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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.

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TABLE OF CONTENTS

[Intervention Review]

Marine-derived n-3 fatty acids therapy for stroke

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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.

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 EBSCO (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)	№ 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 assessed with: SF-36, high score better	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)		-	102 (1 RCT)	⊕⊕○○ Low [56]	Single study. Scoring system not specified Follow-up time: 3 months
Mood assessed with: GHQ-30, lower score better	Mean change from baseline (MD 1.41, 95% CI 0.07 to 2.75)		-	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 burden 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; Orencia 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 subanalysis 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.

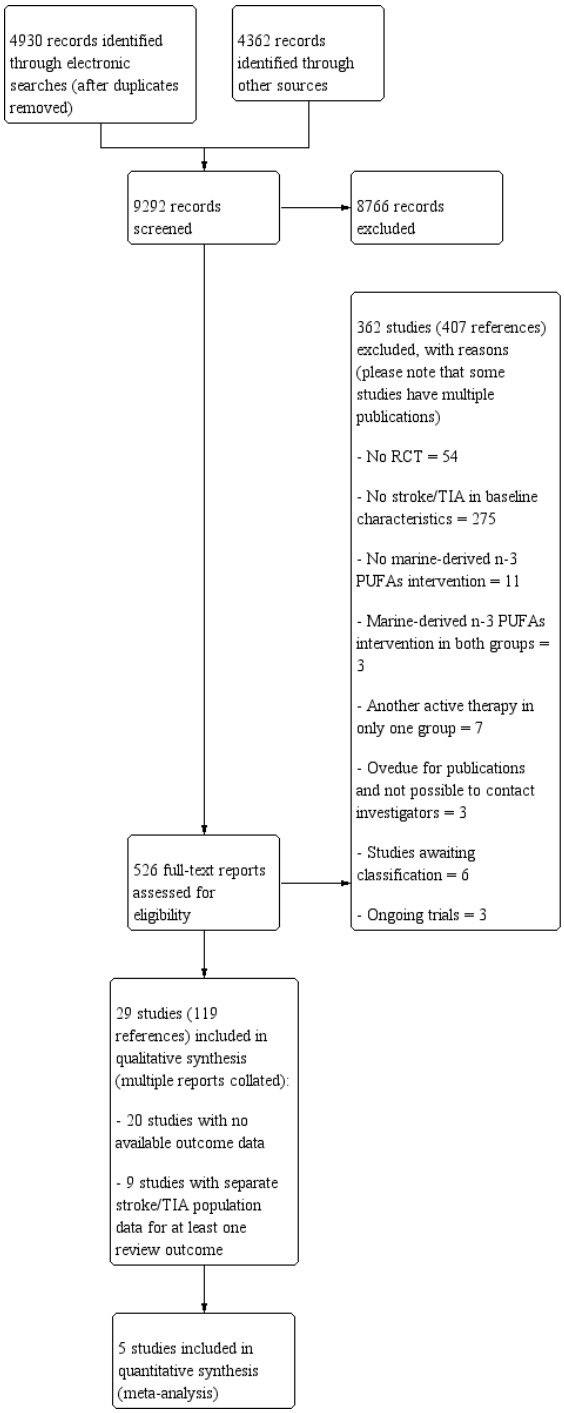
RESULTS

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.

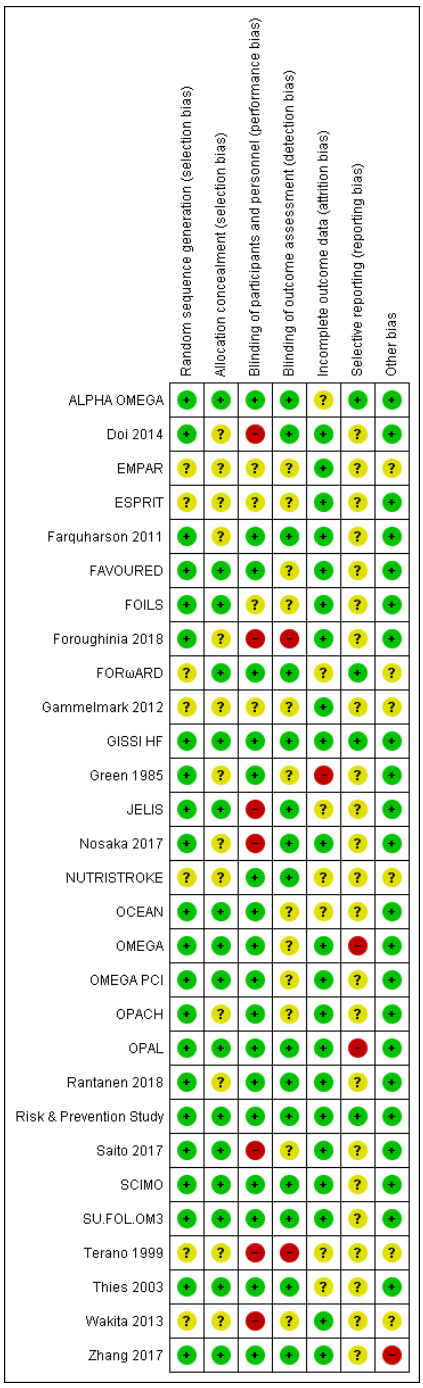
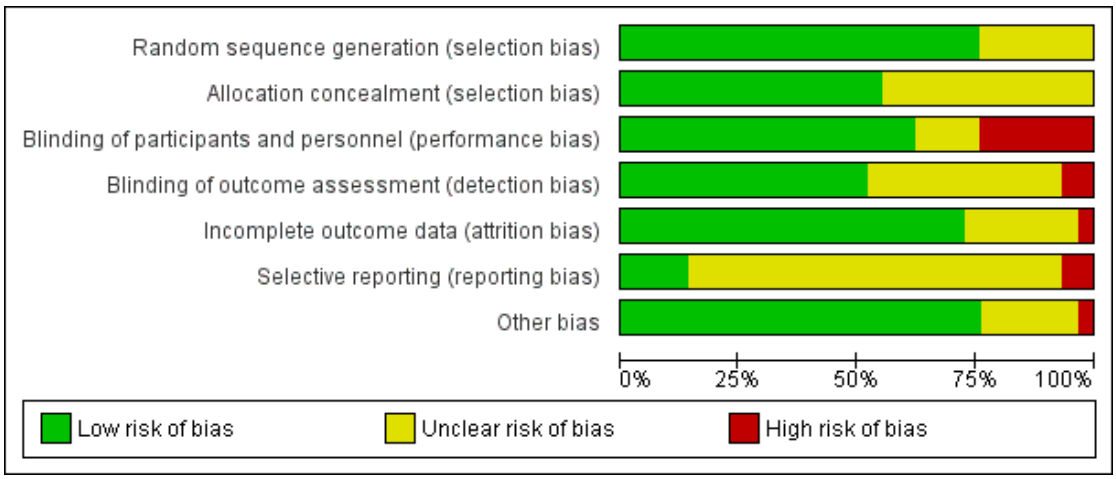


Figure 3. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



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

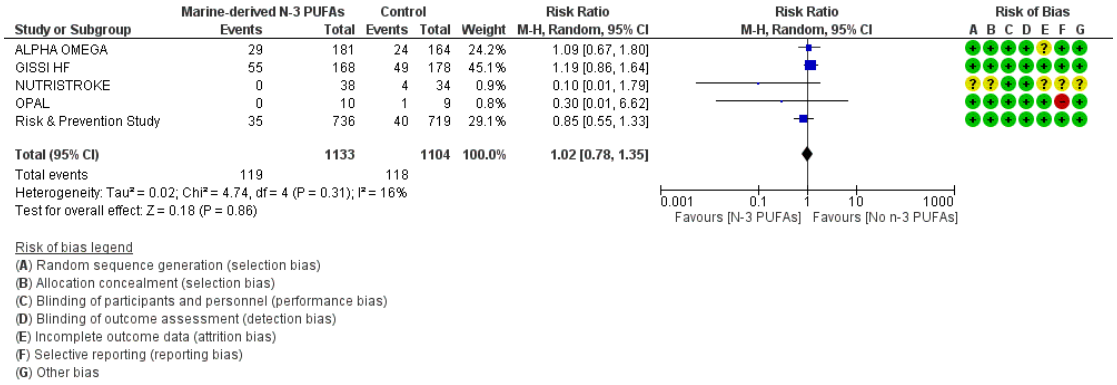
Efficacy (functional outcome or disability/dependency): primary outcome

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.

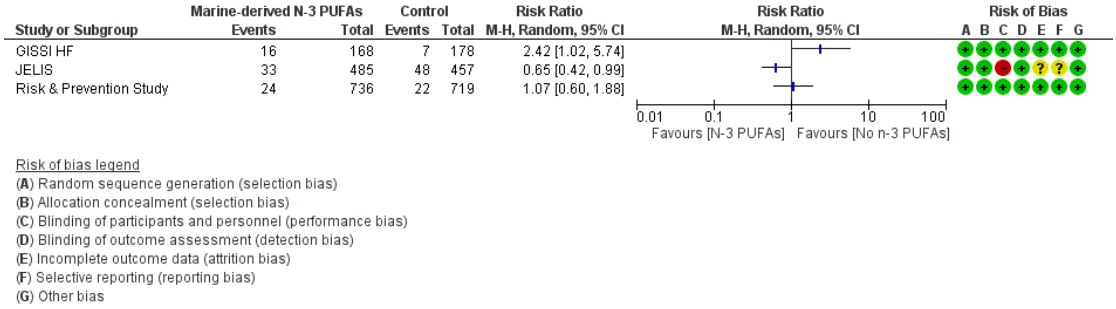
Figure 4. Forest plot of comparison: 2 Marine-derived n-3 fatty acids therapy compared to no marine-derived n-3 fatty acids therapy: follow-up longer than 3 months, outcome: 2.3 Vascular-related death.



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 (I^2 = 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)	№ 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		RR 1.02 (0.78 to 1.35)	2237 (5 RCTs)	⊕⊕◯◯ Low [45]	Follow-up time: from 1 to 5 years
	118 per 1000	120 per 1000 (92 to 159)				
Recurrent events (both ischaemic and haemorrhagic stroke)	Study population		RR 0.69 (0.31 to 1.55)	1819 (3 RCTs)	⊕⊕◯◯ Low [56]	Fatal only Follow-up time: from 2 to 5 years
	30 per 1000	11 per 1000 (9 to 47)				
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 (I^2T^2) (grant number 457349).

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

ALPHA OMEGA

Methods	RCT; parallel; 2 × 2 factorial design Number of study sites: 32 Dates: enrolment between April 2002 and December 2006, follow-up of 41 months (average)
Participants	Inclusion criteria: men and women aged 60 to 80 years; verified clinically diagnosed myocardial infarction up to 10 years before randomisation; written informed consent 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 $\leq$ 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 Sample size: 4837 participants (total population), 345 participants with history of stroke Participants randomised to intervention group (only stroke population): 181 (92 to EPA-DHA only and 89 to EPA-DHA + ALA) Participants randomised to control group (only stroke population): 164 (83 to ALA only and 81 to placebo) 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 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 Time from event (stroke) to start of intervention: not stated Type of baseline stroke: not stated Country: the Netherlands Ethnicity: predominantly of Dutch origin
Interventions	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) 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 Control: average of 20 g/day of margarine supplemented with 2 g of ALA or placebo (oleic acid) 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 Duration of intervention: 40 months Co-interventions: participants randomised also to ALA or placebo (as described above)

ALPHA OMEGA (*Continued*)

Outcomes	Primary outcome of study: major cardiovascular 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: vascular-related death, fatal recurrent events (no data available in non-fatal recurrent stroke) Latest time point of assessment: 6.5 ± 2.5 years Withdrawals or exclusions, n (stroke and/or TIA population only): no withdrawals other than death Study authors' contact status: replied - data provided
Notes	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 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

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)

Doi 2014 (*Continued*)

	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

EMPAR (*Continued*)

	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) Sample size: 653 participants (total population), approximately 9 participants with history of stroke or TIA (reported as percentage of total population) Participants randomised to intervention group (only stroke or TIA population): 6 or 7 (reported as 2% of total) Participants randomised to control group (only stroke or TIA population): 3 (reported as 1% of total) Sex (only stroke or TIA population): not stated Age (only stroke or TIA population): not stated Time from event (stroke or TIA) to start of intervention: not stated Type of baseline stroke: not stated Country: Canada Ethnicity: not stated
Interventions	Comparison groups: fish oil versus placebo (participants were subsequently randomised to LMWH) 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) Control: identical-appearing capsules of corn oil, 6 capsules given 3 times daily with meals Compliance: assessment method unclear Duration of intervention: 4 months Co-interventions: randomisation to LMWH (enoxaparin) 60 mg/day for 6 weeks or standard therapy
Outcomes	Primary outcome of study: reduction of PTCA restenosis Relevant review outcomes measured (in total population): recurrent events (stroke), adverse events Available outcome data for stroke and/or TIA population only: none Latest time point of assessment: 18±2 weeks Withdrawals or exclusions, n (stroke and/or TIA population only): not available Study authors' contact status: replied, no further data available
Notes	Dietary information: none provided Funding: Heart and Stroke Foundation of Ontario and Rhône Poulenc Rorer

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	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 (≥ 70% at visual inspection) amenable to PTCA 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 Sample size: 339 participants (total population), 7 participants with history of stroke and/or TIA Participants randomised to intervention group (only stroke and/or TIA population): 3 (analysed, not stated if more were randomised) Participants randomised to control group (only stroke and/or TIA population): 4 (analysed, not stated if more were randomised) Sex (only stroke and/or TIA population): not stated Age (only stroke and/or TIA population): not stated

ESPRIT (*Continued*)

	Time from event (stroke or TIA) to start of intervention: not stated Type of baseline stroke: not stated Country: Italy Ethnicity: not stated
Interventions	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
Outcomes	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
Notes	Dietary information: none provided Funding: Pharmacia-Upjohn Italia SpA

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

Farquharson 2011 (*Continued*)

Outcomes	Primary outcome of study: occurrence of sustained AF/atrial flutter (duration 10 minutes or requiring intervention) after cardiac surgery Relevant review outcomes measured (in total population): recurrent events (stroke), adverse events Available outcome data for stroke population only: none Latest time point of assessment: up to 4 weeks after start of intervention Withdrawals or exclusions, n (stroke population only): not available Study authors' contact status: no reply up to date
Notes	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 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)

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

FAVOURED

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 × 103/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 (Flexetrials)"
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 ± SD): fish oil group = 64 ± 10, placebo oil group = 65 ± 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 × 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
Risk of bias	

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

Foroughinia 2018 (*Continued*)

	Sex: intervention = 4 men and 4 women, control = 5 men and 5 women Age, years (mean ± SD and range): intervention = 75.2 ± 6.2, range: 65 to 82; control: 71.7 ± 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
Interventions	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)
Outcomes	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
Notes	Dietary information: none provided Funding: Office of Vice Chancellor for Research in Shiraz University of Medical Sciences, Shiraz, Iran

Risk of bias

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"

Foroughinia 2018 (*Continued*)

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

FORωARD

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)

FORωARD (*Continued*)

	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

FORωARD (*Continued*)

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

GISSI HF (*Continued*)

	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 Sample size: 6975 participants (total population), 346 participants with history of stroke Participants randomised to intervention group (only stroke population): 168 Participants randomised to control group (only stroke population): 178 Sex (only stroke population): marine-derived n-3 PUFAs group = 130 men and 38 women; placebo = 145 men and 33 women Age, years (only stroke population) mean ± SD: marine-derived n-3 PUFAs group = 71 ± 8; placebo = 70 ± 9 Time from event (stroke) to start of intervention: not stated Type of baseline stroke: not stated Country: Italy Ethnicity: not stated
Interventions	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 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) Control: matching placebo (no further details) 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 Duration of intervention: median of 3.9 years (IQR 3.0 to 4.5) Co-interventions: participants also randomised to rosuvastatin (10 mg/day) or corresponding placebo
Outcomes	Primary outcome of study: time to death, and time to death or admission to hospital for cardiovascular reasons Relevant review outcomes measured (in total population): vascular-related death; recurrent events; adverse events Available outcome data for stroke population only: vascular-related death; recurrent events (stroke) Latest time point of assessment: median of 3.9 years (IQR 3.0 to 4.5) Withdrawals or exclusions, n (stroke population only): not available Study authors' contact status: replied, data provided
Notes	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" 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

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*)

	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
Interventions	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)
Outcomes	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
Notes	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

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	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 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 Sample size: 18,645 participants (total population), 942 participants with history of stroke or TIA Participants randomised to intervention group (only stroke or TIA population): 485 (analysed, not stated if more were randomised) Participants randomised to control group (only stroke or TIA population): 457 (analysed, not stated if more were randomised) Sex (only stroke or TIA population): no EPA group = 180 men and 277 women, EPA group = 189 men and 296 women Age, years (only stroke or TIA population) mean ± SD: no EPA group = 65 ± 7, EPA group = 66 ± 7 Time from event (stroke or TIA) to start of intervention: not stated, at least 6 months (as per exclusion criteria) 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) Country: Japan Ethnicity: Japanese
Interventions	Comparison groups: EPA versus no EPA Intervention: EPADEL capsules containing 300 mg of highly (> 98%) purified EPA ethyl ester per capsule. Total daily dose of 1800 mg

JELIS (*Continued*)

	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)
Outcomes	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
Notes	Dietary information: participants received "appropriate" dietary advice, no details provided Funding: Mochida Pharmaceutical Co Ltd, Tokyo, Japan

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

Nosaka 2017 (*Continued*)

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 =

	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
Interventions	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)
Outcomes	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
Notes	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
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

OCEAN (*Continued*)

	months prior to start of intervention, not clear if duplicates included) 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) 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: Marine-derived n-3 PUFAs ethyl esters versus placebo Intervention: Omacor capsules (approximately 888 mg EPA and 777 mg DHA per day) Control: olive oil capsules (providing 1.55 g of oleic acid per day) Compliance: returned capsules count Duration of intervention: median 21 days (range: 7 to 102 days) Co-interventions: N/A
Outcomes	Primary outcome of study: atherosclerotic plaque inflammation and stability Relevant review outcomes measured (in total population): none available Available outcome data for stroke and/or TIA population only: none Latest time point of assessment: median 21 days (range: 7 to 102 days) Withdrawals or exclusions, n (stroke and/or TIA population only): not available Study authors' contact status: replied, no data provided
Notes	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. Participants were advised not to change their diet throughout the study Funding: study authors supported by grants from Pronova BioPharma AS and British Heart Foundation

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	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 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 Sample size: 3851 participants (total population), 209 participants with history of stroke Participants randomised to intervention group (only stroke population): 112 (intention-to-treat population) Participants randomised to control group (only stroke population): 97 (intention-to-treat population) 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: Germany Ethnicity: not stated

OMEGA (*Continued*)

Interventions	Comparison groups: marine-derived n-3 PUFAs ethyl esters versus placebo Intervention: 1 g/day of marine-derived n-3 PUFAs ethyl esters (460 mg of EPA and 380 mg of DHA) Control: 1 g/day of olive oil Compliance: 'returned capsules' count and blood concentrations of DHA and EPA at the end of the study Duration of intervention: 12 months 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
Outcomes	Primary outcome of study: rate of sudden cardiac death in participants who survived acute MI Relevant review outcomes measured (in total population): vascular-related death, recurrent events, adverse events, mood (depression, data not provided) 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: 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 Funding: Trommsdorff GmbH & Co. KG Arzneimittel, Alsdorf, Germany and Pronova Biocare, Lysaker, Norway

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, Gö ttingen, 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	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 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)

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	RCT; parallel; placebo-controlled Number of study sites: 11 Dates: enrolment between November 2002 and May 2003. Median follow-up of 558 days
Participants	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 Exclusion criteria: participation in other clinical trials; active malignant disease; and known poor compliance Sample size: 206 participants (total population), 85 participants with history of stroke

OPACH (*Continued*)

	and/or TIA Participants randomised to intervention group (only stroke and/or TIA population): 41 Participants randomised to control group (only stroke and/or TIA population): 44 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: Denmark Ethnicity: not stated
Interventions	Comparison groups: marine-derived n-3 PUFAs versus placebo Intervention: Omacor (marine-derived n-3 PUFAs ethyl esters). 1.7 g/day of n-3 PUFAs Control: olive oil (2 capsules per day, containing 77% oleic acid) Compliance: serum phospholipid fatty acid composition Duration of intervention: 2 years or until reaching a study primary endpoint (median of 558 days, range 219 to 730 days) Co-interventions: N/A
Outcomes	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 Relevant review outcomes measured (in total population): vascular-related death, recurrent events (stroke/TIA), and adverse events Available outcome data for stroke and/or TIA population only: none Latest time point of assessment: median 558 days (range 219 to 730 days) Withdrawals or exclusions, n (stroke and/or TIA population only): not available Study authors' contact status: no reply to date
Notes	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) Funding: The Danish Heart Foundation, The Danish Kidney Foundation, the Research Foundation of the County of Northern Jutland, and Pronova Biocare

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 ± SD (only stroke population): intervention group = 75.16 ± 2.65, control group = 75.04 ± 3.17 Time from event (stroke) to start of intervention: not stated Type of baseline stroke: not stated Country: UK Ethnicity: not stated

OPAL (*Continued*)

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

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

Rantanen 2018 (*Continued*)

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/m2), 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*)

	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 Sample size: 12,513 participants (total population), 1455 participants with history of stroke and/or TIA Participants randomised to intervention group (only stroke and/or TIA population): 736 Participants randomised to control group (only stroke and/or TIA population): 719 Sex (only stroke and/or TIA population): control = 420 men and 299 women, intervention = 473 men and 263 women Age, years + SD (only stroke and/or TIA population): control = 68.3 ± 9.2, intervention = 68.4 ± 9.2 Time from event (stroke or TIA) to start of intervention: not stated Type of baseline stroke: not stated Country: Italy Ethnicity: not stated
Interventions	Comparison groups: marine-derived n-3 PUFAs versus placebo 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 Control: 1g/day of olive oil Compliance: self-report Duration of intervention: median of 5 years (IQR 4.0 to 5.5 years) Co-interventions: N/A
Outcomes	Primary outcome of study: composite of time to death from cardiovascular causes or hospital admission for cardiovascular causes Relevant review outcomes measured (in total population): vascular-related death; recurrent events; adverse events Available outcome data for stroke and/or TIA population only: vascular-related death, recurrent events; adverse events (combined) Latest time point of assessment: median of 5 years (IQR 4.0 to 5.5 years) Withdrawals or exclusions, n (stroke and/or TIA population only): control = 4, intervention = 1 Study authors' contact status: replied, data provided
Notes	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) Funding: Società Prodotti Antibiotici, Pfizer, and Sigma-Tau

Risk of bias

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 $\geq$ 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

	of informed consent Sample size: 40 participants (all stroke population). Initially 41 participants were randomised, however, 1 participant was excluded because baseline diagnosis was other than stroke Participants randomised to intervention group: 20 (initially 21, 1 participant excluded as mentioned above) Participants randomised to control group: 20 Sex: control = 7 men and 13 women, intervention = 8 men and 12 women Age (years), median (range): control = 48 (20 to 67), intervention = 53 (22 to 68) Time from event (stroke) to start of intervention: admission to the emergency department within 72 hours after the initial bleeding episode Type of baseline stroke: haemorrhagic Country: Chile Ethnicity: not stated
Interventions	Comparison groups: marine-derived n-3 PUFAs versus open control 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 Control: normal care Compliance: not stated Duration of intervention: 60 days Co-interventions: medical stabilisation at an ICU/IMCU; 60 mg of oral nimodipine every 4 hours
Outcomes	Primary outcome of study: safety and feasibility of an effectiveness trial 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 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 Latest time point of assessment: 90 days Withdrawals or exclusions, n: 1 participant (aetiology of initial haemorrhage other than stroke) Study authors' contact status: replied, data provided
Notes	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,

	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

SCIMO

Methods	RCT; parallel; placebo-controlled Number of study sites: 1 Dates: recruitment between 1 September 1992 and 19 May 1994. 2 years of follow-up
Participants	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 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 Sample size: 223 participants (total population), 6 participants with history of stroke and/or TIA (with complete follow-up) Participants randomised to intervention group (only stroke and/or TIA population): 3 (only participants with complete follow-up) Participants randomised to control group (only stroke and/or TIA population): 3 (only participants with complete follow-up) 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: ischaemic (including TIA) Country: Germany Ethnicity: not stated
Interventions	Comparison groups: fish oil versus placebo 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) Control: fatty acids mixture without marine-derived n-3 PUFAs and reflecting the fatty acid composition of the average European diet Compliance: 'returned capsules' count and analysis of red cell phospholipids fatty acids Duration of intervention: 24 months Co-interventions: N/A
Outcomes	Primary outcome of study: changes on coronary angiography at 2 years, as assessed by an expert panel Relevant review outcomes measured (in total population): vascular-related death; recurrent events (stroke); adverse events Available outcome data for stroke and/or TIA population only: none Latest time point of assessment: 24 months Withdrawals or exclusions, n (stroke and/or TIA population only): not available Study authors' contact status: replied, no further data available

SCIMO (*Continued*)

Notes	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 Funding: The Bundesministerium fur Forschung und Technologie, Germany, through Gesellschaft fur Strahlenforschung (GSF, 07ERG03) and Deutsche Forschungsanstalt fur 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

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	RCT; parallel; 2 × 2 factorial design Number of study sites: 257 Dates: enrolment between 1 February 2003 and 1 June 2007. Last follow-up 1 July 2009
Participants	Inclusion criteria: men and women aged 45 to 80 years; acute coronary or cerebral ischaemic event within the 12 months before randomisation 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,

SU.FOL.OM3 (*Continued*)

	in particular methotrexate for treating cancer or rheumatoid arthritis and chronic renal failure (plasma creatinine concentration > 200 μmol/L or creatinine clearance < 40 ml/min) Sample size: 2501 participants (total population), 638 participants with history of stroke 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) Participants randomised to control group (only stroke population): 326 (160 to placebo, and 166 to B vitamins) Sex (only stroke population): not stated Age (only stroke population): not stated Time from event (stroke) to start of intervention: median time between the acute CVD event and randomisation was 101 days Type of baseline stroke: ischaemic Country: France Ethnicity: not stated
Interventions	Comparison groups: marine-derived n-3 PUFAs versus placebo. Participants were also randomised to B vitamins or placebo, in a 2 × 2 factorial design Intervention: 600 mg/day of EPA and DHA at a ratio of 2:1 Control: gelatin, fish-oil-flavoured capsules containing liquid paraffin Compliance: self-reported (questionnaire or telephone interview) Duration of intervention: median of 4.7 years (mean ± SD = 4.2 ± 1.0 years) Co-interventions: participants also randomised to 5-methyltetrahydrofolate (560 μg), vitamin B6 (3 mg) and B12 (20 μg) or placebo
Outcomes	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) Relevant review outcomes measured (in total population): vascular-related death; recurrent events (ischaemic stroke); adverse events; and quality of life Available outcome data for stroke population only: none Latest time point of assessment: median of 4.7 years (mean ± SD = 4.2 ± 1.0 years) Withdrawals or exclusions, n (stroke population only): not available Study authors' contact status: no reply to date
Notes	Dietary information: none provided Funding: French Ministry of Research (R02010JJ), Ministry of Health (DGS), Sodexo, Candia, Unilever, Danone, Roche Laboratory, Merck EPROVA GS, and Pierre Fabre Laboratory

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

		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*)

	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

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	RCT; parallel, open label Number of study sites: not stated Dates: not stated
Participants	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)

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

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	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 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 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 Sample size: 240 participants (total population), 22 participants with history of stroke and/or TIA Participants randomised to intervention group (only stroke and/or TIA population): 12 Participants randomised to control group (only stroke and/or TIA population): 10 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
Interventions	Comparison groups: DHA versus placebo Intervention: 2 g/day of algal-derived DHA (Martek Biosciences) containing approximately 45% to 55% of DHA by weight

	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 (*Guides to Enhance Elderly Memory*) 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

		of any exclusion criteria in the published articles

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
Tomiyama 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

8 Mood (GHQ-28)	1	Mean Difference (IV, 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)

Study or subgroup	Marine-derived N-3 PUFAs n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Saito 2017	7/20	9/20		0.78 [0.36, 1.68]

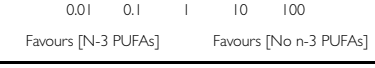
Analysis 1.2. Comparison 1 Marine-derived n-3 fatty acids therapy compared to no marine-derived n-3 fatty acids therapy: follow-up of 3 months or sooner, Outcome 2 Vascular-related death.

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

Study or subgroup	Marine-derived n-3 PUFAs n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
FOILS	0/51	1/51		0.33 [0.01, 8.00]
Saito 2017	0/20	1/20		0.33 [0.01, 7.72]



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)

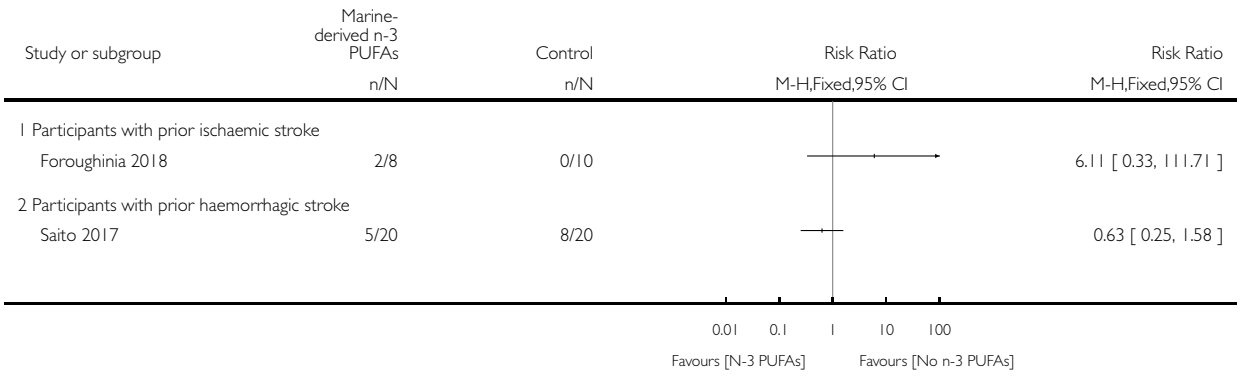
Study or subgroup	Marine-derived n-3 PUFAs n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Foroughinia 2018	0/8	1/10		0.41 [0.02, 8.84]

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

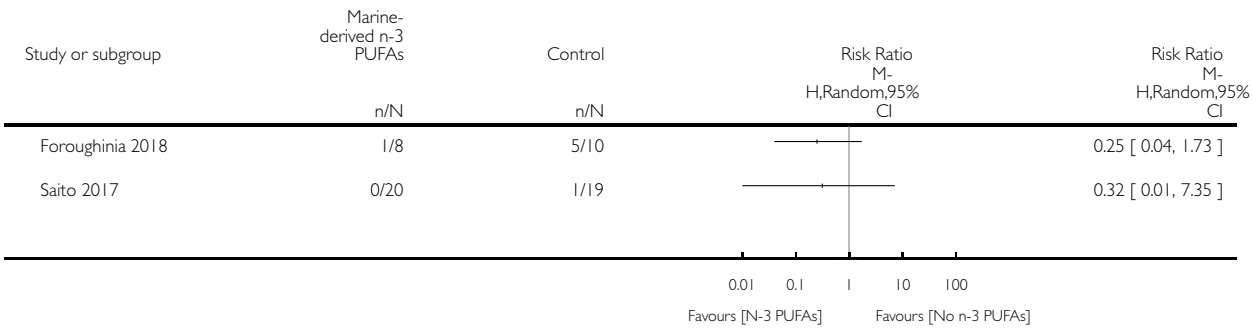


Analysis 1.5. Comparison 1 Marine-derived n-3 fatty acids therapy compared to no marine-derived n-3 fatty acids therapy: follow-up of 3 months or sooner, Outcome 5 Adverse events (all).

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)

Study or subgroup	Marine-derived n-3 PUFAs n/N	No marine n-3 PUFAs n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Foroughinia 2018	1/8	5/10		0.25 [0.04, 1.73]

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)

Study or subgroup	Marine-derived n-3 PUFAs n/N	No marine n-3 PUFAs n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Saito 2017	0/20	1/19		0.32 [0.01, 7.35]

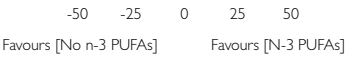
Analysis 1.8. Comparison 1 Marine-derived n-3 fatty acids therapy compared to no marine-derived n-3 fatty acids therapy: follow-up of 3 months or sooner, Outcome 8 Quality of life (mean change from baseline).

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)

Study or subgroup	Marine-derived n-3 PUFAs		Control		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Fixed,95% CI	IV,Fixed,95% CI
1 SF-36 questionnaire Physical component scale						
FOILS	51	0.07 (7.2843)	51	2.38 (5.4989)		-2.31 [-4.81, 0.19]
2 SF-36 questionnaire Mental Component Scale						
FOILS	51	-0.68 (11.0692)	51	1.48 (7.9984)		-2.16 [-5.91, 1.59]



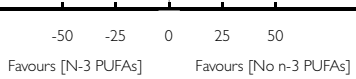
Analysis 1.9. Comparison 1 Marine-derived n-3 fatty acids therapy compared to no marine-derived n-3 fatty acids therapy: follow-up of 3 months or sooner, Outcome 9 Mood (GHQ-30, mean change from baseline).

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)

Study or subgroup	Marine-derived n-3 PUFAs		Control		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Fixed,95% CI	IV,Fixed,95% CI
FOILS	51	-0.67 (3.0708)	51	-2.08 (3.785)		1.41 [0.07, 2.75]



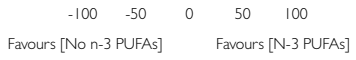
Analysis 2.1. Comparison 2 Marine-derived n-3 fatty acids therapy compared to no marine-derived n-3 fatty acids therapy: follow-up longer than 3 months, Outcome 1 Efficacy (Barthel Index).

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)

Study or subgroup	Marine-derived N-3 PUFAs N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
NUTRISTROKE	32	82.59 (21.41)	20	75.5 (22.25)		7.09 [-5.16, 19.34]



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)

Study or subgroup	Marine-derived N-3 PUFAs N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
NUTRISTROKE	32	11.35 (4.79)	20	10.05 (4.59)		1.30 [-1.31, 3.91]

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

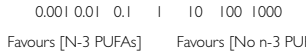
Study or subgroup	Marine-derived N-3 PUFAs n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
ALPHA OMEGA	29/181	24/164		24.2 %	1.09 [0.67, 1.80]
GISSI HF	55/168	49/178		45.1 %	1.19 [0.86, 1.64]
NUTRISTROKE	0/38	4/34		0.9 %	0.10 [0.01, 1.79]
OPAL	0/10	1/9		0.8 %	0.30 [0.01, 6.62]
Risk % Prevention Study	35/736	40/719		29.1 %	0.85 [0.55, 1.33]
Total (95% CI)	**1133**	**1104**		**100.0 %**	**1.02 [0.78, 1.35]**

Total events: 119 (Marine-derived N-3 PUFAs), 118 (Control)

Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 4.74$, df = 4 (P = 0.31); $I^2 = 16\%$

Test for overall effect: Z = 0.18 (P = 0.86)

Test for subgroup differences: Not applicable

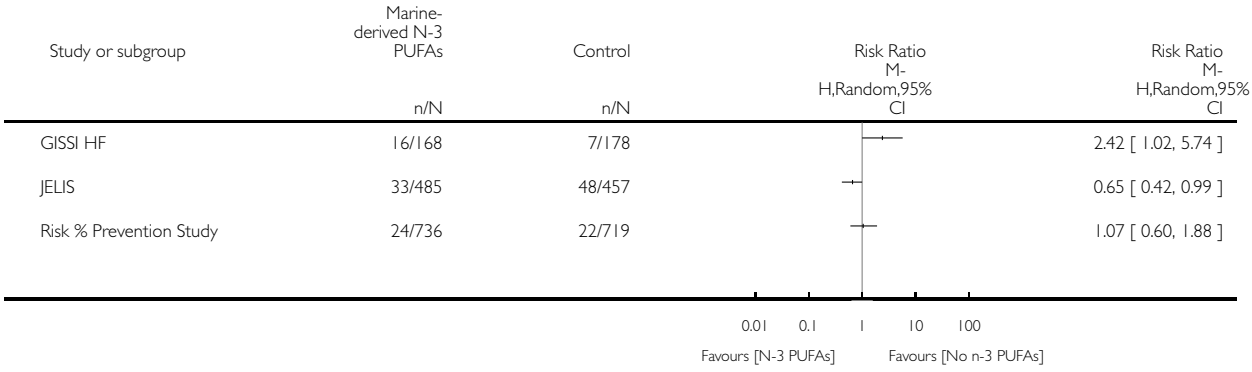


Analysis 2.4. Comparison 2 Marine-derived n-3 fatty acids therapy compared to no marine-derived n-3 fatty acids therapy: follow-up longer than 3 months, Outcome 4 All recurrent events (fatal and non-fatal).

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)

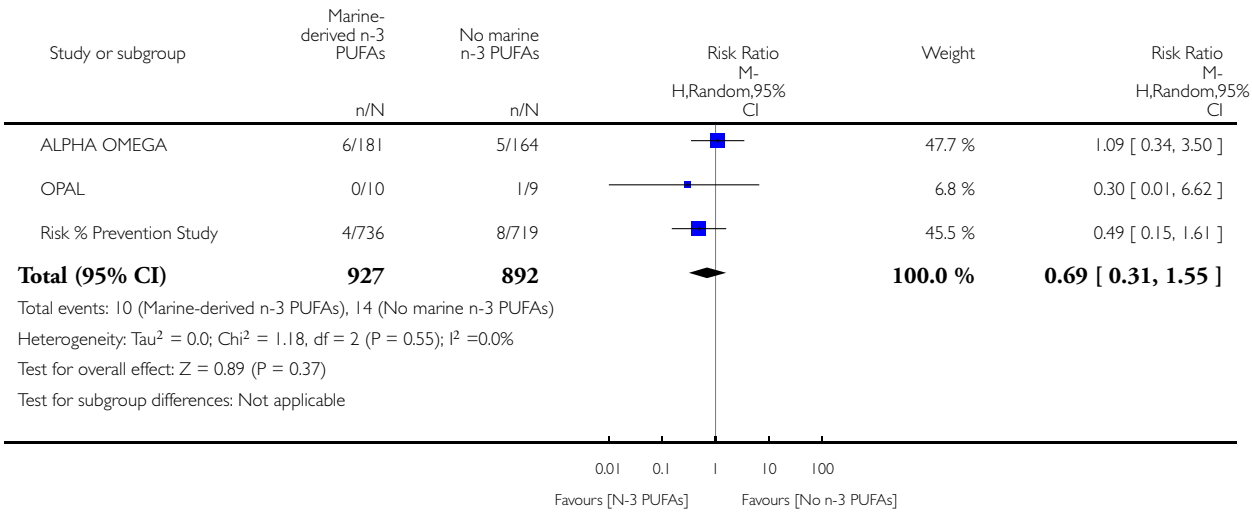


Analysis 2.5. Comparison 2 Marine-derived n-3 fatty acids therapy compared to no marine-derived n-3 fatty acids therapy: follow-up longer than 3 months, Outcome 5 Recurrent events (fatal only).

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)

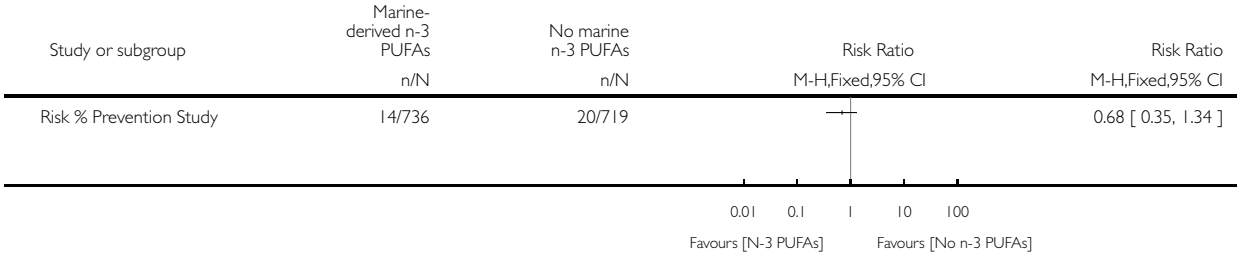


Analysis 2.6. Comparison 2 Marine-derived n-3 fatty acids therapy compared to no marine-derived n-3 fatty acids therapy: follow-up longer than 3 months, Outcome 6 Recurrent events (non-fatal only).

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)

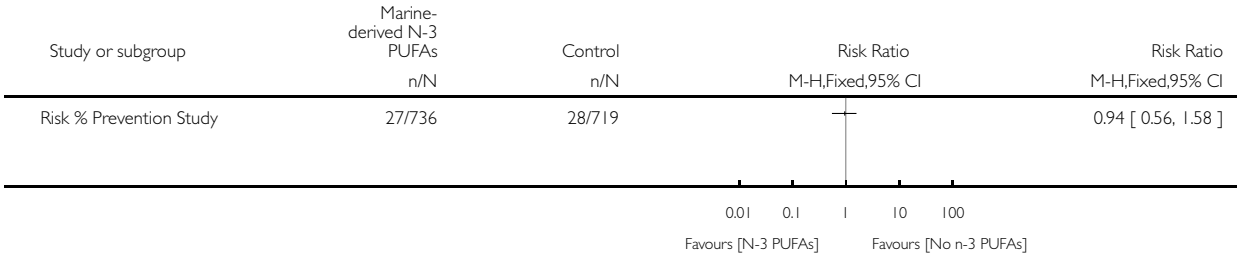


Analysis 2.7. Comparison 2 Marine-derived n-3 fatty acids therapy compared to no marine-derived n-3 fatty acids therapy: follow-up longer than 3 months, Outcome 7 Adverse events (all).

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)



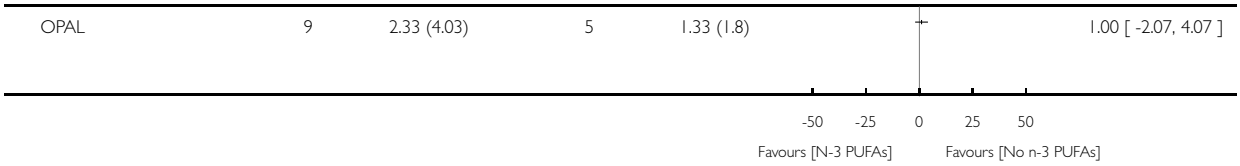
Analysis 2.8. Comparison 2 Marine-derived n-3 fatty acids therapy compared to no marine-derived n-3 fatty acids therapy: follow-up longer than 3 months, Outcome 8 Mood (GHQ-28).

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)

Study or subgroup	Marine-derived n-3 PUFAs N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
OPAL	9	2.33 (4.03)	5	1.33 (1.8)		1.00 [-2.07, 4.07]



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
Studies with follow-up of three months or less					
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	Latest time point of assessment	Co-interventions
Studies with follow-up of three months or less						
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)	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)	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 1. 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 vasc* or cerebral vasc or cva or apoplex or SAH) or AB (stroke or poststroke or post-stroke or cerebrovasc* or brain vasc* or cerebral vasc 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 (I^2T^2) (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".