



Cochrane
Library

Cochrane Database of Systematic Reviews

Marine-derived n-3 fatty acids therapy for stroke (Review)

Alvarez Campano CG, Macleod MJ, Aucott L, Thies F

Alvarez Campano CG, Macleod MJ, Aucott L, Thies F.
Marine-derived n-3 fatty acids therapy for stroke.
Cochrane Database of Systematic Reviews 2019, Issue 6. Art. No.: CD012815.
DOI: 10.1002/14651858.CD012815.pub2.

www.cochranelibrary.com

TABLE OF CONTENTS

| | |
|---|-----|
| HEADER | 1 |
| ABSTRACT | 1 |
| PLAIN LANGUAGE SUMMARY | 2 |
| SUMMARY OF FINDINGS FOR THE MAIN COMPARISON | 4 |
| BACKGROUND | 7 |
| OBJECTIVES | 9 |
| METHODS | 9 |
| RESULTS | 11 |
| Figure 1. | 12 |
| Figure 2. | 15 |
| Figure 3. | 16 |
| Figure 4. | 18 |
| Figure 5. | 19 |
| ADDITIONAL SUMMARY OF FINDINGS | 19 |
| DISCUSSION | 22 |
| AUTHORS' CONCLUSIONS | 23 |
| ACKNOWLEDGEMENTS | 24 |
| REFERENCES | 24 |
| CHARACTERISTICS OF STUDIES | 36 |
| DATA AND ANALYSES | 94 |
| Analysis 1.1. Comparison 1 Marine-derived n-3 fatty acids therapy compared to no marine-derived n-3 fatty acids therapy: follow-up of 3 months or sooner, Outcome 1 Efficacy (poor clinical outcome). | 95 |
| Analysis 1.2. Comparison 1 Marine-derived n-3 fatty acids therapy compared to no marine-derived n-3 fatty acids therapy: follow-up of 3 months or sooner, Outcome 2 Vascular-related death. | 95 |
| Analysis 1.3. Comparison 1 Marine-derived n-3 fatty acids therapy compared to no marine-derived n-3 fatty acids therapy: follow-up of 3 months or sooner, Outcome 3 Recurrent events (all: fatal and non-fatal). | 96 |
| Analysis 1.4. Comparison 1 Marine-derived n-3 fatty acids therapy compared to no marine-derived n-3 fatty acids therapy: follow-up of 3 months or sooner, Outcome 4 Incidence of other type of stroke. | 97 |
| Analysis 1.5. Comparison 1 Marine-derived n-3 fatty acids therapy compared to no marine-derived n-3 fatty acids therapy: follow-up of 3 months or sooner, Outcome 5 Adverse events (all). | 97 |
| Analysis 1.6. Comparison 1 Marine-derived n-3 fatty acids therapy compared to no marine-derived n-3 fatty acids therapy: follow-up of 3 months or sooner, Outcome 6 Adverse events (extracranial haemorrhage). | 98 |
| Analysis 1.7. Comparison 1 Marine-derived n-3 fatty acids therapy compared to no marine-derived n-3 fatty acids therapy: follow-up of 3 months or sooner, Outcome 7 Adverse events (bleeding complications). | 98 |
| Analysis 1.8. Comparison 1 Marine-derived n-3 fatty acids therapy compared to no marine-derived n-3 fatty acids therapy: follow-up of 3 months or sooner, Outcome 8 Quality of life (mean change from baseline). | 99 |
| Analysis 1.9. Comparison 1 Marine-derived n-3 fatty acids therapy compared to no marine-derived n-3 fatty acids therapy: follow-up of 3 months or sooner, Outcome 9 Mood (GHQ-30, mean change from baseline). | 99 |
| Analysis 2.1. Comparison 2 Marine-derived n-3 fatty acids therapy compared to no marine-derived n-3 fatty acids therapy: follow-up longer than 3 months, Outcome 1 Efficacy (Barthel Index). | 100 |
| Analysis 2.2. Comparison 2 Marine-derived n-3 fatty acids therapy compared to no marine-derived n-3 fatty acids therapy: follow-up longer than 3 months, Outcome 2 Efficacy (Rivermead Mobility Index). | 100 |
| Analysis 2.3. Comparison 2 Marine-derived n-3 fatty acids therapy compared to no marine-derived n-3 fatty acids therapy: follow-up longer than 3 months, Outcome 3 Vascular-related death. | 101 |
| Analysis 2.4. Comparison 2 Marine-derived n-3 fatty acids therapy compared to no marine-derived n-3 fatty acids therapy: follow-up longer than 3 months, Outcome 4 All recurrent events (fatal and non-fatal). | 102 |
| Analysis 2.5. Comparison 2 Marine-derived n-3 fatty acids therapy compared to no marine-derived n-3 fatty acids therapy: follow-up longer than 3 months, Outcome 5 Recurrent events (fatal only). | 102 |
| Analysis 2.6. Comparison 2 Marine-derived n-3 fatty acids therapy compared to no marine-derived n-3 fatty acids therapy: follow-up longer than 3 months, Outcome 6 Recurrent events (non-fatal only). | 103 |

| | |
|---|-----|
| Analysis 2.7. Comparison 2 Marine-derived n-3 fatty acids therapy compared to no marine-derived n-3 fatty acids therapy: follow-up longer than 3 months, Outcome 7 Adverse events (all). | 103 |
| Analysis 2.8. Comparison 2 Marine-derived n-3 fatty acids therapy compared to no marine-derived n-3 fatty acids therapy: follow-up longer than 3 months, Outcome 8 Mood (GHQ-28). | 104 |
| ADDITIONAL TABLES | 104 |
| APPENDICES | 108 |
| CONTRIBUTIONS OF AUTHORS | 113 |
| DECLARATIONS OF INTEREST | 114 |
| SOURCES OF SUPPORT | 114 |
| DIFFERENCES BETWEEN PROTOCOL AND REVIEW | 114 |

[Intervention Review]

Marine-derived n-3 fatty acids therapy for stroke

Celia Gabriela Alvarez Campano¹, Mary Joan Macleod², Lorna Aucott³, Frank Thies¹

¹The Rowett Institute, University of Aberdeen, Aberdeen, UK. ²Institute of Medical Sciences, Polwarth Building, Aberdeen, UK.

³Health Services Research Unit, University of Aberdeen, Aberdeen, UK

Contact address: Celia Gabriela Alvarez Campano, The Rowett Institute, University of Aberdeen, Aberdeen, AB25 2ZD, UK.
r01cga16@abdn.ac.uk.

Editorial group: Cochrane Stroke Group.

Publication status and date: New, published in Issue 6, 2019.

Citation: Alvarez Campano CG, Macleod MJ, Aucott L, Thies F. Marine-derived n-3 fatty acids therapy for stroke. *Cochrane Database of Systematic Reviews* 2019, Issue 6. Art. No.: CD012815. DOI: 10.1002/14651858.CD012815.pub2.

Copyright © 2019 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

ABSTRACT

Background

Currently, with stroke burden increasing, there is a need to explore therapeutic options that ameliorate the acute insult. There is substantial evidence of a neuroprotective effect of marine-derived n-3 polyunsaturated fatty acids (PUFAs) in experimental stroke, leading to a better functional outcome.

Objectives

To assess the effects of administration of marine-derived n-3 PUFAs on functional outcomes and dependence in people with stroke.

Our secondary outcomes were vascular-related death, recurrent events, incidence of other type of stroke, adverse events, quality of life, and mood.

Search methods

We searched the Cochrane Stroke Group trials register (6 August 2018), the Cochrane Central Register of Controlled Trials (CENTRAL; Issue 1, January 2019), MEDLINE Ovid (from 1948 to 6 August 2018), Embase Ovid (from 1980 to 6 August 2018), CINAHL EBSICO (Cumulative Index to Nursing and Allied Health Literature; from 1982 to 6 August 2018), Science Citation Index Expanded

– Web of Science (SCI-EXPANDED), Conference Proceedings Citation Index-Science - Web of Science (CPCI-S), and BIOSIS Citation Index. We also searched ongoing trial registers, reference lists, relevant systematic reviews, and used the Science Citation Index Reference Search.

Selection criteria

We included randomised controlled trials (RCTs) comparing marine-derived n-3 PUFAs to placebo or open control (no placebo) in people with a history of stroke or transient ischaemic attack (TIA), or both.

Data collection and analysis

At least two review authors independently selected trials for inclusion, extracted data, assessed risk of bias, and used the GRADE approach to assess the quality of the body of evidence. We contacted study authors for clarification and additional information on stroke/TIA participants. We conducted random-effects meta-analysis or narrative synthesis, as appropriate. The primary outcome was efficacy (functional outcome) assessed using a validated scale e.g. Glasgow Outcome Scale Extended (GOSE) dichotomised into poor or good clinical outcome, Barthel Index (higher score is better; scale from 0 to 100) or Rivermead Mobility Index (higher score is better; scale from 0 to 15).

Main results

We included 29 RCTs; nine of them provided outcome data (3339 participants). Only one study included participants in the acute phase of stroke (haemorrhagic). Doses of marine-derived n-3 PUFAs ranged from 400 mg/day to 3300 mg/day. Risk of bias was generally low or unclear in most trials, with a higher risk of bias in smaller studies. We assessed results separately for short (up to three months) and longer (more than three months) follow-up studies.

Short follow-up (up to three months)

Functional outcome was reported in only one pilot study as poor clinical outcome assessed with GOSE (risk ratio (RR) 0.78, 95% confidence interval (CI) 0.36 to 1.68; 40 participants; very low quality evidence). Mood (assessed with GHQ-30, lower score better), was reported by only one study and favoured control (mean difference (MD) 1.41, 95% CI 0.07 to 2.75; 102 participants; low-quality evidence).

We found no evidence of an effect of the intervention for the remainder of the secondary outcomes: vascular-related death (two studies, not pooled due to differences in population, RR 0.33, 95% CI 0.01 to 8.00, and RR 0.33, 95% CI 0.01 to 7.72; 142 participants; low-quality evidence); recurrent events (RR 0.41, 95% CI 0.02 to 8.84; 18 participants; very low quality evidence); incidence of other type of stroke (two studies, not pooled due to different type of index stroke, RR 6.11, 95% CI 0.33 to 111.71, and RR 0.63, 95% CI 0.25 to 1.58; 58 participants; very low quality evidence); and quality of life (physical component mean difference (MD) -2.31, 95% CI -4.81 to 0.19, and mental component MD -2.16, 95% CI -5.91 to 1.59; one study; 102 participants; low-quality evidence).

Adverse events were reported by two studies (57 participants; very low quality evidence), one trial reporting extracranial haemorrhage (RR 0.25, 95% CI 0.04 to 1.73) and the other one reporting bleeding complications (RR 0.32, 95% CI 0.01 to 7.35).

Longer follow-up (more than three months)

One small trial assessed functional outcome with both Barthel Index (MD 7.09, 95% CI -5.16 to 19.34) for activities of daily living, and Rivermead Mobility Index (MD 1.30, 95% CI -1.31 to 3.91) for mobility (52 participants; very low quality evidence). We carried out meta-analysis for vascular-related death (RR 1.02, 95% CI 0.78 to 1.35; five studies; 2237 participants; low-quality evidence) and fatal recurrent events (RR 0.69, 95% CI 0.31 to 1.55; three studies; 1819 participants; low-quality evidence).

We found no evidence of an effect of the intervention for mood (MD 1.00, 95% CI -2.07 to 4.07; one study; 14 participants; low-quality evidence). Incidence of other type of stroke and quality of life were not reported.

Adverse events (all combined) were reported by only one study (RR 0.94, 95% CI 0.56 to 1.58; 1455 participants; low-quality evidence).

Authors' conclusions

We are very uncertain of the effect of marine-derived n-3 PUFAs therapy on functional outcomes and dependence after stroke as there is insufficient high-quality evidence. More well-designed RCTs are needed, specifically in acute stroke, to determine the efficacy and safety of the intervention.

Studies assessing functionality might consider starting the intervention as early as possible after the event, as well as using standardised clinically-relevant measures for functional outcomes, such as the modified Rankin Scale. Optimal doses remain to be determined; delivery forms (type of lipid carriers) and mode of administration (ingestion or injection) also need further consideration.

PLAIN LANGUAGE SUMMARY

Marine-derived fatty acid therapy for stroke

Review question

To assess the effect of marine-derived omega-3 fatty acids for stroke after a short (up to three months) and a longer (more than three months) follow-up.

Background

The term stroke refers to a group of diseases of blood vessels in the brain. Stroke can be caused by either bleeding or blockage in these vessels that leads to a loss of function of brain cells. Transient ischaemic attack (TIA), also called a 'mini-stroke', is a temporary disruption of blood supply to the brain. Stroke is a disabling disease that usually requires prolonged specialised care and currently there are few

treatment options for stroke patients. Omega-3 fatty acids - eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) - present in oily fish have important functions in the brain. In animal research, they appear to protect the brain cells after stroke particularly if they are administered very early. However, the effects of EPA and DHA as a treatment for stroke in humans are unclear.

Study characteristics

We identified 29 studies that included participants with stroke or TIA and we found relevant information in nine of them (3339 participants in total). Three had a short follow-up (up to three months) and six had a longer follow-up. Three studies compared marine-derived omega-3 fatty acids to normal care and the remainder used a placebo (dummy). Not all the studies assessed all outcomes.

Key results

Effects of marine-derived omega-3 fatty acids are unclear for stroke recovery. Only two very small studies reported it, without finding significant differences. One study found less improvement in mood with marine-derived omega-3 fatty acids but the evidence was of low quality. The effect of marine-derived omega-3 fatty acids on vascular-related death, recurrence of stroke, adverse events, and quality of life after having a stroke or TIA is unclear, due to the small number of studies that have assessed them.

Quality of the evidence

In the short follow-up, we considered the quality of the evidence very low for recovery, recurrence, frequency of other type of stroke (bleeding or blockage), and adverse events, and low for vascular-related death, quality of life, and mood. For the longer follow-up, the evidence was of very low quality for recovery from stroke, and low quality for vascular-related death, recurrence, adverse events, and mood. Frequency of other type of stroke and quality of life were not reported in the long follow-up.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

| Marine-derived n-3 fatty acids therapy compared to no marine-derived n-3 fatty acids therapy for stroke: short follow-up (three months or less) | | | | | | |
|--|---|--|---------------------------|------------------------------|-----------------------------------|--|
| Patient or population: stroke and/or TIA Setting: hospital, outpatient, community, or home Intervention: marine-derived n-3 fatty acids therapy Comparison: no marine-derived n-3 fatty acids therapy | | | | | | |
| Outcomes | Anticipated absolute effects* (95% CI) | | Relative effect (95% CI) | No of participants (studies) | Certainty of the evidence (GRADE) | Comments |
| | Risk with no marine-derived n-3 fatty acids therapy | Risk with marine-derived n-3 fatty acids therapy | | | | |
| Efficacy (functional outcome) assessed with: Glasgow Outcome Scale Extended (GOSE), dichotomised into poor outcome | Study population | | RR 0.78 (0.36 to 1.68) | 40 (1 RCT) | ⊕○○○ Very low ¹²³ | Pilot study. Underpowered to detect effect on efficacy Follow-up time: 3 months |
| | 450 per 1000 | 351 per 1000 (162 to 756) | | | | |
| Vascular-related death | Study population | | - | 142 (2 RCTs) | ⊕⊕○○ Low ²³ | Studies not pooled due to different study populations. 1 study reported RR 0.33 (95%CI 0.01 to 8.00) and the other RR 0.33 (95%CI 0.01 to 7.72) Follow-up time: 3 months |
| | see comment | see comment | | | | |
| Recurrent events: fatal or non-fatal (same type of stroke, i.e. ischaemic or haemorrhagic) | Study population | | RR 0.41 (0.02 to 8.84) | 18 (1 RCT) | ⊕○○○ Very low ²³⁴ | Combined (fatal and non-fatal) Follow-up time: up to 1 month |

| | | | | | | |
|---|--|---------------------------|---|----------------|---------------------------------|--|
| | 100 per 1000 | 41 per 1000 (2 to 884) | | | | |
| Incidence of other type of stroke (ischaemic or haemorrhagic): fatal or non-fatal | Study population | | - | 58 (2 RCTs) | ⊕○○○ Very low ¹²³ | Non-fatal only 1 study reported haemorrhagic stroke (RR 6.11, 95% CI 0.33 to 111.71) and 1 study reported ischaemic stroke (RR 0.63, 95% CI 0.25 to 1.58) Follow-up time: from 1 to 3 months |
| | see comment | see comment | | | | |
| Adverse events | Study population | | - | 57 (2 RCTs) | ⊕○○○ Very low ²³⁴ | Extracranial haemorrhage, 1 study (RR 0.25, 95% CI 0.04 to 1.73). Bleeding complications, 1 study (RR 0.32, 95% CI 0.01 to 7.35) Follow-up time: from 1 to 3 months |
| | see comment | see comment | | | | |
| Health-related quality of life | Mean change from baseline. Physical component (MD -2.31, 95% CI -4.81 to 0.19). Mental component (MD -2.16, 95% CI -5.91 to 1.59) high score better | | - | 102 (1 RCT) | ⊕⊕○○ Low ⁵⁶ | Single study. Scoring system not specified Follow-up time: 3 months |
| Mood | Mean change from baseline (MD 1.41, 95% CI 0.07 to 2.75) lower score better | | - | 102 (1 RCT) | ⊕⊕○○ Low ⁶⁷ | Single study. Scoring system not specified Follow-up time: 3 months |

* **The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **MD:** Mean difference; **OR:** Odds ratio; **RR:** Risk ratio; **TIA:** Transient ischaemic attack

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

¹ High risk of performance bias and unclear risk of detection bias. Downgraded 1 level

² 95% CI crosses no effect and both appreciable benefit and harm. Downgraded 1 level

³ Small number of total events. Downgraded 1 level

⁴ High risk of performance and detection bias. Downgraded 1 level

⁵ Sample size too small for tool employed. Downgraded 1 level

⁶ Small sample size. Downgraded 1 level

⁷ Scoring system not specified. Small sample size might be below tool sensitivity level. Downgraded 1 level

BACKGROUND

Description of the condition

Stroke, defined as the acute onset of a persistent focal neurological deficit related to a specific cerebrovascular location (Barret 2013), is a general term that comprises different diseases involving blood vessels supplying the brain (Caplan 2006). Strokes can be broadly classified as haemorrhagic or ischaemic. Haemorrhagic stroke mainly includes intracerebral haemorrhage (ICH) and subarachnoid haemorrhage (SAH), which account for 5% to 15%, and 5%, respectively, of all acute strokes (Barret 2013). Ischaemic stroke, which can be generated by thrombosis, embolism, or systemic hypoperfusion, leads to a lack of blood supply for normal functioning of the brain tissue (Caplan 2006). From around 790,000 cases of new or recurrent strokes registered each year in the USA, up to 87% are ischaemic (Mozaffarian 2016). Transient ischaemic attacks (TIAs) are temporary disruptions in circulation to a part of the brain (Caplan 2006). Two regions are found within the infarct in ischaemic stroke: the necrotic core, which is irreversibly injured due to rapid cell death; and the ischaemic penumbra, an area that surrounds the core and where neurons remain potentially salvageable (Blondeau 2016; Yao 2013). The penumbra has a life span of only a few hours and, during this period, reperfusion or neuroprotective therapy is needed to prevent irreversible damage (Yao 2013).

In response to stroke, physiological and structural changes take place in neuronal circuits surrounding the infarct in order to stimulate neural repair. These include the formation of new connections in cortical areas (termed axonal sprouting, which is also influenced by neurorehabilitation), neural progenitor responses (neurogenesis and gliogenesis), and changes in neuronal excitability in peri-infarct tissue (Carmichael 2016). However, reperfusion after ischaemia can, paradoxically, result in enhanced tissue injury (Eltzschig 2011). Therefore, neuroprotectants that potentially attenuate damage related to reperfusion injury are also needed. Furthermore, theoretically beneficial compounds may also have adverse effects during the recovery phase, considering that stability and protection are required in the acute phase, whereas neuronal plasticity is needed during the following stages (Carmichael 2016). The timing of intervention is critical for optimal recovery after stroke: alteplase is effective when administered within 4.5 hours from stroke ictus (Hacke 2008), while clot retrieval is beneficial up to 7.3 hours (Saver 2016), and up to 24 hours in selected patients (Nogueira 2018). Due to public awareness campaigns, more people are arriving in emergency departments early after the event, but other than intravenous thrombolysis or thrombectomy, there are no evidence-based neuroprotective agents currently available. In contrast with other cardiovascular events, stroke tends to leave permanent sequelae and generally requires long-term rehabilitation and specialised care (Tanaka 2008). In 2016, there were more than 80 million stroke survivors worldwide and global stroke bur-

den is increasing (Feigin 2019). For these reasons, the need to explore therapeutic options to ameliorate the acute insult remains.

Description of the intervention

High oily fish intake has been related to a reduced mortality from coronary (Hu 2002), and ischaemic heart disease (Zhang 1999), in both sexes. Epidemiological studies have reported mixed results regarding stroke: while some observed an inverse relationship between fish intake and stroke incidence (Gillum 1996; Keli 1994), and mortality (Zhang 1999), others have found no significant effect (Morris 1995; Orenca 1996). Considering the nature of observational studies, potential confounding factors - such as lifestyle and other dietary compounds - need to be taken into account when assessing the evidence. As oily fish is an important source of omega-3 (n-3) polyunsaturated fatty acids (PUFAs), mainly eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) (Saravanan 2010), potential effects of fish intake on cardiovascular diseases have been attributed to these n-3 PUFAs.

EPA and DHA are synthesised by marine algae and are concentrated in fish and marine oils, while terrestrial plant n-3 fatty acids sources contain only the n-3 precursor alpha-linolenic acid (ALA) (Bradbury 2011; Valenzuela 2009). EPA and DHA make up approximately 30% of the fatty acids present in fish oil; however, their proportion varies according to the type of fish (Calder 2012a). Presently, apart from seafood, these fatty acids can be found in supplements of fish oil, fish liver oil, krill oil, and also as pharmaceutical grade ethyl ester formulations (Calder 2009). Availability of n-3 PUFAs has allowed pharmacological intervention trials using highly purified fatty acids concurrently with food-based trials (Yokoyama 2007). Current intake recommendations of marine-derived n-3 PUFAs from different health bodies in Western countries are around 500 mg per day of combined EPA and DHA, the equivalent of two oily-fish meals per week (Kris-Etherton 2009). EPA comprises 20 carbon atoms and five double bonds and it is required for production of eicosanoids (Bradbury 2011). EPA, in its ethyl ester form, has been approved in Japan as a treatment for hyperlipidaemia and peripheral artery disease (Yokoyama 2007). Furthermore, it has been shown to reduce the recurrence of stroke in a Japanese hypercholesterolaemic population (Tanaka 2008). DHA, with the longest side chain (22 carbon atoms) and six double bonds, is particularly concentrated in membrane phospholipids of nervous tissues (Valenzuela 2013), and it is critical for maintaining normal retinal and brain structure and function (Bradbury 2011). DHA is essential for normal brain growth (McNamara 2006), and cognitive function (Bazan 2009): supplies are required for membrane replacement, maintaining synaptic integrity and function, gene regulation, and synthesis of neuroprotectins (Bazinet 2014). DHA also plays a critical role in neuronal survival and is a potent modulator of brain inflammation (Bazinet 2014). DHA, therefore, has potential roles in prevention and attenuation of is-

chaemic injury, and also in facilitating repair and neuroplasticity after stroke (Belayev 2011).

How the intervention might work

Increasing intakes of n-3 PUFAs from fatty fish could positively influence the prevention of stroke (Ikeya 2013). Furthermore, in people with acute ischaemic stroke a low serum n-3/n-6 PUFAs ratio on admission has been shown to predict neurological deterioration (Suda 2013). In patients on a low-dose statin therapy, administration of EPA reduced the risk of a recurrent stroke (Tanaka 2008). Marine-derived n-3 PUFAs are suggested to reduce inflammation, improve endothelial activity, and decrease platelet aggregation (Calder 2012a; Calder 2012b). The antithrombotic effects of marine-derived n-3 PUFAs include reducing thrombin formation, decreasing oxidative stress (Gajos 2011), and increasing plaque stability (Thies 2003).

Recent findings from animal models showed that unesterified DHA injection or infusion with fish oil within three hours after brain ischaemia reduced total infarct volume by 51% in rats (Belayev 2009), and by 36% in mice (Zhang 2014), compared to placebo. It also significantly improved functional outcome after cerebral ischaemia in both models. In a rat model, DHA administration up to five hours after focal ischaemia increased neurobehavioural recovery, reduced brain infarction and oedema, and activated neuroprotectin D1 (NPD1) synthesis in the penumbra (Belayev 2011). NPD1 is a lipid mediator, synthesised from DHA, which stimulates cell-protecting and pro-survival signalling (Belayev 2011), and seems to have a role in neuroprotection (Calder 2012a). NPD1 suppresses apoptosis (Bazan 2005), and promotes neurogenesis (Eady 2014). Additionally, DHA exerts an anti-inflammatory effect during ischaemic injury through the attenuation of microglia activation in both young and aged rat models (Belayev 2011; Eady 2014; Hong 2014; Zendedel 2015). Marine-derived n-3 PUFAs treatment in rats also attenuated the death of both neurons and astrocytes, with the latter being essential for neuronal survival (Belayev 2011). The supplementation with n-3 PUFAs-enriched fish oil for three months before and up to one month after stroke in mice stimulated the expression of angiopoietins (ANGPTs 1 and 2), and improved the migration and survival of neuroblasts (Zhang 2015). Myelin integrity was also preserved and oligodendrogenesis was promoted after ischaemia, facilitating therefore the recovery of white matter and neurological functions (Zhang 2015). Transgenic *fat-1* mice, which overproduce n-3 PUFAs, have been shown to have long-term behavioural and histological protection against transient focal cerebral ischaemia, exhibiting improvements in revascularisation and angiogenesis compared to wild-type littermates (Wang 2014). Taken together, these results suggest that marine-derived n-3 PUFAs may be beneficial not only in the acute phase but also for long-term functional recovery after cerebral ischaemia.

With respect to the risk of haemorrhagic stroke, evidence assessing the impact of marine-derived n-3 PUFAs intake shows conflicting results. Early epidemiological studies in Greenlandic Eskimos (or Inuit) observed a positive relationship between increased fish intake and incidence of haemorrhagic stroke (Dyerberg 1979; Ostergaard Kristensen 1983). This effect is likely due to the EPA component of fish oil, which at high doses inhibits platelet aggregation (Jakubowski 1979). However, an augmented incidence of cerebral haemorrhage was not observed in later studies in women with high consumption of fish and n-3 PUFAs (Iso 2001), nor in patients using fish oil or EPA supplements (Nakase 2015; Pryce 2016).

Why it is important to do this review

Given that stroke is one of the main causes of long-term disability worldwide (Mozaffarian 2016), it is critical to examine the established and potential approaches to protecting the brain during the crucial period of damage and recovery. If marine-derived n-3 PUFAs supplements were shown to reduce cerebral ischaemia severity or improve recovery without increasing the risk of cerebral haemorrhage, this would provide a safe, inexpensive, and simple intervention which is easy to implement. Some studies looking at marine-derived n-3 PUFAs supplementation and human stroke have been reported. One non-randomised study of stroke patients already taking EPA found no increased risk of haemorrhage but was underpowered for recurrent events (Nakase 2015), while a sub-analysis of the Japan EPA Lipid Intervention Study (JELIS) found reduced risk of recurrent stroke in patients also taking low-dose statin (Tanaka 2008). A study using a guideline-recommended moderate dose of fish oil supplement (0.7 g DHA daily) or placebo on cardiovascular biomarkers, mood- and health-related quality of life in patients with a history of ischaemic stroke found no effect after 12 weeks' supplementation (FOILS). Heterogeneity in results might be related to variation in doses or intervention time, different pathophysiologies of the clinical outcomes (Mozaffarian 2006), and the potential oxidation of the fish oils (FOILS). The effects of administration of marine-derived n-3 PUFAs are also likely to differ according to the type of stroke: therefore, assessing their impact on total stroke risk might underestimate the strength of the real association with a specific type of stroke (Kris-Etherton 2002; Zhang 1999).

No systematic review looking specifically at the effect of marine-derived n-3 PUFAs as a treatment for stroke has been published to date. Some systematic reviews of randomised controlled trials have reported the effect of marine-derived n-3 PUFAs on stroke incidence in populations with a history of cardiovascular disease at baseline (Abdelhamid 2018; Chowdhury 2012). However, they did not explore the outcomes considering only participants with previous stroke. Another recent meta-analysis reported a composite of major cardiovascular events following marine-derived n-3 PUFAs intervention in participants with prior stroke

without, however, specifically addressing the recurrence or recovery from stroke (Aung 2018). This Cochrane Review combines and summarises the available outcome evidence from human randomised studies of administration of marine-derived n-3 PUFAs after stroke.

OBJECTIVES

To assess the effects of administration of marine-derived n-3 PUFAs on functional outcomes and dependence in people with stroke.

Our secondary outcomes were vascular-related death, recurrent events, incidence of other type of stroke, adverse events, quality of life, and mood.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials (RCTs) of administration of marine-derived n-3 PUFAs after stroke onset, versus placebo or open control (no placebo), regardless of time lapse between onset and intervention, language, and blinding design. We excluded quasi-randomised, non-randomised, and observational studies.

Types of participants

We included all participants with a diagnosis of stroke (including TIA) on the basis of clinical examination findings, diagnostic test results, or according to the definitions used by researchers to enrol participants in their studies, regardless of severity, comorbidities, age, gender, and phase of the disease (from acute to chronic). We included trials with mixed populations in the analysis when they met our inclusion criteria and separate data for stroke patients were available.

Types of interventions

We included trials comparing administration of marine-derived n-3 PUFAs regardless of duration, dosage, route of administration, or type (fatty acids supplements, marine oils or fish intake) with placebo or no intervention. Eligible interventions included but were not limited to: fish oil, krill oil, microalgae oil, cod liver oil, other marine oils, EPA and/or DHA ethyl esters, and consumption of fish (such as salmon, mackerel, tuna, trout, sprat, pilchard, herring, sardine, swordfish).

We excluded trials in which only one of the groups (treatment or control) received another active therapy. However, we included trials where the addition of marine-derived n-3 PUFAs to another treatment was compared to the other treatment alone, therefore assessing the effect of marine-derived n-3 PUFAs independently.

Types of outcome measures

Primary outcomes

The primary outcome was efficacy (functional outcome or disability/dependency) for the latest time point of assessment, using a validated scale (e.g. modified Rankin Scale (mRS); Barthel index (BI); or change in National Institutes of Health Stroke Scale (NIHSS)). For studies using multiple scales, we included all functional outcome and disability/dependency measures reported. However, for a meta-analysis we would have selected the one with the largest amount of data available or, in the case of equal amounts of data, the one reported first in the study.

Secondary outcomes

We assessed the secondary outcomes as follows: after a short follow-up (up to three months), and after a longer follow-up (over three months).

- Vascular-related death.
- Recurrent events: fatal or non-fatal (same type of stroke, i.e. ischaemic or haemorrhagic).
- Incidence of other type of stroke (ischaemic or haemorrhagic): fatal or non-fatal.
- Adverse events: nausea, vomiting, allergic reaction, or other serious adverse events associated with the intervention.
- Quality of life (scales defined by authors).
- Mood (scales defined by authors).

Search methods for identification of studies

See [Cochrane Stroke's search methods](#) for full search strategies and a list of other resources searched. We searched for trials in all languages and arranged for the translation of relevant articles where necessary.

Electronic searches

We searched the Cochrane Stroke Group trials register and the following electronic databases.

- Cochrane Central Register of Controlled Trials (CENTRAL; Issue 1 of 12, January 2019) in the Cochrane Library ([Appendix 1](#)).
- MEDLINE Ovid (from 1948 to 6 August 2018) ([Appendix 2](#)).
- Embase Ovid (from 1980 to 6 August 2018) ([Appendix 3](#)).

- CINAHL EBSCO (Cumulative Index to Nursing and Allied Health Literature; from 1982 to 06 August 2018) ([Appendix 4](#)).
- Science Citation Index Expanded - Web of Science (SCI-EXPANDED), searched on 6 August 2018 ([Appendix 5](#)).
- Conference Proceedings Citation Index-Science - Web of Science (CPCI-S), searched on 6 August 2018 ([Appendix 5](#)).
- BIOSIS Citation Index, searched on 6 August 2018 ([Appendix 5](#)).

We developed the MEDLINE search strategy ([Appendix 2](#)) with the help of the Cochrane Stroke Group Information Specialist and adapted it for the other databases.

We also searched the following ongoing trial registers.

- US National Institutes of Health Ongoing Trials Register (clinicaltrials.gov), searched on 6 August 2018 ([Appendix 6](#)).
- Stroke Trials Registry (strokecenter.org/trials), searched on 28 January 2019 ([Appendix 7](#)).
- ISRCTN Registry (isrctn.com), searched on 28 January 2019 ([Appendix 8](#)).
- World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (who.int/ictrp/en), searched on 6 August 2018 ([Appendix 9](#)).

Searching other resources

In order to identify other published, unpublished, and ongoing studies we:

- checked the bibliographies of included studies and any relevant systematic reviews identified for further references to relevant trials;
- used the Science Citation Index Reference Search for forward tracking of included trials;
- contacted researchers in the field to obtain additional information on relevant trials;
- contacted original authors for clarification and further data when trial reports were unclear.

Data collection and analysis

Selection of studies

Two review authors (CGAC, and MJM or FT) independently screened titles and abstracts of the references obtained as a result of our searching activities and excluded obviously irrelevant reports. We retrieved the full-text articles for the remaining references and two review authors (CGAC, and MJM or FT) independently screened the full-text articles and identified studies for inclusion, and identified and recorded reasons for exclusion of the ineligible studies. We resolved any disagreements through discussion or, if required, we consulted a third review author. We collated multiple reports of the same study so that each study, not

each reference, is the unit of interest in the review. We recorded the selection process and completed a PRISMA flow diagram.

Data extraction and management

Two review authors (CGAC, and FT or MJM) independently extracted data from included studies. Information extracted included study settings, time frame, type of event, type of intervention, as well as dose and mode of delivery, participants' characteristics, dietary information, outcomes reported, and trial authors' definitions. We resolved discrepancies by discussion or consultation with a third review author.

Assessment of risk of bias in included studies

Two review authors (CGAC, and FT or MJM) independently assessed risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011](#)). We resolved any disagreements by discussion or by involving another review author. We assessed risk of bias considering the following domains.

- Random sequence generation.
- Allocation concealment.
- Blinding of participants and personnel.
- Blinding of outcome assessment.
- Incomplete outcome data.
- Selective outcome reporting.
- Other bias.

We graded the risk of bias for each domain as high, low, or unclear and provided information from the study report together with a justification for our judgement in the 'Risk of bias' tables.

Measures of treatment effect

For continuous outcomes we calculated the mean difference (MD) with 95% confidence intervals (CI) for data measured in the same way between trials. We planned to calculate standardised mean difference (SMD) with 95% CI in case different scales were used for measurement; however, due to the small number of studies assessing continuous outcomes, this was not necessary. For binary outcomes, we calculated the risk ratios (RR) with 95% CI.

Unit of analysis issues

The unit of analysis in all trials was individual participants. For studies where there was more than one follow-up period, we included the longest period recorded to extract outcome data. For non-fatal recurrent events, we planned to only record the first event of each participant. We considered the inclusion of studies with non-standard designs (e.g. cross-over trials, cluster randomised trials) following the guidance in Chapter 16 of the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011](#)).

Dealing with missing data

We contacted study authors to request any missing data. We planned to consider the guidelines from the *Cochrane Handbook for Systematic Reviews of Interventions* for data imputation if necessary (Higgins 2011).

Assessment of heterogeneity

We used the I^2 statistic to measure heterogeneity among the trials in each meta-analysis, with a value above 50% indicating substantial heterogeneity. We explored the reasons for heterogeneity and identified if there were clinical or methodological explanations for differences in treatment effects between studies.

Assessment of reporting biases

As only nine trials in this systematic review contributed any data, we assessed reporting bias qualitatively on the basis of characteristics of included trials.

Data synthesis

Where we considered that studies could be combined, we conducted random-effects model meta-analysis by pooling the appropriate data using Review Manager 5 (Review Manager 2014). When this was not possible, we summarised the results in a narrative manner, including text, figures, and tables.

GRADE and 'Summary of findings' tables

We created 'Summary of findings' tables (Summary of findings for the main comparison; Summary of findings 2) to compare the administration of marine-derived n-3 PUFAs versus placebo or no intervention after both a short (up to three months) and a longer (over three months) follow-up, using the following outcomes: efficacy, vascular-related death, recurrent events, incidence of other type of stroke, adverse events, quality of life, and mood. We used the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness, and publication bias) to assess the quality of a body of evidence as it relates to the studies that contribute data to the review for the prespecified outcomes (Atkins 2004). We used methods and recommendations described in Section 8.5 and Chapter 12 of the *Cochrane Handbook for Systematic*

Reviews of Interventions (Higgins 2011), and used GRADEpro GDT software (GRADEpro GDT). We justified all decisions to downgrade the quality of studies using footnotes, and we made comments to aid the reader's understanding of the review where necessary.

Subgroup analysis and investigation of heterogeneity

We originally planned to carry out subgroup analyses based on type of stroke (ischaemic or haemorrhagic), dose, type of intervention (fatty acids supplements, marine oils or fish intake), length of intervention (up to three months and over three months), and initial time of intervention (up to three months and over three months from event onset). However, there were not sufficient data available for subgroup analysis.

Sensitivity analysis

We originally planned to perform sensitivity analyses by excluding the trials with overall high risk of bias, and excluding studies with substantial missing data. However, due to the small number of studies with available outcome data, sensitivity analysis was not appropriate.

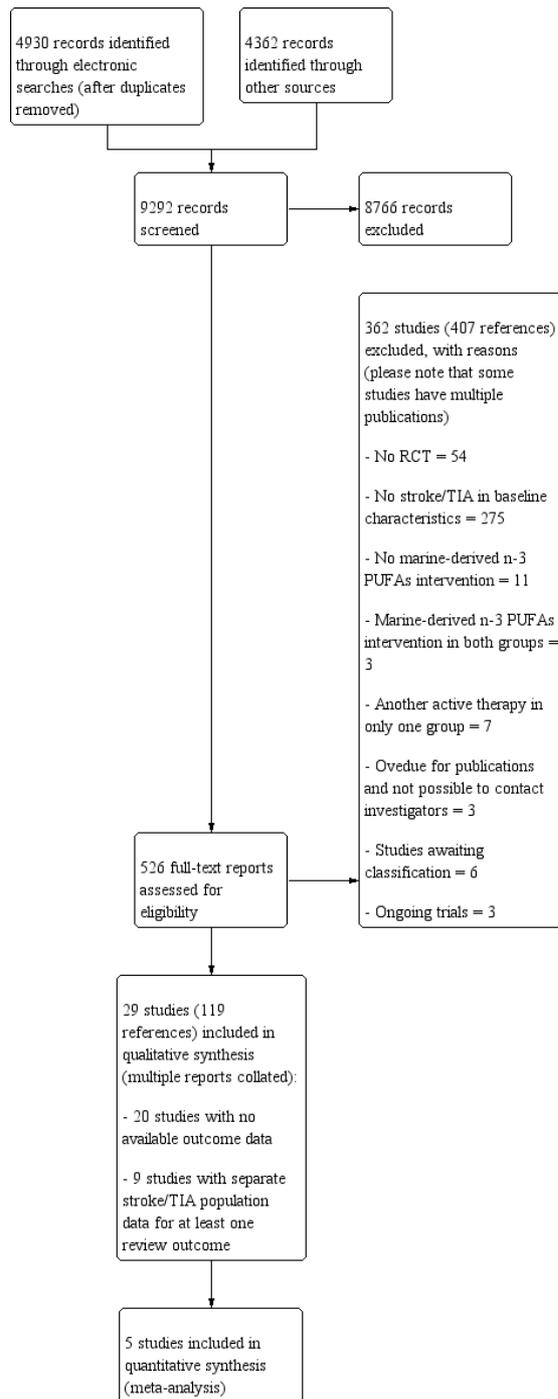
RESULTS

Description of studies

Results of the search

The electronic searches yielded 4930 records after removing duplicates and we identified 4362 additional references through other sources, including Science Citation Index Reference Search, systematic reviews, and references lists (Figure 1). We screened a total of 9292 records of which 8766 were excluded from the titles and abstracts. We assessed the remaining 526 records in full. From these, we identified 29 completed randomised controlled trials (RCTs) eligible for inclusion. Additionally we identified six more studies that need clarification for inclusion, and three ongoing trials.

Figure 1. Study flow diagram.



Included studies

A total of 29 studies were eligible for our review ([Characteristics of included studies](#)). However, in 22 studies the stroke/TIA participants were only a proportion of the study population; and three trials, which fully included stroke/TIA patients, did not report relevant outcomes for the review. We attempted to contact the authors of the 29 studies for more information and relevant outcome data on stroke/TIA population. Twelve study authors replied, and five provided additional data ([ALPHA OMEGA](#); [GISSI HF](#); [OPAL](#); [Risk & Prevention Study](#); [Saito 2017](#)).

Consequently, only nine studies have available data specifically in stroke/TIA populations for at least one outcome of the review. Of these studies, three had a follow-up no longer than three months ([FOILS](#); [Foroughinia 2018](#); [Saito 2017](#)), and the other six had a longer follow-up ([ALPHA OMEGA](#); [GISSI HF](#); [JELIS](#); [NUTRISTROKE](#); [OPAL](#); [Risk & Prevention Study](#)). All studies in the short follow-up included only participants with prior stroke/TIA, whereas for the longer follow-up in all except one ([NUTRISTROKE](#)), stroke/TIA participants constituted a small proportion of their study population.

Sample characteristics

The nine studies providing data for the review involved a total of 3339 participants with stroke or TIA, or both, and consisted of 1954 men and 1385 women. The age of the participants ranged from a median of 48 years ([Saito 2017](#)), to an average of 75.2 years ([Foroughinia 2018](#)). Only one study included participants in the acute phase of stroke ([Saito 2017](#)). Three studies included participants with previous ischaemic stroke only ([FOILS](#); [Foroughinia 2018](#); [NUTRISTROKE](#)), one with previous subarachnoid haemorrhage only ([Saito 2017](#)), one with both ischaemic and haemorrhagic stroke ([JELIS](#)), and the remaining trials did not specify type of baseline stroke ([Table 1](#)). One study was stopped early due to haemorrhagic transformation in two participants ([Foroughinia 2018](#)).

Interventions

On the short follow-up, one study provided fish oil capsules ([FOILS](#)), one a combination of intravenous fish-oil-based lipid emulsion and ethyl ester capsules ([Saito 2017](#)), and the third one just described the intervention as omega-3 fatty acids soft gel capsules ([Foroughinia 2018](#)). Doses ranged from 1.2 g/day to approximately 3.3 g/day of EPA and DHA. Only one of these studies was placebo-controlled ([FOILS](#)), and length of intervention varied across studies from a single dose ([Foroughinia 2018](#)), to 12 weeks ([FOILS](#)). One study included anticoagulants and antiplatelets as co-interventions ([Foroughinia 2018](#)) ([Table 2](#)).

Across the studies with a longer follow-up, four trials provided ethyl ester capsules, three of them included both EPA and DHA ([GISSI HF](#); [OPAL](#); [Risk & Prevention Study](#)), and one only EPA ([JELIS](#)). One study used fish oil capsules ([NUTRISTROKE](#)), and one a margarine supplemented with EPA and DHA ([ALPHA OMEGA](#)). Doses were between 400 mg and 1800 mg of marine-derived n-3 PUFAs. All the studies except one - [JELIS](#) - were placebo controlled and length of intervention ranged from 12 months to more than five years. Two studies had a 2 × 2 factorial design ([ALPHA OMEGA](#); [NUTRISTROKE](#)), with ALA and antioxidants, respectively, as the additional intervention; in one study, participants were also randomised to statins or corresponding placebo ([GISSI HF](#)); and in another all participants were on statins therapy ([JELIS](#)) ([Table 2](#)).

Outcomes

Efficacy - our primary outcome - was reported in two studies. One study had a short follow-up and used the Glasgow Outcome Scale Extended (GOSE), the results being reported as a dichotomised outcome (poor or good clinical outcome) ([Saito 2017](#)). The other study reported our primary outcome as both Barthel Index and Rivermead Mobility Index and the latest time point of assessment was 12 months ([NUTRISTROKE](#)).

Vascular-related death was reported in seven studies: two with short ([FOILS](#); [Saito 2017](#)), and five with long follow-up ([ALPHA OMEGA](#); [GISSI HF](#); [NUTRISTROKE](#); [OPAL](#); [Risk & Prevention Study](#)). Some information on recurrent events was available for one study in the short follow-up ([Foroughinia 2018](#)), and for all studies except [NUTRISTROKE](#) with longer follow-up. Incidence of other type of stroke could only be assessed in two studies ([Foroughinia 2018](#); [Saito 2017](#)), because most of the studies did not state the type of index stroke ([Table 1](#)). Information regarding adverse events was available in two studies with short follow-up ([Foroughinia 2018](#); [Saito 2017](#)), and one with longer follow-up ([Risk & Prevention Study](#)). Quality of life, assessed as SF-36 questionnaire (with physical and mental components separately), was reported only in one study ([FOILS](#)). Mood assessment was available in two studies ([FOILS](#); [OPAL](#)), one in each follow-up category. Assessment was performed using 28-item General Health Questionnaire (GHQ) in one study ([FOILS](#)), and 30-item GHQ in the other one ([OPAL](#)).

Excluded studies

After assessing full-text reports, we excluded 353 studies from this systematic review (see [Figure 1](#) and [Characteristics of excluded studies](#)). The most frequent reasons for exclusion were no indication of stroke/TIA in baseline characteristics of the participants

and no randomised controlled trial design (including studies that used a quasi-randomised method of allocation).

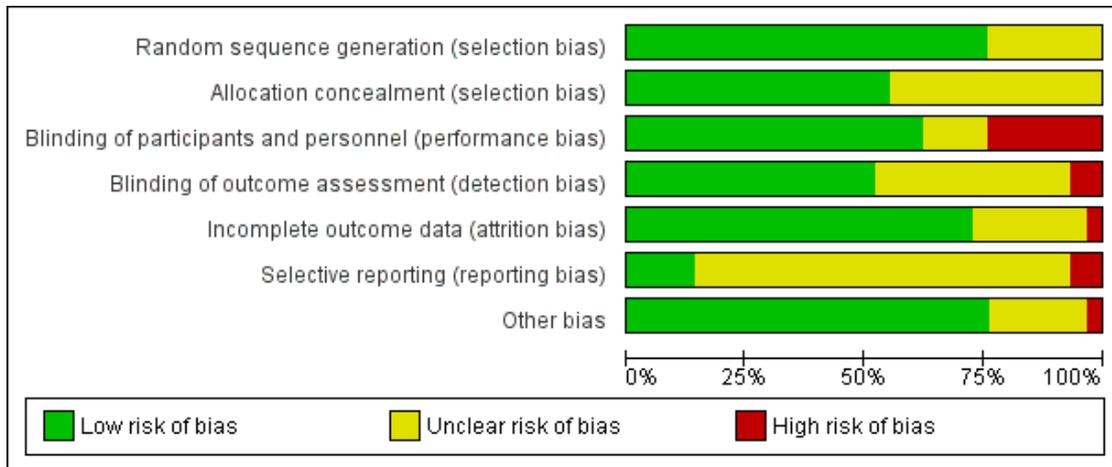
Risk of bias in included studies

We assessed risk of bias in the 29 studies included in the review (see [Figure 2](#) and [Figure 3](#)). However, considering that 20 of those studies do not have outcome data available for stroke/TIA participants only, we provided information regarding each domain for all included studies, and in more detail for the nine studies that are contributing data to the review ([ALPHA OMEGA](#); [FOILS](#); [Foroughinia 2018](#); [GISSI HF](#); [JELIS](#); [NUTRISTROKE](#); [OPAL](#); [Risk & Prevention Study](#); [Saito 2017](#)). We include supporting information for our judgement about the methodological quality of the studies in [Characteristics of included studies](#).

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) | Blinding of participants and personnel (performance bias) | Blinding of outcome assessment (detection bias) | Incomplete outcome data (attrition bias) | Selective reporting (reporting bias) | Other bias |
|-------------------------|---|---|---|---|--|--------------------------------------|------------|
| ALPHA OMEGA | + | + | + | + | ? | + | + |
| Doi 2014 | + | ? | + | + | ? | + | + |
| EMPAR | ? | ? | ? | ? | + | ? | ? |
| ESPRIT | ? | ? | ? | ? | + | ? | + |
| Farquharson 2011 | + | ? | + | + | + | ? | + |
| FAVOURED | + | + | + | ? | + | ? | + |
| FOILS | + | + | ? | ? | + | ? | + |
| Foroughinia 2018 | + | ? | + | + | + | ? | + |
| FORWARD | ? | + | + | + | ? | + | ? |
| Gammelmark 2012 | ? | ? | ? | ? | + | ? | ? |
| GISSI HF | + | + | + | + | + | + | + |
| Green 1985 | + | ? | + | ? | + | ? | + |
| JELIS | + | + | + | ? | ? | ? | + |
| Nosaka 2017 | + | ? | + | + | + | ? | + |
| NUTRISTROKE | ? | ? | + | + | ? | ? | ? |
| OCEAN | + | + | + | ? | ? | ? | + |
| OMEGA | + | + | + | ? | + | + | + |
| OMEGA PCI | + | + | + | ? | ? | ? | + |
| OPACH | + | ? | + | ? | + | ? | + |
| OPAL | + | + | + | + | + | + | + |
| Rantanen 2018 | + | ? | + | + | + | ? | + |
| Risk & Prevention Study | + | + | + | + | + | + | + |
| Saito 2017 | + | + | + | ? | + | ? | + |
| SCIMO | + | + | + | + | + | ? | + |
| SU.FOL.OM3 | + | + | + | + | + | ? | + |
| Terano 1999 | ? | ? | + | + | ? | ? | ? |
| Thies 2003 | + | + | + | ? | ? | ? | + |
| Wakita 2013 | ? | ? | + | ? | + | ? | ? |
| Zhang 2017 | + | + | + | + | ? | ? | + |

Figure 3. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



Allocation

We considered 22 studies to have adequate random sequence generation and 16 studies described appropriate allocation concealment; the remaining studies were 'unclear'.

From the studies providing outcome data, eight had a low risk regarding random sequence generation and one study was unclear. Two studies did not describe allocation concealment methods and we therefore classified them as 'unclear'. We assessed the rest of studies as having a low risk of selection bias (Figure 2).

Blinding

We considered open-label trials (seven studies) as having high risk for performance bias; 18 studies provided enough details about blinding for us to consider them at low risk of bias; and the rest of the studies were at unclear risk of bias (Figure 2).

From the subgroup that is contributing data to the review, three were open-label, assessed as high risk of performance bias (Foroughinia 2018; JELIS; Saito 2017); one was unclear (FOILS); and we considered the remainder to have a low risk of bias (Figure 2).

Regarding detection bias 15 studies, six of them providing data for the review, had a low risk of bias (Figure 2). Two trials, including one that has available outcome data (Foroughinia 2018), had a high risk of detection bias, and the rest were unclear (Figure 2).

Incomplete outcome data

We identified one study with a high risk of attrition bias (Green 1985). This trial, which did not contribute data to the review, had a high rate of dropouts and it provided baseline and outcome data only from participants that completed the study. We deemed 21 studies, including six with relevant outcomes, as having a low risk of bias, and the rest were unclear (Figure 2).

Selective reporting

We considered two studies as having a high risk of selective reporting bias, including one with a relevant review outcome (OPAL). Four studies, three of them providing outcome data (ALPHA OMEGA; GISSI HF; Risk & Prevention Study), had enough information available for us to consider them at low risk of reporting bias, and the remainder of the studies were unclear (Figure 2).

Other potential sources of bias

We considered one study as having a high risk of other bias because in the trial registration, 'stroke' is stated as an exclusion criterion; however, participants with a self-reported history of stroke were included in the report (Zhang 2017). We classified six studies, including one that provided data for the review (NUTRISTROKE), at unclear risk of bias, due to concerns about various aspects of

study design or conduct, or both. We did not detect other potential sources of bias in the remaining studies.

Effects of interventions

See: [Summary of findings for the main comparison](#) Marine-derived n-3 fatty acids therapy compared to No marine-derived n-3 fatty acids therapy for stroke. Short follow-up (three months or less); [Summary of findings 2](#) Marine-derived n-3 fatty acids therapy compared to No marine-derived n-3 fatty acids therapy for stroke. Follow-up longer than three months

Marine-derived n-3 PUFAs therapy for stroke: short follow-up (up to three months)

See [Summary of findings for the main comparison](#)

Efficacy (functional outcome or disability/dependency): primary outcome

There is very low quality evidence of a lack of effect of marine-derived n-3 PUFAs therapy for subarachnoid haemorrhage on clinical outcome (RR 0.78, 95% CI 0.36 to 1.68, $P = 0.52$). Only one study reported this outcome ([Saito 2017](#)). It was assessed by Glasgow Outcome Scale Extended (GOSE) and reported as a binary outcome. The sample size was very small (40 participants), and clinical outcome was not the primary aim of the trial, as this was a pilot study to assess feasibility.

Vascular-related death

Two studies reported vascular-related death ([FOILS](#); [Saito 2017](#)). However, we considered a meta-analysis not to be appropriate due to the small sample size and differences in study populations. One study was carried out in participants with prior subacute and chronic ischaemic stroke ([FOILS](#)), and the other study in people with acute subarachnoid haemorrhage ([Saito 2017](#)). Both studies tended to show a beneficial but non-significant effect ([Analysis 1.2](#)), but we graded the quality of evidence as low, with very serious imprecision issues, as evidenced by small sample size and wide confidence intervals crossing null effect, as well as important benefit and important harm.

Recurrent events

Recurrent events were defined as the same type of stroke as the index event. One study provided very low quality evidence of no effect of marine-derived n-3 PUFAs on recurrent events (ischaemic stroke), with a non-significant reduction in risk (RR 0.41, 95% CI 0.02 to 8.84, $P = 0.57$) in a very small sample (18 participants) ([Foroughinia 2018](#)). The study had high risk of bias and considerable imprecision ([Analysis 1.3](#)).

Incidence of other type of stroke (ischaemic or haemorrhagic)

Two studies reported incidence of other type of stroke (non-fatal); however, each one had a different index stroke type. Therefore, only one study reported incidence of haemorrhagic stroke in participants who previously had ischaemic stroke ([Foroughinia 2018](#)), and one reported ischaemic events in participants with previous subarachnoid haemorrhage ([Saito 2017](#)). One trial tended to favour the intervention ([Saito 2017](#)), and the other to favour control ([Foroughinia 2018](#)); however, in both cases effect was not statistically significant and the quality of the evidence is very low due to imprecision and considerable risk of bias of one of the studies ([Analysis 1.4](#)).

Adverse events

There is very low quality evidence of a lack of effect on adverse events ([Analysis 1.5](#)). One small study reported extracranial haemorrhage (RR 0.25, 95% CI 0.04 to 1.73, $P = 0.16$) ([Foroughinia 2018](#)), and the quality of evidence was downgraded due to risk of bias and imprecision ([Analysis 1.6](#)). Another study reported low-quality evidence on bleeding complications (RR 0.32, 95% CI 0.01 to 7.35, $P = 0.47$) ([Saito 2017](#)), and was also downgraded due to imprecision ([Analysis 1.7](#)).

Quality of life

Health-related quality of life was reported by one study using the SF-36 questionnaire (physical and mental component scales) ([FOILS](#)) ([Analysis 1.8](#)). A higher SF-36 score indicates better health-related quality of life; however, no information about the scoring system used was available. The authors reported mean change from baseline; despite the lack of significant effect, the direction pointed to favour the placebo group. We graded the evidence as low quality, due to imprecision and the fact that the sample size might be too small for the sensitivity threshold of the tool ([Ware 1993](#)).

Mood

One study reported mood, assessed with the 30-item General Health questionnaire (GHQ-30) ([FOILS](#)). A higher GHQ score is worse; however, no additional information about the scoring system used or assessors was available. The study reported mean change from baseline favouring control (MD 1.41, 95% CI 0.07 to 2.75, $P = 0.04$; 102 participants). We considered this evidence as low quality, due to imprecision and unclear scoring system used.

Marine-derived n-3 PUFAs therapy for stroke: longer follow-up (more than three months)

See [Summary of findings 2](#)

Efficacy (functional outcome or disability/dependency): primary outcome

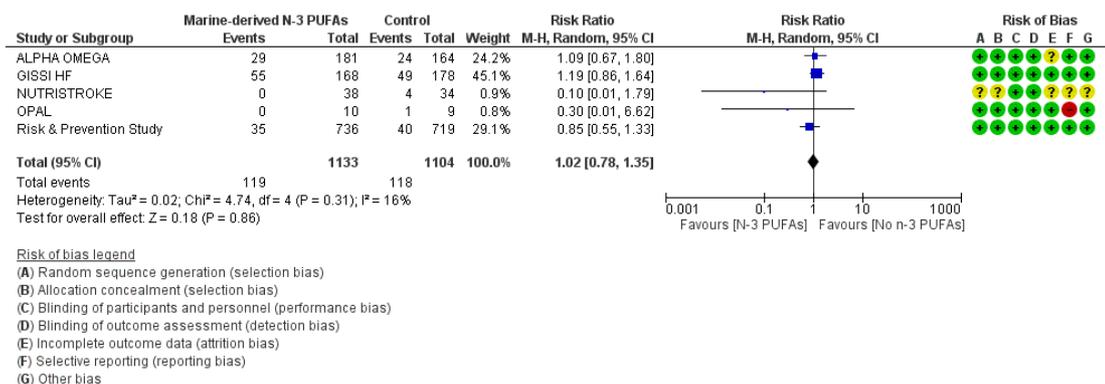
One study reported efficacy at 12 months, measured with Barthel Index score (scale from 0 to 100, higher score is better) for activities of daily living and Rivermead Mobility Index (scale from 0 to 15, higher score is better) for mobility (NUTRISTROKE). The study authors found no effect of marine-derived n-3 therapy for functional outcome (Barthel Index MD 7.09, 95% CI -5.16 to 19.34, P = 0.26; and Rivermead Mobility Index MD 1.30, 95% CI -1.31 to 3.91, P = 0.33; Analysis 2.1 and Analysis 2.2, respectively). However, we considered the quality of the evidence as very low, due to risk of bias (unclear randomisation, allocation concealment, and attrition, as the number of participants completing the

trial was 60% higher in the intervention group (n = 32) compared to the control group (n = 20)), and imprecision, considering that the 95% CIs cross both null effect and important benefit.

Vascular-related death

On the longer follow-up, five studies similar enough to be pooled in a meta-analysis reported vascular-related death. They provided low-quality evidence of no effect with marine-derived n-3 PUFAs (RR 1.02, 95% CI 0.78 to 1.35, P = 0.86) (Analysis 2.3; Figure 4). Reasons for downgrading the evidence were related to imprecision, due to small number of total events and 95% CIs crossing both null effect and appreciable potential harm.

Figure 4. Forest plot of comparison: 2 Marine-derived n-3 fatty acids therapy compared to no marine-derived n-3 fatty acids therapy: follow-up longer than 3 months, outcome: 2.3 Vascular-related death.

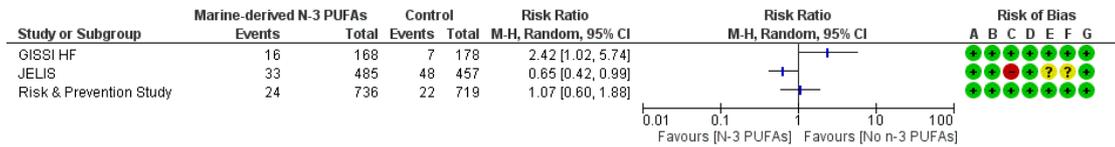


Recurrent events

Most studies with a longer follow-up that reported recurrent events did not state the type of baseline stroke in their population, or did not provide separate information on recurrence by type of index stroke. Therefore, our results include both ischaemic and haemorrhagic strokes. Three studies reported all recurrent events (fatal and non-fatal) (GISSI HF; JELIS; Risk & Prevention Study). However, they were very heterogeneous (I² = 74%) and it was not appropriate to pool their results (Figure 5). Furthermore, the

direction of the effects varied across studies. GISSI HF reported a greater risk of recurrent events with marine-derived n-3 PUFAs (RR 2.42, 95% CI 1.02 to 5.74, P = 0.04), whereas JELIS showed a reduced risk (RR 0.65, 95% CI 0.42 to 0.99, P = 0.05). The Risk & Prevention Study found no effect (RR 1.07, 95% CI 0.60 to 1.88, P = 0.83), with a 95% CI that crosses both null effect and important potential harm. Because of these reasons we considered the quality of the evidence as very low, due to imprecision and inconsistency.

Figure 5. Forest plot of comparison: 2 Marine-derived n-3 fatty acids therapy compared to no marine-derived n-3 fatty acids therapy. Follow-up longer than 3 months, outcome: 2.3 All recurrent events (fatal and non-fatal). Subtotals only, studies not combined due to important heterogeneity ($I^2 = 74\%$).



Risk of bias legend

- (A) Random sequence generation (selection bias)
- (B) Allocation concealment (selection bias)
- (C) Blinding of participants and personnel (performance bias)
- (D) Blinding of outcome assessment (detection bias)
- (E) Incomplete outcome data (attrition bias)
- (F) Selective reporting (reporting bias)
- (G) Other bias

When considering only fatal events, we were able to conduct a meta-analysis for the three studies that reported that outcome (ALPHA OMEGA; OPAL; Risk & Prevention Study). We found low-quality evidence of no effect of marine-derived n-3 PUFAs on fatal recurrent stroke (RR 0.69, 95% CI 0.31 to 1.55, $P = 0.37$) (Analysis 2.5), downgraded by imprecision.

There is low-quality evidence for non-fatal recurrent events, reported by only one study, with a non-significant trend (RR 0.68, 95% CI 0.35 to 1.34, $P = 0.27$) (Risk & Prevention Study).

Incidence of other type of stroke (ischaemic or haemorrhagic)

There was no information available for incidence of other type of stroke with a follow-up longer than three months.

Adverse events

There is low-quality evidence of no effect for adverse events (RR 0.94, 95% CI 0.56 to 1.58, $P = 0.82$), reported by only one

study (Risk & Prevention Study). The quality of the evidence was downgraded for imprecision due to small number of events and very wide confidence intervals crossing null effect, appreciable benefit, and appreciable harm.

Quality of life

No studies with a follow-up longer than three months reported quality of life.

Mood

One study reported mood, assessed with 28-item General Health questionnaire (GHQ-28) (OPAL). A higher GHQ score is worse; however, no additional information about the scoring system used or the assessors was available. The study showed no effect (MD 1.00, 95% CI -2.07 to 4.07, $P = 0.61$), reported by mean score at latest follow-up; we regarded this evidence as low quality, considering the very small sample size and imbalance in groups.

ADDITIONAL SUMMARY OF FINDINGS *[Explanation]*

| Marine-derived n-3 fatty acids therapy compared to no marine-derived n-3 fatty acids therapy for stroke: follow-up longer than three months | | | | | | |
|---|---|--|--------------------------|------------------------------|-----------------------------------|---|
| Patient or population: stroke and/or TIA Setting: hospital, outpatient, community or home Intervention: marine-derived n-3 fatty acids therapy Comparison: no marine-derived n-3 fatty acids therapy | | | | | | |
| Outcomes | Anticipated absolute effects* (95% CI) | | Relative effect (95% CI) | No of participants (studies) | Certainty of the evidence (GRADE) | Comments |
| | Risk with no marine-derived n-3 fatty acids therapy | Risk with marine-derived n-3 fatty acids therapy | | | | |
| Efficacy (functional outcome) assessed with: Barthel Index, higher score better Scale from: 0 to 100 | The mean efficacy (functional outcome) was 82.59 | MD 7.09 higher (5.16 lower to 19.34 higher) | - | 52 (1 RCT) | ⊕○○○ Very low ¹²³ | The same study also reported Rivermead Mobility Index (MD 1.30, 95% CI -1.31 to 3.91), scale from 0 to 15, higher score is better Follow-up time: 1 year |
| Vascular-related death | Study population 118 per 1000 | 120 per 1000 (92 to 159) | RR 1.02 (0.78 to 1.35) | 2237 (5 RCTs) | ⊕⊕○○ Low ⁴⁵ | Follow-up time: from 1 to 5 years |
| Recurrent events (both ischaemic and haemorrhagic stroke) | Study population 30 per 1000 | 11 per 1000 (9 to 47) | RR 0.69 (0.31 to 1.55) | 1819 (3 RCTs) | ⊕⊕○○ Low ⁵⁶ | Fatal only Follow-up time: from 2 to 5 years |
| Incidence of other type of stroke - not measured | | | - | - | - | No studies reported incidence of other type of stroke separately |

| | | | | | | |
|--|------------------------|--|---------------------------|-----------------|---------------------------|---|
| Adverse events | Study population | | RR 0.94 (0.56 to 1.58) | 1455 (1 RCT) | ⊕⊕○○ Low ⁵⁶ | All combined Follow-up time: 5 years |
| | 39 per 1000 | 37 per 1000 (22 to 62) | | | | |
| Quality of life  not measured | | | - | - | - | No studies reported quality of life |
| Mood assessed with: GHQ-28, lower score better | The mean mood was 1.33 | MD 1 higher (2.07 lower to 4.07 higher) | - | 14 (1 RCT) | ⊕⊕○○ Low ⁷⁸ | Follow-up time: 2 years |

* **The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **MD:** Mean difference; **RR:** Risk ratio; **OR:** Odds ratio; **TIA:** Transient ischaemic attack

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

¹ Unclear risk of bias and imbalanced groups. Downgraded 1 level

² 95% confidence intervals cross null effect and appreciable benefit. Downgraded 1 level

³ Small sample size. Downgraded 1 level

⁴ Confidence intervals cross both null effect and potential harm. Downgraded 1 level

⁵ Small number of total events. Downgraded 1 level

⁶ 95% confidence intervals cross null effect, and both appreciable benefit and harm. Downgraded 1 level

⁷ High risk of bias (imbalanced groups and reporting bias). Downgraded 1 level

⁸ Very small sample size. Downgraded 1 level

DISCUSSION

Summary of main results

We identified 29 RCTs of marine-derived n-3 PUFAs that included stroke or TIA participants, or both. From these, only nine studies had available outcome data, involving a population of 3339 participants in total. The age of this population ranged from a median of 48 years in [Saito 2017](#) to an average of 75.2 years in [Foroughinia 2018](#). Three trials had a follow-up of three months or sooner and six studies followed up the participants for longer than three months. Only one study included participants in the acute phase of stroke (subarachnoid haemorrhage). Doses of marine-derived n-3 PUFAs ranged from 400 to 3300 mg/day. Various forms of delivery were also used: marine-derived n-3 PUFAs-enriched margarine, fish oil, and ethyl esters of DHA and EPA. One study also included an initial intravenous triglyceride emulsion load ([Saito 2017](#)).

We assessed the effect of the interventions on relevant outcomes in two categories: studies with a follow-up up to three months; and follow-up longer than three months. Efficacy was reported in two studies, one in each follow-up category. Two trials in the short follow-up and five in the longer one reported vascular-related death. Recurrent events data, either fatal, non-fatal, or combined, were available for one study in the short follow-up and five studies in the long follow-up. Incidence of other type of stroke could be assessed in two studies (one of each type of stroke). Adverse events data were available in two studies of the short follow-up and one of the longer follow-up. One study assessed health-related quality of life and two trials reported mood as well.

It was not possible to pool the results in meta-analyses, except for vascular-related death (RR 1.02, 95% CI 0.78 to 1.35) and fatal recurrent events (RR 0.69, 95% CI 0.31 to 1.55) in the long follow-up.

We found few significant effects regarding marine-derived n-3 PUFAs intervention. Mood, in short follow-up, favoured control (MD 1.41, 95% CI 0.07 to 2.75) with a single study providing low-quality evidence ([FOILS](#)). Two individual studies reported recurrence (fatal and non-fatal combined) in the long follow-up with different direction of effect ([GISSI HF](#): RR 2.42, 95% CI 1.02 to 5.74; and [JELIS](#): RR 0.65, 95% CI 0.42 to 0.99). A third study reported no effect for the same outcome ([Risk & Prevention Study](#): RR 1.07, 95% CI 0.60 to 1.88); therefore, quality of the evidence was very low due to inconsistency and imprecision.

There was a lack of effect of the intervention in the rest of the outcomes, with the quality of the evidence ranging from low to very low. Incidence of other type of stroke and quality of life were not reported in studies with a follow-up of more than three months.

Overall completeness and applicability of evidence

Of a considerable number of studies addressing intervention with marine-derived n-3 PUFAs in cardiovascular diseases, only 29 studies fulfilled all our inclusion criteria and, from these, only nine had available outcome data for stroke population. Most studies did not state the time between the baseline event and start of the intervention. Those which reported such information had participants in different stages (acute, subacute, and chronic) making it difficult to apply the evidence in a practical level, due to the different potential mechanisms of marine-derived n-3 PUFAs therapy post-stroke.

Only three studies with short follow-up ([FOILS](#); [Foroughinia 2018](#); [Saito 2017](#)), and one with a longer follow-up ([NUTRISTROKE](#)) had a study population entirely of stroke or TIA participants, or both. The rest of the studies comprised a mixed population, which rendered a very small number of participants with the condition of interest, making the generalisation of the results not possible.

We originally planned to use funnel plots to assess publication bias. However, this was not possible due to the small number of trials providing outcome data to the review. Through our searches of trial registers we identified three studies seemingly eligible for the review but the results have yet to be published and we could not contact the investigators for clarification. As only nine studies provided data, those three trials, if carried out, represent an important fraction of the evidence that remains unpublished.

Only two studies addressed the primary outcome of the review (efficacy, as functional outcome or disability/dependency), and only one of these was performed in acute stroke (subarachnoid haemorrhage) ([Saito 2017](#)). However, being a pilot study, it was underpowered for efficacy. We did not find adequately controlled studies conducted in acute ischaemic stroke.

Different scales were used to assess functionality (Glasgow Outcome Scale Extended, Barthel Index, and Rivermead Mobility Index). While modified Rankin Scale and Barthel Index are most frequently used for measuring acute stroke outcome, there is still no consensus regarding the most robust assessment. Updates of this review should take into consideration future recommendations in this area ([Broderick 2017](#)).

Another aspect that makes the generalisation and applicability of the evidence difficult is the variation in the form of administering the intervention. Forms of delivery included fish oil capsules, ethyl ester capsules, fish-oil-based intravenous emulsion, and margarine enriched with EPA and DHA derived from fish oil. The bioavailability, and therefore potentially the efficacy, of marine-derived n-3 PUFAs varies according to the type of lipid vector, tending to be more bioavailable when delivered in phospholipids, followed by re-esterified triglycerides, triglycerides, and then ethyl esters ([Cholewski 2018](#)). Bioavailability can be further determined by the site of esterification of EPA and DHA on the glycerol backbone in phospholipids and triglycerides, and is also influenced by

the presence of other lipids that facilitate the formation of micelles in the intestinal lumen and improve digestion and absorption rate (Cholewski 2018).

Quality of the evidence

We considered the quality of the evidence low or very low for each outcome assessed. We found imprecision of the evidence in most outcomes, due to small number of studies assessing them, few total events, and small sample sizes that were, in most cases, subpopulations of larger trials. Risk of bias, especially among the smaller trials, was also a reason for downgrading the quality of the evidence. We did not consider the quality of the evidence high or moderate for any outcome.

Potential biases in the review process

We conducted the electronic searches without language and date restrictions and we made every effort to identify all relevant studies. Considering the population of interest (stroke patients) it is likely that most trials carried out are listed in clinical trial registers or primary databases. Nevertheless, our cited reference search allowed us to gather smaller-scale studies that might have been overlooked otherwise. There were a few studies overdue for publication and we attempted unsuccessfully to contact study authors for clarification; therefore, there is a small possibility that these trials have been carried out and remain unpublished. When we suspected that a trial might have some participants with a history of stroke/TIA, we contacted the authors to request more information; the response rate was low. We also identified older trials whose primary outcomes were not relevant for our review and where additional data were no longer available.

As marine-derived n-3 PUFAs are present in the diet, it was important to consider baseline levels. Dietary information was mostly mentioned briefly, and referred to a similar fish intake across groups and a washout period in case participants were consuming n-3 PUFAs supplements before enrolment. However, not all studies included dietary assessment. Due to the small amount of data available, a sensitivity analysis with only the studies that took into account baseline levels of n-3 PUFAs was not possible, but such an analytical approach could be considered for future updates of this review.

Agreements and disagreements with other studies or reviews

To our knowledge, this is the first review specifically addressing the effect of marine-derived n-3 PUFAs on functional outcomes after stroke. With respect to our secondary outcomes, the only one for

which we found similar, although not identical, approaches was recurrence.

Abdelhamid 2018 reported a higher risk of stroke with long-chain omega-3 PUFAs for secondary prevention (RR 1.21, 95% CI 1.05 to 1.40). However, they included all participants that had a history of cardiovascular disease at baseline, not only stroke history - they did not include JELIS and OPAL in that analysis, as both studies were considered as primary prevention of stroke in that review. Chowdhury 2012 reported no effect (RR 1.17, 95% CI 0.99 to 1.38) of long-chain omega-3 fatty acids on cerebrovascular disease, also in a population with existing cardiovascular disease at baseline, not specifically stroke. Our available data for all recurrent events (fatal and non-fatal) could not be pooled due to the large heterogeneity ($I^2 = 74%$) across the studies that reported them (GISSI HF; JELIS; Risk & Prevention Study). However, we found different directions of effect, with one study favouring control, one favouring marine-derived n-3 PUFAs, and the third one showing a null effect. For non-fatal recurrent events only, we only had data available from one study (Risk & Prevention Study) (RR 0.68, 95% CI 0.35 to 1.34); and for fatal events we carried out a meta-analysis with data from three studies (ALPHA OMEGA; OPAL; Risk & Prevention Study) (RR 0.69, 95% CI 0.31 to 1.55). In contrast with the results presented by Abdelhamid 2018 and Chowdhury 2012, when considering only the participants with stroke/TIA at baseline and non-fatal and fatal events separately, the direction of the effect changed, even when non-significant. As there were few events, small sample sizes, and inconsistency of results, the evidence for the stroke population should be considered of low quality.

Chowdhury 2012 also reported some information on stroke-type incidence (ischaemic or haemorrhagic), but this included all participants in JELIS and GISSI HF, not only participants with prior stroke.

In participants with prior stroke, Aung 2018 reported no effect of marine-derived omega-3 PUFAs intervention on major vascular events (RR 1.07, 95% CI 0.95 to 1.20). Although they included only stroke population in their analysis, our results are not directly comparable because they did not assess the effect of marine-derived n-3 PUFAs in stroke recurrence only, but in a composite of vascular events (first occurrence of non-fatal myocardial infarction or death caused by coronary heart disease; non-fatal or fatal stroke; or any revascularisation procedure).

AUTHORS' CONCLUSIONS

Implications for practice

Currently, there is not sufficient high-quality evidence to indicate therapy with marine-derived n-3 PUFAs after stroke. Only one pilot study has looked at clinical outcome after acute subarachnoid

haemorrhage and no properly controlled studies have looked at acute ischaemic stroke.

Implications for research

Despite the large number of studies addressing marine-derived n-3 PUFAs intervention for cardiovascular diseases, there is only low-quality evidence with respect to the stroke population. There is a lack of studies addressing stroke recovery directly, especially during the acute phase. Only a few studies with small sample sizes have assessed vascular-related death, recurrence, adverse events, quality of life, and mood in a population with a history of stroke or TIA, or both. Adequately-powered studies are needed in haemorrhagic stroke (specifically subarachnoid haemorrhage), considering that the only data available were from a small pilot study. Additionally, there have been no studies specifically addressing acute ischaemic stroke, despite the preclinical evidence suggesting important effects in neuroprotection, especially within six hours from the ischaemic event. Future trials, both in ischaemic and haemorrhagic stroke, should follow the CONSORT guidelines to ensure high quality of evidence (Schulz 2010).

Studies assessing functionality might consider starting the intervention as early as possible after the event, as well as using standardised clinically-relevant measures for functional outcomes, such as the modified Rankin Scale. Optimal doses remain to be determined; delivery forms (type of lipid carriers) and mode of administration (ingestion or injection) also need further consideration, as only one acute study so far has used infusion of fish-oil-based triglyceride emulsion, with potentially positive outcomes. With

regards to oral supplementation, besides the delivery forms included in previous studies, future RCTs may contemplate the use of a self-micro-emulsifying delivery system, which could improve the rate of absorption and bioavailability (Qin 2017).

ACKNOWLEDGEMENTS

Prof Malcolm R Macleod was a co-author for the protocol of this review and he also assisted with the retrieval of some reports.

We thank the Cochrane Stroke Group, and in particular Hazel Fraser (Managing Editor) for her guidance, and Joshua Cheyne (Information Specialist) for his support in the development of the search strategies and performing some of the searches, and for his advice throughout the review process.

We also thank all the authors of the original trials that replied to our information request. In particular, Prof Marianne Geleijnse (ALPHA OMEGA), Dr Aldo P Maggioni (GISSI HF), Prof Alan Dangour and Prof Elizabeth Allen (OPAL), Dr Irene Marzona and Dr Maria Carla Roncaglioni (Risk & Prevention Study), and Dr Rodrigo Zapata (Saito 2017), for providing additional data from their studies.

Dr He Ni, Teresa Grohmann, and Khairun N Sumali provided support with translation of study reports.

CG Alvarez Campano is funded by the Mexican Council for Science and Technology (CONACYT) and the Institute of Innovation and Technology Transfer (I²T²) (grant number 457349).

REFERENCES

References to studies included in this review

ALPHA OMEGA *[published and unpublished data]*

Brouwer I, Geleijnse JM, Klaasen VM, Smit LA, Giltay EJ, de Goede J, et al. Effect of alpha linolenic acid supplementation on serum prostate specific antigen (PSA): results from the Alpha Omega trial. *PLoS ONE* 2013;**8**(12): e81519.

Esmeijer K, Geleijnse JM, Giltay EJ, Stijnen T, Dekker FW, de Fijter JW, et al. Body-fat indicators and kidney function decline in older post-myocardial infarction patients: The Alpha Omega Cohort Study. *European Journal of Preventive Cardiology* 2018;**25**(1):90–9.

Eussen SRBM, Geleijnse JM, Giltay EJ, Rompelberg CJM, Klungel OH, Kromhout D. Effects of n-3 fatty acids on major cardiovascular events in statin users and non-users with a history of myocardial infarction. *European Heart Journal* 2012;**33**(13):1582–8.

Geleijnse JM, Giltay EJ, Kromhout D. Effects of n-3 fatty acids on cognitive decline: a randomized, double-blind,

placebo-controlled trial in stable myocardial infarction patients. *Alzheimer's & Dementia* 2012;**8**(4):278–87.

Geleijnse JM, Giltay EJ, Schouten EG, de Goede J, Oude Griep LM, Teitsma-Jansen AM, et al. Effect of low doses of n-3 fatty acids on cardiovascular diseases in 4,837 post-myocardial infarction patients: design and baseline characteristics of the Alpha Omega Trial. *American Heart Journal* 2010;**159**(4):539–46.

Giltay EJ, Geleijnse JM, Heijboer AC, de Goede J, Oude Griep LM, Blankenstein MA, et al. No effects of n-3 fatty acid supplementation on serum total testosterone levels in older men: the Alpha Omega Trial. *International Journal of Andrology* 2012;**35**(5):680–7.

Giltay EJ, Geleijnse JM, Kromhout D. Effects of n-3 fatty acids on depressive symptoms and dispositional optimism after myocardial infarction. *American Journal of Clinical Nutrition* 2011;**94**(6):1442–50.

Hoogveen EK, Geleijnse JM, Giltay EJ, Soedamah-Muthu SS, Oude Griep LM, Stijnen T, et al. Kidney function and specific mortality in 60-80 years old post-myocardial

infarction patients: a 10-year follow-up study. *PLoS ONE* 2017;**12**(2):e0171868.

Hoogeveen EK, Geleijnse JM, Kromhout D, EJ. No effect of n-3 fatty acids on high-sensitivity C-reactive protein after myocardial infarction: the Alpha Omega Trial. *European Journal of Preventive Cardiology* 2014;**21**(11):1429–36.

Hoogeveen EK, Geleijnse JM, Kromhout D, Stijnen T, Gemen EF, Giltay EJ, et al. Effect of omega-3 fatty acids on kidney function after myocardial infarction: the Alpha Omega Trial. *Clinical Journal of the American Society of Nephrology* 2014;**9**(10):1676–83.

Hoogeveen EK, Geleijnse JM, Kromhout D, Van't Sant P, Gemen EF, Kusters R, et al. No effect of n-3 fatty acids supplementation on NT-proBNP after myocardial infarction: the Alpha Omega Trial. *European Journal of Preventive Cardiology* 2015;**22**(5):648–55.

Kromhout D, Geleijnse JM, de Goede J, Oude Griep LM, Mulder BJ, de Boer MJ, et al. N-3 fatty acids, ventricular arrhythmia-related events, and fatal myocardial infarction in postmyocardial infarction patients with diabetes. *Diabetes Care* 2011;**34**(12):2515–20.

* Kromhout D, Giltay EJ, Geleijnse JM, the Alpha Omega Trial Group. n-3 fatty acids and cardiovascular events after myocardial infarction. *New England Journal of Medicine* 2010;**363**(21):2015–26.

Molenberg FJM, de Goede J, Wanders AJ, Zock PL, Kromhout D, Geleijnse JM. Dietary fatty acid intake after myocardial infarction: a theoretical substitution analysis of the Alpha Omega Cohort. *American Journal of Clinical Nutrition* 2017;**106**(3):895–901.

Rius-Ottenheim N, Geleijnse JM, Kromhout D, van der Mast RC, Zitman FG, Giltay EJ. Physical activity after myocardial infarction: is it related to mental health? *European Journal of Preventive Cardiology* 2012;**20**(3):399–408.

Rius-Ottenheim N, Kromhout D, Sijtsma FPC, Geleijnse JM, Giltay EJ. Dietary patterns and mental health after myocardial infarction. *PLoS ONE* 2017;**12**(10):e0186368. Sijtsma FPC, Soedamah-Muthu SS, de Goede J, Oude Griep LM, Geleijnse JM, Giltay EJ, et al. Healthy eating and lower mortality risk in a large cohort of cardiac patients who received state-of-the-art drug treatment. *American Journal of Clinical Nutrition* 2015;**102**(6):1527–33.

Soedamah-Muthu SS, Geleijnse JM, Giltay EJ, de Goede J, Oude Griep LM, Waterham E, et al. Levels and trends in cardiovascular risk factors and drug treatment in 4837 elderly Dutch myocardial infarction patients between 2002 and 2006. *Netherlands Heart Journal* 2012;**20**:102–9. Soedamah-Muthu SS, Geleijnse JM, Giltay EJ, Kromhout D, Alpha Omega Trial Group. Cardiovascular risk factor management of myocardial infarction patients with and without diabetes in the Netherlands between 2002 and 2006: a cross-sectional analysis of baseline data. *BMJ* 2012;**2**(6):e001360.

de Borst MH, Baia LC, Hoogeveen EK, Giltay EJ, Navis G, Bakker SJ, et al. Effect of omega-3 fatty acid supplementation on plasma fibroblast growth factor 23

levels in post-myocardial infarction patients with chronic kidney disease: the Alpha Omega trial. *Nutrients* 2017;**9**(11):1233–47.

van Dongen LH, Molenberg FJM, Soedamah-Muthu SS, Kromhout D, Geleijnse JM. Coffee consumption after myocardial infarction and risk of cardiovascular mortality: a prospective analysis in the Alpha Omega Cohort. *American Journal of Clinical Nutrition* 2017;**106**(4):1113–20.

Doi 2014 {published data only (unpublished sought but not used)}

Doi M, Nosaka K, Miyoshi T, Iwamoto M, Kajiya M, Okawa K, et al. Early eicosapentaenoic acid treatment after percutaneous coronary intervention reduces acute inflammatory responses and ventricular arrhythmias in patients with acute myocardial infarction: a randomized, controlled study. *International Journal of Cardiology* 2014;**176**(3):577–82.

EMPAR {published data only (unpublished sought but not used)}

Cairns JA, Gill J, Morton B, Roberts R, Gent M, Hirsh J, et al. Fish oils and low-molecular-weight heparin for the reduction of restenosis after percutaneous transluminal coronary angioplasty. *Circulation* 1996;**94**(7):1553–60.

ESPRIT {published data only (unpublished sought but not used)}

Maresta A, Balducci M, Varani E, Marzilli M, Galli C, Heiman F, et al. Prevention of postcoronary angioplasty restenosis by omega-3 fatty acids: main results of the Esapent for Prevention of Restenosis Italian Study (ESPRIT). *American Heart Journal* 2002;**143**(6):1–10.

Farquharson 2011 {published data only (unpublished sought but not used)}

Farquharson AL, Metcalf RG, Sanders P, Stuklis R, Edwards JRM, Gibson RA, et al. Effect of dietary fish oil on atrial fibrillation after cardiac surgery. *American Journal of Cardiology* 2011;**108**(6):851–6.

FAVOURED {published data only (unpublished sought but not used)}

Irish A, Dogra G, Mori T, Beller E, Heritier S, Hawley C, et al. Preventing AVF thrombosis: the rationale and design of the omega-3 fatty acids (fish oils) and aspirin in vascular access outcomes in renal disease (FAVOURED) study. *BMC Nephrology* 2009;**10**:1–12.

* Irish AB, Viecelli AK, Hawley CM, Hooi LS, Pascoe EM, Paul-Brent PA, et al. Effect of fish oil supplementation and aspirin use on arteriovenous fistula failure in patients requiring hemodialysis. A randomized clinical trial. *JAMA Internal Medicine* 2017;**177**(2):184–93.

Viecelli AK, Pascoe EM, Polkinghorne KR, Hawley CM, Paul-Brent PA, Badve SV, et al. Baseline characteristics of the omega-3 fatty acids (fish oils) and aspirin in vascular access outcomes in renal disease (FAVOURED) Study. *Nephrology* 2016;**21**(3):217–28.

Viecelli AK, Pascoe EM, Polkinghorne KR, Hawley CM, Paul-Brent PA, Badve SV, et al. The omega-3 fatty acids (fish oils) and aspirin in vascular access outcomes in renal disease (FAVOURED) study: the updated final trial protocol and rationale of post-initiation trial modifications. *BioMed Central Nephrology* 2015;**16**:89–97.

FOILS {published data only (unpublished sought but not used)}

ACTRN12605000207617. Fish oils (Omega 3) in ischaemic stroke [A randomised placebo-controlled intervention trial of omega -3 PUFA (fish oils) in people with ischaemic stroke]. www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=211&isReview=true (first received 17 August 2005).

Anderson CS, Howe CA, Lithander FE, Silvers KM, Lin R, Poppitt SD. The fish oils in ischemic stroke (FOILS) study: a randomised controlled trial. *Stroke* 2008;**39**:623.

* Poppitt SD, Howe CA, Lithander FE, Silvers KM, Lin RB, Croft J, et al. Effects of moderate-dose omega-3 fish oil on cardiovascular risk factors and mood after ischemic stroke: a randomized, controlled trial. *Stroke* 2009;**40**:3485-92.

Foroughinia 2018 {published data only (unpublished sought but not used)}

Foroughinia F, Jamshidi E, Javanmardi H, Safari A, Borhani-Haghighi A. Effectiveness and safety of omega-3 fatty acids for the prevention of ischemic complications following carotid artery stenting: an early terminated pilot study. *Iranian Journal of Neurology* 2018;**17**(1):11-7.

FORWARD {published data only (unpublished sought but not used)}

Macchia A, Grancelli H, Varini S, Nul D, Ferrante D, Mariani J, et al. Omega-3 fatty acids for the prevention of recurrent symptomatic atrial fibrillation: results of a double-blind randomized clinical trial (FORWARD). *Circulation* 2012;**126**(23):2780-1.

* Macchia A, Grancelli H, Varini S, Nul D, Laffaye N, Javier Mariani, et al. Omega-3 fatty acids for the prevention of recurrent symptomatic atrial fibrillation. Results of the FORWARD (Randomized Trial to Assess Efficacy of PUFA for the Maintenance of Sinus Rhythm in Persistent Atrial Fibrillation) Trial. *Journal of the American College of Cardiology* 2013;**61**(4):463-8.

Macchia A, Varini S, Grancelli H, Nul D, Laffaye N, Ferrante D, et al. The rationale and design of the FORWARD Trial: a randomized, double-blind, placebo-controlled, independent study to test the efficacy of n-3 PUFA for the maintenance of normal sinus rhythm in patients with previous atrial fibrillation. *American Heart Journal* 2009;**157**(3):423-7.

Gammelmark 2012 {published data only (unpublished sought but not used)}

* Gammelmark A, Madsen T, Varming K, Lundbye-Christensen S, Schmidt EB. Low dose fish oil supplementation increases serum adiponectin without affecting inflammatory markers in overweight subjects. *Nutrition Research (New York, N.Y.)* 2012;**32**(1):15-23.

Nielsen MS, Gammelmark A, Madsen T, Obel T, Aardestrup I, Schmid EB. The effect of low-dose marine n-3 fatty acids on the biosynthesis of pro-inflammatory 5-lipoxygenase pathway metabolites in overweight subjects: a randomized controlled trial. *Prostaglandins, Leukotrienes, and Essential Fatty Acids* 2012;**87**(1):43-8.

Venø SK, Skjelbo Nielsen MR, Lundbye-Christensen S, Schmidt EB, Handberg A. The effect of low-dose marine n-3 fatty acids on plasma levels of scd36 in overweight

subjects: a randomized, double-blind, placebo-controlled trial. *Marine Drugs* 2013;**11**(9):3324-34.

GISSI HF {published and unpublished data}

Abdul-Rahim AH, Perez AC, Fulton RL, Jhund PS, Latini R, Tognoni G, et al. Risk of stroke in chronic heart failure patients without atrial fibrillation analysis of the Controlled Rosuvastatin in Multinational Trial Heart Failure (CORONA) and the Gruppo Italiano per lo Studio della Sopravvivenza nell'Insufficienza Cardiaca-Heart Failure (GISSI-HF) Trials. *Circulation* 2015;**131**(17):1486-94.

Aleksova A, Masson S, Maggioni AP, Lucci L, Fabbri G, Beretta L, et al. n-3 polyunsaturated fatty acids and atrial fibrillation in patients with chronic heart failure: the GISSI-HF trial. *European Journal of Heart Failure* 2013;**15**(11):1289-95.

* GISSI-HF investigators. Effect of n-3 polyunsaturated fatty acids in patients with chronic heart failure (the GISSI-HF trial): a randomised, double-blind, placebo-controlled trial. *Lancet* 2008;**372**(9645):1223-30.

Ghio S, Scelsi L, Latini R, Masson S, Eleuteri E, Palvarini M, et al. Effects of n-3 polyunsaturated fatty acids and of rosuvastatin on left ventricular function in chronic heart failure: a substudy of GISSI-HF trial. *European Journal of Heart Failure* 2010;**12**(12):1345-53.

Harris WS, Masson S, Barlera S, Milani V, Pileggi S, MG Franzosi, et al. Red blood cell oleic acid levels reflect olive oil intake while omega-3 levels reflect fish intake and the use of omega-3 acid ethyl esters: the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico-Heart Failure trial. *Nutrition Research* 2016;**36**(9):989-94.

La Rovere MT, Staszewsky L, Barlera S, Maestri R, Mezzani A, Midi P, et al. n-3PUFA and holter-derived autonomic variables in patients with heart failure: data from the gruppo italiano per to studio delta sopravvivenza nell'insufficienza cardiaca (GISSI-HF) holter substudy. *Heart Rhythm* 2013;**10**(2):226-32.

Masson S, Marchioli R, Mozaffarian D, Bernasconi R, Milani V, MS, Dragani L, et al. Plasma n-3 polyunsaturated fatty acids in chronic heart failure in the GISSI-Heart Failure Trial: relation with fish intake, circulating biomarkers, and mortality. *American Heart Journal* 2013;**165**(2):208-15.

Tavazzi L, Tognoni G, Franzosi MG, Latini R, Maggioni AP, Marchioli R, et al. Rationale and design of the GISSI heart failure trial: a large trial to assess the effects of n-3 polyunsaturated fatty acids and rosuvastatin in symptomatic congestive heart failure. *European Journal of Heart Failure* 2004;**6**(5):635-41.

Green 1985 {published data only (unpublished sought but not used)}

Green D, Barreras LR, Borensztajn J, Reddy N, Rovner R, Simon H. A double-blind, placebo-controlled trial of MaxEpa in stroke patients. *Clinical Research* 1984;**32**:309A.

* Green D, Barreras L, Borensztajn J, Kaplan P, Reddy NM, Rovner R, et al. A double-blind, placebo-controlled trial of fish oil concentrate (MaxEpa) in stroke patients. *Stroke* 1985;**16**(4):706-9.

JELIS {published data only (unpublished sought but not used)}

Ikatura H, Yokoyama M, Matsuzaki M, Saito Y, Origasa

H, Ishikawa Y, et al. Relationships between plasma fatty acid composition and coronary artery disease. *Journal of Atherosclerosis and Thrombosis* 2011;**18**(2):99–107.

Ikatura H, Yokoyama M, Matsuzaki M, Saito Y, Origasa H, Ishikawa Y, et al. The change in low-density lipoprotein cholesterol concentration is positively related to plasma docosahexaenoic acid but not eicosapentaenoic acid. *Journal of Atherosclerosis and Thrombosis* 2012;**19**(7):673–9.

Ishikawa Y, Yokoyama M, Saito Y, Matsuzaki M, Origasa H, Oikawa S, et al. Preventive effects of eicosapentaenoic acid on coronary artery disease in patients with peripheral artery disease - subanalysis of the JELIS Trial. *Circulation Journal* 2010;**74**:1451–7.

Matsuzaki M, Yokoyama M, Saito Y, Origasa H, Ishikawa Y, Oikawa S, et al. Incremental effects of eicosapentaenoic acid on cardiovascular events in statin-treated patients with coronary artery disease-secondary prevention analysis from JELIS. *Circulation* 2009;**73**(7):1283–90.

NCT00231738. Protective effect of EPA on cardiovascular events [Effect of eicosapentaenoic acid (EPA) on major cardiovascular events in hypercholesterolemic patients: the Japan EPA lipid intervention study (JELIS)]. clinicaltrials.gov/ct2/show/NCT00231738 (first received 3 October 2005).

Oikawa S, Yokoyama M, Origasa H, Matsuzaki M, Matsuzawa Y, Saito Y, et al. Suppressive effect of EPA on the incidence of coronary events in hypercholesterolemia with impaired glucose metabolism: sub-analysis of the Japan EPA Lipid Intervention Study (JELIS). *Atherosclerosis* 2009;**206**:535–9.

Origasa H, Yokoyama M, Matsuzaki M, Saito Y, Matsuzawa Y, on behalf of the JELIS Investigators. Clinical importance of adherence to treatment with eicosapentaenoic acid by patients with hypercholesterolemia. *Circulation* 2010;**74**: 510–7.

Saito Y, Yokoyama M, Origasa H, Matsuzaki M, Matsuzawa Y, Ishikawa Y, et al. Effects of EPA on coronary artery disease in hypercholesterolemic patients with multiple risk factors: sub-analysis of primary prevention cases from the Japan EPA Lipid Intervention Study (JELIS). *Atherosclerosis* 2008;**200**:135–40.

Sasaki J, Yokoyama M, Matsuzaki M, Saito Y, Origasa H, Ishikawa Y, et al. Relationship between coronary artery disease and non-HDL-C, and effect of highly purified EPA on the risk of coronary artery disease in hypercholesterolemic patients treated with statins: subanalysis of the Japan EPA lipid intervention study (JELIS). *Journal of Atherosclerosis and Thrombosis* 2012;**19**:1974–204.

* Tanaka K, Ishikawa Y, Yokoyama M, Origasa H, Matsuzaki M, Saito Y, et al. Reduction in the recurrence of stroke by eicosapentaenoic acid for hypercholesterolemic patients: subanalysis of the JELIS trial. *Stroke* 2008;**7**:2052–8.

Tanaka K, Ishikawa Y, Yokoyama M, Origasa H, Matsuzaki M, Saito Y, et al. Relationship of ischemic stroke with serum lipid levels, and influence of plasma eicosapentanoic acid (EPA) concentration in patients with hypercholesterolemia.

International Journal of Stroke 2008;**3**(Suppl 1):65–6.

Yokoyama M, Origasa H, Matsuzaki M, Matsuzawa Y, Saito Y, Ishikawa Y, et al. Effects of eicosapentaenoic acid on major coronary events in hypercholesterolaemic patients (JELIS): a randomised open-label, blinded endpoint analysis. *Lancet* 2007;**369**:1090–8.

Yokoyama M, Origasa H, for the JELIS Investigators. Effects of eicosapentaenoic acid on cardiovascular events in Japanese patients with hypercholesterolemia: rationale, design, and baseline characteristics of the Japan EPA Lipid Intervention Study (JELIS). *American Heart Journal* 2003; **146**:613–20.

Nosaka 2017 {published data only (unpublished sought but not used)}

Nosaka K, Miyoshi T, Iwamoto M, Kajiya M, Okawa K, Tsukuda S, et al. Early initiation of eicosapentaenoic acid and statin treatment is associated with better clinical outcomes than statin alone in patients with acute coronary syndromes: 1-year outcomes. *European Heart Journal* 2016; **37**:1391.

* Nosaka K, Miyoshi T, Iwamoto M, Kajiya M, Okawa K, Tsukuda S, et al. Early initiation of eicosapentaenoic acid and statin treatment is associated with better clinical outcomes than statin alone in patients with acute coronary syndromes: 1-year outcomes of a randomized controlled study. *International Journal of Cardiology* 2017;**228**:173–9.

Nosaka K, Miyoshi T, Iwamoto M, Kajiya M, Okawa K, Tsukuda S, et al. Early initiation of eicosapentaenoic acid and statin treatment is associated with better clinical outcomes than statin alone in patients with acute coronary syndromes: 1-year outcomes of a randomized controlled study. *Journal of the American College of Cardiology* 2016; **67**:573.

NUTRISTROKE {published data only (unpublished sought but not used)}

Garbagnati F, Cairella G, De Martino A, Multari M, Scognamiglio U, Venturiero V, et al. Is antioxidant and n-3 supplementation able to improve functional status in poststroke patients? Results from the Nutristroke trial. *Cerebrovascular Disease* 2009;**27**:375–83.

OCEAN {published data only (unpublished sought but not used)}

Cawood AL, Ding R, Napper FL, Young R, Williams J, Ward M, et al. Long-chain n-3 fatty acids enter advanced atherosclerotic plaques and are associated with decreased inflammation and decreased inflammatory gene expression. *Proceedings of the Nutrition Society* 2006;**6**:2A.

* Cawood AL, Ding R, Napper FL, Young RH, Williams JA, Ward MJA, et al. Eicosapentaenoic acid (EPA) from highly concentrated n-3 fatty acid ethyl esters is incorporated into advanced atherosclerotic plaques and higher plaque EPA is associated with decreased plaque inflammation and increased stability. *Atherosclerosis* 2010;**212**:252–9.

NCT00294216. Omacor and placebo in carotid plaque stability [A double blind comparison of Omacor and placebo in patients awaiting endarterectomy to investigate the effect on carotid plaque stability]. clinicaltrials.gov/ct2/show/NCT00294216 (first received 17 February 2006).

Yusuf HM, Cawood AL, Ding R, Williams JA, Napper FL,

et al. Limited impact of 2g/day omega-3 fatty acid Ethyl esters (Omacor) on plasma lipids and inflammatory markers in patients awaiting carotid endarterectomy. *Marine Drugs* 2013;**11**:3579–81.

OMEGA {published data only (unpublished sought but not used)}

Bauer T, Schiele R, Zahn R, Schneider S, Rauch B. Predictors of 1-year mortality in patients with contemporary optimised guideline-adherent secondary prevention therapy after acute myocardial infarction: results from the OMEGA Study. *European Heart Journal* 2012;**33**:346.

Liosis S, Bauer T, Schiele R, Gohlke H, Gottwik M, Katus H, et al. Predictors of 1-year mortality in patients with contemporary guideline-adherent therapy after acute myocardial infarction: results from the OMEGA study. *Clinical Research in Cardiology* 2013;**102**:671–7.

Rauch B, Riemer T, Schwaab B, Schneider S, Diller F, Gohlke H, et al. Short-term comprehensive cardiac rehabilitation after AMI is associated with reduced 1-year mortality: results from the OMEGA study. *European Journal of Preventive Cardiology* 2014;**21**(9):1060–9.

Rauch B, Schiele R, Schneider S, Gohlke H, Katus H, Senges J. Prognostic effect of omega-3 fatty acid supplementation on top of current guideline adjusted therapy of acute myocardial infarction - the OMEGA trial. *European Journal of Cardiovascular Prevention and Rehabilitation* 2010;**17**:S1.

* Rauch B, Schiele R, Schneider S, Diller F, Victor N, Gohlke H, et al. OMEGA, a randomized, placebo-controlled trial to test the effect of highly purified omega-3 fatty acids on top of modern guideline-adjusted therapy after myocardial infarction. *Circulation* 2010;**122**:2152–9.

Rauch B, Schiele R, Schneider S, Gohlke H, Diller F, Gottwik M, et al. Highly purified omega-3 fatty acids for secondary prevention of sudden cardiac death after myocardial infarction - aims and methods of the OMEGA-Study. *Cardiovascular Drugs and Therapy* 2006;**20**:365–75.

Rauch B, Schneider S, Schiele R, Gohlke H, Katus H, Senges J. Prognostic effect of cardiac rehabilitation after acute myocardial infarction - results of the OMEGA-study. *European Journal of Cardiovascular Prevention and Rehabilitation* 2010;**17**:S106.

OMEGA PCI {published data only (unpublished sought but not used)}

* Gajos G, Rostoff P, Undas A, Piwowska W. Effects of polyunsaturated omega-3 fatty acids on responsiveness to dual antiplatelet therapy in patients undergoing percutaneous coronary intervention - the OMEGA-PCI (OMEGA-3 Fatty Acids After PCI to Modify Responsiveness to Dual Antiplatelet Therapy) Study. *Journal of the American College of Cardiology* 2010;**55**(16):1671–8.

Gajos G, Zalewski J, Mostowik M, Konduracka E, Nessler J, Undas A. Polyunsaturated omega-3 fatty acids reduce lipoprotein-associated phospholipase A2 in patients with stable angina. *Nutrition, Metabolism & Cardiovascular Diseases* 2014;**24**:434–9.

Gajos G, Zalewski J, Rostoff P, Nessler P, Piwowska W, Undas A. Reduced thrombin formation and altered fibrin clot properties induced by polyunsaturated omega-

3 fatty acids on top of dual antiplatelet therapy in patients undergoing percutaneous coronary intervention (OMEGA-PCI Clot). *Arteriosclerosis, Thrombosis, and Vascular Biology* 2011;**31**:1696–702.

Mostowik M, Gajos G, Zalewski J, Nessler J, Undas A. Omega-3 polyunsaturated fatty acids increase plasma adiponectin to leptin ratio in stable coronary artery disease. *Cardiovascular Drugs and Therapy* 2013;**27**:289–95.

OPACH {published data only (unpublished sought but not used)}

Harving F, Svensson M, Flyvbjerg A, Schmidt EB, Jørgensen KA, Eriksen HH, et al. n-3 polyunsaturated fatty acids and adiponectin in patients with end-stage renal disease. *Clinical Nephrology* 2015;**83**(5):279–85.

Kirkegaard E, Svensson M, Strandhave C, Schmidt EB, Jørgensen KA, Christensen JH. Marine n-3 fatty acids, atrial fibrillation and QT interval in haemodialysis patients. *British Journal of Nutrition* 2012;**107**:903–9.

Rasmussen LE, Svensson M, Jørgensen KA, Schmidt EB, Christensen JH. The content of docosahexaenoic acid in serum phospholipid is inversely correlated with plasma homocysteine levels in patients with end-stage renal disease. *Nutrition Research* 2010;**30**:535–40.

Svensson M, Frøbert O, Schmidt EB, Jørgensen KA, Simonsen U, Christensen JH. The effect of n-3 fatty acids on levels of methylarginines in patients with end-stage renal disease. *Journal of Nephrology* 2010;**23**(4):459–64.

Svensson M, Schmidt EB, Jørgensen KA, Christensen JH. The effect of n-3 fatty acids on lipids and lipoproteins in patients treated with chronic haemodialysis: a randomized placebo-controlled intervention study. *Nephrology Dialysis Transplantation* 2008;**23**:2918–24.

* Svensson M, Schmidt EB, Jørgensen KA, Christensen JP, OPACH Study Group. N-3 fatty acids as secondary prevention against cardiovascular events in patients who undergo chronic hemodialysis: a randomized, placebo-controlled intervention trial. *Clinical Journal of the American Society of Nephrology* 2006;**1**:780–6.

Svensson M, Schmidt EB, Jørgensen KA, Christensen JH. The effect of n-3 fatty acids on heart rate variability in patients treated with chronic hemodialysis. *Journal of Renal Nutrition* 2007;**17**(4):243–9.

Sørensen GVB, Svensson M, Strandhave C, Schmidt EB, Jørgensen KA, Christensen JH. The effect of n-3 fatty acids on small dense low-density lipoproteins in patients with end-stage renal disease: a randomized placebo-controlled intervention study. *Journal of Renal Nutrition* 2015;**25**(4):376–80.

OPAL {published and unpublished data}

* Dangour AD, Allen E, Elbourne D, Fasey N, Fletcher AE, Hardy P, et al. Effect of 2-y n23 long-chain polyunsaturated fatty acid supplementation on cognitive function in older people: a randomized, double-blind, controlled trial. *American Journal of Clinical Nutrition* 2010;**91**:1725–32.

Dangour AD, Allen E, Elbourne D, Fletcher AE, Neveu MM, Uauy R, et al. n-3 fatty acids and retinal function. *Ophthalmology* 2013;**120**(3):643–e3.

Dangour AD, Clemens F, Elbourne D, Fasey N, Fletcher

- AE, Hardy P, et al. A randomised controlled trial investigating the effect of n-3 long-chain polyunsaturated fatty acid supplementation on cognitive and retinal function in cognitively healthy older people: the Older People And n-3 Long-chain polyunsaturated fatty acids (OPAL) study protocol [ISRCTN72331636]. *Nutrition Journal* 2006;**5**: 20.
- Rantanen 2018** {*published data only (unpublished sought but not used)*}
- Rantanen JM, Riahi S, Johansen MB, Schmidt EB, Christensen JH. Effects of marine n-3 polyunsaturated fatty acids on heart rate variability and heart rate in patients on chronic dialysis: a randomized controlled trial. *Nutrients* 2018;**10**:1313.
- Risk & Prevention Study** {*published and unpublished data*}
- NCT00317707. Risk and prevention study: evaluation of the efficacy of n-3 PUFA in subjects at high cardiovascular risk [Risk and prevention study: optimisation of the preventive strategies and evaluation of the efficacy of n-3 PUFA in subjects at high cardiovascular risk]. clinicaltrials.gov/ct2/show/NCT00317707 (first received 21 April 2006).
- Rischio and Prevenzione Investigators. Efficacy of n-3 polyunsaturated fatty acids and feasibility of optimizing preventive strategies inpatients at high cardiovascular risk: rationale, design and baseline characteristics of the Rischio and Prevenzione study, a large randomised trial in general practice. *Trials* 2010;**11**:68.
- * The Risk and Prevention Study Collaborative Group. n-3 fatty acids in patients with multiple cardiovascular risk factors. *New England Journal of Medicine* 2013;**368**(19): 1800-8.
- Saito 2017** {*published and unpublished data*}
- Saito G, Zapata R, Rivera R, Zambrano H, Rojas D, Acevedo H, et al. Long-chain omega-3 fatty acids in aneurysmal subarachnoid hemorrhage: a randomized pilot trial of pharmaconutrition. *Surgical Neurology International* 2017;**8**:304.
- SCIMO** {*published data only (unpublished sought but not used)*}
- * Angerer P, Kothny W, Stork S, von Schacky C. Effect of dietary supplementation with ω -3 fatty acids on progression of atherosclerosis in carotid arteries. *Cardiovascular Research* 2002;**54**:183-90.
- Angerer P, Kothny W, von Schacky C. Dietary ω -3 fatty acids and human carotid atherosclerosis in patients with coronary artery disease: results of a randomized, double-blind two-year intervention trial. *European Heart Journal* 1998;**19 Suppl 1**:125.
- von Schacky C, Angerer P, Kothny W, Theisen K, Mudra H. The effect of dietary ω -3 fatty acids on coronary atherosclerosis: a randomized, double-blind, placebo-controlled trial. *Annals of Internal Medicine* 1999;**130**: 554-62.
- von Schacky C, Baumann K, Angerer P. The effect of n-3 fatty acids on coronary atherosclerosis: results from SCIMO, an angiographic study, background and implications. *Lipids* 2001;**36**:S99-102.
- SU.FOL.OM3** {*published data only (unpublished sought but not used)*}
- Andreeva VA, Galan P, Torres M, Julia C, Hercberg S, Kesse-Guyot E. Supplementation with B vitamins or n23 fatty acids and depressive symptoms in cardiovascular disease survivors: ancillary findings from the SUpplementation with FOLate, vitamins B-6 and B-12 and/or OMEga-3 fatty acids (SU.FOL.OM3) randomized trial. *American Journal of Clinical Nutrition* 2012;**96**:208-14.
- Andreeva VA, Kesse-Guyot E, Barberger-Gateau P, Fezeu L, Hercberg S, Galan P. Cognitive function after supplementation with B vitamins and long-chain omega-3 fatty acids: ancillary findings from the SU.FOL.OM3 randomized trial. *American Journal of Clinical Nutrition* 2011;**94**:278-86.
- Andreeva VA, Latache C, Hercberg S, Briancon S, Galan P, Kesse-Guyot E. B Vitamin and/or n-3 fatty acid supplementation and health-related quality of life: ancillary findings from the SU.FOL.OM3 randomized trial. *PLOS ONE* 2014;**9**:e84844.
- Blacher J, Czernichow S, Paillard F, Ducimetiere P, Hercberg S, Galan P. Cardiovascular effects of B-vitamins and/or N-3 fatty acids: the Su.Fol.Om3 trial. *International Journal of Cardiology* 2013;**167**:508-13.
- Fezeu LK, Laporte F, Kesse-Guyot E, Andreeva VA, Blacher J, Hercberg S, et al. Baseline plasma fatty acids profile and incident cardiovascular events in the SU.FOL.OM3 Trial: the evidence revisited. *PLOS ONE* 2014;**9**(4):e92548.
- Galan P, Briancon S, Blacher J, Czernichow S, Hercberg S. The SU.FOL.OM3 Study: a secondary prevention trial testing the impact of supplementation with folate and B-vitamins and/or Omega-3 PUFA on fatal and non fatal cardiovascular events, design, methods and participants characteristics. *Trials* 2008;**9**:35.
- * Galan P, Kesse-Guyot E, Czernichow S, Briancon S, Blacher J, Hercberg S, et al. Effects of B vitamins and omega 3 fatty acids on cardiovascular diseases: a randomised placebo controlled trial. *BMJ* 2010;**341**:c6273.
- Galan P, de Bree A, Mennen L, Potier de Courcy G, Preziosi P, Bertrais S, et al. Background and rationale of the SU.FOL.OM3 study: double-blind randomized placebo-controlled secondary prevention trial to test the impact of supplementation with folate, vitamin B6 and B12 and/or omega-3 fatty acids on the prevention of recurrent ischemic events in subjects with atherosclerosis in the coronary or cerebral arteries. *Journal of Nutrition Health and Aging* 2003;**7**(6):428-35.
- ISRCTN41926726. Supplementation with folate (and vitamins B6 and B12) and/or omega 3 fatty acids on the prevention of recurrent ischaemic events in patients who have already experienced a coronary or cerebrovascular event. www.isrctn.com/ISRCTN41926726 (first received 14 September 2005).
- Vesin C, Galan P, Gautier B, Czernichow S, Hercberg S, Blacher J. Control of baseline cardiovascular risk factors in the SU-FOL-OM3 study cohort: does the localization of the arterial event matter?. *European Journal of Cardiovascular*

Prevention and Rehabilitation 2010;**17**:541–8.
de Edelenyi FS, Vergnaud AC, Ahluwalia N, Julia C, Hercberg S, Blacher J, et al. Effect of B-vitamins and n-3 PUFA supplementation for 5 years on blood pressure in patients with CVD. *British Journal of Nutrition* 2012;**107**(6):921–7.

Terano 1999 {published data only (unpublished sought but not used)}

Terano T, Fujishiro S, Ban T, Yamamoto K, Tanaka T, Noguchi Y, et al. Docosahexaenoic acid supplementation improves the moderately severe dementia from thrombotic cerebrovascular diseases. *Lipids* 1999;**34**:S345–6.

Thies 2003 {published data only (unpublished sought but not used)}

Rerkasem K, Shearman CP, Garry JMC, Thies F, Yaqoob P, Williams J, et al. Potential of dietary supplementation in patients with carotid artery disease. *British Journal of Surgery* 2002;**89**:365.

* Thies F, Garry JMC, Yaqoob P, Rerkasem K, Williams J, Shearman CP, et al. Association of n-3 polyunsaturated fatty acids with stability of atherosclerotic plaques: a randomised controlled trial. *Lancet* 2003;**361**:477–85.

Wakita 2013 {published data only (unpublished sought but not used)}

Wakita Y, Wakida Y, Itou T, Mizuno R. Eicosapentaenoic acid in addition to a strong statin makes regression of intima-media thickness in patients with asymptomatic cerebral infarction. *Stroke* 2013;**44**:AWP413.

Zhang 2017 {published data only (unpublished sought but not used)}

Zhang YP, Lou Y, Hu J, Miao R, Ma F. DHA supplementation improves cognitive function via enhancing A β -mediated autophagy in Chinese elderly with mild cognitive impairment: a randomised placebo-controlled trial. *Journal of Neurology, Neurosurgery, and Psychiatry* 2018;**89**(4):382–8.

* Zhang YP, Miao R, Lic Q, Wu T, Ma F. Effects of DHA supplementation on hippocampal volume and cognitive function in older adults with mild cognitive impairment: a 12-month randomized, double-blind, placebo-controlled trial. *Journal of Alzheimer's Disease* 2017;**55**:497–507.

References to studies excluded from this review

ALVINA 2013 {published data only}

Droste DW, Iliescu C, Vaillant M, Gantenbein M, De Braemacker N, Lieunard C, et al. Advice on lifestyle changes (diet, red wine and physical activity) does not affect internal carotid and middle cerebral artery blood flow velocity in patients with carotid atherosclerosis in a randomized controlled trial. *Cerebrovascular Diseases* 2014;**37**:368–75.
Droste DW, Iliescu C, Vaillant M, Gantenbein M, De Braemacker N, Lieunard C, et al. A daily glass of red wine and lifestyle changes do not affect arterial blood pressure and heart rate in patients with carotid arteriosclerosis after 4 and 20 weeks. *Cerebrovascular Diseases Extra* 2013;**3**:121–9.

* Droste DW, Iliescu C, Vaillant M, Gantenbein M, De Braemacker N, Lieunard, et al. A daily glass of red wine associated with lifestyle changes independently improves blood lipids in patients with carotid arteriosclerosis: results

from a randomized controlled trial. *Nutrition Journal* 2013;**12**:147.

NCT01146132. Nutrition and physical activity in patients with cerebrovascular disease [Nutrition and physical activity in patients with cerebrovascular disease (ALVINA)]. clinicaltrials.gov/ct2/show/NCT01146132 (first received 15 June 2010).

ANCHOR {published data only}

Ballantyne CM, Bays HE, Braeckman RA, Philip S, Stirtan WG, Doyle Jr RT, et al. Icosapent ethyl (eicosapentaenoic acid ethyl ester): effects on plasma apolipoproteinC-III levels in patients from the MARINE and ANCHOR studies. *Journal of Clinical Lipidology* 2016;**10**:635–45.

* Ballantyne CM, Bays HE, Kastelein JJ, Stein E, Isaacsohn JL, Braeckman RA, et al. Efficacy and safety of eicosapentaenoic acid ethyl ester (AMR101) therapy in statin-treated patients with persistent high triglycerides (from the ANCHOR Study). *American Journal of Cardiology* 2012;**110**:984–92.

Ballantyne CM, Braeckman RA, Bays HE, Kastelein JJ, Otvos JD, Stirtan WG, et al. Effects of icosapent ethyl on lipoprotein particle concentration and size in statin-treated patients with persistent high triglycerides (the ANCHOR Study). *Journal of Clinical Lipidology* 2015;**9**:377–83.

Bays HE, Ballantyne CM, Braeckman RA, Stirtan WG, Soni PN. Icosapent ethyl, a pure ethyl ester of eicosapentaenoic acid: effects on circulating markers of inflammation from the MARINE and ANCHOR studies. *American Journal of Cardiovascular Drugs* 2013;**13**:37–46.

Bays HE, Ballantyne CM, Doyle RT, Juliano RA, Philip S. Icosapent ethyl: eicosapentaenoic acid concentration and triglyceride-lowering effects across clinical studies. *Prostaglandins & other Lipid Mediators* 2016;**125**:57–64.

Brinton EA, Ballantyne CM, Bays HE, Kastelein JJ, Braeckman RA, Soni PN. Effects of icosapent ethyl on lipid and inflammatory parameters in patients with diabetes mellitus-2, residual elevated triglycerides(200-500 mg/dL), and on statin therapy at LDL-Cgoal: the ANCHOR study. *Cardiovascular Diabetology* 2013;**12**:100.

Bao 2016 {published data only}

Bao J, Chen G, Zhu W, Ye H, Zhang X. Effect of omega-3 fatty acid nutritional therapy on immune function in patients with acute ischemic stroke. *Chinese Journal of Geriatrics* 2016;**35**(10):1094–8.

DOIT 1997 {published data only (unpublished sought but not used)}

Ellingsen I, Seljeflot I, Arnesen H, Tonstad S. Vitamin C consumption is associated with less progression in carotid intima media thickness in elderly men: a 3-year intervention study. *Nutrition Metabolism & Cardiovascular Diseases* 2009;**19**:8–14.

* Hjerkin EM, Abdelnoor M, Breivik L, Bergengen L, Ellingsen I, Seljeflot I, et al. Effect of diet or very long chain omega-3 fatty acids on progression of atherosclerosis, evaluated by carotid plaques, intima-media thickness and by pulse wave propagation in elderly men with

hypercholesterolaemia. *European Journal of Cardiovascular Prevention and Rehabilitation* 2006;**13**:325–33.
NCT00764010. Diet and omega-3 intervention trial on atherosclerosis [Diet and omega-3 intervention trial on atherosclerosis (DOIT)]. clinicaltrials.gov/ct2/show/NCT00764010 (first received 26 September 2008).

EVAS 2004 *{published data only}*

NCT00839449. Eicosapentaenoic acid cerebral vasospasm therapy study [Eicosapentaenoic acid cerebral vasospasm therapy study (EVAS): effect of eicosapentaenoic acid on cerebral vasospasm following subarachnoid hemorrhage]. clinicaltrials.gov/ct2/show/NCT00839449 (first received 4 February 2009).

* Yoneda H, Shirao S, Nakagawa J, Ogasawara K, Tominaga T, Suzuki M. A prospective, multicenter, randomized study of the efficacy of eicosapentaenoic acid for cerebral vasospasm: the EVAS Study. *World Neurosurgery* 2014;**81**(2):309–15.

FISHb Sandesara 2012 *{published data only}*

Sandesara CM, Chung MK, Van Wagoner DR, Barringer TA, Allen K, Ismail HM, et al. A randomized, placebo-controlled trial of omega-3 fatty acids for inhibition of supraventricular arrhythmias after cardiac surgery: the FISH Trial. *Journal of the American Heart Association* 2012; **1**:e000547.

MARINE *{published data only}*

Ballantyne CM, Bays HE, Braeckman RA, Philip S, Stirtan WG, Doyle Jr RT, et al. Icosapent ethyl (eicosapentaenoic acid ethyl ester): effects on plasma apolipoprotein C-III levels in patients from the MARINE and ANCHOR studies. *Journal of Clinical Lipidology* 2016;**10**:635–45.

Bays HE, Ballantyne CM, Braeckman RA, Stirtan WG, Soni PN. Icosapent ethyl, a pure ethyl ester of eicosapentaenoic acid: effects on circulating markers of inflammation from the MARINE and ANCHOR studies. *American Journal of Cardiovascular Drugs* 2013;**13**:37–46.

Bays HE, Ballantyne CM, Doyle Jr. RT, Juliano RA, Philip S. Icosapent ethyl: eicosapentaenoic acid concentration and triglyceride-lowering effects across clinical studies. *Prostaglandins & other Lipid Mediators* 2016;**125**:57–64.

* Bays HE, Ballantyne CM, Kastelein JJ, Isaacsohn JL, Braeckman RA, Soni PN. Eicosapentaenoic acid ethyl ester (AMR101) therapy in patients with very high triglyceride levels (from the multi-center, placebo-controlled, randomized, double-blind, 12-week study with an open-label extension (MARINE) trial). *American Journal of Cardiology* 2011;**108**:682–90.

Bays HE, Braeckman RA, Ballantyne CM, Kastelein JJ, Orvos JD, Stirtan WG, et al. Icosapent ethyl, a pure EPA omega-3 fatty acid: effects on lipoprotein particle concentration and size in patients with very high triglyceride levels (the MARINE study). *Journal of Clinical Lipidology* 2012;**6**:565–72.

Braeckman RA, Manku MS, Bays HE, Stirtan WG, Soni PN. Icosapent ethyl, a pure EPA omega-3 fatty acid: effects on plasma and red blood cell fatty acids in patients with very high triglyceride levels (results from the MARINE study).

Prostaglandins, Leukotrienes and Essential Fatty Acids 2013; **89**:195–201.

Nakagawa 2017 *{published data only}*

Nakagawa I, Park HS, Yokoyama S, Fukutome K, Omoto K, Nishimura F, et al. Effect of eicosapentaenoic/ docosahexaenoic acid for prevention of cerebral vasospasm following aneurysmal subarachnoid hemorrhage. *Cerebrovascular Diseases* 2016;**41**(Suppl 1):129 (Abst.P101).

* Nakagawa I, Yokoyama S, Omoto K, Takeshima Y, Matsuda R, Nishimura F, et al. ω -3 fatty acids ethyl esters suppress cerebral vasospasm and improve clinical outcome following aneurysmal subarachnoid hemorrhage. *World Neurosurgery* 2017;**99**:457–64.

NCT01526824 *{published data only (unpublished sought but not used)}*

NCT01526824. Lovaza's effect on clopidogrel in a neuro population [The effects of polyunsaturated omega-3 fatty acids (Lovaza) on patients taking clopidogrel +/- aspirin who have suffered an ischemic stroke/TIA and/or are candidates for neuroendovascular stenting]. clinicaltrials.gov/ct2/show/NCT01526824 (first received 31 January 2012).

SOFA *{published and unpublished data}*

* Brouwer IA, Zock PL, Camm AJ, Bocker D, Hauer RNW, Wever EFD, et al. Effect of fish oil on ventricular tachyarrhythmia and death in patients with implantable cardioverter defibrillators. The study on omega-3 fatty acids and ventricular arrhythmia (SOFA) randomized trial. *JAMA* 2006;**295**:2613–9.

Brouwer IA, Zock PL, Wever EFD, Hauer RNW, Camm AJ, Bocker D, et al. Rationale and design of a randomised controlled clinical trial on supplemental intake of n-3 fatty acids and incidence of cardiac arrhythmia: SOFA. *European Journal of Clinical Nutrition* 2003;**57**:1323–30.

Suehiro 1994 *{published data only (unpublished sought but not used)}*

Suehiro A, Higasa S, Ueda M, Oura Y, Kakishita E. Combination effect of eicosapentaenoic acid and platelet suppressive agents on platelets. *Current Therapeutic Research* 1994;**55**(6):653–9.

Tomiyama 2005 *{published data only}*

Tomiyama H, Takazawa K, Osa S, Hirose K, Hirai A, Iketani T, et al. Do eicosapentaenoic acid supplements attenuate age-related increases in arterial stiffness in patients with dyslipidemia? A preliminary study. *Hypertension Research* 2005;**28**:651–5.

Yoneda 2008 *{published data only}*

Yoneda H, Shirao S, Kurokawa T, Fujisawa H, Kato S, Suzuki M. Does eicosapentaenoic acid (EPA) inhibit cerebral vasospasm in patients after aneurysmal subarachnoid hemorrhage?. *Acta Neurologica Scandinavica* 2008;**118**: 54–9.

References to studies awaiting assessment

FISH Lok 2012 *{published data only (unpublished sought but not used)}*

Lok CE, Allon M, Donnelly S, Dorval M, Hemmelgarn B, Moist L, et al. Design of the fish oil inhibition of stenosis

in hemodialysis grafts (FISH) study. *Clinical Trials* 2007;**4**:357–67.

* Lok CE, Moist L, Hemmelgarn B, Tonelli M, Vasquez MA, Dorval M, et al. Effect of fish oil supplementation on graft patency and cardiovascular events among patients with new synthetic arteriovenous hemodialysis grafts: a randomized trial. *JAMA* 2012;**307**:1809–16.

Hertantows 2014 {published data only (unpublished sought but not used)}

Hertantows H, Soeharyohs S, Husni AA. Effect of extract supplementation status of snakehead fish in the status of the protein, antioxidant, oxidative stress and outcome in acute ischemic stroke. *International Journal of Stroke* 2014;**9** Suppl 3:95-6 (Abst.WSC-1049).

Nomura 2009 {published data only}

Nomura S, Inami N, Shouzu A, Omoto S, Kimura Y, Takahashi N, et al. The effects of pitavastatin, eicosapentaenoic acid and combined therapy on platelet-derived microparticles and adiponectin in hyperlipidemic, diabetic patients. *Platelets* 2009;**20**(1):16–22.

ORIGIN {published data only (unpublished sought but not used)}

Badings EA, Dyal L, Schoterman L, Lok DJA, Stoel I, Gerding MN, et al. Strategies to detect abnormal glucose metabolism in people at high risk of cardiovascular disease from the ORIGIN (Outcome Reduction with Initial Glargine Intervention) trial population. *Journal of Diabetes* 2011;**3**:232–7.

Bordeleau L, Yakubovich N, Dagenais GR, Rosenstock J, Probstfeld J, Yu PC, et al. The association of basal insulin glargine and/or n-3 fatty acids with incident cancers in patients with dysglycemia. *Diabetes Care* 2014;**37**:1360–6.

Cukierman-Yaffe T, Bosch J, Diaz R, Dyal L, Hancu N, Hildebrandt P, et al. Effects of basal insulin glargine and omega-3 fatty acid on cognitive decline and probable cognitive impairment in people with dysglycaemia: a substudy of the ORIGIN trial. *Lancet Diabetes & Endocrinology* 2014;**2**(7):562–72.

Gerstein HC, Pare G, Hess S, Ford RJ, Sjaarda J, Raman K, et al. Growth differentiation factor 15 as a novel biomarker for metformin. *Diabetes Care* 2017;**40**:280–3.

Gerstein HC, Paré G, McQueen MJ, Haenel H, Lee SF, Pogue J, et al. Identifying novel biomarkers for cardiovascular events or death in people with dysglycemia. *Circulation* 2015;**132**:2297–304.

Hanefeld M, Bramlage P. Insulin use early in the course of Type 2 diabetes mellitus: the ORIGIN trial. *Current Diabetes Reports* 2013;**13**:342–9.

Hanefeld M, Koehler C, Hoffmann C, Wilhelm K, Kamke W, Gerstein H. Effect of targeting normal fasting glucose levels with basal insulin glargine on glycaemic variability and risk of hypoglycaemia: a randomized, controlled study in patients with early Type 2 diabetes. *Diabetic Medicine* 2010;**27**:175–80.

Lamy A, Tong W, Jung H, Gafni A, Singh K, Tyrwhitt J, et al. Cost implications of the use of basal insulin glargine in

people with early dysglycemia: the ORIGIN trial. *Journal of Diabetes and Its Complications* 2014;**28**:553–8.

Lonn E, Bosch J, Diaz R, Lopez-Jaramillo P, Ramachandran A, Hancu N, et al. Effect of insulin glargine and n-3 FA on carotid intima-media thickness in people with dysglycemia at high risk for cardiovascular events. *Diabetes Care* 2013;**36**:2466–74.

Lopez-Jaramillo P, Cohen DD, Gómez-Arbelaez D, Bosch J, Dyal L, Yusuf S, et al. Association of handgrip strength to cardiovascular mortality in pre-diabetic and diabetic patients: a subanalysis of the ORIGIN trial. *International Journal of Cardiology* 2014;**174**(2):458–61.

ORIGIN Trial Investigators. Cardiovascular and other outcomes post intervention with insulin glargine and omega-3 fatty acids (ORIGINALE). *Diabetes Care* 2016;**39**:709–16.

Punthakee Z, Tyrwhitt J, Bosch J, Dagenais GR, Díaz R, Jung H, et al. Outcome reduction with an initial glargine intervention and legacy effects (ORIGINALE). *Diabetologia* 2014;**57**(Suppl 1):S516.

Ramachandran A, Riddle MC, Kabali C, Gerstein HC, ORIGIN Investigators. Relationship between A1C and fasting plasma glucose in dysglycemia or Type 2 diabetes. *Diabetes Care* 2012;**35**:749–53.

Rautio A, Boman K, Gerstein HC, Hernestal-Boman J, Lee SF, Olofsson M, et al. The effect of basal insulin glargine on the fibrinolytic system and von Willebrand factor in people with dysglycaemia and high risk for cardiovascular events: Swedish substudy of the Outcome Reduction with an Initial Glargine Intervention trial. *Diabetes & Vascular Disease Research* 2017;**14**(4):345–52.

The ORIGIN Trial Investigators. Basal insulin and cardiovascular and other outcomes in dysglycemia. *New England Journal of Medicine* 2012;**367**:319–28.

The ORIGIN Trial Investigators. Characteristics associated with maintenance of mean A1C < 6.5% in people with dysglycemia in the ORIGIN Trial. *Diabetes Care* 2013;**36**:2915–22.

The ORIGIN Trial Investigators. Does hypoglycaemia increase the risk of cardiovascular events? A report from the ORIGIN trial. *European Heart Journal* 2013;**34**:3137–44.

The ORIGIN Trial Investigators. Predictors of nonsevere and severe hypoglycemia during glucose-lowering treatment with insulin glargine or standard drugs in the ORIGIN trial. *Diabetes Care* 2015;**38**:22–8.

The ORIGIN Trial Investigators. Rationale, design, and baseline characteristics for a large international trial of cardiovascular disease prevention in people with dysglycemia: the ORIGIN Trial (Outcome Reduction with an Initial Glargine Intervention). *American Heart Journal* 2008;**155**:26–32.e6.

* The ORIGIN Trial Investigators. n-3 fatty acids and cardiovascular outcomes in patients with dysglycemia. *New England Journal of Medicine* 2012;**367**:309–18.

The ORIGIN trial investigators: Gilbert RE, Mann JFE, Hanefeld M, Spinass G, Bosch J, et al. Basal insulin glargine and microvascular outcomes in dysglycaemic individuals:

results of the Outcome Reduction with an Initial Glargine Intervention (ORIGIN) trial. *Diabetologia* 2014;**57**:1325–31.

REDUCE-IT {*published data only (unpublished sought but not used)*}

Bhatt DL, Steg G, Brinton EA, Jacobson TA, Miller M, Tardif JC, et al. Rationale and design of REDUCE-IT: Reduction of Cardiovascular Events with Icosapent Ethyl-Intervention Trial. *Clinical Cardiology* 2017;**40**:138–48.
* Bhatt DL, Steg G, Miller M, Brinton EA, Jacobson TA, Ketchum SB, et al. Cardiovascular risk reduction with icosapent ethyl for hypertriglyceridemia. *New England Journal of Medicine* 2019;**380**:11–22.

Sengoku 2013 {*published data only (unpublished sought but not used)*}

Sengoku R, Sakuta K, Bono K, Yamazaki M, Komatsu T, Mijagawa S, et al. Should eicosapentaenoic acid and/or atorvastatin influence cardio-ankle vascular index?. *Cerebrovascular Diseases* 2013;**36 Suppl 2**:35 (Abst.P-66).

References to ongoing studies

NCT01953705 {*published and unpublished data*}

NCT01953705. n-3 PUFA for vascular cognitive aging [Omega 3 PUFA for the vascular component of age-related cognitive decline]. clinicaltrials.gov/ct2/show/NCT01953705 (first received 24 September 2013).

OMEMI {*published data only*}

Laake K, Myhre P, Nordby LM, Seljeflot I, Abdelnoor M, Smith P, et al. Effects of omega 3 supplementation in elderly patients with acute myocardial infarction: design of a prospective randomized placebo controlled study. *BMC Geriatrics* 2014;**14**:74.

STRENGTH {*published data only*}

Nicholls SJ, Lincoff AM, Bash D, Ballantyne CM, Barter PJ, Davidson MH, et al. Assessment of omega-3 carboxylic acids in statin-treated patients with high levels of triglycerides and low levels of high-density lipoprotein cholesterol: rationale and design of the STRENGTH trial. *Clinical Cardiology* 2018;**41**:1281–8.

Additional references

Abdelhamid 2018

Abdelhamid AS, Brown TJ, Brainard JS, Biswas P, Thorpe GC, Moore HJ, et al. Omega-3 fatty acids for the primary and secondary prevention of cardiovascular disease. *Cochrane Database of Systematic Reviews* 2018, Issue 7. DOI: 10.1002/14651858.CD003177.pub3

Atkins 2004

Atkins D, Best D, Briss PA, Eccles M, Falck-Ytter Y, Flottorp S, et al. GRADE Working Group. Grading quality of evidence and strength of recommendations. *BMJ* 2004;**328**(7454):1490.

Aung 2018

Aung T, Halsey J, Kromhout D, Gerstein HC, Marchioli R, Tavazzi L, et al. Associations of omega-3 fatty acid supplement use with cardiovascular disease risks: meta-

analysis of 10 trials involving 77 917 individuals. *JAMA Cardiology* 2018;**3**(3):225–33.

Barret 2013

Barret KM, Meschia JF (editors). *NIP - Neurology in Practice: Stroke*. 1st Edition. Somerset: Wiley-Blackwell, 2013.

Bazan 2005

Bazan NG. Neuroprotectin D1 (NPD1): a DHA-derived mediator that protects brain and retina against cell injury-induced oxidative stress. *Brain Pathology (Zurich, Switzerland)* 2005;**15**(2):159–66.

Bazan 2009

Bazan NG. Neuroprotectin D1-mediated anti-inflammatory and survival signalling in stroke, retinal degenerations, and Alzheimer's disease. *Journal of Lipid Research* 2009;**50**:S400–5.

Bazinet 2014

Bazinet RP, Laye S. Polyunsaturated fatty acids and their metabolites in brain function and disease. *Nature Reviews Neuroscience* 2014;**15**(12):771–85.

Belayev 2009

Belayev L, Khoutorova L, Atkins KD, Bazan NG. Robust docosahexaenoic acid-mediated neuroprotection in a rat model of transient focal cerebral ischemia. *Stroke* 2009;**40**(9):3121–6.

Belayev 2011

Belayev L, Khoutorova L, Atkins KD, Eady TN, Hong S, Lu Y, et al. Docosahexaenoic acid therapy of experimental stroke. *Translational Stroke Research* 2011;**2**(1):33–41.

Blondeau 2016

Blondeau N. The nutraceutical potential of omega-3 alpha-linolenic acid in reducing the consequences of stroke. *Biochimie* 2016;**120**:49–55.

Bradbury 2011

Bradbury J. Docosahexaenoic acid (DHA): an ancient nutrient for the modern human brain. *Nutrients* 2011;**3**(5):529–54.

Broderick 2017

Broderick JP, Adeoye O, Elm J. The evolution of the modified Rankin Scale and its use in future stroke trials. *Stroke* 2017;**48**(7):2007–12.

Calder 2009

Calder PC, Yaqoob P. Understanding omega-3 polyunsaturated fatty acids. *Postgraduate Medicine* 2009;**121**(6):148–57.

Calder 2012a

Calder PC. Mechanisms of action of (n-3) fatty acids. *Journal of Nutrition* 2012;**142**(3):592S–9S.

Calder 2012b

Calder PC, Yaqoob P. Marine omega-3 fatty acids and coronary heart disease. *Current Opinion in Cardiology* 2012;**27**(4):412–9.

Caplan 2006

Caplan LR. *AAN Press Quality of Life Guide: Stroke*. New York: Demos, 2006.

Carmichael 2016

Carmichael ST. Emergent properties of neural repair: elemental biology to therapeutic concepts. *Annals of Neurology* 2016;**79**(6):895–906.

Cholewski 2018

Cholewski M, Tomczykowa M, Tomczyk M. A comprehensive review of chemistry, sources and bioavailability of omega-3 fatty acids. *Nutrients* 2018;**10**:1662.

Chowdhury 2012

Chowdhury R, Stevens S, Gorman D, Pan A, Warnakula S, Chowdhury S, et al. Association between fish consumption, long chain omega 3 fatty acids, and risk of cerebrovascular disease: systematic review and meta-analysis. *BMJ* 2012;**345**:e6698.

Dyerberg 1979

Dyerberg J, Bang HO. Haemostatic function and platelet polyunsaturated fatty acids in Eskimos. *Lancet* 1979;**2**(8140):433–5.

Eady 2014

Eady TN, Khoutorova L, Obenaus A, Mohd-Yusof A, Bazan NG, Belayev L. Docosahexaenoic acid complexed to albumin provides neuroprotection after experimental stroke in aged rats. *Neurobiology of Disease* 2014;**62**:1–7.

Eltzschig 2011

Eltzschig H, Eckle T. Ischemia and reperfusion - from mechanism to translation. *Nature Medicine* 2011;**17**(11):1391–401.

Feigin 2019

Feigin VL. Anthology of stroke epidemiology in the 20th and 21st centuries: Assessing the past, the present, and envisioning the future. *International Journal of Stroke* 2019;**14**(3):223–37.

Gajos 2011

Gajos G, Zalewski J, Rostoff P, Nessler J, Piwowarska W, Undas A. Reduced thrombin formation and altered fibrin clot properties induced by polyunsaturated omega-3 fatty acids on top of dual antiplatelet therapy in patients undergoing percutaneous coronary intervention (OMEGA-PCI Clot). *Arteriosclerosis, Thrombosis, and Vascular Biology* 2011;**31**(7):1696–702.

Gillum 1996

Gillum RF, Mussolino ME, Madans JH. The relationship between fish consumption and stroke incidence. The NHANES I Epidemiologic Follow-up Study (National Health and Nutrition Examination Survey). *Archives of Internal Medicine* 1996;**156**(5):537–42.

GRADEpro GDT [Computer program]

McMaster University (developed by Evidence Prime). GRADEpro GDT. Hamilton (ON): McMaster University (developed by Evidence Prime), 2015.

Hacke 2008

Hacke W, Kaste M, Bluhmki E, Brozman M, Davalos A, Guidetti D, et al. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. *New England Journal of Medicine* 2008;**359**(13):1317–29.

Higgins 2011

Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

Hong 2014

Hong SH, Belayev L, Khoutorova L, Obenaus A, Bazan NG. Docosahexaenoic acid confers enduring neuroprotection in experimental stroke. *Journal of the Neurological Sciences* 2014;**338**(1-2):135–41.

Hu 2002

Hu FB, Bronner L, Willett WC, Stampfer MJ, Rexrode KM, Albert CM, et al. Fish and omega-3 fatty acid intake and risk of coronary heart disease in women. *JAMA* 2002;**287**(14):1815–21.

Ikeya 2013

Ikeya Y, Fukuyama N, Kitajima W, Ogushi Y, Mori H. Comparison of eicosapentaenoic acid concentrations in plasma between patients with ischemic stroke and control subjects. *Nutrition* 2013;**29**(1):127–31.

Iso 2001

Iso H, Rexrode KM, Stampfer MJ, Manson JE, Colditz GA, Speizer FE, et al. Intake of fish and omega-3 fatty acids and risk of stroke in women. *JAMA* 2001;**285**(3):304–12.

Jakubowski 1979

Jakubowski JA, Ardlie NG. Evidence for the mechanism by which eicosapentaenoic acid inhibits human platelet aggregation and secretion - implications for the prevention of vascular disease. *Thrombosis Research* 1979;**16**(1):205–17.

Keli 1994

Keli SO, Feskens EJ, Kromhout D. Fish consumption and risk of stroke. The Zutphen study. *Stroke* 1994;**25**(2):328–32.

Kris-Etherton 2002

Kris-Etherton PM, Harris WS, Appel LJ. Fish consumption, fish oil, omega-3 fatty acids, and cardiovascular disease. *Circulation* 2002;**106**(21):2747–57.

Kris-Etherton 2009

Kris-Etherton PM, Grieger JA, Etherton TD. Dietary reference intakes for DHA and EPA. *Prostaglandins, Leukotrienes and Essential Fatty Acids* 2009;**81**:99–104.

McNamara 2006

McNamara R, Carlson S. Role of omega-3 fatty acids in brain development and function: potential implications for the pathogenesis and prevention of psychopathology. *Prostaglandins, Leukotrienes and Essential Fatty Acids* 2006;**75**:329–49.

Morris 1995

Morris MC, Manson JE, Rosner B, Buring JE, Willett WC, Hennekens CH. Fish consumption and cardiovascular disease in the physicians' health study: a prospective study. *American Journal of Epidemiology* 1995;**142**(2):166–75.

Mozaffarian 2006

Mozaffarian D, Rimm EB. Fish intake, contaminants, and human health: evaluating the risks and the benefits. *JAMA* 2006;**296**(15):1885–99.

Mozaffarian 2016

Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, et al. Heart disease and stroke statistics - 2016 update. *Circulation* 2016;**133**(4):e38–e360.

Nakase 2015

Nakase T, Sasaki M, Suzuki A. Eicosapentaenoic acid as long-term secondary prevention after ischemic stroke. *Clinical and Translational Medicine* 2015;**4**:21.

Nogueira 2018

Nogueira RG, Jadhav AP, Haussen DC, Bonafe A, Budzik RF, Bhuva P, et al. Thrombectomy 6 to 24 hours after stroke with a mismatch between deficit and infarct. *New England Journal of Medicine* 2018;**378**(1):11–21.

Orencia 1996

Orencia AJ, Daviglius ML, Dyer AR, Shekelle RB, Stamier J. Fish consumption and stroke in men. *Stroke* 1996;**27**(2):204–9.

Ostergaard Kristensen 1983

Ostergaard Kristensen M. Increased incidence of bleeding intracranial aneurysms in Greenlandic Eskimos. *Acta Neurochirurgica* 1983;**67**(1):37–43.

Pryce 2016

Pryce R, Bernaitis N, Davey A, Badrick T, Anoopkumar-Dukie S. The use of fish oil with warfarin does not significantly affect either the International Normalised Ratio or incidence of adverse events in patients with atrial fibrillation and deep vein thrombosis: a retrospective study. *Nutrients* 2016;**8**:578.

Qin 2017

Qin Y, Nyheim H, Haram EM, Moritz JM, Hustvedt SO. A novel self-micro-emulsifying delivery system (SMEDS) formulation significantly improves the fasting absorption of EPA and DHA from a single dose of an omega-3 ethyl ester concentrate. *Lipids in Health and Disease* 2017;**16**:204.

Review Manager 2014 [Computer program]

Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager (RevMan). Version 5.3. Copenhagen: Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

Saravanan 2010

Saravanan P, Davidson NC, Schmidt EB, Calder PC. Cardiovascular effects of marine omega-3 fatty acids. *Lancet* 2010;**376**(9740):540–50.

Saver 2016

Saver JL, Goyal M, van der Lugt A, Menon BK, Majoie CB, Dippel DW, HERMES Collaborators. Time to treatment with endovascular thrombectomy and outcomes from ischemic stroke: a meta-analysis. *JAMA* 2016;**316**(12):1279–88.

Schulz 2010

Schulz KF, Altman DG, Moher D. CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials. *BMJ* 2010;**340**:c332.

Suda 2013

Suda S, Katsumata T, Okubo S, Kanamaru T, Suzuki K, Watanabe Y, et al. Low serum n-3 polyunsaturated fatty acid/n-6 polyunsaturated fatty acid ratio predicts neurological deterioration in Japanese patients with acute ischemic stroke. *Cerebrovascular Diseases (Basel, Switzerland)* 2013;**36**(5-6):388–93.

Tanaka 2008

Tanaka K, Ishikawa Y, Yokoyama M, Origasa H, Matsuzaki M, Saito Y, et al. Reduction in the recurrence of stroke by eicosapentaenoic acid for hypercholesterolemic patients. *Stroke* 2008;**39**(7):2052–8.

Valenzuela 2009

Valenzuela A, Sanhueza J. Marine oils; nutritional and food science relevance [Aceites de origen marino, su importancia en la nutrición y en la ciencia de los alimentos]. *Revista Chilena de Nutrición* 2009;**36**(3):246–57.

Valenzuela 2013

Valenzuela R, Morales J, Sanhueza J, Valenzuela A. Docosahexaenoic acid (DHA), an essential fatty acid at the brain [Acido docosahexaenoico (DHA), un acido graso esencial a nivel cerebral]. *Revista Chilena de Nutrición* 2013;**40**(4):383–90.

Wang 2014

Wang J, Shi Y, Zhang L, Zhang F, Hu X, Zhang W, et al. Omega-3 polyunsaturated fatty acids enhance cerebral angiogenesis and provide long-term protection after stroke. *Neurobiology of Disease* 2014;**68**:91–103.

Ware 1993

Ware JE, Snow KK, Kosinski M, Gandek B. *SF-36 Health Survey Manual & Interpretation Guide*. Boston: The Health Institute New England Medical Center, 1993.

Yao 2013

Yao C, Zhang J, Chen F, Lin Y. Neuroprotectin D1 attenuates brain damage induced by transient middle cerebral artery occlusion in rats through TRPC6/CREB pathways. *Molecular Medicine Reports* 2013;**8**(2):543–50.

Yokoyama 2007

Yokoyama M, Origasa H, Matsuzaki M, Matsuzawa Y, Saito Y, Ishikawa Y. Effects of eicosapentaenoic acid on major coronary events in hypercholesterolaemic patients (JELIS): a randomised open-label, blinded endpoint analysis. *Lancet* 2007;**369**(9567):1090–8.

Zendedel 2015

Zendedel A, Habib P, Dang J, Lammerding L, Hoffmann S, Beyer C, et al. Omega-3 polyunsaturated fatty acids ameliorate neuroinflammation and mitigate ischemic stroke damage through interactions with astrocytes and microglia. *Journal of Neuroimmunology* 2015;**278**:200–11.

Zhang 1999

Zhang J, Sasaki S, Amano K, Kesteloot H. Fish consumption and mortality from all causes, ischemic heart disease, and stroke: an ecological study. *Preventive Medicine* 1999;**28**(5): 520–9.

Zhang 2014

Zhang M, Wang S, Mao L, Leak RK, Shi Y, Zhang W, et al. Omega-3 fatty acids protect the brain against ischemic injury by activating Nrf2 and upregulating heme oxygenase 1. *Journal of Neuroscience* 2014;**34**(5):1903–15.

Zhang 2015

Zhang W, Wang H, Zhang H, Leak RK, Shi Y, Hu X, et al. Dietary supplementation with omega-3 polyunsaturated fatty acids robustly promotes neurovascular restorative dynamics and improves neurological functions after stroke. *Experimental Neurology* 2015;**272**:170–80.

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

ALPHA OMEGA

| | |
|---------------|--|
| Methods | <p>RCT; parallel; 2 × 2 factorial design</p> <p>Number of study sites: 32</p> <p>Dates: enrolment between April 2002 and December 2006, follow-up of 41 months (average)</p> |
| Participants | <p>Inclusion criteria: men and women aged 60 to 80 years; verified clinically diagnosed myocardial infarction up to 10 years before randomisation; written informed consent</p> <p>Exclusion criteria: living in a nursing home or other institution; participation in other scientific study; habitual margarine intake < 10 g/day; habitual alcohol intake > 6 drinks per day; use of fish oil capsules or other supplements containing n-3 fatty acids; presence of cancer with < 1 year of life expectancy; cognitive impairment, as indicated by the MMSE (score ≤ 21); unintended weight loss > 5 kg in the past year; lack of facilities for cooled margarine storage at home; inability or unwillingness to comply with study procedures</p> <p>Sample size: 4837 participants (total population), 345 participants with history of stroke</p> <p>Participants randomised to intervention group (only stroke population): 181 (92 to EPA-DHA only and 89 to EPA-DHA + ALA)</p> <p>Participants randomised to control group (only stroke population): 164 (83 to ALA only and 81 to placebo)</p> <p>Sex (only stroke population): EPA-DHA = 70 men and 22 women, EPA-DHA + ALA = 69 men and 20 women, ALA = 65 men and 18 women, placebo = 60 men and 21 women</p> <p>Age, years (only stroke population) mean ± SD: EPA-DHA = 70.95 ± 5.68, EPA-DHA + ALA = 69.92 ± 5.89, ALA = 70.34 ± 5.39, placebo = 70.38 ± 5.58</p> <p>Time from event (stroke) to start of intervention: not stated</p> <p>Type of baseline stroke: not stated</p> <p>Country: the Netherlands</p> <p>Ethnicity: predominantly of Dutch origin</p> |
| Interventions | <p>Comparison groups: 4 groups: EPA-DHA only, EPA-DHA and ALA, ALA only, and placebo. This review collated the groups in 2: EPA-DHA (including EPA-DHA only and EPA-DHA and ALA) versus no EPA-DHA (ALA only and placebo)</p> <p>Intervention: average of 20 g/day of margarine supplemented with 400 mg of EPA-DHA (derived from fish oil: Marinol®) or 400 mg of EPA-DHA + 2 g of ALA</p> <p>Control: average of 20 g/day of margarine supplemented with 2 g of ALA or placebo (oleic acid)</p> <p>Compliance: amount of margarine tubs returned. Measurement of fatty acid composition in plasma cholesteryl esters in random subgroups of 400 to 800 participants at baseline and after 20 and 40 months of intervention</p> <p>Duration of intervention: 40 months</p> <p>Co-interventions: participants randomised also to ALA or placebo (as described above)</p> |

| | | |
|---|--|---|
| Outcomes | <p>Primary outcome of study: major cardiovascular events</p> <p>Relevant review outcomes measured (in total population): vascular-related death, recurrent events, adverse events</p> <p>Available outcome data for stroke and/or TIA population only: vascular-related death, fatal recurrent events (no data available in non-fatal recurrent stroke)</p> <p>Latest time point of assessment: 6.5 ± 2.5 years</p> <p>Withdrawals or exclusions, n (stroke and/or TIA population only): no withdrawals other than death</p> <p>Study authors' contact status: replied - data provided</p> | |
| Notes | <p>Dietary information: dietary data, including intake of different types of fish, collected by a FFQ. For the total population, median intake of fish was 14 g/day (IQR 5 to 18 g/day), and 12% of the participants never consumed fish. Participants were asked to avoid n-3 fatty acids supplements during the trial</p> <p>Funding: Netherlands Heart Foundation (grant no. 2000T401), US National Institutes of Health (NIH/NHLBI and ODS, grant no. R01HL-076200) and Unilever R&D, Vlaardingen</p> | |
| Risk of bias | | |
| Bias | Authors' judgement | Support for judgement |
| Random sequence generation (selection bias) | Low risk | Quote: "Simple randomization is applied, using a randomization table (with a randomization ratio of 1:1:1:1). The table was produced on the computer by a random-number generator before the start of the trial" |
| Allocation concealment (selection bias) | Low risk | Quote: "Treatment codes (A,B,C,D) are assigned by Unilever to four types of trial margarine and are not known to others involved in the trial. A table linking randomization numbers to treatment codes is stored in a safe, which is only accessible by a third person who is not involved in the Alpha Omega trial" |
| Blinding of participants and personnel (performance bias) All outcomes | Low risk | Quote: "All parties involved will be blinded towards the type of intervention given to the patients" |
| Blinding of outcome assessment (detection bias) All outcomes | Low risk | Quote: "Events were coded by three members of the end-point adjudication committee, who were unaware of the identity of the patient, the identity of the treating physician, and the patient's assigned study group" |

| | | |
|--|--------------|--|
| | | Quote: "Only events for which documentation on the clinical diagnosis (e.g. hospital discharge records or letter) could be retrieved will be considered in the analysis" |
| Incomplete outcome data (attrition bias) All outcomes | Unclear risk | More participants discontinued margarine in intervention group. Insufficient information for discrepancy ("other" or "unknown" reasons) |
| Selective reporting (reporting bias) | Low risk | Endpoints stated in the protocol |
| Other bias | Low risk | None detected |

Doi 2014

| | |
|---------------|---|
| Methods | RCT; parallel; open label Number of study sites: 1 Dates: between November 2010 and December 2012 |
| Participants | Inclusion criteria: acute MI patients treated with PCI within 24 hours of symptom onset Exclusion criteria: cardiogenic shock; severe renal insufficiency requiring dialysis or continuous haemofiltration; cardiopulmonary arrest; emergent coronary artery bypass; and failure of PCI Sample size: 115 participants (total population), 14 participants with history of stroke Participants randomised to intervention group (only stroke population): 7 Participants randomised to control group (only stroke population): 7 Sex (only stroke and/or TIA population): not stated Age (only stroke and/or TIA population): not stated Time from event (stroke or TIA) to start of intervention: not stated Type of baseline stroke: not stated Country: Japan Ethnicity: not stated |
| Interventions | Comparison groups: EPA versus no intervention Intervention: 1800 mg/day of EPA, no further details Control: open label Compliance: not stated Duration of intervention: 30 days Co-interventions: 2 mg/day of pitavastatin. Before PCI, 200 mg aspirin and 300 mg clopidogrel. Intravenous heparin (10,000 IU) was administered after arterial access was obtained and continued for 48 hours after angioplasty. Postprocedural antithrombotic therapy: 100 mg/day and 75 mg/day clopidogrel |
| Outcomes | Primary outcome of study: composite of death, reinfarction, stroke, ventricular fibrillation/ventricular tachycardia (within and after 48 hours), and paroxysmal atrial fibrillation Relevant review outcomes measured (in total population): vascular-related death, recurrent events (stroke) |

| | | |
|---|--|---|
| | Available outcome data for stroke and/or TIA population only: none Latest time point of assessment: 30 days Withdrawals or exclusions, n (stroke and/or TIA population only): not available Study authors' contact status: no reply to date | |
| Notes | Dietary information: there were no significant differences in baseline plasma concentrations of EPA and arachidonic acid before PCI Funding: not stated | |
| Risk of bias | | |
| Bias | Authors' judgement | Support for judgement |
| Random sequence generation (selection bias) | Low risk | Computer-generated randomisation plan, which included stratification by age and sex |
| Allocation concealment (selection bias) | Unclear risk | No details about concealment |
| Blinding of participants and personnel (performance bias) All outcomes | High risk | Open-label trial |
| Blinding of outcome assessment (detection bias) All outcomes | Low risk | Quote: "Diagnosis was confirmed by an investigator who was blinded to treatment allocation" |
| Incomplete outcome data (attrition bias) All outcomes | Low risk | No loss of participants in any group |
| Selective reporting (reporting bias) | Unclear risk | Protocol not available |
| Other bias | Low risk | None detected |

EMPAR

| | |
|--------------|---|
| Methods | RCT; parallel; 2 × 2 factorial design Number of study sites: 4 Dates: recruitment between June 1990 and June 1993, last follow-up in November 1993 |
| Participants | Inclusion criteria: a diagnostic coronary angiogram showing at least 1 localised coronary artery stenosis of ≥ 50% reduction of lumen diameter by visual analysis and age ≥ 18 years Exclusion criteria: certain characteristics of the coronary artery disease (culprit lesion in a saphenous bypass graft, at the site of a previously dilated restenosis, or involving the left main coronary artery; MI < 28 days previously, the presence of very unstable angina necessitating PTCA in < 48 hours, or the presence of variant angina; or the use of Sones' approach); excessive bleeding risk (recent peptic ulcer or gastrointestinal bleeding, platelets < 100000/mm ³ , predisposition to intracranial haemorrhage, or blood |

| | | |
|---|---|---|
| | <p>pressure > 180/105 mmHg); concerns specific to the use of fish oils or LMWH (fish product or LMWH allergy or hypersensitivity, a requirement for anticoagulant therapy, the use of insulin, or significant hepatic or renal disease); or practical patient problems (disease therapy that might interfere with LMWH action or evaluation; concomitant disease likely to limit life span to < 6 months; drug or alcohol abuse; or insurmountable geographic, social, or language barrier)</p> <p>Sample size: 653 participants (total population), approximately 9 participants with history of stroke or TIA (reported as percentage of total population)</p> <p>Participants randomised to intervention group (only stroke or TIA population): 6 or 7 (reported as 2% of total)</p> <p>Participants randomised to control group (only stroke or TIA population): 3 (reported as 1% of total)</p> <p>Sex (only stroke or TIA population): not stated</p> <p>Age (only stroke or TIA population): not stated</p> <p>Time from event (stroke or TIA) to start of intervention: not stated</p> <p>Type of baseline stroke: not stated</p> <p>Country: Canada</p> <p>Ethnicity: not stated</p> | |
| Interventions | <p>Comparison groups: fish oil versus placebo (participants were subsequently randomised to LMWH)</p> <p>Intervention: fish oil capsules (maxEPA), each capsule containing 180 mg EPA and 120 mg DHA in the form of a triglyceride, 6 capsules given 3 times daily with meals (total, 5.4 g/day of marine-derived n-3 PUFAs)</p> <p>Control: identical-appearing capsules of corn oil, 6 capsules given 3 times daily with meals</p> <p>Compliance: assessment method unclear</p> <p>Duration of intervention: 4 months</p> <p>Co-interventions: randomisation to LMWH (enoxaparin) 60 mg/day for 6 weeks or standard therapy</p> | |
| Outcomes | <p>Primary outcome of study: reduction of PTCA restenosis</p> <p>Relevant review outcomes measured (in total population): recurrent events (stroke), adverse events</p> <p>Available outcome data for stroke and/or TIA population only: none</p> <p>Latest time point of assessment: 18±2 weeks</p> <p>Withdrawals or exclusions, n (stroke and/or TIA population only): not available</p> <p>Study authors' contact status: replied, no further data available</p> | |
| Notes | <p>Dietary information: none provided</p> <p>Funding: Heart and Stroke Foundation of Ontario and Rhône Poulenc Rorer</p> | |
| Risk of bias | | |
| Bias | Authors' judgement | Support for judgement |
| Random sequence generation (selection bias) | Unclear risk | No information about random sequence generation |

EMPAR (Continued)

| | | |
|---|--------------|--|
| Allocation concealment (selection bias) | Unclear risk | No details about allocation process |
| Blinding of participants and personnel (performance bias) All outcomes | Unclear risk | No information about blinding of participants or staff |
| Blinding of outcome assessment (detection bias) All outcomes | Unclear risk | No details in how outcomes were assessed |
| Incomplete outcome data (attrition bias) All outcomes | Low risk | Discontinuation of medication was similar across groups |
| Selective reporting (reporting bias) | Unclear risk | Protocol not available |
| Other bias | Unclear risk | Not enough data in some characteristics (standard deviations not provided, percentages given, not actual number of participants) |

ESPRIT

| | |
|--------------|---|
| Methods | RCT; parallel; placebo-controlled Number of study sites: 17 Dates: between March 1993 and May 1995 |
| Participants | <p>Inclusion criteria: clinical indication for PTCA (angina or ischaemia not adequately responsive to medical treatment or significant silent ischaemia after acute MI) in the presence of at least 1 critical coronary artery stenosis ($\geq 70\%$ at visual inspection) amenable to PTCA</p> <p>Exclusion criteria: age < 18 years or > 75 years; recent (< 15 days) acute MI; the presence of unstable disease not allowing the 4-week pretreatment before PTCA; culprit lesions in the left main coronary artery, in a saphenous vein bypass graft, or in a previously dilated site (restenotic lesions); excessive bleeding risk (recent peptic ulcer or gastrointestinal bleeding, platelet count < 100,000/μL, and arterial hypertension not responsive to medical treatment); contraindication to omega-3 fatty acids (such as allergy or hypersensitivity to fish products); requirement for anticoagulant therapy; presence of significant hepatic or renal disease; concomitant disease associated with limited life expectancy; drug or alcohol abuse; or other factors (geographic location or language barriers) possibly precluding follow-up</p> <p>Sample size: 339 participants (total population), 7 participants with history of stroke and/or TIA</p> <p>Participants randomised to intervention group (only stroke and/or TIA population): 3 (analysed, not stated if more were randomised)</p> <p>Participants randomised to control group (only stroke and/or TIA population): 4 (analysed, not stated if more were randomised)</p> <p>Sex (only stroke and/or TIA population): not stated</p> <p>Age (only stroke and/or TIA population): not stated</p> |

| | |
|---------------|---|
| | <p>Time from event (stroke or TIA) to start of intervention: not stated Type of baseline stroke: not stated Country: Italy Ethnicity: not stated</p> |
| Interventions | <p>Comparison groups: marine-derived n-3 PUFAs versus placebo Intervention: Esapent capsules of ethyl ester ω-3 fatty acids concentrates, each containing 85% pure EPA, 50% and DHA, 35%, with 3 mg vitamin E. At a dose of 6 capsules/day for 2 months (starting 1 month before PTCA) and subsequently reduced to 3 capsules/day until the end of follow-up (further 5 months) Control: identically appearing olive oil placebo capsules, with 3 mg vitamin E. Same dose as intervention Compliance: plasma fatty acids evaluation Duration of intervention: 7 months Co-interventions: either aspirin (100 to 500 mg/day) or indobufen (400 mg/day) beginning at least 48 hours before PTCA. Nitrates and anticoagulation with 10,000 IU IV heparin at the start of the PTCA procedure. Heparin administration was subsequently adjusted with 1 or more further boluses or infusion in order to maintain the activated clotting time at > 300 seconds and was then tapered off at least 4 hours before sheath removal and up to 24 hours post-PTCA. After PTCA, either aspirin or indobufen for at least 15 days. Other treatments, such as calcium antagonists, β-blockers, and nitrates were discretionary</p> |
| Outcomes | <p>Primary outcome of study: post-PTCA restenosis Relevant review outcomes measured (in total population): vascular-related death, adverse events Available outcome data for stroke and/or TIA population only: none Latest time point of assessment: 7 months after start of intervention (6 months post-PTCA) Withdrawals or exclusions, n (stroke and/or TIA population only): not available Study authors' contact status: replied, no further data available</p> |
| Notes | <p>Dietary information: none provided Funding: Pharmacia-Upjohn Italia SpA</p> |

Risk of bias

| Bias | Authors' judgement | Support for judgement |
|---|--------------------|---|
| Random sequence generation (selection bias) | Unclear risk | No information about random sequence generation |
| Allocation concealment (selection bias) | Unclear risk | No details about allocation process |
| Blinding of participants and personnel (performance bias) All outcomes | Unclear risk | Described as double-blind; however, no further information provided on blinding process |

ESPRIT (Continued)

| | | |
|---|--------------|---|
| Blinding of outcome assessment (detection bias) All outcomes | Unclear risk | No details about how relevant review outcomes (vascular-related death and adverse events) were determined or assessed |
| Incomplete outcome data (attrition bias) All outcomes | Low risk | Balanced intervention and control groups |
| Selective reporting (reporting bias) | Unclear risk | Protocol not available |
| Other bias | Low risk | None detected |

Farquharson 2011

| | |
|---------------|--|
| Methods | RCT; parallel; placebo-controlled Number of study sites: 1 Dates: study enrolment between April 2006 and December 2009 |
| Participants | Inclusion criteria: patients > 18 years of age who were accepted for cardiac surgery involving CABG and/or valve repair or replacement Exclusion criteria: previous diagnosis of AF or atrial flutter; antiarrhythmic drug use (class 1 or 3) within the previous 3 months; urgent surgery (< 3 weeks); New York Heart Association class IV heart failure; MI within previous 2 weeks; or any condition that might affect the ability to ingest or absorb dietary fat; patients who consumed dietary supplements rich in omega-3 oils, e.g. fish oil or flaxseed oil; or self-reported habitual consumption of ≥ 1 fish meal per week Sample size: 200 participants (total population), 9 participants with history of stroke Participants randomised to intervention group (only stroke population): 5 (analysed, not stated if more were randomised) Participants randomised to control group (only stroke population): 4 (analysed, not stated if more were randomised) Sex (only stroke population): not stated Age (only stroke population): not stated Time from event (stroke) to start of intervention: not stated Type of baseline stroke: not stated Country: Australia Ethnicity: not stated |
| Interventions | Comparison groups: fish oil versus control Intervention: oil supplied in liquid form (Melrose Laboratories, Pty. Ltd., Mitcham, Victoria, Australia), citrus flavoured. At a dose of 15 mL/day, providing EPA -2.7 g/day and DHA -1.9 g/day Control: Sunola oil supplied in liquid form (Melrose Laboratories, Pty Ltd, Mitcham, Victoria, Australia), citrus flavoured, at a dose of 15mL/day Compliance: fatty acid analysis in blood Duration of intervention: up to 4 weeks, commencing 3 weeks before scheduled surgery date until 6 days after surgery or until discharge (whichever came first) Co-interventions: N/A |

| | | |
|---|---|--|
| Outcomes | <p>Primary outcome of study: occurrence of sustained AF/atrial flutter (duration 10 minutes or requiring intervention) after cardiac surgery</p> <p>Relevant review outcomes measured (in total population): recurrent events (stroke), adverse events</p> <p>Available outcome data for stroke population only: none</p> <p>Latest time point of assessment: up to 4 weeks after start of intervention</p> <p>Withdrawals or exclusions, n (stroke population only): not available</p> <p>Study authors' contact status: no reply up to date</p> | |
| Notes | <p>Dietary information: exclusion of patients who consumed dietary supplements rich in omega-3 oils, e.g. fish oil or flaxseed oil, or self-reported habitual consumption of > 1 fish meal per week</p> <p>Funding: the National Health and Medical Research Council of Australia, Canberra, Australia; additionally, the National Heart Foundation of Australia (supporting Dr Sanders) and the National Health and Medical Research Council of Australia (supporting Dr Gibson)</p> | |
| Risk of bias | | |
| Bias | Authors' judgement | Support for judgement |
| Random sequence generation (selection bias) | Low risk | Quote: "Group assignment was based on a computer-generated randomization list using blocks of 20" |
| Allocation concealment (selection bias) | Unclear risk | Quote: "Individual allocation was by sealed envelope". Not stated who prepared the envelopes or description of the process |
| Blinding of participants and personnel (performance bias) All outcomes | Low risk | Quote: "Subjects, physicians, nurses, assessor and data analyst are blinded to treatment allocation" |
| Blinding of outcome assessment (detection bias) All outcomes | Low risk | Quote: "Subjects, physicians, nurses, assessor and data analyst are blinded to treatment allocation" |
| Incomplete outcome data (attrition bias) All outcomes | Low risk | Small and similar amount of participants lost after randomisation |
| Selective reporting (reporting bias) | Unclear risk | Protocol not available |
| Other bias | Low risk | None detected |

FAVORED

| | |
|---------------|---|
| Methods | RCT; parallel; placebo-controlled Number of study sites: 35 Dates: recruitment between 21 August 2008 and 28 February 2014. Last follow-up on 28 February 2015 |
| Participants | Inclusion criteria: adults (age > 19 years) with stage 4 or 5 chronic kidney disease receiving or planned to receive haemodialysis within 12 months and scheduled for AVF surgery in the arm Exclusion criteria: increased bleeding risk (bleeding disorder, recent or active gastrointestinal ulcer, platelet count < 100 × 10 ³ /μL, hepatic insufficiency); taking aspirin within 2 weeks or fish oil within 4 weeks of trial commencement; taking nonsteroidal anti-inflammatory drugs, anticoagulants, or antiplatelet agents; contraindications for taking the study agents. In June 2011, the exclusion criterion of current use of aspirin was removed so that participants currently taking aspirin were eligible for recruitment Sample size: 567 participants (total population), 17 participants with history of stroke Participants randomised to intervention group (only stroke population): 6 Participants randomised to control group (only stroke population): 11 Sex (only stroke population): not stated Age (only stroke population): not stated Time from event (stroke) to start of intervention: not stated Type of baseline stroke: not stated Country: Australia, Malaysia, New Zealand, and the UK Ethnicity: (total population information only). Fish oil group: Asian 92 (32%), White 144 (51%), Indigenous (Aboriginal, Torres Strait Islanders, Maori, and Pacific Islanders) 39 (14%), Other 9 (3%). Placebo group: Asian 89 (32%), White 154 (55%), Indigenous (Aboriginal, Torres Strait Islanders, Maori, and Pacific Islanders) 27 (10%), Other 11 (4%) |
| Interventions | Comparison groups: fish oil versus placebo. Participants not taking open-label aspirin were randomised also to aspirin (100 mg) or matching placebo Intervention: Omacor capsules, 4 g/day of omega-3 PUFAs (46% EPA and 38% DHA) Control: 4 g/day matching placebo capsules (olive oil) Compliance: capsule count at the week 12 visit. Centres in Australia and New Zealand additionally tested erythrocyte fatty acids levels Duration of intervention: 12 months Co-interventions: 100 mg/day of oral aspirin or matching placebo (for participants not taking open-label aspirin) |
| Outcomes | Primary outcome of study: fistula failure, a composite of fistula thrombosis and/or abandonment and/or cannulation failure Relevant review outcomes measured (in total population): adverse events Available outcome data for stroke population only: none Latest time point of assessment: 12 months Withdrawals or exclusions, n (stroke population only): not available Study authors' contact status: replied, no data provided |
| Notes | Dietary information: individuals taking fish oil within 4 weeks of trial commencement were excluded. No further information provided Funding: National Health and Medical Research Council of Australia Project Grant (APP458652), Amgen Australia Pty Ltd and Mylan EPD (at the time of funding was |

FAVoured (Continued)

| | Abbott Products Operations AG). Study medication supplied by Mylan EPD (at the time of supply was Abbott Products Operations AG) (fish oil and placebo) and Bayer Healthcare (aspirin and placebo) free of charge | |
|---|---|--|
| Risk of bias | | |
| Bias | Authors' judgement | Support for judgement |
| Random sequence generation (selection bias) | Low risk | Quote: "Randomisation was achieved using a minimisation method to balance treatments over two stratification factors: study site and AVF location (upper versus lower arm)" |
| Allocation concealment (selection bias) | Low risk | Quote: "Randomisation was performed by a central, web-based system (Flexetrial)" |
| Blinding of participants and personnel (performance bias) All outcomes | Low risk | Quote: "Participants, caregivers, treating physicians and surgeons, laboratory staff, and members of the study team were blinded to treatment allocation." |
| Blinding of outcome assessment (detection bias) All outcomes | Unclear risk | For the primary outcome assessment we consider low risk of bias, as per the following quote: "AVF Access Failure was assessed independently by two observers, each unaware of the participant's treatment assignment, treatment course or medical history". However, there is no indication of who was measuring/reporting adverse events (relevant outcome for this review) |
| Incomplete outcome data (attrition bias) All outcomes | Low risk | Participants excluded from analysis balanced among groups |
| Selective reporting (reporting bias) | Unclear risk | Adverse events in the protocol appear as secondary outcomes; however, in the results are given in separate table, rather than with the rest of the secondary outcomes and in a very general manner (no supplemental data). Tertiary outcomes (not relevant for the review) were not fully reported |
| Other bias | Low risk | None detected |

FOILS

| | |
|---------------------|--|
| Methods | RCT; parallel, placebo-controlled Number of study sites: 1 Dates: randomisation from 29 July 2004 to 23 December 2005. Last follow-up in March 2006 |
| Participants | Inclusion criteria: participants were aged > 45 years, clinically stable, and with a history of CT-confirmed first-ever or recurrent ischaemic stroke of probable noncardioembolic aetiology > 3 months before registration Exclusion criteria: intolerance/hypersensitivity to fish/fish oils; current use of fish oil supplements; malabsorptive bowel diseases; or participation in a concurrent clinical trial Sample size: 102 participants (total population, all with history of ischaemic stroke) Participants randomised to intervention group: 51 Participants randomised to control group: 51 Sex: fish oil = 41 men and 10 women, placebo oil = 31 men and 20 women Age, years (mean \pm SD): fish oil group = 64 \pm 10, placebo oil group = 65 \pm 12 Time from last event (ischaemic stroke) to start of intervention (median and IQR): fish oil group = 1.18 (0.5, 2.1) years, placebo oil group = 0.90 (0.5, 2.3) years Type of baseline stroke: ischaemic Country: New Zealand Ethnicity: not stated |
| Interventions | Comparison groups: fish oil versus placebo oil Intervention: 3 g/day (3 \times 1 g capsules) of fish oil (Hoki liver oil) supplement containing approximately 1.2 g/day total omega-3 PUFA Control: matching placebo (palm and soy oils), 3 g/day Compliance: capsule count and analysis of serum phospholipid fatty acid methyl esters Duration of intervention: 12 weeks Co-interventions: N/A |
| Outcomes | Primary outcome of study: change in serum triglycerides between baseline and 12 weeks Relevant review outcomes measured: vascular-related death (due to MI), quality of life, mood Available outcome data for stroke and/or TIA population only: vascular-related death (due to MI), quality of life, mood Latest time point of assessment: 12 weeks Withdrawals or exclusions, n (stroke and/or TIA population only): fish oil = 4 refused follow-up, placebo oil = 2 refused follow-up, 1 death. Data missing at follow-up were imputed using last value carried forward Study authors' contact status: replied, no data provided |
| Notes | Dietary information: participants advised to abstain from other fish oil supplements, and maintain their habitual diet Funding: The Health Research Council of New Zealand. The Maurice and Phyllis Paykel Trust, New Zealand (LDL particle size and fatty acid analyses). Sea Dragon, New Zealand, provided the fish oil and Nutrition Laboratories, New Zealand, provided the placebo treatment and encapsulated the oils |
| <i>Risk of bias</i> | |

FOILS (Continued)

| Bias | Authors' judgement | Support for judgement |
|---|--------------------|--|
| Random sequence generation (selection bias) | Low risk | Quote: "The randomization was a blocked (varying block sizes), unstratified design sequence." |
| Allocation concealment (selection bias) | Low risk | Quote: "Sequential allocation of packs to patients after confirmation of inclusion criteria [...] generated using an automated Internet-based system held at the Clinical Trials Research Unit, University of Auckland." |
| Blinding of participants and personnel (performance bias) All outcomes | Unclear risk | Quote: "Treatment packs blinded for treatment" |
| Blinding of outcome assessment (detection bias) All outcomes | Unclear risk | It does not state who assessed the outcomes |
| Incomplete outcome data (attrition bias) All outcomes | Low risk | Missing data imputed adequately. Participants lost to follow-up distributed evenly among groups |
| Selective reporting (reporting bias) | Unclear risk | Protocol not available |
| Other bias | Low risk | None detected |

Foroughinia 2018

| | |
|--------------|--|
| Methods | RCT; parallel, open label Number of study sites: 1 Dates: September to December 2016 (study stopped early) |
| Participants | Inclusion criteria: ischaemic stroke confirmed via a brain CT scan, or MRI; patients undergoing carotid stenting (more than 50% stenosis of the internal carotid artery in symptomatic patients, or 70% stenosis in asymptomatic patients); 18 to 80 years old Exclusion criteria: unsatisfactory carotid artery stenting; intraluminal thrombus over the stenosis; pretreatment with glycoprotein IIb/IIIa antagonists or bivalirudin; active bleeding; sensitivity or intolerance to aspirin or clopidogrel or omega-3; severe adverse effects to drugs; percutaneous intervention; surgery less than 30 days; patients with intracranial haemorrhage; cardio-aortic embolic strokes; lacunar infarcts; and non-atherosclerotic causes of carotid stenosis. Additionally: patients with mRS \geq 3; and patients who had contraindications for angiography Sample size: 18 participants (total population, all with history of ischaemic stroke) Participants randomised to intervention group: 8 Participants randomised to control group: 10 |

| | | |
|---|---|---|
| | <p>Sex: intervention = 4 men and 4 women, control = 5 men and 5 women Age, years (mean \pm SD and range): intervention = 75.2 \pm 6.2, range: 65 to 82; control: 71.7 \pm 6.8, range: 57 to 83 Time from event (ischaemic stroke) to start of intervention: not stated Type of baseline stroke: ischaemic Country: Iran Ethnicity: not stated</p> | |
| Interventions | <p>Comparison groups: marine-derived n-3 PUFAs (EPA and DHA) versus no intervention Intervention: 3000 mg loading dose of marine-derived n-3 PUFAs 12 hours before CAS. Providing 990 mg EPA and 660 mg DHA (Premium V Life Company, UK). *The abstract mentions a second dose of 1000 mg the day after the procedure (not mentioned elsewhere) Control: no intervention Compliance: N/A (1-time intervention) Duration of intervention: 1 loading dose (see above) Co-interventions: heparin (during CAS, 80 units per kilogram of body weight); clopidogrel (loading dose of 600 mg and 75 mg/day thereafter); and aspirin (loading dose of 325 mg and 80 mg/day thereafter)</p> | |
| Outcomes | <p>Primary outcome of study: composite outcome of any stroke, MI and/or mortality Relevant review outcomes measured (in total population): recurrent events (ischaemic stroke); incidence of other type of stroke (haemorrhagic stroke); adverse events Available outcome data for stroke and/or TIA population only: recurrent events (ischaemic stroke); incidence of other type of stroke (haemorrhagic stroke); adverse events Latest time point of assessment: 30 days after procedure (planned), actual time not stated Withdrawals or exclusions, n: none (study stopped) Study authors' contact status: no reply to date</p> | |
| Notes | <p>Dietary information: none provided Funding: Office of Vice Chancellor for Research in Shiraz University of Medical Sciences, Shiraz, Iran</p> | |
| <i>Risk of bias</i> | | |
| Bias | Authors' judgement | Support for judgement |
| Random sequence generation (selection bias) | Low risk | Computer-generated sequence |
| Allocation concealment (selection bias) | Unclear risk | They report that the statistician was blinded but they did not specify who allocated the participants |
| Blinding of participants and personnel (performance bias) All outcomes | High risk | Quote: "Only analysts are blinded in this study" |

| | | |
|---|--------------|--|
| Blinding of outcome assessment (detection bias) All outcomes | High risk | Quote: “Only analysts are blinded in this study” |
| Incomplete outcome data (attrition bias) All outcomes | Low risk | Data provided for all the participants enrolled up to early termination of study |
| Selective reporting (reporting bias) | Unclear risk | Death and MI not reported, unclear if there were no cases or if data are missing |
| Other bias | Low risk | None detected |

FORWARD

| | |
|---------------|--|
| Methods | RCT; parallel, placebo-controlled. Number of study sites: 42 Dates: recruitment from January 2008 to March 2011. Last follow-up on February 2012 |
| Participants | Inclusion criteria: patients must have either (1) at least 2 symptomatic episodes of documented AF in the previous 6 months before randomisation, with the last episode occurring in the 14 to 90 days before randomisation (paroxysmal AF), or (2) successful electrical or pharmacologic cardioversion for persistent AF performed in the 14 to 28 days before randomisation. All participants < 65 years of age must present with at least 1 of the following characteristics of moderate-to-high risk of stroke: heart failure (New York Heart Association (NYHA) I to III) or documented ejection fraction < 40%, type II diabetes mellitus, coronary artery disease, peripheral vascular disease, hypertension, previous TIA or stroke Exclusion criteria: contraindications for use n-3 PUFA; heart failure in NYHA class IV; acute coronary syndromes, coronary artery bypass surgery, or valve replacement within the past 3 months; clinically significant valvular disease; known diagnosis of Wolff-Parkinson-White; planned or recent (< 6 months) implantation of pacemaker and/or implantable cardio-defibrillator; planned or recent (< 6 months) ablative treatment for AF; any arrhythmia associated with an acute reversible condition (thyroid dysfunction, hypoxia, anaemia, others); advanced chronic lung disease and pregnancy or lactation Sample size: 586 participants (total population), 27 participants with history of stroke Participants randomised to intervention group (only stroke population): 14 Participants randomised to control group (only stroke population): 13 Sex (only stroke population): not stated Age (only stroke population): not stated Time from event (stroke to start of intervention): not stated Type of baseline stroke: not stated Country: Argentina Ethnicity: not stated |
| Interventions | Comparison groups: marine-derived n-3 PUFAs versus placebo Intervention: capsules containing 1 g/day of marine-derived n-3 PUFAs (850 to 882 mg EpA/DHA ethyl esters) Control: 1 g/day of olive oil (matching odour and fishy aftertaste) |

| | | |
|---|--|--|
| | Compliance: method not described, only time points (2, 4, 8 and 12 months after randomisation) Duration of intervention: 12 months Co-interventions: treatment prescribed for AF (anticoagulants, antiplatelet agents, antiarrhythmics (amiodarone or others), β -blockers, calcium-channel blockers, or other therapies as needed) | |
| Outcomes | Primary outcome of study: time to first recurrence of an AF episode of symptomatic or asymptomatic AF (documented by a 12-lead electrocardiogram) Relevant review outcomes measured (in total population): stroke, adverse events Available outcome data for stroke population only: none Latest time point of assessment: 12 months Withdrawals or exclusions, n (stroke population only): not available Study authors' contact status: no reply to date | |
| Notes | Dietary information: quote "It should be acknowledged as a limitation that we did not track fish consumption among participants. It could be that high fish intake might have mitigated the effect of oral supplementation. Although this is possible, it should also be noted that fish intake is low-to-very-low in Argentina" Funding: SPA and Sigma Tau | |
| Risk of bias | | |
| Bias | Authors' judgement | Support for judgement |
| Random sequence generation (selection bias) | Unclear risk | No details on random sequence generation |
| Allocation concealment (selection bias) | Low risk | Quote: "participants are centrally assigned. . . each study site will be supplied with study drug and placebo in identically appearing packaging" |
| Blinding of participants and personnel (performance bias) All outcomes | Low risk | Quote: "Patients, investigator staff, persons performing the assessments, and data analysts will remain blind to the identity of the treatment from the time of randomization until database lock" |
| Blinding of outcome assessment (detection bias) All outcomes | Low risk | Quote: "Patients, investigator staff, persons performing the assessments, and data analysts will remain blind to the identity of the treatment from the time of randomization until database lock" |
| Incomplete outcome data (attrition bias) All outcomes | Unclear risk | Fewer participants randomised to intervention group |

| | | |
|--------------------------------------|--------------|--|
| Selective reporting (reporting bias) | Low risk | Rationale published before randomisation finished, all outcomes reported |
| Other bias | Unclear risk | Trial stopped before reaching number of volunteers originally sought |

Gammelmark 2012

| | |
|---------------|---|
| Methods | RCT; parallel; placebo-controlled Number of study sites: 1 Dates: between April and December 2009 |
| Participants | Inclusion criteria: participants (age 30 to 75 years) with a waist circumference of more than 80 cm in women or more than 94 cm in men, according to the World Health Organization definition of abdominal obesity in a European population. Women had to be postmenopausal and not receiving hormone replacement therapy Exclusion criteria: taking anti-inflammatory drugs other than low-dose acetylsalicylic acid; chronic or acute inflammatory condition; dysregulated DM (HbA1c > 8%); malignant disease; chronic alcoholism; or severe renal insufficiency (glomerular filtration rate < 30 mL/min). People taking fish oil supplements before inclusion were required to stop the supplements for at least 12 weeks before inclusion Sample size: 50 participants (total population), 4 participants with history of stroke Participants randomised to intervention group (only stroke population): 2 Participants randomised to control group (only stroke population): 2 Sex (only stroke population): not stated Age (only stroke population): not stated Time from event (stroke or TIA) to start of intervention: not stated Type of baseline stroke: not stated Country: Denmark Ethnicity: not stated |
| Interventions | Comparison groups: marine-derived n-3 PUFAs versus placebo Intervention: 2 g/day of fish oil (640 mg of EPA and 480 mg of DHA) Control: 2 g/day of olive oil (similarity to intervention not stated) Compliance: fatty acid composition assessed (granulocytes and adipose tissue) Duration of intervention: 6 weeks Co-interventions: N/A |
| Outcomes | Primary outcome of study: inflammatory markers Relevant review outcomes measured (in total population): adverse events Available outcome data for stroke and/or TIA population only: none Latest time point of assessment: 6 weeks Withdrawals or exclusions, n (stroke and/or TIA population only): not stated Study authors' contact status: no reply to date |
| Notes | Dietary information: the frequency and amount of fish intake (fatty and lean fish) were reported at baseline. Daily intake of n-3 PUFAs was calculated using tabulated values. Participants advised to maintain their regular diet throughout the study |

Gammelmark 2012 (Continued)

| Funding: Spar Nord Foundation, the Obelske Family Foundation and Heinrich Kopp's Grant. Capsules supplied by Napro Pharma, Brattvaag, Norway | | |
|--|--------------------|---|
| Risk of bias | | |
| Bias | Authors' judgement | Support for judgement |
| Random sequence generation (selection bias) | Unclear risk | No details about random sequence generation provided |
| Allocation concealment (selection bias) | Unclear risk | No information about allocation process |
| Blinding of participants and personnel (performance bias) All outcomes | Unclear risk | The study is described as "double blind"; however, no details provided |
| Blinding of outcome assessment (detection bias) All outcomes | Unclear risk | Assessment of adverse events not described |
| Incomplete outcome data (attrition bias) All outcomes | Low risk | Participants balanced across groups |
| Selective reporting (reporting bias) | Unclear risk | Protocol not available |
| Other bias | Unclear risk | It is not stated if the participant that dropped out was included in the analysis. Tables of outcomes do not indicate sample size |

GISSI HF

| | |
|--------------|--|
| Methods | RCT; parallel; placebo-controlled Number of study sites: 357 Dates: randomisation between 6 August 2002 and 28 February 2005. Follow-up concluded on 31 March 2008 |
| Participants | Inclusion criteria: men and women aged 18 years or older, with clinical evidence of heart failure of any cause that was classified according to the European Society of Cardiology guidelines as New York Heart Association (NYHA) class II-IV, provided that they had had their LVEF measured within 3 months before enrolment. When LVEF was greater than 40%, the patient had to have been admitted at least once to hospital for heart failure in the preceding year to meet the inclusion criteria Exclusion criteria: specific indication or contraindication to n-3 PUFA; known hypersensitivity to study treatments; presence of any non-cardiac comorbidity (e.g. cancer) that was unlikely to be compatible with a sufficiently long follow-up; treatment with any investigational agent within 1 month before randomisation; acute coronary syndrome or revascularisation procedure within the preceding 1 month; planned cardiac surgery, expected to be done within 3 months after randomisation; significant liver disease; and |

| | |
|---------------|--|
| | <p>pregnant or lactating women or women of childbearing potential who were not adequately protected against becoming pregnant; conditions that in the opinion of the investigator would be associated with poor adherence to the protocol; background therapy including: (1) for randomisation to n-3 PUFA, an ongoing post-MI treatment with n-3 PUFA; (2) for randomisation to rosuvastatin, lipid-lowering therapy with statins</p> <p>Sample size: 6975 participants (total population), 346 participants with history of stroke</p> <p>Participants randomised to intervention group (only stroke population): 168</p> <p>Participants randomised to control group (only stroke population): 178</p> <p>Sex (only stroke population): marine-derived n-3 PUFAs group = 130 men and 38 women; placebo = 145 men and 33 women</p> <p>Age, years (only stroke population) mean \pm SD: marine-derived n-3 PUFAs group = 71 \pm 8; placebo = 70 \pm 9</p> <p>Time from event (stroke) to start of intervention: not stated</p> <p>Type of baseline stroke: not stated</p> <p>Country: Italy</p> <p>Ethnicity: not stated</p> |
| Interventions | <p>Comparison groups: marine-derived n-3 PUFAs versus placebo. Participants without specific indications or contraindications to statins were further randomised to rosuvastatin or corresponding placebo</p> <p>Intervention: 1 capsule per day of 1 g marine-derived n-3 PUFAs (850 to 882 mg EPA and DHA as ethyl esters in the average ratio of 1:1.2)</p> <p>Control: matching placebo (no further details)</p> <p>Compliance: a participant was regarded as compliant to the treatment if the study drug was administered for at least 80% of the days of observation</p> <p>Duration of intervention: median of 3.9 years (IQR 3.0 to 4.5)</p> <p>Co-interventions: participants also randomised to rosuvastatin (10 mg/day) or corresponding placebo</p> |
| Outcomes | <p>Primary outcome of study: time to death, and time to death or admission to hospital for cardiovascular reasons</p> <p>Relevant review outcomes measured (in total population): vascular-related death; recurrent events; adverse events</p> <p>Available outcome data for stroke population only: vascular-related death; recurrent events (stroke)</p> <p>Latest time point of assessment: median of 3.9 years (IQR 3.0 to 4.5)</p> <p>Withdrawals or exclusions, n (stroke population only): not available</p> <p>Study authors' contact status: replied, data provided</p> |
| Notes | <p>Dietary information: treatment with n-3 PUFA was part of exclusion criteria. Further data not provided for overall study; however, in a sub-study (51 centres) authors report the following (quote): "fish consumption was distributed between never consumers (25.6%), those consuming fish about once per week (36.3%), and those consuming fish 2 or more times per week (38.1%). Baseline levels of n-3 PUFA were positively associated with the frequency of fish consumption [...] There was no specific information on the consumption of types of fish such as oily fish, which have highest levels of EPA and DHA"</p> <p>Funding: pool of financial grants by the companies which are the owners and the suppliers of the study drugs (Pharmacia-Upjohn, Sigma-Tau, and Societa' Prodotti Antibiotici</p> |

GISSI HF (Continued)

| | | |
|---|--|--|
| | supply capsules containing 850 to 882 mg EPA/DHA ethyl esters; rosuvastatin is supplied by Astra-Zeneca) | |
| Risk of bias | | |
| Bias | Authors' judgement | Support for judgement |
| Random sequence generation (selection bias) | Low risk | Quote: "Computerised telephone randomization system" |
| Allocation concealment (selection bias) | Low risk | Quote: "Allocation of patients to treatment groups will be accomplished via a telephone call-in system, and centrally approved at the study Coordinating Centre" |
| Blinding of participants and personnel (performance bias) All outcomes | Low risk | Quote: "All patients and study personnel were blinded to treatment" |
| Blinding of outcome assessment (detection bias) All outcomes | Low risk | Quote: "All the events recorded in the study were adjudicated blindly by an ad-hoc committee on the basis of pre-agreed definitions and procedures" |
| Incomplete outcome data (attrition bias) All outcomes | Low risk | Participants discontinuing study treatment balanced across intervention and control groups |
| Selective reporting (reporting bias) | Low risk | Rationale published before randomisation period finished. All pre-specified outcomes were reported |
| Other bias | Low risk | None detected |

Green 1985

| | |
|--------------|---|
| Methods | RCT; cross-over; placebo-controlled Number of study sites: 1 Dates: not stated |
| Participants | Inclusion criteria: patients with completed stroke or TIAs Exclusion criteria: not stated Sample size: 18 participants (total population, all with history of ischaemic stroke or TIA) with 7 drop outs, all data provided only for the participants that completed the trial (n = 11) Participants randomised to intervention group: 4 on the first period, 7 on the second one Participants randomised to control group: 7 on the first period, 4 on the second one |

Green 1985 (Continued)

| | |
|---------------|--|
| | <p>Sex: 7 men, 4 women Age: range from 53 to 76 years Time from event (stroke or TIA) to start of intervention: not stated Type of baseline stroke: ischaemic Country: USA Ethnicity: not stated</p> |
| Interventions | <p>Comparison groups: MaxEPA versus placebo Intervention: 10 capsules were given daily in divided doses, 180 mg of EPA per capsule (10 mL of MaxEpa daily, i.e. 1.8 g/day of EPA) Control: 10 capsules of olive oil given daily Compliance: not stated Duration of intervention: 6 weeks Co-interventions: vitamin E, 100 mg per 100 g (added to each oil to prevent oxidation)</p> |
| Outcomes | <p>Primary outcome of study: effects on cholesterol, triglycerides, and platelet function Relevant review outcomes measured (in total population): adverse events Available outcome data for stroke and/or TIA population only: none Latest time point of assessment: 6 weeks (cross-over design: therefore 12 weeks of participation in total) Withdrawals or exclusions, n (stroke and/or TIA population only): 7 Study authors' contact status: replied, no further data available</p> |
| Notes | <p>Dietary information: participants remained on the diets prescribed by their attending physicians, and no changes occurred during the course of the study Funding: Seven Seas Health Care Limited provided the study medications</p> |

Risk of bias

| Bias | Authors' judgement | Support for judgement |
|---|--------------------|--|
| Random sequence generation (selection bias) | Low risk | Quote: "A table of random numbers was kept by the pharmacy" |
| Allocation concealment (selection bias) | Unclear risk | Quote: "The pharmacists dispensed either study medication or placebo based on this table". No information about allocation concealment |
| Blinding of participants and personnel (performance bias) All outcomes | Low risk | Quote: "The medications were packaged in opaque capsules". Intervention dispensed by pharmacist |
| Blinding of outcome assessment (detection bias) All outcomes | Unclear risk | It is not specified who is assessing outcomes or the stage at what the code was broken |
| Incomplete outcome data (attrition bias) All outcomes | High risk | High rate of dropouts (data not imputed) |

Green 1985 (Continued)

| | | |
|--------------------------------------|--------------|------------------------|
| Selective reporting (reporting bias) | Unclear risk | Protocol not available |
| Other bias | Low risk | None detected |

JELIS

| | |
|---------------|--|
| Methods | RCT; parallel, open label, blinded end point Number of study sites: multicentre study, number of sites not stated Dates: enrolment between November 1996 and November 1999. Last follow-up November 2004 |
| Participants | <p>Inclusion criteria: serum total cholesterol of 250 mg/dL or more; if taking antihyperlipidaemic drugs for more than 6 months, washout period of 4 weeks (8 weeks for probucol); men aged 40 to 75 years or women after menopause to 75 years; patients who have already received appropriate dietary advice</p> <p>Exclusion criteria: acute MI occurring within last 6 months; unstable angina pectoris; history or complication of serious heart disease (severe arrhythmia, heart failure, cardiac myopathy, valvular disease, congenital disease, etc.); receiving cardiovascular reconstruction within last 6 months; cerebrovascular disorders occurring within last 6 months; complication of serious hepatic disease or renal disease; malignant tumour; uncontrollable diabetes; hyperlipidaemia arising from the following diseases: nephrotic syndrome, hypothyroidism, Cushing's syndrome, secondary hyperlipidaemia due to other disease; hyperlipidaemia due to some drugs such as steroid hormone; haemorrhage (haemophilia, capillary fragility, gastrointestinal ulcer, urinary tract haemorrhage, haemoptysis, vitreous haemorrhage, etc.); haemorrhagic diathesis; hypersensitivity to the study drug formulation; patients intending to undergo surgery; patients judged to be inappropriate by the physician in charge</p> <p>Sample size: 18,645 participants (total population), 942 participants with history of stroke or TIA</p> <p>Participants randomised to intervention group (only stroke or TIA population): 485 (analysed, not stated if more were randomised)</p> <p>Participants randomised to control group (only stroke or TIA population): 457 (analysed, not stated if more were randomised)</p> <p>Sex (only stroke or TIA population): no EPA group = 180 men and 277 women, EPA group = 189 men and 296 women</p> <p>Age, years (only stroke or TIA population) mean \pm SD: no EPA group = 65 \pm 7, EPA group = 66 \pm 7</p> <p>Time from event (stroke or TIA) to start of intervention: not stated, at least 6 months (as per exclusion criteria)</p> <p>Type of baseline stroke: both ischaemic and haemorrhagic (cerebral thrombosis n = 467; cerebral embolism n = 150; TIA n = 86; cerebral haemorrhage n = 80; subarachnoid haemorrhage n = 38; unknown n = 121)</p> <p>Country: Japan</p> <p>Ethnicity: Japanese</p> |
| Interventions | <p>Comparison groups: EPA versus no EPA</p> <p>Intervention: EPADEL capsules containing 300 mg of highly (> 98%) purified EPA ethyl ester per capsule. Total daily dose of 1800 mg</p> |

| | | |
|---|---|--|
| | <p>Control: no intervention (open label) Compliance: process not described. Quote: "Local physicians monitored compliance [.] at every clinic visit" Duration of intervention: maximum of 5 years Co-interventions: either pravastatin (10 to 20 mg/day); or simvastatin (5 to 10 mg/day)</p> | |
| Outcomes | <p>Primary outcome of study: major coronary events Relevant review outcomes measured (in total population): vascular-related death; recurrent events; adverse events Available outcome data for stroke and/or TIA population only: recurrent events Latest time point of assessment: mean 4.6 years (SD 1.1) Withdrawals or exclusions, n (stroke and/or TIA population only): not available Study authors' contact status: no reply to date</p> | |
| Notes | <p>Dietary information: participants received "appropriate" dietary advice, no details provided Funding: Mochida Pharmaceutical Co Ltd, Tokyo, Japan</p> | |
| Risk of bias | | |
| Bias | Authors' judgement | Support for judgement |
| Random sequence generation (selection bias) | Low risk | Quote: "We used a permuted block randomization with a block size of 4. Multiple blocks were assigned according to the number of participants enrolled at each centre. Stratification was based on the prevention stratum (primary or secondary)." |
| Allocation concealment (selection bias) | Low risk | Quote: "The results of the randomization scheme were concealed to the investigators and participants" |
| Blinding of participants and personnel (performance bias) All outcomes | High risk | Open label study |
| Blinding of outcome assessment (detection bias) All outcomes | Low risk | Quote: "Clinical end points are ascertained once a year by the Endpoints Adjudication Committee: expert cardiologists and neurologists who are blinded to the assigned groups. However, the assessment of the end points is performed without breaking a key code, by a blinded-end point approach." |
| Incomplete outcome data (attrition bias) All outcomes | Unclear risk | In total population (no only stroke subsample), considerably more participants withdrew consent in intervention group. Insufficient information about discrepancy |

JELIS (Continued)

| | | |
|--------------------------------------|--------------|--|
| | | reasons and stroke population specifically |
| Selective reporting (reporting bias) | Unclear risk | No protocol available. Rationale published after randomisation period finished |
| Other bias | Low risk | None detected |

Nosaka 2017

| | |
|---------------|--|
| Methods | RCT; parallel; open label. Number of study sites: 1 Dates: recruiting between November 2010 and March 2014 Note: 115 participants from this study overlapped with another included trial (Doi 2014); however, none of them are contributing data to the review |
| Participants | Inclusion criteria: acute coronary syndrome patients treated with percutaneous coronary intervention Exclusion criteria: cardiogenic shock; severe renal insufficiency requiring dialysis; cardiopulmonary arrest; emergent coronary artery bypass; failure of PCI; and expected prognosis less than 1 year because of cancer Sample size: 241 participants (total population), 23 participants with history of stroke Participants randomised to intervention group (only stroke population): 8 (analysed, not stated if more were randomised) Participants randomised to control group (only stroke population): 15 Sex (only stroke population): not stated Age (only stroke population): not stated Time from event (stroke) to start of intervention: not stated Type of baseline stroke: not stated Country: Japan Ethnicity: not stated |
| Interventions | Comparison groups: EPA versus no EPA Intervention: highly (> 98%) purified EPA ethyl ester (ethyl all cis-5,8,11,14,17-icosapentaenoate), at a dose of 1800 mg Control: no placebo Compliance: not stated Duration of intervention: at least 52 weeks Co-interventions: pitavastatin 2 mg/day started within 24 hours after PCI for at least 52 weeks |
| Outcomes | Primary outcome of study: cardiovascular events after acute coronary syndrome Relevant review outcomes measured (in total population): vascular-related death, recurrent events, adverse events Available outcome data for stroke population only: none Latest time point of assessment: 12 months Withdrawals or exclusions, n (stroke population only): not available Study authors' contact status: no reply to date |

| | | |
|---|--|---|
| Notes | Dietary information: not provided Funding: Mochida Pharmaceutical Co, Ltd (speaker honoraria) | |
| Risk of bias | | |
| Bias | Authors' judgement | Support for judgement |
| Random sequence generation (selection bias) | Low risk | Quote: "According to a computer-generated randomization plan that included stratification by gender and acute MI or unstable angina pectoris" |
| Allocation concealment (selection bias) | Unclear risk | Unclear if allocation was concealed |
| Blinding of participants and personnel (performance bias) All outcomes | High risk | Open label trial |
| Blinding of outcome assessment (detection bias) All outcomes | Low risk | Quote: "Diagnoses were confirmed by an investigator (M.I.), who was blind to treatment allocation." |
| Incomplete outcome data (attrition bias) All outcomes | Low risk | Small and similar amount of participants lost after randomisation |
| Selective reporting (reporting bias) | Unclear risk | Protocol not available |
| Other bias | Low risk | None detected |

NUTRISTROKE

| | |
|--------------|--|
| Methods | RCT; parallel; 2 × 2 factorial design Number of study sites: 1 Dates: between June 2004 and February 2006 |
| Participants | Inclusion criteria: first ischaemic stroke survivors admitted to rehabilitation unit Exclusion criteria: onset-admission interval > 60 days; haemorrhagic lesions and the presence of other chronic disabling pathologies and/or medical conditions that would contraindicate physical therapy; and inability or refusal to give consent Sample size: 72 participants (total population, all with history of stroke) Participants randomised to intervention group: 38 (marine-derived n-3 PUFAs and antioxidants + marine-derived n-3 PUFAs groups) Participants randomised to control group: 34 (antioxidants and placebo groups) Sex: antioxidants = 8 men and 8 women; marine-derived n-3 PUFAs = 15 men and 5 women; antioxidants + marine-derived n-3 PUFAs = 13 men and 5 women; placebo = 11 men and 7 women Age, years (article does not indicate if the variance is SD): antioxidants = 65.1 ± 12.8, marine-derived n-3 PUFAs = 61.3 ± 13.6, antioxidants + marine-derived n-3 PUFAs = |

| | |
|---------------|---|
| | <p>66.3 ± 11.4, placebo = 68.4 ± 12.6 Time from event (stroke) to start of intervention: less than 60 days (as per exclusion criteria) Type of baseline stroke: ischaemic Country: Italy Ethnicity: not stated</p> |
| Interventions | <p>Comparison groups: 4 groups: marine-derived n-3 PUFAs; marine-derived n-3 PUFAs + antioxidants; antioxidants; and placebo. This review collated the groups in 2: marine-derived n-3 PUFAs (including marine-derived n-3 PUFAs, and marine-derived n-3 PUFAs + antioxidants) versus no marine-derived n-3 PUFAs (antioxidants, and placebo) Intervention: gelatin capsules from fish oil, 500 mg n-3 PUFAs (250 mg DHA and 250 mg EPA) daily with or without antioxidants (290 mg vitamin E, 240 mg vitamin C, 150 mg polyphenols and 19 mg β-carotene) Control: placebo did not include polyunsaturated fatty acids; however, composition is not detailed Compliance: investigated every month by meetings or telephone interview with the participant, no further details Duration of intervention: 12 months Co-interventions: participants were also randomised to receive antioxidants or placebo (see above)</p> |
| Outcomes | <p>Primary outcome of study: functional status in post-stroke rehabilitation Relevant review outcomes measured (in total population): efficacy (measured by Barthel Index); vascular-related death Available outcome data for stroke and/or TIA population only: efficacy (measured by Barthel Index); vascular-related death Latest time point of assessment: 12 months Withdrawals or exclusions, n: 20 dropouts (including 4 deaths for cardiovascular events) Study authors' contact status: no reply to date</p> |
| Notes | <p>Dietary information: standardised diet for all participants. The nutritional characteristics of the standard diet were established to guarantee restoration and preservation of an optimal nutritional state and to meet energy and nutrient requirements. Specific meals were utilised during the hospitalised rehabilitation period and after the hospital discharge to continue the trial at home (menu Nutristroke). Fulfilment of nutritional needs was reached by increasing the amount of nutrients up to 125% of daily need and providing food of high nutritional density; as is usual in medical facilities, consumption of food is up to 75% of that provided. The meals proposed favoured foods rich in antioxidants and n-3 fatty acids. To verify compliance with the dietetic programme a precise weighing method was used, consisting of 5 surveys over the trial period (2 in the hospital and 3 at home), and each survey lasted a week. During hospitalisation, dietitians weighed and recorded all the food offered to participants before eating and leftovers after eating. Before discharge, participants or their caregivers were trained about the diet and the method of surveying discarded food Funding: Italian Ministry of Health (grant No. RF02.216-BS4B.5.4). Sigma-Tau Health Science, Rome provide n-3 supplements</p> |

Risk of bias

NUTRISTROKE (Continued)

| Bias | Authors' judgement | Support for judgement |
|---|--------------------|---|
| Random sequence generation (selection bias) | Unclear risk | Quote: "Enrolled patients were randomized, by means of a specific list". No information on how the list was generated |
| Allocation concealment (selection bias) | Unclear risk | No details about allocation process |
| Blinding of participants and personnel (performance bias) All outcomes | Low risk | Quote: "No patient, research assistant, investigator or any other medical or nursing staff could distinguish the placebo from the supplements during the study" |
| Blinding of outcome assessment (detection bias) All outcomes | Low risk | Quote: "The code was broken only after data recording had been completed" |
| Incomplete outcome data (attrition bias) All outcomes | Unclear risk | Small study size with big differences in numbers of people lost during follow-up between groups (attenuated after removing deaths) |
| Selective reporting (reporting bias) | Unclear risk | Neurological impairment outcome (not relevant for this review) measured by Canadian Neurological Scale was not reported by intervention group |
| Other bias | Unclear risk | Quote: "No side effects were registered". It does not explain if they were interrogated or not |

OCEAN

| | |
|--------------|--|
| Methods | RCT; parallel; placebo-controlled Number of study sites: 2 Dates: recruitment from March 2003 to December 2004 |
| Participants | Inclusion criteria: awaiting carotid endarterectomy; > 18 years of age; and ability to give written informed consent Exclusion criteria: regular consumption of more than 2 oily fish meals per week; use of fish oil or evening primrose oil supplements; being pregnant or breast feeding; participation in another clinical trial; or requiring surgery within 7 days Sample size: 121 participants (total population), data provided only for participants who completed the trial (n = 100), 85 participants with history of stroke and/or TIA (both within 6 months and more than 6 months prior to start of intervention, not clear if duplicates included) Participants randomised to intervention group (only stroke and/or TIA population): 38 (only participants who completed the trial, both within 6 months and more than 6 |

| | |
|---------------|--|
| | <p>months prior to start of intervention, not clear if duplicates included)</p> <p>Participants randomised to control group (only stroke and/or TIA population): 47 (only participants who completed the trial, both within 6 months and more than 6 months prior to start of intervention, not clear if duplicates included)</p> <p>Sex (only stroke and/or TIA population): not stated</p> <p>Age (only stroke and/or TIA population): not stated</p> <p>Time from event (stroke or TIA) to start of intervention: not stated</p> <p>Type of baseline stroke: not stated</p> <p>Country: UK</p> <p>Ethnicity: not stated</p> |
| Interventions | <p>Comparison groups: Marine-derived n-3 PUFAs ethyl esters versus placebo</p> <p>Intervention: Omacor capsules (approximately 888 mg EPA and 777 mg DHA per day)</p> <p>Control: olive oil capsules (providing 1.55 g of oleic acid per day)</p> <p>Compliance: returned capsules count</p> <p>Duration of intervention: median 21 days (range: 7 to 102 days)</p> <p>Co-interventions: N/A</p> |
| Outcomes | <p>Primary outcome of study: atherosclerotic plaque inflammation and stability</p> <p>Relevant review outcomes measured (in total population): none available</p> <p>Available outcome data for stroke and/or TIA population only: none</p> <p>Latest time point of assessment: median 21 days (range: 7 to 102 days)</p> <p>Withdrawals or exclusions, n (stroke and/or TIA population only): not available</p> <p>Study authors' contact status: replied, no data provided</p> |
| Notes | <p>Dietary information: exclusion of people with a regular consumption of more than 2 oily fish meals per week, as well as those using fish oil or evening primrose oil supplements.</p> <p>Participants were advised not to change their diet throughout the study</p> <p>Funding: study authors supported by grants from Pronova BioPharma AS and British Heart Foundation</p> |

Risk of bias

| Bias | Authors' judgement | Support for judgement |
|---|--------------------|--|
| Random sequence generation (selection bias) | Low risk | Quote: "Randomisation of patients to treatment group was according to a random number table and was performed by PronovaBioPharma" |
| Allocation concealment (selection bias) | Low risk | Quote: "All researchers were blind to treatment allocation. Capsules were provided in sealed containers" |
| Blinding of participants and personnel (performance bias) All outcomes | Low risk | Quote: "All researchers were blind to treatment allocation" Quote: "Capsules were identical in appearance" |

OCEAN (Continued)

| | | |
|---|--------------|---|
| Blinding of outcome assessment (detection bias) All outcomes | Unclear risk | Note: none of the study outcomes available is relevant for the review, no information about relevant outcomes detection |
| Incomplete outcome data (attrition bias) All outcomes | Unclear risk | Baseline information and outcome data provided only of participants who completed the trial. Slightly higher dropout rate in intervention group (no data imputed) |
| Selective reporting (reporting bias) | Unclear risk | Protocol not available |
| Other bias | Low risk | None detected |

OMEGA

| | |
|--------------|--|
| Methods | RCT; parallel, placebo-controlled Number of study sites: 104 Dates: recruitment between October 2003 and June 2007, 1 year of follow-up |
| Participants | <p>Inclusion criteria: male and female patients with a minimum age of 18 years; admitted to hospital for acute ST-elevation or non-ST-elevation MI; written informed consent to participate in the study. 75% of the included patients should have one or more of the following risk factors: age > 70 years, ejection fraction < 40%, diabetes or no reperfusion therapy</p> <p>Exclusion criteria: pre-menopausal woman, who were pregnant, nursing or not practising birth control, and women who did not agree pregnancy testing before participating in the study; known hypersensitivity to any component of the study drugs; patients with haemorrhagic diathesis; patients not willing to discontinue other medications containing fish oil; known or suspected non-compliance; legal incapacity and/or other circumstances rendering the patient unable to understand the study; refusal or withdrawal of the informed consent; history of drug or alcohol abuse within 6 months; any investigational therapy within 1 month of signing the informed consent; and any other clinical condition which would not allow safe completion of the protocol and administration of the study drugs</p> <p>Sample size: 3851 participants (total population), 209 participants with history of stroke</p> <p>Participants randomised to intervention group (only stroke population): 112 (intention-to-treat population)</p> <p>Participants randomised to control group (only stroke population): 97 (intention-to-treat population)</p> <p>Sex (only stroke population): not stated</p> <p>Age (only stroke population): not stated</p> <p>Time from event (stroke) to start of intervention: not stated</p> <p>Type of baseline stroke: not stated</p> <p>Country: Germany</p> <p>Ethnicity: not stated</p> |

| | |
|---------------|---|
| Interventions | <p>Comparison groups: marine-derived n-3 PUFAs ethyl esters versus placebo</p> <p>Intervention: 1 g/day of marine-derived n-3 PUFAs ethyl esters (460 mg of EPA and 380 mg of DHA)</p> <p>Control: 1 g/day of olive oil</p> <p>Compliance: 'returned capsules' count and blood concentrations of DHA and EPA at the end of the study</p> <p>Duration of intervention: 12 months</p> <p>Co-interventions: guideline-adjusted acute and chronic medication, reperfusion therapy (thrombolysis and/or PCI), concomitant hospital care, rehabilitation, bypass surgery or PCI during follow-up if indicated, and lifestyle changes and risk factor management</p> |
| Outcomes | <p>Primary outcome of study: rate of sudden cardiac death in participants who survived acute MI</p> <p>Relevant review outcomes measured (in total population): vascular-related death, recurrent events, adverse events, mood (depression, data not provided)</p> <p>Available outcome data for stroke population only: none</p> <p>Latest time point of assessment: 12 months</p> <p>Withdrawals or exclusions, n (stroke population only): not available</p> <p>Study authors' contact status: no reply to date</p> |
| Notes | <p>Dietary information: assessment of the individual fish consumption based on self-reports at the beginning of the study, at visit 2, and at the end of the study. Categories: no fish, occasionally, several times a week, daily</p> <p>Funding: Trommsdorff GmbH & Co. KG Arzneimittel, Alsdorf, Germany and Pronova Biocare, Lysaker, Norway</p> |

Risk of bias

| Bias | Authors' judgement | Support for judgement |
|---|--------------------|---|
| Random sequence generation (selection bias) | Low risk | Quote: "The randomization code for sequential treatment has been generated by allphamed PHARBIL, Göttingen, Germany" |
| Allocation concealment (selection bias) | Low risk | Quote: "Every container was labelled with a 4-digit number that concealed the actual treatment and was documented by the investigator on the patient's case report form." |
| Blinding of participants and personnel (performance bias) All outcomes | Low risk | Quote: "The appearance of the drugs or the drug containers did not allow patients and physicians to deduce the study arm." |
| Blinding of outcome assessment (detection bias) All outcomes | Unclear risk | Quote: "The randomization code remains unavailable for all investigators and all members of the clinical project team in- |

OMEGA (Continued)

| | | |
|--|-----------|--|
| | | cluding the trial monitors and the steering committee throughout the whole study.” |
| Incomplete outcome data (attrition bias) All outcomes | Low risk | Lost to follow-up balanced across groups |
| Selective reporting (reporting bias) | High risk | Depression, non-fatal resuscitation and re-hospitalisation not reported |
| Other bias | Low risk | None detected |

OMEGA PCI

| | |
|---------------|--|
| Methods | RCT; parallel; placebo-controlled Number of study sites: 1 Dates: not stated |
| Participants | Inclusion criteria: consecutive patients with stable coronary artery disease (age range 30 to 80 years) undergoing PCI with stent implantation Exclusion criteria: acute coronary syndrome; bleeding; concomitant chronic anticoagulant therapy; thienopyridine use before enrolment; platelet count < 100 x 10 ⁹ /L; serum creatinine > 177 μmol/L (2 mg/dL); and liver injury (alanine transaminase level > 1.5 times above the upper limit of the reference range) Sample size: 63 participants (total population), 19 participants with history of stroke or PAD (not reported separately) Participants randomised to intervention group (only stroke population): not stated Participants randomised to control group (only stroke population): not stated Sex (only stroke population): not stated Age (only stroke population): not stated Time from event (stroke) to start of intervention: not stated Type of baseline stroke: not stated Country: Poland Ethnicity: not stated |
| Interventions | Comparison groups: Omacor versus placebo Intervention: 1 g/day of marine-derived n-3 PUFAs ethyl esters (Omacor, 460 mg of EPA and 380 mg of DHA) Control: soybean oil capsules (no further details) Compliance: 'returned tablets' count Duration of intervention: 4 weeks Co-interventions: clopidogrel, 600 mg loading dose (12 hours before PCI), then, 75 mg/day. Aspirin 75 mg/day |
| Outcomes | Primary outcome of study: platelet responsiveness to dual antiplatelet therapy Relevant review outcomes measured (in total population): vascular-related death, adverse events Available outcome data for stroke population only: none Latest time point of assessment: 4 weeks Withdrawals or exclusions, n (stroke population only): not available |

OMEGA PCI (Continued)

| | |
|-------|--|
| | Study authors' contact status: no reply to date |
| Notes | <p>Dietary information: baseline fish consumption was similar in both groups. Participants were asked to comply with a diet recommended by European Society of Cardiology that encouraged increased consumption of oily fish</p> <p>Funding: The Ministry of Science and Higher Education of Poland (N402 095 31/2947 to G.G.) and the Foundation "Helping the Heart" at the Department of Coronary Disease, Jagiellonian University School of Medicine (SKC1 to Dr Gajos)</p> |

Risk of bias

| Bias | Authors' judgement | Support for judgement |
|---|--------------------|--|
| Random sequence generation (selection bias) | Low risk | Quote: "Patients were then randomized in the 1:1 ratio using computerized random-number generation " |
| Allocation concealment (selection bias) | Low risk | Allocation performed by an independent investigator on a double-blind basis |
| Blinding of participants and personnel (performance bias) All outcomes | Low risk | Double-blind study |
| Blinding of outcome assessment (detection bias) All outcomes | Unclear risk | Not clearly stated if assessors were blinded |
| Incomplete outcome data (attrition bias) All outcomes | Low risk | Participants balanced across intervention and control groups |
| Selective reporting (reporting bias) | Unclear risk | Protocol not available |
| Other bias | Low risk | None detected |

OPACH

| | |
|--------------|---|
| Methods | <p>RCT; parallel; placebo-controlled</p> <p>Number of study sites: 11</p> <p>Dates: enrolment between November 2002 and May 2003. Median follow-up of 558 days</p> |
| Participants | <p>Inclusion criteria: established CVD (defined as previously documented MI, angina pectoris, angiographically documented coronary atherosclerosis, stroke, TIA, or PAD) and treatment with stable haemodialysis for at least 6 months</p> <p>Exclusion criteria: participation in other clinical trials; active malignant disease; and known poor compliance</p> <p>Sample size: 206 participants (total population), 85 participants with history of stroke</p> |

| | |
|---------------|---|
| | <p>and/or TIA</p> <p>Participants randomised to intervention group (only stroke and/or TIA population): 41</p> <p>Participants randomised to control group (only stroke and/or TIA population): 44</p> <p>Sex (only stroke and/or TIA population): not stated</p> <p>Age (only stroke and/or TIA population): not stated</p> <p>Time from event (stroke or TIA) to start of intervention: not stated</p> <p>Type of baseline stroke: not stated</p> <p>Country: Denmark</p> <p>Ethnicity: not stated</p> |
| Interventions | <p>Comparison groups: marine-derived n-3 PUFAs versus placebo</p> <p>Intervention: Omacor (marine-derived n-3 PUFAs ethyl esters). 1.7 g/day of n-3 PUFAs</p> <p>Control: olive oil (2 capsules per day, containing 77% oleic acid)</p> <p>Compliance: serum phospholipid fatty acid composition</p> <p>Duration of intervention: 2 years or until reaching a study primary endpoint (median of 558 days, range 219 to 730 days)</p> <p>Co-interventions: N/A</p> |
| Outcomes | <p>Primary outcome of study: a composite of acute MI, angina pectoris that required coronary investigation or intervention, stroke, TIA, peripheral vascular disease that required surgical intervention, or death</p> <p>Relevant review outcomes measured (in total population): vascular-related death, recurrent events (stroke/TIA), and adverse events</p> <p>Available outcome data for stroke and/or TIA population only: none</p> <p>Latest time point of assessment: median 558 days (range 219 to 730 days)</p> <p>Withdrawals or exclusions, n (stroke and/or TIA population only): not available</p> <p>Study authors' contact status: no reply to date</p> |
| Notes | <p>Dietary information: participants evaluated their habitual intake of fish at lunch and dinner and were scored 1 to 6 points for each meal, with 1 point = "never eating fish"; 2 points = "eating fish once a month"; 3 points = "eating fish 2-3 times a month"; 4 points = "eating fish once a week"; 5 points = "eating fish 2-3 times a week"; and 6 points = "eating fish at least once daily". For further analysis, the score for each meal was summed, and patients were divided into 3 groups according to a low fish intake (scores 2 to 5), a moderate fish intake (scores 6 to 8), and a high fish intake (scores 9 to 12)</p> <p>Funding: The Danish Heart Foundation, The Danish Kidney Foundation, the Research Foundation of the County of Northern Jutland, and Pronova Biocare</p> |

Risk of bias

| Bias | Authors' judgement | Support for judgement |
|---|--------------------|---|
| Random sequence generation (selection bias) | Low risk | Quote: "Randomization was performed using an allocation sequence that was generated by computer at an independent firm, GM pack (Hadsund, Denmark), who also packed and delivered the capsules" |

OPACH (Continued)

| | | |
|---|--------------|--|
| Allocation concealment (selection bias) | Unclear risk | Quote: “The allocation sequence was kept at GM pack” |
| Blinding of participants and personnel (performance bias) All outcomes | Low risk | Quote: “All participants, investigators, care providers, and data monitors were blinded, according to treatment, throughout the study. The investigators did not have access to the allocation sequence until the database was closed in September 2005” |
| Blinding of outcome assessment (detection bias) All outcomes | Unclear risk | Quote: “A clinical end point committee, whose members were blinded to treatment, evaluated all end points” |
| Incomplete outcome data (attrition bias) All outcomes | Low risk | Withdrawals similar across groups |
| Selective reporting (reporting bias) | Unclear risk | Protocol not available |
| Other bias | Low risk | None detected |

OPAL

| | |
|--------------|---|
| Methods | RCT; parallel; placebo-controlled Number of study sites: 20 Dates: randomisation between April 2005 and March 2006, 24 months follow-up |
| Participants | Inclusion criteria: healthy, cognitively-normal adults aged 70 to 79 years Exclusion criteria: individuals currently diagnosed with either diabetes (Type I or Type II) or dementia; individuals not deemed suitable to take part in the study (e.g. recent bereavement, terminal illness) were excluded at the discretion of general practitioner at site; current daily use of fish-oil supplements; participants with an MMSE score of less than 24 (out of a maximum of 30) Sample size: 867 participants (total population), 19 participants with history of stroke Participants randomised to intervention group (only stroke population): 10 Participants randomised to control group (only stroke population): 9 Sex (only stroke population): intervention group = 6 men and 4 women, control group = 4 men and 5 women Age, years \pm SD (only stroke population): intervention group = 75.16 \pm 2.65, control group = 75.04 \pm 3.17 Time from event (stroke) to start of intervention: not stated Type of baseline stroke: not stated Country: UK Ethnicity: not stated |

| | |
|---------------|---|
| Interventions | <p>Comparison groups: marine-derived n-3 PUFAs versus placebo</p> <p>Intervention: 700 mg/day of marine-derived n-3 PUFAs ethyl esters (200 mg of EPA and 500 mg of DHA)</p> <p>Control: olive oil (capsules)</p> <p>Compliance: count of capsules, and serum fatty acid concentrations (ethical approval obtained on May 2007)</p> <p>Duration of intervention: 24 months</p> <p>Co-interventions: N/A</p> |
| Outcomes | <p>Primary outcome of study: cognitive function</p> <p>Relevant review outcomes measured (in total population): vascular-related death; recurrent events; adverse events; mood (psychological health assessed by general health questionnaire)</p> <p>Available outcome data for stroke and/or TIA population only: vascular-related death; recurrent events; mood (psychological health assessed by General Health Questionnaire)</p> <p>Latest time point of assessment: 24 months</p> <p>Withdrawals or exclusions, n (stroke population only): intervention group = 1, control group = 4</p> <p>Study authors' contact status: replied, data provided</p> |
| Notes | <p>Dietary information: habitual fish consumption information was collected at baseline. Categories: once a month or less; once a week/fortnight, mainly white; more than once a week, mainly white; once a week/fortnight, mainly oily; more than once a week, mainly oily</p> <p>Funding: UK Food Standards Agency (NO5053) and the UK National Health Service Research and Development</p> |

Risk of bias

| Bias | Authors' judgement | Support for judgement |
|---|--------------------|--|
| Random sequence generation (selection bias) | Low risk | Quote: "Research nurses telephoned a central computerized randomization service to obtain treatment-allocation codes previously generated by the trial statistician" |
| Allocation concealment (selection bias) | Low risk | Quote: "Supplements were packaged into identical pots, each containing 180 capsules, and labelled by staff who were not involved in the study" |
| Blinding of participants and personnel (performance bias) All outcomes | Low risk | Quote: "Supplements were packaged into identical pots, each containing 180 capsules, and labelled by staff who were not involved in the study" |
| Blinding of outcome assessment (detection bias) | Low risk | Quote: "All project staff were unaware of group assignments until the completion of |

OPAL (Continued)

| | | |
|--|-----------|---|
| All outcomes | | the trial and after data analysis.” |
| Incomplete outcome data (attrition bias) All outcomes | Low risk | Participants withdrawing from study balanced across intervention and control groups |
| Selective reporting (reporting bias) | High risk | Some data not shown (psychological health, secondary outcome) in original publication, provided when requested to authors |
| Other bias | Low risk | None detected |

Rantanen 2018

| | |
|---------------|--|
| Methods | Design: RCT; parallel; placebo-controlled Number of study sites: 3 Dates: between June 2014 and March 2016 |
| Participants | Inclusion criteria: dialysis treatment for > 3 months and age > 18 years Exclusion criteria: pregnancy; expected life expectancy < 3 months; inability to give informed consent; known allergy to contents of the supplemental capsules; and expected inability to comply with study protocol Sample size: 112 participants (total population), 31 participants with history of stroke and/or TIA Participants randomised to intervention group (only stroke/TIA population): 18 Participants randomised to control group (only stroke/TIA population): 13 Sex (only stroke/TIA population): not stated Age (only stroke/TIA population): not stated Time from event (stroke or TIA) to start of intervention: not stated Type of baseline stroke: ischaemic, haemorrhagic and/or TIA Country: Denmark Ethnicity: not stated |
| Interventions | Comparison groups: marine-derived n-3 PUFAs versus placebo Intervention: 2 g/day of marine-derived n-3 PUFAs (1 g of EPA and 1 g of DHA) Control: olive oil (capsules) Compliance: count of capsules, and n-3 PUFA content in plasma phospholipids Duration of intervention: 3 months Co-interventions: N/A |
| Outcomes | Primary outcome of study: effect on heart rate variability Relevant review outcomes measured (in total population): adverse events Available outcome data for stroke and/or TIA population only: none Latest time point of assessment: 3 months Withdrawals or exclusions, n (stroke/TIA population only): not available Study authors' contact status: no reply to date |

| | |
|-------|---|
| Notes | Dietary information: fish consumption, evaluated by a questionnaire, was similar at baseline and did not change during the study period Funding: The Danish Council for Strategic Research-(AF Study Group), The Arvid Nilsson Foundation, The Danish Kidney Association, The Danish Society of Nephrology, and Medical Specialist Heinrich Kopp's Grant Supplement provided free of charge by Pharma Marine, Norway |
|-------|---|

Risk of bias

| Bias | Authors' judgement | Support for judgement |
|---|--------------------|--|
| Random sequence generation (selection bias) | Low risk | Quote: "A computer-generated permuted block randomization determined the allocation sequence" |
| Allocation concealment (selection bias) | Unclear risk | No details about process of allocation |
| Blinding of participants and personnel (performance bias) All outcomes | Low risk | Quote: "Patients, investigators and study personal were blinded to the allocation until the trial and all the analyses were completed" |
| Blinding of outcome assessment (detection bias) All outcomes | Low risk | Quote: "Patients, investigators and study personal were blinded to the allocation until the trial and all the analyses were completed" |
| Incomplete outcome data (attrition bias) All outcomes | Low risk | Similar amount of dropouts in both groups |
| Selective reporting (reporting bias) | Unclear risk | Protocol not available |
| Other bias | Low risk | None detected |

Risk & Prevention Study

| | |
|--------------|--|
| Methods | RCT; parallel; placebo-controlled Number of study sites: 57 local health units (860 general practitioners) Dates: enrolment between February 2004 and March 2007, follow-up ended on 31 October 2011 |
| Participants | Inclusion criteria: clinical evidence of atherosclerotic CVD such as angina pectoris, PAD, previous ischaemic stroke, TIA or revascularisation procedure; multiple risk factors (at least 4 cardiovascular risk factors in nondiabetic patients and 1 or more in diabetics) including: old age (≥ 65 years), men, history of arterial hypertension, history of hypercholesterolaemia, smoking, obesity (BMI ≥ 30 kg/m ²), family history of premature CVD (< 55 years in father or brother; < 65 years in mother or sister); other conditions putting the patient at high cardiovascular risk according to the general practitioner's judgement |

Risk & Prevention Study (Continued)

| | | |
|---|--|---|
| | <p>Exclusion criteria: prior MI; allergy to n-3 PUFAs; pregnancy; diseases with predictable poor short-term prognosis; and foreseeable psychological or logistic difficulties that would affect compliance with the project</p> <p>Sample size: 12,513 participants (total population), 1455 participants with history of stroke and/or TIA</p> <p>Participants randomised to intervention group (only stroke and/or TIA population): 736</p> <p>Participants randomised to control group (only stroke and/or TIA population): 719</p> <p>Sex (only stroke and/or TIA population): control = 420 men and 299 women, intervention = 473 men and 263 women</p> <p>Age, years + SD (only stroke and/or TIA population): control = 68.3 ± 9.2, intervention = 68.4 ± 9.2</p> <p>Time from event (stroke or TIA) to start of intervention: not stated</p> <p>Type of baseline stroke: not stated</p> <p>Country: Italy</p> <p>Ethnicity: not stated</p> | |
| Interventions | <p>Comparison groups: marine-derived n-3 PUFAs versus placebo</p> <p>Intervention: 1 g/day of marine-derived n-3 PUFAs ethyl esters with EPA and DHA content not < 85%, in a ratio that could range from 0.9:1 to 1.5:1</p> <p>Control: 1g/day of olive oil</p> <p>Compliance: self-report</p> <p>Duration of intervention: median of 5 years (IQR 4.0 to 5.5 years)</p> <p>Co-interventions: N/A</p> | |
| Outcomes | <p>Primary outcome of study: composite of time to death from cardiovascular causes or hospital admission for cardiovascular causes</p> <p>Relevant review outcomes measured (in total population): vascular-related death; recurrent events; adverse events</p> <p>Available outcome data for stroke and/or TIA population only: vascular-related death, recurrent events; adverse events (combined)</p> <p>Latest time point of assessment: median of 5 years (IQR 4.0 to 5.5 years)</p> <p>Withdrawals or exclusions, n (stroke and/or TIA population only): control = 4, intervention = 1</p> <p>Study authors' contact status: replied, data provided</p> | |
| Notes | <p>Dietary information: baseline fish consumption assessed. A post hoc analysis of the efficacy of n-3 fatty acids in relation to baseline fish consumption (never or seldom, once a week, twice a week, three times a week or more) showed no significant heterogeneity (P = 0.46 for interaction)</p> <p>Funding: Società Prodotti Antibiotici, Pfizer, and Sigma-Tau</p> | |
| <i>Risk of bias</i> | | |
| Bias | Authors' judgement | Support for judgement |
| Random sequence generation (selection bias) | Low risk | Quote: "Computer-generated randomization list stratified by GP" |

Risk & Prevention Study (Continued)

| | | |
|---|----------|--|
| Allocation concealment (selection bias) | Low risk | Quote: "Treatment was centrally allocated by telephone" |
| Blinding of participants and personnel (performance bias) All outcomes | Low risk | Quote: "Patients, general practitioners, coordination and statistical staff, and outcome assessors were unaware of the study assignments until the final analyses were completed" |
| Blinding of outcome assessment (detection bias) All outcomes | Low risk | Quote: "Patients, general practitioners, coordination and statistical staff, and outcome assessors were unaware of the study assignments until the final analyses were completed" |
| Incomplete outcome data (attrition bias) All outcomes | Low risk | In total population (not only stroke subsample), more participants discontinued study treatment in the control group. However, reasons were specified and the only 1 significantly different among groups was "patient's decision". Reasons related to adverse reactions or clinical reasons did not significantly differ between groups |
| Selective reporting (reporting bias) | Low risk | Protocol available. All pre-specified outcomes were reported |
| Other bias | Low risk | None detected |

Saito 2017

| | |
|--------------|---|
| Methods | RCT; parallel; open label Number of study sites: 2 Dates: between March 2013 and October 2016 |
| Participants | Inclusion criteria: 18 to 69 years of age with a modified Fisher grade 3 or 4 SAH (short axis of cisternal blood on CT ≥ 4 mm) who were admitted to the emergency department during the first 72 hours after the initial bleeding episode; ruptured intracranial aneurysm of the anterior circulation demonstrated by CTA or DSA; scheduled for surgical clipping no earlier than 5 hours after CTA/DSA diagnosis; clinical condition at admission or following medical stabilisation or external ventricular drainage placement was required to be World Federation of Neurological Surgeons grades 1 to 4; stable "(hemodynamic: 70 <mean arterial pressure (MAP) <130 mm Hg; 90 <systolic blood pressure (SBP) <180 mm Hg and headache <6 in the visual analogue scale [VAS]) at the intensive or intermediate care unit (ICU or IMCU) before randomization" Exclusion criteria: severe unstable acute or chronic systemic disturbances; antiplatelets, anticoagulants or valproic acid during the 3 weeks before SAH; history of allergy to iodine contrast media, fish or eggs; cerebral sequelae visible on admission CT; and refusal |

| | |
|---------------|--|
| | <p>of informed consent</p> <p>Sample size: 40 participants (all stroke population). Initially 41 participants were randomised, however, 1 participant was excluded because baseline diagnosis was other than stroke</p> <p>Participants randomised to intervention group: 20 (initially 21, 1 participant excluded as mentioned above)</p> <p>Participants randomised to control group: 20</p> <p>Sex: control = 7 men and 13 women, intervention = 8 men and 12 women</p> <p>Age (years), median (range): control = 48 (20 to 67), intervention = 53 (22 to 68)</p> <p>Time from event (stroke) to start of intervention: admission to the emergency department within 72 hours after the initial bleeding episode</p> <p>Type of baseline stroke: haemorrhagic</p> <p>Country: Chile</p> <p>Ethnicity: not stated</p> |
| Interventions | <p>Comparison groups: marine-derived n-3 PUFAs versus open control</p> <p>Intervention: 100 mL/day of the fish-oil-based lipid emulsion (FOLE), Omegaven 10% (Fresenius Kabi Germany), administered intravenously for 5 consecutive days. The first dose of FOLE had to be fully administered before beginning anaesthesia for aneurysm surgery and was continued thereafter every 24 hours. Patients with a body weight less than 50 kg were required to receive an adjusted dose of 0.2 g FOLE/kg/day. Oral treatment: Omacor 4 g/day (Ferrer Chile/Spain, Pronova BioPharma Norway) providing 1840 mg of EPA and 1520 mg of DHA as ethyl esters, beginning the day after the last dose of FOLE until 60th day after SAH. Patients in poor clinical condition and those with swallowing disturbances received the oil contained in the capsules by an emulsion via a nasogastric tube</p> <p>Control: normal care</p> <p>Compliance: not stated</p> <p>Duration of intervention: 60 days</p> <p>Co-interventions: medical stabilisation at an ICU/IMCU; 60 mg of oral nimodipine every 4 hours</p> |
| Outcomes | <p>Primary outcome of study: safety and feasibility of an effectiveness trial</p> <p>Relevant review outcomes measured (in total population): efficacy (measured by Glasgow Outcome Scale Extended score at 90 days); vascular-related death; incidence of other type of stroke; adverse events</p> <p>Available outcome data: efficacy (measured by Glasgow Outcome Scale Extended score at 90 days); vascular-related death; incidence of other type of stroke; adverse events</p> <p>Latest time point of assessment: 90 days</p> <p>Withdrawals or exclusions, n: 1 participant (aetiology of initial haemorrhage other than stroke)</p> <p>Study authors' contact status: replied, data provided</p> |
| Notes | <p>Dietary information: the dietary provision of n-6 PUFAs (by regular diet or enteral formula) did not exceed 9 g/day, and no additional n-3 PUFAs were given during the hospital stay. Thus, the total n-6/n-3 PUFA supplementation ratio did not exceed 2.5/1. Clinical dieticians supervised compliance with these instructions. Participants and their relatives received written nutritional recommendations to be followed during outpatient care: fish and seafood consumption had to be avoided during the treatment. Thereafter,</p> |

| | participants were required to begin eating 2 portions of fatty fish twice weekly until the third month after SAH. Foods with high n-6 PUFAs content (mayonnaise, margarine, spreads and dressings, and vegetable oils except olive and canola) had to be avoided until the third month after SAH Funding: The Public Health Care Service of the VI Region (Servicio de Salud O'Higgins) | |
|---|--|--|
| Risk of bias | | |
| Bias | Authors' judgement | Support for judgement |
| Random sequence generation (selection bias) | Low risk | Quote: "The randomized sequence was created with permuted blocks whose sizes (4 and 6) were unknown until the end of the trial. The randomization process was performed by members of the medical society of the VI Region who were not involved in any other part of the trial or in the treatment of neurosurgical patients" |
| Allocation concealment (selection bias) | Low risk | Quote: "Patients were randomized to treatment groups using sequentially numbered opaque sealed envelopes" |
| Blinding of participants and personnel (performance bias) All outcomes | High risk | Open label trial |
| Blinding of outcome assessment (detection bias) All outcomes | Unclear risk | Only the neuroradiologist was unaware of group assignments (outcomes: incidence of other type of stroke, and adverse events), other assessors were non-blinded (outcome: efficacy) |
| Incomplete outcome data (attrition bias) All outcomes | Low risk | Missing data imputed adequately. Participants lost to follow-up distributed evenly among groups |
| Selective reporting (reporting bias) | Unclear risk | Protocol not available for review (only available in physical format at Regulatory Agency: Instituto de Salud Pública de Chile) |
| Other bias | Low risk | None detected |

| | |
|---------------|--|
| Methods | <p>RCT; parallel; placebo-controlled</p> <p>Number of study sites: 1</p> <p>Dates: recruitment between 1 September 1992 and 19 May 1994. 2 years of follow-up</p> |
| Participants | <p>Inclusion criteria: stenosis greater than 20% in at least 1 vessel and revascularisation (PTCA or coronary bypass surgery) planned or performed in the previous 6 months in no more than 1 vessel</p> <p>Exclusion criteria: history of cardiac transplantation; age younger than 18 years or older than 75 years; haemodynamically relevant left main stenosis or proximal stenosis in all 3 main vessels; biplane left ventricular ejection fraction less than 35%; ventricular tachycardias (≥ 3 QRS complexes); haemodynamically relevant cardiac valve disease; a prognosis severely limited by noncardiac disease; bleeding tendency (e.g. due to thrombocytopenia or anticoagulation); diabetes, or other evidence of increased risk. Additionally: participation in another study; psychiatric disease; history of noncompliance; living too far away; initial coronary angiogram of poor quality; or history of allergic reaction to contrast material</p> <p>Sample size: 223 participants (total population), 6 participants with history of stroke and/or TIA (with complete follow-up)</p> <p>Participants randomised to intervention group (only stroke and/or TIA population): 3 (only participants with complete follow-up)</p> <p>Participants randomised to control group (only stroke and/or TIA population): 3 (only participants with complete follow-up)</p> <p>Sex (only stroke and/or TIA population): not stated</p> <p>Age (only stroke and/or TIA population): not stated</p> <p>Time from event (stroke or TIA) to start of intervention: not stated</p> <p>Type of baseline stroke: ischaemic (including TIA)</p> <p>Country: Germany</p> <p>Ethnicity: not stated</p> |
| Interventions | <p>Comparison groups: fish oil versus placebo</p> <p>Intervention: during the first 3 months, 6 g/day of fish oil, providing 3.3 g/day of marine-derived n-3 PUFAs (EPA plus DHA). For the following 21 months, 3 g/day of fish oil, providing 1.65 g/day of marine-derived n-3 PUFAs (EPA plus DHA)</p> <p>Control: fatty acids mixture without marine-derived n-3 PUFAs and reflecting the fatty acid composition of the average European diet</p> <p>Compliance: 'returned capsules' count and analysis of red cell phospholipids fatty acids</p> <p>Duration of intervention: 24 months</p> <p>Co-interventions: N/A</p> |
| Outcomes | <p>Primary outcome of study: changes on coronary angiography at 2 years, as assessed by an expert panel</p> <p>Relevant review outcomes measured (in total population): vascular-related death; recurrent events (stroke); adverse events</p> <p>Available outcome data for stroke and/or TIA population only: none</p> <p>Latest time point of assessment: 24 months</p> <p>Withdrawals or exclusions, n (stroke and/or TIA population only): not available</p> <p>Study authors' contact status: replied, no further data available</p> |

| | |
|-------|--|
| Notes | <p>Dietary information: overweight patients (body mass index > 25 kg/m²) were advised to restrict caloric intake, and all patients were advised to avoid eating cholesterol-rich foods; no other dietary advice was given</p> <p>Funding: The Bundesministerium für Forschung und Technologie, Germany, through Gesellschaft für Strahlenforschung (GSF, 07ERG03) and Deutsche Forschungsanstalt für Luft- und Raumfahrt (DLR, 01 EA 9501/7); Wilhelm Sander-Stiftung (93.032); Fundacion Federico; and the Deutsche Forschungsgemeinschaft (Scha 398). Pronova, A.S., Lysaker, Norway, provided the capsules and funds for monitoring</p> |
|-------|--|

Risk of bias

| Bias | Authors' judgement | Support for judgement |
|---|--------------------|--|
| Random sequence generation (selection bias) | Low risk | Quote: "A random sequence of study group assignments was computer-generated by the trial monitor in Norway" |
| Allocation concealment (selection bias) | Low risk | Quote: "The medication was prepared, encoded and sent from Norway" |
| Blinding of participants and personnel (performance bias) All outcomes | Low risk | Quote: "All patients, study personnel in contact with patients, and analytical personnel, were blinded with respect to study medication" |
| Blinding of outcome assessment (detection bias) All outcomes | Low risk | Quote: "All patients, study personnel in contact with patients, and analytical personnel, were blinded with respect to study medication" |
| Incomplete outcome data (attrition bias) All outcomes | Low risk | Participants with complete follow-up balanced across groups |
| Selective reporting (reporting bias) | Unclear risk | Protocol not available |
| Other bias | Low risk | None detected |

SU.FOL.OM3

| | |
|--------------|---|
| Methods | <p>RCT; parallel; 2 × 2 factorial design</p> <p>Number of study sites: 257</p> <p>Dates: enrolment between 1 February 2003 and 1 June 2007. Last follow-up 1 July 2009</p> |
| Participants | <p>Inclusion criteria: men and women aged 45 to 80 years; acute coronary or cerebral ischaemic event within the 12 months before randomisation</p> <p>Exclusion criteria: age (< 45 years or > 80 years); ill-defined diagnosis of cardiovascular disease; inability or unwillingness to comply with study treatment; and disease or treatment that might interfere with metabolism of homocysteine or omega-3 fatty acids,</p> |

| | | |
|---|---|--|
| | <p>in particular methotrexate for treating cancer or rheumatoid arthritis and chronic renal failure (plasma creatinine concentration > 200 $\mu\text{mol/L}$ or creatinine clearance < 40 ml/min)</p> <p>Sample size: 2501 participants (total population), 638 participants with history of stroke</p> <p>Participants randomised to intervention group (only stroke population): 312 (148 to marine-derived n-3 PUFAs only, and 164 to marine-derived n-3 PUFAs + B vitamins)</p> <p>Participants randomised to control group (only stroke population): 326 (160 to placebo, and 166 to B vitamins)</p> <p>Sex (only stroke population): not stated</p> <p>Age (only stroke population): not stated</p> <p>Time from event (stroke) to start of intervention: median time between the acute CVD event and randomisation was 101 days</p> <p>Type of baseline stroke: ischaemic</p> <p>Country: France</p> <p>Ethnicity: not stated</p> | |
| Interventions | <p>Comparison groups: marine-derived n-3 PUFAs versus placebo. Participants were also randomised to B vitamins or placebo, in a 2 x 2 factorial design</p> <p>Intervention: 600 mg/day of EPA and DHA at a ratio of 2:1</p> <p>Control: gelatin, fish-oil-flavoured capsules containing liquid paraffin</p> <p>Compliance: self-reported (questionnaire or telephone interview)</p> <p>Duration of intervention: median of 4.7 years (mean \pm SD = 4.2 \pm 1.0 years)</p> <p>Co-interventions: participants also randomised to 5-methyltetrahydrofolate (560 μg), vitamin B6 (3 mg) and B12 (20 μg) or placebo</p> | |
| Outcomes | <p>Primary outcome of study: first major cardiovascular event-non-fatal MI, ischaemic stroke, or death from cardiovascular disease (including fatal MI, stroke, sudden death (within 1 hour of onset of acute symptoms in the absence of violence or accident), aortic dissection, cardiac failure, or other fatal event defined by the medical committee as having a cardiovascular cause)</p> <p>Relevant review outcomes measured (in total population): vascular-related death; recurrent events (ischaemic stroke); adverse events; and quality of life</p> <p>Available outcome data for stroke population only: none</p> <p>Latest time point of assessment: median of 4.7 years (mean \pm SD = 4.2 \pm 1.0 years)</p> <p>Withdrawals or exclusions, n (stroke population only): not available</p> <p>Study authors' contact status: no reply to date</p> | |
| Notes | <p>Dietary information: none provided</p> <p>Funding: French Ministry of Research (R02010JJ), Ministry of Health (DGS), Sodexo, Candia, Unilever, Danone, Roche Laboratory, Merck EPROVA GS, and Pierre Fabre Laboratory</p> | |
| Risk of bias | | |
| Bias | Authors' judgement | Support for judgement |
| Random sequence generation (selection bias) | Low risk | Quote: "Randomization was performed by means of a computerised block sequence stratified by three age groups (44-54, 55- |

SU.FOL.OM3 (Continued)

| | | |
|---|--------------|---|
| | | 64, and 65-80 years), sex, prior disease at enrolment (myocardial infarction, acute coronary syndrome, or ischaemic stroke) and recruitment centre. Permuted block randomization (with block size randomly selected as 8) was used” |
| Allocation concealment (selection bias) | Low risk | Quote: “The allocation of participants was programmed by the statistical coordinating centre. Once participants were randomized, the coordinating centre sent them sufficient treatment capsules for one year (and repeated yearly) in an appropriately labelled package” |
| Blinding of participants and personnel (performance bias) All outcomes | Low risk | Quote “Patients, clinicians, trial coordinators, and outcome investigators were blinded to treatment allocation” |
| Blinding of outcome assessment (detection bias) All outcomes | Low risk | Quote “Patients, clinicians, trial coordinators, and outcome investigators were blinded to treatment allocation” Quote: “All events were adjudicated by two independent committees of cardiologists or neurologists who were blinded to treatment allocation” |
| Incomplete outcome data (attrition bias) All outcomes | Low risk | Participants that withdrew consent were balanced across groups |
| Selective reporting (reporting bias) | Unclear risk | Protocol not available |
| Other bias | Low risk | None detected |

Terano 1999

| | |
|--------------|---|
| Methods | RCT; parallel; open label Number of study sites: 1 Dates: not stated |
| Participants | Inclusion criteria: men and women; living in a care home for the elderly; mild to moderate dementia from cerebrovascular disorder Exclusion criteria: not stated Sample size: 20 participants Participants randomised to intervention group (only stroke population): 10 Participants randomised to control group (only stroke population): 10 Sex (only stroke population): men and women (no details) Age (only stroke population): average of 83 years (no further details) Time from event (stroke) to start of intervention: not stated |

| | |
|---------------|---|
| | Type of baseline stroke: ischaemic (thrombotic) Country: Japan Ethnicity: not stated |
| Interventions | Comparison groups: DHA versus no intervention (open control) Intervention: 6 capsules containing 0.72 g/day of DHA Control: no intervention Compliance: nursing staff provided capsules and ascertained swallowing Duration of intervention: 12 months Co-interventions: N/A |
| Outcomes | Primary outcome of study: effect of DHA on dementia Relevant review outcomes measured (in total population): none Available outcome data for stroke population only: none Latest time point of assessment: 12 months Withdrawals or exclusions, n (stroke population only): not stated Study authors' contact status: contact unsuccessfully attempted |
| Notes | Dietary information: access to the same food (living in the same home) Funding: not stated |

Risk of bias

| Bias | Authors' judgement | Support for judgement |
|---|--------------------|---|
| Random sequence generation (selection bias) | Unclear risk | Quote: "The controller randomly divided the 20 elderly in two groups" No description of the random sequence generation |
| Allocation concealment (selection bias) | Unclear risk | No information on how the process of allocation was conducted |
| Blinding of participants and personnel (performance bias) All outcomes | High risk | Open label study |
| Blinding of outcome assessment (detection bias) All outcomes | High risk | Open label study |
| Incomplete outcome data (attrition bias) All outcomes | Unclear risk | No loss of participants during follow-up |
| Selective reporting (reporting bias) | Unclear risk | Protocol not available |
| Other bias | Unclear risk | Short communication; therefore not enough information about study design, study outcomes (not relevant for this |

Terano 1999 (Continued)

| | | |
|--|--|--|
| | | review) were not fully described. Additionally, no information regarding Ethics Committee approval or funding of the trial |
|--|--|--|

Thies 2003

| | |
|---------------|---|
| Methods | RCT; parallel; placebo-controlled. 3 arms: control oil, sunflower oil, and fish oil. For this review the relevant arms are only control oil and fish oil Number of study sites: 1 Dates: between May 1997 and December 1999 |
| Participants | Inclusion criteria: patients waiting to undergo carotid endarterectomy Exclusion criteria: patients unwilling to participate in the study, patients who went to surgery within 7 days from start of intervention Sample size: 188 participants (total population), participants with history of stroke and/or TIA Participants randomised to intervention group (only stroke and/or TIA population): 46 (only participants who completed the trial, including symptoms within and more than 6 months before study entry, not clear if duplicates included) Participants randomised to control group (only stroke and/or TIA population): 34 (only participants who completed the trial, including symptoms within and more than 6 months before study entry, not clear if duplicates included) Sex (only stroke and/or TIA population): not stated Age (only stroke and/or TIA population): not stated Time from event (stroke or TIA) to start of intervention: not stated Type of baseline stroke: not stated Country: UK Ethnicity: not stated |
| Interventions | Comparison groups: fish oil versus placebo (the study had 3 arms: control oil, sunflower oil, and fish oil. For this review the relevant arms are only control oil and fish oil) Intervention: fish oil 6 g/day Control: blend of palm and soybean oils (80:20) Compliance: 'returned capsules' count and measurement of fatty-acid composition of LDL lipid-fractions Duration of intervention: median of 42 days (range, 7 to 189 days) Co-interventions: N/A |
| Outcomes | Primary outcome of study: plaque morphology indicative of stability or instability Relevant review outcomes measured (in total population): adverse events Available outcome data for stroke and/or TIA population only: none Latest time point of assessment: median of 42 days (range, 7 to 189 days) Withdrawals or exclusions, n (stroke and/or TIA population only): not available Study authors' contact status: replied, no data provided |
| Notes | Dietary information: participants completed a 7-day weighed food diary and were advised not to change their diet Funding: a grant to RFG, PCC, and CPS from the Food Standards Agency (grant number ANO238). JMCG held a postgraduate studentship from the Ministry of Agricul- |

Thies 2003 (Continued)

| | | |
|---|---|---|
| | <p>ture, Fisheries, and Food. KR was supported by the Faculty of Medicine, Chiang Mai University, Thailand, and the Royal Thai Government Note: Dr Frank Thies was not involved in any stage of the analysis of this study for the present review (screening, data extraction, and assessment of risk of bias). Contact author is Prof PC Calder</p> | |
| Risk of bias | | |
| Bias | Authors' judgement | Support for judgement |
| Random sequence generation (selection bias) | Low risk | Quote: "Randomisation of patients was done according to a random number table, by A Chulakadabba and KR. The sequence was generated by computer" |
| Allocation concealment (selection bias) | Low risk | Quote: "Allocation was concealed in a sealed envelope" |
| Blinding of participants and personnel (performance bias) All outcomes | Low risk | Quote: "We randomly allocated patients, in a double-blind manner, to receive one of three types of oil provided in capsules: control oil, sunflower oil, or fish oil" |
| Blinding of outcome assessment (detection bias) All outcomes | Low risk | The only study outcome relevant for this review is adverse events ascribed by participants, who were blinded to intervention |
| Incomplete outcome data (attrition bias) All outcomes | Unclear risk | Slightly more participants allocated to control group, more participants lost to follow-up in fish oil group |
| Selective reporting (reporting bias) | Unclear risk | Protocol not available. Adverse events are only reported as participant's reason to withdraw, not described if they were interrogated for all participants |
| Other bias | Low risk | None detected |

Wakita 2013

| | |
|--------------|--|
| Methods | <p>RCT; parallel, open label Number of study sites: not stated Dates: not stated</p> |
| Participants | <p>Inclusion criteria: patients with asymptomatic cerebral infarction and coronary artery disease receiving 2 mg/day pitavastatin Exclusion criteria: not stated Sample size: 40 participants (all with history of stroke)</p> |

| | |
|---------------|--|
| | <p>Participants randomised to intervention group (only stroke and/or TIA population): 20</p> <p>Participants randomised to control group (only stroke and/or TIA population): 20</p> <p>Sex (only stroke and/or TIA population): not stated</p> <p>Age (only stroke and/or TIA population): not stated</p> <p>Time from event (stroke or TIA) to start of intervention: not stated</p> <p>Type of baseline stroke: ischaemic (cerebral infarction)</p> <p>Country: not stated</p> <p>Ethnicity: not stated</p> |
| Interventions | <p>Comparison groups: EPA versus no EPA</p> <p>Intervention: 1800 mg/day of EPA</p> <p>Control: open control</p> <p>Compliance: not stated</p> <p>Duration of intervention: average of 8 months</p> <p>Co-interventions: 2 mg/day of pitavastatin</p> |
| Outcomes | <p>Primary outcome of study: efficacy of additional EPA to strong statin for carotid plaque using carotid echography and pulse wave velocity</p> <p>Relevant review outcomes measured (in total population): none</p> <p>Available outcome data for stroke and/or TIA population only: none</p> <p>Latest time point of assessment: average of 8 months</p> <p>Withdrawals or exclusions, n (stroke and/or TIA population only): not stated</p> <p>Study authors' contact status: no reply up to date</p> |
| Notes | <p>Dietary information: none provided</p> <p>Funding: not stated</p> <p>Note: only abstract available (conference presentation)</p> |

Risk of bias

| Bias | Authors' judgement | Support for judgement |
|---|--------------------|---|
| Random sequence generation (selection bias) | Unclear risk | Randomisation process not described |
| Allocation concealment (selection bias) | Unclear risk | No information about allocation process |
| Blinding of participants and personnel (performance bias) All outcomes | High risk | Open label study |
| Blinding of outcome assessment (detection bias) All outcomes | Unclear risk | Open label study (no additional information given regarding outcome assessment) |
| Incomplete outcome data (attrition bias) All outcomes | Low risk | No participants lost to follow-up |
| Selective reporting (reporting bias) | Unclear risk | Protocol not available |

Wakita 2013 (Continued)

| | | |
|------------|--------------|---|
| Other bias | Unclear risk | No full report available: therefore large amount of information about study design and conduct is missing |
|------------|--------------|---|

Zhang 2017

| | |
|---------------|--|
| Methods | RCT; parallel; placebo-controlled Number of study sites: not stated (6 geographically convenient communities selected) Dates: enrolment between March and April 2013. Follow-up 12 months |
| Participants | <p>Inclusion criteria: aged 65 years and over; in generally good health, ambulatory, and with sufficient hearing and vision for compliance with testing procedures; absence of terminal illness or mental disorders (i.e. major depression, schizophrenia, bipolar disorder, etc.); not using any nutritional supplementation known to interfere with nutrition status, fatty acid composition metabolism, or cognitive function in the 3 months before recruitment; those able to undergo MRI evaluation (i.e. those without a pacemaker or other metal items within the body, and those with MRI brain abnormalities such as multiple micro haemorrhages, infarcts, or moderate to severe cortical atrophy); not living in a nursing home or on a waiting list for a nursing home. From them, MCI was determined. People with MCI who met the study criteria were selected</p> <p>Exclusion criteria: exclusion criteria are not described in publications; however, they are listed in the trial registration. Such exclusion criteria include history of stroke; nevertheless participants with self-reported history of stroke/TIA were included in the trial</p> <p>Exclusion criteria according to trial registration: neurological examination found the sign of local central nerve obstruction such as obvious paralysis, unilateral sensory disturbance and aphasia etc., history of cerebrovascular diseases (haemorrhagic and ischaemic stroke), brain injury or bone fracture; medical diseases such as asthmatic bronchitis, severe hypertension, angina pectoris and severe infection; psychotic patients with evident anxiety and depressed emotion and people with endocrine system history of disease (hyperthyroidism, thyroid hypofunction, systemic lupus erythematosus, rheumatoid arthritis); newly discovered or advanced tumour; visual perception, auditory perceptual disorders or language communication difficulties, all of which may influence measurement of cognitive function; alcohol dependence and other psychoactive substance abuse such as antipsychotic drug, benzodiazepines or taking medicine influencing cognitive function</p> <p>Sample size: 240 participants (total population), 22 participants with history of stroke and/or TIA</p> <p>Participants randomised to intervention group (only stroke and/or TIA population): 12 Participants randomised to control group (only stroke and/or TIA population): 10</p> <p>Sex (only stroke and/or TIA population): not stated Age (only stroke and/or TIA population): not stated Time from event (stroke or TIA) to start of intervention: not stated Type of baseline stroke: not stated Country: China Ethnicity: Chinese</p> |
| Interventions | <p>Comparison groups: DHA versus placebo</p> <p>Intervention: 2 g/day of algal-derived DHA (Martek Biosciences) containing approximately 45% to 55% of DHA by weight</p> |

| | | |
|---|---|--|
| | Control: identical corn oil capsules (all capsules were orange-flavoured) Compliance: capsule count and blood assessment at baseline, 6, and 12 months Duration of intervention: 12 months Co-interventions: N/A | |
| Outcomes | Primary outcome of study: cognitive function Relevant review outcomes measured (in total population): none Available outcome data for stroke and/or TIA population only: none Latest time point of assessment: 12 months Withdrawals or exclusions, n (stroke and/or TIA population only): not available Study authors' contact status: no reply to date | |
| Notes | Dietary information: at baseline, groups were similar for fish consumption. Dietary recommendations based on a booklet (<i>Guides to Enhance Elderly Memory</i>) were provided to all participants Funding: Chinese Nutrition Society (CNS) Nutrition Research Foundation-DSM Research Fund (grant number: 2014-003) | |
| Risk of bias | | |
| Bias | Authors' judgement | Support for judgement |
| Random sequence generation (selection bias) | Low risk | Quote: "The randomization sequence was computer generated by the study sponsor" |
| Allocation concealment (selection bias) | Low risk | Quote: "The supplements were packaged into identical pots, each containing 180 capsules, and labelled by staff who were not involved in the study" |
| Blinding of participants and personnel (performance bias) All outcomes | Low risk | Quote: "The supplements were packaged into identical pots, each containing 180 capsules, and labelled by staff who were not involved in the study" |
| Blinding of outcome assessment (detection bias) All outcomes | Low risk | Quote: "All project staff were unaware of group assignments until the completion of the trial and after data analysis" |
| Incomplete outcome data (attrition bias) All outcomes | Low risk | Similar amount of participants lost to follow-up across groups |
| Selective reporting (reporting bias) | Unclear risk | Protocol not available |
| Other bias | High risk | As stated above, trial registration includes history of stroke as exclusion criteria; participants with history of stroke are included, however, and there is no mention |

AF: atrial fibrillation
ALA: alpha linolenic acid
AVF: arteriovenous fistula
BMI: body mass index
CABG: coronary artery bypass graft
CAS: carotid angioplasty and stenting
CT: computed tomography
CTA: computed tomographic angiography
CVD: cardiovascular disease
DHA: docosahexaenoic acid
DM: diabetes mellitus
DSA: digital subtraction angiography
EPA: eicosapentaenoic acid
FFQ: food frequency questionnaire
FOLE: fish oil-based lipid emulsion
HbA1c: glycated haemoglobin
ICU: intensive care unit
IQR: interquartile range
LMWH: low molecular weight heparin
LVEF: left ventricular ejection fraction
MCI: mild cognitive impairment
MI: myocardial infarction
MMSE: Mini Mental State Examination
MRI: magnetic resonance imaging
mRS: modified Rankin scale
N/A: not applicable
NYHA: New York Heart Association
PAD: peripheral artery disease
PCI: percutaneous coronary intervention
PTCA: percutaneous transluminal coronary angioplasty
PUFAs: polyunsaturated fatty acids
RCT: randomised controlled trial
SAH: subarachnoid haemorrhage
TIA: transient ischaemic attack

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

| Study | Reason for exclusion |
|--------------------------------------|---|
| ALVINA 2013 | Another active intervention in only 1 group (multiple lifestyle changes) |
| ANCHOR | No stroke participants (baseline characteristics) |
| Bao 2016 | Another active intervention in only 1 group (dietary supplement) |
| DOIT 1997 | No stroke participants (baseline characteristics) |
| EVAS 2004 | Quasi-randomised study (alternation) |
| FISHb Sandesara 2012 | No stroke participants (baseline characteristics) |
| MARINE | No stroke participants (baseline characteristics) |
| Nakagawa 2017 | Not randomised study (participants of each group admitted in 2 different periods) |
| NCT01526824 | No publications. Contact unsuccessfully attempted |
| SOFA | Not clear if stroke participants were included (study authors confirmed that no further information is available) |
| Suehiro 1994 | Study design (randomisation) not indicated |
| Tomiyaama 2005 | Quasi-randomised study (month of birth odd/even) |
| Yoneda 2008 | Quasi-randomised study (alternation) |

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

[FISH Lok 2012](#)

| | |
|---------------|---|
| Methods | RCT; parallel; placebo-controlled |
| Participants | Individuals with end stage renal disease who require a synthetic graft for chronic haemodialysis |
| Interventions | Intervention: fish oil Control: corn oil |
| Outcomes | Primary outcome of study: proportion of AV-grafts with loss of native patency |
| Notes | Pending confirmation from study authors regarding inclusion of participants with stroke/TIA Please note that there exists another study with the same acronym (FISH), see FISHb Sandesara 2012 |

Hertantows 2014

| | |
|---------------|--|
| Methods | RCT; parallel; placebo-controlled |
| Participants | Acute ischaemic stroke patients |
| Interventions | Intervention: snakehead fish extract Control: placebo (no details) |
| Outcomes | Primary outcome of study: protein status, antioxidants and oxidative stress |
| Notes | Pending confirmation from study authors regarding composition of intervention (i.e. proteins or fatty acids) |

Nomura 2009

| | |
|---------------|--|
| Methods | RCT; parallel; 3 arms |
| Participants | Patients with diabetes and hyperlipidaemia and normolipidemic controls |
| Interventions | 3 arms: EPA, pitavastatin, or both interventions. |
| Outcomes | Study primary outcome: effect on platelet-derived microparticles and adiponectin |
| Notes | Pending confirmation from authors regarding distribution of stroke participants across intervention arms |

ORIGIN

| | |
|---------------|--|
| Methods | RCT; parallel; 2 × 2 factorial design |
| Participants | People with high risk for a cardiovascular event and impaired glucose tolerance or diabetes |
| Interventions | Intervention: marine-derived n-3 PUFAs ethyl esters Control: olive oil Participants were randomised at the same time to either insulin glargine (Lantus, Sanofi Aventis) or standard approaches to glycaemic control |
| Outcomes | Primary outcome of study: death from cardiovascular causes (for the marine-derived n-3 PUFAs arm) |
| Notes | Pending confirmation from study authors regarding inclusion and number of stroke/TIA participants. Baseline characteristics grouped “myocardial infarction, stroke, or revascularization” |

REDUCE-IT

| | |
|--------------|---|
| Methods | RCT; parallel; placebo-controlled |
| Participants | People with established cardiovascular disease (≥ 45 years) or age ≥ 50 years with diabetes mellitus in combination with 1 additional risk factor for cardiovascular disease |

REDUCE-IT (Continued)

| | |
|---------------|---|
| Interventions | Intervention: icosapent ethyl (AMR101) Control: mineral oil |
| Outcomes | Primary outcome of study: a composite of cardiovascular death, nonfatal myocardial infarction (including silent myocardial infarction), nonfatal stroke, coronary revascularisation, or unstable angina in a time-to-event analysis |
| Notes | Pending confirmation from authors regarding inclusion of stroke/TIA participants, only described in baseline characteristics as “secondary prevention cohort” from cardiovascular risk stratum |

Sengoku 2013

| | |
|---------------|---|
| Methods | Parallel; open label |
| Participants | Patients with cerebral infarction and dyslipidaemia |
| Interventions | Intervention: EPA plus atorvastatin Control: atorvastatin only |
| Outcomes | Primary outcome of study: Cardio-Ankle Vascular Index |
| Notes | Pending confirmation from study author regarding study design (randomisation) and details |

EPA: eicosapentaenoic acid

MI: myocardial infarction

PUFAs: polyunsaturated fatty acids

RCT: randomised controlled trial

Characteristics of ongoing studies [ordered by study ID]

NCT01953705

| | |
|---------------------|--|
| Trial name or title | n-3 PUFA for vascular cognitive aging |
| Methods | RCT; parallel; placebo-controlled |
| Participants | Older adults at high risk for cognitive decline and dementia of Alzheimer's type |
| Interventions | Intervention: marine-derived n-3 PUFAs Control: soybean oil |
| Outcomes | Primary outcome: total cerebral white matter hyperintensity volume |
| Starting date | May 2014 |

NCT01953705 (Continued)

| | |
|---------------------|--|
| Contact information | Lynne Shinto, ND, MPH Oregon Health and Science University shintol@ohsu.edu |
| Notes | Study author confirmed that lacunar infarcts and TIAs are not exclusions if Clinical Dementia Rating ≤ 0.50 and MMSE ≥ 24 Estimated study completion date: September 2019 |

OMEMI

| | |
|---------------------|--|
| Trial name or title | Omega-3 fatty acids in elderly patients with acute myocardial infarction (OMEMI) |
| Methods | RCT; parallel; placebo-controlled |
| Participants | Elderly population with acute MI |
| Interventions | Intervention: Pikasol® (EPA + DHA) Control: corn oil |
| Outcomes | Primary outcome: combined total mortality, first event of non-fatal MI, stroke and revascularisation |
| Starting date | November 2012 |
| Contact information | Principal Investigator: Kristian Laake, MD Oslo University Hospital |
| Notes | Estimated study completion date: November 2019 |

STRENGTH

| | |
|---------------------|--|
| Trial name or title | Outcomes study to assess statin residual risk reduction with EpaNova in high CV risk patients with hypertriglyceridemia (STRENGTH) |
| Methods | RCT; parallel; placebo-controlled |
| Participants | People with high risk for atherosclerotic cardiovascular disease |
| Interventions | Intervention: Epanova® Control: corn oil |
| Outcomes | Time to the first occurrence of any component of the composite of major adverse cardiovascular events (cardiovascular death, non-fatal MI, non-fatal stroke, emergent/elective coronary revascularisation, or hospitalisation for unstable angina) |
| Starting date | 30 October 2014 |

STRENGTH (Continued)

| | |
|---------------------|--|
| Contact information | Stephen J Nicholls, MBBS, PhD, South Australian Health and Medical Research Institute stephen.nicholls@sahmri.com |
| Notes | Estimated study completion date: October 2019 |

DHA: docosahexaenoic acid

EPA: eicosapentaenoic acid

MI: myocardial infarction

PUFAs: polyunsaturated fatty acids

RCT: randomised controlled trial

DATA AND ANALYSES

Comparison 1. Marine-derived n-3 fatty acids therapy compared to no marine-derived n-3 fatty acids therapy: follow-up of 3 months or sooner

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|--|----------------|---------------------|-------------------------------------|---------------------|
| 1 Efficacy (poor clinical outcome) | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | Totals not selected |
| 2 Vascular-related death | 2 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 3 Recurrent events (all: fatal and non-fatal) | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | Totals not selected |
| 4 Incidence of other type of stroke | 2 | | Risk Ratio (M-H, Fixed, 95% CI) | Totals not selected |
| 4.1 Participants with prior ischaemic stroke | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 4.2 Participants with prior haemorrhagic stroke | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 5 Adverse events (all) | 2 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 6 Adverse events (extracranial haemorrhage) | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | Totals not selected |
| 7 Adverse events (bleeding complications) | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | Totals not selected |
| 8 Quality of life (mean change from baseline) | 1 | | Mean Difference (IV, Fixed, 95% CI) | Totals not selected |
| 8.1 SF-36 questionnaire Physical component scale | 1 | | Mean Difference (IV, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 8.2 SF-36 questionnaire Mental Component Scale | 1 | | Mean Difference (IV, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 9 Mood (GHQ-30, mean change from baseline) | 1 | | Mean Difference (IV, Fixed, 95% CI) | Totals not selected |

Comparison 2. Marine-derived n-3 fatty acids therapy compared to no marine-derived n-3 fatty acids therapy: follow-up longer than 3 months

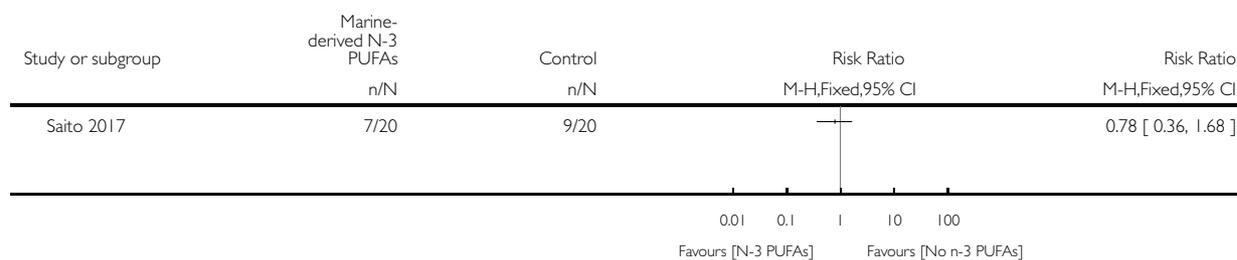
| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|--|----------------|---------------------|-------------------------------------|---------------------|
| 1 Efficacy (Barthel Index) | 1 | | Mean Difference (IV, Fixed, 95% CI) | Totals not selected |
| 2 Efficacy (Rivermead Mobility Index) | 1 | | Mean Difference (IV, Fixed, 95% CI) | Totals not selected |
| 3 Vascular-related death | 5 | 2237 | Risk Ratio (M-H, Random, 95% CI) | 1.02 [0.78, 1.35] |
| 4 All recurrent events (fatal and non-fatal) | 3 | | Risk Ratio (M-H, Random, 95% CI) | Totals not selected |
| 5 Recurrent events (fatal only) | 3 | 1819 | Risk Ratio (M-H, Random, 95% CI) | 0.69 [0.31, 1.55] |
| 6 Recurrent events (non-fatal only) | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | Totals not selected |
| 7 Adverse events (all) | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | Totals not selected |

Analysis 1.1. Comparison 1 Marine-derived n-3 fatty acids therapy compared to no marine-derived n-3 fatty acids therapy: follow-up of 3 months or sooner, Outcome 1 Efficacy (poor clinical outcome).

Review: Marine-derived n-3 fatty acids therapy for stroke

Comparison: 1 Marine-derived n-3 fatty acids therapy compared to no marine-derived n-3 fatty acids therapy: follow-up of 3 months or sooner

Outcome: 1 Efficacy (poor clinical outcome)

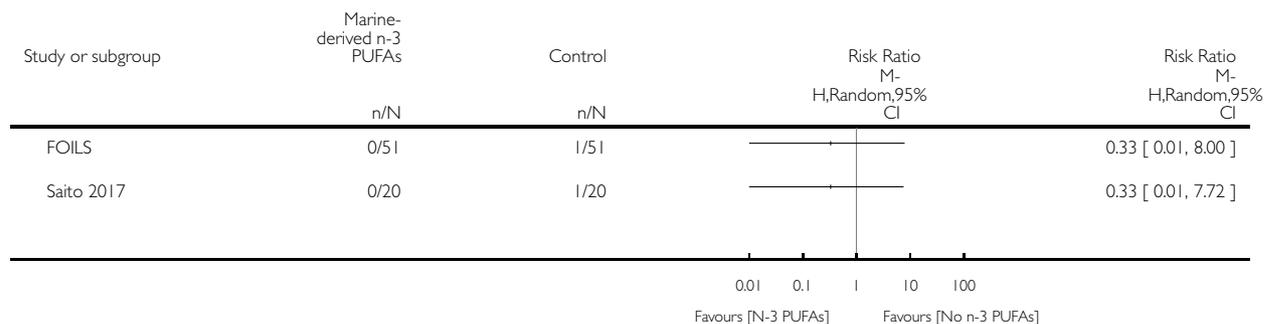


Analysis 1.2. Comparison 1 Marine-derived n-3 fatty acids therapy compared to no marine-derived n-3 fatty acids therapy: follow-up of 3 months or sooner, Outcome 2 Vascular-related death.

Review: Marine-derived n-3 fatty acids therapy for stroke

Comparison: 1 Marine-derived n-3 fatty acids therapy compared to no marine-derived n-3 fatty acids therapy: follow-up of 3 months or sooner

Outcome: 2 Vascular-related death

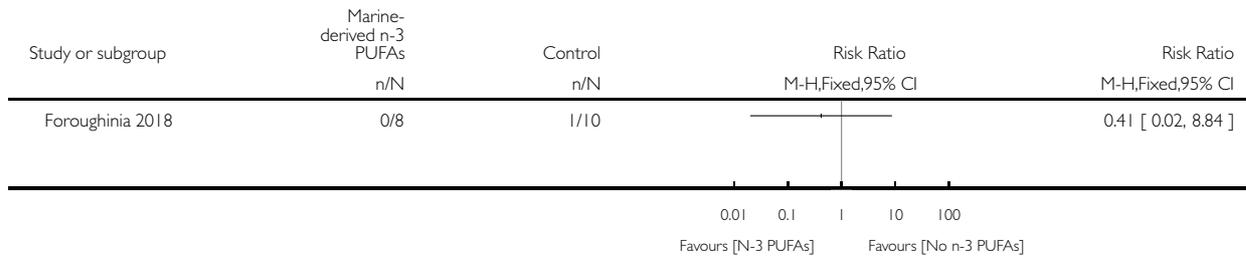


Analysis 1.3. Comparison 1 Marine-derived n-3 fatty acids therapy compared to no marine-derived n-3 fatty acids therapy: follow-up of 3 months or sooner, Outcome 3 Recurrent events (all: fatal and non-fatal).

Review: Marine-derived n-3 fatty acids therapy for stroke

Comparison: 1 Marine-derived n-3 fatty acids therapy compared to no marine-derived n-3 fatty acids therapy: follow-up of 3 months or sooner

Outcome: 3 Recurrent events (all: fatal and non-fatal)

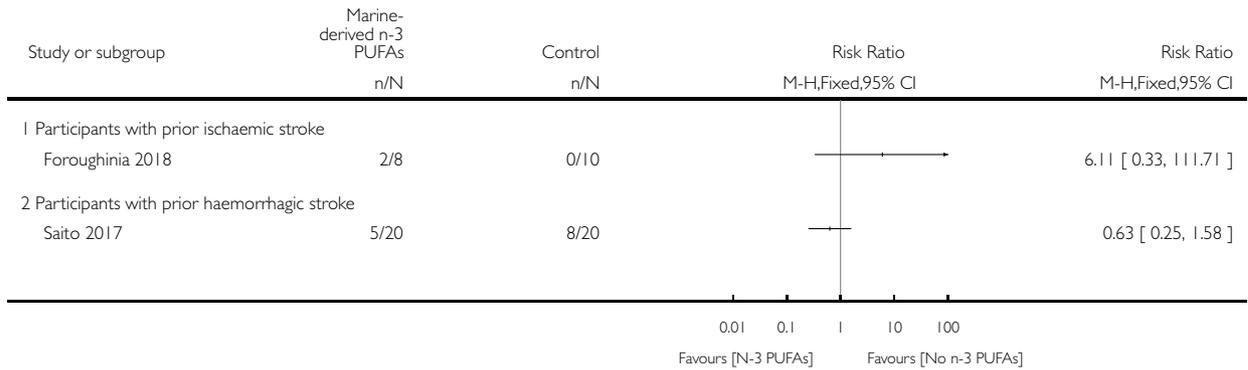


Analysis 1.4. Comparison 1 Marine-derived n-3 fatty acids therapy compared to no marine-derived n-3 fatty acids therapy: follow-up of 3 months or sooner, Outcome 4 Incidence of other type of stroke.

Review: Marine-derived n-3 fatty acids therapy for stroke

Comparison: 1 Marine-derived n-3 fatty acids therapy compared to no marine-derived n-3 fatty acids therapy: follow-up of 3 months or sooner

Outcome: 4 Incidence of other type of stroke

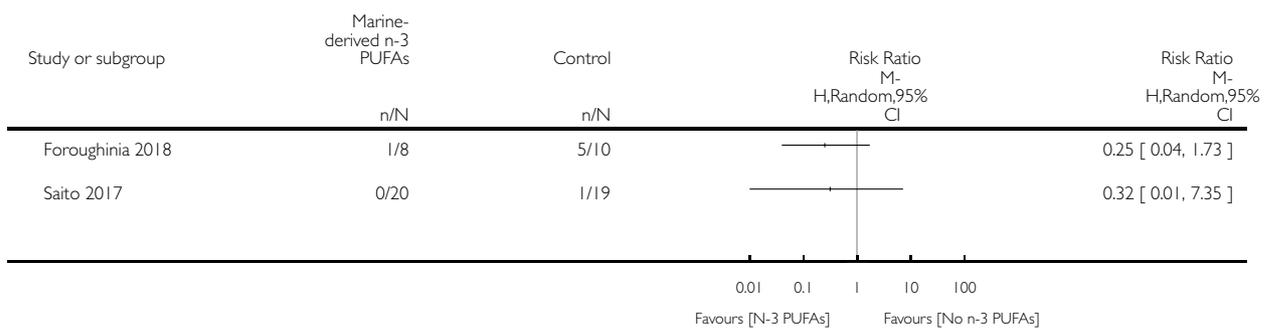


Analysis 1.5. Comparison 1 Marine-derived n-3 fatty acids therapy compared to no marine-derived n-3 fatty acids therapy: follow-up of 3 months or sooner, Outcome 5 Adverse events (all).

Review: Marine-derived n-3 fatty acids therapy for stroke

Comparison: 1 Marine-derived n-3 fatty acids therapy compared to no marine-derived n-3 fatty acids therapy: follow-up of 3 months or sooner

Outcome: 5 Adverse events (all)

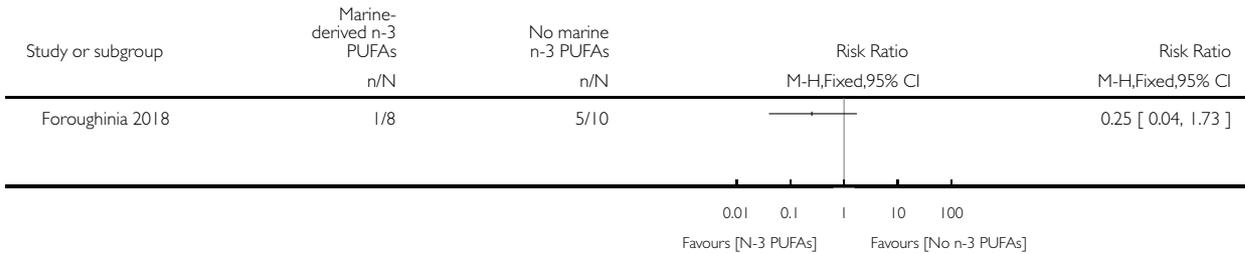


Analysis 1.6. Comparison 1 Marine-derived n-3 fatty acids therapy compared to no marine-derived n-3 fatty acids therapy: follow-up of 3 months or sooner, Outcome 6 Adverse events (extracranial haemorrhage).

Review: Marine-derived n-3 fatty acids therapy for stroke

Comparison: 1 Marine-derived n-3 fatty acids therapy compared to no marine-derived n-3 fatty acids therapy: follow-up of 3 months or sooner

Outcome: 6 Adverse events (extracranial haemorrhage)

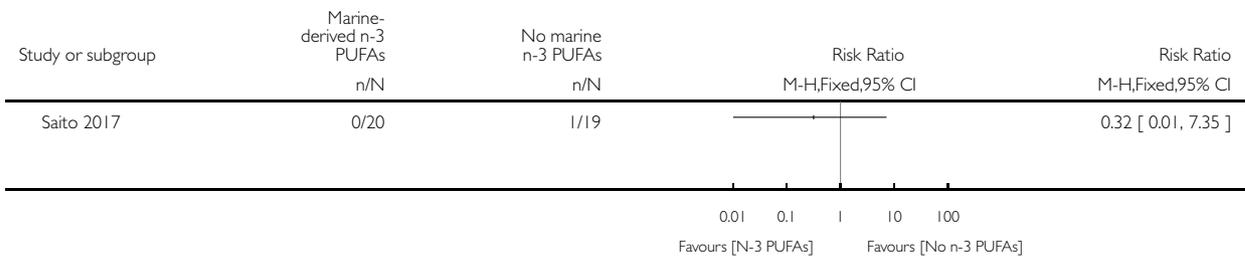


Analysis 1.7. Comparison 1 Marine-derived n-3 fatty acids therapy compared to no marine-derived n-3 fatty acids therapy: follow-up of 3 months or sooner, Outcome 7 Adverse events (bleeding complications).

Review: Marine-derived n-3 fatty acids therapy for stroke

Comparison: 1 Marine-derived n-3 fatty acids therapy compared to no marine-derived n-3 fatty acids therapy: follow-up of 3 months or sooner

Outcome: 7 Adverse events (bleeding complications)

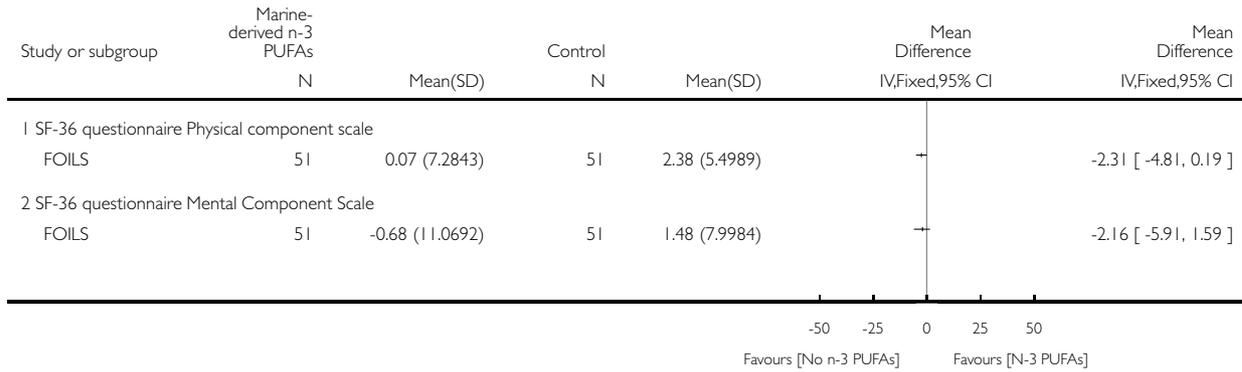


Analysis 1.8. Comparison 1 Marine-derived n-3 fatty acids therapy compared to no marine-derived n-3 fatty acids therapy: follow-up of 3 months or sooner, Outcome 8 Quality of life (mean change from baseline).

Review: Marine-derived n-3 fatty acids therapy for stroke

Comparison: 1 Marine-derived n-3 fatty acids therapy compared to no marine-derived n-3 fatty acids therapy: follow-up of 3 months or sooner

Outcome: 8 Quality of life (mean change from baseline)

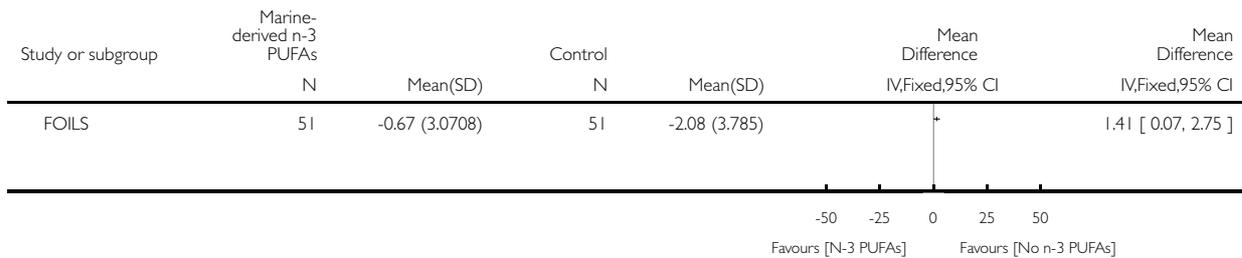


Analysis 1.9. Comparison 1 Marine-derived n-3 fatty acids therapy compared to no marine-derived n-3 fatty acids therapy: follow-up of 3 months or sooner, Outcome 9 Mood (GHQ-30, mean change from baseline).

Review: Marine-derived n-3 fatty acids therapy for stroke

Comparison: 1 Marine-derived n-3 fatty acids therapy compared to no marine-derived n-3 fatty acids therapy: follow-up of 3 months or sooner

Outcome: 9 Mood (GHQ-30, mean change from baseline)

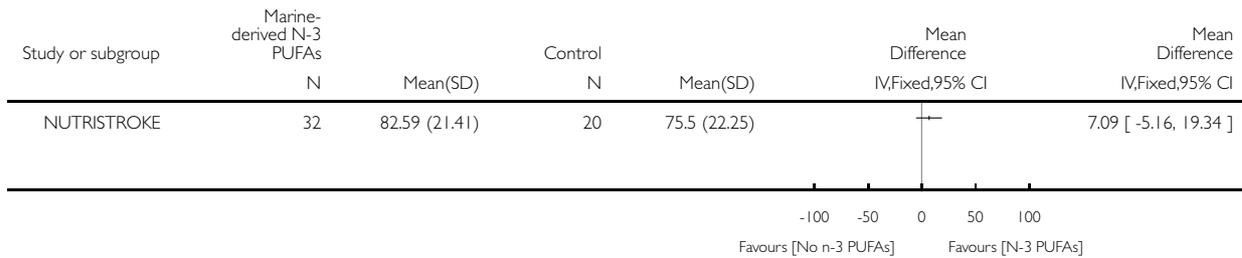


Analysis 2.1. Comparison 2 Marine-derived n-3 fatty acids therapy compared to no marine-derived n-3 fatty acids therapy: follow-up longer than 3 months, Outcome 1 Efficacy (Barthel Index).

Review: Marine-derived n-3 fatty acids therapy for stroke

Comparison: 2 Marine-derived n-3 fatty acids therapy compared to no marine-derived n-3 fatty acids therapy: follow-up longer than 3 months

Outcome: 1 Efficacy (Barthel Index)

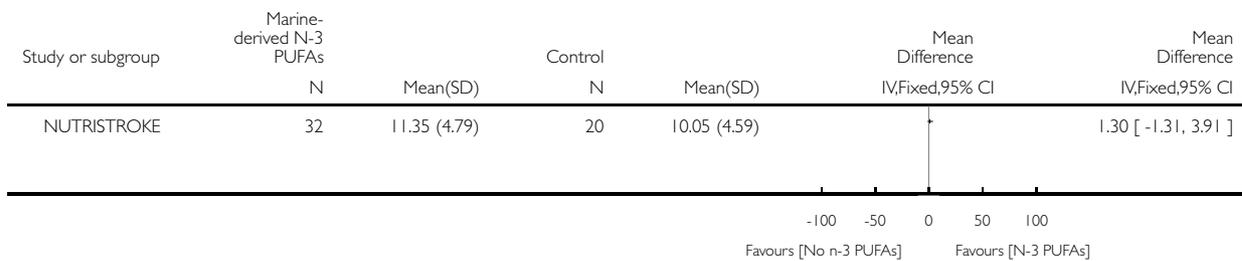


Analysis 2.2. Comparison 2 Marine-derived n-3 fatty acids therapy compared to no marine-derived n-3 fatty acids therapy: follow-up longer than 3 months, Outcome 2 Efficacy (Rivermead Mobility Index).

Review: Marine-derived n-3 fatty acids therapy for stroke

Comparison: 2 Marine-derived n-3 fatty acids therapy compared to no marine-derived n-3 fatty acids therapy: follow-up longer than 3 months

Outcome: 2 Efficacy (Rivermead Mobility Index)

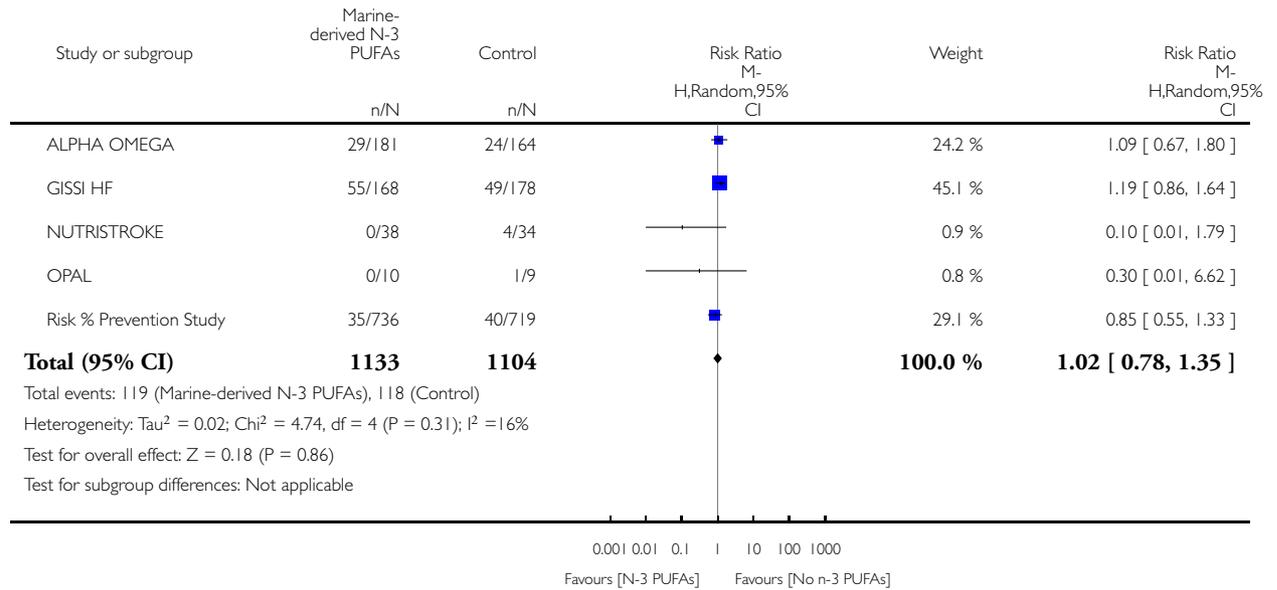


Analysis 2.3. Comparison 2 Marine-derived n-3 fatty acids therapy compared to no marine-derived n-3 fatty acids therapy: follow-up longer than 3 months, Outcome 3 Vascular-related death.

Review: Marine-derived n-3 fatty acids therapy for stroke

Comparison: 2 Marine-derived n-3 fatty acids therapy compared to no marine-derived n-3 fatty acids therapy: follow-up longer than 3 months

Outcome: 3 Vascular-related death

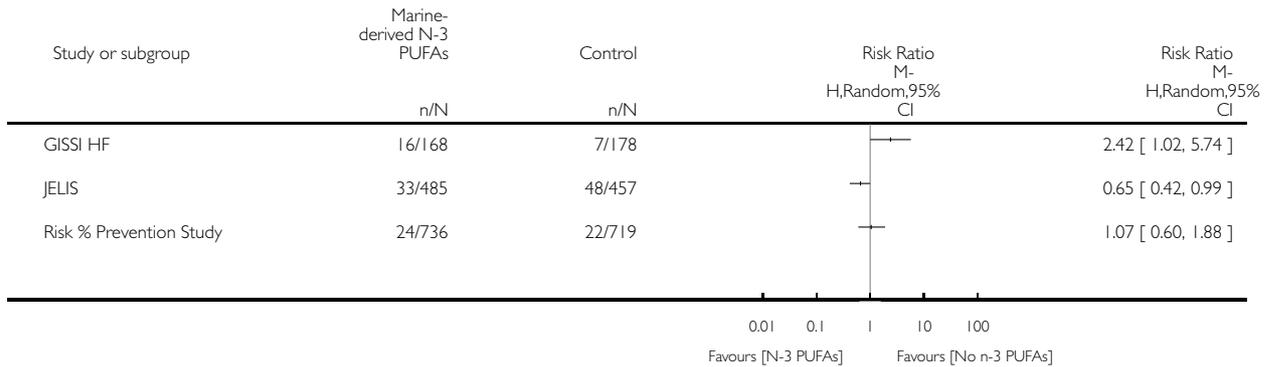


Analysis 2.4. Comparison 2 Marine-derived n-3 fatty acids therapy compared to no marine-derived n-3 fatty acids therapy: follow-up longer than 3 months, Outcome 4 All recurrent events (fatal and non-fatal).

Review: Marine-derived n-3 fatty acids therapy for stroke

Comparison: 2 Marine-derived n-3 fatty acids therapy compared to no marine-derived n-3 fatty acids therapy: follow-up longer than 3 months

Outcome: 4 All recurrent events (fatal and non-fatal)

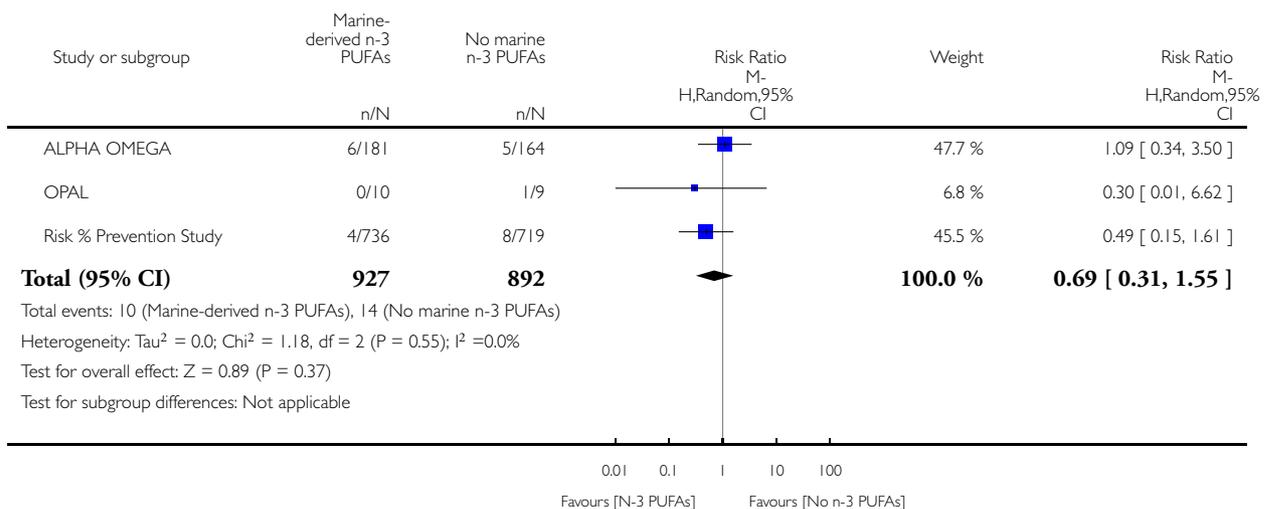


Analysis 2.5. Comparison 2 Marine-derived n-3 fatty acids therapy compared to no marine-derived n-3 fatty acids therapy: follow-up longer than 3 months, Outcome 5 Recurrent events (fatal only).

Review: Marine-derived n-3 fatty acids therapy for stroke

Comparison: 2 Marine-derived n-3 fatty acids therapy compared to no marine-derived n-3 fatty acids therapy: follow-up longer than 3 months

Outcome: 5 Recurrent events (fatal only)

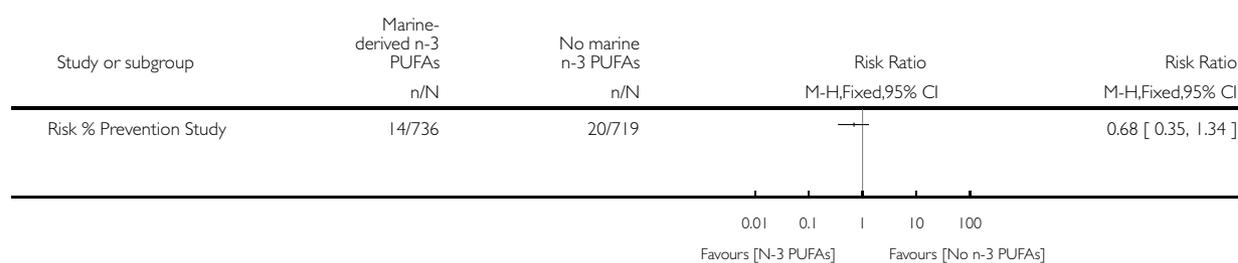


Analysis 2.6. Comparison 2 Marine-derived n-3 fatty acids therapy compared to no marine-derived n-3 fatty acids therapy: follow-up longer than 3 months, Outcome 6 Recurrent events (non-fatal only).

Review: Marine-derived n-3 fatty acids therapy for stroke

Comparison: 2 Marine-derived n-3 fatty acids therapy compared to no marine-derived n-3 fatty acids therapy: follow-up longer than 3 months

Outcome: 6 Recurrent events (non-fatal only)

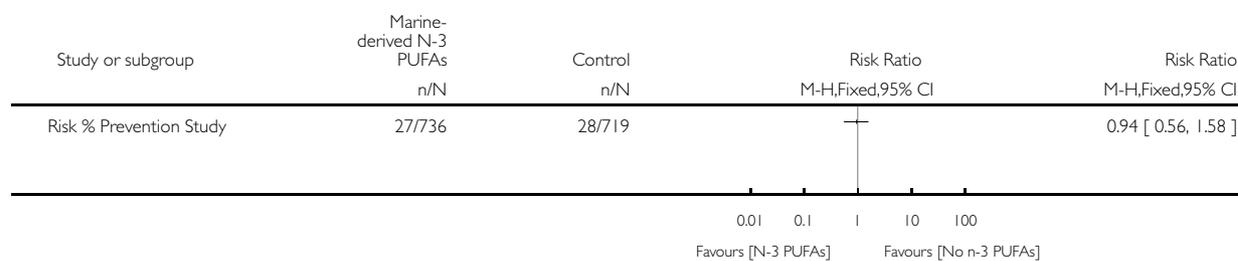


Analysis 2.7. Comparison 2 Marine-derived n-3 fatty acids therapy compared to no marine-derived n-3 fatty acids therapy: follow-up longer than 3 months, Outcome 7 Adverse events (all).

Review: Marine-derived n-3 fatty acids therapy for stroke

Comparison: 2 Marine-derived n-3 fatty acids therapy compared to no marine-derived n-3 fatty acids therapy: follow-up longer than 3 months

Outcome: 7 Adverse events (all)

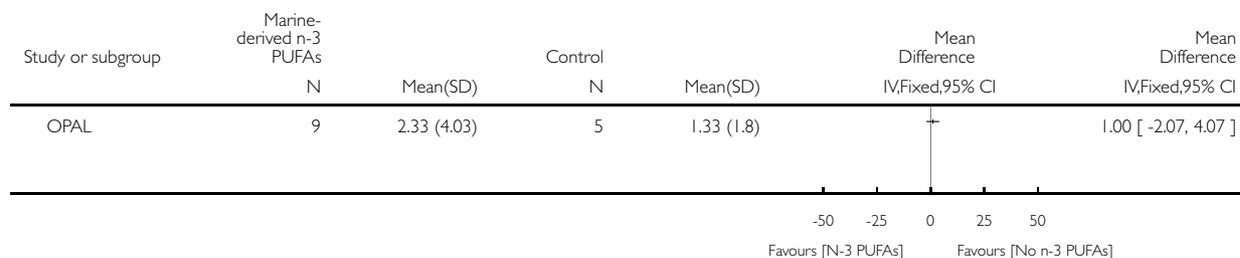


Analysis 2.8. Comparison 2 Marine-derived n-3 fatty acids therapy compared to no marine-derived n-3 fatty acids therapy: follow-up longer than 3 months, Outcome 8 Mood (GHQ-28).

Review: Marine-derived n-3 fatty acids therapy for stroke

Comparison: 2 Marine-derived n-3 fatty acids therapy compared to no marine-derived n-3 fatty acids therapy: follow-up longer than 3 months

Outcome: 8 Mood (GHQ-28)



ADDITIONAL TABLES

Table 1. Sample characteristics in included studies providing outcome data

| Study ID | Stroke/TIA population, n | Sex | Age (years) | Type of baseline stroke | Time between baseline event and intervention |
|---|--------------------------|--------------------|--|-------------------------|---|
| <i>Studies with follow-up of three months or less</i> | | | | | |
| FOILS | 102 | 72 men 30 women | Mean ± SD Intervention group = 64 ± 10 Control group = 65 ± 12 | Ischaemic | Median (IQR) Fish oil group = 1.18 (0.5, 2.1) years Placebo oil group = 0.90 (0.5, 2.3) years |
| Foroughinia 2018 | 18 | 9 men 9 women | Mean (+ SD probably, not specified) and range Intervention group = 75.2 ± 6.2 (Range: | Ischaemic | Not stated |

Table 1. Sample characteristics in included studies providing outcome data (Continued)

| | | | | | |
|---|-----|----------------------|---|--|--|
| | | | 65 to 82) Control group = 71.7 ± 6.8 (Range: 57 to 83) | | |
| Saito 2017 | 40 | 15 men 25 women | Median (range) Intervention = 53 (22 to 68) Control = 48 (20 to 67) | Haemorrhagic (subarachnoid haemorrhage only) | Admission to the emergency department within 72 hours after the initial bleeding episode |
| Studies with follow-up of more than three months | | | | | |
| ALPHA OMEGA | 345 | 264 men 81 women | Mean + SD, Median, Range EPA-DHA = 70.95 ± 5.68, 71.49, 60.1 to 80.9 EPA-DHA + ALA = 69.92 ± 5.89, 70.36, 60.2 to 80.0 ALA = 70.34 ± 5.39, 71.52, 60.4 to 80.2 Placebo = 70.38 ± 5.58, 71.04, 59.8 to 80.6 Overall (n = 345): Mean 70.4 ± 5.6, 71.0, range 60.0 to 80.9 | Not stated | Not stated |
| GISSI HF | 346 | 275 men 71 women | Mean ± SD Intervention group = 71 ± 8 Control group = 70 ± 9 | Not stated | Not stated |
| JELIS | 942 | 369 men 573 women | Mean ± SD Intervention group = 66 ± 7 Control group = 65 ± 7 | Both (ischaemic and haemorrhagic) | Not stated (6 months or more, as per exclusion criteria) |
| NUTRISTROKE | 72 | 47 men 25 women | Mean (± SD probably, not specified) Marine-derived n-3 PUFAs = 61.3 ± 13.6 Marine-derived n-3 | Ischaemic | Less than 60 days (as per exclusion criteria) |

Table 1. Sample characteristics in included studies providing outcome data (Continued)

| | | | | | |
|-------------------------|------|----------------------|---|------------|------------|
| | | | PUFAs + Antioxidants = 66.3 ± 11.4 Antioxidants = 65.1 ± 12.8 Placebo = 68.4 ± 12.6 | | |
| OPAL | 19 | 10 men 9 women | Mean + SD Intervention group = 75.16 ± 2.65 Control group = 75.04 ± 3.17 | Not stated | Not stated |
| Risk & Prevention Study | 1455 | 893 men 562 women | Mean + SD Intervention = 68.4 ± 9.2 Control = 68.3 ± 9.2 | Not stated | Not stated |

ALA: alpha linolenic acid
DHA: docosahexaenoic acid
EPA: eicosapentaenoic acid
IQR: interquartile range
PUFAs: polyunsaturated fatty acids
SD: standard deviation
TIA: transient ischaemic attack

Table 2. Characteristics of the interventions in included studies providing data

| Study ID | Type of intervention | Dose | Control | Length of intervention | Lat-est time point of assessment | Co-interventions |
|---|--|---|--|---|---|--|
| <i>Studies with follow-up of three months or less</i> | | | | | | |
| FOILS | Fish oil (Hoki liver oil) supplement | Approximately 1.2 g/day of marine-derived n-3 PUFAs (3 g/day of fish oil) | Placebo (blend of palm and soy oils) | 12 weeks | 12 weeks | N/A |
| Foroughinia 2018 | Loading dose of marine-derived n-3 PUFAs (soft gel capsules, Premium V Life Company, UK) | 990 mg EPA and 660 mg DHA | Open control (no marine-derived n-3 PUFAs) | Single dose, 12 hours before carotid angioplasty and stenting (CAS) | 30 days after procedure (planned). Actual time not stated | - Heparin (during CAS, 80 units per kilogram of body weight) - Clopidogrel (loading dose of |

Table 2. Characteristics of the interventions in included studies providing data (Continued)

| | | | | | | |
|---|--|--|--|---|-------------------------------------|--|
| | | | | | | 600 mg, then 75 mg/day) - Aspirin (loading dose of 325 mg, then 80 mg/day) |
| Saito 2017 | Intravenous fish oil-based lipid emulsion (Omegaven 10%, Fresenius Kabi, Germany) Ethyl ester capsules (Omacor, Ferrer Chile/Spain Pronova BioPharma Norway) | IV Emulsion = 100 mL/day (adjusted dose of 0.2 g/kg/day to participants with a body weight less than 50 kg) Omacor = 1840 mg of EPA and 1520 mg of DHA per day | Open control (no marine-derived n-3 PUFAs) | 60 days (5 intravenous treatment and 55 oral treatment) | 90 days | - Medical stabilisation - 60 mg of oral nimodipine every 4 hours |
| Studies with follow-up of more than three months | | | | | | |
| ALPHA OMEGA | Margarine supplemented with EPA and DHA (derived from fish oil: Marinol®) | 400 mg of EPA-DHA per day | Placebo (oleic acid) | 40 months | 6.5 ± 2.5 | 2 × 2 design. Participants were also randomised to receive ALA (2 g/day) or Placebo |
| GISSI HF | Ethyl esters capsules | 850-882 mg of EPA and DHA per day (average ratio of 1:1.2) | Placebo (no details) | Median (IQR) 3.9 (3.0 to 4.5) years | Median (IQR) 3.9 (3.0 to 4.5) years | Participants also randomised to rosuvastatin (10 mg/day) or corresponding placebo |
| JELIS | Highly purified ethyl esters capsules (EPADEL) | 1800 mg/day of EPA | Open control (no marine-derived n-3 PUFAs) | Up to 5 years | 4.6 ± 1.1 years | - Pravastatin (10 to 20 mg/day), or - Simvastatin (5 to 10 mg/day) |
| NU-TRISTROKE | Fish oil capsules | 250 mg of DHA and 250 mg of EPA per day | Placebo (no details) | 12 months | 12 months | 2 × 2 design. Participants were also randomised to receive antioxidants (290 mg vitamin E, 240 |

Table 2. Characteristics of the interventions in included studies providing data (Continued)

| | | | | | | | |
|-------------------------|-----------------------|--|---------------------|-------------|-----------------------------------|-----------------------------------|--|
| | | | | | | | mg vitamin C, 150 mg polyphenols and 19 mg β -carotene) or placebo |
| OPAL | Ethyl esters capsules | 200 mg of EPA and 500 mg of DHA per day | Placebo (olive oil) | (olive oil) | 24 months | 24 months | N/A |
| Risk & Prevention Study | Ethyl esters capsules | At least 850 mg per day of EPA and DHA (ratio ranging from 0.9:1 to 1.5:1) | Placebo (olive oil) | (olive oil) | Median (IQR) 5 (4.0 to 5.5) years | Median (IQR) 5 (4.0 to 5.5) years | N/A |

ALA: alpha linolenic acid

CAS: carotid angioplasty and stenting

DHA: docosahexaenoic acid

EPA: eicosapentaenoic acid

IQR: interquartile range

N/A: not applicable

PUFAs: polyunsaturated fatty acids

APPENDICES

Appendix I. CENTRAL search strategy

#1MeSH descriptor: [Cerebrovascular Disorders] this term only

#2MeSH descriptor: [Basal Ganglia Cerebrovascular Disease] this term only

#3MeSH descriptor: [Brain Ischemia] explode all trees

#4MeSH descriptor: [Carotid Artery Diseases] explode all trees

#5MeSH descriptor: [Cerebral Small Vessel Diseases] explode all trees

#6MeSH descriptor: [Intracranial Arterial Diseases] explode all trees

#7MeSH descriptor: [Intracranial Embolism and Thrombosis] explode all trees

#8MeSH descriptor: [Intracranial Hemorrhages] explode all trees

#9MeSH descriptor: [Stroke] this term only

#10MeSH descriptor: [Brain Infarction] explode all trees

#11MeSH descriptor: [Stroke, Lacunar] this term only

#12MeSH descriptor: [Vasospasm, Intracranial] this term only

#13MeSH descriptor: [Vertebral Artery Dissection] this term only

#14(stroke* or poststroke or apoplex* or cerebral vasc* or brain vasc* or cerebrovasc* or cva* or SAH):ti,ab,kw (Word variations have been searched)

#15(((brain or cerebr* or cerebell* or vertebrobasil* or hemispher* or intracran* or intracerebral or infratentorial or supratentorial or middle cerebral artery or MCA* or anterior circulation or posterior circulation or basilar artery or vertebral artery or space-occupying) near/5 (ischaemi* or ischemi* or infarct* or thrombo* or emboli* or occlus* or hypoxi*)):ti,ab,kw (Word variations have been searched)

#16(((brain* or cerebr* or cerebell* or intracerebral or intracran* or parenchymal or intraparenchymal or intraventricular or infratentorial or supratentorial or basal gangli* or putaminal or putamen or posterior fossa or hemispher* or subarachnoid) near/5 (haemorrhag* or haemorrhag* or haematoma* or hematoma* or bleed*)):ti,ab,kw (Word variations have been searched)

#17MeSH descriptor: [Hemiplegia] this term only

#18MeSH descriptor: [Paresis] explode all trees

#19MeSH descriptor: [Gait Disorders, Neurologic] explode all trees

#20(hemipleg* or hemipar* or paresis or paraparesis or paretic):ti,ab,kw (Word variations have been searched)

#21MeSH descriptor: [Gait Disorders, Neurologic] explode all trees

#22(hemipleg* or hemipar* or paresis or paraparesis or paretic):ti,ab,kw (Word variations have been searched)

#23{or #1-#22}

#24MeSH descriptor: [Fish Oils] explode all trees

#25MeSH descriptor: [Fatty Acids] this term only

#26MeSH descriptor: [Fatty Acids, Omega-3] this term only

#27MeSH descriptor: [Docosahexaenoic Acids] this term only

#28MeSH descriptor: [Eicosapentaenoic Acid] this term only

#29MeSH descriptor: [Fishes] explode all trees

#30MeSH descriptor: [Seafood] this term only

#31MeSH descriptor: [Fish Products] this term only

#32MeSH descriptor: [Shellfish] this term only

#33MeSH descriptor: [Dietary Fats] this term only

#34(((fish* or cod or mackerel or kipper* or pilchards or tuna or trout or sprat* or salmon or herring or crab or whitebait or swordfish or sardine* or krill or microalgae or marine) near/3 (oil* or fat* or acid* or "omega-3" or omega3 or "omega 3" or "n-3" or polyunsaturat*)) or PUFA*):ti,ab,kw (Word variations have been searched)

#35((Docosahexaenoic or eicosapentaenoic or icosapentaenoic) near/3 acid*):ti,ab,kw (Word variations have been searched)

#36(EPA or DHA):ti,ab,kw (Word variations have been searched)

#37{or #24-#36}

#38#23 and #37

Appendix 2. MEDLINE (Ovid) search strategy

1. cerebrovascular disorders/ or basal ganglia cerebrovascular disease/ or exp brain ischemia/ or exp carotid artery diseases/ or exp cerebral small vessel diseases/ or exp intracranial arterial diseases/ or exp "intracranial embolism and thrombosis"/ or exp intracranial hemorrhages/ or stroke/ or exp brain infarction/ or stroke, lacunar/ or vasospasm, intracranial/ or vertebral artery dissection/
2. (stroke\$ or poststroke or apoplex\$ or cerebral vasc\$ or brain vasc\$ or cerebrovasc\$ or cva\$ or SAH).tw.
3. ((brain or cerebr\$ or cerebell\$ or vertebrobasil\$ or hemispher\$ or intracran\$ or intracerebral or infratentorial or supratentorial or middle cerebral artery or MCA\$ or anterior circulation or posterior circulation or basilar artery or vertebral artery or space-occupying) adj5 (isch?emi\$ or infarct\$ or thrombo\$ or emboli\$ or occlus\$ or hypoxi\$)).tw.
4. ((brain\$ or cerebr\$ or cerebell\$ or intracerebral or intracran\$ or parenchymal or intraparenchymal or intraventricular or infratentorial or supratentorial or basal gangli\$ or putaminal or putamen or posterior fossa or hemispher\$ or subarachnoid) adj5 (h?emorrhag\$ or h?ematoma\$ or bleed\$)).tw.
5. hemiplegia/ or exp paresis/ or exp Gait Disorders, Neurologic/
6. (hemipleg\$ or hemipar\$ or paresis or paraparesis or paretic).tw.
7. or/1-6
8. exp fish oils/ or fatty acids/ or fatty acids, omega-3/ or docosahexaenoic acids/ or eicosapentaenoic acid/
9. exp Fishes/ or seafood/ or fish products/ or shellfish/ or Dietary Fats/
10. (((fish\$ or cod or mackerel or kipper\$ or pilchards or tuna or trout or sprat\$ or salmon or herring or crab or whitebait or swordfish or sardine\$ or krill or microalgae or marine) adj3 (oil\$ or fat\$ or acid\$ or omega-3 or omega3 or omega 3 or n-3 or polyunsaturat\$)) or PUFA\$).tw.
11. ((Docosahexaenoic or eicosapentaenoic or icosapentaenoic) adj3 acid\$).tw.

12. (EPA or DHA).tw.
13. or/8-12
14. Randomized Controlled Trials as Topic/
15. Random Allocation/
16. Controlled Clinical Trials as Topic/
17. control groups/
18. clinical trials as topic/ or clinical trials, phase i as topic/ or clinical trials, phase ii as topic/ or clinical trials, phase iii as topic/ or clinical trials, phase iv as topic/
19. double-blind method/
20. single-blind method/
21. Placebos/
22. placebo effect/
23. cross-over studies/
24. randomized controlled trial.pt.
25. controlled clinical trial.pt.
26. (clinical trial or clinical trial phase i or clinical trial phase ii or clinical trial phase iii or clinical trial phase iv).pt.
27. (random\$ or RCT or RCTs).tw.
28. (controlled adj5 (trial\$ or stud\$)).tw.
29. (clinical\$ adj5 trial\$).tw.
30. ((control or treatment or experiment\$ or intervention) adj5 (group\$ or subject\$ or patient\$)).tw.
31. (quasi-random\$ or quasi random\$ or pseudo-random\$ or pseudo random\$).tw.
32. ((control or experiment\$ or conservative) adj5 (treatment or therapy or procedure or manage\$)).tw.
33. ((singl\$ or doubl\$ or tripl\$ or trebl\$) adj5 (blind\$ or mask\$)).tw.
34. (cross-over or cross over or crossover).tw.
35. (placebo\$ or sham).tw.
36. trial.ti.
37. (assign\$ or allocat\$).tw.
38. controls.tw.
39. or/14-38
40. 7 and 13 and 39

Appendix 3. Embase (Ovid) search strategy

1. cerebrovascular disease/ or brain disease/ or exp basal ganglion hemorrhage/ or exp brain hemangioma/ or exp brain hematoma/ or exp brain hemorrhage/ or exp brain infarction/ or exp brain ischemia/ or exp carotid artery disease/ or exp cerebral artery disease/ or exp cerebrovascular accident/ or exp cerebrovascular malformation/ or exp intracranial aneurysm/ or exp occlusive cerebrovascular disease/ or exp vertebrobasilar insufficiency/
2. (stroke\$ or poststroke or apoplex\$ or cerebral vasc\$ or brain vasc\$ or cerebrovasc\$ or cva\$ or SAH).tw.
3. ((brain or cerebr\$ or cerebell\$ or vertebrobasil\$ or hemispher\$ or intracran\$ or intracerebral or infratentorial or supratentorial or middle cerebral artery or MCA\$ or anterior circulation or posterior circulation or basilar artery or vertebral artery or space-occupying) adj5 (isch?emi\$ or infarct\$ or thrombo\$ or emboli\$ or occlus\$ or hypoxi\$)).tw.
4. ((brain\$ or cerebr\$ or cerebell\$ or intracerebral or intracran\$ or parenchymal or intraparenchymal or intraventricular or infratentorial or supratentorial or basal gangli\$ or putaminal or putamen or posterior fossa or hemispher\$ or subarachnoid) adj5 (h?emorrhag\$ or h?ematoma\$ or bleed\$)).tw.
5. exp hemiplegia/ or exp paresis/
6. or neurologic gait disorder/
7. (hemipleg\$ or hemipar\$ or paresis or paraparesis or paretic).tw.
8. or/1-7
9. exp fish oil/ or omega 3 fatty acid/ or long chain fatty acid/ or very long chain fatty acid/ or unsaturated fatty acid/ or polyunsaturated fatty acid/ or icosapentaenoic acid/ or icosapentaenoic acid ethyl ester/ or docosahexaenoic acid/
10. exp fish/ or fish meat/ or fish meal/ or fish product/ or sea food/ or shellfish/ or alga/ or cod liver oil/ or edible oil/ or fat intake/

11. (((fish\$ or cod or mackerel or kipper\$ or pilchards or tuna or trout or sprat\$ or salmon or herring or crab or whitebait or swordfish or sardine\$ or krill or microalgae or marine) adj3 (oil\$ or fat\$ or acid\$ or omega-3 or omega3 or omega 3 or n-3 or polyunsaturat\$) or PUFA\$).tw.
12. ((Docosahexaenoic or eicosapentaenoic or icosapentaenoic) adj3 acid\$).tw.
13. (EPA or DHA).tw.
14. 9 or 10 or 11 or 12 or 13
15. Randomized Controlled Trial/ or “randomized controlled trial (topic)”/
16. Randomization/
17. Controlled clinical trial/ or “controlled clinical trial (topic)”/
18. control group/ or controlled study/
19. clinical trial/ or “clinical trial (topic)”/ or phase 1 clinical trial/ or phase 2 clinical trial/ or phase 3 clinical trial/ or phase 4 clinical trial/
20. Crossover Procedure/
21. Double Blind Procedure/
22. Single Blind Procedure/ or triple blind procedure/
23. placebo/ or placebo effect/
24. (random\$ or RCT or RCTs).tw.
25. (controlled adj5 (trial\$ or stud\$)).tw.
26. (clinical\$ adj5 trial\$).tw.
27. ((control or treatment or experiment\$ or intervention) adj5 (group\$ or subject\$ or patient\$)).tw.
28. (quasi-random\$ or quasi random\$ or pseudo-random\$ or pseudo random\$).tw.
29. ((control or experiment\$ or conservative) adj5 (treatment or therapy or procedure or manage\$)).tw.
30. ((singl\$ or doubl\$ or tripl\$ or trebl\$) adj5 (blind\$ or mask\$)).tw.
31. (cross-over or cross over or crossover).tw.
32. (placebo\$ or sham).tw.
33. trial.ti.
34. (assign\$ or allocat\$).tw.
35. controls.tw.
36. or/15-35
37. 8 and 14 and 36

Appendix 4. CINAHL EBSCO search strategy

S1(MH “Cerebrovascular Disorders”) OR (MH “Basal Ganglia Cerebrovascular Disease+”) OR (MH “Carotid Artery Diseases+”) OR (MH “Cerebral Ischemia+”) OR (MH “Cerebral Vasospasm”) OR (MH “Intracranial Arterial Diseases+”) OR ((MH “Intracranial Embolism and Thrombosis”)) OR (MH “Intracranial Hemorrhage+”) OR (MH “Stroke”) OR (MH “Vertebral Artery Dissections”) OR (MH “Stroke Patients”) OR (MH “Stroke Units”)

S2TI (stroke or poststroke or post-stroke or cerebrovasc* or brain vas* or cerebral vas* or cva or apoplex or SAH) or AB (stroke or poststroke or post-stroke or cerebrovasc* or brain vas* or cerebral vas* or cva or apoplex or SAH)

S3TI (brain* or cerebr* or cerebell* or intracran* or intracerebral) or AB (brain* or cerebr* or cerebell* or intracran* or intracerebral)

S4TI (ischemi* or ischaemi* or infarct* or thrombo* or emboli* or occlus*) or AB (ischemi* or ischaemi* or infarct* or thrombo* or emboli* or occlus*)

S5S3 AND S4

S6TI (brain* or cerebr* or cerebell* or intracerebral or intracranial or subarachnoid) or AB (brain* or cerebr* or cerebell* or intracerebral or intracranial or subarachnoid)

S7TI (haemorrhage* or hemorrhage* or haematoma* or hematoma* or bleed*) or AB (haemorrhage* or hemorrhage* or haematoma* or hematoma* or bleed*)

S8S6 AND S7

S9TI transient ischaemic attack* or TI transient ischemic attack* or AB transient ischaemic attack* or AB transient ischemic attack* or TI TIA or TI TIA s or AB TIA or AB TIAs

S10(MH “Hemiplegia”)

S11TI (hemipleg* or hemipar* or paresis or paretic) or AB (hemipleg* or hemipar* or paresis or paretic)

S12S1 OR S2 OR S5 OR S8 OR S9 OR S10 OR S11
 S13(MH "Fish Oils+") OR (MH "Fatty Acids") OR (MH "Fatty Acids, Omega-3") OR (MH "Docosahexaenoic Acids") OR (MH "Eicosapentaenoic Acid")
 S14(MH "Fish+") OR (MH "Seafood") OR (MH "Shellfish") OR (MH "Crustacea") OR (MH "Fats, Unsaturated") OR (MH "Dietary Fats")
 S15TX (((fish* OR cod OR mackerel OR kipper* OR pilchards OR tuna OR trout OR sprat* OR salmon OR herring OR crab OR whitebait OR swordfish OR sardine* OR krill OR microalgae OR marine) N3 (oil* OR fat* OR acid* OR omega-3 OR omega3 OR omega 3 OR n-3 OR polyunsaturat*)) OR PUFA*)
 S16TX ((Docosahexaenoic OR eicosapentaenoic OR icosapentaenoic) N3 acid*)
 S17TX (EPA OR DHA)
 S18S13 OR S14 OR S15 OR S16 OR S17
 S19(MH "Randomized Controlled Trials") or (MH "Random Assignment") or (MH "Random Sample+")
 S20(MH "Clinical Trials") or (MH "Intervention Trials") or (MH "Therapeutic Trials")
 S21(MH "Double-Blind Studies") or (MH "Single-Blind Studies") or (MH "Triple-Blind Studies")
 S22(MH "Control (Research)") or (MH "Control Group") or (MH "Placebos") or (MH "Placebo Effect")
 S23(MH "Crossover Design") OR (MH "Quasi-Experimental Studies")
 S24PT (clinical trial or randomized controlled trial)
 S25TI (random* or RCT or RCTs) or AB (random* or RCT or RCTs)
 S26TI (controlled N5 (trial* or stud*)) or AB (controlled N5 (trial* or stud*))
 S27TI (clinical* N5 trial*) or AB (clinical* N5 trial*)
 S28TI ((control or treatment or experiment* or intervention) N5 (group* or subject* or patient*)) or AB ((control or treatment or experiment* or intervention) N5 (group* or subject* or patient*))
 S29((control or experiment* or conservative) N5 (treatment or therapy or procedure or manage*)) or AB ((control or experiment* or conservative) N5 (treatment or therapy or procedure or manage*))
 S30TI ((singl* or doubl* or tripl* or trebl*) N5 (blind* or mask*)) or AB ((singl* or doubl* or tripl* or trebl*) N5 (blind* or mask*))
 S31TI (cross-over or cross over or crossover) or AB (cross-over or cross over or crossover)
 S32TI (placebo* or sham) or AB (placebo* or sham)
 S33TI trial
 S34TI (assign* or allocat*) or AB (assign* or allocat*)
 S35TI controls or AB controls
 S36TI (quasi-random* or quasi random* or pseudo-random* or pseudo random*) or AB (quasi-random* or quasi random* or pseudo-random* or pseudo random*)
 S37S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35 OR S36
 S38S12 AND S18 AND S37

Appendix 5. Web of Science search strategy

- #1. TS=(stroke or poststroke or post-stroke or apoplex* or cerebral vasc* or brain vasc* or cerebrovasc* or cva or SAH)
- #2. TS=((brain or cerebr* or cerebell* or vertebrobasil* or hemispher* or intracran* or intracerebral or infratentorial or supratentorial or "middle cerebral artery" or MCA* or "anterior circulation" or "posterior circulation" or "basilar artery" or "vertebral artery" or "space-occupying") NEAR/5 (isch\$emi* or infarct* or thrombo* or emboli* or occlus* or hypoxi*))
- #3. TS=((brain* or cerebr* or cerebell* or intracerebral or intracran* or parenchymal or intraparenchymal or intraventricular or infratentorial or supratentorial or "basal gangli*" or putaminal or putamen or "posterior fossa" or hemispher* or subarachnoid) NEAR/5 (h\$emorrhage* or h\$ematoma* or bleed*))
- #4. TS=(hemipleg* or hemipar* or paresis or paraparesis or paretic)
- #5. #1 OR #2 OR #3 OR #4
- #6. TS=((fish* or cod or mackerel or kipper* or pilchards or tuna or trout or sprat* or salmon or herring or crab or whitebait or swordfish or sardine* or krill or microalgae or marine) NEAR/3 (oil* or fat* or acid* or omega-3 or omega3 or "omega 3" or n-3 or polyunsaturat*)) or PUFA*)
- #7. TS=((Docosahexaenoic or eicosapentaenoic or icosapentaenoic) NEAR/3 acid*)
- #8. TS=(EPA or DHA)

#9. #6 OR #7 OR #8
 #10. TS=(random* or RCT or RCTs)
 #11. TS=(controlled NEAR/5 (trial\$ or stud*))
 #12. TS=(clinical* NEAR/5 trial*)
 #13. TS=((control or treatment or experiment* or intervention) NEAR/5 (group\$ or subject\$ or patient\$))
 #14. TS=(quasi-random* or quasi random* or pseudo-random* or pseudo random*)
 #15. TS=((control\$ or experiment* or conservative) NEAR/5 (treatment or therapy or manage* or procedure))
 #16. TS=((doubl* or singl* or tripl* or trebl*) NEAR/5 (blind* or mask*))
 #17. TS=(cross-over or cross over or crossover)
 #18. TS=(placebo* or sham)
 #19. TI=trial
 #20. TS=(assign* or allocat*)
 #21. TS=controls
 #22. #10 #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21
 #24. #5 AND #9 AND #22

Appendix 6. US National Institutes of Health Ongoing Trial Register ClinicalTrials.gov search strategy

(fish OR fatty acid OR dietary fat OR Omega 3 OR docosahexaenoic OR eicosapentaenoic OR sea OR marine)
 AND
 (Brain Infarction OR Intracranial Hemorrhages OR Carotid Artery Diseases OR Brain Ischemia OR Cerebral Hemorrhage OR Cerebrovascular Disorders OR Stroke) [DISEASE]

Appendix 7. Stroke Trials Registry search strategy

Keywords:
 1. Fatty acids
 2. Fish oil
 We adapted the search strategy for each registry

Appendix 8. ISRCTN Registry search strategy

Text search: (fish OR “fish oil” OR “fatty acids” OR “omega 3”) AND stroke

Appendix 9. World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) search strategy

stroke AND fatty acids OR stroke AND dietary fats OR stroke AND marine OR stroke AND fish OR stroke AND sea

CONTRIBUTIONS OF AUTHORS

MJM and FT conceived the review

CGAC developed search strategies and conducted searches

CGAC, MJM and FT screened studies for inclusion

CGAC and MJM retrieved full-text reports

CGAC, FT and MJM extracted data of included studies

CGAC conducted data analysis with support from LA

CGAC and FT assessed quality of the evidence

CGAC drafted the manuscript with contributions from MJM, LA and FT

DECLARATIONS OF INTEREST

Celia Gabriela Alvarez Campano: none known.

Mary Joan Macleod: none known.

Frank Thies: Dr Thies authored one of the studies included in the review ([Thies 2003](#)). However, he was not involved in its assessment at any stage (screening, data extraction and risk of bias assessment) and this study is not contributing any outcome data to the review.

Lorna Aucott: none known.

SOURCES OF SUPPORT

Internal sources

- University of Aberdeen, UK.

External sources

- University of Edinburgh, UK.
- Mexican Council for Science and Technology (CONACyT) and the Institute of Innovation and Technology Transfer (I²T²) (grant number 457349), Mexico.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

In order to improve clarity, we rephrased the secondary outcome “Incidence of different type of stroke (ischaemic or haemorrhagic)” to “Incidence of other type of stroke (ischaemic or haemorrhagic)”. However, the criteria for assessing this outcome were not modified. It refers to incidence, during follow-up, of a stroke different in type from the index event (i.e. if the index stroke was ischaemic, then incidence of haemorrhagic stroke or vice versa).

Additionally, to enhance the reporting of all efficacy outcome measures included, we amended the methodology for the primary outcome from: “For studies using multiple scales, we will select the one with the largest amount of data available or, in the case of equal amounts of data, the one reported first in the study” to the following:

“For studies using multiple scales, we included all functional outcome and disability/dependency measures reported. However, for a meta-analysis we would have selected the one with the largest amount of data available or, in the case of equal amounts of data, the one reported first in the study”.