) compared to placebo. Fish oil effects on lipids were not significantly different from low-dose statins. There was insufficient data to analyse cardiovascular outcomes. Fishy aftertaste and gastrointestinal upset were common but did not result in significant patient drop-out.

### Authors' conclusions

There is insufficient evidence from currently available RCTs to recommend fish oil therapy to improve kidney function, rejection rates, patient survival or graft survival. The improvements in HDL cholesterol and diastolic blood pressure were too modest to recommend routine use. To determine a benefit in clinical outcomes, future RCTs will need to be adequately powered with these outcomes in mind.

## PLAIN LANGUAGE SUMMARY

### Fish oil for kidney transplant recipients

This review set out to assess any benefit or harm in using fish oil to reduce the risk of kidney damage and heart disease in people who have had a kidney transplant and are receiving standard drugs to prevent rejection. Information from 15 studies was used and showed that fish oils provide a slight improvement in HDL cholesterol and diastolic blood pressure. These studies did not provide enough information on the differences in the risk of death, heart disease, kidney transplant rejection or kidney function between patients receiving fish oils and those receiving placebo. There appeared to be no harmful effects of taking fish oil. The benefits of taking fish oil after a kidney transplant are a mild improvement in some heart disease risk factors. There was not enough information to show any benefit in preventing heart disease or reduction in kidney function. Larger, better studies are needed before regular use of fish oil can be recommended.

## BACKGROUND

### Description of the intervention

Fish oils contain high levels of polyunsaturated fatty acids (PUFAs) that may reduce cardiovascular risk and improve kidney transplant graft survival but they are not currently routinely used by kidney transplant recipients. There are two types of PUFAs, namely omega-6 (n-6 PUFA) and omega-3 (n-3 PUFA). n-6 PUFA (linoleic acid) is mainly derived from vegetable oils such as corn oil and sunflower oil. The n-3 PUFAs (linolenic acid) include  $\alpha$ -linolenic acid (ALA, C18:3 n-3), eicosapentaenoic acid (EPA, C20:5 n-3) and docosahexaenoic acid (DHA, C22:6 n-3). While ALA is available from certain plants such as linseed, soy, flaxseed and walnut, EPA and DHA are derived from fish and fish oils. The typical Western diet is abundant in plant n-6 PUFA relative to n-3 PUFA, with a ratio of approximately 10:1 (Kris-Etherton 2000). However, humans lack the enzymes to convert n-6 to n-3 PUFA, and convert only about 5% of ALA to EPA or DHA (Brenna 2002).

Evidence is accumulating in the general population that the very long chain n-3 PUFAs (EPA/DHA) found in fatty fish or fish oil supplements are beneficial in the prevention of cardiovascular disease (Psota 2006). This is probably the most common indication for fish oil supplementation. Potential benefits include antiarrhythmic, antithrombotic (decreased platelet aggregation), antiatherosclerotic and anti-inflammatory actions, lowering of blood pressure, and improvements in endothelial function and lipid profile (Din 2004). The common side effects of fish oil include gastrointestinal upset and fishy aftertaste. The inhibition of platelet aggregation theoretically increases the risk of bleeding but its clinical significance is debatable.

There are special circumstances in the kidney transplant population that increase the risk of graft dysfunction and cardiovascular disease that may be reduced by fish oil. The majority of kidney transplant immunosuppressive regimens include corticosteroids and a calcineurin-inhibitor (CNI), such as cyclosporin A (CSA) and tacrolimus. CNIs can cause endothelial dysfunction by reducing production of vasodilators (nitric oxide and prostaglandins, particularly prostacyclin) and increased release of vasoconstrictors (endothelin and thromboxane A<sub>2</sub>). In the kidney, this imbalance in the arachidonic acid-derived eicosanoid system results in a concentration-dependent vasoconstriction of the glomerular arterioles, decreasing renal plasma flow and glomerular filtration rate (GFR). CNI vasoconstriction causes dose-dependent azotaemia, increasing the risk of acute tubular necrosis and poor graft function. Chronically, CNIs can cause progressive kidney disease with tubular atrophy, striped tubulointerstitial fibrosis and an arteriopathy characterised by hyalinosis of the afferent arteriole (Ader 1998; Andoh 1997; Andoh 1998; de Mattos 2000). This increased risk of kidney failure due to CNI nephrotoxicity is apparent in non-kidney organ recipients (Ojo 2003).

Corticosteroid and CNI use is associated with a higher prevalence of hypertension (Braun 2003), where CSA has been shown to stimulate the renin-angiotensin system and enhance sympathetic nervous system activity (Ader 1998). Furthermore, an abnormal lipid profile occurs in 50% to 80% of kidney transplant recipients treated with prednisolone and CSA, characterised by an increase in total cholesterol, low-density lipoprotein (LDL), very low-density lipoprotein, and apolipoprotein B levels (Braun 2003). Hypertension is an independent risk factor for graft failure (Opelz

1998) and cardiovascular disease is an important contributor to mortality in kidney transplant recipients. For example, 38% of deaths in kidney transplant recipients in Australia and New Zealand are due to cardiovascular causes, where the risk of death is 5 to 10 times that of the age-matched population under 60 (McDonald 2003).

### How the intervention might work

The potential specific benefits of fish oil for the kidney transplant population include:

1. Reversing the endothelial dysfunction caused by CNI-induced disturbance in the eicosanoid pathway: Fish oil treatment is associated with a decreased synthesis of thromboxane and increased synthesis of prostacyclin, and reduced CSA-induced kidney dysfunction in rats (Norris 1990).
2. Immunomodulatory effects: Fish oil has been shown to reduce the pro-inflammatory cytokines involved in acute transplant rejection such as TNF- $\alpha$ , IL-1 and IL-2 (Endres 1989; Ford 1991; Endres 1993; Noronha 1992; Noronha 1993; Vandebroecke 1991; Yard 1994), enhance the immunosuppressive effects of cyclosporine (Kelley 1989), inhibit delayed type hypersensitivity in rat models of cardiac transplant (Otto 1990), and slow the deterioration of graft function in chronic vascular rejection (Sweny 1989).

### Why it is important to do this review

A recent large observational study looking at plasma n-3 PUFA levels in kidney transplant recipients in a Norwegian population noted reduced cardiovascular mortality with higher n-3 PUFA levels (Eide 2015). Furthermore, high levels of n-PUFA were also associated with better kidney allograft survival (Eide 2016). These observations were based on a population with a generally high dietary intake of marine n-3 PUFA.

Hence, fish oil may potentially prolong graft survival in addition to lowering cardiovascular risk. The addition of fish oil to kidney transplant protocols may therefore improve both short- and long-term outcomes for kidney transplant recipients.

## OBJECTIVES

This review aimed to look at the benefits and harms of fish oil treatment in ameliorating the kidney and cardiovascular adverse effects of CNI-based immunosuppressive therapy in kidney transplant recipients.

## METHODS

### Criteria for considering studies for this review

#### Types of studies

All randomised controlled trials (RCTs) and quasi-RCTs (RCTs in which allocation to treatment was obtained by alternation, use of alternate medical records, date of birth or other predictable methods) examining fish oils in kidney transplant recipients. The first period of randomised cross-over studies were included.

## Types of participants

### Inclusion criteria

All recipients of cadaveric or living kidney transplants on a CNI-based immunosuppressive protocol.

### Exclusion criteria

- CNI-free transplant immunosuppression protocol
- Multi-organ combined transplants, e.g. liver-kidney, pancreas-kidney

## Types of interventions

- Fish oil versus control oil
- Fish oil versus statin
- Early versus late introduction (> three months)
- Short-course versus long-course (> three months)

## Types of outcome measures

- Patient survival/death: yes/no
- Graft failure, defined as creatinine clearance (CrCl)/GFR < 15 mL/min OR dialysis: yes/no
- Acute rejection (biopsy proven) present: yes/no
- CNI toxicity (biopsy proven) present: yes/no
- Cardiovascular events (stroke, myocardial infarction and cardiovascular death): yes/no
- Adverse effects (gastrointestinal upset, taste, breath): yes/no
- Compliance (percentage drop-out rate during study period) and satisfaction (quality of life assessment by standard validated method e.g. the SF-36)
- Kidney function (GFR, CrCl, serum creatinine (SCr))
- Blood pressure (systolic, diastolic, mean arterial pressure (MAP))
- Serum lipid levels (total cholesterol, LDL, HDL, triglycerides)

For dichotomous outcomes, the events were combined to 12 months (or earlier for shorter studies). For continuous outcomes, the data was assessed at the 12-month time point (or earlier time point for shorter studies).

## Search methods for identification of studies

### Electronic searches

We searched the [Cochrane Kidney and Transplant Specialised Register](#) (up to 17 March 2016) through contact with the Information Specialist using search terms relevant to this review. The Cochrane Kidney and Transplant Specialised Register contains studies identified from several sources.

1. Monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL)
2. Weekly searches of MEDLINE OVID SP
3. Handsearching of kidney-related journals and the proceedings of major kidney conferences
4. Searching of the current year of EMBASE OVID SP
5. Weekly current awareness alerts for selected kidney journals
6. Searches of the International Clinical Trials Register (ICTRP) Search Portal and ClinicalTrials.gov.

Studies contained in the Specialised Register are identified through search strategies for CENTRAL, MEDLINE, and EMBASE based on the scope of Cochrane Kidney and Transplant. Details of these strategies, as well as a list of handsearched journals, conference proceedings and current awareness alerts, are available in the Specialised Register section of information about the [Cochrane Kidney and Transplant](#).

See [Appendix 1](#) for search terms used in strategies for this review.

### Searching other resources

1. Reference lists of review articles, relevant studies and clinical practice guidelines.
2. Letters seeking information about unpublished or incomplete trials to investigators known to be involved in previous studies.

## Data collection and analysis

### Selection of studies

The review was undertaken by four authors. The search strategy described was used to obtain titles and abstracts of studies that were potentially relevant to the review. The titles and abstracts were screened independently by two authors, who discarded studies that were not applicable. However, studies and reviews that included relevant data or information on studies were retained initially. Two authors independently assessed the retrieved abstracts and, if necessary, the full text of these studies to determine which studies satisfied the inclusion criteria.

### Data extraction and management

Data extraction was carried out by the same authors independently using standard data extraction forms. Studies reported in non-English language journals were translated before assessment. Where more than one publication of the same study existed, reports were grouped together and the publication with the most complete data was used. Disagreements were resolved in consultation with a third author.

### Assessment of risk of bias in included studies

For this update the following items were used to assess the risk of bias ([Higgins 2011](#)) (see [Appendix 2](#)).

- Was there adequate sequence generation (selection bias)?
- Was allocation adequately concealed (selection bias)?
- Was knowledge of the allocated interventions adequately prevented during the study?
  - \* Participants and personnel (performance bias)
  - \* Outcome assessors (detection bias)
- Were incomplete outcome data adequately addressed (attrition bias)?
- Are reports of the study free of suggestion of selective outcome reporting (reporting bias)?
- Was the study apparently free of other problems that could put it at a risk of bias?

### Measures of treatment effect

Results for dichotomous outcomes (death, graft failure, acute rejection, CNI toxicity, cardiovascular events, non-compliance with patient drop-out) were expressed as risk ratio (RR) with 95% confidence intervals (CI). Where continuous scales of measurement

were used to assess the effects of treatment (kidney function, blood pressure, lipid levels), the mean difference (MD) was used, or the standardised mean difference (SMD) if different scales had been used. Adverse effects were tabulated and assessed descriptively, as there was insufficient data to calculate a RR or MD.

#### Dealing with missing data

Further information required from the original authors were requested by written correspondence and information obtained in this manner was included in the review.

#### Assessment of heterogeneity

Heterogeneity was analysed using a Chi<sup>2</sup> test on N-1 degrees of freedom, with an alpha of 0.05 used for statistical significance, and also using the I<sup>2</sup> statistic (Higgins 2003).

#### Assessment of reporting biases

Funnel plots were to be used to assess for the potential existence of small study bias (Higgins 2011) however there were insufficient studies to do this.

#### Data synthesis

Data was pooled using the random effects model but the fixed effects model was also analysed to ensure robustness of the model chosen and susceptibility to outliers.

#### Subgroup analysis and investigation of heterogeneity

Subgroup analyses were planned to assess possible sources of heterogeneity. This was only possible for duration of treatment, dividing treatment courses into short (three months or less) and long (more than three months). The other subgroups which were considered but not analysed due to lack of data include:

1. Heterogeneity among participants related to patient age, underlying risk of graft failure (high if panel reactive antibodies > 50%, previous transplant, cold ischaemia > 24 hours) or diabetes.
2. Heterogeneity in treatments related to the dose of fish oil (g/d) or CNI (as assessed by serum CSA or tacrolimus level), duration and timing of treatment initiation.
3. Blood pressure control and specifically the use of calcium channel antagonists, renin-angiotensin antagonists or both.
4. Different immunosuppressive combinations.

## RESULTS

### Description of studies

#### Results of the search

##### 2007 review

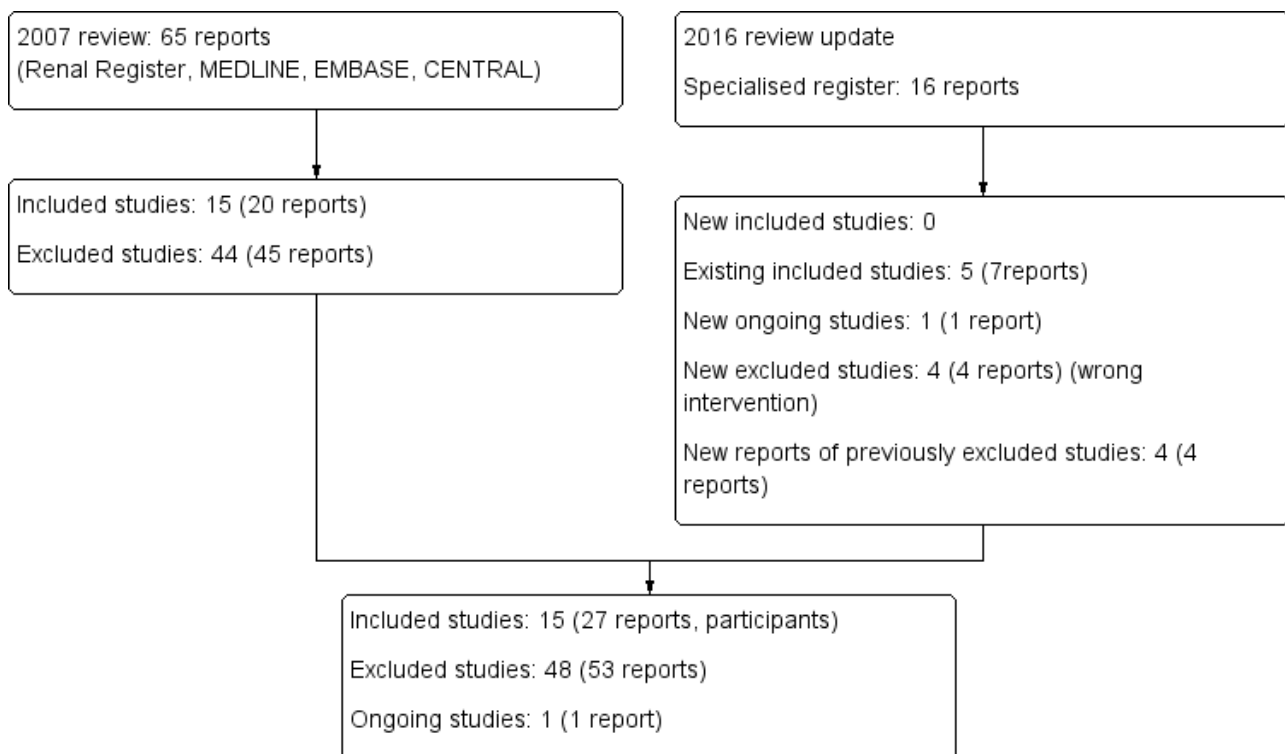
A total of 65 reports were identified after searching the Specialised Register, CENTRAL, MEDLINE and EMBASE. Of these, 45 reports (44 studies) were excluded and 20 reports (15 studies) were included.

##### 2016 review update

A search of the Specialised Register identified 16 new reports: seven new reports of five existing included studies (Busnach 1998; Homan van der Heide 1990a; Homan van der Heide 1990b; Homan van der Heide 1992; Kooijmans-Coutinho 1996); four new reports of two existing excluded studies (Alexander 2005; Levi 1992); four reports of four new excluded studies (Alexander 2006; Alexander 2008; Ramezani 2011; Romo 2012); and one recently completed study which is yet to publish any results (NCT01744067).

See Figure 1.

**Figure 1. Study flow diagram.**



**Included studies**

Of the 15 included studies (733 patients), 13 compared fish oil to control/placebo (658 patients) ([Bennett \(high\) 1995](#); [Bennett \(low\) 1995](#); [Berthoux 1992](#); [Busnach 1998](#); [Hernandez 2002](#); [Homan van der Heide 1990a](#); [Homan van der Heide 1990b](#); [Homan van der Heide 1992](#); [Homan van der Heide 1993](#); [Kooijmans-Coutinho 1996](#); [Maachi 1995](#); [Santos 2000](#); [Schut 1992a](#); [Schut 1992b](#); [Yoa 1994](#)), and two compared fish oil to statin treatment (75 patients) ([Castro 1997](#); [Rodriguez 1997](#)).

[Bennett \(high\) 1995](#) is the same study as [Bennett \(low\) 1995](#). The high dose arm is analysed compared to half of the control group for continuous outcomes. Dichotomous outcomes analysed together. Results for low and high dose corn oil were combined (n = 50) in the published report.

[Schut 1992a](#) is the same study as [Schut 1992b](#). [Schut 1992a](#) presents the data for patients receiving cyclosporin A and [Schut 1992b](#) presents the data for patients receiving cyclosporin A plus prednisone.

Four studies ([Homan van der Heide 1990a](#); [Homan van der Heide 1990b](#); [Homan van der Heide 1992](#); [Homan van der Heide 1993](#)) reported median rather than mean values for several continuous data variables and were not suitable for meta-analysis. Their continuous outcomes were assessed in a separate table but their dichotomous data was included in the analysis. All available studies contained small patient numbers and reporting on outcome measures was highly variable. The duration of treatment and follow-up was also variable, ranging from one to 12 months. No study exceeded 12 months in duration. The dose of fish oil ranged from 2 g/d to 18 g/d, comprising 0.6 g/d to 5.4 g/d of EPA and DHA. Three studies examined delayed introduction of fish oil ([Bennett](#)

[\(high\) 1995](#); [Homan van der Heide 1990b](#); [Schut 1992a](#)). One study ([Hernandez 2002](#)) used soy oil as the control, which is potentially a weak source ALA. However, we considered ALA to be sufficiently different from EPA/DHA to include this study. Two studies were identified which compared fish oil with statins. Both were small, single centre studies with late introduction of fish oil. [Castro 1997](#) compared low-dose simvastatin 10 mg/d to fish oil (duration three months), while [Rodriguez 1997](#) compared lovastatin 20 mg/d with fish oil (six months).

The reporting of outcome measures was variable ([Table 1 - Summary of reported outcome measures](#)). The primary outcomes of interest for most of these studies were kidney function and graft survival (except for the statin studies). The definition of the end points were also variable. Graft failure/loss was generally not defined. Reporting on acute rejection was either in terms of rejection episodes or number of patients with rejection. Some studies did not specify biopsy-proven rejection to define acute rejection episodes. Only [Hernandez 2002](#) provided unpublished data on biopsy-proven CNI toxicity, whereas in [Bennett \(low\) 1995](#) it was physician-diagnosed. Cardiovascular events were not a primary outcome measure for any of the included studies but data on cardiovascular death could be obtained from the reported cause of death. Adverse effects were not quantified but merely stated if present. Some studies reported drop-out rates from non-compliance but no standard quality of life assessment was used. The method of reporting kidney function was inconsistent, with some reports using SCr and CrCl, while others used nuclear GFR (methodology also varied e.g. EDTA, iothalamate, DTPA, inulin). Where data for different time points were available, only data at the latest follow-up was analysed.



**Excluded studies**

A total of 48 studies did not meet our inclusion criteria and were excluded (see [Characteristics of excluded studies](#)). The main reasons for exclusion were:

- Not randomised: 40 studies

- Wrong population: 1 study
- Wrong intervention: 5 studies
- Other: 2 studies (full-text publication not available; crossover study with no outcomes of interest reported or available)

**Risk of bias in included studies**

All studies were small and had variable methodology ([Figure 2](#)).

**Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.**

|                           | Random sequence generation (selection bias) | Allocation concealment (selection bias) | Intention-to-treat analysis | Blinding of participants and personnel (performance bias) | Blinding of outcome assessment (detection bias) | Incomplete outcome data (attrition bias) | Selective reporting (reporting bias) |
|---------------------------|---|---|-----------------------------|---|---|--|--------------------------------------|
| Bennett (high) 1995       | ?   | ?                                       | -                           | +   | ?   | -  | +                                    |
| Bennett (low) 1995        | ?   | ?                                       | -                           | +   | ?   | -  | +                                    |
| Berthoux 1992             | ?   | ?                                       | -                           | -   | -   | ?  | -                                    |
| Busnach 1998              | +   | +                                       | +                           | +   | +   | +  | +                                    |
| Castro 1997               | ?   | ?                                       | +                           | -   | -   | +  | -                                    |
| Hernandez 2002            | ?   | ?                                       | -                           | +   | +   | ?  | +                                    |
| Homan van der Heide 1990a | ?   | ?                                       | +                           | +   | ?   | +  | -                                    |
| Homan van der Heide 1990b | ?   | ?                                       | -                           | +   | ?   | ?  | -                                    |
| Homan van der Heide 1992  | ?   | ?                                       | +                           | +   | ?   | +  | -                                    |
| Homan van der Heide 1993  | ?   | ?                                       | +                           | +   | ?   | ?  | -                                    |
| Kooijmans-Coutinho 1996   | ?   | +                                       | +                           | +   | +   | +  | +                                    |
| Maachi 1995               | ?   | ?                                       | -                           | -   | ?   | ?  | ?                                    |
| Rodriguez 1997            | ?   | ?                                       | +                           | ?   | ?   | ?  | -                                    |
| Santos 2000               | ?   | ?                                       | +                           | ?   | ?   | +  | +                                    |
| Schut 1992a               | ?   | ?                                       | +                           | ?   | ?   | +  | -                                    |
| Schut 1992b               | ?   | ?                                       | +                           | ?   | ?   | +  | -                                    |
| Yoa 1994                  | ?   | ?                                       | +                           | ?   | ?   | +  | -                                    |

## Allocation

Random sequence generation was judged to be at low risk of bias in one study (Busnach 1998) and unclear in the remaining 14 studies.

Allocation concealment was judged to be at low risk of bias in two studies (Busnach 1998; Kooijmans-Coutinho 1996) and unclear in the remaining 13 studies.

Intention-to-treat analysis was not always explicitly stated but was apparent in 10 studies (Busnach 1998; Castro 1997; Homan van der Heide 1990a; Homan van der Heide 1992; Homan van der Heide 1993; Kooijmans-Coutinho 1996; Rodriguez 1997; Santos 2000; Schut 1992a; Schut 1992b; Yoa 1994).

## Blinding

Eight studies were judged to be at low risk of performance bias (Bennett (high) 1995; Bennett (low) 1995; Busnach 1998; Hernandez 2002; Homan van der Heide 1990a; Homan van der Heide 1990b; Homan van der Heide 1992; Homan van der Heide 1993; Kooijmans-Coutinho 1996) (using fish flavour or similar capsules). Three studies were judged to be at high risk of bias (Berthoux 1992; Castro 1997; Maachi 1995), and four studies were judged to be unclear (Rodriguez 1997; Santos 2000; Schut 1992a; Schut 1992b; Yoa 1994).

Three studies were judged to be at low risk of detection bias (Busnach 1998; Hernandez 2002; Kooijmans-Coutinho 1996); two were judged to be at high risk of bias (Berthoux 1992; Castro 1997), and the remaining 10 studies were judged to be unclear (Bennett (high) 1995; Bennett (low) 1995; Homan van der Heide 1990a; Homan van der Heide 1990b; Homan van der Heide 1992; Homan van der Heide 1993; Maachi 1995; Rodriguez 1997; Santos 2000; Schut 1992a; Schut 1992b; Yoa 1994).

## Incomplete outcome data

Studies of three months or less showed complete follow-up of patients, with the exception of Homan van der Heide 1990b (14% lost to follow-up). In studies lasting longer than six months, patients lost to follow-up ranged from 0% to 32%. Eight studies were judged to be at low risk of attrition bias (Busnach 1998; Castro 1997; Homan van der Heide 1990a; Homan van der Heide 1992; Kooijmans-Coutinho 1996; Santos 2000; Schut 1992a; Schut 1992b; Yoa 1994); one study was judged to be at high risk of bias (Bennett (high) 1995; Bennett (low) 1995); and the remaining six studies were judged to be at unclear risk (Berthoux 1992; Hernandez 2002; Homan van der Heide 1990b; Homan van der Heide 1993; Maachi 1995; Rodriguez 1997).

## Selective reporting

Five studies were judged to be at low risk of reporting bias (Bennett (high) 1995; Bennett (low) 1995; Busnach 1998; Hernandez 2002; Kooijmans-Coutinho 1996; Santos 2000), nine studies were judged to be at high risk of bias (Berthoux 1992; Castro 1997; Homan van der Heide 1990a; Homan van der Heide 1990b; Homan van der Heide 1992; Homan van der Heide 1993; Rodriguez 1997; Schut 1992a; Schut 1992b; Yoa 1994), and one study was unclear (Maachi 1995).

## Effects of interventions

### Fish oil versus control

#### All-cause mortality

There were six deaths in 12 studies where survival information was available (Analysis 1.1 (12 studies, 645 participants): RR 1.65, 95% CI 0.34 to 8.10;  $I^2 = 0\%$ ). Deaths were limited to three studies (Busnach 1998; Homan van der Heide 1993; Kooijmans-Coutinho 1996). Of the six deaths, there were three deaths in each of the fish oil and control groups. All patients died with a functioning graft. The cause of deaths were:

- Fish oil group - intestinal infarction (1), haemorrhagic shock post-removal of polycystic native kidney (1), not specified (1)
- Control group - myocardial infarction (1), not specified (2).

#### Graft loss

Twelve studies reported data on graft survival. Two studies in the short-course and five studies in the long-course reported one or more graft loss events. Graft survival was not affected by fish oil (Analysis 1.2 (12 studies, 640 participants): RR 0.91, 95% CI 0.51 to 1.63; participants = 640; studies = 12;  $I^2 = 0\%$ ).

#### Acute rejection

Nine studies contained data on acute rejection but data was only pooled from the eight studies reporting the proportion of patients with rejection as a dichotomous outcome within the study period. Pooled data from three short-course and five long-course studies showed no significant difference in acute rejection (Analysis 1.3 (8 studies, 482 participants): RR 1.00, 95% CI 0.80 to 1.25;  $I^2 = 0\%$ ). There was also no significant difference between short-course (Analysis 1.3.1 (3 studies, 197 participants): RR 1.21, 95% CI 0.82 to 1.79;  $I^2 = 1\%$ ) and long-course (Analysis 1.3.2 (5 studies, 285 participants): RR 0.92, 95% CI 0.70 to 1.20;  $I^2 = 0\%$ ) subgroups. However Homan van der Heide 1993 found less rejection episodes in the fish oil group at 12 months (8 versus 20,  $P = 0.029$ ). The largest difference occurred in the second and third months after transplantation (1 versus 9,  $P = 0.016$ ).

#### Calcineurin inhibitor toxicity

Hernandez 2002 reported biopsy-proven CNI toxicity. In this three-month study, there was no significant difference between fish oil and control (Analysis 1.4 (1 study, 90 participants): RR 1.19, 95% CI 0.56 to 2.51).

#### Calcineurin inhibitor levels

A *post-hoc* analysis of CNI levels was performed to look for any potential differences in CNI levels between the fish oil and control groups. No significant difference was detected in the six studies reporting trough CSA ( $C_0$ ) levels at the end of the studies (Analysis 1.5 (6 studies, 275 participants): MD 4.25 ng/mL, 95% CI -11.57 to 20.07;  $I^2 = 17\%$ ).

#### Cardiovascular events

None of the studies specifically reported myocardial infarction, stroke or cardiovascular death. Three studies had data on myocardial infarction (Bennett (low) 1995; Homan van der Heide 1993; Kooijmans-Coutinho 1996), with only one event in the fish oil and control groups each. Myocardial infarction was not a pre-

specified end-point in these studies but was reported as a reason why patients were not evaluated at the end of the study. One study noted no stroke events (Bennett (low) 1995). Cardiovascular causes of death could be gleaned from the description of the causes of death in some studies. However, events were too infrequent for a reliable estimate to be made.

### Adverse effects

None of the included studies quantitatively reported rates of adverse effects. Reported adverse effects are presented in Table 2: *Fish oil versus control: adverse effects*. Two studies reported no adverse effects (Bennett (low) 1995; Santos 2000). Seven studies reported a fishy aftertaste as the most common problem, with one (Hernandez 2002) reporting a fishy aftertaste in 70% of patients. Gastrointestinal upset such as bloating, nausea, vomiting and diarrhoea was reported in four studies (Berthoux 1992; Homan van der Heide 1993; Kooijmans-Coutinho 1996; Rodriguez 1997). Significant bleeding problems were not encountered.

### Compliance and satisfaction

Reporting of patient compliance was variable, with attempts at monitoring non-compliance having included pill counting, self-monitoring and biochemical measurements. The biochemical assays have included measuring plasma EPA as a percentage of total fatty acids (Bennett (low) 1995) and analyses of plasma cholesterol esters (Homan van der Heide 1993). However, these data could not be pooled due to the lack of a uniform and consistent measure of compliance among the studies. Hence, only data regarding significant non-compliance resulting in patient drop-out was sufficient for analysis. Information on such non-compliant patients was available in eight RCTs (two short-course and six long-course) (Analysis 1.8 (8 studies, 412 participants): RR 1.88, 95% CI 0.56 to 6.26;  $I^2 = 0\%$ ). Patient satisfaction was not assessed quantitatively or qualitatively in any of the included studies.

### Kidney function

#### Serum creatinine

Overall SCr was significantly lower in the fish oil group compared to control (Analysis 1.9 (5 studies, 237 participants): MD -30.63  $\mu\text{mol/L}$ , 95% CI -59.74 to -1.53;  $I^2 = 88\%$ ). In the subgroup analysis, this was only significant in the long-course group (Analysis 1.9.2 (4 studies, 157 participants): MD -37.41  $\mu\text{mol/L}$ , 95% CI -69.89 to -4.94;  $I^2 = 82\%$ ). There was also significant heterogeneity among the studies.

Three other studies used median values, which were not pooled (Table 1). Two (Homan van der Heide 1990a; Homan van der Heide 1992) showed no significant difference between fish oil and control, while another (Homan van der Heide 1990b) found a small difference favouring fish oil (120  $\mu\text{mol/L}$  versus 147  $\mu\text{mol/L}$ ;  $P < 0.05$ ).

#### Creatinine clearance

Overall there was no significant difference in CrCl between fish oil and control (Analysis 1.10 (8 studies, 353 participants): MD -0.61 mL/min, 95% CI -5.67 to 4.45;  $I^2 = 0\%$ ). There was also no difference in subgroup analyses.

Of the three studies reporting median values, two (Homan van der Heide 1990a; Homan van der Heide 1992) found no significant

difference however (Homan van der Heide 1990b) found a better CrCl in the fish oil group (88.4 mL/min versus 79.5 mL/min;  $P < 0.05$ ).

### Glomerular filtration rate

Overall there was no significant difference in GFR between fish oil and control (Analysis 1.11 (9 studies, 343 participants): MD 2.18 mL/min, 95% CI -2.90 to 7.26;  $I^2 = 25\%$ ).

Of the three studies reporting median GFR, Homan van der Heide 1990a and Homan van der Heide 1990b found no difference between the two groups while Homan van der Heide 1993 reported an improved GFR with fish oil (53 mL/min versus 40 mL/min;  $P = 0.038$ ).

### Blood pressure

Systolic pressure, diastolic pressure and MAP were reported variably among the included studies. Generally, MAP was defined as systolic + (2 x diastolic)/3.

Concomitant antihypertensive medication use was poorly reported. Therefore, data on antihypertensive medication use could not be analysed.

#### Systolic/diastolic blood pressure

There was no significant difference in systolic blood pressure between fish oil and control (Analysis 1.12 (4 studies, 200 participants): MD 2.45 mm Hg, 95% CI -5.93 to 10.83;  $I^2 = 66\%$ ); significant heterogeneity was evident. There was a modest but significant reduction in diastolic blood pressure in the fish oil group (Analysis 1.13 (4 studies, 200 participants): MD -4.53 mm Hg, 95% CI -7.60 to -1.45;  $I^2 = 0\%$ ).

#### Mean arterial blood pressure

There was a non-significant reduction in MAP in fish oil-treated patients (Analysis 1.14 (4 studies, 138 participant): MD -3.45 mm Hg, 95% CI -7.43 to 0.53;  $I^2 = 0\%$ ).

Of the four studies reporting median values (Table 1), three (Homan van der Heide 1990a; Homan van der Heide 1990b; Homan van der Heide 1992) found no difference in MAP between fish oil and control groups, while one (Homan van der Heide 1993) found a lower MAP with fish oil (103 mm Hg versus 118 mm Hg;  $P = 0.0011$ ).

### Serum lipids

The full lipid profile was not reported in all the included studies, hence variable patient numbers were available for each parameter for analysis.

#### Total cholesterol

There was no significant difference in TC between fish oil and control (Analysis 1.15 (6 studies, 260 participants): MD -0.11 mmol/L, 95% CI -0.36 to 0.14;  $I^2 = 26\%$ ).

#### LDL cholesterol

There was no significant difference in LDL cholesterol between the two groups (Analysis 1.16.2 (3 studies, 120 participants): MD 0.30 mmol/L, 95% CI -0.62 to 1.22;  $I^2 = 93\%$ ). The high heterogeneity was attributed to Bennett (low) 1995, however removal of this study from the analysis did not change the significance (MD -0.10 mmol/L, 95% CI -0.40 to 0.20;  $I^2 = 0\%$ ).

## HDL cholesterol

Overall there was no significant difference in HDL cholesterol between fish oil and control ([Analysis 1.17](#) (6 studies, 258 participants): MD 0.09 mmol/L, 95% CI -0.01 to 0.19;  $I^2 = 59\%$ ). Subgroup analysis showed long-course fish oil had a small but significant increase in HDL compared to control ([Analysis 1.17.2](#) (5 studies, 178 participants): MD 0.12 mmol/L, 95% CI 0.03 to 0.21;  $I^2 = 47\%$ ).

## Triglycerides

Overall there was no significant difference in triglycerides between fish oil and control ([Analysis 1.18](#) (MD -0.26 mmol/L, 95% CI -0.58 to 0.05; participants = 260; studies = 6;  $I^2 = 73\%$ ). There was substantial heterogeneity which could not be attributed to any one study.

## Fish oil versus statins

Two studies compared fish oil with statins. [Castro 1997](#) compared the effects of simvastatin (10 mg/d) with fish oil (6 g/d) (50% EPA/DHA) in 43 patients over three months. [Rodriguez 1997](#) compared fish oil (2 g/d) (30% EPA/DHA) with lovastatin (20 mg/d) in 34 patients over three months.

Total cholesterol was higher in the fish oil group but this was not significant ([Analysis 2.1](#) (2 studies, 75 participants): MD 0.36 mmol/L, 95% CI -0.10 to 0.82;  $I^2 = 0\%$ ).

LDL cholesterol was higher in the fish oil group but this was not significant ([Analysis 2.2](#) (2 studies, 75 participants): MD 0.41 mmol/L, 95% CI -0.06 to 0.88;  $I^2 = 0\%$ ).

HDL cholesterol was lower in the fish oil group but this was not significant ([Analysis 2.3](#) (2 studies, 75 participants): MD -0.18 mmol/L, 95% CI -0.39 to 0.02;  $I^2 = 44\%$ ).

Triglycerides were higher in the fish oil group but this was not significant ([Analysis 2.4](#) (2 studies, 75 participants): MD 0.18 mmol/L, 95% CI -0.18 to 0.55;  $I^2 = 0\%$ ).

## Patient subgroups

Subgroup analysis could only be performed dividing studies into short (three months or less) and long (greater than three months) courses of treatment. The only difference found was the better HDL result in the long-course as described. When we re-analysed the data using the different patient numbers for the continuous variables reported in [Hernandez 2002](#) (see *Table of included studies*), i.e. 45/40 versus 42/38, no significant change in the any of the results were found.

The results for those studies that only provided median and range for short- and long-course treatment are presented in [Table 3: Short course fish oil versus control/miscellaneous](#) and [Table 4: Long course fish oil versus control/miscellaneous](#).

## Fixed effects model

This model gave different results for the following outcomes.

### Fish oil versus controls

- LDL cholesterol was higher with fish oil treatment (MD 0.49 mmol/L, 95% CI 0.27 to 0.70;  $I^2 = 93\%$ ).

- HDL cholesterol was higher with fish oil treatment (MD 0.14 mmol/L, 95% CI 0.10 to 0.19;  $I^2 = 59\%$ ).
- Triglyceride was lower with fish oil treatment (MD -0.43 mmol/L, 95% CI -0.54 to -0.32;  $I^2 = 73\%$ ).

### Fish oil versus statins

- HDL cholesterol was higher with statin treatment (MD -0.18 mmol/L, 95% CI -0.34 to -0.03;  $P = 0.02$ ).

## DISCUSSION

### Summary of main results

In kidney transplant recipients on CSA-based immunosuppression, fish oil treatment has no effect on patient survival, graft survival, acute rejection and CNI toxicity. There was a modest lowering of diastolic blood pressure, and increased HDL in patients treated for six months or more. Clinical events were small and whilst an effect was not seen, a benefit cannot be ruled out by this analysis. The data on cardiovascular events was particularly limited as these were often not pre-specified end points. Where event data is reported, it has been used, but should be interpreted with caution because it is unclear whether cardiovascular event data was carefully collected for all patients.

The lowering of diastolic blood pressure was a consistent finding, with no heterogeneity. No data on antihypertensive medication use was available to allow stratification by antihypertensives in this analysis to explore the specific influences of calcium-channel or renin-angiotensin antagonists. Calcium channel blockers are known to reduce CSA mediated vasoconstriction, while renin-angiotensin inhibitors are capable of affecting GFR. There was evidence for heterogeneity in the finding of a higher HDL in the long course group ( $I^2 = 47\%$ ). The discrepancy between the  $I^2$  and the  $\text{Chi}^2$  test for heterogeneity ( $\text{Chi}^2 = 7.53$ ,  $P = 0.11$ ) reflects the lower power of the latter test to detect true heterogeneity when the number of studies is low ([Higgins 2003](#)). Such heterogeneity may arise from the use of different fish oil doses and duration, and different methods in measuring serum lipids.

There was no effect on kidney function and a discrepancy existed between serum creatinine and the other measures of kidney function. While SCr appeared lower with fish oil, there was substantial heterogeneity ( $I^2 = 88\%$ ;  $\text{Chi}^2 = 33.96$ ,  $P < 0.00001$ ). In addition to some of the potential sources listed above, heterogeneity between studies may have been impacted by the differing methods of measuring serum creatinine. Given that nuclear GFR is a better measure of kidney function in the transplant population, this is the more important measure on which to base conclusions. A fishy aftertaste was the most common adverse effect followed by gastrointestinal upset. Bleeding did not seem to be a problem despite the potential antithrombotic effect of fish oil. There was a suggestion of poorer compliance with fish oil compared to control but it was not statistically significant and did not significantly effect drop-out rates. The overall deficiencies in patient blinding made the comparisons of adverse effects and compliance difficult to assess. Patient satisfaction or quality of life assessments were not performed by any of the studies. With the exception of HDL cholesterol, there was no difference in short versus longer course treatment. There was also no difference in early versus late introduction of fish oils.

The fixed effects model showed different results for the lipid outcomes of LDL, HDL and triglycerides. This model is based on the assumption that the true effect of treatment (in both magnitude and direction) is the same value in every study, that there is no statistical heterogeneity, and that the observed differences are due to chance. However, there was significant heterogeneity among the studies included for these variables, with an  $I^2$  ranging from 44% to 94%. As the cause of heterogeneity is not readily apparent and the typical treatment effect is not known, the random effects model appears more applicable. However, it does introduce uncertainty as to whether a true effect may be missed.

### Quality of the evidence

There are several limitations of this review. Many of the studies were of poor or average quality due to small patient numbers, inadequate randomisation or allocation concealment, and lack of blinding (Figure 2). Some data from one group publishing several studies were expressed in a way that could not be incorporated in our analysis (Homan van der Heide 1990a; Homan van der Heide 1990b; Homan van der Heide 1992; Homan van der Heide 1993). There were several potential sources of heterogeneity, including differing doses of fish oils, duration of treatment, and timing of initiation of treatment. The studies were too small for these issues to be adequately explored through subgroup analyses. The majority of studies were conducted in the early to mid-1990s, prior to the common use of tacrolimus. Therefore, differences between CSA and tacrolimus could not be examined.

### Agreements and disagreements with other studies or reviews

A recent study in rats has demonstrated that DHA can increase the bioavailability of CSA possibly through inhibition of intestinal CYP 3A enzyme responsible for the first pass metabolism (Hirunpanich 2006). In our post-hoc analysis, we found that fish oil did not effect CSA levels. However, there are limitations to this finding. Firstly, the doses of CSA were not kept constant, as it is usual practice to adjust doses according to levels. Secondly, the studies included in the analysis where a benefit was significant were different to those which reported CSA levels. Thirdly, the use of a single trough level to indicate CNI exposure has limitations. The question whether fish oil influences CSA levels is difficult to answer as all but one of the included studies were not set up to assess CSA pharmacokinetics. In the only study to do so, fish oil treated patients had a higher maximum serum concentration ( $C_{max}$ ) than control patients but the area under curve (AUC) was not significantly higher despite similar trough levels (Busnach 1998). As AUC is probably a better indicator of overall drug exposure, the higher  $C_{max}$  may not necessarily translate to increased CNI toxicity in the long term. However, effects on other outcomes such as blood pressure are theoretically possible but the lower diastolic blood pressure found in our analysis suggests that this positive effect of fish oil may have outweighed any possible adverse pharmacokinetic interactions, or that CNI dose adjustments have compensated for this possible effect.

Overall, this analysis agrees with a published meta-analysis of fish oil supplementation in kidney transplantation (Tatsioni 2005), which demonstrated no difference in clinical outcomes except a modest reduction in triglycerides. The same studies were included in that analysis, however we have included CrCl data from the study by Yoa 1994 which was only reported in an earlier abstract.

They included one study that we excluded (Urakaze 1989) that reported rejection episodes, GFR, lipid and blood pressure data. We excluded the latter study as it was unclear which patients received CSA and which did not. This study was included in their analysis of triglycerides, which found a significant lowering by fish oils whereas we did not. These authors also used different statistical methodology for continuous variables. Rather than calculating MD, these authors calculated the net change in triglyceride for each study (Bonis 2005; Tatsioni 2005) and evaluated the aggregate. Although they appear to include the two studies comparing fish oil to statins in their publication (Tatsioni 2005), they do separate these from the placebo comparison in a separate publication (Bonis 2005).

Systematic reviews of n-3 PUFAs in the general population have demonstrated conflicting results. A reduction in triglycerides, increased HDL and increased LDL has been found with n-3 PUFA supplementation (Balk 2006) but a systematic review by Hooper 2006 showed no reduction in mortality or cardiovascular events. In this review, studies of ALA, EPA and DHA were pooled together, and composite end-points were analysed. In the review by Wang 2006 fish oil reduced rates of all-cause mortality, cardiac and sudden death, and possibly stroke. These authors analysed ALA separately from fish-derived n-3 PUFAs (EPA/DHA) and found that ALA was not associated with these positive findings, suggesting that ALA is sufficiently different from EPA/DHA to be analysed separately. We did not include studies using ALA in our analysis.

An important issue in these studies is the dose of fish oil used, which varied from 0.6 to 5.4 g/d (EPA + DHA). Active n-3 PUFAs (EPA, DHA) constitute only about 30% to 50% of common fish oil supplements, although higher doses may be available. This, and the duration and timing of treatment, may have contributed to the heterogeneity seen in a number of comparisons. There is some suggestion of a dose-dependent effect of fish oil. In the review by Balk 2006 there was an association between the dose of fish oil and reduction in TG. In our analysis, only one study directly compared two different doses (2.7 g/d and 5.4 g/d of EPA/DHA) and found no difference with the higher dose (Bennett (high) 1995).

## AUTHORS' CONCLUSIONS

### Implications for practice

There is insufficient evidence from currently available RCTs to recommend fish oil supplementation to improve kidney function, rejection rates, graft survival or patient survival in kidney transplantation. A dose of at least 6 g/d for longer than three months may be useful for improving HDL and lowering diastolic blood pressure. However, the safety and availability of conventional lipid modifying and antihypertensive agents makes fish oil an unlikely first-line choice. Fish oils were well tolerated with only minor adverse effects.

### Implications for research

Clearly, the studies included in this meta-analysis were too small, and the number of events too few to draw conclusions regarding benefit. These questions can only be answered by larger RCTs powered for specific clinical outcomes and of adequate duration. The introduction of non-CNI immunosuppressive protocols (such as those based on sirolimus) means that further studies with these medications are needed to assess the effects of fish oils in this

subset of kidney transplant recipients. It is recommended that future RCTs use a higher dose of fish oil to compare to controls, ideally 6 g/d or more. No studies have assessed the benefits fish oil as "add-on" therapy to statins and a subgroup of kidney transplant recipients with recurrent IgA nephropathy may also derive benefit from fish oil treatment and could be evaluated. Further studies on the effect of fish oil on CSA pharmacokinetics may be useful and

future studies should report CNI levels (including  $C_{max}$ ) and doses, and AUC where possible.

#### **ACKNOWLEDGEMENTS**

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\* Indicates the major publication for the study

**CHARACTERISTICS OF STUDIES**
**Characteristics of included studies** [ordered by study ID]

**Bennett (high) 1995**

|               |  |
|---------------|--|
| Methods       | <ul style="list-style-type: none"> <li>• Study design: double blind RCT</li> <li>• Time frame: 6 months</li> <li>• Follow-up period: 6 months</li> </ul>   |
| Participants  | <ul style="list-style-type: none"> <li>• Country: USA</li> <li>• Setting: multicentre (3 kidney transplant centres)</li> <li>• 18 to 70 years, clinically stable kidney transplants (16 week open-label baseline evaluation period)</li> <li>• Number: treatment group (18); control group (25)</li> <li>• Mean age <math>\pm</math> SD (years): not reported</li> <li>• Sex (M/F): not reported</li> <li>• Exclusion criteria: MI/arrhythmia &lt; 6 months; liver disease; malignancy &lt; 2 years; investigational drug use &lt; 3 months; severe gastrointestinal malabsorption; severe COPD; pregnancy; lactation; active infection; acute rejection &lt; 2 weeks prior to period 2</li> </ul>   |
| Interventions | <p>Treatment group</p> <ul style="list-style-type: none"> <li>• 18 g MaxEPA (EPA 180 mg/g, DHA 120 mg/g) daily</li> </ul> <p>Control group</p> <ul style="list-style-type: none"> <li>• Corn oil 18 g</li> </ul> <p>Co-interventions: not reported</p>   |
| Outcomes      | <ul style="list-style-type: none"> <li>• Patient survival</li> <li>• Graft survival</li> <li>• Acute rejection</li> <li>• Kidney function (GFR and CrCl)</li> <li>• HDL/LDL cholesterol</li> </ul>   |
| Notes         | <ul style="list-style-type: none"> <li>• <a href="#">Bennett (high) 1995</a> is the same study as <a href="#">Bennett (low) 1995</a></li> <li>• The high dose arm is analysed compared to half of the control group for continuous outcomes. Dichotomous outcomes analysed together (see <a href="#">Bennett (low) 1995</a>)</li> <li>• Results for low and high dose corn oil were combined (n = 50) in the published report</li> <li>• Exclusions post randomisation but pre intervention: none</li> <li>• Unpublished data provided by triallists                             <ul style="list-style-type: none"> <li>* Stroke and myocardial infarction: no events</li> </ul> </li> <li>• Completeness of follow-up: 90/133 patients evaluated (similar number of patients in both groups)</li> <li>• Rate of non-compliant drop-outs not reported (although mentioned)</li> <li>• Results for low and high dose corn oil were combined (n = 50) in the published report</li> </ul> |

**Risk of bias**

**Bennett (high) 1995** (Continued)

| Bias  | Authors' judgement | Support for judgement                         |
|---|--------------------|---|
| Random sequence generation (selection bias)                               | Unclear risk       | Not reported                                  |
| Allocation concealment (selection bias)                                   | Unclear risk       | Not reported                                  |
| Intention-to-treat analysis   | High risk          | No  |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk           | Participants blinded                          |
| Blinding of outcome assessment (detection bias)<br>All outcomes           | Unclear risk       | Not reported                                  |
| Incomplete outcome data (attrition bias)<br>All outcomes                  | High risk          | Loss to follow-up: 43 (32%)                   |
| Selective reporting (reporting bias)                                      | Low risk           | Outcomes relevant to our review were reported |

**Bennett (low) 1995**

|               |  |
|---------------|--|
| Methods       | <ul style="list-style-type: none"> <li>• Study design: double blind RCT</li> <li>• Time frame: 6 months</li> <li>• Follow-up period: 6 months</li> </ul>   |
| Participants  | <ul style="list-style-type: none"> <li>• Country: USA</li> <li>• Setting: multicentre (3 kidney transplant centres)</li> <li>• 18 to 70 years, clinically stable kidney transplants (16 week open-label baseline evaluation period)</li> <li>• Number: treatment group (22); control group (25)</li> <li>• Mean age <math>\pm</math> SD (years): not reported</li> <li>• Sex (M/F): not reported</li> <li>• Exclusion criteria: myocardial infarct/arrhythmia &lt; 6 months; liver disease; malignancy &lt; 2 years; investigational drug use &lt; 3 months; severe gastrointestinal malabsorption; severe COPD; pregnancy; lactation; active infection; acute rejection &lt; 2 weeks prior to period 2</li> </ul> |
| Interventions | <p>Treatment group</p> <ul style="list-style-type: none"> <li>• 9 g MaxEPA (EPA 180 mg/g, DHA 120 mg/g) daily</li> </ul> <p>Control group</p> <ul style="list-style-type: none"> <li>• Corn oil 9 g</li> </ul> <p>Co-interventions: not reported</p>   |
| Outcomes      | <ul style="list-style-type: none"> <li>• Patient survival</li> <li>• Graft survival</li> <li>• Acute rejection</li> </ul>  |

**Bennett (low) 1995** *(Continued)*

- Kidney function (GFR and CrCl)
- HDL/LDL cholesterol

## Notes

- [Bennett \(high\) 1995](#) is the same study as [Bennett \(low\) 1995](#)
- The high dose arm is analysed compared to half of the control group for continuous outcomes. Dichotomous outcomes analysed together
- Results for low and high dose corn oil were combined (n = 50) in the published report
- Exclusions post randomisation but pre intervention: none
- Unpublished data provided by triallists
  - \* Stroke and myocardial infarction: no events
- Completeness of follow-up: 90/133 patients evaluated (similar number of patients in both groups)
- Rate of non-compliant drop-outs not reported (although mentioned)
- Results for low and high dose corn oil were combined (n = 50) in the published report.

**Risk of bias**

| Bias  | Authors' judgement | Support for judgement                         |
|---|--------------------|---|
| Random sequence generation (selection bias)                               | Unclear risk       | Not reported                                  |
| Allocation concealment (selection bias)                                   | Unclear risk       | Not reported                                  |
| Intention-to-treat analysis   | High risk          | No  |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk           | Participants blinded                          |
| Blinding of outcome assessment (detection bias)<br>All outcomes           | Unclear risk       | Not reported                                  |
| Incomplete outcome data (attrition bias)<br>All outcomes                  | High risk          | Loss to follow-up: 43 (32%)                   |
| Selective reporting (reporting bias)                                      | Low risk           | Outcomes relevant to our review were reported |

**Berthoux 1992**

## Methods

- Study design: RCT (non-placebo)
- Time frame: 12 months
- Follow-up period: 12 months

## Participants

- Country: France
- Setting: single-centre university hospital
- Cadaveric donor kidney transplant recipients
- Number: treatment group (14); control group (15)
- Mean age  $\pm$  SD (years): treatment group (46.0  $\pm$  13.9); control group (42.9  $\pm$  10.7)
- Sex (M/F): treatment group (6/8); control group (11/4)

**Fish oil for kidney transplant recipients (Review)**



**Berthoux 1992** (Continued)

- Exclusion criteria: not reported

|               |  |
|---------------|--|
| Interventions | Treatment group <ul style="list-style-type: none"> <li>• 9 g fish oil (MaxEPA 3 g 3 times/d) daily (day 3 to 365)</li> </ul> Control group <ul style="list-style-type: none"> <li>• None</li> </ul> Co-interventions: none |
| Outcomes      | <ul style="list-style-type: none"> <li>• Patient survival</li> <li>• Graft survival</li> <li>• BP (data not shown)</li> <li>• Kidney function (SCr, CrCl, GFR)</li> <li>• Lipids (TC, TG)</li> </ul>                       |
| Notes         | <ul style="list-style-type: none"> <li>• Exclusions post randomisation but pre intervention: none</li> <li>• Additional data requested from authors: no unpublished data provided</li> </ul>                               |

**Risk of bias**

| Bias  | Authors' judgement | Support for judgement             |
|---|--------------------|-----------------------------------|
| Random sequence generation (selection bias)                               | Unclear risk       | Not reported                      |
| Allocation concealment (selection bias)                                   | Unclear risk       | Not reported                      |
| Intention-to-treat analysis   | High risk          | No                                |
| Blinding of participants and personnel (performance bias)<br>All outcomes | High risk          | No blinding                       |
| Blinding of outcome assessment (detection bias)<br>All outcomes           | High risk          | No blinding                       |
| Incomplete outcome data (attrition bias)<br>All outcomes                  | Unclear risk       | Loss to follow-up: 3 (9%)         |
| Selective reporting (reporting bias)                                      | High risk          | BP reported but no data available |

**Busnach 1998**

|              |   |
|--------------|---|
| Methods      | <ul style="list-style-type: none"> <li>• Study design: double blind placebo controlled RCT</li> <li>• Time frame: 12 months</li> <li>• Follow-up period: 12 months</li> </ul> |
| Participants | <ul style="list-style-type: none"> <li>• Country: Italy</li> </ul>  |

**Fish oil for kidney transplant recipients (Review)**

**Busnach 1998** (Continued)

- Setting: single centre
- All kidney transplant recipients
- Number: treatment group (21); control group (21)
- Mean age  $\pm$  SD (years): treatment group ( $44 \pm 2.6$ ); control group ( $39 \pm 2.1$ )
- Sex (M/F): treatment group (10/11); control group (14/7)
- Exclusion criteria: significant lipid disorders, on hypolipaeic drugs in last 3/12 pre-transplant

|               |  |
|---------------|--|
| Interventions | Treatment group <ul style="list-style-type: none"> <li>• 6 g/d fish oil (Esapent) (85% EPA, DHA) for 1 month, 3 g/d to completion</li> </ul> Control group <ul style="list-style-type: none"> <li>• 6 g/d olive oil similar schedule to treatment group</li> </ul> Co-interventions: none  |
| Outcomes      | <ul style="list-style-type: none"> <li>• Patient survival</li> <li>• Graft failure</li> <li>• Acute rejection</li> <li>• Compliance</li> <li>• Kidney function (SCr)</li> <li>• BP (not reported/no longer available)</li> <li>• Lipids</li> </ul>   |
| Notes         | <ul style="list-style-type: none"> <li>• Exclusions post randomisation but pre intervention: none</li> <li>• Additional data requested: unpublished data provided by triallists             <ul style="list-style-type: none"> <li>* Acute rejection: not all rejection episodes were biopsy proven</li> <li>* CSA toxicity: only looked at when biopsy was performed (retrospective)</li> <li>* Compliance: no withdrawals for side-effects; adverse effects not specifically considered</li> <li>* Method of randomisation: centrally processed by sponsor by means of sealed envelopes; active drug and placebo capsules prepared by sponsor</li> </ul> </li> </ul> |

**Risk of bias**

| Bias  | Authors' judgement | Support for judgement                       |
|---|--------------------|---|
| Random sequence generation (selection bias)                               | Low risk           | Central randomisation (sponsor)             |
| Allocation concealment (selection bias)                                   | Low risk           | Closed envelopes                            |
| Intention-to-treat analysis   | Low risk           | Yes   |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk           | Participants and investigators blinded      |
| Blinding of outcome assessment (detection bias)<br>All outcomes           | Low risk           | Outcome assessors and data analysis blinded |
| Incomplete outcome data (attrition bias)<br>All outcomes                  | Low risk           | No losses to follow-up                      |

**Fish oil for kidney transplant recipients (Review)**

**Busnach 1998** (Continued)

|                                      |          |  |
|--------------------------------------|----------|--|
| Selective reporting (reporting bias) | Low risk | All relevant outcomes reported; BP not reported but data no longer available |
|--------------------------------------|----------|--|

**Castro 1997**

|               |  |
|---------------|--|
| Methods       | <ul style="list-style-type: none"> <li>• Study design: RCT of fish oil versus statin (non-placebo, open-label)</li> <li>• Time frame: 3 months</li> <li>• Follow-up: 3 months</li> </ul>   |
| Participants  | <ul style="list-style-type: none"> <li>• Country: Portugal</li> <li>• Setting: single centre</li> <li>• &gt; 1 year post-transplant, stable kidney function, persistent elevated cholesterol after a 12-week lipid lowering diet (AHA, Step 2)</li> <li>• Number: treatment group (18); control group (25)</li> <li>• Mean age <math>\pm</math> SD (years): treatment group (43.4 <math>\pm</math> 11.7); control group (45.6 <math>\pm</math> 9.4)</li> <li>• Sex (M/F): treatment group (6/12); control group (11/14)</li> <li>• Exclusion criteria: non-compliance (13 patients excluded pre-randomisation); diet-normalised patients excluded</li> </ul> |
| Interventions | <p>Treatment group</p> <ul style="list-style-type: none"> <li>• Fish oil 6 g/d (30% EPA; 20% DHA)</li> </ul> <p>Control group</p> <ul style="list-style-type: none"> <li>• Simvastatin 10 mg/d</li> </ul> <p>Co-interventions: none</p>  |
| Outcomes      | <ul style="list-style-type: none"> <li>• Lipids: TC, TG, LDL, HDL</li> </ul>   |
| Notes         | <ul style="list-style-type: none"> <li>• Exclusions post randomisation but pre intervention: none</li> <li>• Additional data requested: none</li> </ul>  |

**Risk of bias**

| Bias  | Authors' judgement | Support for judgement |
|---|--------------------|-----------------------|
| Random sequence generation (selection bias)                               | Unclear risk       | Not reported          |
| Allocation concealment (selection bias)                                   | Unclear risk       | Not reported          |
| Intention-to-treat analysis   | Low risk           | Yes                   |
| Blinding of participants and personnel (performance bias)<br>All outcomes | High risk          | Open-label study      |
| Blinding of outcome assessment (detection bias)<br>All outcomes           | High risk          | No blinding           |

**Castro 1997** (Continued)

|  |           |                           |
|--|-----------|---------------------------|
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk  | No losses to follow-up    |
| Selective reporting (reporting bias)                     | High risk | Only lipids were reported |

**Hernandez 2002**

|               |   |
|---------------|---|
| Methods       | <ul style="list-style-type: none"> <li>Study design: double blind placebo controlled RCT</li> <li>Time frame: 3 months</li> <li>Follow-up period: 12 months</li> </ul>  |
| Participants  | <ul style="list-style-type: none"> <li>Country: Spain</li> <li>Setting: single centre</li> <li>Consecutive recipients of 1st cadaveric kidney graft, 18 to 70 years, no fish oil or immunosuppressive treatment &lt; 6 months, no haemorrhagic disorders</li> <li>Number: treatment group (46); control group (40)</li> <li>Mean age <math>\pm</math> SD (years): treatment group (46.8 <math>\pm</math> 12.1); control group (45.3 <math>\pm</math> 14.5)</li> <li>Sex (M/F): treatment group (26/19); control group (30/10)</li> <li>Exclusion criteria: investigational drug &lt; 3 months; acute liver disease; malignancy &lt; 2 years; fish or iodine allergy; pregnancy or lactation</li> </ul>  |
| Interventions | <p>Treatment group</p> <ul style="list-style-type: none"> <li>6 g/d fish oil (Epaleo) 21% EPA; 11% DHA</li> </ul> <p>Control group</p> <ul style="list-style-type: none"> <li>6 g/d soy oil</li> </ul> <p>Co-interventions: none</p>  |
| Outcomes      | <ul style="list-style-type: none"> <li>Patient survival</li> <li>Graft survival</li> <li>Acute rejection</li> <li>CNI toxicity</li> <li>Adverse effects</li> <li>Compliance</li> <li>Kidney function (SCr, CrCl, GFR)</li> <li>BP</li> <li>Lipids</li> </ul>  |
| Notes         | <ul style="list-style-type: none"> <li>Exclusions post randomisation but pre intervention: 1 patient (post-op thrombosis, graft loss)</li> <li>Additional data requested: unpublished data provided by trialists           <ul style="list-style-type: none"> <li>* Nature of loss to follow-up: 12 patients at 12 months (fish oil: allograft loss (6), acute rejection (5), CAN (1); control: allograft loss (6), acute rejection (4), CAN (2)).</li> <li>* These figures were used for graft survival analysis rather than deriving numbers from percentages in publication. In publication, 5 patients lost grafts (fish oil (3), control (2)). We have assumed that these occurred in the intervention period of the initial 3 months and the remainder of the graft losses occurred from 4 to 12 months. Therefore, we have adjusted the patient numbers to 42/38 for fish oil/control respectively for the analysis of continuous outcomes.</li> <li>* Patients with rejection: 36 (fish oil (20), control (16))</li> <li>* CNI toxicity: all biopsy proven</li> </ul> </li> </ul> |

**Hernandez 2002** (Continued)

- \* Adverse effects: fishy aftertaste 70%
- \* Compliance: no patient drop-out
- \* HDL (LDL calculated using Frederickson formula)
- \* Systolic and diastolic BP

**Risk of bias**

| Bias  | Authors' judgement | Support for judgement                     |
|---|--------------------|---|
| Random sequence generation (selection bias)                               | Unclear risk       | Central (method not specified)            |
| Allocation concealment (selection bias)                                   | Unclear risk       | Not reported                              |
| Intention-to-treat analysis   | High risk          | No  |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk           | Participants and investigators blinded    |
| Blinding of outcome assessment (detection bias)<br>All outcomes           | Low risk           | Outcomes assessors blinded                |
| Incomplete outcome data (attrition bias)<br>All outcomes                  | Unclear risk       | 12/86 (14%) lost to follow-up             |
| Selective reporting (reporting bias)                                      | Low risk           | Outcomes relevant to this review reported |

**Homan van der Heide 1990a**

|               |  |
|---------------|--|
| Methods       | <ul style="list-style-type: none"> <li>• Study design: double blind placebo controlled RCT</li> <li>• Time frame: 1 month</li> <li>• Follow-up period: 1 month</li> </ul>  |
| Participants  | <ul style="list-style-type: none"> <li>• Country: Netherlands</li> <li>• Setting: single centre (unclear)</li> <li>• Inclusion criteria: not reported</li> <li>• Number: treatment group (14); control group (17)</li> <li>• Median age, range (years): treatment group (49, 28 to 63); control group (47, 22 to 64)</li> <li>• Sex (M/F): not reported</li> <li>• Exclusion criteria: not reported</li> </ul> |
| Interventions | Treatment group <ul style="list-style-type: none"> <li>• 6 g/d fish oil (Kortman Intradal) EPA 30%; DHA 20%</li> </ul> Control group <ul style="list-style-type: none"> <li>• 6 g/d coconut oil</li> </ul>   |

**Homan van der Heide 1990a** (Continued)

Co-interventions: none

|          |  |
|----------|--|
| Outcomes | <ul style="list-style-type: none"> <li>• Patient survival</li> <li>• Graft failure</li> <li>• Acute rejection (not defined whether biopsy proven, data not used)</li> <li>• Adverse effects</li> <li>• BP (MAP)</li> <li>• Kidney function (SCr, CrCl, GFR)</li> </ul> |
| Notes    | <ul style="list-style-type: none"> <li>• Exclusions post randomisation but pre intervention: none</li> <li>• Additional data requested: no unpublished data provided</li> </ul>  |

**Risk of bias**

| Bias  | Authors' judgement | Support for judgement   |
|---|--------------------|---|
| Random sequence generation (selection bias)                               | Unclear risk       | Not reported  |
| Allocation concealment (selection bias)                                   | Unclear risk       | Not reported  |
| Intention-to-treat analysis   | Low risk           | Yes   |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk           | Participants blinded  |
| Blinding of outcome assessment (detection bias)<br>All outcomes           | Unclear risk       | Not reported  |
| Incomplete outcome data (attrition bias)<br>All outcomes                  | Low risk           | No losses to follow-up  |
| Selective reporting (reporting bias)                                      | High risk          | Unable to use acute rejection data; median data reported for some continuous outcomes |

**Homan van der Heide 1990b**

|              |   |
|--------------|---|
| Methods      | <ul style="list-style-type: none"> <li>• Study design: double blind placebo controlled RCT</li> <li>• Time frame: 3 months</li> <li>• Follow-up period: 3 months</li> </ul>   |
| Participants | <ul style="list-style-type: none"> <li>• Country: Netherlands</li> <li>• Setting: single centre (unclear)</li> <li>• Patients &gt; 9 months post-transplant, stable kidney function and CSA dosage &gt; 3 months</li> <li>• Number: treatment group (11); control group (10)</li> <li>• Median age, range (years): treatment group (40, 27 to 66); control group (37, 17 to 62)</li> <li>• Sex (M/F): treatment group (5/6); control group (6/4)</li> <li>• Exclusion criteria: not reported</li> </ul> |

**Homan van der Heide 1990b** (Continued)

|               |   |
|---------------|---|
| Interventions | Treatment group <ul style="list-style-type: none"> <li>6 g/d fish oil (Super EPA) EPA 30%; DHA 20%</li> </ul> Control group <ul style="list-style-type: none"> <li>6 g/d corn oil</li> </ul> Co-interventions: none |
| Outcomes      | <ul style="list-style-type: none"> <li>Patient survival</li> <li>Graft failure</li> <li>Acute rejection</li> <li>Compliance</li> <li>BP (MAP)</li> <li>Kidney function (SCr, CrCl, GFR)</li> </ul>                  |
| Notes         | <ul style="list-style-type: none"> <li>Exclusions post randomisation but pre intervention: none</li> <li>Additional data requested: no unpublished data provided</li> </ul>   |

**Risk of bias**

| Bias  | Authors' judgement | Support for judgement                             |
|---|--------------------|---|
| Random sequence generation (selection bias)                               | Unclear risk       | Not reported                                      |
| Allocation concealment (selection bias)                                   | Unclear risk       | Not reported                                      |
| Intention-to-treat analysis   | High risk          | No  |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk           | Participants blinded                              |
| Blinding of outcome assessment (detection bias)<br>All outcomes           | Unclear risk       | Not reported                                      |
| Incomplete outcome data (attrition bias)<br>All outcomes                  | Unclear risk       | Loss to follow-up: 3 (14%)                        |
| Selective reporting (reporting bias)                                      | High risk          | Median data reported for some continuous outcomes |

**Homan van der Heide 1992**

|              |   |
|--------------|---|
| Methods      | <ul style="list-style-type: none"> <li>Study design: double blind placebo controlled RCT</li> <li>Time frame: 1 month</li> <li>Follow-up period: 1 month</li> </ul> |
| Participants | <ul style="list-style-type: none"> <li>Country: Netherlands</li> </ul>  |

**Fish oil for kidney transplant recipients (Review)**

**Homan van der Heide 1992** (Continued)

- Setting: single centre
- Consecutive first cadaveric kidney transplants
- Number: treatment group (40); control group (48)
- Median age, range (years): treatment group (48, 17 to 68); control group (44, 19 to 68)
- Sex (M/F): treatment group (26/14); control group (28/20)
- Exclusion criteria: not reported

|               |   |
|---------------|---|
| Interventions | Treatment group <ul style="list-style-type: none"> <li>• 6 g/d fish oil (Kortman Intradal) EPA 30%; DHA 20%</li> </ul> Control group <ul style="list-style-type: none"> <li>• 6 g/d coconut oil</li> </ul> Co-interventions: none     |
| Outcomes      | <ul style="list-style-type: none"> <li>• Patient survival</li> <li>• Graft survival</li> <li>• Acute rejection</li> <li>• Adverse effects</li> <li>• Compliance</li> <li>• Kidney function (SCr, CrCl)</li> <li>• BP (MAP)</li> </ul> |
| Notes         | <ul style="list-style-type: none"> <li>• Exclusions post randomisation but pre intervention: none</li> <li>• Additional data requested: no unpublished data provided</li> </ul>   |

**Risk of bias**

| Bias  | Authors' judgement | Support for judgement                             |
|---|--------------------|---|
| Random sequence generation (selection bias)                               | Unclear risk       | Not reported                                      |
| Allocation concealment (selection bias)                                   | Unclear risk       | Not reported                                      |
| Intention-to-treat analysis   | Low risk           | Yes   |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk           | Participants blinded; placebo flavour matched     |
| Blinding of outcome assessment (detection bias)<br>All outcomes           | Unclear risk       | Not reported                                      |
| Incomplete outcome data (attrition bias)<br>All outcomes                  | Low risk           | No loss to follow-up                              |
| Selective reporting (reporting bias)                                      | High risk          | Median data reported for some continuous outcomes |



**Homan van der Heide 1993**

|               |   |
|---------------|---|
| Methods       | <ul style="list-style-type: none"> <li>• Study design: double blind placebo control RCT (blinding ceased at 3 months)</li> <li>• Time frame: 12 months</li> <li>• Follow-up period: 12 months</li> </ul>  |
| Participants  | <ul style="list-style-type: none"> <li>• Country: Netherlands</li> <li>• Setting: single centre</li> <li>• First cadaveric kidney transplant</li> <li>• Number: treatment group (33); control group (33)</li> <li>• Median age, range (years): treatment group (41, 17 to 69); control group (47, 19 to 67)</li> <li>• Sex (M/F): treatment group (21/12); control group (19/14)</li> <li>• Exclusion criteria: not reported</li> </ul> |
| Interventions | <p>Treatment group</p> <ul style="list-style-type: none"> <li>• 6 g/d fish oil (Kortman Intradal) EPA 30%; DHA 20%</li> </ul> <p>Control group</p> <ul style="list-style-type: none"> <li>• 6 g/d coconut oil</li> </ul> <p>Co-interventions: none</p>  |
| Outcomes      | <ul style="list-style-type: none"> <li>• Patient survival</li> <li>• Graft survival</li> <li>• Acute rejection</li> <li>• Adverse effects</li> <li>• Compliance</li> <li>• Kidney function (GFR)</li> <li>• BP (MAP)</li> </ul>   |
| Notes         | <ul style="list-style-type: none"> <li>• Exclusions post randomisation but pre intervention: none</li> <li>• Additional data requested: no unpublished data provided</li> </ul>   |

**Risk of bias**

| Bias  | Authors' judgement | Support for judgement                         |
|---|--------------------|---|
| Random sequence generation (selection bias)                               | Unclear risk       | Not reported                                  |
| Allocation concealment (selection bias)                                   | Unclear risk       | Not reported                                  |
| Intention-to-treat analysis   | Low risk           | Yes   |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk           | Participants blinded; placebo flavour matched |
| Blinding of outcome assessment (detection bias)<br>All outcomes           | Unclear risk       | Not reported                                  |
| Incomplete outcome data (attrition bias)                                  | Unclear risk       | Loss to follow-up: 6 (9%)                     |

**Fish oil for kidney transplant recipients (Review)**

**Homan van der Heide 1993** (Continued)

All outcomes

|                                      |           |   |
|--------------------------------------|-----------|---|
| Selective reporting (reporting bias) | High risk | Median data reported for some continuous outcomes |
|--------------------------------------|-----------|---|

**Kooijmans-Coutinho 1996**

|               |  |
|---------------|--|
| Methods       | <ul style="list-style-type: none"> <li>Study design: double blind placebo controlled RCT</li> <li>Time frame: 12 months (May 1990 to November 1991)</li> <li>Follow-up period: 12 months</li> </ul>  |
| Participants  | <ul style="list-style-type: none"> <li>Country: Netherlands</li> <li>Setting: single centre, University hospital</li> <li>First cadaveric kidney transplant recipients</li> <li>Number: treatment group (25); control group (25)</li> <li>Median age, range (years): treatment group (43.5, 22 to 71); control group (47.0, 27 to 68)</li> <li>Sex (M/F): treatment group (13/12); control group (17/12)</li> <li>Exclusion criteria: fish/iodine allergy; non-steroidal anti-inflammatory treatment; diabetes; previous non-compliance</li> </ul> |
| Interventions | <p>Treatment group</p> <ul style="list-style-type: none"> <li>Fish oil 6 g/d (Kortman Intradal) EPA 30%; DHA 20%</li> </ul> <p>Control group</p> <ul style="list-style-type: none"> <li>Coconut oil 6 g/d</li> </ul> <p>Co-interventions: none</p>   |
| Outcomes      | <ul style="list-style-type: none"> <li>Patient survival</li> <li>Graft survival</li> <li>Acute rejection</li> <li>Cardiovascular events</li> <li>Adverse effects</li> <li>Compliance</li> <li>Kidney function (CrCl, GFR)</li> <li>BP (MAP)</li> </ul>   |
| Notes         | <ul style="list-style-type: none"> <li>Exclusions post randomisation but pre intervention: none</li> <li>Additional data requested: no unpublished data provided</li> </ul>  |

**Risk of bias**

| Bias  | Authors' judgement | Support for judgement |
|---|--------------------|-----------------------|
| Random sequence generation (selection bias) | Unclear risk       | Not reported          |
| Allocation concealment (selection bias)     | Low risk           | Sealed envelope       |
| Intention-to-treat analysis                 | Low risk           | Yes                   |

**Kooijmans-Coutinho 1996** (Continued)

|   |          |  |
|---|----------|--|
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | Only first 3 months then code broken           |
| Blinding of outcome assessment (detection bias)<br>All outcomes           | Low risk | Yes  |
| Incomplete outcome data (attrition bias)<br>All outcomes                  | Low risk | No losses to follow-up                         |
| Selective reporting (reporting bias)                                      | Low risk | Outcomes relevant to this review were reported |

**Maachi 1995**

|               |   |
|---------------|---|
| Methods       | <ul style="list-style-type: none"> <li>• Study design: RCT</li> <li>• Time frame: 12 months</li> <li>• Follow-up period: 12 months</li> </ul>   |
| Participants  | <ul style="list-style-type: none"> <li>• Country: France</li> <li>• Setting: single centre, University hospital</li> <li>• Consecutive cadaveric kidney transplant recipients</li> <li>• Number: treatment group (40); control group (40)</li> <li>• Mean age <math>\pm</math> SD (years): treatment group (44.7 <math>\pm</math> 12.7); control group (42.8 <math>\pm</math> 11.2)</li> <li>• Sex (M/F): treatment group (30/10); control group (30/10)</li> <li>• Exclusion criteria: not reported</li> </ul> |
| Interventions | <p>Treatment group</p> <ul style="list-style-type: none"> <li>• Fish oil 8 g/d (Maxepa) EPA 18%; DHA 12%</li> </ul> <p>Control group</p> <ul style="list-style-type: none"> <li>• No placebo</li> </ul> <p>Co-interventions: none</p>   |
| Outcomes      | <ul style="list-style-type: none"> <li>• Patient survival</li> <li>• Graft failure</li> <li>• Acute rejection</li> <li>• Adverse effects</li> <li>• Compliance</li> <li>• Kidney function (SCr, CrCl, GFR)</li> <li>• Hypertension (number of medications to maintain set BP goal)</li> <li>• Lipids (TC,TG)</li> </ul>   |
| Notes         | <ul style="list-style-type: none"> <li>• Exclusions post randomisation but pre intervention: 1 patient failed to received fish oil</li> <li>• Additional data requested: no unpublished data provided</li> </ul>  |

**Risk of bias**
**Fish oil for kidney transplant recipients (Review)**

**Maachi 1995** (Continued)

| Bias  | Authors' judgement | Support for judgement                          |
|---|--------------------|--|
| Random sequence generation (selection bias)                               | Unclear risk       | Not reported                                   |
| Allocation concealment (selection bias)                                   | Unclear risk       | Not reported                                   |
| Intention-to-treat analysis   | High risk          | No   |
| Blinding of participants and personnel (performance bias)<br>All outcomes | High risk          | No blinding                                    |
| Blinding of outcome assessment (detection bias)<br>All outcomes           | Unclear risk       | Not reported                                   |
| Incomplete outcome data (attrition bias)<br>All outcomes                  | Unclear risk       | Loss to follow-up: 2 (2%)                      |
| Selective reporting (reporting bias)                                      | Unclear risk       | Outcomes relevant to this review were reported |

**Rodriguez 1997**

|               |  |
|---------------|--|
| Methods       | <ul style="list-style-type: none"> <li>• Study design: parallel RCT</li> <li>• Time frame: 6 months</li> <li>• Follow-up period: 6 months</li> </ul>   |
| Participants  | <ul style="list-style-type: none"> <li>• Country: Spain</li> <li>• Setting: single centre</li> <li>• Clinically stable kidney transplants with hyperlipidaemia after 3 months dietary intervention, TC &gt; 240 mg/dL (6.2 mmol/L)</li> <li>• Number: treatment group (18); control group (16)</li> <li>• Mean age <math>\pm</math> SD (years): treatment group (43.8 <math>\pm</math> 9.4); control group (42.7 <math>\pm</math> 12.5)</li> <li>• Sex (M/F): treatment group (13/5); control group (11/5)</li> <li>• Exclusion criteria: diabetes; nephrotic syndrome; abnormal liver function; SCr &gt; 3 mg/dL (229 <math>\mu</math>mol/L)</li> </ul> |
| Interventions | Treatment group <ul style="list-style-type: none"> <li>• Fish oil 2 g/d (Beromegan) EPA 18%; DHA 12%</li> </ul> Control group <ul style="list-style-type: none"> <li>• Lovastatin 20 mg/d</li> </ul> Co-interventions: none  |
| Outcomes      | <ul style="list-style-type: none"> <li>• Lipids (TC, TG, LDL, HDL)</li> </ul>  |
| Notes         | <ul style="list-style-type: none"> <li>• Exclusions post randomisation but pre intervention: none</li> <li>• Additional data requested from authors: none</li> </ul>   |

**Fish oil for kidney transplant recipients (Review)**

**Rodriguez 1997** (Continued)

- Paper in Spanish. Translation obtained from Spanish speaking person

**Risk of bias**

| Bias  | Authors' judgement | Support for judgement       |
|---|--------------------|-----------------------------|
| Random sequence generation (selection bias)                               | Unclear risk       | Unclear                     |
| Allocation concealment (selection bias)                                   | Unclear risk       | Unclear                     |
| Intention-to-treat analysis   | Low risk           | Yes                         |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Unclear risk       | Not reported                |
| Blinding of outcome assessment (detection bias)<br>All outcomes           | Unclear risk       | Not reported                |
| Incomplete outcome data (attrition bias)<br>All outcomes                  | Unclear risk       | Loss to follow-up: 2 (6%)   |
| Selective reporting (reporting bias)                                      | High risk          | Only lipid results reported |

**Santos 2000**

|               |  |
|---------------|--|
| Methods       | <ul style="list-style-type: none"> <li>• Study design: placebo controlled RCT</li> <li>• Time frame: 12 months</li> <li>• Follow-up period: 12 months</li> </ul>   |
| Participants  | <ul style="list-style-type: none"> <li>• Country: Portugal</li> <li>• Setting: single centre</li> <li>• First cadaveric kidney transplant with delayed graft function (urine output &lt; 1000 mL/d and no improvement in SCr)</li> <li>• Number: treatment group (15); control group (15)</li> <li>• Mean age ± SD (years): treatment group (37.4 ± 10.9); control group (37.8 ± 11.8)</li> <li>• Sex (M/F): treatment group (7/8); control group (9/6)</li> <li>• Exclusion criteria: primary non-function; diabetes</li> </ul> |
| Interventions | <p>Treatment group</p> <ul style="list-style-type: none"> <li>• Fish oil 6 g/d EPA 30%; DHA 20%</li> </ul> <p>Control group</p> <ul style="list-style-type: none"> <li>• Placebo; not specified</li> </ul> <p>Co-interventions: low sodium diet advised</p>  |
| Outcomes      | <ul style="list-style-type: none"> <li>• Patient survival</li> </ul>   |

**Fish oil for kidney transplant recipients (Review)**

**Santos 2000** (Continued)

- Graft survival
- Acute rejection
- Adverse effects
- Compliance
- Kidney function (SCr, CrCl, GFR)
- BP (systolic, diastolic)
- Lipids (TC, LDL, HDL, TG)

- Notes
- Exclusions post randomisation but pre intervention: none
  - Additional data requested from authors: no unpublished data provided

**Risk of bias**

| Bias  | Authors' judgement | Support for judgement                          |
|---|--------------------|--|
| Random sequence generation (selection bias)                               | Unclear risk       | Not reported                                   |
| Allocation concealment (selection bias)                                   | Unclear risk       | Not reported                                   |
| Intention-to-treat analysis   | Low risk           | Yes  |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Unclear risk       | Not reported                                   |
| Blinding of outcome assessment (detection bias)<br>All outcomes           | Unclear risk       | Not reported                                   |
| Incomplete outcome data (attrition bias)<br>All outcomes                  | Low risk           | No losses to follow-up                         |
| Selective reporting (reporting bias)                                      | Low risk           | Outcomes relevant to this review were reported |

**Schut 1992a**

- Methods
- Study design: double blind cross-over RCT
  - Time frame: 4 months (first period of randomisation) (1979 to 1988)
  - Follow-up period: 8 months (2 periods of crossover)

- Participants
- Country: Netherlands
  - Setting: single centre
  - Cadaveric kidney transplant stable for at least 1 year
  - Number: 10
  - Mean age  $\pm$  SD: 53  $\pm$  14 years
  - Sex (M/F): 4/6
  - Exclusion criteria: not reported

- Interventions
- Treatment group

**Fish oil for kidney transplant recipients (Review)**

**Schut 1992a** (Continued)

- Fish oil 6 g/d (SuperEPA) EPA 30%; DHA 20%

Control group

- Corn oil 6 g/d

Co-interventions: none

|          |  |
|----------|--|
| Outcomes | <ul style="list-style-type: none"> <li>• BP (MAP)</li> <li>• Kidney function (GFR)</li> </ul>  |
| Notes    | <ul style="list-style-type: none"> <li>• Same study as <a href="#">Schut 1992b</a></li> <li>• Data for patients receiving CSA only</li> <li>• Exclusions post randomisation but pre intervention: none</li> <li>• Additional data requested: no unpublished data provided</li> </ul> |

**Risk of bias**

| Bias  | Authors' judgement | Support for judgement    |
|---|--------------------|--------------------------|
| Random sequence generation (selection bias)                               | Unclear risk       | Not reported             |
| Allocation concealment (selection bias)                                   | Unclear risk       | Not reported             |
| Intention-to-treat analysis   | Low risk           | Yes                      |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Unclear risk       | Not reported             |
| Blinding of outcome assessment (detection bias)<br>All outcomes           | Unclear risk       | Not reported             |
| Incomplete outcome data (attrition bias)<br>All outcomes                  | Low risk           | No losses to follow-up   |
| Selective reporting (reporting bias)                                      | High risk          | Only BP and GFR reported |

**Schut 1992b**

|              |  |
|--------------|--|
| Methods      | <ul style="list-style-type: none"> <li>• Study design: double blind cross-over RCT</li> <li>• Time frame: 4 months (first period of randomisation) (1979 to 1988)</li> <li>• Follow-up period: 8 months (2 periods of crossover)</li> </ul>                              |
| Participants | <ul style="list-style-type: none"> <li>• Country: Netherlands</li> <li>• Setting: single centre</li> <li>• Cadaveric kidney transplant stable for at least 1 year</li> <li>• Number: 10</li> <li>• Mean age <math>\pm</math> SD: 51 <math>\pm</math> 14 years</li> </ul> |

**Fish oil for kidney transplant recipients (Review)**

**Schut 1992b** (Continued)

- Sex (M/F): 9/1
- Exclusion criteria: not reported

|               |   |
|---------------|---|
| Interventions | <p>Treatment group</p> <ul style="list-style-type: none"> <li>• Fish oil 6 g/d (SuperEPA) EPA 30%; DHA 20%</li> </ul> <p>Control group</p> <ul style="list-style-type: none"> <li>• Corn oil 6 g/d</li> </ul> <p>Co-interventions: none</p> |
| Outcomes      | <ul style="list-style-type: none"> <li>• BP (MAP)</li> <li>• Kidney function (GFR)</li> </ul>   |
| Notes         | <ul style="list-style-type: none"> <li>• Same study as <a href="#">Schut 1992a</a></li> <li>• Data from CSA and prednisone group only</li> </ul>  |

**Risk of bias**

| Bias  | Authors' judgement | Support for judgement    |
|---|--------------------|--------------------------|
| Random sequence generation (selection bias)                               | Unclear risk       | Not reported             |
| Allocation concealment (selection bias)                                   | Unclear risk       | Not reported             |
| Intention-to-treat analysis   | Low risk           | Yes                      |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Unclear risk       | Not reported             |
| Blinding of outcome assessment (detection bias)<br>All outcomes           | Unclear risk       | Not reported             |
| Incomplete outcome data (attrition bias)<br>All outcomes                  | Low risk           | No losses to follow-up   |
| Selective reporting (reporting bias)                                      | High risk          | Only BP and GFR reported |

**Yoa 1994**

|              |  |
|--------------|--|
| Methods      | <ul style="list-style-type: none"> <li>• Study design: double blind placebo controlled RCT</li> <li>• Time frame: 6 months</li> <li>• Follow-up period: 6 months</li> </ul>        |
| Participants | <ul style="list-style-type: none"> <li>• Country: France</li> <li>• Setting: university hospital</li> <li>• All kidney transplant patients stable for at least 3 months</li> </ul> |

**Fish oil for kidney transplant recipients (Review)**



**Yoa 1994** (Continued)

- Number: treatment group (12); control group (11)
- Mean age  $\pm$  SD (years): treatment group ( $38.5 \pm 11.01$ ); control group ( $37 \pm 14.15$ )
- Sex (M/F): treatment group (6/6); control group (7/4)
- Exclusion criteria: not reported

|               |   |
|---------------|---|
| Interventions | Treatment group <ul style="list-style-type: none"> <li>• Fish oil 6 g/d (MaxEPA) EPA 18%; DHA 12%</li> </ul> Control group <ul style="list-style-type: none"> <li>• Olive oil 6 g/d</li> </ul> Co-interventions: none |
| Outcomes      | <ul style="list-style-type: none"> <li>• Lipids</li> <li>• Kidney function (CrCl)</li> </ul>  |
| Notes         | <ul style="list-style-type: none"> <li>• Exclusions post randomisation but pre intervention: none</li> <li>• Additional data requested: none</li> </ul>   |

**Risk of bias**

| Bias  | Authors' judgement | Support for judgement         |
|---|--------------------|-------------------------------|
| Random sequence generation (selection bias)                               | Unclear risk       | Not reported                  |
| Allocation concealment (selection bias)                                   | Unclear risk       | Not reported                  |
| Intention-to-treat analysis   | Low risk           | Yes                           |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Unclear risk       | Not reported                  |
| Blinding of outcome assessment (detection bias)<br>All outcomes           | Unclear risk       | Not reported                  |
| Incomplete outcome data (attrition bias)<br>All outcomes                  | Low risk           | No losses to follow-up        |
| Selective reporting (reporting bias)                                      | High risk          | Only lipids and CrCl reported |

AHA - American Heart Association; BP - blood pressure; CAN - chronic allograft nephropathy; CNI - calcineurin inhibitor; COPD - chronic obstructive pulmonary disease; CrCl - creatinine clearance; CSA - cyclosporin A; DHA - docosahexaenoic acid; EPA - eicosapentaenoic acid; GFR - glomerular filtration rate; HDL - high density lipoprotein; LDL - low density lipoprotein; MAP - mean arterial pressure; M/F - male/female; MI - myocardial infarction; RCT - randomised controlled trial; SCr - serum creatinine; SD - standard deviation; TC - total cholesterol; TG - triglycerides

**Characteristics of excluded studies** [ordered by study ID]

| Study                    | Reason for exclusion  |
|--------------------------|---|
| A-Echevarria 2004        | Non-interventional, non-RCT, cross-sectional dietary assessment study, examining dietary influences on the plasma profile of fatty acids.   |
| Alexander 2005           | This RCT has dual therapy (arginine + canola oil) in the intervention arm. Fish oil is not used, although canola oil does contain small amounts of omega-3. Arginine alone may have impact on outcome measures. |
| Alexander 2006           | Dual intervention with arginine and fish oil. Arginine alone may have impact on outcome measure   |
| Alexander 2008           | Dual intervention with arginine and fish oil  |
| Arnadottir 1997          | Non-RCT, review article on treatment of hyperlipidaemia in kidney transplant recipients   |
| Balasubramaniam 1998     | A conference abstract looking at treatment of donors, not recipients  |
| Bellomo 2002             | Non-RCT, conference paper on nutritional support in ICU patients with kidney failure  |
| Bennett 1992             | Non-RCT, review article on arachidonic acid metabolism in transplant-associated acute kidney failure  |
| Bloomgarden 2004         | Non-RCT, review article   |
| Butani 2000              | Non-RCT, case report on the effect of fish oil in post-transplantation IgA nephropathy  |
| Clark 1994               | Non-RCT, review article on the treatment of lupus nephritis   |
| Davis 2002               | Non-RCT, review article on kidney disease and liver transplantation   |
| de Mattos 1996           | Non-RCT, review article on immunosuppressive medications  |
| Donadio 1997             | Non-RCT, review article on IgA nephropathy  |
| Donadio 2002             | Non-RCT, review article on IgA nephropathy  |
| Endres 1995              | Non-RCT, review article on n-3 fatty acids  |
| Endres 1996              | Non-RCT, review article on n-3 PUFA and human cytokine synthesis  |
| Farbakhsh 2005           | Non-RCT, review article on dyslipidaemia in CKD   |
| Gerster 1995             | Non-RCT, review article on fish oil in enteral nutrition  |
| Grekas 2001              | Non-RCT. There is no control group in this clinical trial of dyslipidaemia, where treatment consists of statin + fish oil   |
| Grimble 2001             | Non-RCT, review article on stress proteins  |
| Hansen 1995a             | Non-RCT, cohort study in stable transplants looking at the effects of fish oil on kidney haemodynamics  |
| Hansen 1995b             | No control group - All patients and "controls" received fish oil. No randomisation  |
| Hejaili 2003             | Non-RCT, review article on lupus nephritis  |
| Homan van der Heide 1994 | Non-RCT. Journal note/commentary on another trial   |

| Study                            | Reason for exclusion   |
|----------------------------------|--|
| <a href="#">Julian 1997</a>      | Non-RCT, conference paper on IgA nephropathy   |
| <a href="#">Kasiske 2003</a>     | Non-RCT, K/DOQI practice guidelines on treatment of dyslipidaemia in CKD   |
| <a href="#">Kasiske 2004</a>     | Non-RCT, K/DOQI practice guidelines on treatment of dyslipidaemia in kidney transplantation  |
| <a href="#">Kho 1989</a>         | Non-RCT, study examining effects of dopamine infusion and fish oil administration on urinary prostaglandins  |
| <a href="#">Kobashigawa 1997</a> | Non-RCT. Review article on hyperlipidaemia in solid organ transplantation  |
| <a href="#">Levi 1992</a>        | Fish oil versus corn oil crossover trial, which did not include any of the outcome measures examined in the review   |
| <a href="#">Maes 2000</a>        | Non-RCT, short survey on IgA nephropathy   |
| <a href="#">Mathis 2004</a>      | Non-RCT, review article on drug-related dyslipidaemia after kidney transplantation   |
| <a href="#">Naber 2003</a>       | Non-RCT, conference paper on lipids in artificial nutrition  |
| <a href="#">Nakamura 1998</a>    | Non-RCT, uncontrolled cohort study on the effects of fish oil on hyperlipidaemia post transplantation  |
| <a href="#">Ramezani 2011</a>    | Immunosuppression protocol could not be determined (in relation of CNI exposure) and the lipid data presented represents change in values rather than absolute numbers. No further information was available from study authors. Authors contacted 24 July 2015 - no reply as of 10 Feb 2016 |
| <a href="#">Rodicio 1993</a>     | No fish oil intervention   |
| <a href="#">Romo 2012</a>        | Abstract only available. All patients received omega-3, with the control group receiving placebo and intervention group receiving atorvastatin. Unclear if all patients on CNI   |
| <a href="#">Schiele 1999</a>     | Non-RCT, review article on IgA nephropathy   |
| <a href="#">Shah 1994</a>        | Non-RCT, no fish oil intervention  |
| <a href="#">Shihab 1996</a>      | Non-RCT, review article on cyclosporine nephropathy  |
| <a href="#">Singer 2004</a>      | Non-RCT study of parenteral fish oil given to donors and recipients  |
| <a href="#">Soylu 2002</a>       | Non-RCT, conference paper on paediatric kidney transplant experience   |
| <a href="#">Urakaze 1989</a>     | Not all patients were on CNI (separate data for patients on CNI not provided)  |
| <a href="#">Wierzbicki 1999</a>  | Non-RCT, review article on lipid lowering in transplantation   |
| <a href="#">Young 1995</a>       | Non-kidney transplant patients. Conference paper   |
| <a href="#">Zak 1996</a>         | Non-RCT, non-transplant patients, trial on fish oil in diabetic patients   |
| <a href="#">Zolotarski 2003</a>  | Non-RCT, conference paper on effects of parenteral fish oil given to donors and kidney transplant recipients   |

CKD - chronic kidney disease; CNI - calcineurin inhibitor; ICU - intensive care unit; RCT - randomised controlled trial

**Characteristics of studies awaiting assessment** [ordered by study ID]

**NCT01744067**

|               |   |
|---------------|---|
| Methods       | Allocation: randomised<br>Endpoint classification: safety/efficacy study<br>Intervention model: parallel assignment<br>Masking: double blind (subject, caregiver, investigator, outcomes assessor)<br>Primary purpose: treatment  |
| Participants  | Inclusion criteria <ul style="list-style-type: none"> <li>Patients over the age of 18 who have received a kidney transplant. Patients with a functioning kidney transplant, defined as eGFR&gt;30 ml/min. Signed informed consent.</li> </ul> Exclusion criteria <ul style="list-style-type: none"> <li>Patients participating in clinical trials with other investigational drugs. Patients who received a deceased donor kidney from a donor &gt;75 years. Patients with a history of an allergic reaction or significant sensitivity to the study drug or drugs similar to the study drug.</li> </ul>  |
| Interventions | Active comparator<br><br>Omega-3 fatty acids 2,7 g omega-3 fatty acids / day: Omacor 1 g 1 capsule by mouth 3 times a day for 44 weeks.<br><br>Placebo comparator<br><br>Placebo: 1 capsule containing 1 g of olive oil by mouth 3 times a day for 44 weeks.  |
| Outcomes      | Primary outcome measures<br><br>Glomerular filtration rate. Time frame: 44 weeks. Iohexol clearance<br><br>Secondary outcome measures<br><br>Proteinuria. Time frame: 44 weeks. Both ACR and FEPR<br>Inflammation in the renal transplant. Time frame: 44 weeks. Degree of total inflammation in renal transplant biopsies, scores by PI and rescored by two pathologists.<br>Fibrosis in the renal transplant. Time frame: 44 weeks. As for inflammation<br>Blood pressure. Time frame: 44 weeks.<br>Heart rate variability. Time frame: 44 weeks.<br>Flow mediated dilation. Time frame: 44 weeks.<br>Pulse wave velocity and augmentation index. Time frame: 44 weeks.<br>Blood glucose. Time frame: 44 weeks. HbA1c and oral glucose tolerance test<br>Lipids. Time frame: 44 weeks. Total, LDL and HDL cholesterol, triglyceride and ratios<br>Body composition. Time frame: 44 weeks. Visceral fat volume and weight, visceral to subcutaneous fat ratio.<br>Bone mineral density. Time frame: 44 weeks. Regular BMD in the lumbar spine, hips, femur and arms and also selected to trabecular bone.<br>Body mass index. Time frame: 44 weeks.<br>Vitamin D levels. Time frame: 44 weeks.<br>Fatty acid composition in plasma and renal tissue. Time frame: 44 weeks.<br>Tacrolimus pharmacokinetics. Time frame: 12 weeks. Substudy of 15 patients, where we study tacrolimus trough levels, T <sub>max</sub> and AUC at the end of the ORENTRA trial, after a minimum of 4 weeks wash-out and again after 4 weeks of 2.7 g omega-3 fatty acid supplementation<br><br>Other outcomes<br>Incidence of post-transplant complications. Time frame: 44 weeks + 8 weeks.<br>Adverse events. Time frame: 44 weeks + 8 weeks.<br>Adverse reactions. Time frame: 44 weeks. |

NCT01744067 (Continued)

Frequency of clinically significant safety laboratory variables [Time Frame: 44 weeks]. Especially INR and tacrolimus trough concentrations. Follow-up by local nephrologist plus five Telephone Controls during follow-up.

Quality of life. Time frame: 44 weeks. The participants fill out SF-36 at baseline and the 1 year post transplant control for both safety reasons and measurement of differences between the groups with regards to quality of life.

Food questionnaire. Time frame: 44 weeks. Two specially designed food questionnaires to obtain data on dietary habits in general and type and amount of fish consumed

Comorbidity, concomitant medication and life-style factor interview. Time frame: 44 weeks.

Notes

## DATA AND ANALYSES

### Comparison 1. Fish oil versus control

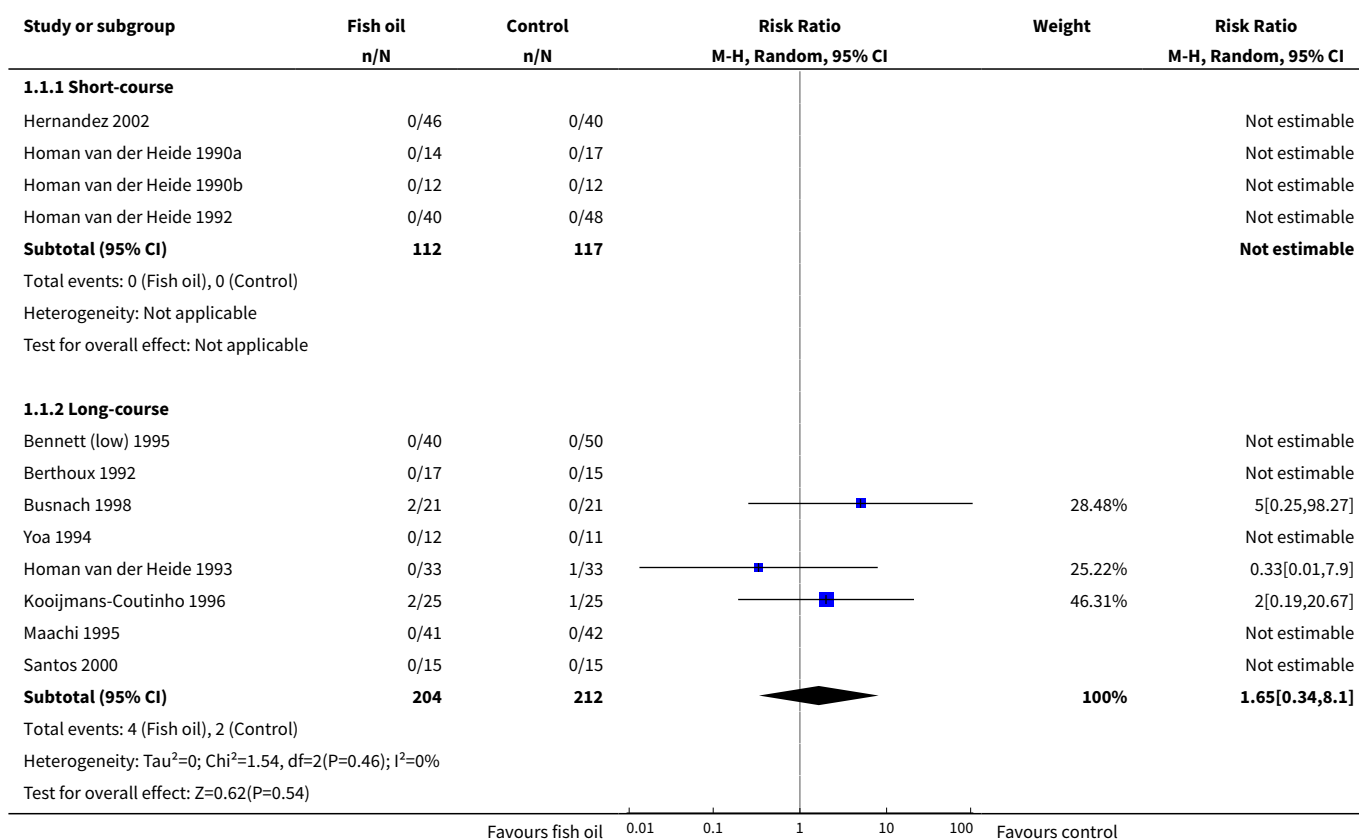
| Outcome or sub-group title              | No. of studies | No. of participants | Statistical method                   | Effect size            |
|---|----------------|---------------------|--------------------------------------|------------------------|
| <a href="#">1 All-cause mortality</a>   | 12             | 645                 | Risk Ratio (M-H, Random, 95% CI)     | 1.65 [0.34, 8.10]      |
| 1.1 Short-course                        | 4              | 229                 | Risk Ratio (M-H, Random, 95% CI)     | 0.0 [0.0, 0.0]         |
| 1.2 Long-course                         | 8              | 416                 | Risk Ratio (M-H, Random, 95% CI)     | 1.65 [0.34, 8.10]      |
| <a href="#">2 Graft loss</a>            | 12             | 640                 | Risk Ratio (M-H, Random, 95% CI)     | 0.91 [0.51, 1.63]      |
| 2.1 Short-course                        | 4              | 229                 | Risk Ratio (M-H, Random, 95% CI)     | 1.17 [0.33, 4.17]      |
| 2.2 Long-course                         | 8              | 411                 | Risk Ratio (M-H, Random, 95% CI)     | 0.86 [0.45, 1.65]      |
| <a href="#">3 Acute rejection</a>       | 8              | 482                 | Risk Ratio (M-H, Random, 95% CI)     | 1.00 [0.80, 1.25]      |
| 3.1 Short-course                        | 3              | 197                 | Risk Ratio (M-H, Random, 95% CI)     | 1.21 [0.82, 1.79]      |
| 3.2 Long-course                         | 5              | 285                 | Risk Ratio (M-H, Random, 95% CI)     | 0.92 [0.70, 1.20]      |
| <a href="#">4 CNI toxicity</a>          | 1              |                     | Risk Ratio (M-H, Random, 95% CI)     | Totals not selected    |
| 4.1 Short-course                        | 1              |                     | Risk Ratio (M-H, Random, 95% CI)     | 0.0 [0.0, 0.0]         |
| 4.2 Long-course                         | 0              |                     | Risk Ratio (M-H, Random, 95% CI)     | 0.0 [0.0, 0.0]         |
| <a href="#">5 CNI levels</a>            | 6              | 275                 | Mean Difference (IV, Random, 95% CI) | 4.25 [-11.57, 20.07]   |
| 5.1 Short-course                        | 1              | 80                  | Mean Difference (IV, Random, 95% CI) | -19.10 [-52.19, 13.99] |
| 5.2 Long-course                         | 5              | 195                 | Mean Difference (IV, Random, 95% CI) | 9.02 [-5.60, 23.64]    |
| <a href="#">6 Myocardial infarction</a> | 3              |                     | Risk Ratio (M-H, Random, 95% CI)     | Subtotals only         |
| 6.1 Long-course                         | 3              | 206                 | Risk Ratio (M-H, Random, 95% CI)     | 1.00 [0.11, 9.37]      |

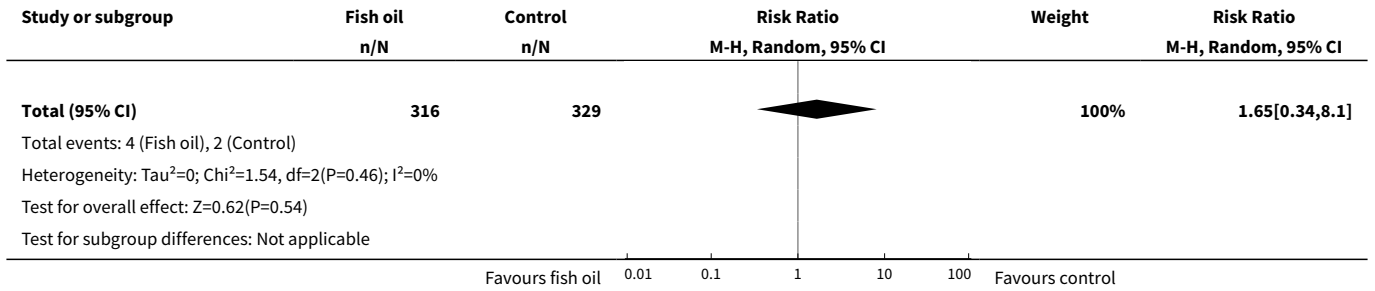
### Fish oil for kidney transplant recipients (Review)

| Outcome or sub-group title           | No. of studies | No. of participants | Statistical method                   | Effect size            |
|--------------------------------------|----------------|---------------------|--------------------------------------|------------------------|
| <b>7 Cardiovascular death</b>        | 3              |                     | Risk Ratio (M-H, Random, 95% CI)     | Subtotals only         |
| 7.1 Long-course                      | 3              | 138                 | Risk Ratio (M-H, Random, 95% CI)     | 1.01 [0.11, 9.37]      |
| <b>8 Compliance</b>                  | 8              | 412                 | Risk Ratio (M-H, Random, 95% CI)     | 1.88 [0.56, 6.26]      |
| 8.1 Short-course                     | 2              | 109                 | Risk Ratio (M-H, Random, 95% CI)     | 3.0 [0.13, 67.06]      |
| 8.2 Long-course                      | 6              | 303                 | Risk Ratio (M-H, Random, 95% CI)     | 1.73 [0.47, 6.38]      |
| <b>9 Serum creatinine</b>            | 5              | 237                 | Mean Difference (IV, Random, 95% CI) | -30.63 [-59.74, -1.53] |
| 9.1 Short-course                     | 1              | 80                  | Mean Difference (IV, Random, 95% CI) | -8.84 [-26.31, 8.63]   |
| 9.2 Long-course                      | 4              | 157                 | Mean Difference (IV, Random, 95% CI) | -37.41 [-69.89, -4.94] |
| <b>10 Creatinine clearance</b>       | 8              | 353                 | Mean Difference (IV, Random, 95% CI) | -0.61 [-5.67, 4.45]    |
| 10.1 Short-course                    | 1              | 80                  | Mean Difference (IV, Random, 95% CI) | -3.70 [-15.73, 8.33]   |
| 10.2 Long-course                     | 7              | 273                 | Mean Difference (IV, Random, 95% CI) | 0.06 [-5.52, 5.63]     |
| <b>11 Glomerular filtration rate</b> | 9              | 343                 | Mean Difference (IV, Random, 95% CI) | 2.18 [-2.90, 7.26]     |
| 11.1 Short-course                    | 1              | 80                  | Mean Difference (IV, Random, 95% CI) | 2.0 [-9.53, 13.53]     |
| 11.2 Long-course                     | 8              | 263                 | Mean Difference (IV, Random, 95% CI) | 1.86 [-4.08, 7.80]     |
| <b>12 Systolic blood pressure</b>    | 4              | 200                 | Mean Difference (IV, Random, 95% CI) | 2.45 [-5.93, 10.83]    |
| 12.1 Short-course                    | 1              | 80                  | Mean Difference (IV, Random, 95% CI) | -6.0 [-13.46, 1.46]    |
| 12.2 Long-course                     | 3              | 120                 | Mean Difference (IV, Random, 95% CI) | 5.97 [-1.59, 13.53]    |
| <b>13 Diastolic blood pressure</b>   | 4              | 200                 | Mean Difference (IV, Random, 95% CI) | -4.53 [-7.60, -1.45]   |
| 13.1 Short-course                    | 1              | 80                  | Mean Difference (IV, Random, 95% CI) | -4.0 [-9.04, 1.04]     |
| 13.2 Long-course                     | 3              | 120                 | Mean Difference (IV, Random, 95% CI) | -4.85 [-9.90, 0.21]    |
| <b>14 Mean arterial pressure</b>     | 4              | 138                 | Mean Difference (IV, Random, 95% CI) | -3.45 [-7.43, 0.53]    |
| 14.1 Short-course                    | 1              | 80                  | Mean Difference (IV, Random, 95% CI) | -4.70 [-9.85, 0.45]    |
| 14.2 Long-course                     | 3              | 58                  | Mean Difference (IV, Random, 95% CI) | -1.61 [-7.87, 4.66]    |
| <b>15 Total cholesterol</b>          | 6              | 260                 | Mean Difference (IV, Random, 95% CI) | -0.11 [-0.36, 0.14]    |

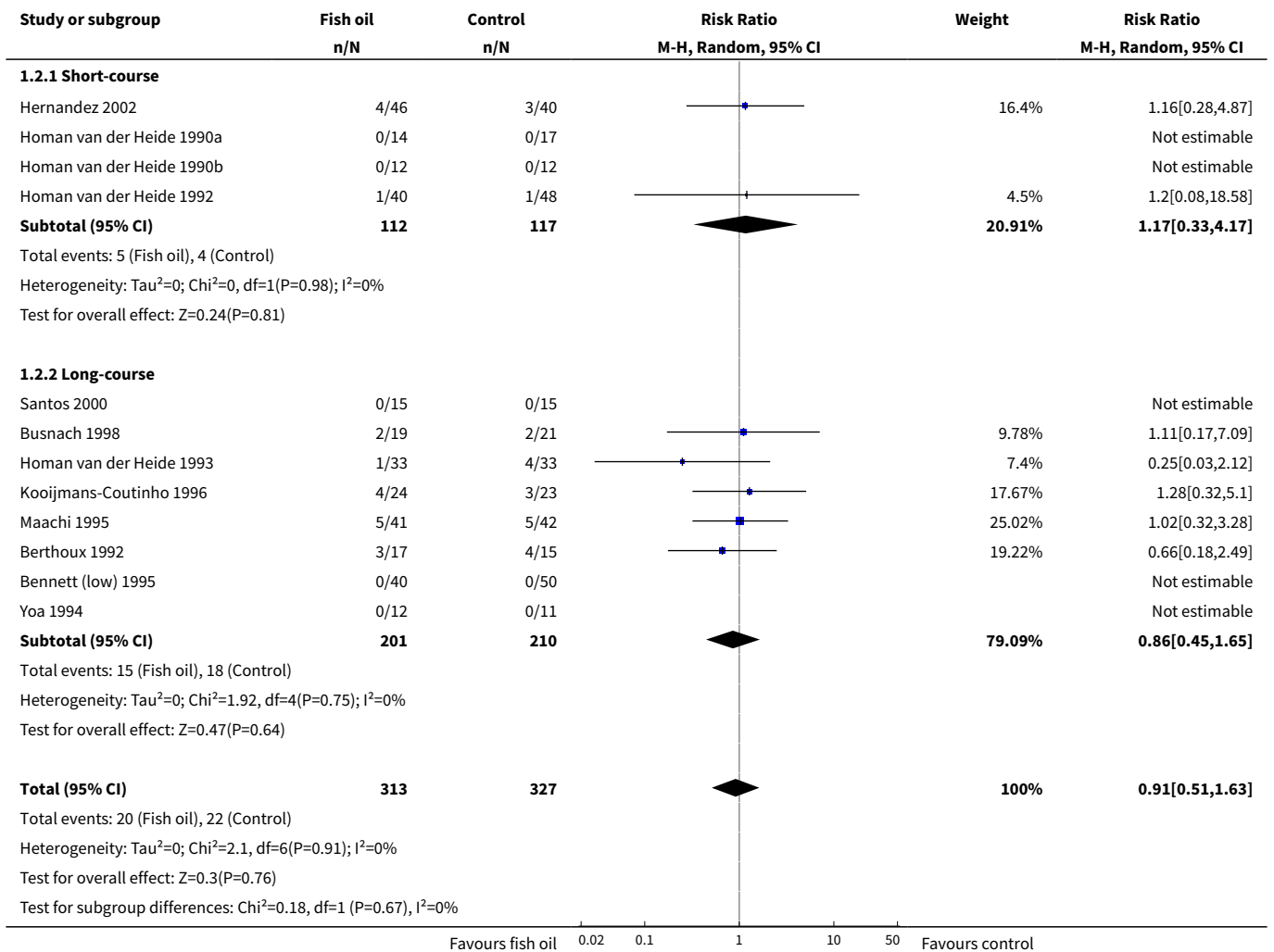
| Outcome or sub-group title | No. of studies | No. of participants | Statistical method                   | Effect size          |
|----------------------------|----------------|---------------------|--------------------------------------|----------------------|
| 15.1 Short-course          | 1              | 80                  | Mean Difference (IV, Random, 95% CI) | -0.44 [-0.88, -0.00] |
| 15.2 Long-course           | 5              | 180                 | Mean Difference (IV, Random, 95% CI) | 0.06 [-0.12, 0.24]   |
| <b>16 LDL cholesterol</b>  | 3              |                     | Mean Difference (IV, Random, 95% CI) | Subtotals only       |
| 16.1 Short-course          | 0              | 0                   | Mean Difference (IV, Random, 95% CI) | 0.0 [0.0, 0.0]       |
| 16.2 Long-course           | 3              | 120                 | Mean Difference (IV, Random, 95% CI) | 0.30 [-0.62, 1.22]   |
| <b>17 HDL cholesterol</b>  | 6              | 258                 | Mean Difference (IV, Random, 95% CI) | 0.09 [-0.01, 0.19]   |
| 17.1 Short-course          | 1              | 80                  | Mean Difference (IV, Random, 95% CI) | -0.08 [-0.29, 0.13]  |
| 17.2 Long-course           | 5              | 178                 | Mean Difference (IV, Random, 95% CI) | 0.12 [0.03, 0.21]    |
| <b>18 Triglycerides</b>    | 6              | 260                 | Mean Difference (IV, Random, 95% CI) | -0.26 [-0.58, 0.05]  |
| 18.1 Short-course          | 1              | 80                  | Mean Difference (IV, Random, 95% CI) | -0.09 [-0.49, 0.31]  |
| 18.2 Long-course           | 5              | 180                 | Mean Difference (IV, Random, 95% CI) | -0.30 [-0.67, 0.07]  |

**Analysis 1.1. Comparison 1 Fish oil versus control, Outcome 1 All-cause mortality.**



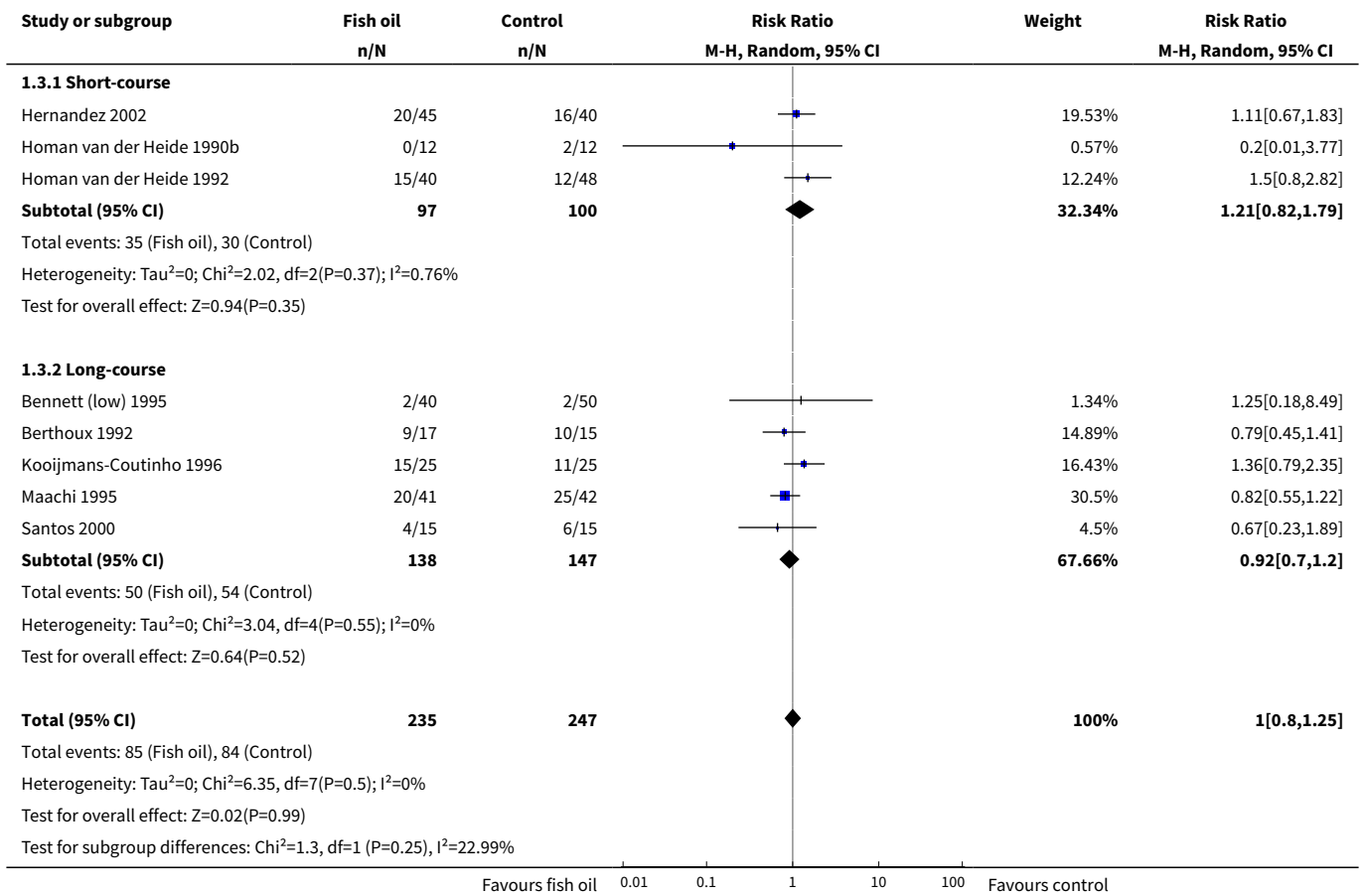


**Analysis 1.2. Comparison 1 Fish oil versus control, Outcome 2 Graft loss.**

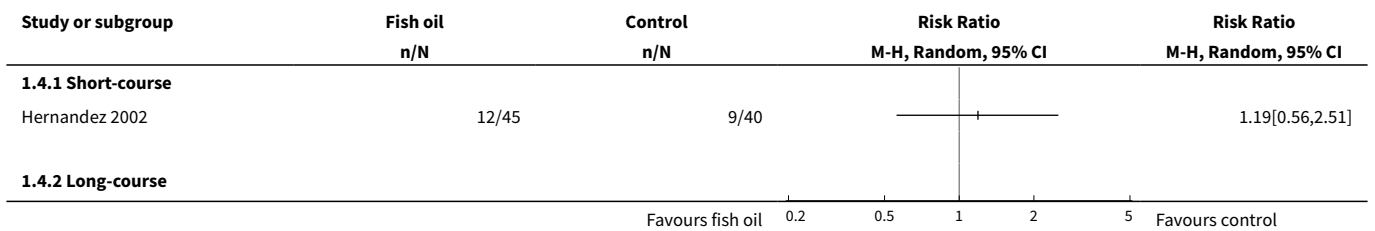




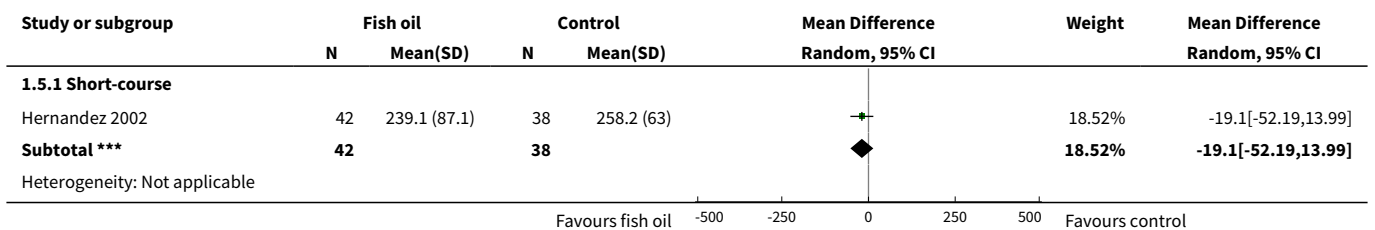
**Analysis 1.3. Comparison 1 Fish oil versus control, Outcome 3 Acute rejection.**

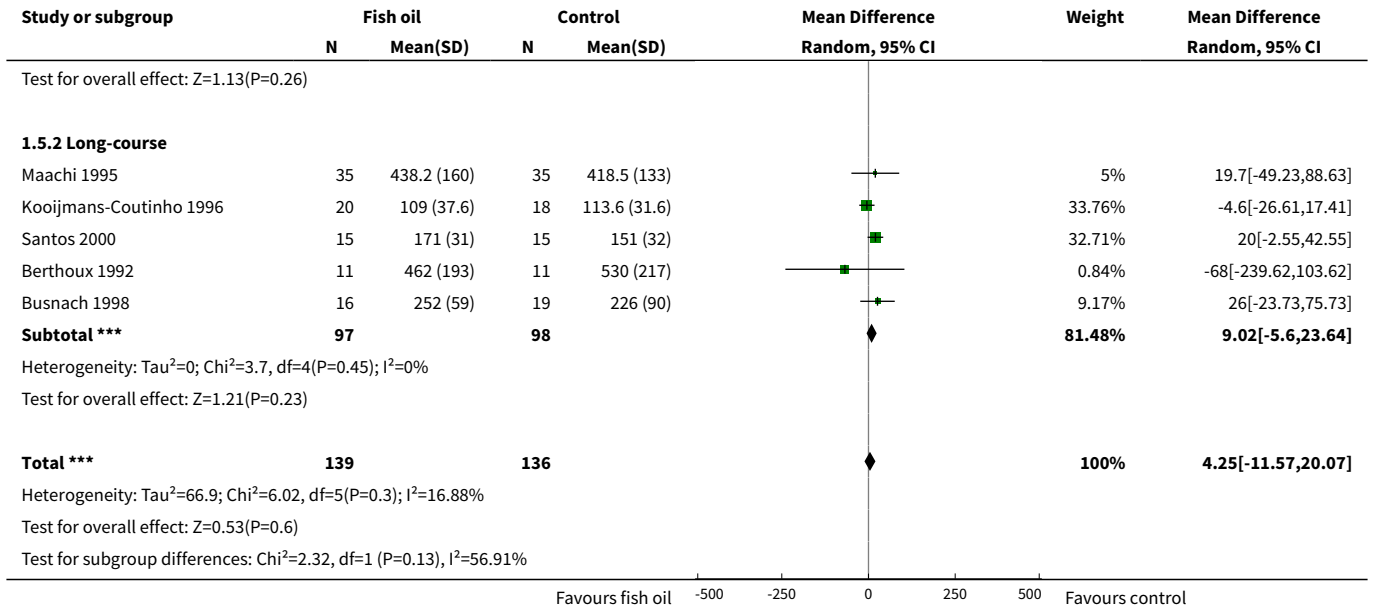


**Analysis 1.4. Comparison 1 Fish oil versus control, Outcome 4 CNI toxicity.**

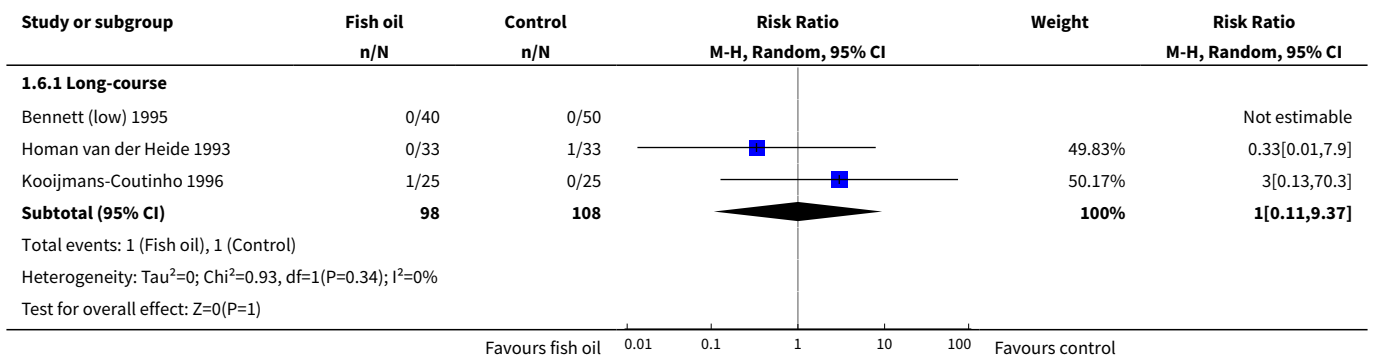


**Analysis 1.5. Comparison 1 Fish oil versus control, Outcome 5 CNI levels.**

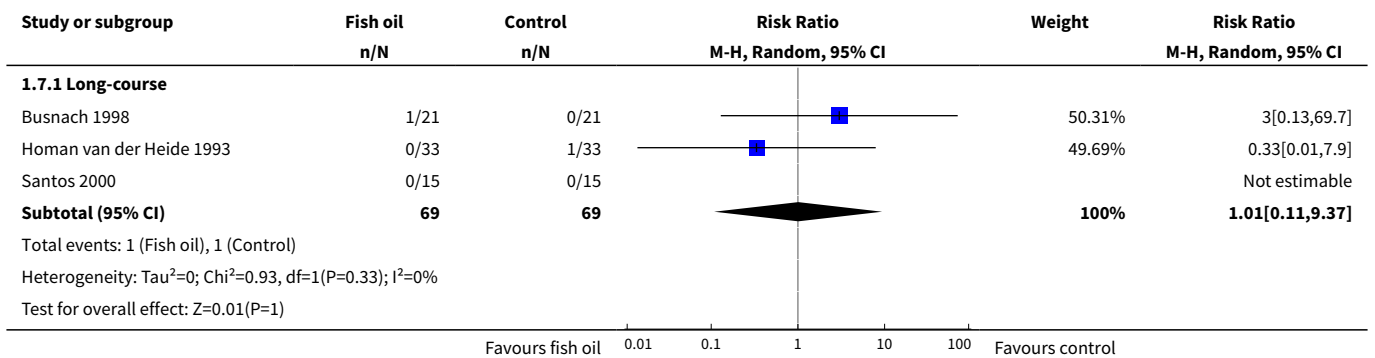




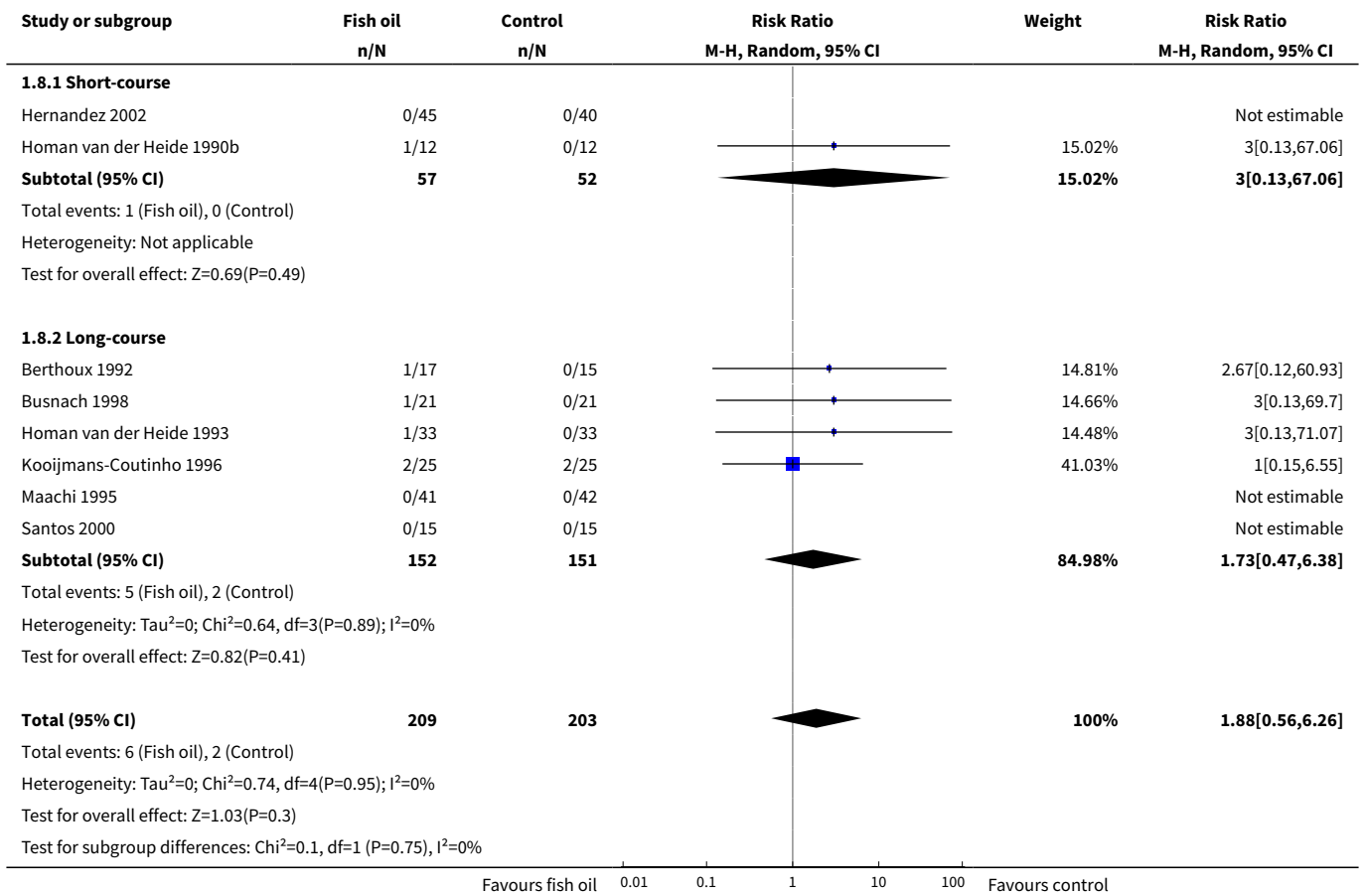
**Analysis 1.6. Comparison 1 Fish oil versus control, Outcome 6 Myocardial infarction.**



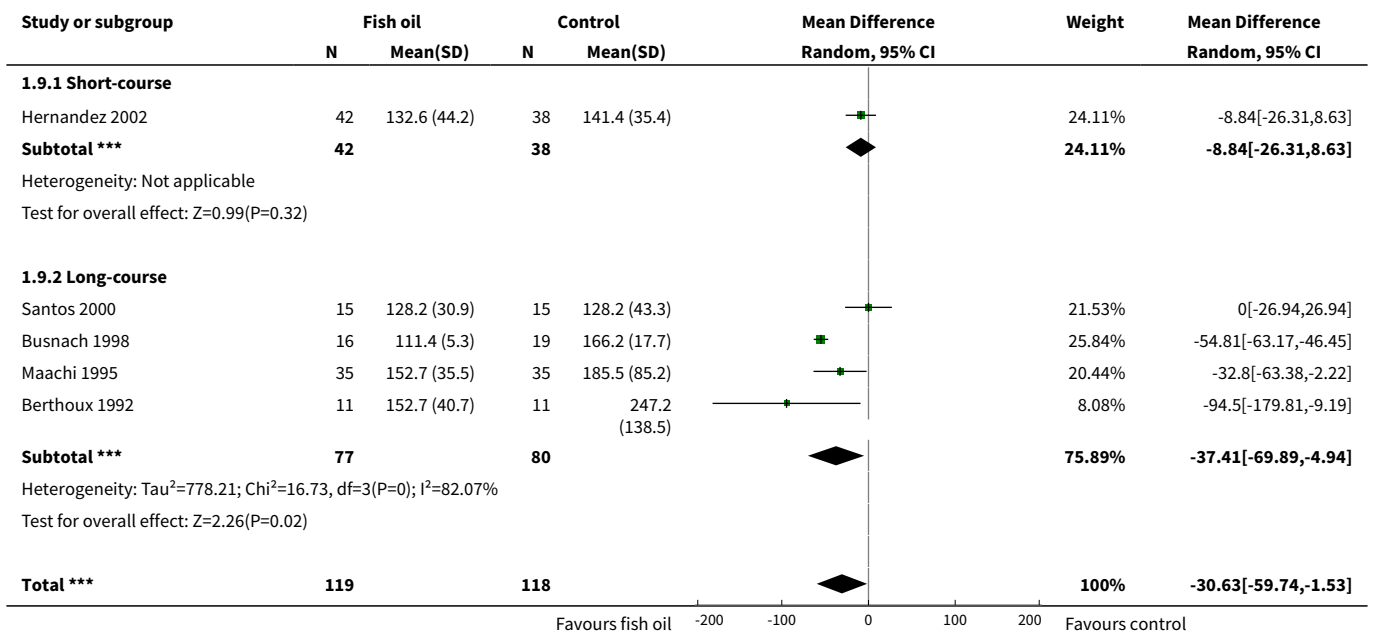
**Analysis 1.7. Comparison 1 Fish oil versus control, Outcome 7 Cardiovascular death.**



**Analysis 1.8. Comparison 1 Fish oil versus control, Outcome 8 Compliance.**



**Analysis 1.9. Comparison 1 Fish oil versus control, Outcome 9 Serum creatinine.**



| Study or subgroup | Fish oil |          | Control |          | Mean Difference<br>Random, 95% CI | Weight | Mean Difference<br>Random, 95% CI |
|-------------------|----------|----------|---------|----------|-----------------------------------|--------|-----------------------------------|
|                   | N        | Mean(SD) | N       | Mean(SD) |                                   |        |                                   |

Heterogeneity: Tau<sup>2</sup>=835.44; Chi<sup>2</sup>=33.96, df=4(P<0.0001); I<sup>2</sup>=88.22%  
 Test for overall effect: Z=2.06(P=0.04)  
 Test for subgroup differences: Chi<sup>2</sup>=2.31, df=1 (P=0.13), I<sup>2</sup>=56.65%

Favours fish oil    -200    -100    0    100    200    Favours control

**Analysis 1.10. Comparison 1 Fish oil versus control, Outcome 10 Creatinine clearance.**

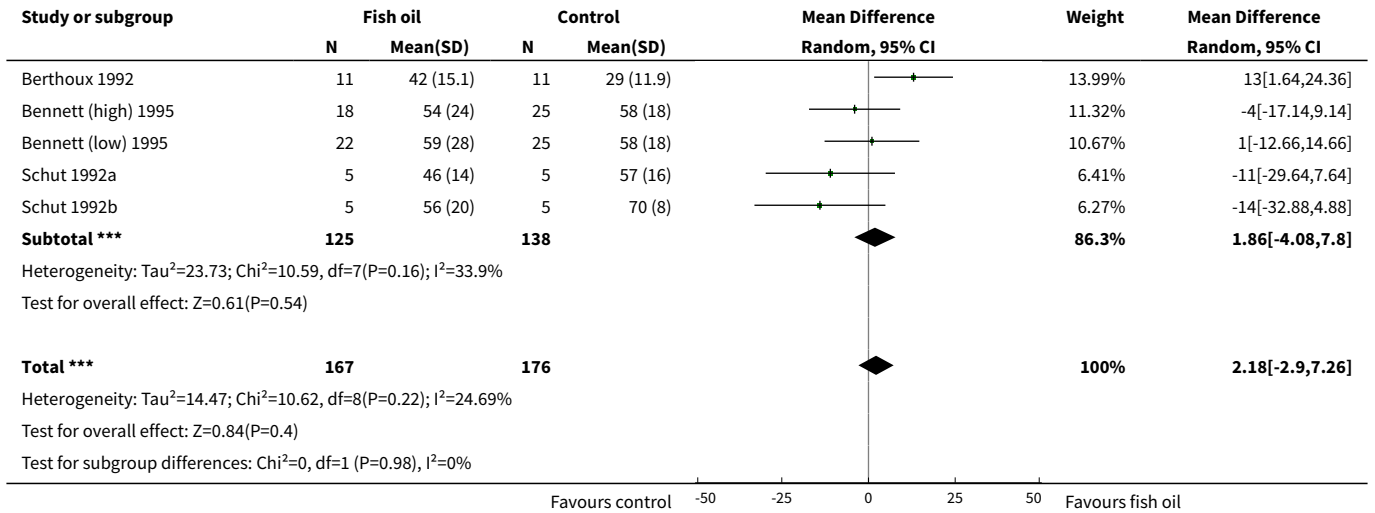
| Study or subgroup  | Fish oil   |             | Control    |             | Mean Difference<br>Random, 95% CI | Weight        | Mean Difference<br>Random, 95% CI |
|--|------------|-------------|------------|-------------|-----------------------------------|---------------|-----------------------------------|
|  | N          | Mean(SD)    | N          | Mean(SD)    |                                   |               |                                   |
| <b>1.10.1 Short-course</b>   |            |             |            |             |                                   |               |                                   |
| Hernandez 2002   | 42         | 61 (35)     | 38         | 64.7 (18)   |                                   | 17.68%        | -3.7[-15.73,8.33]                 |
| <b>Subtotal ***</b>  | <b>42</b>  |             | <b>38</b>  |             |                                   | <b>17.68%</b> | <b>-3.7[-15.73,8.33]</b>          |
| Heterogeneity: Tau <sup>2</sup> =0; Chi <sup>2</sup> =0, df=0(P<0.0001); I <sup>2</sup> =100%<br>Test for overall effect: Z=0.6(P=0.55)  |            |             |            |             |                                   |               |                                   |
| <b>1.10.2 Long-course</b>  |            |             |            |             |                                   |               |                                   |
| Santos 2000  | 15         | 74.2 (28.8) | 15         | 70.4 (19.4) |                                   | 8.29%         | 3.8[-13.77,21.37]                 |
| Kooijmans-Coutinho 1996  | 20         | 70 (32.1)   | 18         | 65 (22.5)   |                                   | 8.37%         | 5[-12.49,22.49]                   |
| Maachi 1995  | 35         | 49 (17.2)   | 35         | 48.6 (23.5) |                                   | 27.5%         | 0.4[-9.25,10.05]                  |
| Berthoux 1992  | 11         | 53.2 (13.9) | 11         | 43.7 (28.9) |                                   | 7.13%         | 9.5[-9.45,28.45]                  |
| Bennett (high) 1995  | 18         | 61 (15)     | 25         | 67 (33)     |                                   | 11.89%        | -6[-20.67,8.67]                   |
| Bennett (low) 1995   | 22         | 63 (28)     | 25         | 67 (33)     |                                   | 8.41%         | -4[-21.44,13.44]                  |
| Yoa 1994   | 12         | 60.2 (18.3) | 11         | 64.1 (19.4) |                                   | 10.73%        | -3.96[-19.41,11.49]               |
| <b>Subtotal ***</b>  | <b>133</b> |             | <b>140</b> |             |                                   | <b>82.32%</b> | <b>0.06[-5.52,5.63]</b>           |
| Heterogeneity: Tau <sup>2</sup> =0; Chi <sup>2</sup> =2.56, df=6(P=0.86); I <sup>2</sup> =0%<br>Test for overall effect: Z=0.02(P=0.98)  |            |             |            |             |                                   |               |                                   |
| <b>Total ***</b>   | <b>175</b> |             | <b>178</b> |             |                                   | <b>100%</b>   | <b>-0.61[-5.67,4.45]</b>          |
| Heterogeneity: Tau <sup>2</sup> =0; Chi <sup>2</sup> =2.87, df=7(P=0.9); I <sup>2</sup> =0%<br>Test for overall effect: Z=0.24(P=0.81)<br>Test for subgroup differences: Chi <sup>2</sup> =0.31, df=1 (P=0.58), I <sup>2</sup> =0% |            |             |            |             |                                   |               |                                   |

Favours control    -50    -25    0    25    50    Favours fish oil

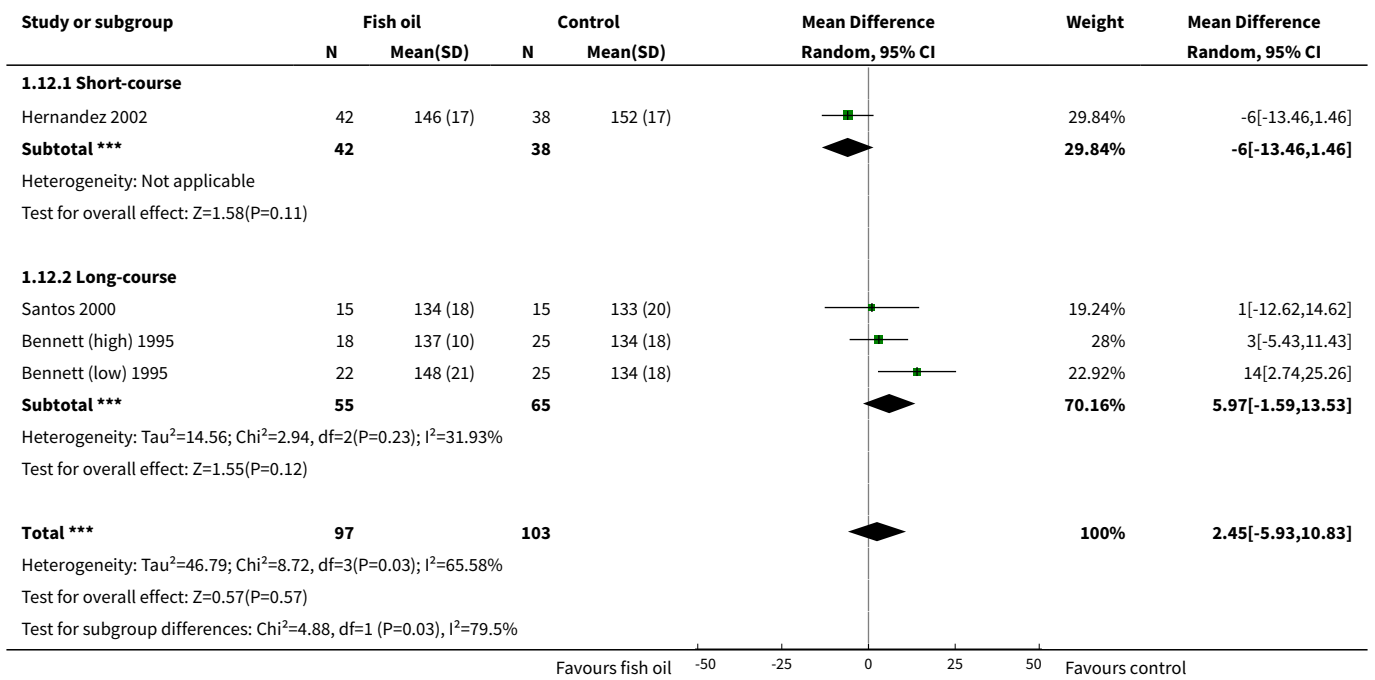
**Analysis 1.11. Comparison 1 Fish oil versus control, Outcome 11 Glomerular filtration rate.**

| Study or subgroup  | Fish oil  |             | Control   |             | Mean Difference<br>Random, 95% CI | Weight       | Mean Difference<br>Random, 95% CI |
|--|-----------|-------------|-----------|-------------|-----------------------------------|--------------|-----------------------------------|
|  | N         | Mean(SD)    | N         | Mean(SD)    |                                   |              |                                   |
| <b>1.11.1 Short-course</b>   |           |             |           |             |                                   |              |                                   |
| Hernandez 2002   | 42        | 61 (35)     | 38        | 59 (14.4)   |                                   | 13.7%        | 2[-9.53,13.53]                    |
| <b>Subtotal ***</b>  | <b>42</b> |             | <b>38</b> |             |                                   | <b>13.7%</b> | <b>2[-9.53,13.53]</b>             |
| Heterogeneity: Not applicable<br>Test for overall effect: Z=0.34(P=0.73) |           |             |           |             |                                   |              |                                   |
| <b>1.11.2 Long-course</b>  |           |             |           |             |                                   |              |                                   |
| Santos 2000  | 15        | 92.6 (37.6) | 15        | 88.5 (20.4) |                                   | 4.93%        | 4.1[-17.55,25.75]                 |
| Kooijmans-Coutinho 1996  | 14        | 54.4 (21.6) | 17        | 52.5 (18.9) |                                   | 9.78%        | 1.9[-12.55,16.35]                 |
| Maachi 1995  | 35        | 50.1 (18)   | 35        | 43 (14)     |                                   | 22.93%       | 7.1[-0.45,14.65]                  |

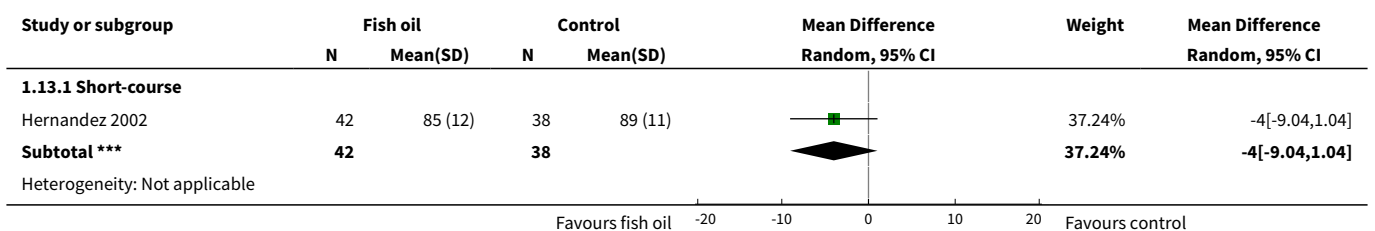
Favours control    -50    -25    0    25    50    Favours fish oil

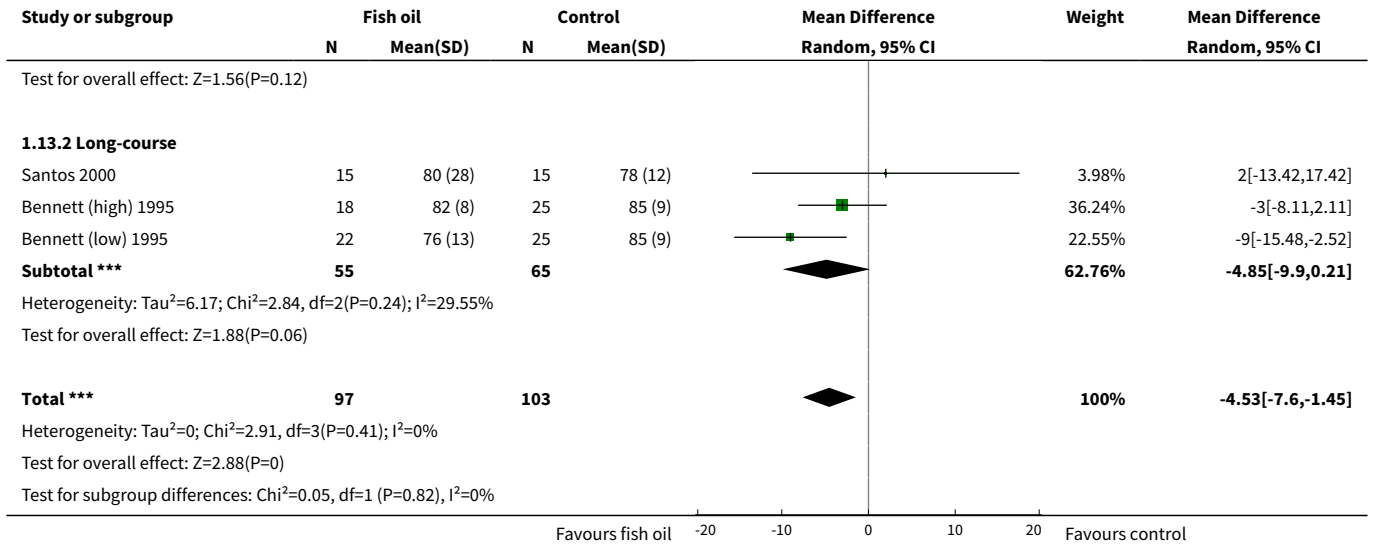


**Analysis 1.12. Comparison 1 Fish oil versus control, Outcome 12 Systolic blood pressure.**

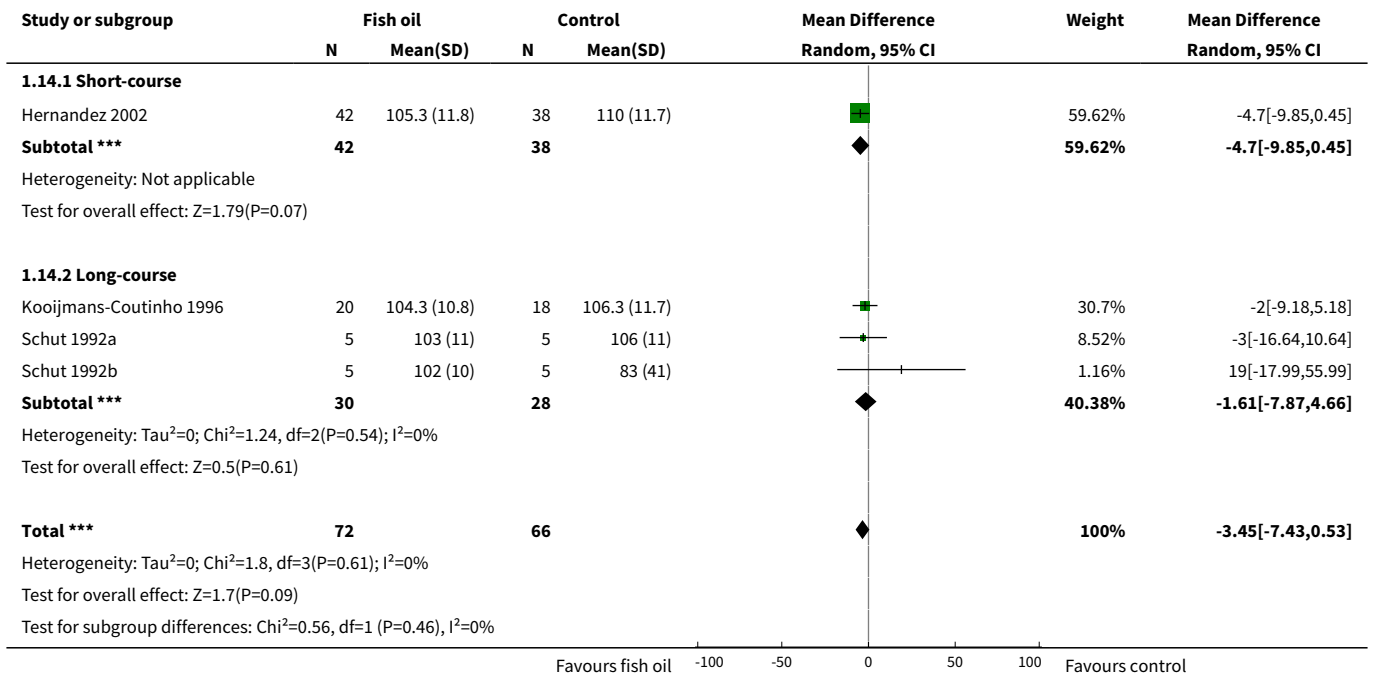


**Analysis 1.13. Comparison 1 Fish oil versus control, Outcome 13 Diastolic blood pressure.**

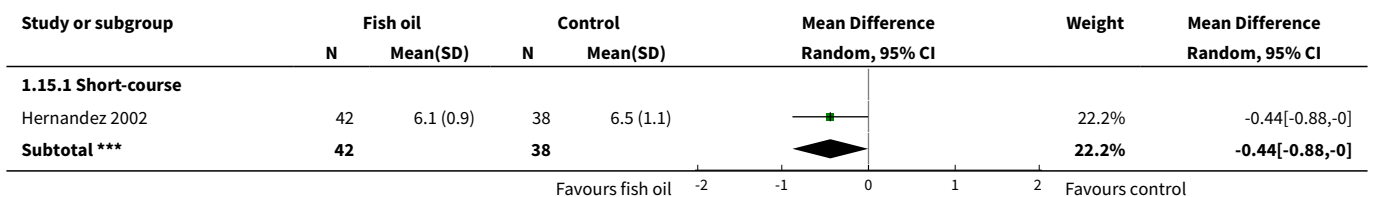


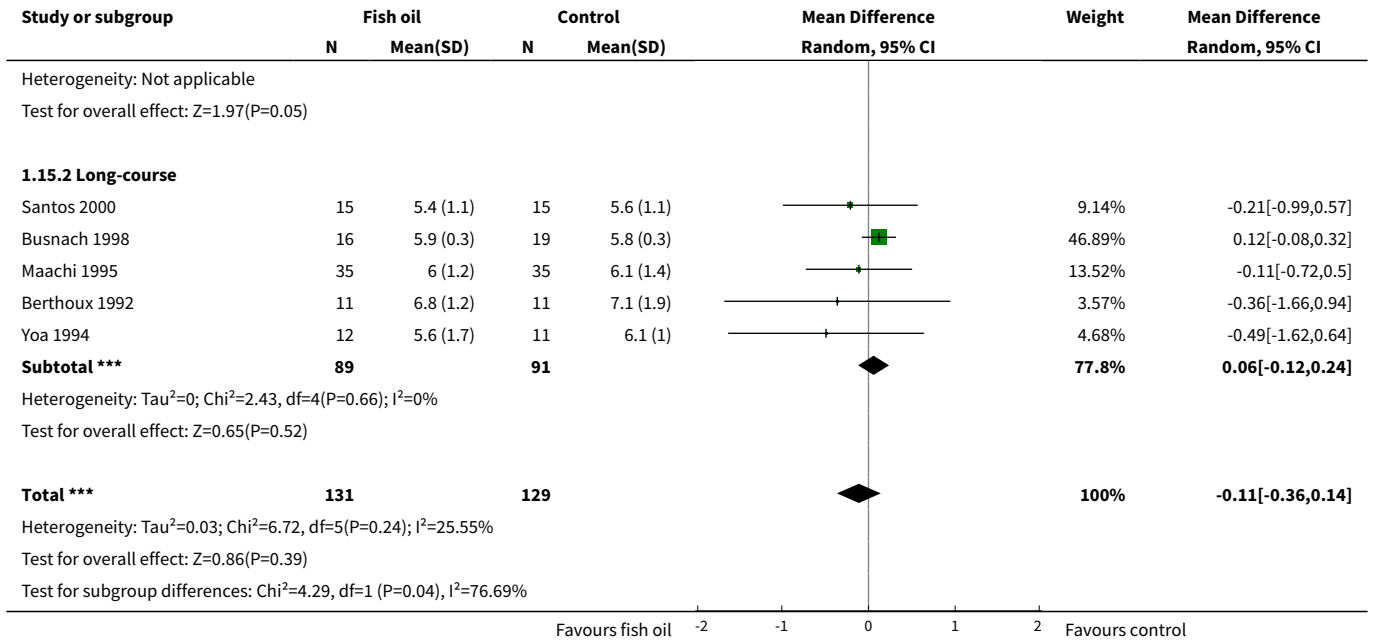


**Analysis 1.14. Comparison 1 Fish oil versus control, Outcome 14 Mean arterial pressure.**

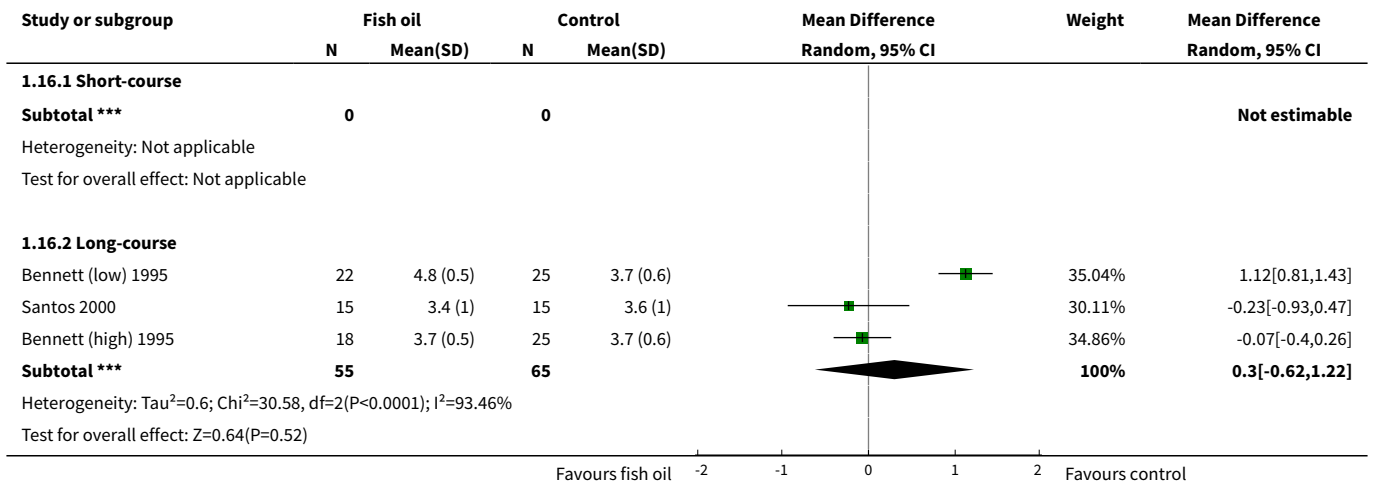


**Analysis 1.15. Comparison 1 Fish oil versus control, Outcome 15 Total cholesterol.**

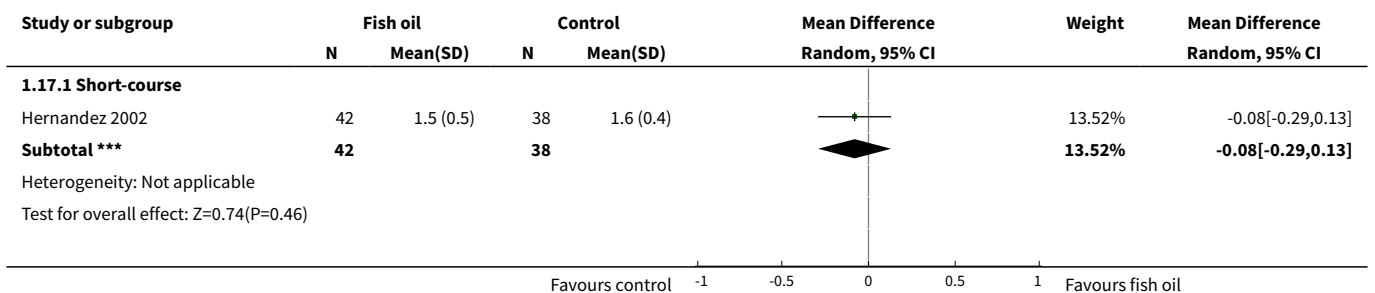


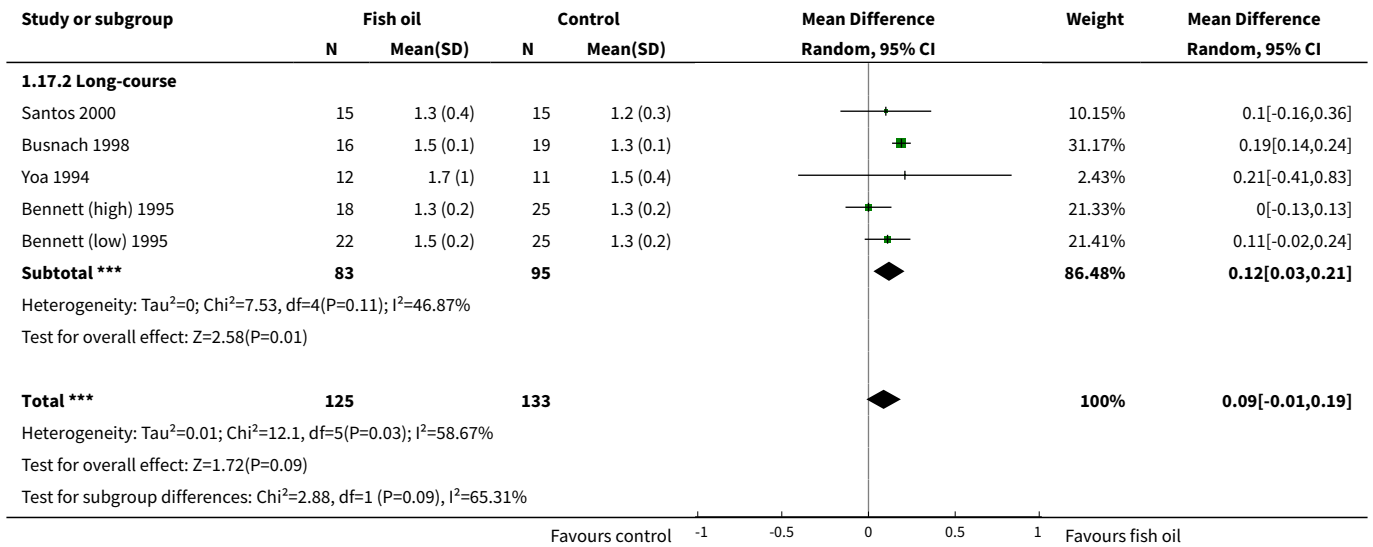


**Analysis 1.16. Comparison 1 Fish oil versus control, Outcome 16 LDL cholesterol.**

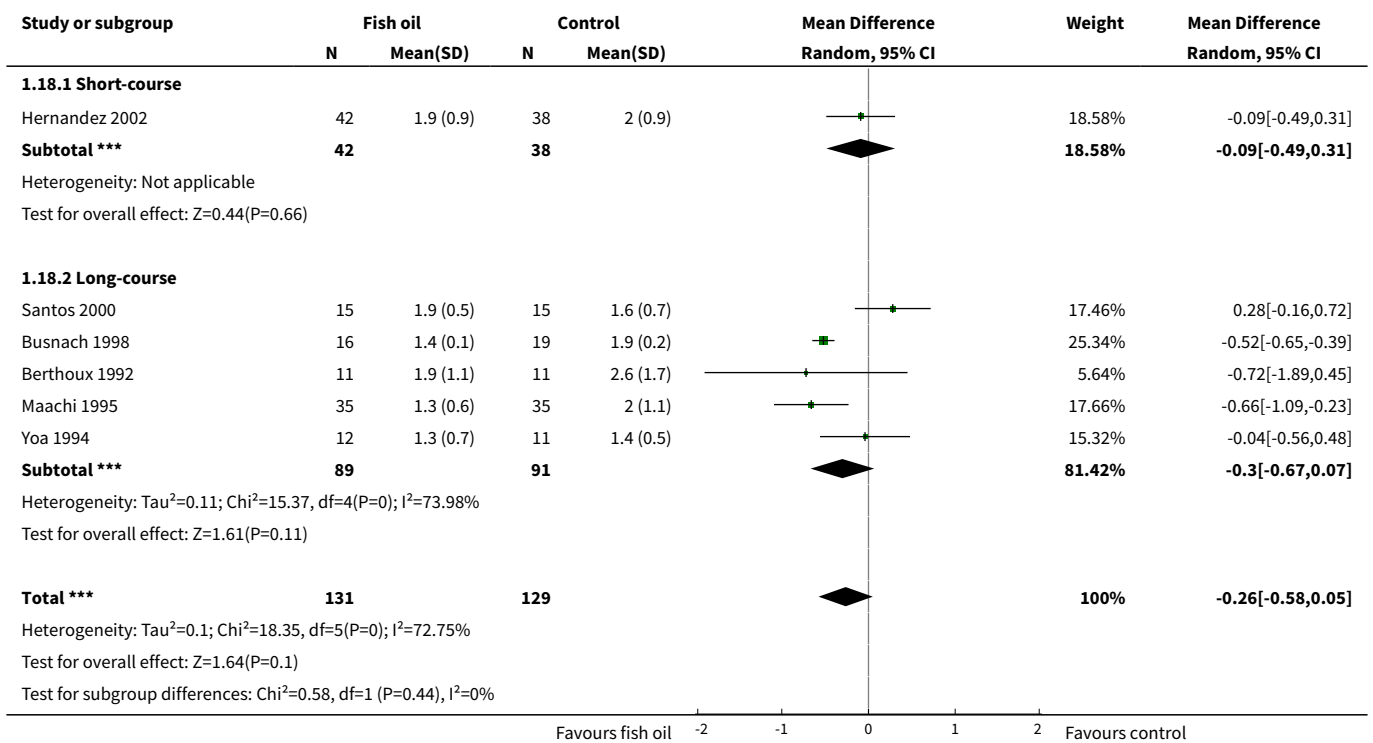


**Analysis 1.17. Comparison 1 Fish oil versus control, Outcome 17 HDL cholesterol.**





**Analysis 1.18. Comparison 1 Fish oil versus control, Outcome 18 Triglycerides.**

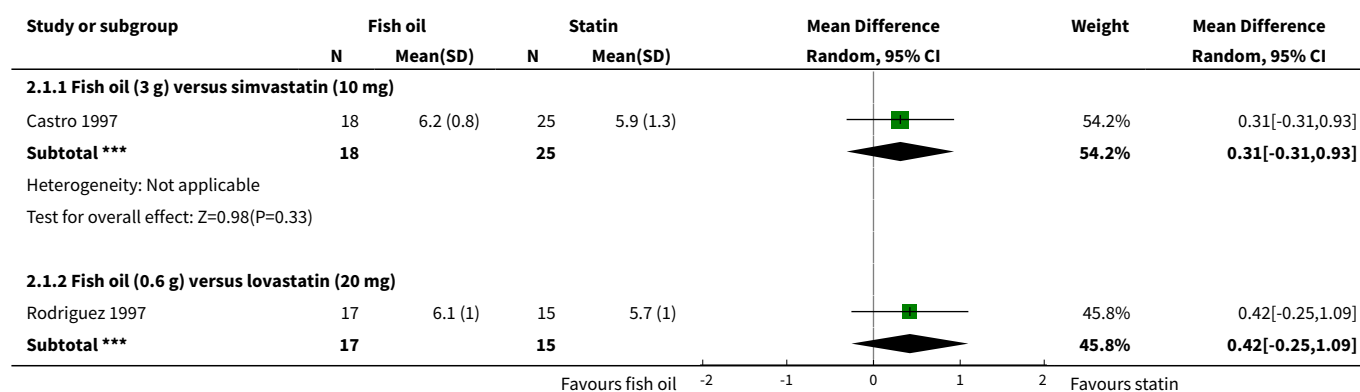


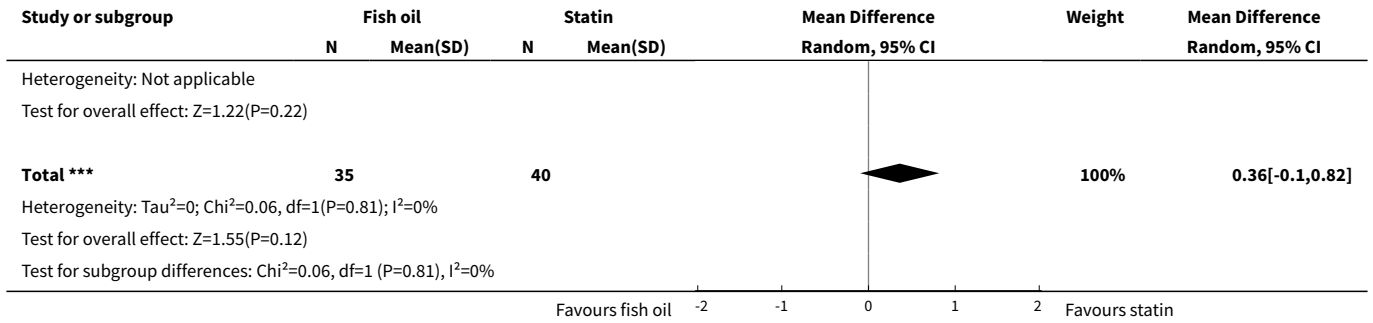


**Comparison 2. Fish oil versus statins**

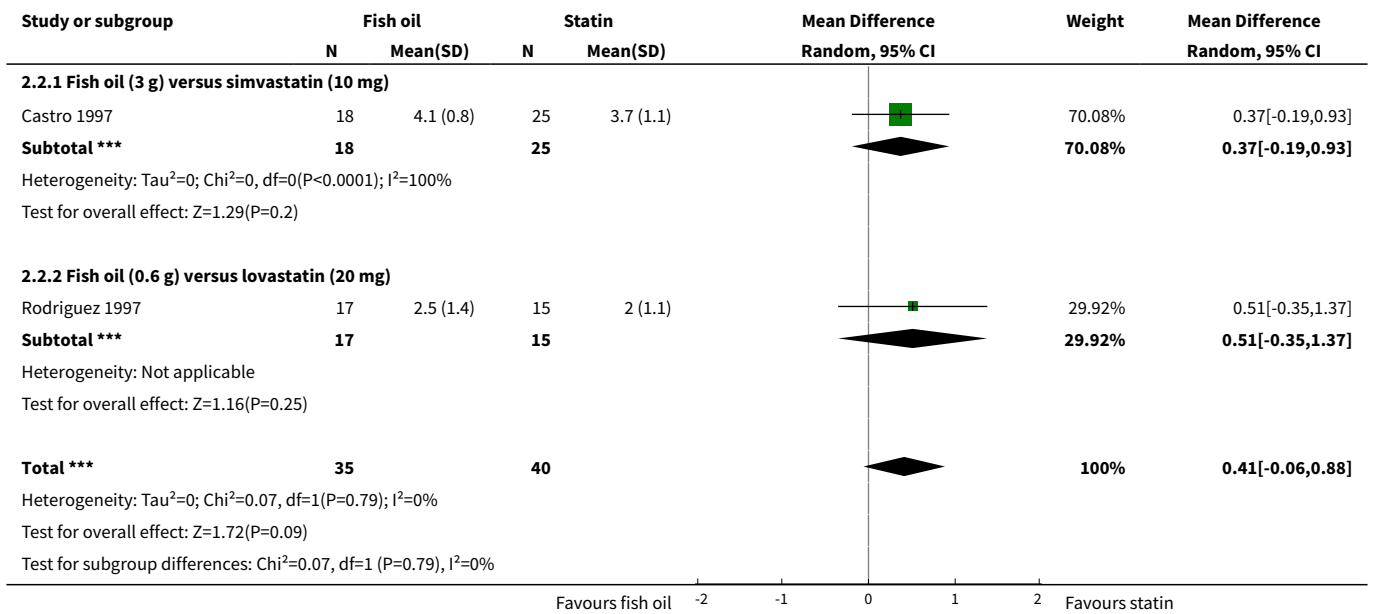
| Outcome or subgroup title                      | No. of studies | No. of participants | Statistical method                   | Effect size          |
|--|----------------|---------------------|--------------------------------------|----------------------|
| <b>1 Total cholesterol</b>                     | 2              | 75                  | Mean Difference (IV, Random, 95% CI) | 0.36 [-0.10, 0.82]   |
| 1.1 Fish oil (3 g) versus simvastatin (10 mg)  | 1              | 43                  | Mean Difference (IV, Random, 95% CI) | 0.31 [-0.31, 0.93]   |
| 1.2 Fish oil (0.6 g) versus lovastatin (20 mg) | 1              | 32                  | Mean Difference (IV, Random, 95% CI) | 0.42 [-0.25, 1.09]   |
| <b>2 LDL cholesterol</b>                       | 2              | 75                  | Mean Difference (IV, Random, 95% CI) | 0.41 [-0.06, 0.88]   |
| 2.1 Fish oil (3 g) versus simvastatin (10 mg)  | 1              | 43                  | Mean Difference (IV, Random, 95% CI) | 0.37 [-0.19, 0.93]   |
| 2.2 Fish oil (0.6 g) versus lovastatin (20 mg) | 1              | 32                  | Mean Difference (IV, Random, 95% CI) | 0.51 [-0.35, 1.37]   |
| <b>3 HDL cholesterol</b>                       | 2              | 75                  | Mean Difference (IV, Random, 95% CI) | -0.18 [-0.39, 0.02]  |
| 3.1 Fish oil (3 g) versus simvastatin (10 mg)  | 1              | 43                  | Mean Difference (IV, Random, 95% CI) | -0.08 [-0.30, 0.14]  |
| 3.2 Fish oil (0.6 g) versus lovastatin (20 mg) | 1              | 32                  | Mean Difference (IV, Random, 95% CI) | -0.29 [-0.51, -0.07] |
| <b>4 Triglycerides</b>                         | 2              | 75                  | Mean Difference (IV, Random, 95% CI) | 0.18 [-0.18, 0.55]   |
| 4.1 Fish oil (3 g) versus simvastatin (10 mg)  | 1              | 43                  | Mean Difference (IV, Random, 95% CI) | 0.25 [-0.17, 0.67]   |
| 4.2 Fish oil (0.6 g) versus lovastatin (20 mg) | 1              | 32                  | Mean Difference (IV, Random, 95% CI) | -0.02 [-0.75, 0.71]  |

**Analysis 2.1. Comparison 2 Fish oil versus statins, Outcome 1 Total cholesterol.**

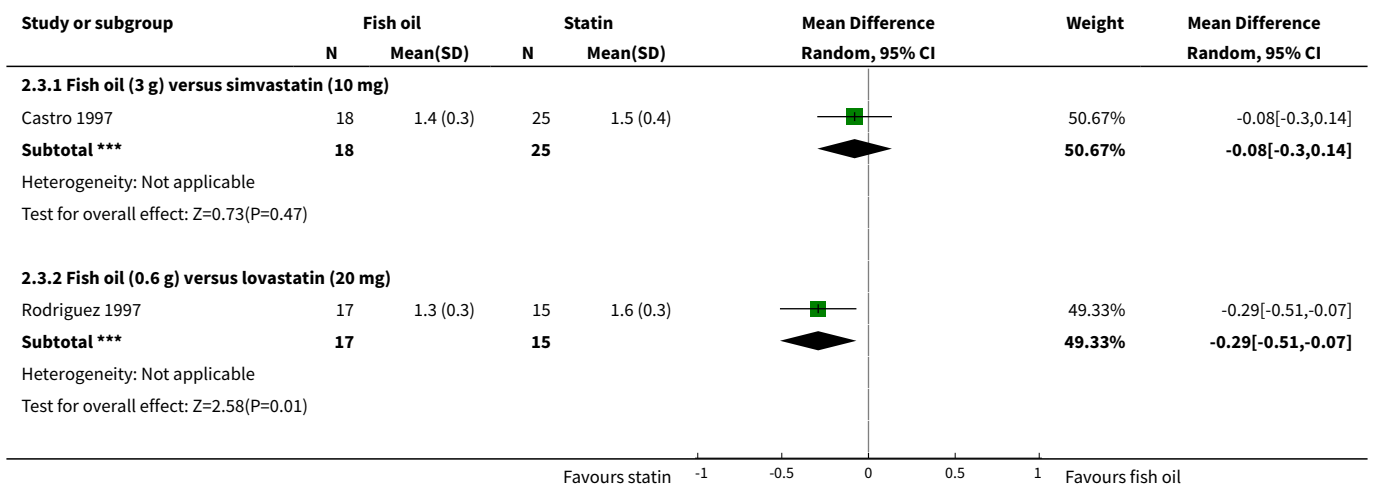


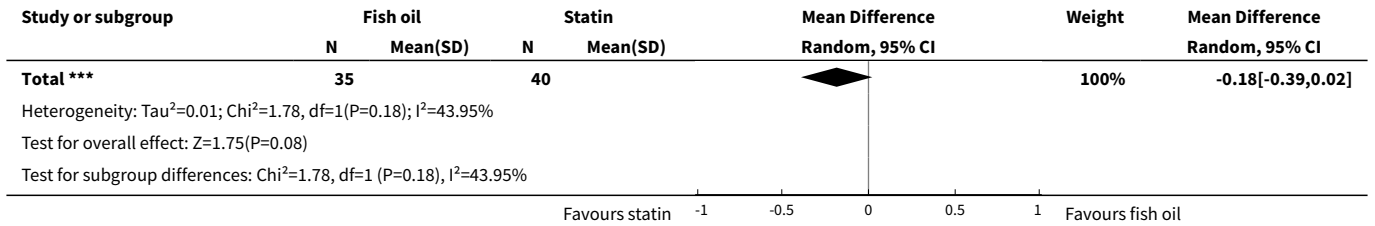


**Analysis 2.2. Comparison 2 Fish oil versus statins, Outcome 2 LDL cholesterol.**

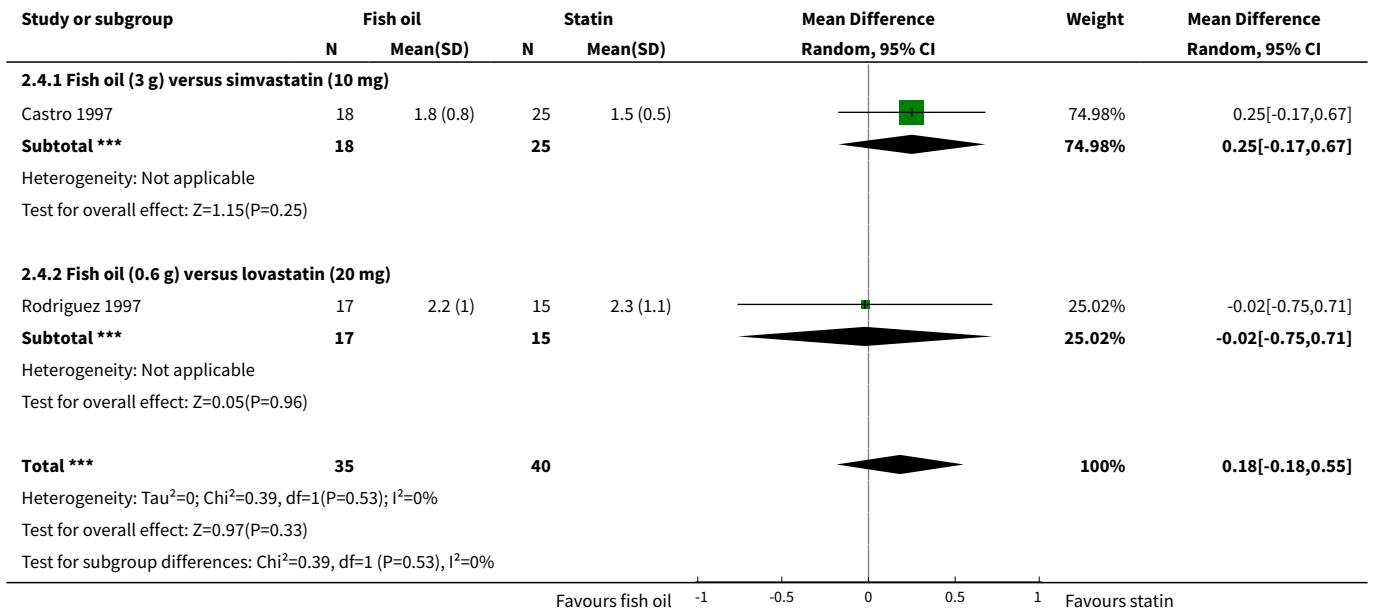


**Analysis 2.3. Comparison 2 Fish oil versus statins, Outcome 3 HDL cholesterol.**





**Analysis 2.4. Comparison 2 Fish oil versus statins, Outcome 4 Triglycerides.**



**ADDITIONAL TABLES**
**Table 1. Summary of reported outcome measures**

| Study ID                                | Patient survival | Graft survival | Acute rejection | CNI toxicity | Adverse effects | Compliance | Kidney function | Blood pressure | Lipid profile |
|---|------------------|----------------|-----------------|--------------|-----------------|------------|-----------------|----------------|---------------|
| Bennett (high) 1995; Bennett (low) 1995 | X                | X              | X               | -            | -               | -          | X               | -              | X             |
| Berthoux 1992                           | X                | X              | -               | -            | -               | -          | X               | X              | X             |
| Busnach 1998                            | X                | X              | X               | -            | -               | X          | X               | X              | X             |
| Castro 1997                             | -                | -              | -               | -            | -               | -          | -               | -              | X             |
| Hernandez 2002                          | X                | X              | X               | X            | X               | X          | X               | X              | X             |
| Homan van der Heide 1990a               | X                | X              | X               | -            | X               | -          | X               | X              | -             |
| Homan van der Heide 1990b               | X                | X              | X               | -            | -               | X          | X               | X              | -             |
| Homan van der Heide 1992                | X                | X              | X               | -            | -               | X          | X               | X              | -             |
| Homan van der Heide 1993                | X                | X              | X               |              | X               | X          | X               | X              | -             |
| Kooijmans-Coutinho 1996                 | X                | X              | X               | -            | X               | X          | X               | X              | -             |
| Maachi 1995                             | X                | X              | X               | -            | X               | X          | X               | -              | X             |
| Rodriguez 1997                          | -                | -              | -               | -            | -               | -          | -               | -              | X             |
| Santos 2000                             | X                | X              | X               | -            | X               | X          | X               | X              | X             |
| Schut 1992a; Schut 1992b                | -                | -              | -               | -            | -               | -          | X               | X              | -             |
| Yoa 1994                                | -                | -              | -               | -            | -               | -          | X               | -              | X             |

CNI - calcineurin inhibitor

**Table 2. Fish oil versus control: adverse effects**

| Study ID  | Fishy taste                      | GI upset | Breath | Bleeding | Other                            |
|---|----------------------------------|----------|--------|----------|----------------------------------|
| <a href="#">Bennett (high) 1995; Bennett (low) 1995</a> | No                               | No       | No     | No       | -                                |
| <a href="#">Berthoux 1992</a>                           | Yes                              | Yes      | No     | No       | -                                |
| <a href="#">Hernandez 2002</a>                          | Yes (70%)                        | No       | No     | No       | -                                |
| <a href="#">Homan van der Heide 1990a</a>               | Yes                              | No       | No     | No       | -                                |
| <a href="#">Homan van der Heide 1992</a>                | Yes                              | No       | No     | No       | -                                |
| <a href="#">Homan van der Heide 1993</a>                | Yes                              | Yes      | No     | No       | "Pyrosis"<br>Swallowing problems |
| <a href="#">Kooijmans-Coutinho 1996</a>                 | Yes (1 patient in control group) | Yes      | No     | No       | -                                |
| <a href="#">Maachi 1995</a>                             | Yes                              | No       | No     | No       | -                                |
| <a href="#">Rodriguez 1997</a>                          | No                               | Yes      | No     | No       | -                                |
| <a href="#">Santos 2000</a>                             | No                               | No       | No     | No       | -                                |

GI - gastrointestinal

**Table 3. Short-course fish oil versus control/miscellaneous**

| Study ID                                  | Serum creatinine: median (range)                                   | Creatinine clearance: (range)   | GFR: median (range)   | Blood pressure (MAP): median (range)  | Lipids       | Other |
|---|--|---|---|---|--------------|-------|
| <a href="#">Homan van der Heide 1990a</a> | Fish oil: 170 (93 to 224)<br>Control: 172 (101 to 540)<br>P = NS   | Fish oil: 51 (35 to 75)<br>Control: 48 (10 to 88)<br>P = NS                 | Fish oil: 44 (26 to 60)<br>Control: 40 (10 to 80)<br>P = NS   | Fish oil: 106 (82 to 137)<br>Control: 107 (80 to 132)<br>P = NS   | Not reported | -     |
| <a href="#">Homan van der Heide 1990b</a> | Fish oil: 120 (88 to 159)<br>Control: 147 (106 to 189)<br>P < 0.05 | Fish oil: 88.4 (57.7 to 158.6)<br>Control: 79.5 (52.3 to 113.3)<br>P < 0.05 | Fish oil: 68 (29 to 93)<br>Control: 60 (32 to 84)<br>Per cent change<br>Fish oil: 20.3 (8.9 to 33.3)<br>Control: -2.6 (-38 to -7.2)<br>P < 0.01 | Fish oil: 98 (76 to 106)<br>Control: 109 (103 to 116)<br>Per cent change<br>Fish oil: -8.6 (-23.8 to 0)<br>Control: 0.9 (-6.9 to 9.4)<br>P < 0.01 | Not reported | -     |

**Table 3. Short-course fish oil versus control/miscellaneous** (Continued)

|                          |                           |                         |              |                           |              |                            |
|--------------------------|---------------------------|-------------------------|--------------|---------------------------|--------------|----------------------------|
| Homan van der Heide 1992 | Fish oil: 163 (93 to 406) | Fish oil: 53 (22 to 80) | Not reported | Fish oil: 105 (76 to 137) | Not reported | Rejecting patients         |
|                          | Control: 200 (100 to 850) | Control: 49 (12 to 88)  |              | Control: 108 (76 to 142)  |              |                            |
|                          | P = NS                    | P = NS                  |              | P = NS                    |              |                            |
|                          |                           |                         |              |                           |              | SCr median (range)         |
|                          |                           |                         |              |                           |              | Fish oil: 183 (127 to 406) |
|                          |                           |                         |              |                           |              | Control: 283 (132 to 860)  |
|                          |                           |                         |              |                           |              | P < 0.05                   |
|                          |                           |                         |              |                           |              | CrCl median (range)        |
|                          |                           |                         |              |                           |              | Fish oil: 43 (22 to 69)    |
|                          |                           |                         |              |                           |              | Control: 27 (12 to 50)     |
|                          |                           |                         |              |                           |              | P < 0.05                   |

CrCl - creatinine clearance; NS - not significant; SCr - serum creatinine

**Table 4. Long-course fish oil versus control/miscellaneous**

| Study ID                 | Serum creatinine | Creatinine clearance | GFR (median)   | Mean arterial pressure (range)                                      | Lipids       | Other |
|--------------------------|------------------|----------------------|--|---|--------------|-------|
| Homan van der Heide 1993 | Not reported     | Not reported         | Fish oil: 53 mL/min<br>Control: 40 mL/min<br>P = 0.038 | Fish oil: 103 (80 to 141)<br>Control: 118 (98 to 131)<br>P = 0.0011 | Not reported | -     |

## APPENDICES

### Appendix 1. Electronic search strategies

| Database | Search terms  |
|----------|---|
| CENTRAL  | <ol style="list-style-type: none"> <li>1. MeSH descriptor Fish Oils explode all trees in MeSH products</li> <li>2. (fish oil*) in Clinical Trials</li> <li>3. (cod liver oil*) in Clinical Trials</li> <li>4. (fish liver oil*) in Clinical Trials</li> <li>5. "omega-3" in Clinical Trials</li> <li>6. "n-3 fatty acid*" in Clinical Trials</li> <li>7. (icosapentaenoic acid* or eicosapentaenoic acid*) in Clinical Trials</li> <li>8. (docosahexaenoate* or docosahexenate\$) in Clinical Trials</li> <li>9. (ameu* or efamed* or epax* or feniko* or fish oil* or himega*) in Clinical Trials</li> </ol> |

(Continued)

10. ("k-85\*" or "lachs 550\*" or lipitac\* or maxepa\* or olemar\* or optimepa\* or pikasol\*) in Clinical Trials
11. (promega\* or "super era" or superepa\*) in Clinical Trials
12. (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11)
13. MeSH descriptor Kidney Transplantation, this term only
14. (kidney transplant\* or renal transplant\*) in Clinical Trials
15. (13 OR 14)
16. (12 AND 15)

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**MEDLINE**

1. kidney transplantation/
2. exp Fish Oils/
3. (fish adj2 oil).tw.
4. fish oil\$.tw.
5. (cod adj2 oil\$).tw.
6. omega 3 fatty acid\$.tw.
7. n-3 fatty acid\$.tw.
8. Eicosapentaenoic Acid\$.tw.
9. Docosahexaenoic acid\$.tw.
10. timnodonic acid\$.tw.
11. (icosapentaenoic acid\$ or eicosapentaenoic acid\$).tw.
12. omega-3.tw.
13. (docosahexaenoate\$ or docosahexenoate\$).tw.
14. ameu.tw.
15. efamed.tw.
16. epax\$.tw.
17. feniko.tw.
18. himega.tw.
19. k-85.tw.
20. lachs 550.tw.
21. lipitac.tw.
22. maxepa.tw.
23. olemar.tw.
24. optimepa.tw.
25. pikasol.tw.
26. promega.tw.
27. (super epa or superepa).tw.
28. or/2-27
29. and/1,28

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**EMBASE**

1. exp kidney transplantation/
2. Fish Oil/
3. ameu.tw.
4. efamed.tw.
5. epax\$.tw.
6. feniko.tw.
7. fish oil\$.tw.
8. himega.tw.
9. k-85.tw.
10. lachs 550.tw.
11. lipitac.tw.
12. maxepa.tw.
13. olemar.tw.

(Continued)

- 14.optimepa.tw.
- 15.pikasol.tw.
- 16.promega.tw.
- 17.(super EPA or superepa).tw.
- 18.or/2-17
- 19.Omega 3 Fatty Acid/
- 20.bilantin omega.tw.
- 21.conchol 36.tw.
- 22.(eicosa e or eicosapen).tw.
- 23.epaisdin.tw.
- 24.omacor.tw.
- 25.omega 3.tw.
- 26.omega 3 fatty acid\$.tw.
- 27.sakana.tw.
- 28.sanhelios.tw.
- 29.eicosapentaenoic acid\$.tw.
- 30.docosahexaenoic acid\$.tw.
- 31.Docosahexaenoic Acid/
- 32.Icosapentaenoic Acid/
- 33.timnodonic acid\$.tw.
- 34.icosapentaenoic acid\$.tw.
- 35.(docosahexaenoate\$ or docosahexenoate\$).tw.
- 36.or/2-35
- 37.and/1,36

## Appendix 2. Risk of bias assessment tool

| Potential source of bias   | Assessment criteria   |
|--|---|
| <p><b>Random sequence generation</b></p> <p>Selection bias (biased allocation to interventions) due to inadequate generation of a randomised sequence</p>        | <p><i>Low risk of bias:</i> Random number table; computer random number generator; coin tossing; shuffling cards or envelopes; throwing dice; drawing of lots; minimisation (minimisation may be implemented without a random element, and this is considered to be equivalent to being random).</p> <p><i>High risk of bias:</i> Sequence generated by odd or even date of birth; date (or day) of admission; sequence generated by hospital or clinic record number; allocation by judgement of the clinician; by preference of the participant; based on the results of a laboratory test or a series of tests; by availability of the intervention.</p> <p><i>Unclear:</i> Insufficient information about the sequence generation process to permit judgement.</p>                  |
| <p><b>Allocation concealment</b></p> <p>Selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment</p> | <p><i>Low risk of bias:</i> Randomisation method described that would not allow investigator/participant to know or influence intervention group before eligible participant entered in the study (e.g. central allocation, including telephone, web-based, and pharmacy-controlled, randomisation; sequentially numbered drug containers of identical appearance; sequentially numbered, opaque, sealed envelopes).</p> <p><i>High risk of bias:</i> Using an open random allocation schedule (e.g. a list of random numbers); assignment envelopes were used without appropriate safeguards (e.g. if envelopes were unsealed or non-opaque or not sequentially numbered); alternation or rotation; date of birth; case record number; any other explicitly unconcealed procedure.</p> |



(Continued)

*Unclear:* Randomisation stated but no information on method used is available.

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**Blinding of participants and personnel**

Performance bias due to knowledge of the allocated interventions by participants and personnel during the study

*Low risk of bias:* No blinding or incomplete blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding; blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken.

*High risk of bias:* No blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding; blinding of key study participants and personnel attempted, but likely that the blinding could have been broken, and the outcome is likely to be influenced by lack of blinding.

*Unclear:* Insufficient information to permit judgement

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**Blinding of outcome assessment**

Detection bias due to knowledge of the allocated interventions by outcome assessors.

*Low risk of bias:* No blinding of outcome assessment, but the review authors judge that the outcome measurement is not likely to be influenced by lack of blinding; blinding of outcome assessment ensured, and unlikely that the blinding could have been broken.

*High risk of bias:* No blinding of outcome assessment, and the outcome measurement is likely to be influenced by lack of blinding; blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome measurement is likely to be influenced by lack of blinding.

*Unclear:* Insufficient information to permit judgement

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**Incomplete outcome data**

Attrition bias due to amount, nature or handling of incomplete outcome data.

*Low risk of bias:* No missing outcome data; reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias); missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate; for continuous outcome data, plausible effect size (difference in means or standardised difference in means) among missing outcomes not enough to have a clinically relevant impact on observed effect size; missing data have been imputed using appropriate methods.

*High risk of bias:* Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate; for continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size; 'as-treated' analysis done with substantial departure of the intervention received from that assigned at randomisation; potentially inappropriate application of simple imputation.

*Unclear:* Insufficient information to permit judgement

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**Selective reporting**

Reporting bias due to selective outcome reporting

*Low risk of bias:* The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way; the study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon).

*High risk of bias:* Not all of the study's pre-specified primary outcomes have been reported; one or more primary outcomes is reported using measurements, analysis methods or subsets of the data (e.g. sub-scales) that were not pre-specified; one or more reported primary outcomes were not pre-specified (unless clear justification for their reporting is provided, such as an unexpected adverse effect); one or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis; the study report fails to include results for a key outcome that would be expected to have been reported for such a study.

*Unclear:* Insufficient information to permit judgement

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**Other bias**

*Low risk of bias:* The study appears to be free of other sources of bias.

(Continued)

Bias due to problems not covered elsewhere in the table

*High risk of bias:* Had a potential source of bias related to the specific study design used; stopped early due to some data-dependent process (including a formal-stopping rule); had extreme baseline imbalance; has been claimed to have been fraudulent; had some other problem.

*Unclear:* Insufficient information to assess whether an important risk of bias exists; insufficient rationale or evidence that an identified problem will introduce bias.

## WHAT'S NEW

| Date          | Event  | Description   |
|---------------|--|---|
| 17 March 2016 | New citation required but conclusions have not changed | New search, 1 ongoing study identified                          |
| 17 March 2016 | New search has been performed                          | New search; subheadings added; risk of bias assessment included |

## HISTORY

Protocol first published: Issue 2, 2005

Review first published: Issue 2, 2007

| Date        | Event   | Description                     |
|-------------|---------|---------------------------------|
| 12 May 2008 | Amended | Converted to new review format. |

## CONTRIBUTIONS OF AUTHORS

AL: researched background, established protocol, performed search and reviewed identified studies, co-author of review

KM: researched background, established protocol, performed search and reviewed identified studies, co-author of review

MR: conflict arbitration as independent third author, co-author of review

MF: project supervisor, proof-reading, editorial comments

## DECLARATIONS OF INTEREST

- Andy KH Lim: none known
- Karen J Manley: none known
- Matthew A Roberts: none known
- Margaret B Fraenkel: none known

## DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Risk of bias assessment tool has replaced the Quality checklist.

## INDEX TERMS

### Medical Subject Headings (MeSH)

\*Calcineurin Inhibitors; Blood Pressure [drug effects] [physiology]; Fish Oils [adverse effects] [\*therapeutic use]; Graft Rejection [\*prevention & control]; Graft Survival [\*drug effects]; Kidney [drug effects] [physiology]; Kidney Transplantation [\*mortality]; Lipids [blood]; Randomized Controlled Trials as Topic

**MeSH check words**

Humans