Supplementary File 1, Dataset 1.
Omega-3, omega-3 and total PUFA long-term RCT Database

(Supplementary File 1 for for Hooper et al “Creation of a database to assess effects of omega-3, omega-6 and total polyunsaturated fats on health: methodology for a set of systematic reviews”)

Characteristics of 211 included trials (RCTs included in at least one of our systematic reviews)

ADCS 2010 - NCT00440050 [1-3]

Methods	Alzheimer's Disease Cooperative Study (ADCS) RCT, parallel, (n-3 DHA vs n-6 LA), 18 months Summary risk of bias: low
Participants	Individuals with mild to moderate Alzheimer's disease N: 238 intervention, 164 control Level of risk for CVD: low Men: 52.9% intervention, 40.2% control Mean age in years (SD): 76 (9.3) intervention, 76 (7.8) control Age range: unclear Smokers: 24.4% intervention, 21.9% control Hypertension: not reported Medications taken by at least 50% of those in the control group: cholinesterase inhibitor, memantine Medications taken by 20%-49% of those in the control group: none Medications taken by some, but less than 20% of the control group: none Location: USA Ethnicity: not reported
Interventions	Type: supplement (capsule) Comparison: DHA vs omega 6 Intervention: 2 × 1 g algal-derived DHA capsules (Neuromins) per day for a total daily dose of 2 g, each capsule contain 45% to 55% of DHA and does not contain EPA (950 mg soft-gel capsules which contain approximately 510 mg DHA). Dose: +DHA 1.02 g/d. Control: 2 × 1 g placebo capsules per day (made up of corn or soy oil) Compliance: measured by pill counts at every visit Length of intervention: 18 months
Outcomes	Main study outcome: change in the cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-cog) and change in the Clinical Dementia Rating (CDR) Dropouts: 67 intervention, 40 control (discontinued treatment but included in main analyses) Available outcomes: mortality, measures of cognition, baseline & change in plasma DHA, adverse events Response to contact: no data provided
Notes	Study funding; quote: "grant UO1-AG10483 from the National Institute on Aging. The National Institute on Aging was not otherwise involved in the design and conduct of the study, or in the analysis of data or preparation of the manuscript". "The placebo and DHA study drugs were provided by Martek Biosciences. Martek also provided plasma and cerebrospinal fluid measurements of fatty acids, as well as partial financial support for the magnetic resonance imaging sub study. (Martek Biosciences produces nutritional supplements from cultivated fungi and microalgae). Martek employees participated in design of the study and in revision of the manuscript, but were not involved in data management or data analysis." (Quinn 2010, p. 1910).

Risk of bias table

Bias	Authors' judgement	Support for judgement

Random sequence generation (selection bias)	Low risk	Randomisation was achieved with a centralised interactive voice response system, using a block design with a block size of 5 (3 in the DHA group and 2 in the placebo group.
Allocation concealment (selection bias)	Low risk	Randomisation was achieved with a centralised interactive voice response system, using a block design with a block size of 5 (3 in the DHA group and 2 in the placebo group.
Blinding of participants and personnel (performance bias)	Low risk	Placebo capsules (made up of corn or soy oil) were identical in appearance. The adequacy of blinding was assessed by questionnaires completed by caregivers, study coordinators, and site physicians.
Blinding of outcome assessment (detection bias)	Low risk	The adequacy of blinding was assessed by questionnaires completed by caregivers, study coordinators, and site physicians with results showing no difference between groups and the majority did not know.
Incomplete outcome data (attrition bias)	Low risk	Intention-to-treat analysis. At 12 months data were available for > 80% (ITT analysis)
Selective reporting (reporting bias)	Low risk	Prospectively registered February 2007, study started February 2007, completed May 2009. Primary outcomes were rate of change in ADAS-Cog11 and CDR-SOB, which are both reported in main report. NPI and ADL were secondary outcomes also reported.
Attention	Low risk	Both study arms had the same follow-up and care.
Compliance	Unclear risk	Measured by pill count at every visit. 28% intervention and 24% control discontinued supplement with a minority discontinuing due to adverse events. A further 8% were excluded for < 80% compliance in both intervention and control arms.
Other bias	Low risk	None noted

AFFORD 2013 – NCT01235130, ISRCTN 52203885 [4 5]

Methods	Multi-centre study to evaluate the effect of n-3 fatty acids on arrhythmia recurrence in atrial fibrillation (AFFORD) RCT, parallel, (n-3 EPA + DHA vs n-6), 12 months Summary risk of bias: moderate or high
Participants	People with symptomatic paroxysmal or persistent AF N: 165 intervention, 172 control. (analysed, intervention: 153 control: 163) Level of risk for CVD: high Men: 69% intervention, 65% control Mean age in years (SD): 60 (12) intervention, 62 (13) control Age range: not reported Smokers: not reported Hypertension: 45% intervention, 42% control Medications taken by at least 50% of those in the control group: oral anticoagulant Medications taken by 20%-49%: beta-blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers Medications taken by some, but < 20%: none Location: Canada Ethnicity: not reported
Interventions	Type: supplement (fish oil) Comparison: EPA + DHA vs omega 6 safflower oil

	Intervention: 4 × 1 g enteric-coated fish oil capsules/d (1.6 g/d EPA + 0.8 g/d DHA, Genuine Health, Toronto, Ontario, Canada). Dose: +2.4 g/d EPA + DHA, Control: 4 ×1 g matching placebo capsules, 4 g/d safflower oil Compliance: omega-3 index increased in intervention group, but not control, over the study Duration of intervention: 6 to 16 months
Outcomes	Main study outcome: AF recurrence Dropouts: 21 intervention, 19 control Available outcomes: all-cause mortality, stroke, AF recurrence, TIA, CV events, CRP (not usable) Response to contact: no
Notes	Authors contacted about QoL, resource use and dietary habits Study funding: Canadian Institutes for Health Research and the Heart and Stroke Foundation of Quebec

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"[R]andomised"
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias)	Unclear risk	Described as double-blind, but blinding not described or tested
Blinding of outcome assessment (detection bias)	Unclear risk	An independent events committee adjudicated AF recurrences, bleeding, strokes, transient ischemic attacks, and deaths, but unclear if blinded to allocation.
Incomplete outcome data (attrition bias)	Low risk	Participant flow well described. ITT analysis
Selective reporting (reporting bias)	High risk	NCT01235130 registered July 2010, recruitment March 2009-March 2012, follow-up finished December 2012. Results published 2014, but no data on quality of life, resource utilisation, or dietary habits (stated in registry) found
Attention	Low risk	No problem with attention bias
Compliance	Low risk	Omega-3 index measured
Other bias	Low risk	None noted

Ahn 2016 [6]

Methods	RCT, parallel, (EPA + DHA + statins vs statins), 12 months Summary risk of bias: moderate to high
Participants	Statin treated CAD patients undergoing PCI N: 38 intervention, 36 control Level of risk for CVD: high Men: 63.2% intervention, 72.2% control Mean age in years (SD): 59.6 (9.1) intervention, 60.7 (0.8) [sic] control Age range: unclear Smokers: 36.8% intervention, 58.3% control Hypertension: 50% in both groups Medications taken by at least 50% of those in the control group: aspirin, clopidogrel, ACE inhibitors/ARB, beta-blockers, atorvastatin Medications taken by 20%-49% of those in the control group: cilostazol Medications taken by some, but less than 20% of the control group: rosuvastatin, nitrates, calcium antagonists Location: South Korea Ethnicity: not reported
Interventions	Type: supplement (capsule)

	Comparison: EPA + DHA vs unclear (nil) Intervention: 3 g of ω-3 PUFA containing 1395 mg of EPA and 1125 mg of DHA per day. No further details. Dose: +2.52 g/d EPA + DHA Control: unclear whether control group were given placebo or only statins Compliance: unclear how it was measured but reported good compliance with no numbers Length of intervention: 12 months
Outcomes	Main study outcome: change in atherosclerotic burden Dropouts: none Available outcomes: lipids (TG reported as median, IQR so not used), atheroma volume, neointimal volume index Response to contact: no
Notes	Study funding: the study was supported by clinical research grant from Pusan National University Hospital

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Simple randomisation was carried out using random number tables to assign each participant to the intervention or control group
Allocation concealment (selection bias)	Low risk	Participants were assigned randomisation numbers sequentially on recruitment to the study, and the randomisation codes were retained by the clinical research coordinator.
Blinding of participants and personnel (performance bias)	Unclear risk	No details
Blinding of outcome assessment (detection bias)	Low risk	The personnel responsible for randomisation as well as those performing laboratory measurements were blinded to the randomisation assignments.
Incomplete outcome data (attrition bias)	Low risk	No dropouts reported
Selective reporting (reporting bias)	Unclear risk	No protocol or trial register entry found
Attention	Unclear risk	No details
Compliance	Unclear risk	No details on how it was measured and no fatty acid levels reported
Other bias	High risk	It's unclear whether the study was placebo controlled or the control group had no intervention. Also, some of the SDs appear to be incorrectly reported.

Almallah 1998 [7-12]

Methods	Pilot 2 arm double-blind RCT, placebo controlled (n3 EPA+DHA vs n6 LA), 6 months Summary risk of bias: Moderate to high Aim: "to evaluate the in situ effect of n-3 PUFAs on distal proctocolitis"
Participants	Individuals with ulcerative colitis with only distal disease (to enable assessment via sigmoidoscopy) attending the outpatients clinic. No participant was on steroids before starting supplementation. All were taking a standard western diet and were identified as having UC via rectal biopsy. N: 9 int., 9 control (analysed – int: 9 cont: 9) Level of risk for CVD: Low Male: 44.4% int., 55.6% control. Mean age (sd): 54 int.; 41 cont. (SD not reported) Age range: 29-64 int., 32-74 cont. Smokers: NR Hypertension: NR Medications taken by at least 50% of those in the control group: Sulphasalazine, mesalazine (for ethical reasons patients were maintained on their existing long-term medication with either preparation) Medications taken by 20-49% of those in the control group:

	Medications taken by some, but less than 20% of the control group Location: Scotland Ethnicity: NR
Interventions	Type: supplement (food: fish oil or sunflower oil) Comparison: EPA+DHA vs MUFA/n6 FA Intervention: 15mls/day fish oil (including 3.2g/d EPA + 2.4g/d DHA; supplied by Callanish Ltd, Isle of Lewis, Scotland): EPA+DHA 5.6g/d Control: 15mls/day sunflower oil (including 2.6g oleic acid and 7.9g linoleic acid; supplied by Callanish Ltd, Isle of Lewis, Scotland) Compliance: used bottles of oil counted but data not provided; no FA status data. Duration of intervention: 6 months
Outcomes	Main study outcome: Disease activity (clinical and sigmoidoscopic scores) Dropouts: 0 int., 0 control Available outcomes: histological evaluation of mucosal biopsies, inflammatory markers (IL-2, soluble IL2 receptors, LTB_4), circulating levels of natural killer (NK) and lymphokine activated killer (LAK) cells.
Notes	Oil preparations supplied by Callanish Ltd; research publically funded; no conflict of interest statement

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomly assigned by hospital pharmacy but method not specified
Allocation concealment (selection bias)	Unclear risk	Timing of allocation Vs randomisation not reported; insufficient detail
Blinding of participants and personnel (performance bias)	Unclear risk	Free oils used – no information provided about attempt to mask/match colour, smell or taste.
Blinding of outcome assessment (detection bias)	Unclear risk	Although intervention provided by pharmacy, if outcome assessor is assessing compliance by bottle count and oils differ in colour, then they could have determined allocation.
Incomplete outcome data (attrition bias)	Unclear risk	Numbers analysed not explicitly stated
Selective reporting (reporting bias)	Unclear risk	No study registration or protocol found
Attention	Low risk	Identical follow-up described for participants in each arm.
Compliance	Unclear risk	No data provided on oil consumption or fatty acid status.
Other bias	Low risk	None noted

AlphaOmega - ALA 2010 NCT00127452 [13-27]

Methods	RCT, (n-3 ALA vs MUFA), 40 months Summary risk of bias: low
Participants	60-80 year-olds with previous MI N: 1197 ALA intervention, 1236 control (1212 ALA + EPA/DHA intervention group) Level of risk for CVD: high Men: 77.9% intervention, 78.7% control Mean age in years (SD): 69.0 (5.6) intervention, 68.9 (5.6) control Age range: 60-80 years Smokers: 17.4% intervention, 18% control Hypertension: unclear Medications taken by at least 50% of those in the control group: lipid lowering medication, antihypertensives, antithrombotics Medications taken by 20%-49% of those in the control group: not reported

	Medications taken by some, but less than 20% of the control group: antiarrhythmic drugs, antidiabetic drugs Location: the Netherlands Ethnicity: not reported
Interventions	Type: supplementary margarine Comparison: ALA vs MUFA Intervention 20 g of enriched margarine per day incorporating: 2 g ALA. 8 × 250 g margarine tubs delivered every 12 weeks. Dose: average achieved +1.9 g/d ALA Control: 20 g of margarine per day. No additional n-3 PUFAs. Identical margarine (oleic acid) placebo. Compliance: unused margarine tubs were returned- daily intakes of margarine and n-3 fatty acids were calculated on the basis of the amount unused. Adherence was measured by levels of fatty acids in plasma cholesteryl esters, margarine and questionnaires. 90.5% of patients adhered to the protocol and consumed 20.6 (SD 2.8) g of margarine/d. Length of intervention: 40 months
Outcomes	Main study outcome: cardiovascular disease events Dropouts: 91 died, 98 discontinued intervention, 93 died, 93 discontinued control Available outcomes: deaths, MI, cardiovascular events, ventricular arrhythmia, Incident cardiovascular disease Response to contact: yes (data provided)
Notes	The study has 3 intervention arms (ALA margarine, EPA/DHA margarine, mixture of the two interventions). This table represents the ALA only intervention. Outcome data is used for the ALA group where reported separately or for the combined (ALA arm, ALA + EPA/DHA arm) Study funding: Netherlands Heart Foundation, National Institutes of Health and Unilever R&D (latter provided unrestricted grant for distribution of trial margarines)

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	On the computer by a random number generator before the start of the trial
Allocation concealment (selection bias)	Low risk	Author confirmed allocation was concealed from clinicians/ researchers
Blinding of participants and personnel (performance bias)	Low risk	The 4 types of margarine were "similar in taste, texture and colour". A trained test panel did not perceive a fishy taste or odour. Randomisation tables were stored safely under supervision.
Blinding of outcome assessment (detection bias)	Low risk	Randomisation tables were stored safely under supervision. There was an independent statistician for data analysis. 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 patients assigned study group".
Incomplete outcome data (attrition bias)	Low risk	All patients were followed up for events computerised linkage with municipal registries. 2531 patients were only followed up for baseline anthropometric and medical measurements.
Selective reporting (reporting bias)	High risk	Sudden cardiac death endpoint omitted. Registered in August 2005, recruitment was from 2002 to 2006. Outcomes papers published in 2010
Attention	Low risk	All participants appear to have had similar frequency and quantity of attention and follow-up
Compliance	Low risk	Unused margarine tubs were returned; daily intakes of margarine and n-3 fatty acids were calculated on the basis of the amount unused. Adherence was measured by levels of fatty acids in plasma cholesteryl esters, margarine and questionnaires. 90.5% of patients adhered to the protocol and consumed 20.6 (SD 2.8) g of margarine/d

Other bias	Low risk	None noted

AlphaOmega - EPA+DHA 2010 NCT00127452 [13-27]

Methods
RCT, (EPA + DHA vs MUFA), 40 months
Summary risk of bias: low

Participants
60-80 year-olds with previous MI
N: 1192 EPA/DHA intervention, 1236 control (1212 ALA + EPA/DHA intervention group)
Level of risk for CVD: high
Men: 78.1% intervention, 78.7% control
Mean age in years (SD): 69.1 (5.6) intervention, 68.9 (5.6) control
Age range: 60-80 years
Smokers: 16.8%, intervention, 18% control
Hypertension: unclear
Medications taken by at least 50% of those in the control group: lipid-lowering medication, antihypertensives, antithrombotics
Medications taken by 20%-49% of those in the control group: not reported
Medications taken by some, but less than 20% of the control group: antiarrhythmic drugs, antidiabetic drugs
Location: the Netherlands
Ethnicity: not reported

Interventions
Type: supplementary margarine
Comparison 1: EPA + DHA vs MUFA
Intervention: 20 g of enriched margarine per day incorporating 400 mg EPA-DHA (240 mg EPA and 160 mg DHA). Dose: average achieved 376 mg/d EPA + DHA
Control: 20 g of margarine per day. No additional n-3 PUFAs. Identical margarine (oleic acid) placebo
Compliance: unused margarine tubs were returned; daily intakes of margarine and n-3 fatty acids were calculated on the basis of the amount unused. Adherence was measured by levels of fatty acids in plasma cholesteryl esters, margarine and questionnaires. 90.5% of patients adhered to the protocol.
Length of intervention: 40 months

Outcomes
Main study outcome: cardiovascular disease events
Dropouts: 95 died, 119 discontinued intervention, 93 died, 93 discontinued control
Available outcomes: deaths, MI, cardiovascular events, ventricular arrhythmia, incident cardiovascular disease
Response to contact: yes (data provided)

Notes
The study has three intervention arms (ALA margarine, EPA/DHA margarine, mixture of the two interventions). This table represents the EPA/DHA only intervention. Outcome data is used for the EPA/DHA group where available or for the combined (EPA/DHA arm, EPA/DHA + ALA arm)
Study funding: Netherlands Heart Foundation, National Institutes of Health and Unilever R&D (latter provided unrestricted grant for distribution of trial margarines)

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	On the computer by a random number generator before the start of the trial
Allocation concealment (selection bias)	Low risk	Author confirmed allocation was concealed from clinicians/ researchers
Blinding of participants and personnel (performance bias)	Low risk	The 4 types of margarine were "similar in taste, texture and colour". A trained test panel did not perceive a fishy taste or odour. Randomisation tables were stored safely under supervision.
Blinding of outcome assessment (detection bias)	Low risk	Randomisation tables were stored safely under supervision. There was an independent statistician for data analysis. 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 patients assigned study group".
Incomplete outcome data (attrition bias)	Low risk	All patients were followed up for events computerised linkage with municipal registries. 2531 patients were only followed up for baseline anthropometric and medical measurements.
Selective reporting (reporting bias)	High risk	Sudden cardiac death endpoint omitted. Registered from August 2005, recruitment was from 2002 to 2006. Outcomes papers published in 2010
Attention	Low risk	All participants appear to have had similar frequency and quantity of attention and follow-up
Compliance	Low risk	Unused margarine tubs were returned; daily intakes of margarine and n-3 fatty acids were calculated on the basis of the amount unused. Adherence was measured by levels of fatty acids in plasma cholesteryl esters, margarine and questionnaires. 90.5% of patients adhered to the protocol and consumed 20.6 (SD 2.8) g of margarine/d
Other bias	Low risk	None noted

Araujo 2014 [28]

Methods	RCT, 3 arms (n3 vs unclear control), 6 months Summary risk of bias: moderate to high
Participants	People with rheumatoid arthritis (RA) N: 11 int, 15 cont Level of risk for CVD: low Men: NR Mean age in years (SD): NR Age range: NR Smokers: NR Hypertension: NR Medications taken by at least 50% of those in the control group: NR Medications taken by 20%-49% of those in the control group: NR Medications taken by some, but less than 20% of the control group: NR Location: Portugal Ethnicity: NR
Interventions	Type: supplements (probably capsules) Comparison: n3 vs control Intervention: n3 (no details of type or dose) Control: control (unclear whether placebo or not) Compliance: NR Length of intervention: 6 months
Outcomes	Main study outcome: RA activity Dropouts: NR Available outcomes: ESR, CRP, tender joints, swollen joints, global health (EVA GH), disease activity (DAS-28) Response to contact: not attempted
Notes	The study has three intervention arms (n3, control and Mediterranean diet) Study funding: NR Reported as abstract only

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"randomised"

Allocation concealment (selection bias)	Unclear risk	no further information
Blinding of participants and personnel (performance bias)	Unclear risk	unclear whether there was a placebo
Blinding of outcome assessment (detection bias)	Unclear risk	not stated
Incomplete outcome data (attrition bias)	Unclear risk	no information
Selective reporting (reporting bias)	Unclear risk	No protocol or trials register found
Attention	Unclear risk	No information
Compliance	Unclear risk	Not reported
Other bias	Low risk	None noted

AREDS2 2014 – NCT00345176 [29-35]

Methods
Age-Related Eye Disease Study 2 (AREDS2)
RCT, parallel, 2 × 2 factorial (n-3 EPA + DHA vs nil) also randomised to lutein and zeaxanthin vs nil), 5 years
Summary risk of bias: low

Participants
People aged 50-85 years at high risk of progression to advanced age-related macular degeneration (AMD)
N: 2147 intervention (1068 DHA/EPA, 1079 DHA/EPA + lutein/zeaxanthin), 2056 control (1012 placebo, 1044 lutein/zeaxanthin)
Level of risk for CVD: low (however ~20% had previous CV event)
Men: intervention 42.1%, control 44.4%
Age in years: intervention median 74.6 (IQR 11.1), control median 74 (IQR 11.1)
Age range: 68-79 years
Smokers: intervention 6.3%, control 7.2%
Hypertension: unclear
Medications taken by at least 50% of those in the control group: multivitamins
Medications taken by 20%-49% of those in the control group: cholesterol lowering drugs, aspirin
Medications taken by some, but less than 20% of the control group: NSAID, paracetamol
Location: USA
Ethnicity: white 96.5% intervention, 96.6% control; Hispanic: 2.6 intervention, 1.3 control

Interventions
Type: supplement (capsule)
Comparison: EPA + DHA vs nil
Intervention 350 mg/d DHA plus 650 mg/d EPA added to the standard AREDS supplement of Vitamin C (500 mg/d), Vitamin E (440 IU/d), beta-carotene (15 mg/d), zinc oxide (80 mg/d) and cupric oxide (2 mg/d). Dose: +1 g/d EPA + DHA
Control: standard AREDS supplement of Vitamin C (500 mg/d), Vitamin E (400IU/d), beta-carotene (15 mg/d), zinc oxide (80 mg/d) and cupric oxide (2 mg/d).
Compliance: assessed by pill count – 84% of participants in each group took at least 75% of study medications
Length of intervention: 60 months

Outcomes
Main study outcome: development of advanced AMD
Dropouts: intervention 200 died, 165 discontinued, 80 were lost to follow-up; control 168 died, 140 discontinued, 61 were lost to follow-up
Available outcomes: deaths, cardiovascular death, MI, stroke, angina, heart failure, revascularisation, cognition, eye health, (authors provided data on diabetes diagnosis, depression diagnosis, breast cancer)
Response to contact: yes (data provided)

Notes
Study funding: National Eye Institute/National Institutes of Health, Department of Health and Human Services

Risk of bias table

Bias	Authors' judgement	Support for judgement

Random sequence generation (selection bias)	Low risk	Quote: "random block design was implemented using the AREDS2 Advantage Electronic Data Capture system by the AREDS2 Coordinating Center"
Allocation concealment (selection bias)	Low risk	Each treatment was assigned 5 bottle numbers. Bottle numbers were issued via an electronic randomisation system for each participant once study eligibility was verified. The assigned bottle number was used to distribute the study treatment(s). AREDS2 Coordinating centre personnel involved in creating the randomisation system had access to the bottle number/treatment assignments.
Blinding of participants and personnel (performance bias)	Low risk	"Participants, investigators, study coordinators, and all other study personnel are masked to treatment assignment". However, no information was given regarding the taste, smell, or appearance of the active or placebo capsules.
Blinding of outcome assessment (detection bias)	Low risk	The coordinating centre randomly assigned the event to a study adjudicator, who made the final determination of these study endpoints through review of the medical records and applying the endpoint criterion defined a priori. All adjudicators were masked to study assignment.
Incomplete outcome data (attrition bias)	Low risk	< 20% attrition over 5 years, balanced reasons for dropouts
Selective reporting (reporting bias)	Low risk	Outcomes in trials registry entry appear to all be reported (NCT00345176). Entry received June 2006, recruitment September 2006 – October 2012
Attention	Low risk	Participants, investigators, study coordinators, and all other study personnel are masked to treatment assignment, so attention bias not feasible
Compliance	Unclear risk	Assessed by pill count – 84% of participants in each group took at least 75% of study medications
Other bias	Low risk	None noted

ASCEND - NCT00135226 [36 37]

Methods	A Study of Cardiovascular Events iN Diabetes (ASCEND) RCT, parallel, 2 × 2 factorial (n-3 EPA + DHA vs MUFA) also randomised to aspirin vs placebo), median 7.4 years Summary risk of bias: low
Participants	Patients with diabetes, without apparent vascular disease N: 7740 intervention, 7740 control (ITT so 7740 in each arm analysed) Level of risk for CVD: moderate (DM) Men: intervention 62.6%, control 62.6% Age in years (SD): intervention 63.3 (9.2), control 63.3 (9.2) Age range: 40+ years Smokers: intervention 8.3%, control 8.3% Hypertension: intervention 61.6%, control 61.6% Medications taken by at least 50% of those in the control group: statins, metformin, ACE inhibitors or ARBs Medications taken by 20%-49% of those in the control group: aspirin, insulin, sulphonylurea, calcium channel blockers Medications taken by some, but less than 20% of the control group: NSAID, thiazolidinedione, beta-blockers, thiazide or related diuretics, PPI Location: UK Ethnicity: white 96.5% intervention, 96.5% control
Interventions	Type: supplement (capsule) Comparison: EPA + DHA vs MUFA

	Intervention: 840mg/d EPA+DHA (460mg/d EPA plus 380mg/d DHA) as 1 capsule daily, provided by Mylan, Solvay and Abbott. Arm 1: omega-3 (1 g/d: 0.41 g EPA, 0.34 g DHA) and placebo tablets for aspirin Arm 3: omega-3 (1 g/d) and aspirin (100 mg/d) Control: 1 capsule/d of olive oil provided by Mylan, Solvay and Abbott. Arm 2: aspirin (100 mg/d) and olive oil placebo capsule Arm 4: olive oil placebo and placebo tablets for aspirin Compliance: assessed through posted questionnaires, suggesting 77% compliance in intervention group, 76% in control. 10% also took over-the-counter fish oil. Length of intervention: mean 7.4 years
Outcomes	Main study outcome: serious vascular events (first of MI, stroke, TIA or vascular death) Dropouts: intervention 2879 stopped taking meds for some reason, but were included in analysis; control 2938 stopped taking meds, but were included in analysis Available outcomes: deaths, cardiovascular death, MI, stroke, heart failure, revascularisation, atrial fibrillation, diabetes complications, cancer diagnosis, breast cancer, prostate cancer (and other types of cancer), TIA, IBD, dementia, depressive disorders, anxiety, suicidal and injurious behaviour, Parkinsons disease, body weight, serum cholesterol, HDL cholesterol, HbA1c Response to contact: not yet attempted
Notes	NCT00135226 Trial website: ascend.medsci.ox.ac.uk; rum.ctsu.ox.ac.uk/ascend Study funding: British Heart Foundation, medications provided by Mylan, Solvay and Abbott.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised using minimisation
Allocation concealment (selection bias)	Low risk	Almost no direct contact with trial personnel - all via questionnaires and GP appointments, central randomisation appears to follow consent
Blinding of participants and personnel (performance bias)	Low risk	Blinding of participants, care providers, investigators and outcome assessors stated in trials register. This appears feasible given the dispersed design with mainly postal contact.
Blinding of outcome assessment (detection bias)	Low risk	Outcomes self-reported (questionnaire) but investigated by masked adjudication committee
Incomplete outcome data (attrition bias)	Low risk	Intention to treat analysis
Selective reporting (reporting bias)	Low risk	Prospective trial registration (registered Aug 2005, recruitment June 2005 to July 2011), and all outcomes in register reported (plus extensive adverse event list)
Attention	Low risk	Almost no contact that could differ between groups
Compliance	Unclear risk	All information was via questionnaires, so unclear.
Other bias	Low risk	None noted.

Baldassarre 2006 [38]

Methods	RCT, (n-3 EPA + DHA vs MUFA), 24 months Summary risk of bias: moderate or high
Participants	45-70 year olds with combined hyperlipoproteinaemia N: 32 intervention, 32 control Level of risk for CVD: moderate Men: 29% intervention, 29% control Mean age in years (SD): 53.7 (7.2) intervention, 53.7 (6.9) control Age range: 45-70 years (inclusion)

Smokers: 28.1% intervention, 28.1% control
Hypertension: none (exclusion criteria)
Medications taken by at least 50% of those in the control group: not reported
Medications taken by 20%-49% of those in the control group: not reported
Medications taken by some, but less than 20% of the control group: not reported (patients on HRT, anti-hypertensive drugs, lipid lowering drugs, or who smoked > 10 cigarettes were excluded)
Location: Italy
Ethnicity: not reported

Interventions Type: capsules
Comparison: LCn3 vs MUFA
Intervention: 1 g × 6 soft gelatin capsules/d of fatty acid mixture (19% EPA), 13% DHA, 19% palmitic acid, 18% oleic acid, 2% LA and 29% other minor components) providing 1.08 g/d EPA, 0.72 g/d DHA, 0.01 g/d tocopherol acetate, divided to three doses. Dose: 1.8 g/d EPA + DHA
Control: 1 g × 6 opaque identical soft gelatin capsules/d of olive oil divided in 3 doses.
Compliance: assessed by counting returned capsules at each visit and by measuring EPA and DHA levels at month 24
Length of intervention: 24 months

Outcomes Main study outcome: carotid atherosclerosis measures
Dropouts: 2 intervention, 5 control
Available outcomes: deaths (nil), MI (lipids, weight, BP and heart rate reported but not in a usable format; lipid data were presented at various times without clear numerical data, suggesting falls in TGs in the intervention but not control arms, and rises in LDL and HDL cholesterol in intervention but not control arms. For the other outcomes the text states "a rise in body weight (+ 3%, P < 0.01) was observed at the end of the study in both groups. Blood pressure and heart rate were unchanged". Effects on IMT and platelets also reported but not used)
Response to contact: not yet attempted

Notes Study funding: supported by Institut De Recherche Pierre Fabre, Departement Recherche Clinique

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	An appropriate software was used to obtain 2 groups balanced for sex, age and smoking
Allocation concealment (selection bias)	Unclear risk	No further details
Blinding of participants and personnel (performance bias)	Unclear risk	Double-blind and placebo capsules were opaque and identical looking to intervention. However no information provided on capsules taste or smell
Blinding of outcome assessment (detection bias)	Unclear risk	No details
Incomplete outcome data (attrition bias)	Low risk	All dropouts are accounted for. "One patient left the study after 3 months because he moved to another city and was therefore excluded from statistical analyses. Two patients were excluded because of major deviation from the protocol during the follow-up (anti-hypertensive assumption) and four because of non-compliance on the basis of returning capsules (compliance < 70%). The final analysed group included 57 patients (30 on active treatment)."
Selective reporting (reporting bias)	Unclear risk	No protocol or trial register record
Attention	Low risk	Both groups had the same contact and number of visits.
Compliance	Low risk	Pill count, we know they excluded 4/64 who returned > 70% of capsules. So 60/64 had > 70% compliance with significant increase in serum EPA and DHA in the intervention group.
Other bias	Low risk	None noted

Baleztena 2015 – NCT01817101 [39 40]

Methods	RCT, parallel, (n3 EPA+DHA assumed vs nil), 12 months Summary risk of bias: Moderate or high
Participants	Institutionalised older adults without cognitive problems or MCI N: NR int., NR control. (analysed, int: NR cont: NR), total given as 99 Level of risk for CVD:NR Male: NR% int., NR% control. Overall given as 68% Mean age (sd): NR int., NR control, overall given as 89.9(6.2) Age range: 75 and above Smokers: NR Hypertension: NR Medications taken by at least 50% of those in the control group: NR Medications taken by 20-49% of those in the control group: NR Medications taken by some, but less than 20% of the control group: NR Location: Spain Ethnicity: NR
Interventions	Type: omega-3 supplement (capsule) Comparison: Omega-3 vs placebo (empty gelatine capsule) Intervention: omega-3 supplement (0.35g n-3 capsule, 3 times daily): EPA+DHA 1.05g/d (probably) Control: placebo (empty gelatine capsule) **PUFA Dose**: (intended) increase 0.4g/d, **0.5%E n-3, 0.5%E PUFA** Compliance: NR Duration of intervention: 12 months
Outcomes	Main study outcome: levels of cognition (MMSE). Secondary outcomes: Short Portable Mental Status Questionnaire (SPMSQ), verbal fluency test, clock drawing test Dropouts: NR int., NR control Available outcomes: MEC (Spanish MMSE), MEC (memory section)
Notes	Study funding: Clinica Universidad de Navarra, Universidad de Navarra

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Little information as final publication is still pending. information gathered so far from two conference abstract and trial register
Allocation concealment (selection bias)	Unclear risk	As above
Blinding of participants and personnel (performance bias)	Unclear risk	As above
Blinding of outcome assessment (detection bias)	Unclear risk	As above
Incomplete outcome data (attrition bias)	Unclear risk	As above
Selective reporting (reporting bias)	Unclear risk	Participants were recruited from Jan 2012, trial registered in March 2013.
Attention	Unclear risk	Little information
Compliance	Unclear risk	Little information
Other bias	Unclear risk	Little information

Balfego 2016 – NCT02294526 [41]

Methods	RCT, parallel, (n3 vs lower n3), 6 months Summary risk of bias: Moderate or high
Participants	Drug-naive patients with type 2 diabetes N: 19 int., 16 control. (analysed, int: 17 cont: 15)

	Level of risk for CVD: Moderate Male: 42.1% int., 50.0% control. Mean age (sd): 60 (7.41) int., 61.2 (9.6) control Age range: Inclusion 40-70 years Smokers: NR Hypertension: NR Medications taken by at least 50% of those in the control group: NR Medications taken by 20-49% of those in the control group: NR Medications taken by some, but less than 20% of the control group: Statins, beta blockers Location: Spain Ethnicity: NR
Interventions	Type: supplemented food (sardine-enriched diet or control diet) Comparison: n3 vs lower n3 Intervention: Standard diet for type 2 diabetes enriched with sardines plus dietary advice Control: Standard diet for type 2 diabetes plus dietary advice Compliance: Erythrocyte omega-3 index; and 3-d food record and food frequency questionnaire Duration of intervention: 6 months
Outcomes	Main study outcome: Metabolic control, inflammation and gut microbiota Dropouts: 2 int., 1 control Available outcomes: Weight, BMI, glucose, insulin, HOMA, HbA1c, inflammatory markers (weight and BMI not used due to baseline differences)
Notes	Study funding: Catalunya-La Pedrera Foundation, Government of Catalonia

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised using online software
Allocation concealment (selection bias)	Unclear risk	An external person was involved in allocating
Blinding of participants and personnel (performance bias)	High risk	Sardine vs control diet
Blinding of outcome assessment (detection bias)	Unclear risk	NR
Incomplete outcome data (attrition bias)	Low risk	Balanced drop outs and <10% in 6 months
Selective reporting (reporting bias)	Unclear risk	Retrospectively registered
Attention	Unclear risk	Not specified and diets differ (sardines or control diet)
Compliance	Low risk	Significant increase in EPA and DHA erythrocyte fatty acids in the intervention group at intervention end
Other bias	Low risk	None noted

Bassey 2000-Post [42]

Methods	RCT, (high PUFA GLA+DHA+EPA vs low PUFA, both with Ca), 12 months Summary risk of bias: moderate or high
Participants	Healthy postmenopausal women N: 21 intervention, 24 control (total randomised 57) Level of risk for CVD: low Male: 0% intervention, 0% control Mean age (SD): 58 (4.6) intervention, 55 (4.6) control Age range: 50-65 years (inclusion) Smokers: 20.8% intervention, 19% control Hypertension: not reported Medications taken by ≥ 50% of those in the control group: not reported Medications taken by 20%-49% of those in the control group: not reported

Medications taken by some, but < 20% of the control group: not reported (Women on confounding drug therapy were excluded.)
Location: UK
Ethnicity: not reported

Interventions

Type: capsules
Comparison: evening primrose oil + fish oil vs nil
Intervention 10 large capsules/d of efacal (Ca 1.0 g, evening primrose oil 4.0 g (85% or 3.4 g/d PUFA) and marine fish oil 440 mg), divided in doses with meals
Control: large capsules of 1 g Ca
Dose aim: increase ~3.5 g/d PUFA, **1.6% E PUFA**
Baseline PUFA unclear
Compliance by biomarkers: neither biomarkers nor TC data reported
Compliance by dietary intake: not reported

- Energy intake: not reported
- Total fat intake: not reported
- SFA intake: not reported
- PUFA intake: not reported
- PUFA n-3 intake: not reported
- PUFA n-6 intake: not reported
- Trans fat intake: not reported
- MUFA intake: not reported
- CHO intake: not reported
- Sugars intake: not reported
- Protein intake: not reported
- Alcohol intake: not reported

Compliance, other methods: assessed by counting returned capsules at each visit, reported compliance > 90%
Inclusion basis: no intention to increase total PUFA, planned dose ~3.5 g/d PUFA, 1.6% E PUFA, > 10% higher than assumed 6% E from total PUFA at baseline
PUFA dose: 1.6% E PUFA
Length of intervention: 12 months

Outcomes

Main trial outcome: BMD
Dropouts: 23% (unclear by arm)
Available outcomes: weight
Response to contact: not attempted

Notes

Trial funding: Scotia Pharmaceuticals Plc, Guildford, UK
Mortality reported (1 death but unclear in which arm)

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "women were randomized by staff at Scotia Pharmaceuticals Plc"
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias)	Unclear risk	Double-blind stated but no further details
Blinding of outcome assessment (detection bias)	Unclear risk	Assessors were blinded for the BMD measurements but unclear for other outcomes
Incomplete outcome data (attrition bias)	High risk	23% were lost to follow-up, unclear by arm and not all were accounted for
Selective reporting (reporting bias)	Unclear risk	No protocol or trial registry record
Attention	Low risk	No difference was noted for intervention/control groups
Compliance	Unclear risk	Neither biomarkers nor TC data reported
Other bias	Low risk	None noted

Bassey 2000-Pre [42]

Methods RCT, (high PUFA GLA+DHA+EPA vs low PUFA, both with Ca), 12 months
Summary risk of bias: moderate or high

Participants Healthy pre-menopausal women
N: 19 intervention, 24 control (total randomised 64)
Level of risk for CVD: low
Male: 0% intervention, 0% control
Mean age (SD): 34 (4.4) intervention, 35 (4.9) control
Age range: 25-40 years (inclusion)
Smokers: 0% intervention, 0% control
Hypertension: not reported
Medications taken by ≥ 50% of those in the control group: not reported
Medications taken by 20%-49% of those in the control group: not reported
Medications taken by some, but < 20% of the control group: not reported (Women on confounding drug therapy were excluded)
Location: UK
Ethnicity: not reported

Interventions Type: capsules
Comparison: evening primrose oil + fish oil vs nil
Intervention 10 large capsules/d of efacal (Ca 1.0 g, evening primrose oil 4.0 g and marine fish oil 440 mg), divided in doses with meals
Control: large capsules of 1 g Ca
Dose aim: increase ~3.5 g/d PUFA, 1.6% E PUFA
Baseline PUFA unclear
Compliance by biomarkers: neither biomarkers nor TC data reported
Compliance by dietary intake: not reported

- Energy intake: not reported
- Total fat intake: not reported
- SFA intake: not reported
- PUFA intake: not reported
- PUFA n-3 intake: not reported
- PUFA n-6 intake: not reported
- Trans fat intake: not reported
- MUFA intake: not reported
- CHO intake: not reported
- Sugars intake: not reported
- Protein intake: not reported
- Alcohol intake: not reported

Compliance, other methods: assessed by counting returned capsules at each visit, reported compliance > 90% (median > 9 capsules/d in both treatment and control groups)
Inclusion basis: no intention to increase total PUFA, planned dose ~3.5 g/d PUFA, 1.6% E PUFA, > 10% higher than assumed 6% E from total PUFA at baseline
PUFA dose: 1.6% E PUFA
Length of intervention: 12 months

Outcomes Main trial outcome: BMD
Dropouts: 31% (unclear by arm)
Available outcomes: weight
Response to contact: not attempted

Notes Trial funding: Scotia Pharmaceuticals Plc, Guildford, UK

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "women were randomized by staff at Scotia Pharmaceuticals Plc"
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias)	Unclear risk	Double-blind stated but no further details

Blinding of outcome assessment (detection bias)	Unclear risk	Assessors were blinded for the BMD measurements but unclear for other outcomes
Incomplete outcome data (attrition bias)	High risk	31% were lost to follow-up, unclear by arm and not all were accounted for
Selective reporting (reporting bias)	Unclear risk	No protocol or trial registry record
Attention	Low risk	No difference was noted for intervention/control groups
Compliance	Unclear risk	Neither biomarkers nor TC data reported
Other bias	Low risk	None noted

Bates 1977 [43 44]

Methods RCT, parallel, 4 arms (n6 GLA+LA vs MUFA), 2 years
Summary risk of bias: moderate to high

Participants People with chronic progressive multiple sclerosis
CVD risk: low
N; intervention A, C: 38 per arm; control B, D: 38 per arm
Mean years in trial: 2
% male: unclear (no statistically significant difference between groups)
Age: unclear (no statistically significant difference between groups)
Age range: unclear
Smokers: unclear
Hypertension: unclear
Medications taken by ≥ 50% of those in the control group: not reported
Medications taken by 20%-49% of those in the control group: not reported
Medications taken by some, but < 20% of the control group: not reported
Location: UK
Ethnicity: not reported

Interventions Type: supplement
Comparison: GLA + linoleic (n6) vs oleic (MUFA)
Intervention aims A: increase PUFAs with addition of 8 x 0.6 mL/d of Naudicelle oil in capsules (360 mg/d GLA plus 3.42 g/d linoleic acid plus < 1% ALA)
Control aims B: increase MUFAs with addition of 8 x 0.6 mL/d of oleic acid in capsules (4.8 g oleic acid/d)
A vs B dose aim: increase 0.34 g/d GLA, 3.78 g/d or 34 kcal or **1.7% E n-6**
Intervention aims C: increase linoleic acid with addition of 11.5 g/d in a spread
Control aims D: increase oleic acid with addition of 4 g/d in a spread
C vs D dose aim: increase 11.5 g/d or 104 kcal or **5% E n-6**
Baseline PUFA: unclear
Compliance by biomarkers: unclear, no serum TC reported, no tissue fatty acids reported
Compliance by dietary intake assessment: unclear, not reported

- Energy intake: not reported
- Total fat intake: not reported
- SFA intake: not reported
- PUFA intake: not reported
- PUFA n-3 intake: not reported
- PUFA n-6 intake: not reported
- Trans fat intake: not reported
- MUFA intake: not reported
- CHO intake: not reported
- Sugars intake: not reported
- Protein intake: not reported
- Alcohol intake: not reported

Compliance, other methods: not reported
Inclusion basis: aimed to increase total PUFA intake
PUFA dose: A vs B 1.7% E PUFA, C vs D 5% E PUFA
Duration of intervention: 2 years

Outcomes Main trial outcome: progression or regression of multiple sclerosis
Dropouts: unclear in all arms (deaths and dropouts reported together)
Available outcomes: multiple sclerosis progression (deaths occurred but reported with dropouts, so numbers and arms unclear)
Response to contact: yes, Professor Bates stated that data on mortality are no longer available.

Notes Trial funding: Multiple Sclerosis Society, Van den Berghs provided intervention and control spreads free

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomly allocated"
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias)	Low risk	Paper states "double blind", capsules of "identical appearance" and "similar spread"
Blinding of outcome assessment (detection bias)	Unclear risk	Paper states "double blind" with no further details
Incomplete outcome data (attrition bias)	Unclear risk	Deaths and dropouts combined, no reasons for dropping out provided
Selective reporting (reporting bias)	Unclear risk	No protocol or trials registry entry located
Attention	Low risk	Capsules and spreads provided to all participants, no suggestion of attention bias
Compliance	Unclear risk	Neither tissue PUFA biomarkers nor TC data reported
Other bias	Low risk	None found

Bates 1978 [44-46]

Methods RCT, parallel, 2 arms (n6 GLA+LA vs MUFA), using supplements (further 2 arms of n6 LA vs MUFA using supplementary foods not included as no outcome data), 2 years
Summary risk of bias: moderate to high

Participants People with acute remitting multiple sclerosis
CVD risk: low
N; intervention A, C: 29 per arm; control B, D: 29 per arm
Mean years in trial: 2
% male: intervention A 34.48%; intervention C 17.24%; control B 34.48%; control D 37.93%
Age (SD) years: intervention A 35 (9); intervention C 34 (8); control B 32 (7); control D 33 (5)
Age range: unclear
Smokers: unclear
Hypertension: unclear
Medications taken by ≥ 50% of those in the control group: not reported
Medications taken by 20%-49% of those in the control group: not reported
Medications taken by some, but < 20% of the control group: not reported
Location: UK
Ethnicity: not reported

Interventions Type: supplement
Comparison: GLA and linoleic (n6) vs oleic (MUFA)
Intervention aims A: 8 x Naudicelle capsules/d, 2.92 g/d LA plus 0.34 g/d GLA
Control aims B: 8 x capsules/d (4 g/d oleic acid), 4 g/d MUFA
A vs B dose aim: increase 0.34 g/d GLA, 3.26 g/d or 29 kcal or **1.5% E n-6**
Intervention aims C: linoleic acid spread (23 g/d linoleic acid)
Control aims D: oleic acid spread (16 g/d oleic acid)
C vs D dose aim: increase 23 g/d LA or 207 kcal or **10.4% E n-6**
Baseline PUFA: unclear
Compliance by biomarkers: good for C vs D, poor for A vs B, no serum TC reported, "estimations of total fatty acids in patients before and after 12-24 months' treatment showed that the percentage of

linoleic and arachidonic acids increased significantly only in those patients taking the linoleic acid spread (group C)".
Compliance by dietary intake: unclear, not reported

- Energy intake: not reported
- Total fat intake: not reported
- SFA intake: not reported
- PUFA intake: not reported
- PUFA n-3 intake: not reported
- PUFA n-6 intake: not reported
- Trans fat intake: not reported
- MUFA intake: not reported
- CHO intake: not reported
- Sugars intake: not reported
- Protein intake: not reported
- Alcohol intake: not reported

Compliance, other methods: not reported
Inclusion basis: aimed to increase PUFA intake, but C vs D had no outcome data so was excluded.
PUFA dose: A vs B 1.5% E PUFA, C vs D 10.4% E PUFA (assumed from omega-6 doses)
Duration of intervention: 2 years

Outcomes Main trial outcome: progression or regression of multiple sclerosis
Dropouts: A 0, B 1, C 3, D 6
Available outcomes: multiple sclerosis progression, deaths (nil in arms A, C and D)
Response to contact: contact with Dr Bates

Notes Trial funding: Multiple Sclerosis Society, Van den Berghs provided intervention and control spreads free

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomly allocated"
Allocation concealment (selection bias)	Unclear risk	Quote: "randomly allocated"
Blinding of participants and personnel (performance bias)	Low risk	Paper states "double blind", capsules of "identical appearance" and "similar spread"
Blinding of outcome assessment (detection bias)	Unclear risk	Paper states "double blind" with no further details
Incomplete outcome data (attrition bias)	Low risk	Fairly well described, from 0-6 dropouts per arm over 2 years (each 29 randomised)
Selective reporting (reporting bias)	Unclear risk	No protocol or trials registry entry located
Attention	Low risk	Appears equivalent
Compliance	High risk	No serum TC reported. Paper reports Quote: "estimations of total fatty acids in patients before and after 12-24 months' treatment showed that the percentage of linoleic and arachidonic acids increased significantly only in those patients taking the linoleic acid spread (group C)". Only A vs B had outcomes for this review, data suggests poor compliance in this group.
Other bias	Low risk	None found

Bates 1989 [47 48]

Methods RCT, parallel, (n-3 EPA + DHA vs MUFA), 24 months
Summary risk of bias: moderate or high

Participants People with multiple sclerosis

N: 155 intervention, 157 control. (analysed, intervention: 145 control: 147)
Level of risk for CVD: low
Men: 34.2% intervention, 30.6% control
Mean age in years (SD): 34.0 (6.6) intervention, 33.7 (6.3) control
Age range: not reported but 16-45 years inclusion criteria
Smokers: not reported
Hypertension: not reported
Medications taken by at least 50% of those in the control group: not reported
Medications taken by 20%-49%: not reported
Medications taken by some, but < 20%: not reported
Location: UK
Ethnicity: not reported

Interventions Type: supplement (fish oil capsule)
Comparison: EPA + DHA vs MUFA
Intervention: 20 × 0.5 g/d capsules MaxEPA fish body oil (10 g/d fish oil providing 1.71 g/d EPA +1.14 g/d DHA +10 IU/d vitamin E), plus all advised to reduce animal fat and ensure plentiful omega-6 fats.
Dose: +2.85 g/d EPA + DHA
Control: 20 × 0.5 g/d capsules olive oil (10 g/d olive oil), plus all advised to reduce animal fat and ensure plentiful omega-6 fats. All capsules contained 0.5 IU vit E and 100 ppm dodecyl gallate to minimise peroxide formation
Compliance: serum EPA and DHA rose in intervention group but fell in controls
Duration of intervention: 24 months (5 years mentioned but outcomes not reported)

Outcomes Main study outcome: multiple sclerosis progress
Dropouts: 10 intervention, 10 control
Available outcomes: all-cause mortality, progress of MS, rate of MS relapse
Response to contact: yes (no data provided)

Notes Study funding: Multiple Sclerosis Society of Great Britain and Northern Ireland, but Marfleet Refining provided fish oil and placebo capsules

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomised"
Allocation concealment (selection bias)	Unclear risk	No further details
Blinding of participants and personnel (performance bias)	Low risk	Paper states research was "double blind" and control capsules "had the same appearance and flavour as the fish oil capsules and were packed and dispensed in identical fashion"
Blinding of outcome assessment (detection bias)	Unclear risk	Not stated
Incomplete outcome data (attrition bias)	Low risk	Low risk at reported time points
Selective reporting (reporting bias)	High risk	No protocol or trials registration entries found. Study was intended to run for 5 years, but outcomes only appear to be reported for the first 2 years.
Attention	Low risk	Unlikely as each had capsules
Compliance	Low risk	Serum EPA and DHA rose in intervention group but fell in controls
Other bias	Low risk	Not noted

Baxheinrich 2012 [49]

Methods RCT, parallel, (n3 ALA vs MUFA), 6 months
Summary risk of bias: Moderate or high

Participants Participants with metabolic syndrome
N: 47 int., 48 control. (analysed, int: 40 cont: 41)

Level of risk for CVD: Moderate
Male: 32.10% in both groups combined
Mean age (sd): 52.3 (10.6) int., 50.3 (9.8) control
Age range: NR
Smokers: NR
Hypertension: NR
Medications taken by at least 50% of those in the control group: NR
Medications taken by 20-49% of those in the control group: NR
Medications taken by some, but less than 20% of the control group: NR
Location: Germany
Ethnicity: NR

Interventions Type: supplementary food (advice to consume hypo energetic diet with rapeseed oil or olive oil)
Comparison: ALA vs MUFA
Intervention: Rapeseed oil (Brokelmann) and a rapeseed-based margarine (Othuna): ALA 3.5g/d
Control: Olive oil (including <1g/d ALA, Lamotte Oils)
PUFA Dose: (intended) increase 3.5g/d ALA, **1.6%E n-3, 1.6%E PUFA**
Compliance: Dietary record
Duration of intervention: 6 months

Outcomes Main study outcome: Body weight and cardiovascular risk profile
Dropouts: 6 int., 7 control
Available outcomes: Adiposity, lipids, glucose, insulin (bp and metabolic syndrome- 6 months only)

Notes Study funding: Union for Promoting Oil and Protein Plants and the International Foundation for the Promotion of Nutrition Research and Nutrition Education

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"randomly assigned"
Allocation concealment (selection bias)	Unclear risk	As above
Blinding of participants and personnel (performance bias)	High risk	Appears open- control participants consumed a different oil once weekly
Blinding of outcome assessment (detection bias)	Unclear risk	NR
Incomplete outcome data (attrition bias)	Low risk	Analysis for completers only. Similar drop-out and reasons by arm
Selective reporting (reporting bias)	Unclear risk	No registry or protocol identified
Attention	Low risk	Counselling about lifestyle, dietary behaviour and physical activity was identical for both groups
Compliance	Low risk	Significant difference in dietary intake for ALA recorded at 6 months
Other bias	Low risk	None identified

Belch 1988 [50]

Methods RCT, parallel, 2 arms (n-6 evening primrose oil vs non-fat paraffin), 12 months
Summary risk of bias: moderate to high

Participants People with rheumatoid arthritis (RA)
CVD risk: low
Intervention 16 randomised, 16 analysed
Control 18 randomised, 18 analysed
Mean years in trial: 1
% male: intervention 6%; control 6%
Age, years: intervention median 46 years, control 48 years
Age range: intervention 35-68 years, control 30-74 years
Smokers: unclear

Hypertension: unclear
Medications taken by at least 50% of those in the control group: NSAIDs
Medications taken by 20%-49% of those in the control group: not reported
Medications taken by some, but less than 20% of the control group: not reported
Location: UK
Ethnicity: not reported

Interventions Type: supplement
Comparison: GLA (n-6) vs non-fat
Intervention aims: 12 capsules of evening primrose oil (Efamol), including 540 mg of gamma linolenic acid (GLA) per day
Control aims B: 12 capsules of liquid paraffin per day
Dose aim: increase 0.54 g/d GLA, 5 kcal or **0.25% E GLA**, assume 70% LA*, 4.2 g/d or 37.8 kcal/d or **1.9% E LA**, **2.2% E n-6**
Baseline n-6: unclear
Compliance by biomarkers: no serum total cholesterol or blood markers reported
Compliance by dietary intake: unclear, not reported

- Energy intake: not reported
- Total fat intake: not reported
- Saturated fat intake: not reported
- PUFA intake: not reported
- PUFA n-3 intake: not reported
- PUFA n-6 intake: not reported
- Trans fat intake: not reported
- MUFA intake: not reported
- CHO intake: not reported
- Sugars intake: not reported
- Protein intake: not reported
- Alcohol intake: not reported

Duration of intervention: 1 year

Outcomes Main study outcome: RA activity and NSAID dose
Dropouts: intervention 0, control 0
Available outcomes: ESR, CRP, functional status, RA status, NSAID use (authors stated that no deaths or CVD events occurred during the trial)

Notes Study funding: Action Research for the Crippled Child, and Efamol Ltd provided the supplements
Response to contact: Dr Belch contacted and provided some additional information, stating that no deaths or CVD events occurred

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomized double blind fashion", no detail provided
Allocation concealment (selection bias)	Unclear risk	As above, randomisation method not described.
Blinding of participants and personnel (performance bias)	Low risk	Quote: "All three types of capsules were supplied by Efamol Ltd and were visually identical. The capsules were issued to the patients in a randomized double blind fashion". Participants and personnel were probably blinded.
Blinding of outcome assessment (detection bias)	Unclear risk	Not stated
Incomplete outcome data (attrition bias)	Low risk	Quote: "Table 2 shows the number of patients withdrawn from the study by 12 months. One patient in the EPO group and two in the EPO/fish oil group were withdrawn owing to increasing symptoms of RA, compared with 10/18 of the placebo patients (both P < 0.001, Mann-Whitney). The results from all patients who were withdrawn were analyzed throughout the study on an intention to treat basis".
Selective reporting (reporting bias)	Unclear risk	No trial protocol or trials registry entry located

Attention	Low risk	Appears equivalent, capsules to both arms
Compliance	Unclear risk	No serum lipid, serum fatty acid or dietary intake data provided
Other bias	Low risk	None noted

Belluzzi 1996 [51 52]

Methods RCT, double blind, parallel, placebo controlled (n3 EPA+DHA vs mixed fat), 12 months
Summary risk of bias: Low
Aim "to investigate the effects of a new fish-oil preparation in the maintenance of remission in 78 patients with Crohn's disease"

Participants Individuals with established diagnosis of Crohn's Disease in clinical remission
N: 39 int., 39 control. (analysed – primary outcome, int: 34 cont: 37)
Level of risk for CVD: Low
Male: 51.3% int., 48.7% control.
Mean age (sd): NR. Median age: 34 int., 39 control
Age range: 18-67 int., 20-65 control
Smokers: 35.9% int., 33.33% control
Hypertension: NR
Medications taken by at least 50% of those in the control group: NR
Medications taken by 20-49% of those in the control group: NR
Medications taken by some, but less than 20% of the control group: NR
Location: Italy
Ethnicity: NR
% with diseased small bowel: 51.3% int., 51.3% control
% with diseased colon: 12.8% int., 10.3% control
% with small and large bowel disease: 35.9% int., 38.5% control

Interventions Type: supplement (capsules with EPA+DHA or capric/caprylic acid)
Comparison: EPA+DHA vs SFA
Intervention: 9x500mg capsules per day (including 1.8g/d EPA + 0.9g/d DHA; Purepa, Tillotts Pharma, Switzerland): EPA+DHA 2.7g/d
Control: 9x500mg capsules per day (including 1.8g/d capric acid + 2.7g/d caprylic acid, types of MCT; Myglyol 812, Dynamit Nobel Chemicals, Germany)
PUFA Dose: (intended) increase 2.7g/d, **1.2%E n-3, 1.2%E PUFA**
Compliance: capsule count, adiposity (RBCs)
Duration of intervention: 12 months

Outcomes Main study outcome: incidence of relapse/remission of CD
Dropouts: 5 int., 2 control
Available outcomes: Inflammatory markers: ESR, Serum alpha-2 globulins, Serum alpha 1-acid glycoprotein; changes in major FAs in red cells in patients remaining in remission at the end of the study

Notes Study funding: supported by Tillotts Pharma, Switzerland

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"balanced block randomisation scheme"
Allocation concealment (selection bias)	Low risk	Confirmed in personal communication
Blinding of participants and personnel (performance bias)	Low risk	"study medications were packed identically and labelled with each patient's code number; no difference in odour provided capsules were not broken"
Blinding of outcome assessment (detection bias)	Low risk	Confirmed in personal communication

Incomplete outcome data (attrition bias)	Low risk	Primary outcome reported only for participants who completed the trial (71/78, 9% drop-out)
Selective reporting (reporting bias)	Unclear risk	No study registration or protocol was found
Attention	Low risk	Identical follow up
Compliance	Low risk	Erythrocyte plasma membrane EPA and DHA measured at 12 months, both statistically significantly higher in the intervention group than control at 12 months; result of capsule count not stated.
Other bias	Low risk	None noted

Berbert 2005 [53]

Methods	3x parallel arm, placebo-controlled RCT (n3 EPA+DHA vs n6 LA), 24 weeks/6 months Summary risk of bias: Moderate or high Aim: "whether supplementation with olive oil could improve clinical and laboratory parameters of disease activity in patients who had rheumatoid arthritis and were using fish oil supplements"
Participants	People with rheumatoid arthritis according to the American College of Rheumatology criteria. N: 18 int., 17 control. (analysed: 13 int., 13 cont.) Level of risk for CVD: Low Male: 30.8% int., 15.4% control. Mean age (sd): 51 (13) int., 48 (10) control Age range: NR Smokers: NR Hypertension: NR Medications taken by at least 50% of those in the control group: One SAARD (slow-acting anti-rheumatic drub Medications taken by 20-49% of those in the control group: NSAID & 2xSAARD Medications taken by some, but less than 20% of the control group: 3xSAARD Location: Brazil Ethnicity: NR
Interventions	Type: supplement (capsules containing EPA+DHA or soy oil) Comparison: EPA + DHA vs MUFA/n6 Intervention: 3g/d (20 capsules) containing 1.8g EPA & 1.2g DHA (total n3 PUFA 3g/d) manufactured by R>P Scherer do Brasil Encapsulacoes, Sao Paulo, Brazil: EPA+DHA 3.0g/d Control: soy oil (20 capsules/d reported by author contact, composition unknown) Compliance: capsule count Duration of intervention: 24 wk/ 6 months
Outcomes	Main study outcome: Clinical and laboratory parameters of RA disease activity Dropouts: 5 int., 4 control Available outcomes: RA clinical and functional outcomes, laboratory measures of RA activity (ESR, CRP, rheumatoid factor, a1-acid antitrypsin, a1-acid glycoprotein, Hb) Author contact: Dr Dichi reports that they did not collect data on further inflammatory markers and recorded no CVD, diabetes, cancer, adiposity, depression or IBD event data.
Notes	Study funding: Capsules provided by R.P.Scherer do Brasil Encapsulacoes. No other indication of funding or conflict of interest.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient detail about method
Allocation concealment (selection bias)	Unclear risk	No details provided
Blinding of participants and personnel (performance bias)	Unclear risk	No information provided
Blinding of outcome assessment (detection bias)	Unclear risk	Insufficient information provided

Incomplete outcome data (attrition bias)	Low risk	“we used intention to treat as primary analysis” 16% drop-out
Selective reporting (reporting bias)	Unclear risk	No trial registration found
Attention	Low risk	Participants in both arms appear to have identical follow-up
Compliance	Unclear risk	Measured by capsule count but result not reported; no fatty acid status data provided
Other bias	Low risk	None noted

Berson 2004 [54 55]

Methods RCT, parallel, (n-3 DHA vs n-6 LA), 48 months
Summary risk of bias: low

Participants People with retinitis pigmentosa aged 18-55 years
N: 221 randomised overall, analysed 105 intervention, 103 control
Level of risk for CVD: low
Men: 48% intervention, 54% control
Mean age in years (SD): 37.8 (6.5) intervention, 36.0 (7.2) control
Age range: unclear (18-55 inclusion criterion)
Smokers: not reported
Hypertension: not reported
Medications taken by at least 50% of those in the control group: vitamin A
Medications taken by 20%-49% of those in the control group: multivitamins
Medications taken by some, but less than 20% of the control group: not reported
Location: USA
Ethnicity: unclear (6% of the study population were minorities)

Interventions Type: supplement (DHA capsules)
Comparison: DHA vs omega 6
Intervention: 6 × 500 mg capsules/d of DHA (1.2 g/d DHA plus 1.8 g vegetable oil) plus < 0.0006 mg/d tocopherols plus 15,000 IU retinyl palmitate (vitamin A). Dose: +1.2 g/d DHA
Control: 6 × 500 mg capsules/d of soy and corn oils (half each) with 120 mg/d ALA, plus < 0.0006 mg/d tocopherols plus 15000 IU retinyl palmitate (vitamin A)
Compliance: 92% of capsules taken by both intervention and control groups (assessed by monthly calendars), Plasma DHA much higher in intervention than control
Length of intervention: 48 months

Outcomes Main study outcome: retinal degeneration
Dropouts: 5 or 6 intervention, 7 or 8 control
Available outcomes: mortality, cancer diagnoses, lipids, eyesight
Response to contact: yes (no data provided)

Notes Study funding: National Eye Institute and Foundation Fighting Blindness

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random numbers
Allocation concealment (selection bias)	Low risk	Random numbers available only to programmer who provided assignments to data manager, all staff in contact with patients were masked to group assignment
Blinding of participants and personnel (performance bias)	Low risk	States that all staff in contact with participants were masked to group assignment, as were participants. However no information was provided regarding the taste, smell and appearance of the active and placebo capsules
Blinding of outcome assessment (detection bias)	Low risk	All assessments were performed blind to study allocation. Each ocular examination was performed

		without review of previous records. All serum samples were analysed without knowledge of treatment group assignment.
Incomplete outcome data (attrition bias)	Unclear risk	Numbers of dropouts and reasons for dropouts not stated. 221 participants randomised, data presented on 208 participants
Selective reporting (reporting bias)	Unclear risk	No trials registry entry or protocol found.
Attention	Low risk	Staff in contact with patients were masked, so unable to bias time, etc.
Compliance	Low risk	92% of capsules taken by both intervention and control groups (assessed by monthly calendars), Plasma DHA much higher in intervention than control
Other bias	Low risk	None noted

Black 1994 [56-58]

Methods RCT, parallel, (low fat diet vs usual diet), 24 months
Summary risk of bias: moderate or high

Participants People with non-melanoma skin cancer
N: 66 intervention, 67 control (analysed, 57 int, 58 cont)
Level of risk for CVD: low
Male: 54% intervention, 67% control
Mean age (SD): 50.6 (9.7) intervention, 52.3 (13.2) control
Age range: not reported
Smokers: not reported
Hypertension: not reported
Medications taken by ≥ 50% of those in the control group: not reported
Medications taken by 20%-49% of those in the control group: not reported
Medications taken by some, but < 20% of the control group: not reported
Location: USA
Ethnicity: white 100% (excluded from trial if of Asian, Black, Hispanic or American Indian ancestry)

Interventions Type: dietary advice
Comparison: reduced fat (lower omega-6 and total PUFA) vs usual diet
Intervention: aims total fat 20% E, protein 15% E, CHO 65% E; methods 8 x weekly classes plus monthly follow-up sessions, with behavioural techniques being taught following individual approach (not clear if in a group or individual). 4-month intervals clinic examination by dermatologist.
Intervention delivered face to face by a dietitian
Control: aims usual diet; methods no dietary change, 4-month intervals clinic examination by dermatologist
Dose aim: reduce total fat to 20% E, 15% E protein, 65% E CHO, particularly complex CHO (fat reduction included reducing omega-6 and total PUFA, no aim provided)
Baseline PUFA 8% E
Compliance by biomarkers: unclear, no serum TC reported, no tissue fatty acids
Compliance by dietary intake: all assessed "during study", months 4-24, using 7-day food records verified by a dietitian

- Energy intake, kcal/d: control 2196 (SD 615), intervention 1995 (SD 564)
- Total fat intake, % E: control 37.8 (SD 4.1), intervention 20.7 (SD 5.5) (MD -17.10, 95% CI -18.88 to -15.320 significant reduction
- SFA intake, % E: control 12.8 (SD 2.0), intervention 6.6 (SD 1.8), (MD -6.20, 95% CI -6.90 to -5.50) significant reduction
- PUFA intake, % E: control 7.8 (SD 1.4), intervention 4.5 (SD 1.3), (MD -3.30, 95% CI -3.79 to -2.81) significant reduction
- PUFA n-3 intake: not reported
- PUFA n-6 intake: LA, Control 16.9 (SD 5.6) g, intervention 8.5 (SD 3.3) g
- Trans fat intake: not reported
- MUFA intake, % E: control 14.4 (SD 1.7), intervention 7.6 (SD 2.2), (MD -6.80, 95% CI -7.52 to -6.08) significant reduction
- CHO intake, % E: control 44.6 (SD 6.9), intervention 60.3 (SD 6.3), (MD 15.70, 95% CI 13.29 to 18.11) significant increase

- Sugars intake: not reported
- Protein intake, % E: control 15.7 (SD 2.4), intervention 17.7 (SD 2.2), (MD 2.00, 95% CI 1.16 to 2.84) significant increase
- Alcohol intake, % E: control 3.2 (SD 3.9), intervention 3.2 (SD 3.4)

Inclusion basis: dietary intake data suggested total PUFA intake 3.3% E higher in control than intervention
PUFA dose: -3.3% E
Duration of intervention: 24 months (mean 1.9 years in trial)

Outcomes Main trial outcome: incidence of actinic keratosis and non-melanoma skin cancer
Dropouts: unclear intervention, unclear control
Available outcomes: deaths, CVD deaths, cancer deaths (none), (weight data provided but without variance)
Response to contact: Prof Black provided data on mortality

Notes Trial funding: National Cancer Institute
NOTE: for this trial the higher PUFA arm is the control, and lower PUFA arm is the intervention

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"list of randomly generated numbers"
Allocation concealment (selection bias)	Unclear risk	Randomisation method not clearly described
Blinding of participants and personnel (performance bias)	High risk	Dietary advice provided, so participants not blinded
Blinding of outcome assessment (detection bias)	Low risk	"examined .... by dermatologists unaware of their treatment assignments". Deaths (all-cause and CVD) not considered relevant to the intervention
Incomplete outcome data (attrition bias)	Low risk	For mortality. Unclear for other outcomes
Selective reporting (reporting bias)	Unclear risk	No protocol or trials registry entry found
Attention	High risk	Weekly classes and monthly follow-up in intervention group, 4-monthly check-ups only in control
Compliance	Unclear risk	Neither tissue PUFA biomarkers nor TC data reported
Other bias	Low risk	None noted

Bo 2017 – ChiCTR-TRC-14004625 [59]

Methods RCT, parallel, (n3 EPA+DHA vs MUFA), 6 months
Summary risk of bias: Moderate or high
Aim: "investigate the effect of n-3 PUFA supplementation on cognitive function in the Chinese elderly with mild cognitive impairment"

Participants Older adults with mild cognitive impairment
N: 44 int., 42 control. (analysed, int: 44 cont: 42)
Level of risk for CVD: low
Male: 59% int., 60% control.
Mean age (sd) yrs: 71.8 (5.7) int., 70.5 (6.8) control
Age range: NR but inclusion criteria were ≥60 years
Smokers: NR
Hypertension: NR
Medications taken by at least 50% of those in the control group: NR
Medications taken by 20-49% of those in the control group: NR
Medications taken by some, but less than 20% of the control group: NR
Location: China
Ethnicity: NR

Interventions Type: supplement
Comparison: EPA+DHA vs MUFA

Intervention: 4x1g capsules every nine days (each capsule contained 120 mg DHA & 180 mg EPA, Royal DSM Company of Holland, Shanghai, 480 mg/d DHA and 720 mg/d EPA): EPA+DHA 1.2g/d
Control: 4x1g isocaloric placebo olive oil capsules every nine days (each containing 550 mg of oleic acid)
Compliance: NR
Duration of intervention: 6 months

Outcomes Main study outcome: cognitive function
Dropouts: 12 of 44 int., 10 of 42 control (but ITT analysis included everyone randomised)
Available outcomes: Basic Cognitive Aptitude Test (BCAT) and subcategories, IL-6, IL-10, TNFα, cyclooxygenase, lipoxygenase, secretory phospholipase A2 (MMSE also assessed but not reported)

Notes Study funding: Chinese Nutrition Society (CNS) Nutrition Research Foundation-DSM Research Fund, State Key Program of National Natural Science Foundation of Tianjin. The capsules were supplied by the Royal DSM Company of Holland
Author contact: Author response, no further outcome data available (no deaths occurred, other health problems were not recorded), some methodology details provided.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"The randomization sequence was computer-generated by a blinded statistician not involved in data collection or analysis according to age and gender"
Allocation concealment (selection bias)	Low risk	Randomisation occurred after screening for MMSE and BCAT, with details above this suggests good allocation concealment.
Blinding of participants and personnel (performance bias)	Unclear risk	Study described as double blind. However no information was provided regarding the taste, smell and appearance of the active and placebo capsules.
Blinding of outcome assessment (detection bias)	Unclear risk	No clear information
Incomplete outcome data (attrition bias)	Low risk	ITT analysis, though drop out was 22 of 86 (26%) over 6 months
Selective reporting (reporting bias)	High risk	Trials registry entry March 2014, eligible participants were screened between February 2014 and May 2014, study ran Oct 2013 to Oct 2015. MMSE, blood membrane fatty acids and ADLs were the primary outcomes, but of these only fatty acids reported in this paper.
Attention	Low risk	Appeared similar in the two groups
Compliance	Low risk	Peripheral blood plasma DHA and EPA of the intervention group were significantly higher than in the placebo group
Other bias	Low risk	None noted

Boespflug 2016 – NCT01746303 [60]

Methods RCT, parallel (n3 EPA + DHA vs n6 LA, 6 months
Summary risk of bias: moderate or high

Participants Population: older adults with subjective memory impairment
N: 15 int., 12 control. (analysed, int: 11 cont: 10)
Level of risk for CVD: Low
Male: 45.5% int., 30.0% control.
Mean age (sd): 70.1 (6.12) int., 66.4 (3.75) control
Age range:62-80
Smokers: NR
Hypertension: 36.4% int., 40.0% control

Medications taken by at least 50% of those in the control group: NR
Medications taken by 20-49% of those in the control group: NR
Medications taken by some, but less than 20% of the control group: NR
Location: USA
Ethnicity: NR

Interventions Type: food supplement (fish oil with DHA +EPA)
Comparison: DHA + EPA vs n-6
Intervention: fish oil capsule (1.6g/d EPA + 0.8g/d DHA; 4 capsules/d): EPA + DHA 2.4g/d
Control: placebo (corn oil, no other information)
Compliance: NR but erythrocyte fatty acid composition was determined)
Duration of intervention: 6 months

Outcomes Main study outcome: working memory and executive ability
Dropouts: 4 int., 2 control
Available outcomes: cognitive measures (n-back task)

Notes Clinical dementia 'sum of boxes score' and geriatric depression scale reported at baseline but not at the end of the study, so may be available.
Study funding: in part by a National Institute of Health
grant AG034617-01S2 to R.K. and R.K.M. (Co-PIs).
Inflammation Research Foundation provided fish oil or placebo capsules.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Participants were randomized to fish oil or placebo (corn oil)
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias)	Unclear risk	Placebo corn oil capsules that are identical in size, shape, and colour to omega-3 capsules. However no information provided on capsules taste or smell.
Blinding of outcome assessment (detection bias)	Low risk	All samples were processed by a technician blinded to treatment.
Incomplete outcome data (attrition bias)	High risk	27 became 21. 5 left because dietary restrictions too onerous, one missed assessment visit, one had a bad attitude. > 20% loss in just 24 weeks.
Selective reporting (reporting bias)	High risk	Most outcomes are missing and not reported.
Attention	Low risk	Evaluations at baseline, 12 wks, 24 wks. It reads the same for all 4 arms.
Compliance	Unclear risk	Fatty acid status of erythrocyte reported for both arms but this was not linked to compliance.
Other bias	Low risk	None noted

Bonnema 1995 [61]

Methods RCT, parallel, (n3 EPA+DHA vs MUFA), 6 months
Summary risk of bias: Moderate or high

Participants Adults with insulin-treated diabetes and microalbuminurea
N: 14 int., 14 control. (analysed, int: 14 cont: 13)
Level of risk for CVD: moderate (diabetes)
Male: 57% int., 50% control.
Mean age (sd) years: 47 (16) int., 41 (12) control
Age range: NR
Smokers: 71% int., 57% control
Hypertension: 0% int., 0% control
Medications taken by at least 50% of those in the control group: insulin
Medications taken by 20-49% of those in the control group: NR
Medications taken by some, but less than 20% of the control group: NR

(Diuretics allowed, and vasoactive and lipid lowering drugs prohibited)
Location: Denmark
Ethnicity: NR

Interventions Type: supplement
Comparison: fish oil capsules vs olive oil capsules
Intervention: 6x1g fish oil capsules (Pikasol) daily (with conventional diabetic diet) including 2g/d EPA plus 1.32g/d DHA: EPA+DHA 3.32g/d
Control: 6x1g olive oil capsules daily (with conventional diabetic diet)
PUFA Dose: (intended) increase 3.32g/d EPA+DHA, **1.5%E n-3, 1.5%E PUFA**
Compliance: Capsule count, average daily consumption was >95% expected amount
Duration of intervention: 6 months

Outcomes Main study outcome: peripheral arterial compliance
Dropouts: 0 int., 1 control
Available outcomes: glucose, total & HDL cholesterol (HbA1c no variance; BP, urinary albumin, serum creatinine, arterial & venous compliance - these not used, TG not used as 2 arms very different at baseline), no deaths or CVD events occurred, insulin doses not altered. 2 in intervention group, 0 in control developed albumin excretion.

Notes Study funding: Esbjerg Fonden, Fonden for laegevidenskabelig forskning i Rignkoebing, Ribe and Soenderjyllands Amter, capsules from Lube Ltd, Denmark.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomization was done by sealed envelopes", and was "blinded through a third person without involvement of the investigators"
Allocation concealment (selection bias)	Low risk	As above.
Blinding of participants and personnel (performance bias)	Unclear risk	Authors replied to reviewers stating that the recipients and providers were unaware of the assigned treatment, but it is unclear how this was achieved given that fish oil is easy to taste.
Blinding of outcome assessment (detection bias)	Unclear risk	Unclear.
Incomplete outcome data (attrition bias)	Low risk	One withdrawal only of 28 randomised, due to adverse effects
Selective reporting (reporting bias)	Unclear risk	No trials registry entry or study protocol identified.
Attention	Unclear risk	Participants all visited every 2 months, no suggestion of differential treatment
Compliance	Low risk	Pill counts suggested high compliance.
Other bias	Low risk	None noted

Brox 2001 [62]

Methods RCT, parallel, 3 arms (n-3 EPA + DHA from cod liver vs n-3 EPA + DHA from seal oil vs nil), 14 months
Summary risk of bias: moderate or high

Participants Subjects with moderate hypercholesterolaemia
N: 40 seal oil (SO), 40 cod liver oil (CLO), 40 control (numbers analysed vary by outcome)
Level of risk for CVD: moderate (dyslipidaemia)
Men: 53% seal oil, 50% cod liver oil, 48% control
Mean age in years: 53.2 seal oil, 55.0 cod liver oil, 55.8 control
Age range: 43-66 years
Smokers: unclear
Hypertension: unclear
Medications taken by at least 50% of those in the control group: none allowed
Medications taken by 20%-49% of those in the control group: not reported

Medications taken by some, but less than 20% of the control group: not reported
Location: Norway
Ethnicity: not reported

Interventions Type: supplement (oil)
Comparison: EPA + DHA vs nil
Intervention: Intervention: seal oil – 15 mL/d (2.6 g, 1.1 g/d EPA + 1.5/d DHA) (total n-3 3.9 g/d, total PUFA 4.2 g/d): SO dose: EPA + DHA 2.6 g/d
Cod liver oil – 15 mL/d (3.3 g, 1.5 g /d EPA + 1.8 g/d DHA) (total n-3 4.1 g/d, total PUFA 4.35 g/d): CLO dose: EPA + DHA 3.3 g/d
Control: nil, no supplement
Compliance: serum omega-3 fatty acids, rose from around 1 mmol/L to 2.4 (seal oil), 2.1 (cod liver oil) and 1.2 mmol/L (control)
Length of intervention: 14 months

Outcomes Main study outcome: serum lipids
Dropouts: 8 seal oil, 2 cod liver oil, 1 control
Available outcomes: total and cardiovascular deaths, MI, combined CV events, lipids, adverse events
Response to contact: yes (author provided methodological details)

Notes Data of two intervention groups combined for dichotomous outcomes and CLO vs control data used for continuous outcomes
Study funding: the study was supported by the programme Medical Research in Finnmark County, University of Tromsø

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	J Brox stated (personal communication, January 2017): "The randomization of the 120 participants was done by first generating 3 groups (seal oil, cod liver oil, control), then giving each participant a number (1-120), "'putting all the numbers into the same hat' and blindly drawing one number at the time from the hat. The first 40 numbers (1-40) were allocated to the seal oil group, the next 40 numbers (41-80) to the cod liver oil group and the rest (81-120) were allocated to the control group."
Allocation concealment (selection bias)	Low risk	J Brox stated (personal communication, January 2017): "The researcher/clinician who invited the participants had no knowledge of to which group the participants would be allocated."
Blinding of participants and personnel (performance bias)	High risk	Quote: "controls were aware – not given a supplement"
Blinding of outcome assessment (detection bias)	Low risk	J Brox stated (personal communication, 2003): "All the persons involved in the drawing & analysing of blood were unaware of treatment. The technicians analysing the blood did not have any personal contact with the participants except K. Olaussen who did the FA analysis … she only had access to the sample numbers not names and code. The participants did not know their number (says elsewhere that K Olaussen did not know allocations). The only outcome assessor was J Brox who did not have personal contact with participants, randomising, collecting results or analysing process." "The only assessor was J Brox who did not have any personal contact with the participants, had nothing to do with the randomising or analysing process, or the collecting of results."
Incomplete outcome data (attrition bias)	High risk	Control group 3 dropouts, seal oil group 10 dropouts, cod liver oil 3 dropouts. So substantial differences in rates of dropouts between the groups

Selective reporting (reporting bias)	Unclear risk	No study protocol or trials register entry was found
Attention	Low risk	No suggestion of differential attention
Compliance	Low risk	Serum omega-3 fatty acids, rose from around 1 mmol/L to 2.4 (seal oil), 2.1 (cod liver oil) and 1.2 mmol/L (control)
Other bias	Low risk	No further bias noted

Brzeski 1991 [63]

Methods RCT, parallel, (n6 GLA vs MUFA), 6 months
Summary risk of bias: Moderate to high
Aim "we studied EPO in patients with RA who already had upper gastrointestinal lesions attributable to NSAIDs"

Participants People with rheumatoid arthritis and upper GI lesions due to NSAID intake
N: 19 int., 21 control. (analysed, int: 13 cont: 17)
Level of risk for CVD: low
Male: 11% int., 29% control.
Mean age (sd) yrs: 60 (NR) int., 61 (NR) control
Age range: int 54-77, cont 51-67 yrs
Smokers: NR
Hypertension: NR
Medications taken by at least 50% of those in the control group: all used NSAIDs and analgesics, some used H2 blockers (numbers not stated)
Medications taken by 20-49% of those in the control group: second line therapy (not stated what, 48%)
Medications taken by some, but less than 20% of the control group: NR
Location: UK
Ethnicity: NR

Interventions Type: supplement
Comparison: GLA vs MUFA
Intervention: 6g/d evening primrose oil (EPO), including 0.54g/d GLA, 60mg/d alpha-tocopherol
Control: 6g/d olive oil in capsules, including 60mg/d alpha-tocopherol
Compliance: Of 13 completing EPO 10 showed a significant rise in plasma DGLA (a GLA metabolite), int 4.85 (SD 1.52)%, control 3.48 (SD 0.57)%, statistically significantly different
Duration of intervention: 6 months

Outcomes Main study outcome: NSAID use and dosage
Dropouts: 6 of 19 int., 4 of 21 control
Available outcomes: NSAID dose reduction, pain, articular index, morning stiffness, HAQ, wellbeing (inflammatory markers inc ESR and CRP were measured, but no data shown, text states "there were no changes in laboratory parameters of inflammation".

Notes Study funding: Efamol provided funding, materials and fatty acid analyses.
Author contact: No response to attempts

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Paper only states "randomised"
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias)	Low risk	Paper states double-blind and EPO and olive oil capsules are said to appear identical
Blinding of outcome assessment (detection bias)	Unclear risk	No description of how this was achieved
Incomplete outcome data (attrition bias)	High risk	6 of 19 and 4 of 21 lost by 6 months (25%), reasons given

Selective reporting (reporting bias)	Unclear risk	No protocol or trials register entry found
Attention	Low risk	The study only differed by the content of the capsules, but the assessment schedule was not stated to differ between the two arms
Compliance	Low risk	Plasma DGLA significantly different between int and control at 6 months.
Other bias	Low risk	None noted

Caldwell 2011 NCT00681408 [64-67]

Methods RCT, parallel, (n-3 EPA + DHA vs n-6 LA), 12 months
Summary risk of bias: low

Participants Participants with non-cirrhotic NASH (non-alcoholic steatohepatitis)
N: 20 intervention, 21 control (analysed 17 intervention, 17 control)
Level of risk for CVD: moderate
Men: 35.3% intervention, 41.2% control
Mean age in years (SD): 46.4 (12.1) intervention, 47.2 (12) control
Age range: 25-72 years
Smokers: not reported
Hypertension: not reported
Medications taken by at least 50% of those in the control group: not reported
Medications taken by 20%-49% of those in the control group: not reported
Medications taken by some, but less than 20% of the control group: not reported
Location: USA
Ethnicity: intervention, 100% white, control 94.% white, 5.9% other

Interventions Type: supplement (capsule)
Comparison: EPA + DHA vs omega 6
Intervention: 3 × 1 g fish oil capsules/d (Nordic Natural) for a total 2.1 g/d n-3, each capsule contained 70% of n-3 (1050 mg EPA, 750 mg DHA + 300 mg other n-3). Dose: 1.8 g/d EPA + DHA
Control: 3 × 1 g identical placebo (soybean) capsules per day containing 8% fish oils
Both groups had dietary counselling on caloric intake and physical activity
Compliance: unclear (measured n-6-n-3 ratio due to its link to hepatic lipid composition)
Length of intervention: 12 months

Outcomes Main study outcome: NASH activity score
Dropouts: 3 intervention, 3 control
Available outcomes: lipids (TG too unbalanced at baseline to use), measures of adiposity (weight, BMI, visceral fat – all unbalanced at baseline so not used), fasting glucose, insulin, HOMA-IR, QUICKI (also NASH progression, hepatic fat, ALT, VO_2 max, activity level, markers of cell injury, adiponectin not used)
Response to contact: yes, change data supplied for BMI and body weight, confirmed no deaths, cardiovascular events, diabetes, depression, breast cancer or IBD diagnoses

Notes Data on; BMI, weight, visceral fat, TG and glucose were not used as they were different between groups at baseline.
Study funding: study was supported by NIH NCCAM Grant 5R21AT2901–2 and 5 M01 RR00847. Study medication and identical appearing placebo was provided at no charge by Nordic Natural. RBC phospholipid profile was performed by Metametrix (www.metametrix.com). M30, M65, adiponectin, and IGFBP-1 electro chemiluminescence assays were performed by Wellstat Diagnostics (www.wellstatdiagnostics.com).

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomised to n-3 or placebo using a stratified block 1:1 randomisation scheme. An independent biostatistician generated the randomisation list which was confidentially forwarded to the Investigational pharmacy

Allocation concealment (selection bias)	Low risk	As above
Blinding of participants and personnel (performance bias)	Low risk	All staff and subjects were blinded to therapy assignment throughout the study period. Both capsules were identical. However no information provided on capsules taste or smell
Blinding of outcome assessment (detection bias)	Low risk	Blinded for main outcome
Incomplete outcome data (attrition bias)	Low risk	15% dropouts explained and equal in both groups
Selective reporting (reporting bias)	Low risk	The trial was prospectively registered
Attention	Low risk	Both groups had the same attention
Compliance	Unclear risk	No details on compliance measurement
Other bias	Low risk	None noted

Chiu 2008 - NCT00628017 [68]

Methods	RCT, parallel, omega 3 supplements (n3 EPA + DHA vs MUFA), 6 months Summary risk of bias: Moderate or high
Participants	pop: Older adults with Alzheimer's Disease or Mild Cognitive Impairment N: 24 int., 22 control. (analysed, int: 17 cont: 12) Level of risk for CVD: Low Male: 35% int., 53.3% control. Mean age (sd): 74 (NR) int., 76.5 (NR) control Age range: 70.1-77.8 (int), 71.8-81.1 (control) Smokers: NR Hypertension: NR Medications taken by at least 50% of those in the control group: NR Medications taken by 20-49% of those in the control group: NR Medications taken by some, but less than 20% of the control group: NR Location: Taiwan (Taipei City Psychiatric Center, Taipei City Hospital, Taipei) Ethnicity: NR
Interventions	Type: supplement (capsule DHA + EPA) Comparison: DHA & EPA vs olive oil Intervention: Dietary supplement (180mg EPA + 120mg DHA/capsule), 3 capsules twice daily, total dosage of 1.08mg/d EPA + 0.72 mg/d DHA: EPA+DHA 1.8g/d Control: Olive oil (placebo), 3 capsules twice daily containing olive oil esters. **PUFA Dose**: (intended) increase 1.8g/d, **0.8%E n-3, 0.8%E PUFA** Compliance: 92.4%, intervention; 81.8%, control Duration of intervention: 6 months
Outcomes	Main study outcome: the Clinician's Interview-Based Impression of Change Scale (CIBIC-plus), the cognitive portion of the Alzheimer's Disease Assessment Scale (ADAS-cog) Dropouts: 7 int., 10 control Available outcomes: ADAS-cog, MMSE, CIBIC-plus, adverse effects, Hamilton Depression Scale (HDRS, but data too unbalanced at baseline to use), plasma fatty acid status, adherence
Notes	Study funding: Taipei City Psychiatric Center, Taiwan Collaborator: Department of Health, Executive Yuan, R.O.C. (Taiwan)

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The randomization was not stratified, which may make an unbalanced distribution of participants with AD and MCI in the two groups, especially in small sample size study although there was no significant difference in the distribution of patients with AD or

		MCI in the two groups at the post hoc comparison. Further details not provided.
Allocation concealment (selection bias)	Unclear risk	The randomization process was carried out by another member of staff independent of the study and blind to the assessment.
Blinding of participants and personnel (performance bias)	Low risk	Placebo capsules were identical to the capsules used in the intervention group. Both treatment and placebo capsules were vacuum deodorized and supplemented with tertiary-butyl hydroquinone, 0.2 mg/g, and tocopherols, 2 mg/g, as antioxidants.
Blinding of outcome assessment (detection bias)	Low risk	Laboratory measures were conducted on coded samples by workers blinded to other data, including intervention group.
Incomplete outcome data (attrition bias)	High risk	Over 25% lost from both arms of the study over 24 weeks, 8 from intervention, & 10 from control group.
Selective reporting (reporting bias)	High risk	Results submitted for publication before trial registration (Paper submitted in Dec 2007 Trial registered Feb 2008)
Attention	Low risk	Participants were assessed and the capsules replenished every 6 weeks after starting the trial…. Measurements were assessed at baseline and at weeks 6, 12, 18, and 24.Seems the same in both arms.
Compliance	Low risk	Compliance was 92.4% in the intervention group and 2 *were removed for non-compliance.* Compliance for the control group was 81.8%, with *3 removed due to non-compliance.*
Other bias	Unclear risk	None stated

Clark 2016 – NCT01241474 [69 70]

Methods	RCT, parallel, (n3 EPA+DHA vs n6 LA), 9 months Summary risk of bias: Moderate or high
Participants	Adults with impaired glucose metabolism or type 2 diabetes mellitus N: 36 randomised (not specified by arm) (analysed, int: 16 cont: 17) Level of risk for CVD: Low Male: 63% int., 59% control. Mean age (sd): 61.8 (NR) int., 58.1 (NR) control Age range: 52-67 int, 51-68 cont, years Smokers: NR Hypertension: NR Medications taken by at least 50% of those in the control group: NR Medications taken by 20-49% of those in the control group: NR Medications taken by some, but less than 20% of the control group: NR Non-steroidal anti-inflammatory medication and diabetic medications were not allowed, statins were allowed (but unclear how many used them) Location: Scotland, UK Ethnicity: NR
Interventions	Type: supplement (capsule) Comparison: fish oil vs maize oil Intervention: 6g/d fish oil from menhaden & pacific herring as 6x1g EPAX 6000 TG (EPAX AS), 3.9g/d omega 3: EPA+DHA 3.9g/d Control: 6g/d as 6x1g maize oil (<2% EPA+DHA) **PUFA Dose**: (intended) increase 3.9g/d EPA+DHA, **1.8%E n-3, 1.8%E PUFA** Compliance: monthly capsule count plus phospholipid composition of erythrocyte membranes Duration of intervention: 9 months
Outcomes	Main study outcome: insulin sensitivity Dropouts: NR (36 randomised, 16 int, 17 cont analysed)

Available outcomes: Diabetes diagnosis, weight, %body fat, lipids, fasting glucose & insulin , HOMA2-IR, , fasting endogenous glucose production, branched chain amino acids, C-peptide measured but not used)
Response to contact: Yes (data provided)

Notes Study funding: core grant from the Scottish Government to the Rowett Institute, EPAX AS provided the intervention and control capsules.
Diabetes diagnosis: only data on confirmed diagnosis was used. Data provided by authors included participants with raised HbA1c not used.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Author confirmed the Statistician (head of the local Biomathematics and Statistics (BioSS) team) generated a random list (computer generated) for oil distribution; the contents of this list were known only to him.
Allocation concealment (selection bias)	Low risk	As above
Blinding of participants and personnel (performance bias)	Unclear risk	"Capsules of the two oils were identical in outward appearance and were provided via the double-blind procedure in similar containers labelled sequentially under the supervision of an independent nutritionist. Neither volunteers nor researchers knew which treatment was allocated". However no information provided on capsules taste or smell.
Blinding of outcome assessment (detection bias)	Low risk	Author confirmed: At the end of the trial and following data analysis, the final codes were disclosed by the Statistician. So throughout the trial neither the volunteers nor the Experimenters knew which oil was allocated to whom
Incomplete outcome data (attrition bias)	Low risk	3 dropouts only of 36 randomised (8%), reasons provided
Selective reporting (reporting bias)	Unclear risk	All outcomes mentioned in the registry were presented, but study started in Feb 2009 and study was registered in Nov 2010, unclear how many participants had completed by this time
Attention	Low risk	Intervention and control participants appeared to have the same time and procedures at each appointment
Compliance	Low risk	Erythrocyte membrane long chain omega 3 fatty acids were significantly different in intervention and control participants
Other bias	Low risk	None noted

Connor 1993 [71 72]

Methods RCT, cross-over, (n3 EPA+DHA vs MUFA), 6 months
Summary risk of bias: Moderate or high

Participants Participants with non-insulin dependent diabetes and hypertriglyceridemia
N: 16 int., 16 control. (analysed, int: 16 cont: 16)
Level of risk for CVD: Moderate
Male: NR
Mean age (sd): 58.7 (7.8) in both groups combined
Age range: 46-72 years overall
Smokers: NR
Hypertension: NR

Medications taken by at least 50% of those in the control group: 15/16 pts were on oral hypoglycaemic agents
Medications taken by 20-49% of those in the control group: insulin
Medications taken by some, but less than 20% of the control group: NR
Location: USA
Ethnicity: NR

Interventions Type: supplement (fish oil or olive oil)
Comparison: EPA+DHA vs MUFA
Intervention: 15g fish oil/d (including 4.1g/d EPA and 1.9g/d DHA, Promegae, Parke David Warner Lambert): EPA+DHA 6.0g/d
Control: 15g olive oil/d (Perke David Warner Lambert)
PUFA Dose: (intended) increase 6.0g/d EPA+DHA, **2.7%E n-3, 2.7%E PUFA**
Compliance: Plasma fatty acids
Duration of intervention: 2 consecutive 6 month periods of intervention or control

Outcomes Main study outcome: Lipids and diabetic control
Dropouts: 0 int., 0 control
Available outcomes: Lipids, glucose (plasma and urinary), HbA1c, weight, mortality
Response to contact: yes

Notes Author response confirming no mortality/ cardiovascular events
Study funding: Institutes of health, Oregon sea grant

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"randomized" "coin"
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias)	Unclear risk	No details
Blinding of outcome assessment (detection bias)	Unclear risk	No details
Incomplete outcome data (attrition bias)	Low risk	No drop outs
Selective reporting (reporting bias)	Unclear risk	No registry or protocol identified
Attention	Low risk	Identical treatment is described
Compliance	Unclear risk	No p-values supplied
Other bias	Low risk	None noted

Darghosian 2015 - NCT00552084 [73]

Methods RCT, double blind, parallel, placebo-controlled (n3 EPA+DHA vs n6 LA), 6 months
Summary risk of bias: Moderate or high
Aim: examined the effects of high-dose marine n-3 PUFAs added to conventional therapy on the recurrence of AF and on markers of inflammation and oxidative stress"

Participants People with paroxysmal or persistent AF
N: 126 int., 64 control. (analysed, int: 126 cont: 64)
Level of risk for CVD: High
Male: 53% int., 66% control.
Mean age (sd): 62 (12) int., 61 (11) control
Age range: NR
Smokers: NR
Hypertension: 62% int., 69% control
Medications taken by at least 50% of those in the control group: Beta-blocker (64%)
Medications taken by 20-49% of those in the control group: Class I agent (23%), Solatol/dofetilide (31%), Statin (44%), ACE inhibitor (25%), Warfarin (44%)

	Medications taken by some, but less than 20% of the control group: Angiotensin receptor blocker (9%), Amiodarone (12%) Location: USA Ethnicity: int. 94% white, control 95% white
Interventions	Type: supplement (capsules containing EPA+DHA or corn oil) Comparison: EPA + DHA vs SFA/MUFA Intervention: 4g/d capsules containing 1.86g/d EPA & 1.5g/d DHA (total n3 PUFA 3.36g/d) manufactured as Lovaza by GlaxoSmithKline: EPA+DHA 3.36g/d Control: 4g/day capsules containing corn oil, manufactured by GlaxoSmithKline. Identical in appearance to intervention. Compliance: capsule count Duration of intervention: 6 months
Outcomes	Main study outcome: AF/atrial flutter – instance of recurrence Dropouts: 8 int., 9 control Available outcomes: inflammatory markers: IL-6, IL-8, IL-10, TNF-alpha, MCP-1; cardiac disease biomarkers: VEGF, NTpBNP; markers of oxidative stress: urinary F_2-IsoPs, urinary F_3-IsoPs
Notes	Study funding: Capsules provided free by GSK, cardiac monitoring devices provided free by eCardio. Authors state no conflicts of interest, no involvement of these companies in data analysis/interpretation of findings/publication.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"computer generated permuted block scheme"
Allocation concealment (selection bias)	Unclear risk	Unclear, no details provided.
Blinding of participants and personnel (performance bias)	Unclear risk	"placebo identical in appearance to placebo." However no information provided on capsules taste or smell. Measures to mask taste not mentioned
Blinding of outcome assessment (detection bias)	Low risk	"ECGs coded, de-identified and evaluated blindly by 2 cardiac electrophysiologists"
Incomplete outcome data (attrition bias)	Low risk	"we used intention to treat as primary analysis." Findings reported for full sample
Selective reporting (reporting bias)	Low risk	Primary outcome reported matches trials register. NCT00552084, First registered: October 31, 2007. Patients recruited between November 2007-April 2014
Attention	Low risk	Participants in both arms appear to have identical follow-up
Compliance	Unclear risk	Measured by capsule count but result not reported; no fatty acid status data provided
Other bias	Low risk	None noted.

DART fat 1989 [74-83]

Methods	Diet And Reinfarction Trial (DART) RCT, 2 x 2 x 2 factorial (n6 LA vs mixed fats), also increased fish and increased fibre arms, 2 years Summary risk of bias: moderate to high
Participants	Men recovering from an MI CVD risk: high N: intervention: randomised 1018, analysed unclear; control: randomised 1015, analysed unclear Mean years in trial: control 1.9, randomised 1.9 % male: 100% Age: mean control 56.8, intervention 56.4 years Age range: all < 70 years Smokers: control 62.7%, intervention 61.2% Hypertension: intervention 24%, control 23.3%

Medications taken by ≥ 50% of those in the control group: not reported
Medications taken by 20%-49% of those in the control group: beta-blockers, other anti-hypertensives, anti-anginals
Medications taken by some, but < 20% of the control group: anti-coagulant, aspirin, other anti-platelet, digoxin, other cardiac drugs
Location: UK
Ethnicity: not reported

Interventions Type: dietary advice
Comparison: ↑ polyunsaturated oil and margarines (n6) vs usual dietary fats (SFA)
Intervention aims: reduce fat intake to 30% E, increase P/S to 1.0 (using polyunsaturated oils and margarines), weight-reducing advice if BMI > 30 (dietitians provided the participants and their wives with initial individual advice and a diet information sheet, participants were revisited for further advice, recipes, encouragement at 1, 3, 6, 9, 12, 15, 18 and 21 months)
Control aims: no dietary advice on fat, weight-reducing advice if BMI > 30 (dietitians provided 'sensible eating' advice without specific information on fats)
Dose aim: unclear
Baseline n-6: unclear, but control PUFA intake 6.8% E
Compliance by biomarkers: good, serum TC significantly reduced in intervention compared to control (-0.26 mmol/L, 95% CI -0.37 to -0.15)
Compliance by dietary intake: assessed using a 7-day weighted food diary, of a 25% random subsample

- Energy intake, MJ/d: intervention 7.3 (SD 1.8), control 7.7 (SD 1.9)
- Total fat intake, % E: intervention 31 (SD 7), control 35 (SD 6)
- SFA intake: intervention 11% E (SD 3), control 15% E (SD 3), dose -4% E
- PUFA intake: intervention 9.4% E, control 6.6% E, dose +2.8% E (most of which omega-6)
- PUFA n-3 intake: not reported
- PUFA n-6 intake: not reported, but PUFA/SFA ratio was 0.85 (SD 0.33) in intervention, implying PUFA of 9.4% E. In control ratio was 0.45 (SD 0.24), implying PUFA of 6.8% E
- Trans fat intake: not reported
- MUFA intake: not reported
- CHO intake: intervention 46% E (SD 7), control 44% E (SD 6)
- Sugars intake: not reported
- Protein intake: % E: intervention 18 (SD 4), control 17 (SD 4)
- Alcohol intake: intervention 5% E (SD 6), control 4% E (SD 6)

Compliance, other measures: no other data
Inclusion basis: intended to increase PUFA/SFA ratio, as well as reduce total fat. TC was lower in intervention than control, and intake data suggest PUFA intake higher by 2.8% E in intervention than control, > 10% greater than baseline of 6.8% E.
PUFA dose: 2.8% E
Duration of intervention: 2 years

Outcomes Main trial outcomes: mortality, reinfarction
Dropouts: all followed for events regardless of compliance (ITT)
Available outcomes: CV events (CV deaths plus non-fatal MI), cancer deaths, total MI, non-fatal MI, TC, HDL cholesterol
Response to contact: yes, Professor Burr provided additional data and information on methodology

Notes Note: this was a 2 x 2 x 2 factorial trial, and so some in each group were randomised to increased fatty fish and/or increased cereal fibre.
Trial funding: Welsh Scheme for Development of Health and Social Research, Welsh Heart Research Foundation, Flora Project (commercial), Health Promotion Research Trust

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised using sealed envelopes
Allocation concealment (selection bias)	Unclear risk	Unclear if envelopes were opaque

Blinding of participants and personnel (performance bias)	High risk	Very difficult to blind trials where participants need to make their own dietary changes
Blinding of outcome assessment (detection bias)	Low risk	Quote: "outcome assessors were not aware of study allocation" (Prof Burr, personal communication). Method of blinding not stated
Incomplete outcome data (attrition bias)	Low risk	GPs contacted for information on mortality and morbidity when participants did not attend, data collected from mortality register
Selective reporting (reporting bias)	Unclear risk	No protocol or trials registry entry located
Attention	High risk	Those given dietary advice almost certainly given more time and attention than those in the control group (with no dietary advice)
Compliance	Low risk	TC significantly reduced in intervention compared to control (-0.26 mmol/L, 95% CI -0.37 to -0.15)
Other bias	Low risk	None found

DART fish 1989 [74-83]

Methods
Diet And Reinfarction Trial (DART) – oily fish advice (or capsule) arm
RCT – parallel, 2 × 2 × 2 factorial (n-3 EPA + DHA vs nil or fat advice vs not, oily fish advice (or capsule) vs not, dietary fibre advice vs not)), 2 years
Summary risk of bias: moderate or high

Participants
Men recovering from myocardial infarction
N: 1015 intervention, 1018
Level of risk for CVD: high (post-MI)
Men: 100%
Mean age, SD: 56.7 intervention, 56.4 control (SDs not stated)
Age range: unclear
Smokers: 61.7% intervention, 62.2% control
Hypertension: 22.7% intervention, 24.6% control
Medications taken by at least 50% of those in the control group: none reported
Medications taken by 20%-49%: beta-blockers, other antihypertensives, antianginals
Medications taken by some, but < 20%: anticoagulant, aspirin/antiplatelet, digoxin/antiarrhythmic
Location: UK
Ethnicity: not stated

Interventions
Type: dietary advice (to eat more oily fish)
Comparison: EPA + DHA vs SFA + MUFA (by dietary achievement below)
Intervention: advised to eat at least 2 weekly portions of 200-400 g fatty fish (mackerel, herring, kipper, pilchard, sardine, salmon, trout). If this was not possible, given MaxEPA capsules, 3/d (0.5 g EPA/d). 191/883 participants were taking MaxEPA at 2 years. Advice was reinforced 3-monthly. Dose: aimed for 0.5 g/d EPA
Control: No such dietary advice or capsules

Compliance: 7 day weighed food diary of a random sub-sample indicated intake of 2.5 g/week EPA intervention, 0.8 g/week EPA control
Dietary achievements
Total fat intake, %E (through study): control 35 (SD 6), intervention 31 (SD 7) (MD −4.00, 95% CI −4.57 to −3.43); significant reduction
Saturated fat intake, %E (through study): control 15 (SD 3), intervention 11 (SD 3), (MD −4.00, 95% CI −4.26 to −3.74); significant reduction
PUFA intake (through study), %E‡: control 7 (SD unclear), intervention 9 (SD unclear), (MD 2.00, 95% CI 1.57 to 2.43 assuming SDs of 5) significant increase
PUFA n-3 intake: EPA, control 0.6 (SD 0.7) g/week, intervention 2.4 (SD 1.4) g/week
PUFA n-6 intake: not reported
MUFA intake (through study), %E‡: control 13 (SD unclear), intervention 11 (SD unclear) (MD −2.00, 95% CI −2.43 to −1.57 assuming SDs of 5); significant reduction
CHO intake (through study), %E: control 44 (SD 6),intervention 46 (SD 7) (MD 2.00, 95% CI 1.43 to 2.57); significant increase
Protein intake (through study), %E: control 17(SD 4), intervention 18 (SD 4) (MD 1.00, 95% CI 0.65 to 1.35); significant increase
Trans fat intake: not reported
Length of intervention: 24 months

Outcomes Main study outcome: total mortality, reinfarction, CHD death
Dropouts: none for mortality
Available outcomes: total and CV deaths, MI, CHD events, lipids, blood pressure, cancer deaths
Response to contact: yes (data provided)

Notes Some of each group were also advised on low fat and high PUFA and/or high fibre diets, all participants who smoked were advised to stop and all with a BMI > 30 kg/m^2 were given weight reduction advice, regardless of randomisation arm. The low fat high PUFA comparison was included in the omega-6 review.
Study funding: by the Welsh Scheme for the Development of Health and Social Research, the Welsh Heart Foundation and the Health Promotion, Research Trust. Seven Seas Health Care and Duncan Flockhart provided MaxEPA capsules

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "randomised" confirmed by author
Allocation concealment (selection bias)	Unclear risk	Pre-prepared sequentially numbered enveloped opened by dietitian (unclear if envelopes were opaque)
Blinding of participants and personnel (performance bias)	High risk	Blinding of dietary advice (or lack of it) is not possible
Blinding of outcome assessment (detection bias)	Low risk	Outcome assessors were not aware of study allocation (Prof Burr stated he did not know assignments)
Incomplete outcome data (attrition bias)	Low risk	Hospital notes and death registers were flagged to catch all outcome data
Selective reporting (reporting bias)	Unclear risk	No study protocol or trials register entry was found
Attention	High risk	More attention was paid to those given dietary advice
Compliance	Unclear risk	7 day weighed food diary of a random sub-sample indicated intake of 2.5 g/week EPA intervention, 0.8 g/week EPA control
Other bias	Low risk	None noted

DART2 2003 [84-88]

Methods Diet and Angina Randomised Trial (DART2)

RCT, 2 × 2, (oily fish or capsulesn-3 EPA + DHA vs nil, also no specific advice, also fruit, vegetables and oats vs no specific advice), 3-9 years
Summary risk of bias: moderate or high

Participants

Men treated for angina
N: 1571 intervention, 1543 control (all analysed for events)
Control level of risk for CVD: high
Men: 100%
Mean age in years (SD): 61.1 (NR) intervention, 61.1 (NR) control
Age range: unclear
Smokers: 25% intervention, 23% control
Hypertension: 49% intervention, 47% control
Medications taken by at least 50% of those in the control group: not reported
Medications taken by 20%-49%: lipid lowering, beta-blockers
Medications taken by some, but less than 20% of the control group: not reported
Location: UK
Ethnicity: not reported

Interventions

Type: dietary advice (to eat more oily fish or take fish oil capsules)
Comparison: EPA + DHA vs unclear (not total fat, SFA or alcohol, presumably CHO and/or protein but not clear)
Intervention: most (1109) advised to eat at least 2 weekly portions of fatty fish OR take MaxEPA capsules, 3/d (0.5 g EPA/d). But 462 participants were sub-randomised to receive only fish oil capsules, not dietary fish advice. Dose: aimed for 0.5 g/d EPA.
Control: none specific sensible eating advice that did not include either of the interventions.
Compliance: postal dietary questionnaire suggested dietary EPA intake increased by 2.4 g /week intervention, 0.2 g /week control
Dietary achievements
Total fat intake, (change from baseline to 6 months): control −8.6 g/d (SD 20.9), intervention −5.2 (g/d SD 21.4) (MD 3.4 g/d)
Saturated fat intake, (change from baseline to 6 months): control −3.5 g/d (SD 9.3), intervention −2.8 g/d (SD 9.4), (MD 0.7 g/d)
PUFA intake (change from baseline to 6 months): control −1.6 g/d (SD 5.4), intervention −0.1 g/d (SD 5.8) (MD 1.5 g/d)
PUFA n-3 intake (change from baseline to 6 months): EPA, control 0.12 g/week (SD 0.73), intervention 2.65 g/week (SD 1.35) (MD 2.53 g/week)
PUFA n-6 intake: not reported
MUFA intake: not reported
CHO intake: not reported
Protein intake: not reported
Trans fat intake: not reported
Duration of intervention: 36 to 108 months

Outcomes

Main study outcome: total mortality
Dropouts: none for mortality
Available outcomes: total and CV deaths, sudden death, stroke, heart failure, cancer deaths
Response to contact: yes (data provided)

Notes

Some of each group were also advised on high fruit, vegetables and oat diets, and those who received neither fish nor fruit advice received 'non-specific' dietary advice. All those whose BMI > 30 kg/m^2 in both groups received weight reduction advice.
Study funding: probably British Heart Foundation, Seven Seas Ltd, Novex Pharma Ltd and the Fish Foundation (these were acknowledged)

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomly allocated"
Allocation concealment (selection bias)	Unclear risk	Pre-prepared sequentially numbered enveloped opened by dietitian (unclear if envelopes were opaque)
Blinding of participants and personnel (performance bias)	High risk	Dietary advice, so not possible for participants to be blinded to intervention

Blinding of outcome assessment (detection bias)	Low risk	Outcome assessors were not aware of study allocation (Prof Burr stated he did not know assignments)
Incomplete outcome data (attrition bias)	Low risk	Hospital notes and death registers were flagged to catch all outcome data
Selective reporting (reporting bias)	Unclear risk	No study protocol was found, or trials registry entry
Attention	High risk	More attention was paid to those given dietary advice
Compliance	Unclear risk	Postal dietary questionnaire suggested dietary EPA intake increased by 2.4 g/week intervention, 0.2 g/week control
Other bias	Low risk	None noted

Dasarathy 2015 – NCT00323414 [89 90]

Methods	RCT, parallel, (n3 EPA & DHA vs n6 LA), 11 months Summary risk of bias: Moderate or high
Participants	NASH patients with type 2 diabetes N: 18 int., 19 control. (analysed, int: 18 cont: 19) Level of risk for CVD: Moderate Male: 33.3% int., 10.5% control Mean age (sd): 51.5 (6.9) int., 49.8 (12.1) control Age range: NR Smokers: NR Hypertension: 94.4% int., 68.4% control Medications taken by at least 50% of those in the control group: inclusion criteria required stable regiment of anti-diabetic agents. Medications taken by 20-49% of those in the control group: NR Medications taken by some, but less than 20% of the control group: NR Location: USA Ethnicity: 94.4% Caucasian & 5.6% Black int., 89.5% Caucasian & 10.5% Hispanic in control
Interventions	Type: supplement (capsules with EPA+DHA or corn oil) Comparison: EPA & DHA vs n6 LA Intervention: 6 capsules/d “Opti-EPA” fish oil concentrate (including 2.16g/d EPA + 3.6g/d DHA, Douglas Laboratories): EPA+DHA 5.76g/d Control: 6 capsules/d corn oil Compliance: Pill counts and patient self-report Duration of intervention: 48 weeks
Outcomes	Main study outcome: Histology and liver function Dropouts: 0 int., 0 control Available outcomes: Adiposity, lipids, glucose, HOMA, HbA1c, insulin (BMI, total cholesterol, triglycerides and insulin not used due to baseline differences)
Notes	Study funding: National Institutes of Health

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	“using a random numbers table”
Allocation concealment (selection bias)	Unclear risk	No methodology supplied
Blinding of participants and personnel (performance bias)	Low risk	Capsules had no visual/odour/taste differences
Blinding of outcome assessment (detection bias)	Low risk	“codes were broken only after primary analysis was completed”
Incomplete outcome data (attrition bias)	Low risk	All included in analysis

Selective reporting (reporting bias)	Unclear risk	Not all registry outcomes clearly reported
Attention	Low risk	No suggestion of this
Compliance	Unclear risk	Pill count or intake data not reported in percentage terms or equivalent
Other bias	Low risk	None noted

de Luis 2016 – NCT01865448 [91]

Methods RCT, single blind, placebo-controlled (n3 DHA vs MUFA), 6 months
Summary risk of bias: Moderate or high

Participants Generally healthy individuals with obesity (BMI 30-35)
N: 17 int., 17 control. (analysed, int: 14 cont: 15)
Level of risk for CVD: low
Male: 35.7% int., 46.7% control.
Mean age (sd): 47.4(9.1) int., 44.3(11.7) control
Age range: 18-65 (inclusion)
Smokers: NR
Hypertension: NR
Medications taken by at least 50% of those in the control group: NR
Medications taken by 20-49% of those in the control group: NR
Medications taken by some, but less than 20% of the control group: NR
Location: Spain
Ethnicity: NR

Interventions Type: supplement (capsules/pills containing DHA or olive oil
Comparison: Higher DHA vs MUFA
Intervention: 500mg/d DHA for first 60 days followed by 250mg/d until 180 days manufactured by Polaris, Pleuven, France
Control: placebo pill containing 5 ml olive oil
PUFA Dose: (intended) increase average 0.33g/d EPA+DHA, **0.2%E n-3, 0.2%E PUFA**
Compliance: Erythrocyte fatty acid status
Duration of intervention: 6 months

Outcomes Main study outcome: modification in inflammation-resolving eicosanoid levels
Dropouts: 3 int., 2 control
Available outcomes: body weight; waist circumference; BMI; fat mass; HOMA-IR; plasma glucose levels; insulin levels; serum total cholesterol, triglyceride, HDL & LDL concentrations; resistin, leptin, adiponectin levels; inflammatory markers: CRP, IL-6, TNF-alpha; red cell membrane fatty acid status (LDL not used due to baseline differences)
Response to contact: Yes (details provided)

Notes No conflicts of interest declared; PNKDIET, SLU, Spain provided free of charge the diet of the ketogenic phases in both groups & oral supplementation of DHA/placebo

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	randomised using table of numbers
Allocation concealment (selection bias)	Unclear risk	Unclear, no details provided.
Blinding of participants and personnel (performance bias)	High risk	Single blinded, only participants blinded. Insufficient detail regarding appearance, smell or taste of intervention or placebo to assess blinding performance
Blinding of outcome assessment (detection bias)	Unclear risk	Insufficient information provided
Incomplete outcome data (attrition bias)	High risk	Outcome data reported for 85.3% of randomised participants

Selective reporting (reporting bias)	Low risk	Primary outcome reported matches trials register
Attention	Low risk	Participants in both arms appear to have identical follow-up
Compliance	Low risk	Measured by fatty acid status data. C-RoB low as p<0.05 in FA DHA levels between arms at 6m
Other bias	Low risk	None noted

DeFina 2010 [92]

Methods RCT, parallel, (n3 EPA+DHA vs n6 LA), 6 months
Summary risk of bias: Moderate or high

Participants Sedentary men and women with a BMI between 26 and 40
N: 64 int., 64 control. (analysed, int: 64 cont: 64)
Level of risk for CVD: Low
Male: 31.3% int., 31.3% control.
Mean age (sd): 45.6 (8.3) int., 47.0 (7.8) control
Age range: 30-60 years
Smokers: NR
Hypertension: 17.2% int., 18.8% control
Medications taken by at least 50% of those in the control group: NR
Medications taken by 20-49% of those in the control group: NR
Medications taken by some, but less than 20% of the control group: NR
Location: USA
Ethnicity: NR

Interventions Type: supplement (capsules with n3 EPA+DHA; or soybean+corn oil)
Comparison: n3 EPA+DHA vs n6 LA
Intervention: 5 capsules/d (including 3.0g EPA+DHA in ratio 5:1, Cooper Advanced Omega-3): EPA+DHA 3.0g/d
Control: 5 capsules/d (soybean and corn oil in ratio 1:1)
Compliance: Plasma fatty acids, pill counts, 3-d dietary records
Duration of intervention: 6 months

Outcomes Main study outcome: Weight loss and body composition
Dropouts: 23 int., 22 control
Available outcomes: Anthropometrics, lipids, glucose, insulin, fatty acids. Profile of mood states (POMS). CRP measured, not reported (bp 6 months not used; insulin and HDL cholesterol not used, baseline differences)
Response to contact: Yes, methodological details provided

Notes Study funding: Cooper Concepts Inc.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	author confirmed: *Participants were randomized to intervention and control arms using a sex and 2-level BMI stratified random block method. The clinical observers were blinded to the randomization process.*
Allocation concealment (selection bias)	Low risk	As above
Blinding of participants and personnel (performance bias)	Unclear risk	States capsules were identical in colour, shape, and flavour; but smell not reported
Blinding of outcome assessment (detection bias)	Unclear risk	NR
Incomplete outcome data (attrition bias)	Low risk	Attrition >20%, however balanced by arm, reasons given and intention-to-treat analysis
Selective reporting (reporting bias)	Unclear risk	No registry or protocol identified
Attention	Low risk	Schedule appears comparable and differs only by capsule

Compliance	Low risk	Significant increase in plasma EPA and DHA in intervention group
Other bias	Low risk	None noted

Delamaire 1991 [93]

Methods	RCT, parallel, (n3 EPA & DHA vs n6 LA), 6 months Summary risk of bias: Moderate or high
Participants	People with well-controlled insulin-dependent diabetes mellitus (DM) N: 11 int., 17 control. (analysed, int: NR cont: NR) Level of risk for CVD: Moderate Male: NR Mean age (sd): NR Age range: NR Smokers: NR Hypertension: NR Medications taken by at least 50% of those in the control group: NR Medications taken by 20-49% of those in the control group: NR Medications taken by some, but less than 20% of the control group: NR Location: France Ethnicity: NR
Interventions	Type: supplement Comparison: MaxEPA vs peanut oil Intervention: 4 capsules/d of MaxEPA (0.7g/d EPA + 0.5g/d DHA): EPA+DHA 1.2g/d Control: 4 capsules/d peanut oil Compliance: NR Duration of intervention: 6 months
Outcomes	Main study outcome: haemorheological parameters Dropouts: NR Available outcomes: (sheer rate viscosity, erythrocyte aggregation, fibrinogen - not used) No usable outcomes were reported, but blood sugar parameters were clearly collected as the abstract states "glycaemic balance was unchanged in either group".
Notes	Study funding: NR Only abstract found. No replies despite several attempts to contact the author.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias)	Unclear risk	Not reported
Blinding of outcome assessment (detection bias)	Unclear risk	Not reported, but biochemistry type outcomes so likely low risk
Incomplete outcome data (attrition bias)	Unclear risk	Not reported
Selective reporting (reporting bias)	Unclear risk	No protocol or trials registry entry found
Attention	Unclear risk	Not reported
Compliance	Unclear risk	Not reported
Other bias	Low risk	None noted

Derosa 2009 [94]

Methods	RCT, parallel, (n3 EPA+DHA vs non-fat placebo), 6 months Summary risk of bias: Moderate or high
Participants	Italian Caucasian adults with combined dyslipidaemia N: 168 int., 164 control. (analysed, int: 165 cont: 162) Level of risk for CVD: moderate Male: 49% int., 50% control Mean age (sd): 51.3 (7.2) int., 50.7 (6.8) control Age range: unclear, but inclusion criteria were aged ≥18 years Smokers: 22% int, 25% cont Hypertension: NR Medications taken by at least 50% of those in the control group: NR Medications taken by 20-49% of those in the control group: NR Medications taken by some, but less than 20% of the control group: NR (no participants were allowed to have taken or be taking medication that would influence lipid metabolism) Location: Pravia & Bologna areas of Italy Ethnicity: Caucasian
Interventions	Type: supplement Comparison: omega 3 capsules vs sugar pills Intervention: 1.125g/d EPA plus 1.875g/d DHA as ethylic esters, split over 3 meals (SPA Societa Produtti Antibiotici): EPA+DHA 3.0g/d Control: pills of sucrose, mannitol and mineral salts, 3g/d split over 3 meals **PUFA Dose**: (intended) increase 3.0g/d EPA+DHA, **1.4%E n-3, 1.4%E PUFA** Compliance: assessed by pill count returned at clinic visits, but compliance data not reported Duration of intervention: 6 months
Outcomes	Main study outcome: lipid profile, coagulation, inflammatory and fibrinolytic parameters Dropouts: 4 of 168 int., 3 of 165 control Available outcomes: lipids, glucose, insulin, HOMA, hsCRP (no deaths or MI occurred, 1 cancer diagnosed in each arm but 6 month data), PAI1, homocysteine and several inflammatory markers reported but not used, BMI provided but too different at baseline to use
Notes	Study funding: SPA (Societa Produtti Antibiotici) provided medication and paid for publication charges, no other funding reported

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomization was done using a drawing of envelopes containing randomization codes prepared by a statistician. A copy of the code was provided only to the responsible person performing the statistical analysis. The code was only broken after a database lock, but could have been broken for individual subjects in case of an emergency."
Allocation concealment (selection bias)	Unclear risk	As above- no information provided on opacity of envelopes.
Blinding of participants and personnel (performance bias)	High risk	No suggestion that pills were similar, and given different compositions there were unlikely to be
Blinding of outcome assessment (detection bias)	Unclear risk	Unclear, code was masked, but participants were likely to have known their allocation
Incomplete outcome data (attrition bias)	Unclear risk	Low dropout level, though no explanations of attrition provided
Selective reporting (reporting bias)	Unclear risk	No trials registry entry or protocol found
Attention	Low risk	Appointments appeared similar in schedule and duration between arms
Compliance	Unclear risk	No body tissue levels or pill count data provided
Other bias	Low risk	None noted

Derosa 2011 [95 96]

Methods RCT, parallel, (EPA+DHA vs non-fat placebo), 6 months
Summary risk of bias: Moderate or high

Participants White adults with combined lipidaemia (raised total cholesterol and TG)
N: 84 int., 83 control (analysed 78 int., 79 control).
Level of risk for CVD: Moderate
Male: 49% int., 49% control.
Mean age (sd): 54.5 (7.0) overall, not given by arm
Age range: NR but inclusion criteria were 18-75 years
Smokers: 27% int., 31% control
Hypertension: 51.5% with history of hypertension (not given by arm)
Medications taken by at least 50% of those in the control group: NR
Medications taken by 20-49% of those in the control group: NR
Medications taken by some, but less than 20% of the control group: ACE inhibitors, ARBs, calcium antagonists, beta-blockers, diuretics, alpha-blockers
Location: Italy
Ethnicity: White

Interventions Type: Capsule (n-3 PUFA)
Comparison: EPA & DHA vs filler (non-fat)
Intervention: 3x1g capsule/ day n-3 PUFAs (ethyl esters, each 1-g capsule of n-3 PUFAs contains 85% n3 ethyl esters), total 1.2g/d EPA + 1.35g/d DHA plus controlled diet with 600kcal deficit, 50% CHO, 30% fat, 6% SFA, 20% protein, increased physical activity: EPA+DHA 2.55g/d
Control: placebo (capsule containing sucrose, mannitol and mineral salts magnesium stearate and silicon dioxide, used as anti-caking agents) plus controlled diet with 600kcal deficit, 50% CHO, 30% fat, 6% SFA, 20% protein, increased physical activity
PUFA Dose: (intended) increase 2.55g/d EPA+DHA, **1.2%E n-3, 1.2%E PUFA**
Compliance: measured by counting the number of pills returned at the time of specified clinic visits, no data found
Length of intervention: 6 months

Outcomes Main study outcome: insulin-resistance
Dropouts: 6 int, 4 control
Available outcomes: weight, lipids, fasting glucose, HOMA-IR, other markers of insulin sensitivity, hsCRP, s-ICAM, s-VCAM, TNF alpha, E-selectin, IL-6 (BP reported but not used as 6 month data, metalloproteinases reported, fasting insulin, HOMA, BMI reported but not used as too unbalanced at baseline)
Response to contact: Not yet attempted

Notes Study funding: NR, "The authors certify that they have no affiliation with, or financial involvement in, any organization or entity with a direct financial interest in the subject matter or materials discussed in the manuscript"

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"randomisation was done using a drawing of envelopes containing randomisation codes prepared by a statistician"
Allocation concealment (selection bias)	Unclear risk	Unclear whether envelopes were thick enough to be opaque
Blinding of participants and personnel (performance bias)	Unclear risk	n-3 and placebo supplied as identical, opaque, white capsules in coded bottles to ensure the blind status of the study - However no information provided on capsules taste or smell
Blinding of outcome assessment (detection bias)	Low risk	States "double blind", and code only broken after database lock
Incomplete outcome data (attrition bias)	Unclear risk	Numbers shown at baseline don't add up to the total number randomised, but ITT analysis for those receiving at least one dose of the capsules
Selective reporting (reporting bias)	Unclear risk	No registry entry or protocol found

Attention	Unclear risk	Frequency of contact appears similar for both groups, and blinded
Compliance	Unclear risk	Unclear as data not provided on compliance
Other bias	Low risk	None noted

Derosa 2016 [97]

Methods RCT, parallel, (n-3 PUFA capsules vs placebo), 18 months
Summary risk of bias: low

Participants White overweight/obese patients with impaired fasting glucose (IFG) or impaired glucose tolerance (IGT)
N: 138 intervention, 143 control (analysed 128 intervention, 130 control)
Level of risk for CVD: low
Men: 50.72% intervention, 48.95% control
Mean age in years (SD): 53.4 (11.2) intervention, 54.8 (12.1) control
Age range: unclear
Smokers: not reported
Hypertension: not reported
Medications taken by at least 50% of those in the control group: not reported
Medications taken by 20%-49% of those in the control group: not reported
Medications taken by some, but less than 20% of the control group: not reported
Location: Italy
Ethnicity: white

Interventions Type: capsule (n-3 PUFA)
Comparison: EPA + DHA vs CHO + SFA
Intervention: 3 ×1 g capsule/ day n-3 PUFAs (ethylic esters, each 1-g capsule of n-3 PUFAs contains highly concentrated ethyl esters of omega-3 fatty acids, primarily EPA, and DHA in the proportion of 0.9–1.5). Dose: unclear (approx. 2-3 g/d)
Control: placebo (a capsule containing sucrose, mannitol and mineral salts, magnesium stearate (a saturated fat) and silicon dioxide, used as anti-caking agents)
Both groups were given diet advice to follow a controlled-energy diet based on AHA recommendations (50% of calories from carbohydrates, 30% from fat (6% saturated), and 20% from proteins, with a maximum cholesterol content of 300 mg/day and 35 g/day of fibre). Individuals were also encouraged to increase their physical activity by walking briskly for 20 to 30 min, 3 to 5 times per week, or by cycling
Compliance: measured by counting the number of pills returned at the time of specified clinic visits
Length of intervention: 18 months

Outcomes Main study outcome: insulin resistance
Dropouts: 23 across arms (no details on groups but stated that there were no difference between groups)
Available outcomes: mortality, CV mortality, CHD event, stroke, combined CVD events, MI, AF, weight, BMI, lipids, diabetes mellitus
Response to contact: yes (data provided)

Notes Study funding: "The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties"

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was done using a drawing of envelopes containing randomisation codes prepared by a statistician.
Allocation concealment (selection bias)	Low risk	Author stated that allocation was concealed from clinicians and researchers, but no methodology provided

Blinding of participants and personnel (performance bias)	Low risk	Both n-3 PUFAs and placebo were supplied as identical, opaque, white capsules in coded bottles to ensure the blind status of the study. However no information provided on capsules taste or smell
Blinding of outcome assessment (detection bias)	Low risk	A copy of the code was provided only to the person performing the statistical analysis
Incomplete outcome data (attrition bias)	Low risk	An intention-to-treat analysis was conducted for patients who received 1 dose of study medication
Selective reporting (reporting bias)	Unclear risk	No trial registry or protocol found
Attention	Low risk	No difference reported
Compliance	Unclear risk	Measured by counting the number of pills returned at the time of specified clinic visits
Other bias	Low risk	None noted

Deslypere 1992 [98-100]

Methods RCT 4 arms, (n-3 EPA + DHA (3 different doses) vs MUFA), 12 months
Summary risk of bias: moderate or high

Participants Healthy monks
N: 14 high, 15 medium, 15 low dose intervention, 14 control
Level of risk for CVD: low
Men: 100%
Mean age in years (SD): 56.2 (16.5) (not reported by arm)
Age range: 21-87
Smokers: none
Hypertension: not reported
Medications taken by at least 50% of those in the control group: not reported
Medications taken by 20%-49% of those in the control group: not reported
Medications taken by some, but less than 20% of the control group: not reported (no medications influencing lipid metabolism or non-steroidal anti-inflammatory drugs were allowed)
Location: the Netherlands
Ethnicity: not reported

Interventions Type: capsules
Comparison: LCn3 vs MUFA
Intervention 9 capsules (9 g vol.) per day, of which 3, 6 or 9 were fish oil (Labaz, Brussels, Belgium) and any remainder were placebo (providing respectively 1.12; 2.24 or 3.37 g n-3 FA/day). Dose: 1.12 g/d; 2.24 g/d or 3.37 g/d EPA + DHA)
Control: 9 placebo capsules made up of olive oil (Puget Marseille, France) and Palmoil (Loders-Kroklaan Wormerveen, the Netherlands) with the same SFA, cholesterol and vitamin E as the fish oil capsules.
Compliance: assessed by counting remaining capsules every 2 months and by measuring EPA concentration. Excellent compliance reported and shown by the EPA concentration results
Length of intervention: 12 months

Outcomes Main study outcome: effect on coronary risk factors
Dropouts: none
Available outcomes: deaths (nil), CVD events (nil), lipids, BP, HbA1c, weight (measured but only text suggests "no significant changes in the anthropometric parameters (weight, length, waist, hip and thigh circumferences) during the study"), IL-6, TNF-alpha and several IL-1s (IL-6 reported as below detection range, for the others there was "no significant difference between the two treatment groups at any point in time")
Response to contact: yes

Notes Study funding: capsules supplied by Labaz (Brussels Belgium). The placebo capsules contained olive oil (Puget) and palm oil (Loders-Kroklaan, Wormerveer). Financial support by Sanofi-Labaz.
Data entered for high fish oil versus placebo groups

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (author correspondence): "The manufacturer provided envelopes containing numbers corresponding with boxes of capsules. For each enrolled subject, random envelope was opened."
Allocation concealment (selection bias)	Low risk	Allocation concealed from all this way
Blinding of participants and personnel (performance bias)	High risk	Although double blind, the fishy taste of the active treatment was not matched (author states that the fishy taste was clear in the intervention capsules)
Blinding of outcome assessment (detection bias)	Low risk	Authors confirmed outcome assessors were unaware until afterwards.
Incomplete outcome data (attrition bias)	Low risk	No dropouts
Selective reporting (reporting bias)	Unclear risk	No protocol or trial registry record
Attention	Low risk	No difference between groups
Compliance	Low risk	Significant difference in EPA concentration
Other bias	Low risk	None noted

DIPP 2015 – UMIN000000461 [101 102]

Methods Dietary Intervention for Patients Polypectomized for tumours of the colorectum (DIPP)
RCT, parallel, 2 arms (n-3 EPA + DHA + n-3 ALA vs nil), 24 months
Summary risk of bias: moderate or high

Participants Patients previously polypectomised for colorectal tumours
N: 104 intervention, 101 control
Level of risk for CVD: low
Men: 73.1% intervention, 74.3% control
Mean age in years (SD): 58.3 (9.5) intervention, 59.7 (8.9) control
Age range: 35-75
Smokers: 65.4% intervention, 61.4% control
Hypertension: not reported
Medications taken by at least 50% of those in the control group: supplements
Medications taken by 20%-49% of those in the control group: none
Medications taken by some, but less than 20% of the control group: oral contraceptive pills
Location: Japan
Ethnicity: not reported

Interventions Type: advice + supplement (fish oil capsules)
Comparison: EPA + DHA + ALA vs omega-6
Intervention: advice to reduce total fat intake, decrease consumption of n-6 PUFAs, increase intake of n-3 PUFAs from fish/marine foods, increase intake of n-3 PUFAs from perilla oil rich in ALA, take 8 capsules of fish oil/day (equivalent to 96 mg/day of EPA and 360 mg/day of DHA). Dose: 456mg/d EPA + DHA and unknown dose of ALA
Control: advice to decrease intake of fats/oils as a whole
Compliance: measured via semi-quantitative food frequency questionnaire, plasma fatty acid concentrations, fatty acid compositions in the membranes of red blood cells and the sigmoid colon. Reported satisfactorily high compliance with protocol in both groups but no figures provided.
Length of intervention: 24 months

Outcomes Main study outcome: number and size of colorectal tumours
Dropouts: 3 intervention, 5 control
Available outcomes: all-cause mortality, dietary intake, plasma fatty acids, lipids, side effects, glucose
Response to contact: yes (methodological details provided)

Notes Study funding: all were either government or charity grants

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomly allocated using random digit number for allocation of participants
Allocation concealment (selection bias)	Low risk	Author confirmed "Allocation information was blinded to clinicians and researchers"
Blinding of participants and personnel (performance bias)	Unclear risk	From the 2015 paper, "The attending physicians as well as the participants were blinded to the assignment information". However in the discussion section they say "complete participant blinding could not have been achieved because free living participants might have exchanged information on their dietary intervention, say in the hospital waiting room". Author confirmed blinding
Blinding of outcome assessment (detection bias)	Low risk	Quote: "physicians, including colonoscopists, a scientist who conducted blood and specimen analyses, and pathologists were blinded"
Incomplete outcome data (attrition bias)	Low risk	All those randomised were accounted for
Selective reporting (reporting bias)	High risk	The researchers chose not to report data on the number, size and pathological type of the colorectal tumours as they said they would in the trials register. They reported more outcomes in the paper than initially stated. UMIN000000461 Registered 3 August 2006, recruitment completed 1 March 2007
Attention	Low risk	Participants were given equal follow-up
Compliance	Unclear risk	Reported satisfactorily high compliance with protocol was noted in both groups but no figures
Other bias	Low risk	None noted

DISAF 2003 – ISRCTN16448451 [103-108]

Methods
Dietary Intervention Study for AF (DISAF)
RCT, parallel, 2 arms (n-3 EPA + DHA vs nil), 12 months
Summary risk of bias: moderate or high

Participants
People presenting for first treatment of acute/persistent atrial fibrillation or flutter, confirmed by ECG
N: intervention 201, control 206
Level of risk for CVD: high (patients with atrial fibrillation)
Men: intervention 64.7%, control 63.6%
Mean age in years (SD): intervention 67.7 (9.4), control 68.7 (9.5)
Age range: unclear
Smokers: intervention 10.9%, control 12.1%
Hypertension: intervention 48.2%, control 40.8%
Medications taken by at least 50% of those in the control group: not reported
Medications taken by 20%-49% of those in the control group: antiarrhythmics, antithrombotics
Medications taken by some, but less than 20% of the control group: not reported
Location: UK
Ethnicity: white British

Interventions
Type: dietary advice
Comparison: EPA + DHA vs unclear
Intervention: dietary assistants gave advice and support to eat 2 to 3 portions of oily fish per week (providing up to 10 g LCn3/ week), plus 2 to 3 portions of fruit and vegetables per day. Dose: 1.4 g/d EPA + DHA.
Control: dietary assistants gave advice and support to eat 2 to 3 portions of fruit and vegetables per day. No other health/lifestyle given as part of the trial
Compliance: assessed red blood cell fatty acids and found some increases in EPA and DHA in intervention compared to control (no further intake data)

Length of intervention: 12 months

Outcomes Main study outcome: sinus rhythm after 12 months
Dropouts: unclear
Available outcomes: deaths, AF recurrence
Response to contact: yes (data provided)

Notes Study funding: not reported

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was by phone to an independent randomisation office, which used pre-printed random number tables
Allocation concealment (selection bias)	Low risk	Randomisation was by phone to an independent randomisation office, which used pre-printed random number tables
Blinding of participants and personnel (performance bias)	High risk	Dietary advice was clear, so allocation known by participants
Blinding of outcome assessment (detection bias)	Unclear risk	Unclear
Incomplete outcome data (attrition bias)	High risk	Some discrepancies between papers, reasons unclear
Selective reporting (reporting bias)	High risk	ISRCTN16448451 registered 23 January 2004, recruitment from 1 July 1998 to 1 July 2002; some secondary outcomes were not reported
Attention	Low risk	Intervention (advice to eat more oil-rich fish, fruit and vegetables) and control (advice to eat more fruit and vegetables) groups appeared to be given equivalent time and attention.
Compliance	Low risk	Assessed red blood cell fatty acids and found some increases in EPA and DHA in intervention compared to control
Other bias	High risk	The trial was stopped early

DO IT 2010 – NCT00764010 [109-126]

Methods Diet and Omega 3 Intervention Trial on Atherosclerosis (DO IT)
Randomisation: RCT, parallel, 2 × 2 factorial, (n-3 DHA + EPA vs n-6 LA also dietary advice intervention), 36 months
Summary risk of bias: moderate or high

Participants Elderly men with longstanding dyslipidaemia or hypertension (a subset of Oslo Diet heart study)
N: intervention 282 (140 n-3 capsules + 142 n-3 capsules and dietary advice), control 281 (142 placebo capsules + 139 placebo capsules and dietary advice)
Level of risk for CVD: moderate
Men: intervention 100%, control 100%
Mean age in years (SD): intervention 70.4 (2.9), control 69.7 (3.0) years
Age range: 64-76 years
Smokers: intervention 35%, control 33%
Hypertension: intervention 29%, control 27%
Medications taken by at least 50% of those in the control group: none
Medications taken by 20%-49% of those in the control group: statins and acetylsalicylic acid
Medications taken by some, but less than 20% of the control group: β-blockers, ACE inhibitors and nitrates
Location: Norway
Ethnicity: not reported

Interventions Type: supplement/ capsule (also dietary advice as the factorial intervention)
Comparison: EPA + DHA vs omega-6
Intervention: 2 × 2 capsules/d incl 2.4 g/d of omega-3 PUFA (Pikasol, 0.84 g/d EPA plus 0.48 g/d DHA plus 8.4 mg/d tocopherols). Dose: 1.32 g/d EPA + DHA
Control: 2 × 2 capsules/d inc 4 g/d corn oil (2.24 g/d linoleic, 1.28 g/d oleic acid, 16 mg/d tocopherols)
Compliance: pharmacy records suggested that > 90% of supplements were taken, and plasma EPA and DHA were raised in intervention compared to control participants.
Duration of intervention: 36 months

Outcomes Main study outcome: atherosclerosis progression.
Dropouts: intervention 14 died, 20 others discontinued, control 24 died, 18 others discontinued
Available outcomes: mortality, cardiovascular deaths, CHD events, CV events, MI, stroke, diabetes, glucose, lipids, cancer diagnosis, cancer deaths, sudden death, BMI (waist circumference reported as median, IQR)
Response to contact: yes (data provided)

Notes The other 2 × 2 intervention was dietary counselling to increase both omega-3 and omega-6 fats as well as fruit and vegetables.
Study funding: Norwegian Cardiovascular Council, Norwegian retail company RIMI, vegetable oil and margarine supplied by the Norwegian food company Mills DA and placebo capsules by LUBE

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Permuted block randomisation, no clear mechanism provided
Allocation concealment (selection bias)	Unclear risk	No details provided
Blinding of participants and personnel (performance bias)	Unclear risk	Capsules of fish oil or placebo taken, but unclear whether blinded and if so, how well or successfully
Blinding of outcome assessment (detection bias)	Low risk	"Mortality data were supplied from the Norwegian Cause of Death Registry, and all clinical events were confirmed by hospital records and verified by an independent cardiologist"
Incomplete outcome data (attrition bias)	Low risk	No attrition as deaths and events collected from centralised register
Selective reporting (reporting bias)	Unclear risk	Trials registry entry submitted after the outcomes papers were published.
Attention	Low risk	No suggestion of attention bias between verum and placebo supplement arms
Compliance	Low risk	Pharmacy records suggested that > 90% of supplements were taken, and plasma EPA and DHA were raised in intervention compared to control participants
Other bias	Low risk	None noted

Dodin 2005 [127 128]

Methods RCT, parallel, (n-3 ALA vs n-6 LA), 12 months
Summary risk of bias: moderate or high

Participants Healthy menopausal women
N: 101 intervention, 98 control. (analysed, intervention: 85 control: 94)
Level of risk for CVD: low
Men: 0% intervention, 0% control
Mean age in years (SD): 54.0 (4.0) intervention, 55.4 (4.5) control
Age range: 49-65
Smokers: 8% intervention, 6% control
Hypertension: not reported
Medications taken by at least 50% of those in the control group: not reported

Medications taken by 20%-49% of those in the control group: not reported
Medications taken by some, but less than 20% of the control group: not reported
Location: Canada
Ethnicity: French Canadian

Interventions Type: food supplement (flaxseed)
Comparison: ALA vs unclear (probably includes lipids, CHO and protein, but not clear)
Intervention: 40 g/d flaxseed incorporated into diets (providing 21,071 g total lignans, 180 calories, 16 g lipids (57% ALA), and 11 g total dietary fibre). Dose: 9.1 g/d ALA
Control: 40 g/d wheat germ incorporated into diets (providing 196 g total lignans, 144 calories, 4 g lipids (6.9% ALA), and 6 g total dietary fibre
Compliance: first morning urine collection was performed at randomisation and at month 12 to measure urinary lignin levels. In addition, study participants recorded their daily intake of seeds on diary cards and were asked to return unused bread and packages of seeds at each visit. Good compliance reported
Duration of intervention: 12 months

Outcomes Main study outcome: bone mineral density
Dropouts: 26 intervention, 17 control (but 13/17 had an endpoint evaluation)
Available outcomes: weight, BMI, QoL, blood pressure, lipids, glucose, adverse events, dietary intake, plasma fatty acids
Response to contact: yes

Notes Authors replied to tell us that there were no deaths or CV events during the study
Study funding: not reported

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The randomisation schedule was prepared by the clinical unit of the research centre using computer generated randomisation in blocks of 4-8
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias)	Low risk	Participants, investigators, staff, and statisticians were blinded to dietary assignments for the duration of the study. Quote: "a local baker prepared loaves of bread. Each week, the loaves of bread were delivered in sealed, opaque unmarked wrappers to the Department of Food and Nutrition Sciences at Laval University. The seeds were ground up and vacuum-packed in the same laboratory. The Department of Food and Nutrition Sciences was responsible for labelling the bags of bread and packages of seeds with the subject's randomization number. Bread and packages of seeds were provided on a 3-month basis. The foods that both groups received was similar in appearance and packaging and was kept frozen until consumption to avoid essential fatty acid
Blinding of outcome assessment (detection bias)	Low risk	Participants, investigators, staff, and statisticians were blinded to dietary assignments for the duration of the study
Incomplete outcome data (attrition bias)	Low risk	Intention-to-treat analysis. Loss to follow-up 10%, reasons given
Selective reporting (reporting bias)	Unclear risk	No protocol or clinical trial registry entry found
Attention	Low risk	All participants had same number of visits
Compliance	Low risk	First morning urine collection was performed at randomisation and at month 12 to measure urinary lignin levels. In addition, study participants recorded their daily intake of seeds on diary cards and were asked to return unused bread and packages of seeds at each visit. Good compliance reported

Other bias	Low risk	None noted

Doi 2014 – UMIN000016723 [129-132]

Methods	RCT, parallel, (n-3 EPA vs nil), 12 months Summary risk of bias: moderate or high
Participants	Patients having PCI after acute MI N: 119 intervention, 119 control analysed Level of risk for CVD: high Men: 77% intervention, 76% control Mean age in years (SD): 70 (11) intervention, 71 (12) control Age range: unclear Smokers: 28% intervention, 32% control Hypertension: 71% intervention, 69% control Medications taken by at least 50% of those in the control group: aspirin, ticlopidine, beta-blockers, statins (as part of treatment) Medications taken by 20%-49% of those in the control group: ARB/ACE inhibitors Medications taken by some, but less than 20% of the control group: none Location: Japan Ethnicity: not reported
Interventions	Type: supplement (EPA) Comparison: EPA vs nil Intervention: purified EPA ethyl esters (> 98%) 1800 mg EPA/day within 24 hours after PCI plus statins. Dose: 1.8 g/d EPA Control: statins with no EPA Compliance: not reported Length of intervention: 12 months
Outcomes	Main study outcome: cardiovascular events Dropouts: 1 intervention, 2 control Available outcomes: mortality, stroke, MI, sudden death, CV death, revascularisation Response to contact: no
Notes	Study funding: trial registry state "self-funded". The authors received honoraria from Mochida Pharmaceutical Co.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A computer-generated, randomisation plan, which included stratification by age and sex
Allocation concealment (selection bias)	Unclear risk	Carried out by research technician but unclear
Blinding of participants and personnel (performance bias)	High risk	Open label but blind endpoint
Blinding of outcome assessment (detection bias)	Unclear risk	Data on outcomes were collected from clinical charts. Unclear if blinded. Diagnoses were confirmed by investigator blind to treatment allocation
Incomplete outcome data (attrition bias)	Low risk	Only 3 dropouts, similar rates between the groups and reasons given
Selective reporting (reporting bias)	High risk	Data collection completed before trial registry entry. Only 1% dropouts
Attention	Low risk	Timing of follow-up similar
Compliance	Unclear risk	Not reported
Other bias	Low risk	None observed

Dullaart 1992 [133]

Methods RCT, parallel, 2 arms (n6 LA vs mixed fats), 2 years
Summary risk of bias: moderate to high

Participants People with type I diabetes with elevated urinary albumin
CVD risk: moderate
Intervention: randomised 18, analysed 16
Control: randomised 20, analysed 20
% male: 81% intervention, 75% control
Age: mean (SD) intervention 44 (12), control 41 (14)
Age range: unclear (21-65 inclusion)
Smokers: intervention 50%, control 55%
Hypertension: intervention 6%, control 10%
Medications taken by ≥ 50% of those in the control group: insulin
Medications taken by 20%-49% of those in the control group: not reported
Medications taken by some, but < 20% of the control group: anti-hypertensives
Location: Netherlands
Ethnicity: not reported

Interventions Type: dietary advice
Comparison: LA (n6) vs usual diet
Intervention: diet advice given at every visit throughout the 2-year period to increase linoleic acid achieving a polyunsaturated: saturated fatty acid ratio close to 1.0. Advice to replace butter or saturated margarines by polyunsaturated margarines and to restrict the intake of SFA from meat and milk products
Control: to continue their usual diet. All participants were urged not to alter total fat and protein content.
Dose: aim unclear
Baseline PUFA: 6.6% E PUFA
Compliance: TC fell more in intervention (-0.45 mmol/L) than control (0.10 mmol/L) from baseline to 2 years. Significant difference between plasma cholesteryl ester LA in intervention and control at 2 years
Plasma cholesteryl esters at 2 years

- LA mol%: intervention 62.2 (SD 4.2), control 57.4 (SD 4.9)
- oleic acid mol%: intervention13.7 (SD 1.8), control 16.5 (SD 1.4)

Dietary assessment using 1 week dietary recall, reported at 2 years.

- Energy intake, MJ/d: intervention 7.42 (SD 2.02), control 8.48 (SD 2.48)
- Total fat intake, % E: intervention 37 (SD 4), control 40 (SD 7)
- SFA intake, % E: intervention 13 (SD 2), control 16 (SD 3)
- PUFA intake, % E: (calculated from P/S and SFA intake) intervention 12.5 (SD not reported), control 9.0 (SD not reported), increase 3.5%E
- PUFA n-3 intake: not reported
- PUFA n-6 intake, % E: not reported, but intervention 11%E LA (SD 2), control 7%E LA (SD 3)
- PUFA/SFA ratio: intervention 0.96 (SD 0.16), control 0.56 (SD 0.25)
- MUFA intake: not reported
- CHO intake, % E: intervention 43 (SD 4), control 41 (SD 7)
- Protein intake, % E: intervention 18 (SD 4), control 17 (SD 3)
- Trans fat intake: not reported
- Cholesterol intake, mg/d: intervention 174 (SD 49), control 245 (SD 120)

Compliance, other methods: not reported
Inclusion basis: aimed to increase LA rather than total PUFA intake. Intake data suggests 3.5% E PUFA dose, > 10% increase from control 9% E intake Supported by plasma cholesteryl ester LA and TC
PUFA dose: 3.5% E PUFA
Duration of intervention: 2 years

Outcomes Main trial outcomes: albuminuria and lipids
Dropouts: intervention 2 of 20, control 4 of 20
Available outcomes: weight, HDL cholesterol, TGs, HbA1c (TC, glucose, insulin reported but too different at baseline to use, LDL not reported in control group, renal outcomes such as glomerular filtration rate, albuminuria, mean arterial pressure not used)
Response to contact: yes, trial author confirmed no MI or other CVD events occurred during trial

Notes Most outcomes are estimated from figures.
Trial funding: Dutch Diabetes Research Fund

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "patients were stratified according to sex and randomised in blocks of ten men and six women"
Allocation concealment (selection bias)	Low risk	Assigned using opaque sealed envelopes by independent statistical investigator with no contact with participants
Blinding of participants and personnel (performance bias)	High risk	No information on blinding. Participants could not be blinded as they received dietary advice.
Blinding of outcome assessment (detection bias)	Unclear risk	No details
Incomplete outcome data (attrition bias)	Unclear risk	No details on dropouts apart from the exclusion of 2 intervention participants from the trial due to pregnancy and decision not to participate.
Selective reporting (reporting bias)	Unclear risk	No protocol or trial registration located
Attention	High risk	Likely that diet-advice group had more time and attention
Compliance	Low risk	TC fell more in intervention (-0.45 mmol/L) than control (0.10 mmol/L) from baseline to 2 years. Significant difference between plasma cholesteryl ester LA in intervention and control at 2 years
Other bias	Low risk	None noted

Ebrahimi 2009 [134 135]

Methods	RCT, parallel, (n3 EPA+DHA vs nil), 6 months Summary risk of bias: Moderate or high
Participants	People with metabolic syndrome N: 60 int., 60 control. (analysed, int: 47 cont: 43) Level of risk for CVD: moderate Male: 15% int., 9% control. Mean age (sd): 53.5 (12.7) int., 52.3 (11.1) control Age range: NR but 40-70yrs inclusion criteria Smokers: 4% int., 2% control Hypertension: 32% int., 32% control Medications taken by at least 50% of those in the control group: NR Medications taken by 20-49% of those in the control group: NR Medications taken by some, but less than 20% of the control group: antihypertensives (14.3%), antidiabetic medication (16.7%) Location: Iran Ethnicity: NR
Interventions	Type: supplement Comparison: EPA+DHA vs nil (no placebo) Intervention: 1x1g capsule of fish oil/d (180mg/d EPA, 120mg/d DHA): EPA+DHA 3.0g/d Control: nil, no placebo **PUFA Dose**: (intended) increase 3.0g/d EPA+DHA, **1.4%E n-3, 1.4%E PUFA** Compliance: assessed by counting tablets at weekly visits and those who did not take their capsules were excluded but unclear how many this was (and not feasible in control group) Duration of intervention: 6 months
Outcomes	Main study outcome: "several anthropometric and biochemical parameters" Dropouts: 13/60 int., 17/60 control (this probably combines dropouts and exclusions) Available outcomes: weight, BMI, total chol, HDL & LDL chol, fasting glucose (TGs and hsCRP provided as medians, BP given but only 6 months, heat shock protein not relevant)
Notes	Study funding: Mashhad University of Medical Science Research Council

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"randomly allocated" - no further details
Allocation concealment (selection bias)	Unclear risk	no information
Blinding of participants and personnel (performance bias)	High risk	No placebo used
Blinding of outcome assessment (detection bias)	Unclear risk	Blinding not mentioned
Incomplete outcome data (attrition bias)	High risk	30/120 (25%) lost over 6 months
Selective reporting (reporting bias)	Unclear risk	No protocol or trials register entry found
Attention	High risk	Paper states that weekly visits were used to promote and assess compliance, but presumably these did not happen in the control group as there was no placebo to encourage or assess.
Compliance	Unclear risk	Unclear how many did not comply fully (and so were excluded)
Other bias	Low risk	None noted

ELIA - Takaki 2011 UMIN000002171 [136]

Methods RCT, parallel, (n3 EPA vs nil), 11 months
Summary risk of bias: Moderate or high
Aim: "examined the anti-oxidant mechanisms of... EPA plus statin on the progression of atherosclerosis"

Participants People with CAD and dyslipidaemia on statins
N: 25 int., 25 control. (analysed, int: 23 or 24 cont: 23 or 24)
Level of risk for CVD: high
Male: 84% int., 80% control.
Mean age (sd) yrs: 61.6 (5.6) int., 60.9 (7.0) control
Age range: NR but 20-70 years inclusion criteria
Smokers: 20% int., 24% control.
Hypertension: 56% int., 64% control.
Medications taken by at least 50% of those in the control group: statins (100%, inclusion criterion), antihypertensive agents (80%), antiplatelet agents (88%)
Medications taken by 20-49% of those in the control group: NR
Medications taken by some, but less than 20% of the control group: antidiabetic agents (16%)
Location: Japan
Ethnicity: NR

Interventions Type: supplement
Comparison: EPA vs nil
Intervention: 1.8g/d EPA (no further details) plus statin treatment (from before trial) plus dietary advice (not specified): EPA 1.8g/d
Control: no placebo, only statin treatment (from before trial) plus dietary advice (not specified)
Compliance: assessed by questionnaire on adherence at each clinic appointment and blood EPA/AA ratio. Reports good adherence (receipt of at least 80% of meds) was seen in both (sic) groups, and blood EPA/AA was significantly higher in intervention than control group.
Duration of intervention: x months

Outcomes Main study outcome: progression of atherosclerosis
Dropouts: 0 of 25 int., 0 of 25 control
Available outcomes: hs-CRP (CHD events, serum lipids presented, but only 11 months so not used, also aortic stiffness, arterial stiffness, carotid atherosclerosis, oxidative stress not used)

Notes Study funding: None reported
Author contact: Not attempted

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Trials register states individual randomisation, paper mentions block stratification.
Allocation concealment (selection bias)	Unclear risk	"Central registration" mentioned, otherwise unclear.
Blinding of participants and personnel (performance bias)	High risk	Open trial (no placebo)
Blinding of outcome assessment (detection bias)	Low risk	States that outcome assessors were blinded in the trials register, biochemical analysis results used
Incomplete outcome data (attrition bias)	Unclear risk	1 person excluded, but unclear from which arm
Selective reporting (reporting bias)	High risk	Trials registry entry was retrospective
Attention	Unclear risk	Follow up frequency was unclear
Compliance	Low risk	Blood EPA/AA ratio was significantly different in intervention and control at 11 months (p<0.001)
Other bias	Low risk	None noted

EPE-A - Sanyal 2014 NCT01154985 [137]

Methods
EPE-A
RCT, parallel, 3 arms (n-3 EPA, low dose vs high dose vs unclear placebo), 12 months
Summary risk of bias: moderate or high

Participants
People with non-alcoholic steatohepatitis (NASH) and non-alcoholic fatty liver disease (NAFLD)
N: 86 intervention-high, 82 int low, 75 control (analysed 64, 55, 55 respectively, ITT analysis for primary outcomes)
Level of risk for CVD: low (although 35% had type II diabetes)
Men: 33.7% intervention-high, 41.5% intervention-low, 42.7% control
Mean age in years (SD): 47.8 (11.1) intervention-high, 47.8 (12.5) intervention-low, 50.5 (12.5) control
Age range: not reported
Smokers: not reported
Hypertension: not reported
Medications taken by at least 50% of those in the control group: not reported
Medications taken by 20%-49% of those in the control group: not reported
Medications taken by some, but less than 20% of the control group: not reported
Location: USA
Ethnicity: white intervention-low: 94%, intervention-high: 87%, control: 90.7%
African American intervention-low: 3.7%, intervention-high: 2.3%, control: 4.0%
Others intervention-low: 2.4%, intervention-high: 10.5%, control: 5.3%

Interventions
Type: supplement (omega 3 capsule)
Comparison 1: high EPA vs low EPA (unclear what replaced EPA)
Comparison 2: EPA vs unclear (placebo contents not reported)
Intervention-high: EPA-E 2.7 g/d, 3 × EPA-E 300 mg capsules. Dose: 2.7 g/d EPA + DHA
Intervention-low: EPA-E 1.8 g/d, 2 × EPA-E 300 mg capsules + 1 placebo capsule
Dose: 1.8 g/d EPA + DHA
Control: 3 × placebo capsules. The pills were identical with respect to size, colour and smell
Compliance: estimated by pill count and measuring the ratio of serum EPA to arachidonic acid. compliance rates for the 3 groups (placebo vs EPA-E 1800 mg/d vs EPA-E 2700 mg/d) were 89.5% (6.8%), 90.3% (5.7%) and 89.5% (5.3%), respectively
Length of intervention: 12 months

Outcomes
Main study outcome: histological response in standardised scoring of liver biopsies and change in ALT level
Dropouts: 22 intervention-high, 27 intervention-low, 20 control
Available outcomes: cardiac events, deaths (none), angina, adverse events (weight, BMI, lipids, glucose, HbA1c, HOMA, hsCRP all reported as medians so not useable in meta-analyses)
Response to contact: yes (provided methodological details)

Notes Data combined for the 2 intervention groups for binary outcomes and higher dose data vs control used for continuous outcomes
Study funding: supported entirely by Mochida Pharmaceuticals

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Block randomisation using an interactive voice-response system to assign subjects in a 1:1:1 ratio between the 2 arms for each site separately. Participants were stratified by the presence of type 2 diabetes. The total fraction of such individuals was capped at 40% of the study cohort
Allocation concealment (selection bias)	Low risk	As above (remote computer-generated randomisation)
Blinding of participants and personnel (performance bias)	Low risk	Double-blind stated, but no further details. Author confirmed researchers and outcome assessors were blinded to treatment allocation and pills were identical with respect to size, colour and smell
Blinding of outcome assessment (detection bias)	Unclear risk	No details
Incomplete outcome data (attrition bias)	High risk	Number and characteristics of participants lost to follow-up similar across arms, however < 80% provided outcome data relevant to this systematic review
Selective reporting (reporting bias)	Low risk	Registered June 2010, study started June 2010, completed October 2012. All outcomes in trials registry entry were also reported in the trials registry. Secondary outcomes reported were not planned (compared with first version of clinicaltrials.gov entry)
Attention	Low risk	All participants had same follow-up visits.
Compliance	Low risk	Compliance was estimated by pill count and measuring the ratio of serum EPA to arachidonic acid. Compliance rates for the 3 groups (placebo vs EPA-E 1800 mg/d vs EPA-E 2700 mg/d) were 89.5% (6.8%), 90.3% (5.7%) and 89.5% (5.3%) respectively
Other bias	Low risk	None noted

EPIC-1 – Feagan 2008 – NCT00613197 [138]

Methods EPANOVA in Crohn's disease, study 1 (EPIC-1)
RCT, parallel, 2-arm (omega 3 vs MCT), 52 weeks
Summary risk of bias: moderate or high

Participants Adults with quiescent Crohn's disease (CDAI) score < 150
N: 188 intervention, 186 control
Level of risk for CVD: low
Men: 48.1% intervention, 41.1% control
Mean age in years (SD): 40.5 (15.2) intervention, 38.2 (13.1) control
Age range: 18-70 years
Smokers: 30.6% intervention, 34.4% control
Hypertension: unclear
Medications taken by at least 50% of those in the control group: oral 5-ASA therapy, Systemic corticosteroids – prednisolone, budesonide
Medications taken by 20%-49% of those in the control group: not reported
Medications taken by some, but less than 20% of the control group: antibiotic therapy, topical rectal therapy, immune-modifying agents, immune modifiers/biologics
Location: Canada, Europe, Israel, USA
Ethnicity: not reported

Interventions Type: supplement (capsule)
Comparison: EPA + DHA vs SFA (medium chain triglycerides of short SFAs)
Intervention: 2 × 2 1 g gelatin capsules omega-3 free fatty acids (Epanova- 2.2 g EPA, 0.8 g DHA).
Dose: 3 g/d EPA + DHA
Control: 4 x1 g capsules medium chain triglycerides
Compliance: pill counts, 79.2% adhered intervention, 75.6% adhered control
Length of intervention: mean 52 weeks

Outcomes Main study outcome: Cohn's relapse-free time
Dropouts: 80 intervention, 91 control
Available outcomes: total deaths, non-fatal arrhythmias, cancer diagnoses, cancer deaths, adverse events
Response to contact: yes (data provided)

Notes Study funding: Tillotts Pharma, authors had extensive financial disclosures

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation by number generator. Used a centralised randomisation procedure via interactive voice recognition system.
Allocation concealment (selection bias)	Low risk	Centralised randomisation (see above)
Blinding of participants and personnel (performance bias)	Low risk	Double blinding stated, identical capsule (slow-release capsules). Neither investigator nor participant knew the allocation.
Blinding of outcome assessment (detection bias)	Unclear risk	Study states double-blind but does not state that outcome assessors were blinded or provide a mechanism for this
Incomplete outcome data (attrition bias)	Low risk	Number of dropouts and reasons provided. 171 of 187 in intervention group and 174 of 184 in control group provided data for primary outcome, (7% dropout), though 80 in the intervention group and 91 in the control group terminated early.
Selective reporting (reporting bias)	High risk	Trials registration (NCT00613197) first received in 2008, but study started in 2003 and was published in 2008
Attention	Low risk	As investigators were blinded attention bias was not possible.
Compliance	Unclear risk	Pill counts, 79.2% adhered intervention, 75.6% adhered control
Other bias	Low risk	No further bias noted

EPIC-2 – Feagan 2008 – NCT00074542 [138]

Methods EPANOVA in Crohn's Disease, Study 2 (EPIC-2)
RCT, parallel, 2 arms (omega 3 vs MCT), 58 weeks
Summary risk of bias: moderate or high

Participants Adults with a confirmed diagnosis of Crohn's Disease and a Crohn's Disease Activity Index (CDAI) score < 150 who are responding to steroid induction therapy
N: intervention, 189, control 190 (187 intervention, 188 control analysed)
Level of risk for CVD: low (people with quiescent Crohn's disease)
Men: 48.1% intervention, 41.1% control
Mean age in years (SD): 38.5 (13.8) intervention, 40.0 (13.6) years control
Age range: > 16 years
Smokers: 25.1% intervention, 37.2% control
Hypertension: unclear

Medications taken by at least 50% of those in the control group: systemic corticosteroids – prednisolone, budesonide (but tapered and discontinued during the study)
Medications taken by 20%-49% of those in the control group: only reported for prior 12 months
Medications taken by some, but less than 20% of the control group: only reported for prior 12 months
Location: Canada, Europe, Israel, USA
Ethnicity: not reported

Interventions Type: supplement (capsule)
Comparison: EPA + DHA vs SFA (medium chain triglycerides of short SFAs)
Intervention: 2 × 2 1 g gelatin capsules omega-3 free fatty acids (Epanova) providing total dose ~2.2 g/d EPA, 0.8 g/d DHA. Dose: ~3.0 g/d EPA + DHA
Control: 2 × 2 1 g capsules medium chain triglyceride oil
Compliance: measured by patient interviews and pill counts, 75.4% adhered intervention, 81.4% adhered control
Length of intervention: mean 58 weeks

Outcomes Main study outcome: maintain Cohn's symptomatic remission
Dropouts: 114 intervention, 112 control
Available outcomes: mortality, CV events (nil), cancer diagnoses, adverse events
Response to contact: yes (data provided)

Notes Study funding: Tillotts Pharma, authors had extensive financial disclosures

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation by number generator. Used a centralised randomisation procedure via interactive voice recognition system
Allocation concealment (selection bias)	Low risk	Centralised randomisation (see above)
Blinding of participants and personnel (performance bias)	Unclear risk	Double blinding stated, identical capsule (slow-release capsules). Neither investigator nor participant knew the allocation. However no information provided on capsules taste or smell
Blinding of outcome assessment (detection bias)	Unclear risk	Study states double-blind but does not state that outcome assessors were blinded or provide a mechanism for this
Incomplete outcome data (attrition bias)	High risk	Number of dropouts and reasons provided, however 114 of 189 in intervention group and 112 of 190 in control group terminated early.
Selective reporting (reporting bias)	High risk	NCT00074542. First received 2003, study start 2002. Published 2008. Some outcomes, such as quality of life, stated in trials registry but not in published papers
Attention	Low risk	As investigators were blinded, attention bias was not possible.
Compliance	Unclear risk	Measured by patient interviews and pill counts, 75.4% adhered intervention, 81.4% adhered control
Other bias	Low risk	No further bias noted

EPOCH – Danthiir 2014 – ACTRN2607000278437 [139] [140]

Methods Older People, Omega-3 and Cognitive Health (EPOCH)
RCT, parallel (n-3 EPA + DHA vs MUFA), 18 months
Summary risk of bias: low

Participants Healthy older adults with no cognitive impairment
N: 195 intervention, 196 control (reported by author)
Level of risk for CVD: low
Men: not reported
Mean age in years (SD): not reported

Age range: not reported, but 65-90 recruited
Smokers: not reported
Hypertension: not reported
Medications taken by at least 50% of those in the control group: not reported
Medications taken by 20%-49% of those in the control group: not reported
Medications taken by some, but less than 20% of the control group: not reported
Location: Australia
Ethnicity: not reported

Interventions Type: supplement (fish oil capsules)
Comparison: EPA + DHA vs MUFA
Intervention: 4 capsules/d (1.72 g/d DHA and 0.60 g/d EPA). Dose: 2.32 g/d EPA + DHA
Control: 4 capsules/d (3.960 g/d olive oil and 40 mg/d fish oil)
Compliance: count of all unused supplements returned at three-monthly intervals, plus self-report calendars, mailed back on a monthly basis. If compliance fell below 85% (re calendars), they were contacted by a researcher who noted the reasons. Compliance also assessed by erythrocyte membrane n-3 LC PUFA status
Length of intervention: 18 months

Outcomes Main study outcome: change in cognitive performance
Dropouts: not reported
Available outcomes: mortality (nil), MI, stroke, revascularisation, arrhythmias, CV events
Response to contact: yes (data provided)

Notes Authors reported some events, but don't appear to be published.
Study funding: EPAX donated the Omega-3 concentrate and Blackmores Pty Ltd donated the placebo and packaging of the Omega-3 concentrate. The trial was supported by the Brailsford Robertson Award 2007-2008 (University of Adelaide and CSIRO Food and Nutritional Sciences), and is funded by a National Health and Medical Research Project Grant (#578800).

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Age-stratified, permuted-block randomisation, with mixed block-sizes (2-8, size unknown to study investigators), 1:1 allocation. Computer-generated randomisation schedule
Allocation concealment (selection bias)	Low risk	An independent researcher prepared allocation to treatment
Blinding of participants and personnel (performance bias)	Low risk	The researchers, project staff, and participants remained blinded to treatment allocation until the trial was completed and the database locked. However, no information provided on capsules appearance, taste or smell
Blinding of outcome assessment (detection bias)	Low risk	As above
Incomplete outcome data (attrition bias)	Unclear risk	No data for each group presented, and no attrition data presented
Selective reporting (reporting bias)	High risk	Only cognitive functions reported for whole population (not by arm). No secondary outcomes reported (MMSE; perceived health status, depressive symptoms, positive and negative affect, life satisfaction, self-reported cognitive functioning, and functional capacity; blood pressure; biomarkers of glucose, glycated haemoglobin, triglycerides, total cholesterol, HDL, LDL, homocysteine, CRP, MDA, and telomere length)
Attention	Low risk	All had the same contact and attention
Compliance	Unclear risk	Count of all unused supplements returned at 3-monthly intervals, plus self-report calendars, mailed back on a monthly basis. If compliance fell below 85% (re calendars), they were contacted by a researcher who noted the reasons. Compliance also

		assessed by erythrocyte membrane n-3 LC PUFA status but results not reported
Other bias	Low risk	None noted

Erdogan 2007 [141-143]

Methods	RCT, parallel (n-3 EPA + DHA vs unclear), 12 months Summary risk of bias: moderate to high
Participants	People with successful external cardioversion N: unclear intervention, unclear control (54 analysed intervention, 54 control) Level of risk for CVD: high Men: 70% intervention, 74% control Mean age in years (SD): 65.0 (mean for whole group, SD not reported) Age range: not reported Smokers: not reported Hypertension: not reported Medications taken by at least 50% of those in the control group: not reported Medications taken by 20%-49% of those in the control group: not reported Medications taken by some, but less than 20% of the control group: not reported Location: Germany Ethnicity: not reported
Interventions	Type: supplement (probably, not described) Comparison: high EPA + DHA vs unclear placebo Intervention: described only as "PUFA" but included in systematic review (Mariani 2013) by Erdogan et al on effects of n-3 PUFA. Dose: unclear Control: described only as "placebo" Compliance: not reported Length of intervention: 12 months
Outcomes	Main study outcome: atrial fibrillation relapse Dropouts: not reported Available outcomes: recurrent AF (reported in Mariani 2013), mortality (none) Response to contact: no reply to date
Notes	Funding source: not reported

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomly assigned"
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias)	Unclear risk	Described as triple blind, but no further details provided (only an abstract with some details in a related trial publication and some in a systematic review by the same author)
Blinding of outcome assessment (detection bias)	Unclear risk	Not described, but analysis appears to have been carried out blind to intervention/control status
Incomplete outcome data (attrition bias)	Unclear risk	Number randomised not described
Selective reporting (reporting bias)	Unclear risk	Unclear, no trial registry entry or protocol found
Attention	Unclear risk	Not described
Compliance	Unclear risk	Not described
Other bias	Low risk	None noted

Eschen 2010 [144]

Methods RCT, parallel, (n3 EPA+DHA vs MUFA), 6 months
Summary risk of bias: Moderate or high
Aim: "supplementation with marine n-3 PUFA will reduce markers associated with inflammation in patients with" chronic heart failure (CHF)

Participants People with chronic heart failure
N: 69 int., 69 control. (analysed, int: NR cont: NR)
Level of risk for CVD: High
Male: 83% int., 88% control.
Mean age (sd) yrs: 58 (10) int., 61 (8) control
Age range: NR but inclusion criteria were 19-80 years
Smokers: 13% int., 17% control.
Hypertension: 46% int., 39% control.
Medications taken by at least 50% of those in the control group: beta blockers (84%), RAS inhibitors (angiotensin converting enzyme inhibitor or angiotensin II receptor blocker, 97%), Aspirin (53%), statins (52%)
Medications taken by 20-49% of those in the control group: NR
Medications taken by some, but less than 20% of the control group: NR
Location: Italy
Ethnicity: NR

Interventions Type: supplement
Comparison: EPA+DHA vs MUFA
Intervention: 1 capsule/d of EPA and DHA as ethyl esters (including 0.9g/d EPA+DHA, Società Prodotti Antibiotici S.p.A., Milano): EPA+DHA 0.9g/d
Control: 1 capsule/d of olive oil (including 1g/d olive oil, Società Prodotti Antibiotici S.p.A., Milano)
Compliance: assessed by analysis of plasma EPA and DHA, both were significantly greater at 24 weeks in the intervention than control groups ($p<0.001$).
Duration of intervention: 6 months (24 weeks)

Outcomes Main study outcome: soluble adhesion molecules
Dropouts: NR int., NR control - this was reported as a substudy, and no details of study flow are given (or what study it is a substudy of)
Available outcomes: hsCRP, ICAM-1, VCAM-1, P-selectin

Notes Study funding: Società Prodotti Antibiotici S.p.A., Milano
Author contact: not yet

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"randomised" - no further details
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias)	Unclear risk	The study is referred to as "double-blind" and it is stated that the intervention and control capsules were "similar" but no further details are provided. No information provided on capsules taste or smell.
Blinding of outcome assessment (detection bias)	Low risk	States double blind and all useable outcomes are biochemical in nature
Incomplete outcome data (attrition bias)	Low risk	States that 138 were recruited, and that 138 samples were available for analysis
Selective reporting (reporting bias)	Unclear risk	No protocol or trials register entry were found
Attention	Low risk	Assessment schedule identical for the two groups
Compliance	Low risk	Statistically significantly more EPA and DHA in intervention arms at 24 weeks
Other bias	High risk	This study is referred to as a sub-study but the main study is not referenced, and it is not clear whether this is published and what proportion of participants are included in this study.

FAAT – Leaf 2005 – NCT00004559 [145]

Methods	Fatty Acid Antiarrhythmia Trial – FAAT Randomisation: RCT, parallel, 2 arms, (n-3 EPA + DHA vs MUFA), 12 months Summary risk of bias: moderate or high
Participants	People with implanted cardioverter defibrillators (ICDs) N: intervention 200, control 202 Level of risk for CVD: high (patients with ICDs). Men: intervention 84.5%, control 81.7% Mean age in years (SD): intervention 65.7 (11.6), control 65.3 (11.7) Age range: unclear Smokers: intervention 15%, control 11.4% Hypertension: unclear Medications taken by at least 50% of those in the control group: ACE inhibitors, beta-blockers Medications taken by 20% - 49%: diuretics Medications taken by some, but < 20%: calcium channel blockers, amiodarone, sotalol, type 1 antiarrhythmics Location: USA Ethnicity: intervention 95.5% white, control 96.5% white
Interventions	Type: supplement/capsule Comparison: EPA + DHA vs MUFA Intervention: 4 ×1 g/d fish oil gelatin capsules, 2.6 g/d EPA + DHA (Pronova Biocare, quantities of EPA + DHA unclear). Dose: 2.6 g/d EPA + DHA Control: 4 ×1 g/d olive oil capsules, 4 g/d (in identical gelatin capsules, < 0.06 g/d EPA and < 0.06 g/d DHA) All were advised to use olive oil rather than the common plant seed oils for cooking, dressings, and sauces Compliance: pill counts and platelet phospholipid data suggested greater omega 3 intake in intervention participants. 35% were non-compliers (36.5% intervention, 34.2% control) Duration of intervention: 12 months
Outcomes	Main study outcome: fatal ventricular arrhythmias Dropouts: intervention 13 deaths, unclear no. of dropouts, control 12 deaths, dropouts unclear Available outcomes: deaths, cardiovascular deaths, CVD events, deaths from heart failure, fatal arrhythmias, MI, angina Response to contact: yes (data provided)
Notes	Study funding: the study was supported in part by a grant from the NHLBI, NIH (HL62154)

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation tables for each collaborating site, stratified by site
Allocation concealment (selection bias)	Low risk	Author confirmed allocation was concealed from investigators
Blinding of participants and personnel (performance bias)	Unclear risk	Study referred to as "double blind" and gelatin capsules (verum and placebo) were stated as being of identical appearance but no discussion of taste or smell. Author confirmed that investigators and patients were blinded.
Blinding of outcome assessment (detection bias)	Low risk	VT and VF events were assessed blinded to allocation
Incomplete outcome data (attrition bias)	High risk	Large numbers dropped out so some deaths, etc. may have been missed, 35% discontinued early due to non-compliance but were assessed at study end, data censored for some participants
Selective reporting (reporting bias)	High risk	Trials registry data received September 2005, paper published November 2005

Attention	Low risk	Time and attention appeared similar between the 2 arms
Compliance	High risk	Pill counts and platelet phospholipid data suggested greater omega 3 intake in intervention participants. 35% were non-compliers (36.5% intervention, 34.2% control)
Other bias	Low risk	None noted

Fakhrzadeh 2010 [146 147]

Methods RCT, parallel, (n3 EPA+DHA vs mixed fat MCT), 6 months
Summary risk of bias: Moderate or high

Participants Elderly residents (65 yrs or over)
N: 134 in both groups combined. (analysed, int: 62 cont: 62)
Level of risk for CVD: Low
Male: 43.5% int., 38.7% control
Mean age (sd): 74.7 (10.1) int., 74.9 (8.8) control
Age range: NR
Smokers: 21.0% int., 14.8% control
Hypertension: NR
Medications taken by at least 50% of those in the control group: NR
Medications taken by 20-49% of those in the control group: NR
Medications taken by some, but less than 20% of the control group: Statins
Location: Iran
Ethnicity: NR

Interventions Type: supplement (fish oil capsule vs placebo)
Comparison: n-3 vs nil
Intervention: 1g/d fish oil capsule (180mg EPA, 120mg DHA, Zahravi Pharmacy Company, Iran): EPA+DHA 0.3g/d
Control: 1g/d placebo capsule (medium-chain triglycerides, Zahravi Pharmacy Company, Iran)
Compliance: Capsule consumption observed by two nurses
Duration of intervention: 6 months

Outcomes Main study outcome: Lipids, insulin resistance
Dropouts: 10 in both groups combined
Available outcomes: Lipid profiles, insulin, glucose, HOMA-IR (glucose, insulin and HOMA-IR data not useable- baseline differences)

Notes Study funding: Tehran University of Medical Science

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"randomly assigned"
Allocation concealment (selection bias)	Unclear risk	As above
Blinding of participants and personnel (performance bias)	Unclear risk	"participants and investigators were blinded to the intervention"
Blinding of outcome assessment (detection bias)	Unclear risk	As above
Incomplete outcome data (attrition bias)	Unclear risk	Drop out numbers by group unclear
Selective reporting (reporting bias)	Unclear risk	No registry or protocol identified
Attention	Unclear risk	Not reported and blinding unclear
Compliance	Unclear risk	Nurses observed participants taking capsules
Other bias	Low risk	None noted

Ferrara 2000 [148]

Methods RCT, crossover, (n6 LA vs MUFA), 6 months
Summary risk of bias: Moderate or high

Participants Hypertensive patients
N: 23 overall (analysed, int: 23 cont: 23)
Level of risk for CVD: Moderate
Male: 43% int., 43% control.

Mean age (sd): NR
Age range: 25-70 years
Smokers: NR
Hypertension: All
Medications taken by at least 50% of those in the control group: Antihypertensives
Medications taken by 20-49% of those in the control group: (atenolol, nifedipine, lisinopril)
Medications taken by some, but less than 20% of the control group: (hydrochlorothiazide, doxazosin)
Location: Italy
Ethnicity: NR

Interventions Type: supplemented food (diets enriched with sunflower oil or olive oil)
Comparison: PUFA vs MUFA
Intervention: Spoons of sunflower oil added after cooking (40g men, 30g women): assuming 59% LA, 23.6g/d LA men, 17.7g/d women
Control: Spoons of olive oil added after cooking (40g men, 30g women)
PUFA Dose: (intended) increase ~20g/d LA, **9%E n-6, 9%E PUFA**
Compliance: 7-d food records
Duration of intervention: 6 months

Outcomes Main study outcome: Antihypertensive use and bp
Dropouts: none
Available outcomes: BMI, weight, lipids, glucose

Notes Study funding: NR

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"randomly assigned"
Allocation concealment (selection bias)	Unclear risk	"randomly assigned"
Blinding of participants and personnel (performance bias)	Unclear risk	"double-blind"- however, given as spoonsful of oil (olive oil and sunflower oil)
Blinding of outcome assessment (detection bias)	Unclear risk	BP measures by author "unaware of the patient's dietary treatment". Method of blinding not described
Incomplete outcome data (attrition bias)	Low risk	No dropouts
Selective reporting (reporting bias)	Unclear risk	No registry or protocol identified
Attention	Low risk	The study only differed by the content of the spoonsful of oil added to participants diets. Assessment schedule did not appear to differ between the two arms.
Compliance	Unclear risk	3 patients not fully compliant, however included in the analysis "since they had complied with the indications for the intake of MUFA or PUFA"
Other bias	Low risk	None noted

Ferreira 2015 [149]

Methods RCT, parallel, (n3 EPA vs unclear), 6 months
Summary risk of bias: moderate or high

Participants Population: Adults with Huntington's disease
N: 147 int., 143 control. (analysed, int: 97 cont: 87)
Level of risk for CVD: Low
Male: 54.4% int., 51% control.
Mean age (sd): 52.9 (10.28) int., 52.2 (10.70) control
Age range: NR
Smokers: NR
Hypertension: NR
Medications taken by at least 50% of those in the control group: NR

Medications taken by 20-49% of those in the control group: NR
Medications taken by some, but less than 20% of the control group: NR
Location: UK, Germany, Portugal, Spain, Italy, and Austria
Ethnicity: int: Caucasian 145, Asian 1 other 1; cont: Caucasian 141, Oriental, other 1
Depression: Long term condition (high risk)
Anxiety: Long term condition (high risk)

Interventions Type: supplement
Comparison: EPA vs placebo
Intervention: 4x500mg/d capsules of ethyl-EPA (2 g/d EPA)
Control: placebo (identical in appearance to the test product, but not clear what it constitutes)
Compliance: NR
Duration of intervention: 6 months

Outcomes Main study outcome: change in TMS-4 (Total Motor Score 4)
Dropouts: 17 participants withdrew but their group allocation was not given
Available outcomes: Depression incidence, adverse events

Notes The authors only reported data on their subgroup analysis, which had a certain range of CAG repeats.
Study funding: Trial was funded by Amarin Neuroscience Ltd. According to their website this is a biopharmaceutical company with a commercial focus on “the potential therapeutic benefits of polyunsaturated fatty acids”. Furthermore, one of the authors works for them.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Patients were randomly assigned by the investigator in each site by allocation of a pre numbered treatment pack (block balanced randomisation codes were computer generated by Catalent Pharma Solutions, Bolton, UK).
Allocation concealment (selection bias)	Low risk	Patients were randomly assigned by the investigator in each site by allocation of a pre numbered treatment pack (block balanced randomisation codes were computer generated by Catalent Pharma Solutions, Bolton, UK).
Blinding of participants and personnel (performance bias)	Unclear risk	Paper states that this was a double-blind study, placebo was identical in appearance to the test product, however no details provided
Blinding of outcome assessment (detection bias)	Unclear risk	Unclear
Incomplete outcome data (attrition bias)	Low risk	Seventeen subjects (6%) withdrew from the study.
Selective reporting (reporting bias)	Unclear risk	No protocol in a trial register found
Attention	Low risk	Treated equally
Compliance	Unclear risk	Not reported
Other bias	Low risk	None seen.

Finnegan 2003 [150-153]

Methods RCT, parallel, 5 arms (n3 EPA+DHA vs n3 ALA vs n6 LA), 6 months
Summary risk of bias: Moderate or high

Participants People with hyperlipidaemia
N: 200 randomised into study (NR by arm), (analysed, high EPA+DHA 31, low EPA+DHA 30, high ALA 29, low ALA 30, cont 30)
Level of risk for CVD: moderate
Male: high EPA+DHA 58%, low EPA+DHA 57%, high ALA 59%, low ALA 57%, cont 60%
Mean age (sd): high EPA+DHA 54(11), low EPA+DHA 53(11), high ALA 54(11), low ALA 52(11), cont 55(11)

Age range: NR
Smokers: NR
Hypertension: NR
Medications taken by at least 50% of those in the control group: NR
Medications taken by 20-49% of those in the control group: NR
Medications taken by some, but less than 20% of the control group: NR
Location: UK
Ethnicity: NR

Interventions Type: supplement / supplemented food
Comparison: high EPA+DHA vs low EPA+DHA vs high ALA vs low ALA 30 vs n6 PUFA
Intervention: **high EPA+DHA** 1.7g/d EPA+DHA including 25g of margarine containing 0.5g/d EPA+DHA (Unilever) plus 3 fish oil capsules inc 0.8g/d EPA+DHA (Roche): EPA+DHA 1.7g/d
low EPA+DHA 0.8g/d EPA+DHA including 25g of margarine containing 0.5g/d EPA+DHA (Unilever) plus control capsules (Roche): EPA+DHA 0.8g/d
high ALA 9.5g/d ALA including 25g/d of margarine containing rapeseed & linseed oils plus control capsules (Roche): ALA 9.5g/d
low ALA 4.5g/d ALA including 25g/d margarine containing rapeseed & linseed oils plus control capsules (Roche): ALA 4.5g/d
Control: 25g/d linoleic-acid rich margarine plus control capsules (Roche)
Compliance: assessed through return of margarine pots and capsule packs, plus through measurement of plasma phospholipid fatty acid composition, compliance with margarine was >92% across groups, with capsules was >88% across groups and not significantly different between groups
Duration of intervention: 6 months

Outcomes Main study outcome: fasting and postprandial insulin and glucose
Dropouts: NR but 50 were lost across all 5 arms
Available outcomes: weight, lipids, glucose, insulin, TNFα, IL-1,2,4,6&10 (postprandial TG and glucose AUC and IAUCs, coagulation and fibrinolytic factors, BP, phagocytic activity, oxidative burst, thymidine and interferon gamma reported but not used)

Notes Study funding: DEFRA, BBSRC, Roche Vitamins & Unilever research under the Agri-Food LINK programme

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Blocked stratified randomisation
Allocation concealment (selection bias)	Unclear risk	No methods discussed
Blinding of participants and personnel (performance bias)	Unclear risk	Reported as "double blind" but their similarity in appearance, taste and packaging was not discussed
Blinding of outcome assessment (detection bias)	Unclear risk	As above
Incomplete outcome data (attrition bias)	High risk	25% of participants were lost
Selective reporting (reporting bias)	Unclear risk	No trials registry entry or protocol found
Attention	Low risk	No suggestion of differential attention in the 5 groups
Compliance	Low risk	Statistically significant changes in fatty acids
Other bias	Low risk	None noted

FISHGASTRO - Pot 2009 – NCT00145015 [154-157]

Methods Fish Consumption and Gastro-Intestinal Health (FishGastro)
RCT, parallel, multicentre (n3 EPA+DHA rich fish vs low n3 EPA+DHA fish, n3 vs nil), both arms included dietary advice, and the third arm is dietary advice only, 6 months
Summary risk of bias: Low (as food trial)
Aim: "to investigate the effects of fish on genotoxicity markers in the colon"

Participants Attendees visiting the hospital for colonoscopy as part of their regular medical care, subdivided into 3 groups: 1. People with colorectal polyps; 2. People with inactive ulcerative colitis; 3. People with no macroscopic signs of disease.
N: 82 int.1 (advice & salmon), 78 int.2 (advice & cod), 82 control (advice only). (analysed: 74 int.1, 70 int.2, 69 cont.)
Level of risk for CVD: Low
Male: 49% int.1, 59% int.2, 46% control.
Mean age (SEM): 55.1(11.5) int.1, 57.4(10.3) int.2, 55.3(9.5) control
Age range: NR
Smokers: 26% int.1, 11.4% int.2, 15.9% cont.
Hypertension: NR
Medications taken by at least 50% of those in the control group: NR
Medications taken by 20-49% of those in the control group: NR
Medications taken by some, but less than 20% of the control group: NR
(Excluded if taking ASAs or NSAIDs)
Location: UK & Netherlands
Ethnicity: NR

Interventions Type: dietary advice and supplement (supplement containing either higher EPA+DHA or lower EPA/DHA) or dietary advice only
Comparison: high n3 fish diet vs low n3 fish diet vs low fish diet
Intervention 1: 300g/wk salmon containing 2.1g/wk EPA & 4.2g/wk DHA (total n3 PUFA 9.9g/wk PLUS 3.9g/wk n6 PUFA): EPA+DHA 1.4g/d
Intervention 2: 300g/wk cod containing 1.8g/wk total n3 PUFA: EPA+DHA 0.26g/d
Control: dietary advice only
Fish provider: salmon provided by Marine Harvest, Norway; cod provided by Pescanova, Spain
Compliance: post-intervention serum FA composition & food diaries
Duration of intervention: 24 wks/6 months

Outcomes Main study outcome: Risk of colorectal cancer
Dropouts: 8 int.1, 7 int.2, 11 control
Available outcomes: serum CRP, faecal calprotectin, cytokines/chemokines in faecal water, IL-6 from biopsy (provided by study authors).

Notes None of the authors had any personal or financial conflicts of interest to disclose

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Treatment codes were generated by country and patient group in blocks of 6 by using a computer generated randomization schedule.
Allocation concealment (selection bias)	Low risk	Randomly allocated by an independent person
Blinding of participants and personnel (performance bias)	High risk	Participants not blinded as fish delivered to participants' homes and consumed by them with regular diet
Blinding of outcome assessment (detection bias)	Low risk	Outcome assessment undertaken without knowledge of allocation
Incomplete outcome data (attrition bias)	Low risk	10% drop out rate; pre-specified outcomes reported
Selective reporting (reporting bias)	Low risk	Registered outcomes reported
Attention	Low risk	Participants in all arms appear to have identical follow-up
Compliance	Low risk	Fatty acid status data suggests C-RoB is low
Other bias	Low risk	None noted

FLAX-PAD 2013 – NCT00781950 [158-166] [158 160 161 167-169]

Methods	Effects of Dietary Flaxseed on Symptoms of Cardiovascular Disease in Patients With Peripheral Arterial Disease (FLAX PAD) RCT, parallel, (n-3 ALA vs mixed fat), 12 months Summary risk of bias: low
Participants	Patients with peripheral artery disease, over 40 years old N: 58 intervention, 52 control Level of risk for CVD: high (all had peripheral artery disease, 80% had hyperlipidaemia) Men: 74.1% intervention, 73.1% control Mean age in years (SD): 67.4 (8.06) intervention, 65.3 (9.4) control Age range: unclear Smokers: 19.2% intervention, 34.6% control Hypertension: 81% intervention, 69.2% control Medications taken by at least 50% of those in the control group: lipid lowering medication, antihypertensives, antithrombotics Medications taken by 20%-49% of those in the control group: not reported Medications taken by some, but less than 20% of the control group: insulin or blood sugar-lowering drugs Location: Canada Ethnicity: unclear
Interventions	Type: food supplement (milled flaxseed) Comparison: ALA vs unclear (mix of wheat, wheat germ and mixed dietary oils) Intervention: food products (i.e. bagels, muffins, bars, pasta, buns, and milled seeds) containing 30 g of milled flaxseed daily. Dose: ~6.8 g/d ALA (calculated based on 30 g milled flaxseed/d) Control: placebo food products (i.e. bagels, muffins, bars, pasta, buns, and milled seeds) containing a mixture of wheat, wheat bran, and mixed dietary oils to replace the flaxseed daily Compliance: plasma levels of enterolignans and the n-3 fatty acid ALA were used as markers of dietary compliancy Length of intervention: 12 months
Outcomes	Main study outcome: all-cause mortality, cardiovascular mortality, stroke, and myocardial infarctions Dropouts: 15 intervention, 11 control Available outcomes: blood pressure, lipids, adverse events, plasma ALA Response to contact: yes (but no data provided)
Notes	Different intervention dropout figures reported in two publications (13 or 15) Study funding: funded by government organisations but foods created and provided by a company

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomly selected by a computer programme
Allocation concealment (selection bias)	Low risk	Allocation was concealed. The person who determined if a participant was eligible for inclusion in the trial was unaware, when this decision was made, of which group the subject would be allocated
Blinding of participants and personnel (performance bias)	Low risk	Product colour and texture were similar to disguise the composition of the product. Participants, personnel administering the intervention and those assessing the outcomes were blinded to group assignment
Blinding of outcome assessment (detection bias)	Low risk	All personnel that collected or analysed data were blinded to the intervention
Incomplete outcome data (attrition bias)	Low risk	All randomised accounted for in main outcomes
Selective reporting (reporting bias)	High risk	Prospectively registered October 2008, study start October 2008, primary outcome data completed March 2011, end date December 2017. Cardiovascular mortality and measures of adiposity not reported in a useable way
Attention	Low risk	Both groups had the same care

Compliance	Unclear risk	12 in intervention group and 8 in placebo group unwilling to comply with diet
Other bias	Low risk	None noted

FORWARD – Macchia 2013 – NCT00597220 [170-172]

Methods Randomized trial to assess efficacy of PUFA for the maintenance of sinus rhythm in persistent atrial fibrillation (FORWARD)
RCT, parallel, (n-3 EPA + DHA vs MUFA), 12 months
Summary risk of bias: low

Participants Patients with paroxysmal atrial fibrillation
N: 289 intervention, 297 control
Level of risk for CVD: high
Men: 57.8% intervention, 51.9% control
Mean age in years (SD): 66.3 (12) intervention, 65.9 (10.5) control
Age range: > 21
Smokers: 9% intervention, 6.2% control
Hypertension: 92.2% intervention, 90.8% control
Medications taken by at least 50% of those in the control group: aspirin, amiodarone, 'any antithrombotic treatment', beta-blockers
Medications taken by 20%-49% of those in the control group: anticoagulants
Medications taken by some, but less than 20% of the control group: none reported
Location: Argentina
Ethnicity: not reported

Interventions Type: supplement (capsule)
Comparison: EPA + DHA vs MUFA
Intervention: one capsule/ day containing 1 g of n-3 PUFA (Societá Prodotti Antibiotici and SigmaTau, Italy) (provided 850 mg to 882 mg EPA/DHA). Dose: 0.85 g/d EPA + DHA
Control: identical placebo capsule containing olive oil
Compliance: not reported.
Length of intervention: 12 months

Outcomes Main study outcome: survival free of atrial fibrillation
Dropouts: 20 intervention, 25 control
Available outcomes: mortality, MI, AF, heart failure, stroke, hospitalisation, side effects. Authors supplied further info on CVD events and methodology
Response to contact: yes

Notes Study funding: through unrestricted grants provided by companies that supplied study drugs, however "these companies did not have representatives on the Steering Committee" who terminated the trial after 1 year

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Participants were centrally assigned to receive either 1 g of n-3 PUFA or placebo in a ratio of 1:1" – computer generated in blocks of 4 and 6 stratified by study location
Allocation concealment (selection bias)	Low risk	As above, centrally allocated. Communication from authors was ambiguous, stated that the person recruiting *was* aware of which arm the individual would be allocated to, but that the "study was double-blind, placebo-controlled."
Blinding of participants and personnel (performance bias)	Low risk	Quote: "Each study site will be supplied with study drug and placebo in identically appearing packaging". "Both placebo and active treatment have the same odour and produce a comparable degree of fishy aftertaste"
Blinding of outcome assessment (detection bias)	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 randomisation until database lock" "The adjudication committee members are unaware of participant allocation and assess all available data and documentation with reference to pre-established criteria".
Incomplete outcome data (attrition bias)	High risk	Quote: "the study was cut short by the trial steering committee due to 'a slower-than-expected recruitment rate and lower event rates'. This 'resulted in an underpowered clinical trial unable to verify its hypothesis'. Therefore the outcome data were not as complete as they were initially meant to be".
Selective reporting (reporting bias)	Low risk	Prospectively registered January 2008, study start January 2008, completion August 2011. All outcomes in trials registry appear to have been reported.
Attention	Low risk	Both intervention and control given the same exposure to research personnel. 2013 paper: "Clinical outcomes, adherence, and adverse events were assessed 2, 4, 8, and 12 months after randomization"
Compliance	Unclear risk	Not reported
Other bias	Low risk	None noted

FOSTAR 2016 – ACTRN12607000415404 [173-177]

Methods	Fish Oil in knee OSTeoARthritis (FOSTAR) RCT, parallel, (n-3 EPA + DHA vs low n-3), 24 months Summary risk of bias: low
Participants	Adults aged 40+ years with knee osteoarthritis N: 101 intervention, 101 control Level of risk for CVD: low Men: 41% intervention, 60% control Mean age in years (SD): 60.8 (10) intervention, 61.1 (10) control Age range: > 40 Smokers: not reported Hypertension: not reported Medications taken by at least 50% of those in the control group: none reported Medications taken by 20%-49% of those in the control group: not reported at baseline, but 'during' includes Vit. D ~ 32% Medications taken by some, but less than 20% of the control group: not reported at baseline, but 'during' includes Glucocorticoid, HRT/anti-resorptive, both ~ 10% Location: Australia Ethnicity: not reported
Interventions	Type: supplementary food (enriched orange juice) Comparison: high EPA + DHA vs low EPA + DHA plus ALA (replacement unclear, but low omega 3) Intervention: 1-3 × a day drink of fruit juice mixed with day total = 15 mL of fish oil supplement (18% EPA, 12% DHA, 4.5 g/day total omega 3). Dose: 4.5 g/d EPA + DHA Control: liquid oral oil 15 mL sunola oil/day (which contains fish oil 2 mL plus 13 mL canola oil) (total omega-3 fat: ≥ 0.45 g EPA + DHA from 15 mL) Compliance: assessed by measuring the oil volume in returned bottles, compliance was > 80% in both groups. Both groups had increases from baseline in plasma EPA and DHA with the high-dose group having substantially larger increases, consistent with compliance with study oil Length of intervention: 24 months
Outcomes	Main study outcome: change in pain scale of WOMAC index Dropouts: 18 intervention, 16 control Available outcomes: mortality, CVD events, adverse events, analgesic use, bone marrow density, weight gain and serum fatty acids Response to contact: yes
Notes	Data on quality of life and pain score are presented in a figure and not in a usable format Study funding: government funding

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random allocation sequence
Allocation concealment (selection bias)	Low risk	A security-protected central automated allocation procedure was used to allocate participants to one of the 2 treatment arms. This was performed centrally at one pharmacy and then used to allocate and administer the oil at each site
Blinding of participants and personnel (performance bias)	Low risk	Citrus flavouring was added to both oils to achieve comparable taste and optimise masking. Both were provided in identical dark 500-mL bottles with *similar* labelling. At the end of the study, 52% of participants were unsure which group to which they had been allocated (50% high dose, 50% low dose). Of the remaining who thought they knew which group they were allocated, only 57% answered correctly, suggesting that blinding had been well maintained
Blinding of outcome assessment (detection bias)	Low risk	Participants and staff involved in patient care and assessment of BMD remained blinded throughout the study.
Incomplete outcome data (attrition bias)	Unclear risk	Oil intolerance in 1st year differed, others appear similar, but numbers confused
Selective reporting (reporting bias)	High risk	Prospectively registered August 2007, recruitment started July 2007, outcomes published 2016. Variety of outcomes such as quality of life stated in trials registry but not published.
Attention	Low risk	Same contact and instruction schedule for all participants.
Compliance	Low risk	Assessed by measuring the oil volume in returned bottles, compliance was > 80% in both groups. Both groups had increases from baseline in plasma EPA and DHA with the high-dose group having substantially larger increases, consistent with compliance with study oil
Other bias	Low risk	None noted

Franzen 1993 [178-180]

Methods RCT, parallel (n-3 EPA + DHA vs MUFA), 12 months
Summary risk of bias: moderate to high

Participants Adults with documented coronary heart disease
N: 15 intervention, 15 control
Level of risk for CVD: high
Men: unclear
Mean age in years (SD): 52 (9) intervention, 54 (7) control
Age range: not reported
Smokers: 87% intervention, 100% control
Hypertension: not reported
Medications taken by at least 50% of those in the control group: aspirin, beta-blockers
Medications taken by 20%-49% of those in the control group: not reported
Medications taken by some, but less than 20% of the control group: not reported
Lipid lowering medications were not allowed
Location: Germany
Ethnicity: not reported

Interventions Type: fish oil capsules

Comparison: EPA + DHA vs MUFA
Intervention: 9 × 1 g capsules/day of fish oils (20% EPA, 15% DHA, 3.15 g/day total omega 3). Dose: 3.15 g/d EPA + DHA
Control: 9 × 1 g capsules/day olive oil (which contains 6.3 g/day MUFA, 1.35 g/day SFA, 1.35 g/d total omega 6 fat)
Compliance: assessed by pill counts and FA in body tissue analysis
Length of intervention: 12 months

Outcomes Main study outcome: blood lipids and FA in body tissues
Dropouts: 0 intervention, 0 control
Available outcomes: mortality (nil death), CVD events (nil), lipids (only TC used as the others were different at baseline), adverse events, serum fatty acids
Response to contact: yes

Notes Study funding: unclear

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated list
Allocation concealment (selection bias)	Unclear risk	No details. They received their initial allocation in a sealed box in person; subsequent doses arrived in the post
Blinding of participants and personnel (performance bias)	Unclear risk	No further details beyond stating "double blind"
Blinding of outcome assessment (detection bias)	Unclear risk	No details
Incomplete outcome data (attrition bias)	Low risk	No attrition
Selective reporting (reporting bias)	Unclear risk	No trial register or protocol found
Attention	Low risk	No difference between groups
Compliance	Unclear risk	Measured but no results
Other bias	Low risk	None noted

Gill 2012 – NCT00350194 [181 182]

Methods RCT, parallel, (EPA + DHA vs unclear), 24 months
Summary risk of bias: moderate or high

Participants Adults with Metabolic syndrome
N: unclear, total randomised 101
Level of risk for CVD: low
Men: 47% total, no details by group
Mean age in years (SD): 55 (10) total
Age range: 18-75 years
Smokers: 0% intervention, 0% control
Hypertension: not reported
Medications taken by at least 50% of those in the control group: not reported
Medications taken by 20%-49% of those in the control group: not reported
Medications taken by some, but less than 20% of the control group: not reported
Location: USA
Ethnicity: unclear

Interventions Type: supplement (fish oil capsules)
Comparison: EPA + DHA vs placebo (unclear what)
Intervention: fO3FA capsules 1.8 g of EPA + DHA daily. Dose: 1.8 g/d EPA + DHA
Control: matching placebo supplement
Compliance: not reported
Length of intervention: 12 months

Outcomes Main study outcome: change in carotid IMT
Dropouts: unclear
Available outcomes: lipids, insulin and glucose are stated as secondary outcomes but no usable data published
Response to contact: no

Notes Results cannot be used as numbers are not reported by study arm.
Study funding: unclear, but mentions that Pfizer, NIH and "Northwest Lipids Clinic" are partners

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias)	Unclear risk	No data
Blinding of outcome assessment (detection bias)	Unclear risk	No data
Incomplete outcome data (attrition bias)	Unclear risk	No data
Selective reporting (reporting bias)	High risk	Inadequate detail in reporting as no full text publication found; Gill 2014 does give detail on carotid IMT, but not on other primary or secondary outcomes. The trial was prospectively registered (registered July 2006, unclear when recruitment started, final data collection 2011, first data published 2012).
Attention	Unclear risk	No data
Compliance	Unclear risk	No data
Other bias	Unclear risk	No data

GISSI-HF 2008 – NCT00336336 [183-210]

Methods Gruppo Italiano per la Sperimentazione della Streptochinasi nell'Infarto Miocardico – Heart Failure (GISSI-HF)
RCT, parallel, 2 arms (n-3 EPA + DHA vs MUFA), 3.9 years
Summary risk of bias: moderate or high

Participants Patients with chronic heart failure
N: 3494 intervention, 3481 control
Level of risk for CVD: high
Men: 77.8% intervention, 78.8% control
Mean age: 67 (11) intervention,67 (11) control
Age range: 18+ years
Smokers: 14.4% intervention, 13.9% control
Hypertension: 54.0% intervention, 55.2% control
Medications taken by at least 50% of those in the control group: ACE inhibitors, beta-blockers, diuretics
Medications taken by 20%-49% of those in the control group: spironolactone, digitalis, oral anticoagulants, aspirin, nitrates, statin
Medications taken by some, but less than 20% of the control group: ARBs, other antiplatelets, calcium channel blockers, amiodarone
Location: Italy
Ethnicity: unclear

Interventions Type: supplement (capsule)
Comparison: EPA + DHA vs MUFA

	Intervention:1 capsule per day of 1 g n-3 mainly EPA and DHA as ethyl esters in the average ratio of 1:1.2. Dose: ~0.866 g/d EPA + DHA Control: 1 g/d matching olive oil placebo capsule Compliance: unclear Length of intervention: median 3.9 years
Outcomes	Main study outcome: time to death or admission to hospital for cardiovascular reasons Dropouts: 34 intervention, 46 control (1004 intervention and 1029 control stopped study treatment) Available outcomes: mortality, CV mortality, MI, stroke, new heart failure, incident AF, resumed arrhythmia gatalitis Response to contact: yes (no data provided)
Notes	Study funding: funders included Pfizer, AstraZeneca and others

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomly assigned (with stratification by site) to treatment groups
Allocation concealment (selection bias)	Low risk	Randomly assigned (with stratification by site) to treatment groups by a concealed computerised telephone randomisation system
Blinding of participants and personnel (performance bias)	Unclear risk	Double blinding stated, but taste not reported as masked and blinding of participants not checked
Blinding of outcome assessment (detection bias)	Low risk	All events "adjudicated blindly by an ad-hoc committee on the basis of pre-agreed definitions and procedures"
Incomplete outcome data (attrition bias)	Low risk	Reasons for attrition and exclusion were stated and addressed. Numbers in each intervention compared to numbers were similar.
Selective reporting (reporting bias)	Unclear risk	Published rationale and design (Tavazzi 2004) suggested primary outcomes were deaths and death or CV hospitalisation (published). Secondary outcomes not stated and no trials registry entry found
Attention	Low risk	Scheduled clinic visits at 1, 3, 6 months then 6-monthly until the end of the trial (for both arms)
Compliance	Unclear risk	No details
Other bias	Low risk	No further bias noted

GISSI-P 1999 [211-227]

Methods	Gruppo Italiano per la Sperimentazione della Streptochinasi nell'Infarto Miocardico – Prevention (GISSI-P) RCT, 2 × 2 (n-3 EPA + DHA vs nil), 42 months Summary risk of bias: moderate or high
Participants	People with recent (≤ 3 months) myocardial infarction N: 5666 intervention, 5658 control (99.9% follow-up at study end) Level of risk for CVD: high Men: 85.7% intervention, 84.9% control Mean age in years (SD): 59.3 (10.6) intervention, 59.5 (10.5) years control Age range: < 50 to > 80 Smokers: 42.6% intervention, 42.3% control Hypertension: 36.2% intervention, 34.9% control Medications taken by at least 50% of those in the control group: anti-platelet Medications taken by 20%-49% of those in the control group: ACE inhibitors, beta-blockers Medications taken by some, but less than 20% of the control group: lipid lowering Location: Italy Ethnicity: not reported
Interventions	Type: supplement (capsule)

Comparison: EPA + DHA vs nil
Intervention: gelatin capsules of omega-3-acid ethyl esters 90 (Omacor), 1/d (850-882 mg/d EPA + DHA daily, ratio 1:2)
Dose: ~0.866 g/d EPA + DHA
Control: nil (no placebo)
Compliance: capsule counts, 11.6% had stopped taking Omacor by 12 months, 28.5% by the end of the study
Duration of intervention: median follow-up 40 months

Outcomes Main study outcome: all-cause mortality, CV mortality, stroke, MI
Dropouts: unclear (however, all randomised were included in analyses)
Available outcomes: total, sudden and CV deaths, MI, stroke, angioplasty or CABG, angina, CHD, cancer diagnosis, cancer death, combined CV events, side effects
Response to contact: no

Notes Numbers are slightly different in different publications (Lancet 1999 paper used as main source). Half of both groups were on vitamin E supplements (300 mg/d synthetic α-tocopherol) as this was the other 2 × 2 intervention.
Study funding: Bristol Meyers Squibb, Pharmacia Upjohn, Societa Produtti Antibiotici, Pfizer

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Telephone/computer network, stratified by hospital, based on a biased coin algorithm
Allocation concealment (selection bias)	Low risk	Randomisation by telephone with the coordinating centre
Blinding of participants and personnel (performance bias)	High risk	No placebo intervention (capsule vs nil) so participants not blinded
Blinding of outcome assessment (detection bias)	Low risk	"validation of clinical events ... was assured by an ad-hoc committee of expert cardiologists and neurologists blinded to patients treatment assignment"
Incomplete outcome data (attrition bias)	Low risk	Clearly described, good follow-up (< 28% dropped out over 3.5 years)
Selective reporting (reporting bias)	Unclear risk	No study protocol or trials registry entry was found
Attention	Low risk	Slight as no placebo, otherwise similar
Compliance	Unclear risk	Capsule counts, 11.6% had stopped taking Omacor by 12 months, 28.5% by the end of the study
Other bias	Low risk	No further bias noted

GLAMT 1993 [228]

Methods Gamma Linolenic Acid Multicentre Trial (GLAMT)
RCT, 2-arm, parallel (n6 GLA vs non-fat), 1 year
Summary risk of bias: moderate to high

Participants People with mild diabetic neuropathy
CVD risk: moderate
Control: randomised 57, analysed 48 (with ≥ 1 evaluation)
Intervention: randomised 54, analysed 52
Mean years in trial: control 1.0, randomised 1.0
% male: intervention 67%, control 79%,
Age, mean (SD) years: intervention 53.3 (11.1), control 52.9 (11.4)
Age range: unclear
Smokers: unclear
Hypertension: unclear
Medications taken by ≥ 50% of those in the control group: insulin
Medications taken by 20%-49% of those in the control group: not reported
Medications taken by some, but < 20% of the control group: not reported

Location: UK and Finland
Ethnicity: not reported

Interventions Type: supplement
Comparison: GLA (n-6) vs placebo (paraffin)
Control aims: 12 capsules/d paraffin
Intervention aims: 12 capsules/d evening primrose oil (EP4, equivalent to Epogam): 0.48 g/d GLA plus LA (stated as the major constituent, dose not given, if assume 0.7 g/capsule then 8.4 g/d*)
Dose aim: increase 0.48 g/d GLA or 4 kcal or **0.2% E GLA,** increase ~8.4 g/d LA or 76 kcal or **3.8% E LA, total 4% E n6**
Baseline PUFA: unclear
Compliance by biomarkers: unclear, no serum TC or tissue fatty acid levels reported
Compliance by dietary intake: unclear

- Energy intake: not reported
- Total fat intake: not reported
- SFA intake: not reported
- PUFA intake: not reported
- PUFA n-3 intake: not reported
- PUFA n-6 intake: not reported
- Trans fat intake: not reported
- MUFA intake: not reported
- CHO intake: not reported
- Sugars intake: not reported
- Protein intake: not reported
- Alcohol intake: not reported

Compliance, other methods: not reported
Inclusion basis: aimed to increase GLA intake rather than total PUFA.
Dose aim appeared to be ~4% E PUFA (from omega-6 data), >10% more than assumed baseline of 6% E PUFA. No confirmatory biomarker or intake data
PUFA dose: 4% E PUFA (estimated from aim)
Duration of intervention: 1 year

Outcomes Main trial outcome: measures of diabetic neuropathy
Dropouts: intervention 10, control 17
Available outcomes: MI, cancer (no deaths)
Response to contact: contact attempted but no response to date.

Notes Trial funding: Scotia Pharmaceuticals

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias)	Low risk	Described as double-blind, and Quote: "Active and placebo capsules were indistinguishable in taste or appearance"
Blinding of outcome assessment (detection bias)	Unclear risk	Unclear, though trial described as double-blind no methods or statement of blinding of outcome assessors was mentioned
Incomplete outcome data (attrition bias)	High risk	Reasons for withdrawal usually given, but high and dissimilar
Selective reporting (reporting bias)	Unclear risk	No clear protocol or trials registry entry found
Attention	Low risk	Appeared similar
Compliance	Unclear risk	Neither tissue PUFA biomarkers nor TC data reported
Other bias	Low risk	None identified

Greenfield 1993 [229]

Methods RCT, parallel, 3 arms (n3 EPA vs n6 GLA vs MUFA), 6 months
Summary risk of bias: Moderate to high
Aim: "to determine whether fatty acid supplementation could alter the composition of cell membranes... and controlling symptoms, reducing relapse rates and improving histological proctitis in patients with ulcerative colitis"

Participants People with stable (treatment unchanged for at least 6 weeks) ulcerative colitis (diagnosed by standard endoscopic, histological and radiological criteria) for more than a year and receiving less than 10mg prednisolone/day.
N: 16 int.1, 19 int.2, 8 control. (analysed: 13 int.1, 13 int.2, 7 cont.)
Level of risk for CVD: Low
Male: 75% int.1, 68.4% int.2, 62.5% control.
Mean age (SEM): 57.3(4.4) int.1, 51.3(3.4) int.2, 35 (6.8) control
Age range: NR
Smokers: NR
Hypertension: NR
Medications taken by at least 50% of those in the control group: 5ASA (mesalazine/ sulphasalazine)
Medications taken by 20-49% of those in the control group:
Medications taken by some, but less than 20% of the control group: Rectal steroids
Location: UK
Ethnicity: NR

Interventions Type: supplement (capsules containing EPA+DHA or borage/EPO or olive oil)
Comparison: EPA + DHA vs n6 vs MUFA
Intervention 1: 6g/d (6 capsules) containing 1.116g/d EPA & 0.726g/d DHA (total n3 PUFA 1.842g/d PLUS 0.318g/d n6 PUFA)*: EPA+DHA 1.84g/d
Intervention 2: 1.5g/d (6 capsules) containing 0.840g/d LA & 0.232g/d GLA (total n6 PUFA 1.072g/d)*
Control: olive oil 6g/day (6 capsules)*
*each patient received a loading dose of 12 capsules per day for one month at the start of the trial followed by 6 capsules daily for the remaining 5 months, all oils provided by Seven Seas Healthcare, Kingston upon Hull, UK
PUFA Dose n3: (intended) increase 1.84g/d EPA+DHA, 0.8**%E n3, 0.8%E PUFA**
PUFA Dose n6: (intended) increase 1.07g/d EPA+DHA, 0.5**%E n6, 0.5%E PUFA**
Compliance: erythrocyte FA composition
Duration of intervention: 24 wks/6 months

Outcomes Main study outcome: Relapse rate for UC measured by stool frequency, stool consistency and rectal bleeding
Dropouts: 3 int.1, 3 int.2, 1 control
Available outcomes: UC relapse, stool frequency, stool consistency, rectal bleeding, FA composition of red cell membranes (ESR reported as follows “there were no differences in erythrocyte sedimentation rate between the three treatment arms at any time point”)

Notes Study stated as supported by and capsules provided by Seven Seas Healthcare.
Author response: author replied that there were no deaths and provided details on study methodology

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient detail re method – envelope randomisation method with help of clinic nurse
Allocation concealment (selection bias)	Low risk	According to author correspondence, allocation could not be altered following assignment
Blinding of participants and personnel (performance bias)	High risk	Participants and outcome assessors unaware of allocation but capsules likely to be different sizes between placebo/int.1 (1g caps) and int.2 (250mg caps); peppermint oil used to mask taste but fishy taste reported as a side-effect for some participants.
Blinding of outcome assessment (detection bias)	Unclear risk	Insufficient information provided
Incomplete outcome data (attrition bias)	Low risk	Data not used in final analysis for 7 patients who dropped out (16%)

Selective reporting (reporting bias)	Unclear risk	No trial registration found
Attention	Low risk	The study only differed by the content of the capsules, but the assessment schedule was not stated to differ between the two arms
Compliance	Low risk	Fatty acid status data suggests C-RoB is low
Other bias	Low risk	None noted

Gruenwald 2009 [230]

Methods RCT, 2arm, parallel (EPA+DHA vs non), 6 months
Summary risk of bias: Low

Participants People with moderate to severe hip/knee osteoarthritis
CVD risk: Low
N: 90 int., 87 control (analysed 80 int, 84 control for the valid case analysis)
% male: cont 36.4%, int 36.7%
Age, mean (sd) yrs: control 62.4 (8), intervention 62.2 (7.7)
Age range: 41-75 control, 40-74 int.
Smokers: unclear. BMI, mean (SD): 29.1 (5.2) cont., 29.6 (5.1) int.
Hypertension: unclear
Medications taken by at least 50% of those in the control group: Glucosamine sulfate, Vitamin D, Vitamin A
Medications taken by 20-49% of those in the control group: NR
Medications taken by some, but less than 20% of the control group: NR
Location: Germany
Ethnicity: NR

Interventions Type: Supplement
Comparison: LCN3+ glucosamine sulfate vs glucosamine sulfate alone
Intervention: 1 capsule tid. Each capsule contained 500mg glucosamine sulfate 2 KCl; 444 mg fish oil; 200mg omega-3-fatty acids; 120µg vitamin A; 0.75µg vitamin D; 1.5mg vitamin E. **Dose:** 600mg/d EPA+DHA
Control: 1 capsule tid. Each capsule contained 500mg glucosamine sulfate 2 KCl; 444 mg mixture of several oils [oils without EPA and DHA] containing palm oil [70%], rapeseed oil [15%], and sunflower oil [15%]; 120 µg vitamin A; 0.75 µg vitamin D; 1.5 mg vitamin E.
Compliance: Measured by counting returned capsules. Defined as taking not less than 75% of the product for 25-27 weeks. 44% int., 32% control.
Duration of intervention: 6 months

Outcomes Main study outcome: WOMAC score
Dropouts: unclear (ITT analysis performed as well as valid case analysis excluding 13 participants for protocol violations)
Available outcomes: WOMAC total, pain, stiffness and function sub-scores. However, no variance provided and hence data doesn't contribute to the meta-analysis.
Response to contact: Not attempted

Notes Study funding: funded by Seven Seas

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Block randomization, with a block size of four, and the randomization code were created externally using the randomization scheme EDGAR
Allocation concealment (selection bias)	Low risk	Codes were created externally
Blinding of participants and personnel (performance bias)	Low risk	Capsules did not differ in colour, size, smell, or taste. Personnel gave sealed polythene containers of the investigational product.
Blinding of outcome assessment (detection bias)	Low risk	Physical outcomes assessed by investigators who were blinded to the treatment.

Incomplete outcome data (attrition bias)	Low risk	Full case analysis was conducted and few losses evenly distributed.
Selective reporting (reporting bias)	Unclear risk	No protocol or trial registration
Attention	Low risk	Same attention
Compliance	High risk	Only 44% of the intervention group and 32% of the control group were considered compliant (i.e. consumed a minimum 75% for at least 25 weeks)
Other bias	Unclear risk	None noted

HARP 1995 – NCT00000461 [231-233]

Methods	Harvard Atherosclerosis Reversibility Project (HARP) RCT, (n-3 EPA + DHA vs MUFA), 24 months Summary risk of bias: moderate or high
Participants	Patients with coronary heart disease N: 41 intervention, 39 control (99.9% follow-up at study end) Level of risk for CVD: high Men: 93.5% intervention, 92.9 % control Mean age in years (SD): 62 (7) intervention, 62 (7) years control Age range: 30-75 Smokers: 0% (exclusion criteria) Hypertension: 48% intervention, 36% control Medications taken by at least 50% of those in the control group: beta blockers, antiplatelet agents Medications taken by 20%-49% of those in the control group: calcium channel blockers, nitrates Medications taken by some, but less than 20% of the control group: ACE inhibitors, oral hypoglycaemic drugs Location: USA Ethnicity: not reported
Interventions	Type: supplement (capsule) Comparison: LCn3 vs MUFA Intervention: 12 fish oil capsules/day (Promega, Parke-Davis) in divided doses, preferably after meals. Each fish oil capsule contained 500 mg of n-3 polyunsaturated fatty acids composed of EPA (240 mg), DHA (160 mg) and other (100 mg) (mainly DPA) providing total daily dose of 6 g of n-3 fatty acids. Dose: 6 g/d LCn3 Control: olive oil capsules identical in appearance to the fish oil capsules. Compliance: capsule counts and serum level measurements. Adherence averaged 80% intervention, and 90% control with significant levels of adipose n-3 fatty acids in the fish oil group. Duration of intervention: average 28 months
Outcomes	Main study outcome: regression of coronary artery lesions Dropouts: 10 intervention, 11 control Available outcomes: all-cause and CV deaths, fatal and non-fatal MI, stroke, angioplasty or CABG, unstable angina, CHD, cancer diagnosis, combined CV events, side effects Response to contact: yes
Notes	Study funding: National Heart, Lung, and Blood Institute (NHLBI), National Institutes of Health, Bethesda, Maryland, Warner Lambert-Parke Davis, East Hanover, New Jersey; and by an Established Investigator Award to Dr Sacks from the American Heart Association, Dallas, Texas

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "randomization" stratified by clinical management regime and total/HDL cholesterol ratio
Allocation concealment (selection bias)	Unclear risk	No further details
Blinding of participants and personnel (performance bias)	Unclear risk	Quote: "patients and personnel responsible for lab measurements, cardiac catheterization, and analysis of angiography films were blinded to the treatment

		assignment". Although capsules were identical in appearance, no information on their taste and smell
Blinding of outcome assessment (detection bias)	Low risk	Quote: "patients and personnel responsible for lab measurements, cardiac catheterization, and analysis of angiography films were blinded to the treatment assignment"
Incomplete outcome data (attrition bias)	Low risk	Low attrition rate over 28 months and all reasons are well documented
Selective reporting (reporting bias)	High risk	Trial registered retrospectively after publication
Attention	Low risk	Nothing in description implies the arms were treated differently
Compliance	Low risk	Very clear (P < 0.001) differences between arms for the 3 main n-3 components in the fish oil
Other bias	Low risk	None noted

Hashimoto 2012 [234 235]

Methods	RCT, parallel, (n3 EPA+DHA vs MUFA), 12 months Summary risk of bias: Moderate or high
Participants	Healthy older people from Japan N: 57 int., 54 control. (analysed, int: 53 cont: 48) Level of risk for CVD: Low Male: 63% int., 61% control. Mean age (sd): 72.0 (7.6) int., 72.9 (7.8) control Age range: NR but ≥57 years inclusion criteria Smokers: NR Hypertension: NR Medications taken by at least 50% of those in the control group: NR Medications taken by 20-49% of those in the control group: NR Medications taken by some, but less than 20% of the control group: NR Location: Japan Ethnicity: Japanese
Interventions	Type: food supplement (fish sausage with EPA+DHA or olive oil) Comparison: EPA & DHA vs MUFA Intervention: 2 fish sausages/d (including 1.72g/d DHA + 0.4g/d EPA, Resara, Maruha Nichiro Foods): EPA + DHA 2.12g/d Control: 2 fish sausages/d (including 0.1g/d DHA + 0.02g/d EPA plus olive oil). The sausages were indistinguishable re colour taste and flavour. Compliance: Sausages eaten were recorded in a diary and assessed monthly to encourage compliance. Plasma DHA and EPA levels increased in the intervention group, and decreased in controls Duration of intervention: 12 months
Outcomes	Main study outcome: cognitive decline Dropouts: 6 int., 6 control Available outcomes: cognitive outcomes (but not in a useable format)
Notes	The study was 24 months long, but in the second 12 months all participants received the DHA +EPA supplemented sausages. Study funding: Ministry of Education, Culture, Sports, Sciences and Technology of Japan

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"randomised"
Allocation concealment (selection bias)	Unclear risk	Not reported

Blinding of participants and personnel (performance bias)	Low risk	"All study staff and subjects were blinded to the food products". The sausages were reported as indistinguishable re colour, taste and flavour.
Blinding of outcome assessment (detection bias)	Low risk	"double blind" and "All study staff and subjects were blinded to the food products".
Incomplete outcome data (attrition bias)	Unclear risk	Flow described but reasons for exclusion and causes of disease not documented. However, <10% lost over 3 years.
Selective reporting (reporting bias)	Unclear risk	No trials registry entry or protocol found.
Attention	Low risk	Sausages equivalent, and staff blinded
Compliance	Low risk	Sausages eaten were recorded in a diary and assessed monthly to encourage compliance. Plasma DHA and EPA levels increased in the intervention group, and decreased in controls
Other bias	Low risk	None noted

Hashimoto 2016 [236-238]

Methods	RCT, parallel, (n3 DHA high dose vs n3 DHA low dose), 12 months Summary risk of bias: Moderate or high
Participants	Healthy older people from Japan N: 43 int., 32 control. (analysed, int: 39 cont: 27) Level of risk for CVD: Low Male: 12% int., 16% control. Mean age (sd): 87.6 (3.3) int., 89.6 (5.1) control Age range: NR but ≥75 years inclusion criteria Smokers: NR Hypertension: NR Medications taken by at least 50% of those in the control group: NR Medications taken by 20-49% of those in the control group: NR Medications taken by some, but less than 20% of the control group: NR Location: Japan Ethnicity: Japanese Depression: General population (low risk) Anxiety: General population (low risk)
Interventions	Type: food supplement (fish sausage with EPA+DHA or olive oil) Comparison: EPA & DHA vs MUFA Intervention: daily fish sausages (including 0.86g DHA + 0.20g EPA, Resara, Maruha Nichiro Corp) Control: daily fish sausages/d (including 0.05g DHA + 0.02g EPA, Kururunpack, Maruha Nichiro Corp). Compliance: Unclear how well sausages were eaten, but erythrocyte DHA fell in control group and was maintained in the intervention group. Erythrocyte plasma membrane EPA was statistically significantly higher in the intervention group than control at 12 months. Duration of intervention: 12 months
Outcomes	Main study outcome: cognitive decline Dropouts: 4 int., 5 control Available outcomes: cognitive outcomes (MMSE, Hasegawa's Dementia Scale-Revised), caregiver burden, depression
Notes	Study funding: Ministry of Education, Culture, Sports, Sciences and Technology of Japan, sausages provided free by the food company

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"randomly allocated"

Allocation concealment (selection bias)	Unclear risk	Unclear, no details provided.
Blinding of participants and personnel (performance bias)	Unclear risk	"all study participants were blinded to the food products, as all participant meals were cooked by staff in the kitchen of the care facility or nursing home" - taste and appearance not mentioned.
Blinding of outcome assessment (detection bias)	Unclear risk	"scales were self-administered, with possible assistance from neuropsychologists and/or hospital nurses if necessary"
Incomplete outcome data (attrition bias)	High risk	Aside from those who dropped out, not all participants provided data for all outcome tests - numbers and reasons are unclear
Selective reporting (reporting bias)	Unclear risk	No study registration or protocol was found
Attention	Low risk	The only difference appears to be the type of sausages provided
Compliance	Low risk	Erythrocyte plasma membrane EPA and DHA measured at 12 months, and EPA was statistically significantly higher in the intervention group than control at 12 months.
Other bias	Low risk	None noted

Hawthorne 1992 [239]

Methods RCT, parallel arm, placebo controlled (n3 EPA vs MUFA), 12 months
Summary risk of bias: Moderate or high
Aim: "to evaluate the clinical effects of fish oil supplementation in ulcerative colitis"

Participants Individuals with established diagnosis of ulcerative colitis diagnosed on the basis of rectal biopsy and barium enema or colonoscopy. Entry restricted to patients who had had two or more relapses in the previous three years.
N: 46 int., 50 control [entry in relapse: 26 int., 30 cont; entry in remission: 20 int., 20 cont] (analysed – int: 45 cont: 42; states ITT analysis but figures reported are for those who completed the trial only)
Level of risk for CVD: Low
Male: 69% int., 40.5% control.
Mean age (sd): 44 int.; 49 cont. (SD not reported)
Age range: 17-73 int., 20-77 control
Smokers: 2.2% int., 2.4% control
Hypertension: NR
Medications taken by at least 50% of those in the control group: sulphasalazine or mesalazine (71%)
Medications taken by 20-49% of those in the control group: all patients entering the trial in relapse appear to be on 20mg prednisolone or less = 27% control group
Medications taken by some, but less than 20% of the control group: NSAIDs (5%)
Location: UK
Ethnicity: NR
UC distribution in colorectum:
Whole colorectum: 33% int., 43% control
Left-sided disease only: 27% int., 24% control
Sigmoid disease only: 38% int., 33% control
Proctitis only: 2% int.; 0% control
Mean duration of colitis (years): 7 int., 9 cont.
Median number of relapses in previous year: 2 int., 3 cont.

Interventions Type: supplement (free fish oil triglyceride concentrate HiEPA or olive oil)
Comparison: EPA+DHA vs MUFA
Intervention: 20mls free oil per day (including 25% EPA + 6% DHA, or 4.5g/d EPA plus 1.08g/d DHA; Scotia Pharmaceuticals, Surrey, UK): EPA+DHA 5.58g/d
Control: 20mls olive oil per day (including 73% MUFA; Scotia Pharmaceuticals, Surrey, UK)
PUFA Dose: (intended) increase 5.58g/d EPA+DHA, 2.5**%E n-3, 2.5 %E PUFA**
Compliance: count of bottles of oil used during each two month period, adiposity (red cell membrane EPA incorporation), 2 x 7-day semi-weighted diet diaries in both first and last 2m of study (pts enrolled in Nottingham only, n=76). Median consumption of oil: 20ml daily in both arms; bottle counts:

intervention - median 650 (360-720) ml/month; control – median 635 (270-720) ml/month, with no fall during the year. Good compliance confirmed by red cell membrane incorporation of EPA in int. group only throughout follow-up period.
Duration of intervention: 12 months

Outcomes Main study outcome: relapse rate of UC for all patients achieving stable remission during the trial
Dropouts: 4 int., 5 control
Available outcomes: overall time spent in remission; treatment of relapse; rate of achieving remission off corticosteroids; corticosteroid usage at 1 and 2 months; red cell membrane fatty acid levels.

Notes Standard drug therapy was given in addition to intervention/placebo throughout trial. Study funding: supported by a research grant from Scotia Pharmaceuticals and the British Digestive Foundation, UK

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"double-blind randomisation in blocks of 4 – code held by pharmacy"
Allocation concealment (selection bias)	Low risk	Confirmed in personal communication – author states that those recruiting participants were not able to alter allocation once assigned.
Blinding of participants and personnel (performance bias)	High risk	Although placebo used, study oils taken as free oils so taste not disguised.
Blinding of outcome assessment (detection bias)	Unclear risk	Although personal communication states that the outcome assessors were not aware of the assigned treatment and 'patients were asked not to comment on the taste to the clinician', patients could have revealed this information during assessment
Incomplete outcome data (attrition bias)	Unclear risk	Primary outcome reported only for participants who completed the trial even though ITT analysis is stated as having been performed as a secondary analysis (actual figures not provided).
Selective reporting (reporting bias)	Unclear risk	No study registration or protocol was found
Attention	Unclear risk	Patients were able to make unscheduled visits if symptoms suggesting relapse developed – no indication of how many patients from each arm attended an unscheduled visit.
Compliance	Low risk	Median consumption of oil: 20ml daily in both arms; bottle counts: intervention - median 650 (360-720) ml/month; control – median 635 (270-720) ml/month, with no fall during the year. Good compliance confirmed by red cell membrane incorporation of EPA in int. group only throughout follow-up period.
Other bias	Low risk	None noted

Heine 1989 [240]

Methods RCT, cross-over, (n6 LA vs mixed fat), 6 months
Summary risk of bias: Moderate or high

Participants Non-insulin dependent diabetic patients
N: 17 patients overall (analysed, int: 14 cont: 14)
Level of risk for CVD: Moderate
Male: 57% int., 57% control.
Mean age (sd): 51.9 (11.6) int., 51.9 (11.6) control
Age range: 30-70 years
Smokers: NR
Hypertension: NR
Medications taken by at least 50% of those in the control group: NR

Medications taken by 20-49% of those in the control group: Glibenclamide
Medications taken by some, but less than 20% of the control group: Gliclazide, tolbutamide
Location: The Netherlands
Ethnicity: NR

Interventions Type: supplemented food (oils and margarines with LA or SFA)
Comparison: LA vs SFA
Intervention: LA enriched oils and margarines (P:S ratio 1.0): LA quantity unclear
Control: Substitution of LA oils and margarines for SFA (P:S ratio 0.3)
PUFA Dose: (intended) increase unclear
Compliance: 1-wk dietary recall and assessment of fatty acids of cholesteryl esters
Duration of intervention: 30 weeks

Outcomes Main study outcome: Lipoproteins and insulin sensitivity
Dropouts: 3 overall
Available outcomes: Lipids, glucose, HbA1c, weight, insulin (HDL subfractions as means over the period and bp at 6 months not used)

Notes Study funding: NR

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"randomized"
Allocation concealment (selection bias)	Unclear risk	"randomized"
Blinding of participants and personnel (performance bias)	Unclear risk	NR
Blinding of outcome assessment (detection bias)	Unclear risk	NR
Incomplete outcome data (attrition bias)	High risk	Drop out >20% in 3 months
Selective reporting (reporting bias)	Unclear risk	No registry or protocol identified
Attention	Low risk	The study only differed by the content of the oils and margarines. The assessment schedule was not stated to differ between the two arms
Compliance	Low risk	Dietary recall confirmed by significant increase in LA in the intervention group
Other bias	Low risk	None noted

HERO 2009 – ACTRN12607000600448 [241 242]

Methods Healthy Eating to Reduce Overweight in people with type 2 diabetes (HERO)
RCT, parallel, (n-3 ALA vs low n-3), 12 months
Summary risk of bias: moderate or high

Participants Overweight adults with non-insulin treated diabetes
N: 26 intervention, 24 control (analysed, intervention: 18 control: 17)
Level of risk for CVD: moderate
Male %: not reported
Mean age in years (SD): 54 (8.7), not reported by arm
Age range: 33-70 years
Smokers: not reported
Hypertension: not reported
Medications taken by at least 50% of those in the control group: lipid lowering drugs, oral hypoglycaemics
Medications taken by 20%-49% of those in the control group: not reported
Medications taken by some, but less than 20% of the control group: not reported
Location: Australia
Ethnicity: not reported

Interventions Type: food supplement (walnuts)

Comparison: ALA vs nil
Intervention: 30 g/d snack portions of walnuts (provided 10% MUFA, 10% E PUFA, and a P/S ratio of 1.0) and advised not to take fish oil supplements. ALA dose not reported. Dose: ~3 g/d ALA based on 30 g/d intake of walnuts
Control: no supplements
Both groups were given low-fat isocaloric dietary advice (30% E fat (10% E SFA, 15% E MUFA; 5% E PUFA, P/S ratio of 0.5), 20% E protein and 50% E CHO) plus advice to brisk walk 30 min × 3 times/week
Compliance: measured by erythrocyte membrane fatty acid levels which were similar in both groups
Duration of intervention: 12 months

Outcomes Main study outcome: change in body weight and % body fat
Dropouts: 8 intervention, 5 control
Available outcomes: all-cause mortality (nil deaths), weight, visceral adipose tissue, lipids, glucose, insulin, HbA1c (body fat % and subcutaneous adipose tissue measured but too different at baseline to use)
Response to contact: not yet attempted

Notes Body fat % was too different between groups at baseline hence data not used
Study funding: California Walnuts Commission

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was conducted using a computerised random number generator by a researcher independent of the subject interface.
Allocation concealment (selection bias)	Unclear risk	No further details
Blinding of participants and personnel (performance bias)	High risk	Quote: "Subjects, but not dietitians, were blinded to the type of overall diet (a pre-packaged 30 g snack portion of walnuts was given to the walnut group unbeknown to the controls)". However, there was no placebo supplement, so blinding easily broken
Blinding of outcome assessment (detection bias)	Unclear risk	Paper states "code was concealed from the researchers collecting data, as well as from subjects." However as participants could not be blinded outcome assessors may not have been (problem for measures of adiposity, not for biochemical measures)
Incomplete outcome data (attrition bias)	High risk	High dropout rate 35 of 50 analysed (30% attrition rate)
Selective reporting (reporting bias)	Unclear risk	Trial was registered post analysis
Attention	Low risk	Both groups appear to have had same level of attention
Compliance	High risk	ALA levels almost exactly the same in intervention and control
Other bias	Low risk	None noted

Higashihara 2010 [243]

Methods RCT, parallel, (n3 EPA vs nil), 24 months
Summary risk of bias: Moderate or high

Participants Prostate cancer patients whose PSA levels were less than 0.2 ng/ml 3 months after prostatectomy (n=62)
N: 34 int., 34 control. (analysed, int: 32 cont: 30)
Level of risk for CVD: low
Male: 100% int., 100% control.
Mean age (sd): 58 (5) int., 58 (7) control
Age range: unclear
Smokers: NR

Hypertension: NR
Medications taken by at least 50% of those in the control group: NR
Medications taken by 20-49% of those in the control group: NR
Medications taken by some, but less than 20% of the control group: NR
Location: Japan
Ethnicity: NR

Interventions Intervention EPA 2.4 g/d for 2 years
Control group: no treatment
Dose: increase 2.4g/d, **1.1%E EPA, 1.1%E PUFA**

Outcomes Main study outcome: PSA
Dropouts: 2 int., 4 control
Available outcomes: Changes to Prostate-specific antigen (PSA) after prostatectomy
Luteinizing hormone (mIU/ml) at 6 months, 24 months and recurrence
Total testosterone (ng/dl) at 6 months, 24 months and recurrence

Notes Study funding: EPA ethyl ester capsules (Epadel-S®) and research funds were provided by Mochida Pharmaceutical Co., Ltd. (Tokyo, Japan) to each institute.
Author contact: not yet

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation process not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias)	High risk	The control group received no treatment, so blinding unlikely
Blinding of outcome assessment (detection bias)	Unclear risk	Not described
Incomplete outcome data (attrition bias)	Low risk	Attrition reported with reasons (9%)
Selective reporting (reporting bias)	Unclear risk	No trials registry entry found
Attention	Unclear risk	Not described (N.B. the control group received no treatment)
Compliance	Low risk	Semi-quantitative food-frequency questionnaire. Erythrocyte EPA, DHA and DPA all statistically significantly higher in intervention group than control at 24 months.
Other bias	Low risk	None noted

Houtsmuller 1979 [244-246]

Methods RCT, parallel, (increase LA vs usual diet), 72 months maximum
Summary risk of bias: moderate or high

Participants Adults with newly diagnosed diabetes
N: 51 intervention, 51 control (analysed unclear intervention, unclear control)
Level of risk for CVD: moderate
Male: 56% overall (not stated by intervention arm)
Mean age (SD): not reported intervention, not reported control
Age range: not reported
Smokers: not reported
Hypertension: not reported
Medications taken by ≥ 50% of those in the control group: not reported
Medications taken by 20%-49% of those in the control group: not reported
Medications taken by some, but < 20% of the control group: statins (probably)
Location: Netherlands
Ethnicity: not reported

Interventions Type: dietary advice

Comparison: omega-6 vs SFA and CHO
Intervention: aims total fat 40% E, 1/3 LA, CHO 45% E, protein 15% E; methods unclear, surveyed by dietitian. Intervention appears to have been delivered by dietitian but no details on format or frequency.
Control: aims SFA 35% E, CHO 50% E, protein 15% E; methods unclear, surveyed by dietitian
Dose aims: increase **~9% E LA** (aims imply no LA in control, but paper states LA was 4 x higher in intervention than control, est 3% E control, 12% E int, so increase of ~9% E)
Baseline PUFA: unclear
Compliance by biomarkers: good, serum TC significantly reduced in intervention compared to control (-0.47 mmol/L, 95% CI -0.76 to -0.18), no significant differences in men, but significant improvements in women from 3 years.
Compliance by dietary intake: unclear (not reported)

- Energy intake: not reported
- Total fat intake: not reported
- SFA intake: not reported
- PUFA intake: not reported
- PUFA n-3 intake: not reported
- PUFA n-6 intake: not reported
- Trans fat intake: not reported
- MUFA intake: not reported
- CHO intake: not reported
- Sugars intake: not reported
- Protein intake: not reported
- Alcohol intake: not reported

Compliance, other measures: not reported
Inclusion basis: aimed to increase LA, not total PUFA. Appears to have increased LA by ~9% E so assume increase in total PUFA also ~9% E, > 10% increase from control group baseline of ~3% E from PUFA
PUFA dose: 9% E PUFA
Duration of intervention: 72 months

Outcomes Main trial outcome: progression of diabetic retinopathy
Dropouts: unclear intervention, unclear control
Available outcomes: CV events (total MI and angina), TC, TGs (data read off graph), CHD mortality (fatal MI), CHD events (MI, angina), progression of retinopathy
Response to contact: contact attempted but no response to date.

Notes Trial funding: Dutch Heart Foundation

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Participants matched in pairs then randomised
Allocation concealment (selection bias)	Unclear risk	Randomisation method not clearly described
Blinding of participants and personnel (performance bias)	Unclear risk	Unclear, though unlikely as dietary advice provided
Blinding of outcome assessment (detection bias)	Unclear risk	Blinding of outcome assessors not mentioned
Incomplete outcome data (attrition bias)	Unclear risk	Unclear, deaths, cancer and CV events are dropouts, trialists asked for data - unclear if any data missing
Selective reporting (reporting bias)	Unclear risk	No protocol or trials registry entry found
Attention	Unclear risk	No details provided
Compliance	Low risk	TC significantly reduced in intervention compared to control (-0.47 mmol/L, 95% CI -0.76 to -0.18)
Other bias	High risk	Some concerns around fraud in the first author's later research on diet in cancer. No allegations found regarding his research in diabetes (but much information is in Dutch).

Huang 1996 [247]

Methods	RCT, parallel, (n3 EPA+DHA vs n6 LA), 12 months Summary risk of bias: Moderate or high
Participants	Post-surgery patients with Dukes A or B adenocarcinoma of the colon or rectum or severely dysplastic adenomatoid polyps N: 17 int., 10 control. (analysed, int: 12 cont: unclear) Level of risk for CVD: low Male: NR Mean age (sd): NR Age range: NR Smokers: NR Hypertension: NR Medications taken by at least 50% of those in the control group: NR Medications taken by 20-49% of those in the control group: NR Medications taken by some, but less than 20% of the control group: NR Location: USA Ethnicity: NR
Interventions	Type: supplement Comparison: n3 EPA vs n6 Intervention: n3 capsules: 9x 1g/d. EPA: 9x 0.44= 4g DHA: 9 x 0.24 = 2g. Total 4g/d EPA + 2g/d DHA: EPA+DHA 6.0g/d Control: corn oil capsules Compliance: plasma fatty acid levels and capsule counts assessed (82% capsule counts) Duration of intervention: 12 months
Outcomes	Biopsies at baseline, 3 and 6 months for epithelial cells (polyps at 12 months) Main study outcome: colonic epithelial cell proliferation Dropouts: 5 int., unclear control Available outcomes: Plasma phospholipid n6/n3 ratio and Bromodeoxyuridine uptake
Notes	Author contacted re. control group at 12 months (number of participants and number of events) and reasons for attrition from the intervention group (12th May and 7th June 2017)

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	States that they were randomised but no further information
Allocation concealment (selection bias)	Unclear risk	No information given
Blinding of participants and personnel (performance bias)	Unclear risk	No information given
Blinding of outcome assessment (detection bias)	Unclear risk	No information given
Incomplete outcome data (attrition bias)	High risk	Numbers of participants not well explained. Participants in the intervention arm at 12 months drop from n=17 to n=12 without explanation. n for control group at 12 months not given.
Selective reporting (reporting bias)	Unclear risk	No trials registry entry or protocol found
Attention	Low risk	Little information given but appears both had the same follow up
Compliance	Low risk	Plasma fatty acid levels (assessed by plasma phosphorid n-6/n-3 ratio) and capsule counts (which indicate 82% compliance). States that: fish oil supplement was well tolerated with no side effects
Other bias	Low risk	None noted

Hutchins-Wiese 2013 – NCT00634686 [248-251]

Methods RCT, 2arm, parallel (EPA+DHA vs MUFA), 6 months
Summary risk of bias: Moderate/high

Participants Older post-menopausal women.
CVD risk: Low
N: 85 int., 41 control (analysed 79 int., 39 control)
% male: 0%
Age, mean (sd) yrs: control 75 (7), intervention 75 (6)
Age range: ≥65 years
Smokers: 0% control, 2% int. BMI, mean (SD): 26.6 (5) cont., 26.5 (4.9) int.
Hypertension: 93% control, 49% int.
Medications taken by at least 50% of those in the control group: Statins
Medications taken by 20-49% of those in the control group: Diuretics, B blockers, ACE inhibitors, ARB
Medications taken by some, but less than 20% of the control group: Ca channel blockers, NSAID
Location: USA
Ethnicity: Int., 97% white, 2% black & 1% Asian. Control, 99% white, 1% Hispanic

Interventions Type: Supplement
Comparison: LCN3 vs Oleic acid (MUFA)
Intervention: 2 fish oil capsules/ day, Vital Nutrients, Middletown, CT. Each capsule provided 360mg EPA and 240mg DHA. **Dose:** 1.2g/d EPA+DHA
Control: 2 olive oil placebo capsules, 1.8g oleic acid per day, Vital Nutrients, Middletown, CT.
All participants received Citracal tablets (315mg calcium citrate, 200 IU cholecalciferol each; Bayer, Morristown, NJ) and 1000 IU cholecalciferol (Nature's Products Inc., Sunrise, FL) daily. Participants were counselled to maintain a calcium intake of 1500mg per day from diet and supplementation (amounting to 3-4 Citrical/day).
Compliance: Measured by pill counting and erythrocyte FA level. 82% int., & 78% control were compliant with significant increase in DHA level in int.
Duration of intervention: 6 months

Outcomes Main study outcome: Bone turnover markers
Dropouts: 6 int., 2 control
Available outcomes: BMD, Osteocalcin, BAP, NTX, PTH, walking speed, repeated chair rises, hand grip, dietary intake and serum fatty acids.
Response to contact: Not attempted

Notes Study funding: Study supported by the Patrick and Catherine Donaghue Research Foundation and the University of Connecticut Health Center General Clinical Research Center (MO1-RR06192). Vital Nutrients provided fish oil supplement to the study free of charge.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Blocked randomisation 2:1 generated by a research pharmacist with no direct contact with patients.
Allocation concealment (selection bias)	Low risk	Randomised in a double-masked manner. A research pharmacist with no direct contact with patients generated randomisation and labelled all supplement bottles.
Blinding of participants and personnel (performance bias)	Unclear risk	No details
Blinding of outcome assessment (detection bias)	Low risk	All measures were collected by a research assistant blind to treatment randomisation.
Incomplete outcome data (attrition bias)	Low risk	Drop outs similar between groups and reasons explained
Selective reporting (reporting bias)	Unclear risk	Although a trial registration was found, there was no mention/ link between the record and publications. Some of the listed secondary outcomes are not reported.
Attention	Low risk	Appear similar between groups
Compliance	Low risk	See characteristics table

Other bias	Low risk	None noted

IFOMS- Sirtori 1997 [252-256]

Methods Italian Fish Oil Multicentre Study (IFOMS)
RCT, parallel, (n3 EPA+DHA vs MUFA), 6 months
Summary risk of bias: Moderate or high

Participants Patients with hypertriglyceridemia
N: 470 int., 465 control. (analysed, int: 442 cont: 426)
Level of risk for CVD: Moderate
Male: 62.6% int., 62.2% control
Mean age (sd): 58.2 (9.09) int., 58.8 (8.99) control
Age range: NR
Smokers: NR
Hypertension: 67% int., 68% control
Medications taken by at least 50% of those in the control group: Antihypertensives
Medications taken by 20-49% of those in the control group: NR
Medications taken by some, but less than 20% of the control group: NR
Location: Italy
Ethnicity: NR

Interventions Type: supplement (n-3 or olive oil capsules)
Comparison: n-3 vs MUFA
Intervention: n-3 capsules (3g/d for 2 months [1.53g EPA and 1.05g DHA], then 2g/d [1.02g EPA and 0.70g DHA] for 4 months, Escapent, Italy): EPA+DHA 1.72g/d
Control: Olive oil capsules (3g/d for 2 months, then 2g/d for 4 months)
PUFA Dose: (intended) increase ~2.0g/d EPA+DHA, **0.9%E n-3, 0.9%E PUFA**
Compliance: Pill counts and plasma and erythrocyte EPA and DHA
Duration of intervention: 6 months (followed by a 6 month open phase)

Outcomes Main study outcome: Lipids and glucose metabolism
Dropouts: 28 int., 39 control
Available outcomes: Mortality (nil), lipids, glucose, OGTT (area under curve), HbA1c, insulin
Response to contact: Yes

Notes Study funding: Consiglio delle Ricerche of Italy and by a grant-in-aid by Pharmacia and Upjohn, Milan, Italy

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	SAS system “randomized-block technique”
Allocation concealment (selection bias)	Unclear risk	Not detailed
Blinding of participants and personnel (performance bias)	Unclear risk	Not detailed
Blinding of outcome assessment (detection bias)	Unclear risk	Not detailed
Incomplete outcome data (attrition bias)	Low risk	Intention to treat analysis and seemingly balanced drop outs
Selective reporting (reporting bias)	Unclear risk	No registry or protocol identified
Attention	Unclear risk	Not detailed and blinding unclear
Compliance	Unclear risk	Overall compliance >90% (by pill count)
Other bias	Low risk	None noted

Jackson 2016 – NCT01185379 [257]

Methods	RCT, parallel, (n3 DHA vs MUFA), 6 months Summary risk of bias: Moderate or high
Participants	Population: Healthy adults with subjective memory deficit (MMSE ≥26, MAC-Q score > 24) N: 33 int., 32 control. (analysed, int: 30 cont: 28) Level of risk for CVD: Low Male: 39% int., 36% control. Mean age (sd): 60.3 (4.9) int., 59.6 (5.3) control Age range: 50-70 Smokers: NR Hypertension: NR Medications taken by at least 50% of those in the control group: NR Medications taken by 20-49% of those in the control group: NR Medications taken by some, but less than 20% of the control group: NR Location: UK Ethnicity: NR Depression: General population (low risk) Anxiety: General population (low risk)
Interventions	Type: supplement Comparison: DHA-rich fish oil vs high oleic acid sunflower oil & fish oil Intervention: 4 x 500 mg DHA rich tuna oil (896mg DHA, 128mg EPA) / day Control: 2.24 g high oleic acid sunflower oil and 120 mg fish oil (32 mg DHA + EPA) / day (Efalex Active 50+, a dietary supplement containing a number of potentially cognition enhancing components including DHA, phosphatidylserine, vitamin B12, folic acid and Ginkgo biloba), Compliance: Duration of intervention: 6 months
Outcomes	Cerebral haemodynamics Cognitive performance Available outcomes: depression, anxiety, rapid visual information processing accuracy, reaction time, mental fatigue, adverse events, fatty acid status data
Notes	Study funding: Efamol Ltd. provided the capsules and the funding for the study

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Eligible volunteers were randomized to one of three treatment groups according to a computer-generated randomization schedule
Allocation concealment (selection bias)	Low risk	'All capsules were packaged, labelled and randomized on-site by a third party who had no further involvement in the study. In addition, due to the fact that the color of the DHA-rich fish oil capsules did not match the other two treatments, all treatments were collected and counted by a third party who had no further involvement in the study' Jackson et al (2016), 'study design' section, p 3
Blinding of participants and personnel (performance bias)	High risk	'The placebo capsules contained 2.24 g high oleic acid sunflower oil and 120 mg fish oil (32 mg DHA + EPA) for masking purposes'. However "the color of the DHA-rich fish oil capsules did not match the other two treatments".
Blinding of outcome assessment (detection bias)	Unclear risk	Unclear.
Incomplete outcome data (attrition bias)	Low risk	All participant recruited to the study was accounted for. Fig 1, consort diagram, p3. Communication with the authors stated that all data cleaning was carried out blinded. 4 Cases were removed due to data capture errors/technical issues relating to the NIRS data.
Selective reporting (reporting bias)	High risk	Primary outcome in trial registry reported in published data. However, a secondary outcome measure

		(mood/wellbeing) listed in the trial register was not reported in the published data. clinicaltrials.gov registry number: NCT01185379 Date registered: August 18th 2010 date data collection began: July 2010
Attention	Low risk	'Participants attended the laboratory on four separate occasions.' Jackson et al. 2016, p5.
Compliance	Low risk	capsule count at 3 and 6 months and verified with fingertip capillary whole blood measurements
Other bias	Low risk	None noted

JELIS 2007 – NCT00231738 [258-272]

Methods	Japan Eicosapentaenoic acid Lipid Intervention Study (JELIS) RCT, parallel, 2-arm (EPA capsule vs nil), 5 years Summary risk of bias: moderate or high
Participants	People with hypercholesterolaemia N: intervention, 9326, control 9319 (analysed intervention 9326, control 9319) Level of risk for CVD: moderate (Patients with hypercholesterolaemia) Men: 32% intervention, 31% control Mean age in years (SD): 61 (8) intervention 61 (9) control Age range: 40-75 years Smokers: 20% intervention, 18% control Hypertension: 36% intervention, 35% control Medications taken by at least 50% of those in the control group: statins Medications taken by 20%-49% of those in the control group: calcium channel blockers, other antihypertensives Medications taken by some, but less than 20% of the control group: beta-blockers, antiplatelet, hypoglycaemics, nitrates Location: Japan Ethnicity: Japanese
Interventions	Type: supplement (EPA capsule) Comparison 1: EPA vs nil Intervention: 3 × 2 × 300 mg capsules/d EPA ethyl ester (total dose of 1.8 g/d EPA), after meals. Dose: 1.8 g/d EPA Control: nothing (though all in both groups received "appropriate" dietary advice). All patients in both groups were on statins. Compliance: monitored by local physicians and measuring plasma fatty acids concentrations. Study drug regimens, 71% adhered EPA intervention, 73% adhered EPA control, 74% adhered statin Duration of intervention: maximum 5 years, mean 4.7 (1.1) years
Outcomes	Main study outcome: major coronary events Dropouts: 1766 intervention, 1582 control (but all had endpoint evaluation) Available outcomes: major coronary events: sudden cardiac death, fatal or non-fatal MI, unstable angina, angioplasty or CABG. Also all-cause mortality, stroke, peripheral artery disease, cancer, lipids, rise in blood sugar, fasting glucose, HbA1c Response to contact: no
Notes	Study funding: Mochida Pharmaceutical Company

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Statistical co-ordination centre: "permitted block randomisation with a block size of 4"
Allocation concealment (selection bias)	Low risk	Centralised. Statistical coordinating centre (see above)
Blinding of participants and personnel (performance bias)	High risk	Not blinded as there was no placebo. Quote: "[o]pen label blinded end point"

Blinding of outcome assessment (detection bias)	Low risk	"Clinical endpoints ... reported by local physicians were checked by members of a regional organizing committee in a blinded fashion. Then an endpoints adjudication committee ... confirmed them once a year without knowledge of the treatment allocation"
Incomplete outcome data (attrition bias)	Low risk	Well documented, dropout numbers low
Selective reporting (reporting bias)	Unclear risk	NCT00231738 registered October 2005, recruitment November 1996 to November 1999, main results published 2007. Rationale and design paper published in 2003 (reported baseline characteristics, so before completed follow-up, but after data collection began). All reported outcomes appear to have been published.
Attention	Low risk	Slight, as no placebo provided to control group, but only capsules to intervention group. Otherwise 2 groups appeared to be treated equally
Compliance	Unclear risk	Monitored by local physicians and measuring plasma fatty acids concentrations. Study drug regimens,71% adhered EPA intervention, 73% adhered EPA control, 74% adhered statin
Other bias	Low risk	No further bias noted

Kanorsky 2007 [273]

Methods RCT, 2 arms (n3 vs nil), 12 months
Summary risk of bias: moderate to high

Participants People with persistent atrial fibrillation
N: 45 sotalol + n3 int., 48 sotalol alone control (analysed unclear)
Level of risk for CVD: high
Male: NR% int., NR% control.
Mean age (sd): NR
Age range: NR
Smokers: NR
Hypertension: NR
Medications taken by at least 50% of those in the control group: NR
Medications taken by 20-49% of those in the control group: NR
Medications taken by some, but less than 20% of the control group: NR
Location: Russia
Ethnicity: NR

Interventions Type: Supplement (capsules)probably
Comparison: n3 vs nil
Intervention: n3 (dose and type unclear) with sotalol
Control: sotalol alone (no placebo)
PUFA Dose: (intended) increase NR %**E n-3, NR%E LCn3, NR %E PUFA**
Duration of intervention: 12 months

Outcomes Main study outcome: maintenance of sinus rhythm
Dropouts: NR
Available outcomes: sinus rhythm, hs-CRP, perhaps more
Response to contact: not yet attempted

Notes Funding: NR
Note: paper in Russian, details only taken from English abstract to date

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Paper states "randomised", no further details

Allocation concealment (selection bias)	Unclear risk	No details of allocation
Blinding of participants and personnel (performance bias)	High risk	No placebo
Blinding of outcome assessment (detection bias)	Unclear risk	No details provided
Incomplete outcome data (attrition bias)	Unclear risk	Attrition unclear
Selective reporting (reporting bias)	Unclear risk	No protocol or trials registry entry found
Attention	Unclear risk	Unclear, no details provided
Compliance	Unclear risk	Unclear, no details provided
Other bias	Low risk	None noted

Krebs 2006 [274]

Methods	RCT, parallel, (n3 EPA+DHA vs n6 LA, both with weight loss programme), 6 months Summary risk of bias: Moderate or high
Participants	Overweight hyperinsulinaemic women N: 39 int., 38 control. (analysed, int: 35 cont: 32) Level of risk for CVD: Moderate Male: 0% int., 0% control. Mean age (sd): 44.7 (13.2) in both groups combined Age range: 21-69 years Smokers: 0 (smokers were excluded) Hypertension: NR Medications taken by at least 50% of those in the control group: NR Medications taken by 20-49% of those in the control group: NR Medications taken by some, but less than 20% of the control group: NR Location: UK Ethnicity: NR
Interventions	Type: supplement (capsules with n3 EPA+DHA or LA+oleic acid) Comparison: n3 EPA+DHA vs n6 LA, both with weight loss programme Intervention: Weight loss programme plus 5 capsules/d (including 1.3g EPA+ 2.9g DHA, EPAX, Pronova): EPA+DHA 4.2g/d Control: Weight loss programme plus 5 capsules/d (including 2.8g LA + 1.4g oleic acid, Pronova): LA 2.8g/d Compliance: Plasma and adipose fatty acids Duration of intervention: 6 months
Outcomes	Main study outcome: Cardiovascular risk factors Dropouts: 4 int., 6 control Available outcomes: Adiposity, insulin, glucose, HOMA, HbA1c, lipids, inflammatory markers (bp 6 months not used). All as geometric means. Change data for weight, fat mass, waist circumference, triglycerides, AUC insulin
Notes	3 arm study, with the no weight-loss arm not discussed here Study funding: Medical Research Council and SMILES

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"randomly assigned"
Allocation concealment (selection bias)	Unclear risk	"randomly assigned"
Blinding of participants and personnel (performance bias)	Unclear risk	"double blind"

Blinding of outcome assessment (detection bias)	Unclear risk	"double blind"
Incomplete outcome data (attrition bias)	High risk	>10% lost over 6 months
Selective reporting (reporting bias)	Unclear risk	No registry or protocol identified
Attention	Low risk	For the arms discussed here, schedules appeared comparable and only differed by capsule content
Compliance	Low risk	Significant increase in n-3 and DHA in adipose tissue of intervention group
Other bias	Low risk	None noted

Kremer 1995 [275]

Methods RCT, 4 x parallel arm, placebo controlled (n3 EPA+DHA vs n6 LA), 6 months / 7 months
Summary risk of bias: moderate to high
Aim: "To determine ...: 1) whether dietary supplementation with fish oil will allow the discontinuation of ...NSAIDs in patients with rheumatoid arthritis (RA); 2) the clinical efficacy of high-dose dietary n3 fatty acid ... in RA patients; and 3) the effect of fish oil supplements on the production of multiple cytokines in this population"

Participants Individuals with definite or classic active rheumatoid arthritis as demonstrated by the presence of three of the following four criteria: ≥6 tender joints, ≥3 swollen joints, ≥30 min morning stiffness, a Westergren ESR of ≥28 mmol/hour.
N: 37 int., 29 control (analysed – int: 15 cont: 14)
Level of risk for CVD: Low
Male: 43.5% int., 46.2% control.
Mean age (sd): 58 int.; 57 cont. (SD not reported)
Age range: NR
Smokers: NR
Hypertension: NR
Medications taken by at least 50% of those in the control group: None reported
Medications taken by 20-49% of those in the control group: prednisolone (mean 4.5mg/day) 23%; hydroxychloroquine 34%
Medications taken by some, but less than 20% of the control group: methotrexate (11%), intramuscular gold (11%), sulphasalazine (11%), D-penicillamine (8%), Auranofin (4%), Azathioprine (4%)
Location: USA
Ethnicity: NR
Baseline Westergren ESR (mean +/- SEM): int. 31 +/- 3.9 mm/hr; cont. 41 +/- 8.1 mm/hr

Interventions Type: supplement (fish oil capsule or corn oil)
Comparison: EPA+DHA vs MUFA/SFA
Intervention: 130mg/kg/day (including 44% EPA + 24% DHA; supplied by National marine Fisheries Association for the National Institutes of Health): EPA+DHA ~6.2g/d
Control: 9 x corn oil capsules per day, capsule weight unspecified (supplier not reported)
Compliance: capsule count showed 93% overall compliance in patients consuming fish oil and 88% overall compliance in patients taking corn oil. Authors state that analysis of 3-day food diaries revealed a consistent pattern of nutrient intake in both study groups (data not shown).
Duration of intervention: 6/7 months (depending on allocation)

Outcomes Main study outcome: Diclofenac use
Dropouts: 24 int., 18 control
Available outcomes: clinical outcomes for RA, blood pressure, cytokine production.

Notes This study involved a combined, staggered intervention of n3 FAs/placebo and Diclofenac, with all patients starting the trial on a combination of either Diclofenac & n3FAs or Diclofenac & corn oil placebo, and the Diclofenac stopped eight weeks before the n3/corn oil at either 18 or 22 weeks, depending on the allocated arm. While it is possible to separate the n3 & corn oil findings, it is more difficult with this combined intervention and the numbers involved in this trial to be confident that differences were attributable to the n3FAs.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Random sequence generation method not reported
Allocation concealment (selection bias)	Unclear risk	Timing of allocation Vs randomisation not reported
Blinding of participants and personnel (performance bias)	High risk	Intervention provided as 130mg/kg/day so participants in the intervention arms would have potentially been taking a different number of capsules compared to control arms.
Blinding of outcome assessment (detection bias)	Unclear risk	As performance bias – stated to be the same assessor used throughout from screening to end of study
Incomplete outcome data (attrition bias)	High risk	High drop-out rate (44%) with no ITT analysis
Selective reporting (reporting bias)	Unclear risk	No study registration or protocol was found; very limited outcome reporting
Attention	Low risk	Identical follow-up described for participants in each arm.
Compliance	Low risk	Capsule count showed 93% overall compliance in patients consuming fish oil and 88% overall compliance in patients taking corn oil. EAIC stat 0.93 int/0.88 cont.
Other bias	Unclear risk	Unclear as to extent to which diclofenac may have influenced findings as data between diclofenac cessation and n3/placebo cessation not provided.

Kristensen 2016 – NCT01818804 [276-278]

Methods
RCT, 2 arm (LCn3 vs MUFA), 6 months
Summary risk of bias: moderate to high
Aim: "Investigate the effect of [LCn3] on cardiac autonomic function and vascular function in patients with psoriatic arthritis"

Participants
People with psoriatic arthritis
N: 72 int., 71 control (analysed – int: 68 cont: 60)
Level of risk for CVD: Low
Male: 44% int., 39% control.
Mean age (sd): 53 (11) int.; 51 (12) cont.
Age range: NR
Smokers: int 13% current smokers, cont 23%
Hypertension: 29% int, 28% cont
Medications taken by at least 50% of those in the control group: None reported
Medications taken by 20-49% of those in the control group: NR
Medications taken by some, but less than 20% of the control group: NR
Location: Denmark
Ethnicity: NR
Baseline CRP, mean (sd): int. 4.6 (4.2) mg/l; cont. 6.1 (7.7) mg/l

Interventions
Type: supplement (capsules)
Comparison: LCn3 vs MUFA
Intervention: 3g/d LCn3 (1.5g/d EPA, 1.5g/d DHA) in 6 daily capsules
Control: 3g/d olive oil (2.4g/d oleic acid, 0.6g/d LA) in 6 daily capsules
Compliance: 10 int, 4 cont non-compliant (missed >15% capsules), granulocyte fatty acids increased in int, not in control, significantly different (EPA 1.99 vs 0.50 weight %, DHA 2.1 vs 1.1 weight %), $p<0.01$ for both
Duration of intervention: 24 weeks

Outcomes
Main study outcome: heart rate velocity
Dropouts: 3 int., 5 control
Available outcomes: cardiac autonomic and hemodynamic function - RR and HR (not defined), pulse wave velocity. NSAID and paracetamol intake, disease activity score (arthritis), tender joint count,

enthesitis, psoriasis area and leukotriene B4, B5 & 5-HEPE reported in abstract only (BP, hip to waist ratio, BMI, CRP, PASI, cholesterol (TC) were measured but data not found)

Notes NCT01818804

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"randomly assigned in blocks of 5 by a computer-generated block sequence"
Allocation concealment (selection bias)	Unclear risk	Unclear, as above
Blinding of participants and personnel (performance bias)	Low risk	Defines itself as "double-blind" and includes placebo, but taste and appearance of capsules not mentioned
Blinding of outcome assessment (detection bias)	Low risk	Unclear for clinical outcomes, appears fine for immunological outcomes
Incomplete outcome data (attrition bias)	Low risk	All accounted for
Selective reporting (reporting bias)	High risk	More outcomes reported than mentioned in trials registry (including BP, BMI, lipids)
Attention	Low risk	Likely to be little difference
Compliance	Low risk	Appears good using both counts and fatty acid changes
Other bias	Low risk	None noted

Kruger 1998 [279]

Methods RCT, 2arm, parallel (N6+LCN3 vs SFA), 18 months
Summary risk of bias: Moderate/high

Participants Women from old age homes with osteoporosis/ osteopenia.
CVD risk: Low
N: 66 randomised overall (analysed 29 int., 31 control)
% male: 0%
Age, mean (sd) yrs: control 77.2 (6.4), intervention 78.66 (5.77)
Age range: NR
Smokers: NR. BMI, mean (SD): NR
Hypertension: NR
Medications taken by at least 50% of those in the control group: Calcium carbonate
Medications taken by 20-49% of those in the control group: NR
Medications taken by some, but less than 20% of the control group: NR
Location: South Africa
Ethnicity: NR

Interventions Type: Supplement
Comparison: PUFA (N3+N6 vs coconut oil (SFA)
Intervention: 4x 500mg capsules tid providing 6g of a mixture of evening primrose oil and fish oil [60% LA, 8% GLA), 4% EPA and 3% DHA], **Dose:** 3.6g/d LA, 0.48g/d GLA, 240 mg/d EPA & 180mg/d DHA (N6 4.08g & N3 0.42g/d)
Control: 12 capsules (4 capsules x 3) providing 6g of coconut oil as placebo (97% saturated fat; 0.2% LA).
All participants received 600mg/d calcium carbonate and all were fed the same diet.
Compliance: Measured by patient log book and plasma FAs level. There was significant increase in EPA, DHA & GLA level in int compared to control.
Duration of intervention: 18 months

Outcomes Main study outcome: BMD
Dropouts: 6 int., 2 control
Available outcomes: BMD, bone biomarkers, dietary intake and plasma fatty acids.
Response to contact: Not attempted

Notes Study funding: Study supported by Scotia Pharmaceuticals Pty (Ltd), South Africa and Stirling, Scotland

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Just stated, no details.
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias)	Unclear risk	No details
Blinding of outcome assessment (detection bias)	Unclear risk	No details
Incomplete outcome data (attrition bias)	Low risk	Few drop outs balanced between groups.
Selective reporting (reporting bias)	Unclear risk	No protocol found.
Attention	Low risk	Equal attention
Compliance	Low risk	See table
Other bias	Unclear risk	None noted

Kumar 2008 [280]

Methods RCT, parallel, (n6 GLA vs MUFA), 9 months
Summary risk of bias: Moderate to high
Aim: "whether ... borage (starflower) oil could be substituted for ...NSAIDs, without exacerbation/worsening of clinical measures of disease activity in patients with" rheumatoid arthritis (RA).

Participants People with rheumatoid arthritis
N: 14 int., 14 control. (analysed, int: 12 cont: 7)
Level of risk for CVD: low
Male: 21% int., 21% control.
Mean age (sd) yrs: 62.3 (11.4) int., 56.5 (8.0) control
Age range: NR
Smokers: NR
Hypertension: NR
Medications taken by at least 50% of those in the control group: NR
Medications taken by 20-49% of those in the control group: NR
Medications taken by some, but less than 20% of the control group: NR
Location: UK
Ethnicity: NR

Interventions Type: supplement
Comparison: GLA n6 vs MUFA & n6
Intervention: 12 capsules/d borage (or starflower) oil, 6g/d including 1.32g/d GLA
Control: 12 capsules/d peanut oil, including MUFA and LA (0.76g/d LA but peanut oil contains more MUFA than n6)
Compliance: assessed by capsule count at each visit, and red cell membrane EFA. Erythrocyte DGLA and GLA and plasma DGLA and GLA were all significantly different between intervention and control arms at 36 weeks
Duration of intervention: 9 months

Outcomes Main study outcome: NSAID requirements
Dropouts: 2 of 14 int., 7 of 14 control
Available outcomes: pain (VAS), subjective response, NSAID use, morning stiffness, grip strength, CRP, ESR, side effects (CRP and ESR only reported as "no significant changes were seen in CRP or ESR when comparing the treatment to the control group", also "there were no adverse effects on blood biochemistry, full blood count, pulse rate or body weight. Blood pressures in both groups were in the normal range and remained so during the study period").

Notes Study funding: Not reported
Author contact: Not yet

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"randomised"
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias)	Unclear risk	Study stated as double blind, but few details provided
Blinding of outcome assessment (detection bias)	Unclear risk	Not detailed
Incomplete outcome data (attrition bias)	High risk	9 of 28 were lost over 9 months (32%)
Selective reporting (reporting bias)	Unclear risk	No protocol or trials register entry found
Attention	Low risk	The study only differed by the content of the capsules, but the assessment schedule was not stated to differ between the two arms
Compliance	Low risk	Significant differences between intervention and control in erythrocyte DGLA and GLA and plasma DGLA and GLA at 36 weeks
Other bias	Low risk	None noted

Kumar 2012 – NCT00232219 [281-286]

Methods RCT, parallel, (fish oil vs nil), 12 months
Summary risk of bias: moderate or high

Participants Patients with persistent atrial fibrillation (AF) on warfarin
N: 92 intervention, 90 control (91 and 87 analysed ITT)
Level of risk for CVD: high
Male %: 82.4 intervention, 72.4 control
Mean age in years (SD): 63 (10) intervention, 61(13) control
Age range: 18-85 years (inclusion criteria)
Smokers: 22.2% intervention, 11.5% control
Hypertension: 45.6% intervention, 58.6% control
Medications taken by at least 50% of those in the control group: anti-arrhythmic drugs, renin-angiotensin system inhibitors
Medications taken by 20%-49% of those in the control group: statins
Medications taken by some, but less than 20% of the control group: not reported
Location: Australia
Ethnicity: not reported

Interventions Type: fish oil capsule
Comparison: EPA + DHA vs nil
Intervention: 6 capsules/day of a fish oil preparation containing a total dose of 1.02 g of EPA and 0.72 g DHA. Participants in the omega-3 group were asked to continue fish oils till a maximum of 1 year or till return of persistent AF. Dose: 1.7 g/d EPA + DHA
Control: no supplements. Patients were advised not to take any fish oil supplements.
All patients underwent cardioversion following randomisation.
Compliance: was monitored on a weekly basis via telephone and during follow-up by using a pill count plus serum EPA and DHA levels which were significantly increased
Duration of intervention: 1 year (or AF recurrence)

Outcomes Main study outcome: atrial fibrillation recurrence
Dropouts: 4 intervention, 0 control
Available outcomes: all-cause mortality (nil death), AF recurrence, time to AF recurrence, adverse events
Response to contact: contact not yet established

Notes Study funding: the study was funded in part by the National Heart Foundation of Australia and the Pfizer Cardiovascular Lipid Research Grant.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Patients were randomised to a control or an omega-3 group in a 1:1 fashion (no details of method)
Allocation concealment (selection bias)	Unclear risk	No further details
Blinding of participants and personnel (performance bias)	High risk	Open label with no placebo control
Blinding of outcome assessment (detection bias)	High risk	Open label
Incomplete outcome data (attrition bias)	Low risk	ITT analysis was conducted
Selective reporting (reporting bias)	Unclear risk	Trial registered 2005 but data collection started 2003
Attention	Unclear risk	Intervention group had capsules, while control group did not. Potential for greater contact and checking with intervention group on this basis, although otherwise both groups seem to have had the same care.
Compliance	Low risk	EPA and DHA levels were significantly higher in intervention group
Other bias	Low risk	None noted

Kumar 2013 – NCT00232245 [287]

Methods RCT, parallel, (fish oil vs nil), 12 months
Summary risk of bias: moderate or high

Participants Patients > 60 years with sinoatrial node disease and dual chamber pacemakers
N: 39 intervention, 39 control randomised (18 intervention vs 39 control at 12 months)
Level of risk for CVD: moderate/high
Male %: 46% intervention, 56% control
Mean age in years (SD): 78 (7) intervention, 77(8) control
Age range: not reported
Smokers: not reported
Hypertension: 72%
Medications taken by at least 50% of those in the control group: statin, renin-angiotensin system inhibitors
Medications taken by 20%-49% of those in the control group: anti-arrhythmic drugs
Medications taken by some, but less than 20% of the control group: not reported
Location: Australia
Ethnicity: not reported

Interventions Type: omega 3 capsule
Comparison: EPA + DHA vs nil
Intervention: a triglyceride preparation containing a total of 6 g/day of omega-3 polyunsaturated fatty acids of which 1.8 g/day were n-3 (1.02 g EPA and 0.72 g DHA). Dose: 1.8 g/d EPA + DHA
Control: no supplements
Compliance: measured by weekly dietary history and pill count. Fatty acid status measured at randomisation and between 1-3 months post randomisation (blood samples).
Duration of intervention: median 378 days

Outcomes Main study outcome: atrial fibrillation burden
Dropouts: 1 intervention, 0 control
Available outcomes: all-cause mortality, CV mortality, AF (frequency and duration but not recurrence so not used), adverse events
Response to contact: written but no contact yet

Notes Study funding: unclear

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was performed using sequentially numbered, opaque, sealed envelopes.
Allocation concealment (selection bias)	Low risk	As above
Blinding of participants and personnel (performance bias)	High risk	Open label design
Blinding of outcome assessment (detection bias)	High risk	Quote: "At each visit, stored AT/AF diagnostic data were retrieved in an un-blinded fashion"
Incomplete outcome data (attrition bias)	High risk	Only 1 lost, and reason explained. 21 of the 39 randomised to the intervention were crossed over to control at 6 months so 12-month outcomes are reported for 17/18 intervention while baseline characteristics are reported for the 39 patients.
Selective reporting (reporting bias)	Low risk	Trial prospectively registered and outcomes stated were reported
Attention	Unclear risk	As only the intervention group had supplements there was potential for attention differences. Other contact appears the same.
Compliance	Low risk	EPA was 3-fold higher and DHA 1.8 fold higher compared with controls. EPA and DHA did not change significantly in controls upon repeat testing
Other bias	High risk	Odd design – 21 of the 39 randomised to the intervention were crossed over to control at 6 months

Lalia 2015 – NCT01686568 [288]

Methods
RCT, parallel, (n3 EPA+DHA vs MUFA), 6 months
Summary risk of bias: Moderate or high

Participants
Insulin resistant adults
N: 16 int., 15 control. (analysed, int: 14 cont: 11)
Level of risk for CVD: low
Male: 36% int., 18% control.
Mean age (sd): 35.3 (2.9) int., 32.6 (2.5) control
Age range: NR (recruitment criterion was ≥18 years)
Smokers: 0% (exclusion criterion)
Hypertension: NR
Medications taken by at least 50% of those in the control group: NR
Medications taken by 20-49% of those in the control group: NR
Medications taken by some, but less than 20% of the control group: NR
(Those taking medications that might affect muscle metabolism, such as beta-blockers, corticosteroids, anticoagulants were excluded)
Location: USA
Ethnicity: NR

Interventions
Type: supplement
Comparison: EPA+DHA vs ethyl oleate
Intervention: EPA+DHA as 2x2 softgel capsules/d (2.7g/d EPA+ 1.2g/d DHA): EPA+DHA 3.9g/d
Control: ethyl oleate as 2x2 softgel capsules/d (4.8g/d ethyl oleate)
PUFA Dose: (intended) increase 3.9g/d EPA+DHA, **1.8%E n-3, 1.8%E PUFA**
Compliance: plasma EPA and DHA assessed, both levels were higher in the intervention group at 6 months (p values between 0.05 and 0.10).
Duration of intervention: 6 months

Outcomes
Main study outcome: hepatic and peripheral insulin sensitivity
Dropouts: 2 of 16 int., 4 of 15 control
Available outcomes: BMI, glucose, insulin, HOMA-IR (weight, lipids, CRP, IL-6 too different at baseline to use, leptin & adiponectin reported but not used)

Notes Study funding: Clinical and translational science award, Strickland Career Development Award, Sancilio & Co supplied materials for the study, senior author was member of the Sancilio Scientific Advisory Board.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"randomly assigned individuals to groups based on a table prepared by a statistician"
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias)	Unclear risk	Reported as "double blind" but no further details of how this was attained or whether it was successful provided.
Blinding of outcome assessment (detection bias)	Unclear risk	Not described
Incomplete outcome data (attrition bias)	High risk	31 randomised, 25 completed so 20% dropout over 6 months. Further 4 participants missed out on several measures.
Selective reporting (reporting bias)	Low risk	All outcomes reported in trials register were reported in the paper or on the registry site. Study registered in Sept 2012, data collection began in Dec 2012.
Attention	Low risk	Appeared similar in both arms
Compliance	High risk	Difference in lipid composition between arms was not statistically significant
Other bias	Low risk	None noted

Lau 1993 [289-291]

Methods RCT, parallel arm, double-blind, placebo controlled (n3 EPA+DHA vs nil), 12 months
Summary risk of bias: moderate to high
Aim: "to investigate the effects of MaxEPA on NSAID usage in patients with" rheumatoid arthritis (RA)

Participants Individuals with definite or classical rheumatoid arthritis as defined by the 1987 American Rheumatism Association criteria and requiring use of non-steroidal anti-inflammatory medication (NSAIDs).
N: 32 int., 32 control (analysed – not reported, drop-out rate suggests int: 23, cont: 16 as no ITT analysis reported)
Level of risk for CVD: Low
Male: 28% int., 31% cont.
Mean age (sd): 49.3 int.; 53.4 cont. (SD not reported)
Age range: 26-73 int., 27-70 cont.
Smokers: NR
Hypertension: NR
Medications taken by at least 50% of those in the control group: None reported
Medications taken by 20-49% of those in the control group: Diclofenac (28.1%)
Medications taken by some, but less than 20% of the control group: Piroxicam (18.8%), Ibuprofen (12.5%), Naproxen (9.4%), Fenbufen (9.4%), Aspirin (9.4%), Ketoprofen (6.3%), Indomethacin (3.1%), Orudis (3.1%)
Location: Scotland
Ethnicity: NR/British
Baseline ESR (mean + range): int. 27 (5-87) mm/hr; cont. 28.5 (5-85) mm/hr
Baseline CRP (mean + range): int. 1.1 (0-8) mg/l; cont. 1.3 (0-4.3) mg/l

Interventions Type: supplement (fish oil capsule or air-filled capsule)
Comparison: EPA+DHA vs air
Intervention: 10 capsules per day (including 1.71g EPA + 1.14g DHA [MaxEPA]; manufactured and supplied by Glaxo Pharmaceuticals Ltd.: EPA+DHA 2.85g/d
Control: 10 air-filled capsules per day (supplier not reported)
Compliance: capsule count undertaken but result not reported. In MaxEPA treatment group: EPA levels significantly elevated at 6m & 12m and returned to baseline at 15m; DHA significantly elevated

at 12m, which persisted to 15m. No significant changes in the levels of EPA, DHA or AA in red cell membrane in placebo group.
Duration of intervention: 12 months (but followed up for 15m)

Outcomes Main study outcome: Requirement for NSAID therapy over a 15-month period
Dropouts: 24 int., 18 control
Available outcomes: NSAID requirement, clinical assessment of disease activity for RA, laboratory variables of disease activity (ESR, FBC, IgM RF titre, CRP), patients assessment of RA condition (CRP measured, but paper stated that "no statistically significant or trend of changes in any of the clinical and laboratory variables was observed within and between the two groups of patients studied" including articular index, grip strength, duration of morning stiffness, VAS of severity of pain, ESR, haemoglobin level, leucocyte and platelet count, haematocrit, mean corpuscular volume or haemoglobin, IgM RF titre, CRP. Quantitative data (in graphic form) only provided for ESR and NSAID requirement.
Author contact: Established, information provided on methodology, deaths and cardiovascular events (none occurred)

Notes Supported by Glaxo Pharmaceuticals Ltd.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random sequence generation method not reported in paper but described in personal communication as 'assigned by computer software in blocks of 10'
Allocation concealment (selection bias)	Low risk	Allocation concealment and inability to alter allocation after assignment confirmed in personal communication
Blinding of participants and personnel (performance bias)	Unclear risk	Personal communication confirms that neither the recipients, providers of care nor outcome assessors were aware of the assigned treatment during the intervention period BUT no attempt to conceal smell or taste of intervention reported and air-filled capsules may be different in appearance and feel in mouth to oil-filled.
Blinding of outcome assessment (detection bias)	Low risk	'Neither the physician nor the metrologist handled the trial medication throughout the whole study' (p.983). Author communication confirms blinding of outcome assessor.
Incomplete outcome data (attrition bias)	Unclear risk	Numbers analysed not stated in paper so unable to assess. Withdrawals reported as 9 in int. group and 16 in cont. group (table 3)
Selective reporting (reporting bias)	Unclear risk	No trials pre-registration/protocol found
Attention	Low risk	Identical follow-up described for participants in each arm.
Compliance	Unclear risk	In MaxEPA treatment group: EPA levels significantly elevated at 6m & 12m and returned to baseline at 15m; DHA significantly elevated at 12m, which persisted to 15m. No significant changes in the levels of EPA, DHA or AA in red cell membrane in placebo group. However, this does not confirm degree of compliance in intervention group.
Other bias	Low risk	None noted

Lee 2012 [292 293]

Methods RCT, parallel, (n3 DHA vs n6 LA), 12 months
Summary risk of bias: Moderate or high

Participants	Population: elderly individuals aged 60 and above, living in 15 low to middle socioeconomic public flats. N: 18 int., 18 control. (analysed, int: 17 cont: 18) Level of risk for CVD: Low Male: 17.6% int., 28% control. Mean age (sd): 66.4 (5.1) int., 63.5 (3.0) control Age range: NR Smokers: 11.8% int; 16.7% control Hypertension: NR Medications taken by at least 50% of those in the control group: NR Medications taken by 20-49% of those in the control group: NR Medications taken by some, but less than 20% of the control group: NR Location: Malaysia Ethnicity: NR Depression: General population (low risk) Anxiety: General population (low risk)
Interventions	Type: supplement Comparison: Docosahexaenoic acid-concentrated fish oil vs corn oil (n6) Intervention: 3x 1-g soft gelatine capsule daily, containing 430mg of DHA and 150mg of EPA (EPAX 1050TG; EPAX AS, Lysaker, Norway) Control: Isocaloric placebo corn oil 0.6g linoleic acid. (EPAX AS, Lysaker, Norway) Compliance: Monthly capsule counts found compliance was high: capsule consumption rate 94.5% int., 93.8% control Duration of intervention: 12 months
Outcomes	Main study outcome: Cognition Dropouts: 1 int., 0 control Available outcomes: neuropsychological tests (WMS-R, RAVLT, WAIS-R, CDT, WAIS-III, & MMSE) and depression (GDS)
Notes	Study funding: Both the fish oil and placebo capsules were provided by the EPAX AS, Lysaker, Norway.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was achieved using computer-generated random numbers in stratified permuted blocks of size four. Stratification factors considered were age 60-74 and age over 75 and gender.
Allocation concealment (selection bias)	Unclear risk	Method of concealment of allocation not stated
Blinding of participants and personnel (performance bias)	Unclear risk	Study was stated as double-blind but unclear exactly whom this included. Both the [fish oil] EPAX 1050TG and placebo were visually identical and odourless. The present study used two distinct substances as the supplementation agents. However, there appears to be some doubtful blindness between the fish oil and placebo due to the fishy taste after consumption.
Blinding of outcome assessment (detection bias)	Low risk	Study was double-blinded. Both the [fish oil] EPAX 1050TG and placebo were visually identical and odourless. The treatment code was released once data analyses had been completed.
Incomplete outcome data (attrition bias)	Low risk	1 patient was excluded from the intervention group (3% drop-out). Data was analysed on a per protocol basis.
Selective reporting (reporting bias)	Unclear risk	Protocol was not published
Attention	Low risk	All subjects were scheduled for a monthly appointment
Compliance	Low risk	Compliance with the trial was high, with a capsule consumption rate for the fish oil and placebo groups of 94.5% & 93.8% respectively.

Other bias	Low risk	None noted

Leventhal 1993 [294]

Methods	2x parallel arm, double-blind, placebo-controlled RCT (n6 GLA vs mixed fats including LA), 24 weeks/6 months Summary risk of bias: Moderate to high Aim: "To assess the clinical efficacy and side effects of [GLA on]....inflammation and joint tissue injury"
Participants	People with rheumatoid arthritis and active synovitis N: 19 int., 18 control (analysed: 14 int., 13 cont.) Level of risk for CVD: Low Male: 21% int., 27.78% control. Mean age (sd): 58 (13) int., 50 (16) control Age range: 18-80y for inclusion Smokers: NR Hypertension: NR Medications taken by at least 50% of those in the control group: non-steroidal anti-inflammatory drugs (100%), corticosteroids (50%) Medications taken by 20-49% of those in the control group: Medications taken by some, but less than 20% of the control group: Location: USA Ethnicity: NR
Interventions	Type: supplement (capsules containing borage seed oil or cottonseed oil) Comparison: higher GLA n6 vs lower GLA n6 Intervention: 12 capsules per day of borage seed oil (including 1.4g/d (23%) GLA, 62% c/s linoleic acid, 8% oleic acid, manufactured by Bio Oil Research Ltd, Nantwich, Cheshire, UK) Control: 12 capsules per day of cottonseed oil (including 54% linoleic acid, 18% oleic acid, 24% palmitic acid, manufactured by Bio Oil Research Ltd, Nantwich, Cheshire, UK) Compliance: capsule count at week 12 and week 24 – data not reported Duration of intervention: 24 wks/6 months
Outcomes	Main study outcome: Clinical response measured by a selection of measures of RA disease activity Dropouts: 5 int., 5 control Available outcomes: clinical response, laboratory outcomes (ESR, rheumatoid factor, platelet count)
Notes	None of the authors disclosed any personal or financial conflicts of interest; study funded by public body in USA

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Methods for randomisation not described
Allocation concealment (selection bias)	Unclear risk	Insufficient detail.
Blinding of participants and personnel (performance bias)	Low risk	Identical appearance – unlikely to have distinctive smell or taste
Blinding of outcome assessment (detection bias)	Unclear risk	Insufficient detail
Incomplete outcome data (attrition bias)	High risk	28% attrition
Selective reporting (reporting bias)	Unclear risk	No trials registration
Attention	Low risk	The study only differed by the content of the capsules, but the assessment schedule was not stated to differ between the two arms
Compliance	Unclear risk	Results of capsule count not reported and no fatty acid status data so C-RoB is unclear
Other bias	Low risk	None noted

Leventhal 1994 [295]

Methods	2x parallel arm, double-blind, placebo-controlled RCT (n6 GLA & n3 ALA vs n6 LA), 24 weeks/6 months Summary risk of bias: Moderate to high Aim: "to assess the clinical efficacy and side effects of blackcurrant seed oil (BCSO...rich in GLA and ALA) .... in patients with RA and active synovitis"
Participants	People with rheumatoid arthritis and active synovitis N: 11 int., 14 control (analysed: 7 int., 7 cont.) Level of risk for CVD: Low Male: 27.3% int., 7% control. Mean age (sd): 55 (15) int., 55 (11) control Age range: 18-80y for inclusion Smokers: NR Hypertension: NR Medications taken by at least 50% of those in the control group: non-steroidal anti-inflammatory drugs (78.6%) Medications taken by 20-49% of those in the control group: corticosteroids (43%), methotrexate (36%), hydroxychloroquine (21.5%) Medications taken by some, but less than 20% of the control group: Gold salts (14%), minocycline (7%) Location: USA Ethnicity: int. black 27%, white 73%; cont. black 50%, white 50%
Interventions	Type: supplement (capsules containing blackcurrant seed oil or soybean oil) Comparison: higher GLA vs lower GLA Intervention: 15x 700mg (10.5g) capsules per day of blackcurrant seed oil (including 2g/d (19%) GLA, 5g/d (48%) cis-linoleic acid, 1.9g/d ALA (18%) n3 FA [ALA/stearidonic acid] manufactured by Nestec Ltd, Lausanne, Switzerland) Control: 15x700mg capsules per day of soybean oil (including 5.67g (54%) linoleic acid, 1.9g (18%) MUFA, 1.9g (18%) n3 FA [ALA/stearidonic] manufactured by Nestec Ltd, Lausanne, Switzerland) Compliance: capsule count at 6, 12, 18 and 24 weeks – data not reported Duration of intervention: 24 wks/6 months
Outcomes	Main study outcome: Clinical response measured by a selection of measures of RA disease activity Dropouts: 7 int., 13 control Available outcomes: clinical response, laboratory outcomes (ESR, rheumatoid factor, platelet count)
Notes	Supported by grants from US Public Health Service and Nestec Ltd; none of the authors disclosed any personal or financial conflicts of interest.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Methods for randomisation not described
Allocation concealment (selection bias)	Unclear risk	Insufficient detail.
Blinding of participants and personnel (performance bias)	Unclear risk	Identical appearance – no detail about differences in smell or taste
Blinding of outcome assessment (detection bias)	Unclear risk	Insufficient detail
Incomplete outcome data (attrition bias)	High risk	Over 50% attrition
Selective reporting (reporting bias)	Unclear risk	No trials registration
Attention	Low risk	The study only differed by the content of the capsules, but the assessment schedule was not stated to differ between the two arms
Compliance	Unclear risk	Results of capsule count not reported and no fatty acid status data so C-RoB is unclear

Other bias	Low risk	None noted

Ley 2004 [296-298]

Methods RCT, parallel, (reduced total fat vs usual diet), 12 months
Summary risk of bias: low (dietary advice trial)

Participants Adults with impaired glucose intolerance or high normal blood glucose
N: 85 intervention, 90 control (176 between both groups) (analysed 66 intervention: 70 control at 1 year, 112 between both groups at 5 years)
Level of risk for CVD: moderate
Male: 80% intervention, 68% control
Mean age (SD): 52.5 (SE 0.8) intervention, 52.0 (SE 0.8) control
Age range: not reported
Smokers: 23% intervention, 9% control
Hypertension: not reported
Medications taken by ≥ 50% of those in the control group: not reported
Medications taken by 20%-49% of those in the control group: not reported
Medications taken by some, but < 20% of the control group: BP medication taken by 27% intervention, 18% control
Location: New Zealand
Ethnicity: European 67% intervention, 77% control, Maori 11% intervention, 7% control, Pacific islander 20% intervention, 13% control, other 3% intervention, 4% control (outcomes not provided by ethnicity)

Interventions Type: diet advice
Comparison: reduced fat vs usual diet
Intervention: aim reduced fat diet (no specific goal stated); methods monthly small group meetings to follow a 1-year structured programme aimed at reducing dietary fat, includes education, personal goal setting, self-monitoring
Control: aim usual diet; methods usual intake plus general advice on healthy eating consistent with the New Zealand guidelines and standard dietary information for people with nutrition-related problems upon entering the trial.
Dose aim: no goal stated
Baseline PUFA: unclear but lower PUFA arm 4% E PUFA
Compliance by biomarkers: erythrocyte ALA increased by 28% in control, reduced by 17% in intervention (in a subsample of participants, % of total fatty acids in red blood cells also increased in control group compared to intervention), no other erythrocyte fatty acids reported. TC fell by 0.15 mmol/L (SE 0.09) in control, and by 0.05 mmol/L (SE 0.17) in intervention to 1 year
Compliance by dietary intake: mean of five, 24-h diet recalls over 2 years of trial

- Energy intake, kcal/d: intervention 1821 (SD not reported), control 1593 (SD not reported)
- Total fat intake, % E: intervention 33.6 (SE 7.8), control 26.1 (SE 7.7)
- SFA intake, %E: intervention 10.0 (SE 0.6), control 13.4 (SE 0.6)
- PUFA intake, % E: intervention 4.0 (SE 0.2), control 4.8 (SE 0.2)
- PUFA n-3 intake: not reported
- PUFA n-6 intake: not reported
- Trans fat intake: not reported
- MUFA intake, % E: intervention 8.9 (SE 0.4), control 11.8 (SE 0.4)
- CHO intake, % E: intervention 54.2 (SE 1.5), control 45.8 (SE 1.4)
- Sugars intake: not reported
- Protein intake, % E: intervention 18.4 (SE 0.5), control 16.6 (SE 0.5)
- Alcohol intake, % E: intervention 3.6 (SE 1.0), control 5.7 (SE 0.9)

Compliance, other methods: not reported
Inclusion basis: aimed to reduce total fat, not to alter total PUFA. Resulted in fall of 0.8% E total PUFA in intervention, > 10% increase from 5.3% E PUFA at baseline
PUFA dose: 0.8% E PUFA (from dietary intake data)
Duration of intervention: 12 months (later data reported, but intervention only lasted 1 year)

Outcomes Main trial outcome: lipids, glucose, BP
Dropouts: unclear intervention, unclear control
Available outcomes: mortality, CVD mortality, combined CV events (including MI, angina, stroke, heart failure), diabetes diagnosis, total MI, stroke, cancer diagnoses, cancer deaths, CHD events (MI or angina), weight, total, LDL and HDL cholesterol, TGs, BP

Author contact: Dr Metcalf provided additional methodology and outcome data

Notes Trial funding: National Heart Foundation of New Zealand, Aukland Medical Research Foundation, Lotteries Medical Board and the Health Research Council of New Zealand
NOTE: total PUFA intake lower in intervention than control group

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Unmarked opaque envelopes were opened by the person recruiting, unable to alter allocation later (trial author stated in their reply to us that randomisation and preparation of the envelopes was by people not involved in recruitment).
Allocation concealment (selection bias)	Low risk	Unmarked opaque envelopes were opened by the person recruiting, unable to alter allocation later
Blinding of participants and personnel (performance bias)	High risk	Dietary advice, not blinded
Blinding of outcome assessment (detection bias)	Low risk	Trial authors stated that those assessing lipids were blinded
Incomplete outcome data (attrition bias)	Unclear risk	Unclear, deaths, cancer and CV events are dropouts, trialists asked for data but they were unable to provide any - unclear if any data missing
Selective reporting (reporting bias)	Low risk	No protocol or trials registry entry found
Attention	High risk	Regular meetings in intervention group, not in control
Compliance	Low risk	Erythrocyte ALA increased by 28% in control, reduced by 17% in intervention (in a subsample of participants, % of total fatty acids in red blood cells also increased in control group compared to intervention), no other erythrocyte fatty acids reported. TC fell by 0.15 mmol/L (SE 0.09) in control (the arm higher in PUFA), and by 0.05 mmol/L (SE 0.17) in intervention to 1 year (control group should have been higher in total PUFA in this trial).
Other bias	Low risk	None noted

Li 2015 [299]

Methods 2x parallel arm, prospective, un-blinded RCT (n3 EPA+DHA vs nil), 6 months
Summary risk of bias: Moderate or high
Aim: "To examine whether ...PUFA therapy is beneficial for improving non-alcoholic steatohepatitis (NASH)"

Participants People diagnosed with pathological non-alcoholic steatohepatitis (NASH)
N: 39 int., 39 control (analysed: 39 int., 39 cont.)
Level of risk for CVD: Moderate
Male: 87.2% int., 92.3% control.
Mean age (sd): 52.6 (6.6) int., 50.4 (7.2) control
Age range: NR
Smokers: 59% int., 56.4% cont.
Hypertension: NR
Medications taken by at least 50% of those in the control group: NR
Medications taken by 20-49% of those in the control group: NR
Medications taken by some, but less than 20% of the control group: NR
Location: China
Ethnicity: NR

Interventions Type: supplement (oil containing PUFA or normal saline)
Comparison: higher EPA+DHA n3 vs lower EPA+DHA n3
Intervention: 50mls PUFA oil (with 1:1 ratio of EPA+DHA) Manufacturer not stated: EPA+DHA unclear

Control: normal saline (volume not stated)
Compliance: NR
Duration of intervention: 24 wks/6 months

Outcomes Main study outcome: primary outcome unspecified (improvement in NASH) Dropouts: 0 int., 0 control
Available outcomes: liver enzymes, lipid profiles, markers of inflammation and oxidation, and histological changes

Notes Study funding source not stated; authors declare no conflicts of interest.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Methods for randomisation not described in detail
Allocation concealment (selection bias)	Unclear risk	Insufficient detail.
Blinding of participants and personnel (performance bias)	High risk	Unblinded study – no placebo
Blinding of outcome assessment (detection bias)	Low risk	All working staff involved in evaluating parameters were blinded to the information about both groups
Incomplete outcome data (attrition bias)	Low risk	Outcome data reported for all participants randomised
Selective reporting (reporting bias)	Unclear risk	No trials registration found; side effects and compliance not reported.
Attention	Low risk	Follow-up appears identical for both arms
Compliance	Unclear risk	Compliance measures not reported so C-RoB is unclear
Other bias	Low risk	None noted

Loeschke 1996 [300]

Methods RCT, parallel, (n3 EPA+DHA vs n6 LA), 24 months
Summary risk of bias: Moderate or high
Aim: "test the protective potential of n-3 fatty acids [in ulcerative colitis]"

Participants People with ulcerative colitis in remission
N: 31 int., 33 control. (analysed, int: 31 cont: 33)
Level of risk for CVD: low
Male: 48% int., 55% control.
Mean age (sd) years: 40 (13) int., 39 (11) control
Age range: NR
Smokers: NR
Hypertension: NR
Medications taken by at least 50% of those in the control group: 5-ASA
Medications taken by 20-49% of those in the control group: NR
Medications taken by some, but less than 20% of the control group: NR
Location: Germany
Ethnicity: NR

Interventions Type: supplement
Comparison: fish oil (LCn3) vs maize oil (n6)
Intervention: 2 capsules 3x/d, each capsule contained 1ml of 85% ethyl esters of LC n-3 fatty acids from fish oil (Fresenius AG, Homburg). Included 1 IU/ml tocopherol and orange flavour: EPA+DHA 5.1g/d
Control: 2 capsules 3x/d of maize oil (Fresenius AG, Homburg). Included 1 IU/ml tocopherol and orange flavour.
Compliance: assessed by detailed interview and capsule count, blood samples were drawn at every presentation. 2 intervention and 1 control participant were found to be noncompliant.
Duration of intervention: 24 months

Outcomes Main study outcome: UC relapse

Dropouts: 8/31 int., 9/33 control suggested
Available outcomes: hematologic and clinical chemistry, fatty acid composition, liver enzymes
Inflammatory marker data were not presented, but the publication states "Inflammatory laboratory parameters were rather, low corresponding to the clinical condition of these patients in remission and not further reduced by n-3 fatty acids"

Notes Study funding: Supported in part by Bundesministerium ffir Forschung und Technologie, Bonn
Author contact: replied to queries about data and risk of bias.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"After entry documentation, patients were allocated the next free number in one of four strata"...."Matched placebo or active medication had been prepacked according to a random list in blocks of two for each stratum and coded with consecutive numbers"
Allocation concealment (selection bias)	Low risk	Similarity of capsule and packaging not stated, but researcher stated that those responsible for participant recruitment were not aware of allocation or able to affect allocation.
Blinding of participants and personnel (performance bias)	Unclear risk	Stated as double blind, and "Matched placebo or active medication" but no details provided on appearance, smell or taste
Blinding of outcome assessment (detection bias)	Unclear risk	Methodology for blinding assessment of relapse not reported, though double blind stated, and author confirmed assessor blinding
Incomplete outcome data (attrition bias)	Low risk	ITT analysis
Selective reporting (reporting bias)	Unclear risk	No protocol or trials registry entry found
Attention	Low risk	Appeared similar for both groups
Compliance	Low risk	Of 64 patients randomized, 47 adhered to the protocol in that "pill count revealed that over 95% of all capsules had been taken as requested. Seventeen patients stopped taking the study medication prematurely". This suggests 70% compliance overall
Other bias	Low risk	None noted.

Lorenz-Meyer 1996 [301]

Methods RCT- parallel, 2 arms (omega 3 vs corn oil), 12 months
Summary risk of bias: low

Participants People with Crohn's disease in remission (but with a recent relapse)
N: 70 intervention, 63 control
Level of risk for CVD: low
Men: 35.7% intervention, 27.0% control
Mean age in years (SD): 29.5 (9.6) intervention, 31.8 (10.9) control
Age range: 17-62 years intervention, 17-65 years control
Smokers: not reported
Hypertension: not reported
Medications taken by at least 50% of those in the control group: methylprednisolone (all for 1st 8 weeks)
Medications taken by 20%-49%: not reported
Medications taken by some, but < 20%: not reported
Location: Germany
Ethnicity: not reported

Interventions Type: supplement (fish oil)
Comparison: EPA + DHA vs omega 6

	Intervention: 2 × 3 1 g gelatin capsules/d of ethylester fish oil concentrate (3.3 g/d EPA + 1.8 g/d DHA). Dose: 5.1 g/d EPA + DHA Control: 2 × 3 1 g gelatin capsules/d of corn oil Compliance: pill count, 5 non-compliant patients, among compliant patients, 18 were censored (for not using the medication for 3 continuous weeks) Duration of intervention: 12 months
Outcomes	Main study outcome: Crohn's disease duration of remission Dropouts: unclear Available outcomes: mortality (nil), Crohn's disease activity and relapses, serum triglycerides Response to contact: yes (methodological details provided)
Notes	There was a third arm of dietary advice (for low CHO diet) Study funding: not reported

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised within the centres in blocks of six (block size blinded to the centres)
Allocation concealment (selection bias)	Low risk	Author reported allocation was concealed
Blinding of participants and personnel (performance bias)	Low risk	Quote: "Double blind conditions were intended for the verum-placebo comparisons". Author stated that capsules were identical in appearance (taste not mentioned).
Blinding of outcome assessment (detection bias)	Low risk	Primary outcome was relapses "classified in a blind fashion by a primary end-point committee"
Incomplete outcome data (attrition bias)	High risk	Participants were accounted for based on the main outcome of the study (relapses), however 20% omitted from analyses and numbers confusing
Selective reporting (reporting bias)	Unclear risk	No trials registry entry or protocol found
Attention	Low risk	All patients were seen by their physician in the respective centre after regular time intervals (1, 2, 3, 6, 9 and 12 months).
Compliance	Unclear risk	Pill count, 5 non-compliant patients, among compliant patients, 18 were censored (for not using the medication for three continuous weeks). 23 of 133 non-compliant
Other bias	Low risk	None noted

Macsai 2008 [302]

Methods	RCT, 2 arms (ALA vs MUFA), 12 months Summary risk of bias: moderate to high
Participants	People with meibomian gland dysfunction N: 18 ALA int., 20 control (analysed, int: 14 cont: 16) Level of risk for CVD: low Male: 22% int., 10% control. Mean age (sd): 46.9 (8.6) int., 54.5 (9.5) control Age range: NR (recruitment criterion was ≥18 years) Smokers: NR Hypertension: NR Medications taken by at least 50% of those in the control group: NR Medications taken by 20-49% of those in the control group: NR Medications taken by some, but less than 20% of the control group: NR (Those taking aspirin, Cox-2 inhibitors, anticoagulants and long-term NSAIDs were excluded) Location: USA Ethnicity: NR

Interventions Type: Supplement (capsules)
Comparison: ALA vs MUFA
Intervention: 6 capsules/d, 6g/d of which 55% was ALA, so 3.3g/d ALA, 1.14g/d LA.
Control: 6g/d olive oil capsules, 0.5%E from n3 (0.04%E EPA, 0.01%E DHA) low LCn3 & high polyphenol, 0.5%E from n3 (0.02%E EPA, 0.01%E DHA) low LCn3 & low polyphenol.
PUFA Dose: (intended) increase **1.5%E n-3, 0%E LCn3, 0.4% n-6, 1.9%E PUFA**
Duration of intervention: 12 months

Outcomes Main study outcome: eye outcomes
Dropouts: 4 int, 4 cont
Available outcomes: clinical measures (including Schirmer, tear breakup time, staining), meibomian gland health and scores, ocular surface disease index (authors report no deaths or CVD disease, no diabetes diagnoses, 1 diagnosis of breast cancer in control group, none in intervention)
Response to contact: yes, data provided

Notes Funding: Natrol donated all capsules, other funders included Pearl Vision Foundation, Research for Prevention of Blindness

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random number generator in Excel, managed by research coordinator
Allocation concealment (selection bias)	Unclear risk	No details of concealment
Blinding of participants and personnel (performance bias)	Low risk	Capsules were made to look as much alike as possible and coded by content. Only research staff, not involved in patient care, had access to assignments
Blinding of outcome assessment (detection bias)	Low risk	As above.
Incomplete outcome data (attrition bias)	Unclear risk	38 randomised, 30 assessed at 1 year (7 lost to follow up, 1 diagnosed with Sjogren's disease)
Selective reporting (reporting bias)	Unclear risk	No protocol or trials registry entry found
Attention	Low risk	Appeared equivalent
Compliance	Unclear risk	Appeared fine, but full data not provided for plasma or red blood cell fatty acids for control group
Other bias	Low risk	None noted.

Mansel 1990 [303-305]

Methods RCT, 2 arm, parallel (n-6 GLA vs non-fat), 1 year
Summary risk of bias: moderate to high

Participants Women with macroscopic breast cysts
CVD risk: low
N; Intervention 100, Control 100
Mean years in trial: 1
% male: 0
Age: unclear (no statistically significant difference between groups)
Age range: 35 to 60 years
Smokers: unclear
Hypertension: unclear
Medications taken by at least 50% of those in the control group: not reported
Medications taken by 20%-49% of those in the control group: not reported
Medications taken by some, but less than 20% of the control group: not reported
Location: UK
Ethnicity: not reported

Interventions Type: supplement
Comparison: GLA (n-6) vs placebo (paraffin)

Intervention aims: 6 capsules/d EPO (Efamol) containing ≥ 9% GLA (total volume unclear)
Control aims: 6 capsules/d paraffin (total volume unclear)
Dose: (assuming each capsule is 1 g) increase **0.54 g/d GLA**, increase 6 g/d or 54 kcal or **2.7% E n-6**
Baseline n-6: unclear
Compliance: unclear
Duration of intervention: 1 year

Outcomes Main study outcome: unclear, recurrent cysts?
Dropouts: intervention 7, control 8
Available outcomes: breast cancer (no deaths or CVD events appear to have occurred)
Response to contact: no response to attempted contact

Notes Study funding: not stated

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomised"
Allocation concealment (selection bias)	Unclear risk	Randomisation process not discussed
Blinding of participants and personnel (performance bias)	Unclear risk	Placebo controlled but similarity of placebo unclear; paper suggests that participants and physicians were blinded to allocation
Blinding of outcome assessment (detection bias)	Unclear risk	Quote: "examined by a clinician who was blind to the treatment allocated" but method of this blinding unclear
Incomplete outcome data (attrition bias)	Low risk	Attrition below 20% and well documented
Selective reporting (reporting bias)	Unclear risk	No protocol or trials registry entry found
Attention	Unclear risk	Unclear
Compliance	Unclear risk	Not reported
Other bias	Low risk	None noted

Mantzaris 1996 [306]

Methods RCT, parallel arm, placebo-controlled (n3 EPA+DHA Vs MUFA), 12 months
Summary risk of bias: moderate to high
Aim: "to evaluate the potential role of EPA as an adjunct to [aspirin] in the maintenance treatment of ulcerative colitis"

Participants People with ulcerative colitis in clinical, endoscopic & histological remission
N: 27 int., 23 control. (analysed, int: 22 cont: 18)
Level of risk for CVD: Low
Male: 45% int., 50% control.
Mean age (sd): 35 int., 37 control (no SD)
Age range: 18-65 int., 17-60 cont.
Smokers: NR
Hypertension: NR
Medications taken by at least 50% of those in the control group: oral mesalazine (1.2g tid) to 100%
Medications taken by 20-49% of those in the control group:
Medications taken by some, but less than 20% of the control group:
Location: Greece
Ethnicity: NR

Interventions Type: supplement (oil containing EPA+DHA or olive oil)
Comparison: EPA+DHA vs MUFA
Intervention: 20ml/d oil containing 3.2g/d EPA & 2.1g/d DHA, manufactured as MaxEPA: EPA+DHA 5.3g/d
Control: 20ml/day olive oil
PUFA Dose: (intended) increase 5.3g/d EPA+DHA, 2.4**%E n-3, 2.4 %E PUFA**

Compliance: unclear
Duration of intervention: 12 months

Outcomes Main study outcome: Ulcerative colitis relapse
Dropouts: 5 int., 5 control
Available outcomes: relapse rate, colectomy

Notes Study funding source: not stated

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	States randomised but method of randomisation not reported
Allocation concealment (selection bias)	Unclear risk	No details provided
Blinding of participants and personnel (performance bias)	Unclear risk	Intervention and placebo appear to have been given as free oil but measures to mask taste and smell not reported
Blinding of outcome assessment (detection bias)	Unclear risk	Not reported
Incomplete outcome data (attrition bias)	High risk	20% participants omitted for non-compliance
Selective reporting (reporting bias)	High risk	Known outcomes not reported fully
Attention	Low risk	FU appears identical and rigorous for both groups
Compliance	Unclear risk	Not reported in-depth but 20% dropped out because of non-compliance
Other bias	Low risk	No trials registration found; funding source not reported

MAPT 2017 - NCT00672685[307-317] & MAPT Plus - NCT01513252 [318]

Methods Multidomain Alzheimer Preventive Trial (MAPT)
4 arms RCT, parallel, (n-3 ± multidomain intervention vs placebo ± multidomain intervention), 36 months
Summary risk of bias: low

Participants Population: people aged at least 70 years without dementia but with memory complaint, IADL limitation or slow gait speed
N: 840 intervention (arms 1 and 3), 840 control (arms 2 and 4) randomised. Numbers analysed differ by outcome.
Level of risk for CVD: low
Men: 37.2% intervention, 34.5% control. (combined groups)
Mean age in years (SD): 75.6 (4.7) and 74.4 (4.4) intervention, 75.1 (4.3) and 75 (4.1) control
Age range: not reported
Smokers: not reported
Hypertension: not reported
Medications taken by at least 50% of those in the control group: not reported
Medications taken by 20%-49% of those in the control group: not reported
Medications taken by some, but less than 20% of the control group: not reported
Location: France and Monaco
Ethnicity: not reported

Interventions Type: supplement (capsule)
Comparison: EPA + DHA vs paraffin oil (non-fat)
Intervention
Arm 1: omega-3 (V0137 CA 800 mg/d DHA; 225 mg/d EPA in soft caps). Dose for arms 1 and 3: 1.025 g/d EPA + DHA
Arm 3: omega 3 (V0137 CA 800 mg/d DHA; 225 mg/d EPA in soft caps) plus multi-domain intervention (nutrition, physical exercise, cognitive stimulation, social activities)
Control:

Arm 2: placebo capsules containing flavoured paraffin oil. All capsules were supplied by Pierre Fabre Médicament (Castres, France)
Arm 4: placebo capsules plus multi-domain intervention (nutrition, physical exercise, cognitive stimulation, social activities)
Compliance: adherence to study interventions was assessed every 6 months. For supplementation, adherence was assessed by counting the number of capsules returned by participants (or based on treatment dates if the number of capsules was missing). Furthermore, biological samples were obtained at baseline and after 12 months to assess concentrations of DHA and EPA in red blood cell membranes.
Duration of intervention: 36 months

Outcomes Main study outcome: change in cognitive function)
Dropouts: 200 intervention, 194 control
Available outcomes: mortality, CVD events, haemorrhagic stroke, adverse events, functional capacity, other cognitive functions, safety and tolerability
Response to contact: no

Notes Study funding: Gérontopôle of Toulouse, the French Ministry of Health (PHRC 2008, 2009), the Pierre Fabre Research Institute (manufacturer of the polyunsaturated fatty acid supplement), Exhonit Therapeutics, and Avid Radiopharmaceuticals

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomly assigned (1:1:1:1) to the combined intervention (i.e. the multidomain intervention plus polyunsaturated fatty acids), the multidomain intervention plus placebo, polyunsaturated fatty acids only, or placebo only. A computer-generated randomisation procedure (done by ClinInfo, a subcontractor) was used with block sizes of 8 and stratification by centre.
Allocation concealment (selection bias)	Low risk	A clinical research assistant, who was not involved in the assessment of participants, used a centralised interactive voice response system to identify which group to allocate the participant to, and which lot number to administer.
Blinding of participants and personnel (performance bias)	Low risk	All participants and study staff were blinded to polyunsaturated fatty acid or placebo assignment – both sets of capsules looked and tasted identical. In view of the nature of the multidomain intervention, the study was unblinded for this component, but the independent neuropsychologists who were trained to assess cognitive outcomes were blinded to group assignment.
Blinding of outcome assessment (detection bias)	Low risk	All participants and study staff were blinded to polyunsaturated fatty acid or placebo assignment—both sets of capsules looked and tasted identical. In view of the nature of the multidomain intervention, the study was unblinded for this component, but the independent neuropsychologists who were trained to assess cognitive outcomes were blinded to group assignment. Data analysts were not blinded to group assignment, but two data managers, one statistician (CC) and two physicians (SA and BV) did a blinded data review.
Incomplete outcome data (attrition bias)	Low risk	1680 participants were enrolled and randomly allocated, the modified intention-to-treat population (N = 1525), i.e. 155 excluded (9% over 3 years)
Selective reporting (reporting bias)	Low risk	Protocol registered ClinicalTrials.gov (NCT00672685) – outcomes match report. Because of advances in the field since our trial was designed in 2007, we decided to modify the primary outcome from one

		cognitive test to a composite cognitive score, which is now thought to be a better endpoint. This protocol amendment was submitted to the local ethical committee on 2 February 2015 and was subsequently approved
Attention	Low risk	Both groups assessed at baseline, 6, 12, 24, 36 months. Groups 1 and 2 only differed by content of capsules.
Compliance	Unclear risk	Adherence to study interventions was assessed every 6 months, by counting the number of capsules returned (or based on treatment dates if the number of capsules was missing). Biological samples were obtained at baseline and after 12 months to assess concentrations of DHA and EPA in red blood cell membranes, but outcomes not reported.
Other bias	Low risk	None noted

MARGARIN 2002 [319-325]

Methods Mediterranean alpha-linolenic enriched Groningen dietary intervention study (MARGARIN)
RCT, factorial 2 × 2 (ALA rich margarine vs LA rich margarine, also nutrition education vs no education but this is not included), 2 years
Summary risk of bias: low

Participants Hypercholesterolemia adults with 2 or more CVD risk factors
N: total 282 randomised; 114 intervention (51 with nutrition education, 58 without NE) 157 control (52 with NE, 105 without NE)
Level of risk for CVD: moderate (multiple cardiovascular risk factors, 10-year IHD risk ~20%)
Men: 41.9% intervention, 45.7% control
Mean age in years (SD): 54.4 (9.5) intervention, 53.9 (9.8) control
Age range: 30-70
Smokers: 49.1% intervention, 49.3% control
Hypertension: 52.9% intervention, 45.3% control (on anti-hypertensives)
Medications taken by at least 50% of those in the control group: antihypertensives
Medications taken by 20%-49%: not reported
Medications taken by some, but < 20%: not reported
Location: the Netherlands
Ethnicity: not reported

Interventions Type: supplementary food (ALA enriched margarine)
Intervention: provided with ALA rich margarine (80% fat of which 15% was ALA and 46% LA) to be eaten ad libitum. Dose: average intake 6.3 g/d ALA (was also 1 g/d ALA in the control group).
Control: provided with linoleic rich margarine (80% fat of which 0.3% was ALA and 58% LA), identical in taste and packaging. Both margarines contained 0.66 mg vit E/g, 9 micro-g vit A/g and 0.023 micro-g vit D/g
Comparison: ALA vs omega 6
Compliance: serum fatty acids used to assess, ALA rose by 0.47 mol % (SD 0.04) and 0.36 mol% (SD 0.04) intervention arms (with and without NE) and fell by 0.06 mol % (SD 0.04) and 0.11 mol % (SD 0.03) control arms (with and without NE), significantly different.
Duration of intervention: 24 months

Outcomes Main study outcome: cardiovascular risk factors and IHD risk
Dropouts: unclear
Available outcomes: total and CV deaths, non-fatal MI, stroke, CABG and angioplasty, BMI, lipids, BP
Response to contact: yes

Notes Study funding: Prevent fund and Unilever Research
Other intervention (2 × 2) was educational, teaching a multifactorial dietary intervention. It was excluded as multifactorial.

Risk of bias table

Bias	Authors' judgement	Support for judgement

Random sequence generation (selection bias)	Low risk	Computer-generated random allocation, allocated by an independent trial coordination centre that organised masked distribution of margarines
Allocation concealment (selection bias)	Low risk	Allocated by an independent trial coordination centre which organised masked distribution of margarines
Blinding of participants and personnel (performance bias)	Low risk	Double-blind; the 2 margarines are described as identical as to taste and packaging (though not reported as checked)
Blinding of outcome assessment (detection bias)	Low risk	2 independent physicians, a cardiologist and a general practitioner validated and classified results in a blinded fashion
Incomplete outcome data (attrition bias)	Low risk	The number randomised to each arm was unclear, but one publication clarifies (55 randomised to each arm, 51 intervention and 52 control analysed).
Selective reporting (reporting bias)	Unclear risk	No study protocol or trials registry entry was found.
Attention	High risk	There was no difference in attention between margarine types, but the dietary advice group spent more time with study staff than the control group, and some (not quite randomly allocated) were sent individual motivational letters (Siero 2000).
Compliance	Low risk	Serum fatty acids used to assess, ALA rose by 0.47 mol% (SD 0.04) and 0.36 mol % (SD 0.04) intervention arms (with and without NE) and fell by 0.06 mol % (SD 0.04) and 0.11 mol % (SD 0.03) control arms (with and without NE), Significantly different
Other bias	Low risk	No further bias noted

MARINA 2011 – ISRCTN66664610 [326-333]

Methods	Modulation of Atherosclerosis Risk by Increasing dose of n-3 fatty Acids (MARINA) RCT, parallel, 4 arms (n-3 PUFA 3 different doses or olive oil placebo), 12 months Summary risk of bias: low
Participants	Non-smoking men and women aged 45-70 years N: intervention. 279 in 3 groups (G1 0.45 g/d n = 94, G2 0.9 g/d n = 93, G3 1.8 g/d n = 92); control: 88 (analysed G1 0.45 g/d n = 81, G2 0.9 g/d n = 80, G3 1.8 g/d n = 80, control 71) Level of risk for CVD: low Men: 38.7% intervention, 38.6% control Mean age in years (CI): G1: 55 (53, 56), G2: 55 (54, 56), G3: 55 (54, 57) intervention 55 (54,57) control Age range: 45-70 Smokers: 0% intervention, 0% control Hypertension: 5.4% intervention, 5% control Medications taken by at least 50% of those in the control group: none Medications taken by 20%-49% of those in the control group: none Medications taken by some, but less than 20% of the control group: statins, antihypertensives, HRT, thyroxine Location: UK Ethnicity: G1: white 80.9%, black 4.3%, Asian 6.4%, East Asian 4.3%, other 4.3% G2: white 78.5%, black 6.5%, Asian 10.8%, East Asian 0%, other 4.3% G3: white 85.9%, black 1.1%, Asian 2.2%, East Asian 4.3%, other 6.5% Control: white 77.3%, black 10.2%, Asian 6.8%, East Asian 2.3%, other 3.4%
Interventions	Type: supplement (fish oil capsules) Comparison 1: EPA + DHA vs MUFA Comparison 2: high EPA + DHA vs low EPA + DHA Intervention: 3 × 1 g oil gelatin capsule/day consisting of blend of EPA concentrate, DHA concentrate, refined olive oil and 0.1% peppermint oil. Providing a daily dose of: 0.45 g, 0.9 g, or 1.8 g per day (all with EPA/DHA ratio of 1.51). Dose: 1.8 g/d EPA + DHA (G3 used for outcomes)

Control: 3 gelatin capsules/ day containing refined olive oil + 0.1% peppermint oil
Compliance: measured by capsule counting and erythrocyte lipids for proportion of EPA/DHA @ baseline, 6 months, 12 months. 88.5% of participants consumed > 90% of capsules provided. EPA and DHA in erythrocyte lipids increased in dose-dependent manner compared with placebo, indicating long-term compliance with intervention.
Length of intervention: 12 months

Outcomes Main study outcome: endothelial function, arterial stiffness
Dropouts: 38 intervention (13,13,12), 17 control
Available outcomes: lipids, dietary intake, CRP, BP (supine and ambulatory – numeric data not provided, but study states that there were no significant differences between arms). Weight data not used as baseline is different between groups (FMD, arterials stiffness, carotid intima media thickness, heart rate variability, heart rate, endothelial progenitor cells reported but not used)
Contact with authors: yes (many outcomes above provided in end of study report from authors)

Notes Outcome data used G3 (highest dose) vs placebo for continuous outcomes and combined the 3 intervention groups vs placebo for dichotomous outcomes
Study funding: Food Standards Agency

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "the random allocation sequence was generated with a computer program by using the process of minimisation to balance age, sex and ethnicity between treatment groups."
Allocation concealment (selection bias)	Low risk	Quote: "We enrolled eligible participants and the study database program allocated a serious of capsules to the participant. The treatments associated with the capsule codes were concealed from all investigators and associated clinical staff until the data analysis was complete. The code breaker was an employee of MedSciNet who constructed the trial database."
Blinding of participants and personnel (performance bias)	Low risk	Quote: "We enrolled eligible participants and the study database program allocated a serious of capsules to the participant. The treatments associated with the capsule codes were concealed from all investigators and associated clinical staff until the data analysis was complete. The code breaker was an employee of MedSciNet who constructed the trial database." "blends of the test fat with 0.1% peppermint oil to disguise the fish taste of the EPA and DHA" (peppermint oil in both intervention and control capsules)
Blinding of outcome assessment (detection bias)	Low risk	Quote: "We enrolled eligible participants and the study database program allocated a serious of capsules to the participant. The treatments associated with the capsule codes were concealed from all investigators and associated clinical staff until the data analysis was complete. The code breaker was an employee of MedSciNet who constructed the trial database."
Incomplete outcome data (attrition bias)	Low risk	15% withdrawal, reasons for attrition reported
Selective reporting (reporting bias)	Low risk	Outcomes published match trials register. Registered September 2008, trial started June 2008, ended December 2010, main publication 2011
Attention	Low risk	No difference between groups
Compliance	Low risk	Statistically significant difference in erythrocyte omega 3 fats at 12 months between different arms
Other bias	Low risk	None noted

Martinez 2014 [334]

Methods RCT, parallel, (n3 EPA+DHA vs unclear), 12 months
Summary risk of bias: Moderate or high

Participants People treated for chronic periodontitis
N: 7 int., 8 control. (analysed, int: 7 cont: 8)
Level of risk for CVD: low
Male: 43% int., 38% control.
Mean age (sd) yrs: 43.1 (6.0) int., 46.1 (11.6) control
Age range: NR
Smokers: 0% int., 13% control
Hypertension: NR
Medications taken by at least 50% of those in the control group: NR
Medications taken by 20-49% of those in the control group: NR
Medications taken by some, but less than 20% of the control group: NR
Location: Brazil
Ethnicity: non-white 4 of 7 (57%) int, 2 of 8 (25%) placebo, others white

Interventions Type: supplement
Comparison: EPA+DHA vs "placebo"
Intervention: 3 capsules/d EPA+DHA (Quintaessencia, 0.18g/d EPA, 0.12g/d DHA): EPA+DHA 0.9g/d
Control: 3 capsules/d "placebo" - not defined (Quintaessencia)
Compliance: assessed by return of empty capsule containers and weekly discussion about intake, difference between intervention and control at 12 months was statistically significant for EPA but not DHA or DPA.
Duration of intervention: 12 months

Outcomes Main study outcome: serum fatty acids
Dropouts: 0 int., 0 control
Available outcomes: periodontal outcomes (probing depth, clinical attachment levels, visible plaque index, bleeding on probing), lipids, hsCRP, leucocytes, HbA1c, Insulin, glucose (all reported as medians, so not useable in meta-analyses).

Notes Study funding: Not reported
Author contact: Not yet

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"randomly assigned using a coin toss"
Allocation concealment (selection bias)	Unclear risk	No further detail
Blinding of participants and personnel (performance bias)	Unclear risk	Unclear how similar intervention and control were
Blinding of outcome assessment (detection bias)	Low risk	Probable as paper states "bottles were not decoded until all of the follow up evaluations and statistical analyses had been performed to ensure proper double-blind study protocol"
Incomplete outcome data (attrition bias)	Low risk	No participants were lost
Selective reporting (reporting bias)	Unclear risk	No protocol or trials register entry found
Attention	Low risk	Capsules provided monthly, discussion about intake weekly, dental follow up every 4 months
Compliance	Unclear risk	Only EPA but not DHA or DPA was significantly different at 12 months (due to small sample size?)
Other bias	Low risk	None noted

Maté 1991 [335]

Methods 2 arm parallel RCT (n3 EPA+DHA vs nil), 24 months
Summary risk of bias: Moderate or high
Aim: "to assess the effect of a diet high in" EPA and DHA on maintenance of remission in Crohn's disease

Participants People with Crohn's Disease in remission
N: 19 int., 19 control. (analysed, int: 15 cont: 13)
Level of risk for CVD: Low
Male: 42% int., 58% control.
Mean age (sd): 35 int., 34 control (no SD)
Age range: NR
Smokers: NR
Hypertension: NR
No meds allowed
Location: Spain
Ethnicity: NR

Interventions Type: supplement/dietary advice (diet with high content fish oil [100-200g/wk cold water fish meat OR 100g/wk fish pate OR 250g/wk fish oil supplements] or free diet)
Comparison: more EPA+DHA vs less EPA+DHA
Intervention: 100-200g/wk cold water fish meat OR 100g/wk fish pate OR 250g/wk fish oil supplements (no dose or goal for omega 3 fats stated): EPA+DHA dose unclear
Control: free diet
PUFA Dose: (intended) increase unclear EPA+DHA, unclear **%E n-3, unclear %E PUFA**
Compliance: NR
Duration of intervention: 24 months

Outcomes Main study outcome: Crohn's Disease relapse
Dropouts: 4 int., 6 control
Available outcomes: relapse rate

Notes Study funding: not stated

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer randomisation
Allocation concealment (selection bias)	Unclear risk	Unclear, no details of method provided.
Blinding of participants and personnel (performance bias)	High risk	Participants knew allocation
Blinding of outcome assessment (detection bias)	Unclear risk	No detail reported
Incomplete outcome data (attrition bias)	High risk	Over 20% dropped out from both arms
Selective reporting (reporting bias)	Unclear risk	No trials registration
Attention	Unclear risk	Not reported
Compliance	Unclear risk	Not reported although stated as assessed
Other bias	Low risk	None noted

McIllmurray 1987 [336]

Methods RCT, parallel, 2 arms (GLA vs "inert placebo"), 40 months
Summary risk of bias: moderate to high

Participants People within 1 month following operation to remove Dukes' C colorectal cancer
N: intervention 25 (plus some dropouts), control: 24 (plus some dropouts (analysed intervention 25, control 24). 5 dropped out, but arms unclear
Level of risk for CVD: low

Male: not reported
Mean age (SD) years: intervention 62.1 (not reported), control 64.8 (not reported)
Age range: intervention 48-81, control 45-77
Smokers: not reported
Hypertension: not reported
Medications taken by ≥ 50% of those in the control group: not reported
Medications taken by 20%-49% of those in the control group: not reported
Medications taken by some, but < 20% of the control group: not reported
Location: UK
Ethnicity: not reported

Interventions Type: supplement (Efamol)
Comparison: GLA vs "inert placebo" (unclear what)
Intervention: 6 capsules/d containing 500 mg GLA plus 10 mg natural vitamin E (Efamol). GLA 0.5 g/d, 60 mg/d vitamin E. Plus vitamin supplements including vitamin C, zinc sulphate and pyridoxine.
Control: 6 capsules/d containing an inert placebo, identical in appearance (not specified what). Plus vitamin supplements including vitamin C, zinc sulphate and pyridoxine.
Dose aim: (assuming placebo contains no PUFA) increase **0.5 g/d GLA**, 5 kcal or **0.2% E GLA,** assume 70% LA*, 4.2 g/d or 37.8 kcal/d or **1.9% E LA**, **2.1% E n6**
Baseline PUFA: unclear
Compliance by biomarkers: unclear, no serum TC or tissue fatty acid levels reported.
Compliance by dietary intake: unclear, states that one participant stopped taking the supplements at 12 months

- Energy intake: not reported
- Total fat intake: not reported
- SFA intake: not reported
- PUFA intake: not reported
- PUFA n-3 intake: not reported
- PUFA n-6 intake: not reported
- Trans fat intake: not reported
- MUFA intake: not reported
- CHO intake: not reported
- Sugars intake: not reported
- Protein intake: not reported
- Alcohol intake: not reported

Compliance, other methods: not reported
Inclusion basis: aimed to increase GLA rather than total PUFA. Aimed to increase omega-6 by 2.1% E, assume 2.2% E increase for PUFA, > 10% of assumed 6% E PUFA baseline. No confirmatory biomarker, TC or intake data.
PUFA dose: 2.2% E PUFA
Duration of intervention: 40 months

Outcomes Main trial outcome: unclear, "survival", probably mortality
Dropouts: 5 (unclear from which groups)
Available outcomes: mortality, cancer mortality (face flushing reported as a side effect, but no numbers provided and assumed due to concomitant pyridoxine)
Response to contact: Professor McIllmurray replied, "I don't have the records...so I have nothing more than what appears in the publication. I do not recall there being any cardiovascular events."

Notes Trial funding: not stated, Efamol Ltd provided the Efamol capsules and inert capsules.
*EPO described as being ~70% LA in some publications, this and a 1 g capsule size have been assumed where no other details are provided

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "assigned at random"
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias)	Unclear risk	No details apart from the placebo was identical in appearance to the Efamol capsules
Blinding of outcome assessment (detection bias)	Unclear risk	Not stated

Incomplete outcome data (attrition bias)	Unclear risk	5 dropouts, unclear from which arms
Selective reporting (reporting bias)	Unclear risk	No protocol or trials register entry found
Attention	Low risk	Supplement provided, no suggestion of attention bias
Compliance	Unclear risk	Neither tissue PUFA biomarkers nor TC data reported
Other bias	Unclear risk	None noted, but contents of placebo capsules unclear

MEMO 2008 – NCT00124852, ISRCTN46249783 [337-340]

Methods Mental health in Elderly Maintained with Omega-3 (MEMO)
RCT, 3 arm parallel (n3 EPA+DHA high vs low dose vs MUFA), 6 months
Summary risk of bias: Moderate or high

Participants Independently living people aged at least 65 years
N: 96 int high dose, 100 int low dose, 106 control. (analysed, 96 int high dose, 100 int low dose, 103 cont)
Level of risk for CVD: low
Male: 55% int high dose, 55% int low dose, 56% control
Mean age (sd), years: 69.9 (3.4) int high dose, 69.5 (3.2) int low dose, 70.1 (3.7) control
Age range: unclear, ≥65 years
Smokers (current): 8% int high dose, 8% int low dose, 10% control
Hypertension: NR
Medications taken by at least 50% of those in the control group: NR
Medications taken by 20-49% of those in the control group: NR
Medications taken by some, but less than 20% of the control group: NR
(pharmacologic antidepressants and medication for dementia were not allowed)
Location: Netherlands
Ethnicity: NR
Depression: General population (low risk)
Anxiety: General population (low risk)

Interventions Type: supplement
Comparison: high EPA+DHA vs low EPA+DHA vs MUFA
Intervention high dose:1800mg/d EPA+DHA (1093mg/d EPA, 847mg/d DHA), 6 soft gelatine capsules/d, Banner pharmacaps
Intervention low dose: 400mg/d EPA+DHA (226mg/d EPA, 176mg/d DHA), 6 soft gelatine capsules/d, Banner pharmacaps
Control: sunflower oil high in oleic, 6 soft gelatine capsules/d, Banner pharmacaps
Compliance: "judged according to counts of capsules returned and a diary", “Adherence was excellent and did not differ between the treatment groups"
Duration of intervention: 26 weeks

Outcomes Main study outcome: cognitive function and mental well-being
Dropouts: 1 high dose int (discontinued), 0 low dose int, 4 control (2 died, 2 discontinued)
Available outcomes: cognition, depression, anxiety, lipids (quality of life data were collected but not reported).
Meta-analysis of high EPA+DHA capsules vs MUFA groups only

Notes Study funding: Netherlands Organization for Health Research and Development

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	An independent person randomized subjects using computer-generated random numbers in stratified permuted blocks of size six. Stratification factors included age (<69 and ≥69), sex, MMSE (<28 and ≥28), and CES-D screening test score (<5 and ≥5)”
Allocation concealment (selection bias)	Unclear risk	States "Staff members and participants were blinded toward treatment allocation until completion of the

		trial and after completion of data analysis" and does describe foil packs of 6 tablets identical between groups, but not how participants got their capsules, and timing and concealment methods unclear.
Blinding of participants and personnel (performance bias)	Low risk	"capsules with fish oil or placebo oil were indistinguishable in appearance", "staff members and participants were blinded toward treatment allocation until completion of the trial and after completion of data analysis", "At the end of the study, blinding of subjects toward treatment allocation (fish oil, placebo, or "no idea") was evaluated. The proportion of participants who thought they had received fish oil or placebo did not differ between the groups (*P*=0.15). In the high-dose fish-oil group, 25% correctly thought that they had received fish oil and 54% had no idea. In the low-dose group, 19% correctly thought that they had received fish oil and 64%had no idea. In the placebo group 25% correctly thought that they had received placebo and 60% had no idea."
Blinding of outcome assessment (detection bias)	Low risk	as above
Incomplete outcome data (attrition bias)	Low risk	Low attrition & well explained
Selective reporting (reporting bias)	Low risk	Outcomes mentioned in (prospectively registered 5 months before recruitment started) trials register are all detailed in published papers. ISRCTN46249783 registered August 2005. Date data collection began: Nov 2005
Attention	Low risk	The 3 arms appear to have been treated very similarly, with several tests at each visit.
Compliance	Low risk	Apart from the 3 who discontinued "average adherence to treatments based on counts of returned capsules was high (99%, with only 3 subjects <80%) and did not differ between the treatment groups".
Other bias	Low risk	None noted

Mendis 2001 [341]

Methods RCT, 2 arms, parallel (n6 LA vs non-fat) dietary advice, 1 year
Summary risk of bias: moderate to high

Participants Healthy volunteers responding to survey. Some had hyperlipidaemia.
CVD risk: low
N: 30 intervention, 30 control (analysed 26 intervention, 28 control)
% male: 78% (total)
Mean age: not reported
Age range: 20-65 years
Smokers: not reported
Hypertension: not reported
Medications taken by ≥ 50% of those in the control group: not reported
Medications taken by 20%-49% of those in the control group: not reported
Medications taken by some, but < 20% of the control group: not reported
*lipid-lowering medications as well as many others were not allowed.
Location: Sri Lanka
Ethnicity: 100% Sri Lanakan

Interventions Type: diet advice plus test fat supplement
Comparison: n-6 vs non-fat (unclear if CHO, protein or both)
Intervention: group B received a diet containing 20% E as fat (4.7% coconut fat) plus 7.5 g/d test fat containing soybean fat-sesame fat (3:1, v/v containing PUFA:MUFA ratio 2). Fat intake in group B was, therefore, 24% energy intake. (test fat provided additional 5 g/d PUFA mainly LA)
Control: Group A received a diet containing 20% E as fat (4.7% E coconut fat).

Dose aim: increase 5 g/d PUFA, **2.2% E PUFA**
Baseline PUFA: unclear
Compliance by biomarkers: poor, serum TC was not significantly reduced in intervention compared to control (0.16 mmol/L, 95% CI -0.18 to 0.50). The intervention group were stated as having higher dietary PUFA:SFA ratio than controls, but no blood levels of FAs were reported.
Compliance by dietary intake: unclear, measured by field workers' visits and using food diaries.

- Energy intake, kJ/d: intervention 7962 (SD 1568), control 8030 (SD 1465)
- Total fat intake, % E: intervention 24 (SD not reported), control 20 (SD not reported)
- SFA intake % E: intervention 11.4 (SD not reported), control 11.8 (SD not reported)
- PUFA intake: not reported (unsaturated fat intake intervention 12.6% E, control 8.2% E, test fat reported as mainly LA)
- PUFA n-3 intake: not reported
- PUFA n-6 intake: (unsaturated fat intake intervention 12.6% E, control 8.2% E, test fat reported as mainly LA)
- Trans fat intake: not reported
- MUFA intake: not reported
- CHO intake, % E: intervention 64 (SD not reported), control 67 (SD not reported)
- Sugars intake: not reported
- Protein intake, % E: intervention 12.2 (SD not reported), control 12.1 (SD not reported)
- Alcohol intake: not reported

Compliance, other methods: not reported
Inclusion basis: did not aim to increase PUFA (but replace SFA with unsaturated fats). Did appear to increase unsaturated fat by 4.4% E, and test fat reported as mainly LA. Aim was to increase PUFA by 2.2% E, assume this achieved though no biomarker or dietary intake data and TC was not reduced in intervention.
PUFA dose: 2.2% E PUFA
Duration of intervention: 1 year

Outcomes Main trial outcome: serum lipids
Dropouts: intervention 4, control 2
Available outcomes: lipids
Response to contact: contact attempted but no response to date.

Notes Trial funding: funded by the National Science Foundation of Sri Lanka

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Participants were randomised to 2 groups (groups A and B). This was done in such a way that the 38 hyperlipidaemic participants were equally divided between the two groups.
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias)	High risk	The groups had different diets with test fat added to intervention group
Blinding of outcome assessment (detection bias)	Unclear risk	No details
Incomplete outcome data (attrition bias)	High risk	Six participants dropped out at 6 months but their data are not included in the analysis at all
Selective reporting (reporting bias)	Unclear risk	No protocol or trial register entry found
Attention	Low risk	Appeared similar
Compliance	High risk	TC was higher in intervention than control (0.16 mmol/L, 95% CI -0.18 to 0.50). The intervention group were stated as having higher dietary PUFA:SFA ratio than controls, but no blood levels of FAs were reported.
Other bias	Unclear risk	No details provided on the form or method of supply of diet or test fat

MENU 2016 – NCT01424007 [342 343]

Methods Metabolism, Exercise and Nutrition at UCSD (MENU)
RCT, parallel, (walnut rich moderate fat diet vs moderate fat diet), 12 months
Summary risk of bias: moderate or high

Participants Overweight and obese women, of whom half were insulin resistant
N: 82 intervention, 81 control (analysed, intervention: 65 control: 61)
Level of risk for CVD: low
Men: 0% intervention, 0% control
Mean age (SD) years: 51 (NR) intervention, 50 (NR) control
Age range: 22-67 years intervention, 25-72 years control
Smokers: not reported
Hypertension: not reported
Medications taken by at least 50% of those in the control group: not reported
Medications taken by 20%-49% of those in the control group: not reported
Medications taken by some, but less than 20% of the control group: 10% were on cholesterol medications
Location: USA
Ethnicity: Hispanic 18% intervention, 14% control; black 9% intervention, 3% control; Asian American 1% intervention, 4% control; white non-Hispanic 71% intervention, 78% control.

Interventions Type: food and advice
Comparison: walnut rich moderate fat diet (ALA) vs moderate fat diet (MUFA)
Intervention: advice to follow walnut-rich higher fat diet (35%E fat with limited SFA, MUFA encouraged, including 42 g/d walnuts (provided by study), 45%E CHO, 20%E protein). Participants given print materials on diet and exercise, attended group sessions weekly for 1st 4 months, biweekly for next 2 months, then monthly to 1 year), provided web-based tracking for dietary constituents, scale, pedometer, measuring cups and exercise videos. Regular dietetic and group leader support. Clinic visits were at 0, 6 and 12 months. Dose: ~4.2 g/d ALA (calculated based on 42 g/d intake of walnuts)
Control: exactly as intervention for goals, materials and support except higher fat diet did not include walnuts (35% E fat with limited SFA, MUFA encouraged, 45%E CHO, 20%E protein)
Compliance: walnut consumption reported on form and nuts provided. Red blood cell ALA significantly higher in intervention at 12 months than control
Duration of intervention: 12 months

Outcomes Main study outcome: body weight
Dropouts: 13 of 82 intervention, 12 of 81 control
Available outcomes: weight, waist circumference, HDL and LDL cholesterol, triglycerides, insulin, glucose, HOMA-IR, HOMA-beta, CRP and IL-6 (estradiol, SHBG, nutrient gene interactions, physical activity and heart rate also presented)
Response to contact: no reply received to date

Notes Study funding: National Cancer Institute and California Walnut Commission

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation stratified by age and insulin resistance
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias)	High risk	Open study, participants were advised on their diets extensively
Blinding of outcome assessment (detection bias)	Unclear risk	Blinding not mentioned, so unclear for their primary outcome, weight
Incomplete outcome data (attrition bias)	Low risk	Paper states ITT analysis but 25 dropouts (15%) not included in 1 year data, but dropout reasons clear
Selective reporting (reporting bias)	Low risk	Pre-registered, all mentioned outcomes reported at 12 months
Attention	Low risk	Appear very equal

Compliance	Low risk	Statistically significant difference between intervention and control arms for ALA in blood cell membranes at 12 months
Other bias	Low risk	None noted

MIDAS 2010 – NCT0027813 [344-346]

Methods RCT, parallel (n3 DHA vs n6 LA), 24 weeks.
Summary risk of bias: Low

Participants Healthy older American people with subjective memory complaints (not meeting threshold for dementia diagnosis)
N: 242 int., 243 control. (analysed, int: 219 cont: 218)
Level of risk for CVD: Low
Male: 44% int., 40% control.
Mean age (sd): 70 (9.3) int., 70 (8.7) control
Age range: NR but ≥55 years inclusion criteria
Smokers: NR
Hypertension: 43% (both arms)
Medications taken by at least 50% of those in the control group: Lipophilic statins
Medications taken by 20-49% of those in the control group: Other statins, diuretics, aspirin, multivitamins.
Medications taken by some, but less than 20% of the control group: ACE inhibitors, Ca++ channel blockers, Beta-blockers
Location: USA
Ethnicity: ~84% white American

Interventions Type: supplement
Comparison: DHA vs corn and soy oil
Intervention: 3x 300mg capsule/d (total = 900mg/d DHA , *DSM Nutritional Products, Inc.*)
Control: 3 capsules/d (comprised of 50% corn oil & 50% soy oil).All capsules were orange-flavoured and orange colour to protect blinding.
Compliance: Capsule count at each visit, week 24 change from baseline plasma phospholipid DHA level. Change greater than 1.5 wt% (based on historical dose response plasma DHA levels) was considered compliant for the DHA group. Mean plasma DHA levels at 24 weeks met this criterion, and were significantly greater for intervention group compared to controls.
Duration of intervention: 24 weeks

Outcomes Main study outcome: cognitive decline
Dropouts: 23 int., 24 control
Available outcomes: cognitive outcomes, geriatric depression

Notes Study funding: The chief investigator was an employee of DSM Nutritional Produces, Inc. With the exception of Drs. Dror Rom, Andrew Blackwell, and Mary Stedman, the other authors are employed by Martek Biosciences Corporation. The study was funded by Martek Biosciences Corporation.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	(from main paper) *Eligible subjects were stratified by age (55–69; ≥70) and randomized 1:1 in blocks of four to active or placebo by site.*
Allocation concealment (selection bias)	Low risk	(from main paper) *using a centralized interactive voice randomization system (Fisher Clinical, FACTS services, Allentown, PA). Yurko-Mauro et al 2010, section 2.2, pg 458.*
Blinding of participants and personnel (performance bias)	Low risk	(double-blind, from main paper) *capsules were identical in size and appearance. All capsules were orange-flavored and orange color to protect the study blind. Subjects were instructed to take capsules with food at the same time each day (e.g., 1 capsule/ meal), starting at the baseline visit, and to not alter*

		their normal diet during the study. Yurko-Mauro et al 2010, section 2.2, pg 458.
Blinding of outcome assessment (detection bias)	Low risk	(from protocol) Masking: Double Blind (Subject, Caregiver, Investigator)
Incomplete outcome data (attrition bias)	Low risk	(from main paper) *The flow of study participants shown in FIGURE 1, described randomisation, enrolment and those who did not complete the study. Yurko-Mauro et al 2010, pg. 459.*
Selective reporting (reporting bias)	Low risk	*Outcomes in the trial register* NCT00278135 *matched with outcomes reported in publication.*
Attention	Low risk	
Compliance	Low risk	Very different plasma levels of target supplement (p< 0.01).
Other bias	Low risk	No other bias found

Mita 2007 [347]

Methods	RCT, parallel, (EPA capsules vs nil), 2 years Summary risk of bias: moderate to high
Participants	Japanese type 2 diabetics N: intervention. 40, control: 41 (analysed 30, 30) Level of risk for CVD: moderate Men: 53% intervention, 67% control Mean age in years (SD): 59 (11.2) intervention 61.2 (8.4) control Age range: not reported Smokers: 40% intervention, 43% control Hypertension: not reported Medications taken by at least 50% of those in the control group: oral hypoglycaemics Medications taken by 20%-49% of those in the control group: insulin, lipid lowering drugs, antihypertensives Medications taken by some, but less than 20% of the control group: antithrombotics Location: Japan Ethnicity: 100% Japanese
Interventions	Type: supplement (EPA oil capsules) Comparison: EPA vs nil Intervention: 1800 mg/d EPA EPADEL capsules (Mochida Pharmaceutical Co Ltd Japan)- 98% pure ethyl-ester EPA (unclear how many caps). Dose: ~1.8 g/d EPA Control: no intervention Compliance: checked during 3 month reviews throughout trial and 5 participants were excluded for poor compliance but no details on method or results Length of intervention: mean 2.1 (0.2) years
Outcomes	Main study outcome: progression of diabetic macroangiopathy measured by carotid intima-media thickness and brachial-ankle pulse wave velocity Dropouts: 10 intervention, 11 control Available outcomes: BMI, lipids, BP, HbA1c, cancer diagnosis Response to contact: not yet attempted
Notes	Blood pressure data not used as groups are different at baseline Study funding: not stated

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Patients randomly divided into 2 groups matched for age and gender
Allocation concealment (selection bias)	Unclear risk	No details

Blinding of participants and personnel (performance bias)	High risk	Open label
Blinding of outcome assessment (detection bias)	Low risk	Assessors of main study outcomes were blinded to the treatment
Incomplete outcome data (attrition bias)	Low risk	Dropout rate (26%) over 2 years. All dropouts explained, however, 5 were excluded for poor compliance but no clear predefined protocol for exclusion
Selective reporting (reporting bias)	Unclear risk	No protocol
Attention	Low risk	All participants had the same contact
Compliance	Unclear risk	Compliance measured but no clear methods or reported results
Other bias	Low risk	None noted

Moore 2006 [348]

Methods RCT, 5 arms in parallel, (high LCn3 & high ALA vs high LCn3 & n6 vs low LCn3 & high ALA vs low LCn3 & n6, also a control arm), 6 months
Summary risk of bias: moderate to high

Participants Overweight or obese adults
N: high LCn3 & high ALA 32 (analysed 29), high LCn3 & n6 32 (analysed 27), low LCn3 & high ALA 30 (analysed 22), low LCn3 & n6 29 (analysed 27)
Level of risk for CVD: moderate
Men: 33% overall
Mean age in years (SD): 50 (9) overall
Age range: not reported
Smokers: NR
Hypertension: NR
Medications taken by at least 50% of those in the control group: NR
Medications taken by 20%-49% of those in the control group: NR
Medications taken by some, but less than 20% of the control group: NR
Location: UK
Ethnicity: NR

Interventions Type: food - oily or white fish plus fat spreads and cooking oils
Comparison: high LCn3 & high ALA vs high LCn3 & n6 vs low LCn3 & high ALA vs low LCn3 & n6, also a control arm
Intervention: study foods were collected from trial every 4 weeks
high LCn3 & high ALA: 2 portions oily fish/wk or 4.5g/wk LCn3, rapeseed oil for oils and fats
high LCn3 & n6: 2 portions oily fish/wk or 4.5g/wk LCn3, sunflower oil for oils and fats
low LCn3 & high ALA: 2 portions white fish/wk or 0.7g/wk LCn3, rapeseed oil for oils and fats
low LCn3 & n6: 2 portions white fish/wk or 0.7g/wk LCn3, sunflower oil for oils and fats
Control: no intervention
Compliance: assessed by food diary and by plasma fatty acids - suggesting good compliance
Length of intervention: 24 weeks

Outcomes Main study outcome: cardiovascular risk factors
Dropouts: 2, 5, 7, 3 dropped out
Available outcomes: adiposity (weight, waist, DXA%), lipids, BP, inflammatory markers (plasma cytokines, leptin, acute phase proteins, TNF alpha, ACT reported but not in enough detail to include in meta-analysis), insulin sensitivity (glucose and insulin, but only states "no significant group x time interactions").
Response to contact: not yet attempted

Notes Study funding: not stated but Matthew foods provided fat spreads

Risk of bias table

Bias	Authors' judgement	Support for judgement

Random sequence generation (selection bias)	Low risk	minimisation was used to assign participants and ensure groups were balanced
Allocation concealment (selection bias)	Unclear risk	unclear
Blinding of participants and personnel (performance bias)	High risk	Not blinded as foods were used
Blinding of outcome assessment (detection bias)	Unclear risk	Unclear
Incomplete outcome data (attrition bias)	Low risk	Clearly described
Selective reporting (reporting bias)	Unclear risk	No trials registry or protocol found
Attention	Low risk	Food interventions so equivalent attention likely
Compliance	Low risk	Good changes in plasma fatty acids
Other bias	Low risk	None noted

MRC 1968 [349-351]

Methods Medical Research Council (MRC)
RCT, 2 arm, parallel (n6 LA vs mixed fats), 4 years
Summary risk of bias: moderate to high

Participants Free-living men who have survived a first MI (UK)
CVD risk: high
Control: randomised 194, analysed 181 at 2 years
Intervention: randomised 199, analysed 172 at 2 years
Mean years in trial: control 3.7, intervention 3.8
% male: 100
Age: unclear
Age range: all < 60 years
Smokers: control 84%, intervention 81%
Hypertension: control 12%, intervention 8%
Medications taken by ≥ 50% of those in the control group: not reported
Medications taken by 20%-49% of those in the control group: not reported
Medications taken by some, but < 20% of the control group: not reported
Location: UK
Ethnicity: not reported

Interventions Type: diet advice plus supplement
Comparison: ↑ soya oil (n-6) vs usual diet (some SFA replacement, otherwise unclear)
Control aims: usual diet
Intervention aims: reduce dietary fat to 35 g/d fat, add 84 g/d soya oil
Dose aim: increase 84 g/d soya oil or 756 kcal or **37.8% E soya** (assume 50% LA, so **18.9% E LA**, assume 58% PUFA so **21.9% E PUFA)**
Baseline PUFA: unclear
Compliance by biomarkers: serum TC reported but without variance info, but TC lower in intervention than control consistently post-baseline. Report stated that, "tissue fat of the men on the soya-bean oil diet was less saturated than that of the controls" and that further information would be published elsewhere. No statistical significance or variance data mentioned.
Compliance by dietary intake: unclear

- Energy intake, kcal/d: intervention 2380 (SD not reported), control 2274 (SD not reported)
- Total fat intake: not reported
- SFA intake: not reported
- PUFA intake: not reported
- PUFA n-3 intake: not reported
- PUFA n-6 intake: not reported
- Trans fat intake: not reported
- MUFA intake: not reported
- CHO intake, g/d: intervention 243 (SD not reported), control 228 (SD not reported)
- Sugars intake, g/d: intervention 66 (SD not reported), control 60 (SD not reported)

- Protein intake, g/d: intervention 80 (SD not reported), control 88 (SD not reported)
- Alcohol intake: not reported

Compliance, other methods: not reported
Inclusion basis: aimed to replace SFA with PUFA.
PUFA dose: 21.9% E PUFA (aim)
Duration of intervention: 4 years

Outcomes Main trial outcomes: MI or sudden death
Dropouts: intervention 199 randomised, 181 at 2 years, 91 at 4 years. Control: 194 randomised, 172 at 2 years, 85 at 4 years
Available outcomes: mortality, CV mortality (CV deaths plus non-fatal MI), total MI, non-fatal MI (data for weight, TC and BP, but no variance info)
Response to contact: reply from trial statistician, JA Heady, in 1999

Notes Some data not usable due to lack of variance. For all, data at 4 years, control N = 89, intervention N = 88
Weight change: intervention 0 kg, control -3 kg
TC change: intervention -1.11 mmol/L, control -0.47 mmol/L
Systolic BP change: intervention +2 mmHg, control 0 mmHg
Diastolic BP change: intervention -1 mmHg, control +3 mmHg
Trial funding: Medical Research Council

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "using random numbers, by blocks within hospitals"
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias)	High risk	Big changes to fat intake in intervention group while control group ate their usual diet
Blinding of outcome assessment (detection bias)	Low risk	Quote: "Suspected relapses were assessed at regular intervals by a review committee unaware of the patients diet group"
Incomplete outcome data (attrition bias)	High risk	Data collection was thorough, but some participants dropped out and contact was lost.
Selective reporting (reporting bias)	Unclear risk	No protocol or trials registry entry located
Attention	High risk	Dietary intervention, control ate usual diet, so likely that intervention group received more time and support, though this is not clear from paper
Compliance	Low risk	TC lower in intervention than control consistently post-baseline. Report stated that "tissue fat of the men on the soya-bean oil diet was less saturated than that of the controls" and that further information would be published elsewhere.
Other bias	Low risk	None noted

MUFFIN Miller 2016 [352]

Methods RCT, prospective, open label, parallel group (n6 LA vs MUFA), 6 months
Summary risk of bias: Moderate or high

Participants Middle-aged men and women with metabolic syndrome
N: total randomised: 88 (analysed: int: 16; cont: 23)
Level of risk for CVD: Moderate
Male: 40% of all participants; NR by group.
Mean age (sd): 60.9 (8.5) for all participants; NR by group
Age range: 38-76 (all participants)
Smokers: NR
Hypertension: NR
Medications taken by at least 50% of those in the control group: NR

Medications taken by 20-49% of those in the control group: statins, ACE inhibitors
Medications taken by some, but less than 20% of the control group: NR
Location: USA
Ethnicity: 79% of total participants were African-American

Interventions Type: food supplement (PUFA enriched muffins with safflower oil or MUFA enriched with high oleic acid sunflower oil)
Comparison: PUFA vs MUFA
Intervention: 3x 3.5oz PUFA enriched muffins per day (including 27.6g/d PUFA; prepared in the metabolic kitchen of the USDA [Beltsville, MD]): PUFA 27.6g/d
Control: 3x 3.5oz MUFA enriched muffins per day (including 30.9g/d MUFA; prepared in the metabolic kitchen of the USDA [Beltsville, MD])
PUFA Dose: (intended) increase 27.6g/d LA, **12.4%E n-3, 12.4%E PUFA**
Compliance: 7 day food records at baseline and at end of 6m testing, including number of muffins consumed.
Duration of intervention: 6 months

Outcomes Main study outcome: Cardiometabolic benefit
Dropouts: 49 in total (n=88/110 randomised post AHA dietary baseline phase; n=39 completed 6-month dietary intervention)
Available outcomes: Adiposity, glucose, HOMA, insulin, lipids, Inflammatory markers: hs-CRP, IL-8, TNFα (glucose and HOMA not used due to baseline differences; bp. 6 months, not used)

Notes Supported by the Baltimore VA Geriatric Research Education and Clinical Center and Nutrition Obesity Research Center. No conflicts of interest declared

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation stated but no method
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias)	Unclear risk	Taste blinded for participants but no information about personnel blinding
Blinding of outcome assessment (detection bias)	Unclear risk	No detail provided for relevant outcomes
Incomplete outcome data (attrition bias)	High risk	Primary outcomes reported only for participants who completed the trial (39/88)
Selective reporting (reporting bias)	Unclear risk	No study registration or protocol was found
Attention	Low risk	Follow up appeared identical
Compliance	Unclear risk	No data provided regarding muffin compliance over trial; FA status data provided for 34/88 participants only
Other bias	Low risk	None noted

NAT2 2013 – ISRCTN98246501 [353-356]

Methods Nutritional AMD Treatment-2 (NAT2)
RCT, parallel, (EPA + DHA vs MUFA), 36 months
Summary risk of bias: low

Participants Patients with early age related macular degeneration
N: 150 intervention, 150 control
Level of risk for CVD: high (92.5% intervention and 79.8 controls had past CVD)
Men: 31.3% intervention, 39.5% control
Mean age in years (SD): 73.9 (6.6) intervention, 73.2 (6.8) control
Age range: 55-85
Smokers: 6.7% intervention, 8.5% control
Hypertension: 58% total (not reported by study arm)
Medications taken by at least 50% of those in the control group: lipid-lowering medication

Medications taken by 20%-49% of those in the control group: agents acting on renin-angiotensin system, anti-inflammatory and anti-rheumatic products
Medications taken by some, but less than 20% of the control group: insulin or blood sugar lowering drugs
Location: France
Ethnicity: unclear

Interventions Type: supplement (fish oil capsule)
Comparison: EPA + DHA vs MUFA
Intervention: 3 daily fish oil capsules containing 1110 total n-3 FAs (EPA: 270 mg/day DHA: 840 mg/day) and vit E: 6 mg/day. Dose: 1.1 g/d EPA + DHA
Control: 3 × 602 mg olive oil capsules a day containing 0.2 g total PUFA and vit E: 0.09 g/d
Compliance: assessed during visits from unused capsules and serum PUFA levels. Overall compliance over the 3 years; 69.4% intervention, 70.5% control
Length of intervention: 36 months

Outcomes Main study outcome: time to occurrence of choroidal new vessels (CNV) in the study eye from prospective assessment of fluorescein angiography
Dropouts: 29 intervention, 34 control
Available outcomes: all cause mortality, plasma lipids, adverse events, serum FAs
Response to contact: yes (no added data)

Notes TG data not used as presented as median (5th-95th percentile)
Study funding: Laboratoire Chauvin, Bausch & Lomb Inc

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	QL Ranclin software was used to generate the randomisation list before enrolment. The patients and the study personnel both were blinded to the treatment assignment
Allocation concealment (selection bias)	Low risk	As above
Blinding of participants and personnel (performance bias)	Low risk	The capsules had the same appearance, the same size, and the same weight (602 mg) in both DHA and placebo groups. No masking flavour was added to the capsules, which were otherwise odourless
Blinding of outcome assessment (detection bias)	Low risk	Author confirmed blinding of outcome assessors
Incomplete outcome data (attrition bias)	Low risk	Any temporary discontinuation of the treatment was considered to be a deviation from the study protocol. Discontinuation for more than 5 months was considered to be a major deviation from the study protocol. Participants who dropped out were taken in account in the survival analysis and occurrence of CNV and were counted at last angiography performed.
Selective reporting (reporting bias)	Unclear risk	ISRCTN98246501. Retrospectively registered May 2007, recruitment started December 2003, completed November 2008, key publication 2013
Attention	Low risk	Same amount of time spend with both study arms
Compliance	Low risk	Assessed during visits from unused capsules and serum PUFA levels. Overall compliance over the 3 years; 69.4% intervention, 70.5% control
Other bias	Low risk	None noted

NDHS Faribault 1968 [349 357-361]

Methods National Diet-Heart Study (NDHS) - Faribault site
RCT, several arms, parallel (n6 LA vs SFA), 1 year

Summary risk of bias: low

Participants Men living in a mental health institute
CVD risk: low
N: interventions B, C, E combined: randomised 167, analysed 143; control: randomised 57, analysed 52
Mean years in trial: interventions 0.9, control 1.0,
% male: 100
Age: unclear
Age range: all 45-54 years
Smokers: 55%-59% current smokers in each arm
Hypertension: unclear
Medications taken by ≥ 50% of those in the control group: not reported
Medications taken by 20%-49% of those in the control group: not reported
Medications taken by some, but < 20% of the control group: not reported
Location: USA
Ethnicity: not reported

Interventions Type: diet provided (residential institution)
Comparison: ↑ PUFA (n-6) vs usual institutional diet (SFA and MUFA)
Control aims: total fat 40% E, SFA 16%-18% E, dietary cholesterol 650-750 mg/d, P/S 0.4 (so PUFA 6.8% E) (whole diet provided)
Intervention aims: B (C, E) total fat 30% E (40% E, 40% E), SFA < 9% E (< 9% E, not stated), dietary cholesterol 350-450 mg/d (350-450 mg/d, not stated), PUFA 15% E (18-20% E, not stated), P/S 1.5 (2.0, 4.4) (equivalent to Minnesota Coronary Trial diet) (whole diet provided)
Dose aim: increase **B 8.2% E, C 12.2% E, E unclear n-6**
Baseline n-6 (table IX2): 4.4% E LA, 4.8% E PUFA
Compliance by biomarkers: serum TC significantly reduced in intervention compared to control (-0.91 mmol/L, 95% CI -1.17 to -0.65). Fatty acid composition of red blood cells suggests that LA was higher in intervention arms (table X6: LA rose by 4 in control, by 5-7 in other arms, at the expense of MUFA, which rose by 1 in control, fell by 4 or 5 in other arms. Palmitic acid fell by 5 in control, and fell by 4 in intervention arms, stearic did not alter in control, rose by 1 or 2 in intervention arms - no statistical significance or variance info provided, units unclear, probably % of LA+oleic+palmitic+stearic)
Compliance by dietary intake: good. Assessed from 7-day food records after 28 and 44 weeks combined (tables IX8&9)

- Energy intake, kcal/d: intervention B 2549, intervention C 2599, intervention E 2560, control D 2593
- Total fat intake, % E: intervention B 29.0, intervention C 38.5, intervention E 37.1, control 39.5 (decrease **B 10.5% E, C 1.0% E, E 2.4 total fat)**
- SFA intake, % E: intervention B 6.1, intervention C 7.0, intervention E 4.6, control D 15.6 (decrease **B 9.5% E, C 8.6% E, E 11.0% E SFA)**
- PUFA intake, % E: intervention B 12.1, intervention C 17.8, intervention E 22.3, control D 4.6 (increase **B 7.5%E, C 13.2% E, E 17.7% E PUFA)**
- PUFA n-3 intake: not reported
- PUFA n-6 intake, % E LA: intervention B 11.6, intervention C 16.9, intervention E 21.9, control D 4.3 (increase **B 7.3% E, C 12.6% E, E 17.6% E LA)**
- Trans fat intake: not reported
- MUFA intake, % E: intervention B 10.8, intervention C 13.7, intervention E 10.2, control D 19.3 (decrease **B 8.5% E, C 5.6% E, E 9.1% E MUFA)**
- CHO intake, % E: intervention B 55.3, intervention C 45.8, intervention E 48.6, control D 45.1 (increase **B 10.1% E, C 0.7% E, E 3.5% E CHO)**
- Sugars intake: not reported
- Protein intake, % E: intervention B 17.0, intervention C 16.7, intervention E 15.7, control D 16.4 (increase **B 0.6% E, C 0.3% E, E -0.7% E protein)**
- Alcohol intake: not reported

Compliance, other methods: 3.6% of days were lost (diet not eaten)
Inclusion basis: aimed to increase PUFA intake as well as increase PUFA/SFA, reduce SFA slightly and reduce dietary cholesterol.
PUFA dose: B 7.5% E, C 13.2% E, E 17.7% E PUFA
Duration of intervention: 1 year

Outcomes Main trial outcomes: lipid levels and dietary assessment
Dropouts: B 7, C 10, E 7, D (control) 5
Available outcomes: mortality, TC (weight and TG data available but without SDs)

Response to contact: not attempted as trial completed in 1967

Notes

Data entered as all interventions combined (B+C+E) vs control (D)
Dose calculations
Interventions: B PUFA 15% E, ↑8.2% E
Control: 17% E SFA, P/S 0.4 so PUFA 6.8% E
C PUFA 19% E, ↑12.2% E
D unclear ↑% E?
Mean for all interventions ↑10.2% E
Trial funding: National Heart Institute

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Stratified randomisation by the statistical centre
Allocation concealment (selection bias)	Low risk	As above
Blinding of participants and personnel (performance bias)	Low risk	Institution so all participants and trial staff blinded to allocation
Blinding of outcome assessment (detection bias)	Low risk	Outcome assessors were reported as blinded to treatment allocation
Incomplete outcome data (attrition bias)	Low risk	Institution so able to follow-up all participants through trial.
Selective reporting (reporting bias)	Unclear risk	No protocol or trials registry entry found
Attention	Low risk	Equivalent, diet provided to both groups
Compliance	Low risk	TC significantly reduced in intervention compared to control (-0.91 mmol/L, 95% CI -1.17 to -0.65). Fatty acid composition of red blood cells suggests LA was higher in intervention arms
Other bias	Low risk	None found

NDHS Open 1st 1968 [349 357-361]

Methods

National Diet-Heart Study (NDHS) - open first phase
RCT, several arms, parallel (n6 LA vs SFA), 1 year
Summary risk of bias: low

Participants

Free-living men aged 45-54 years
CVD risk: low
Interventions B, C, X combined: randomised 829, analysed 726
Control: randomised 382, analysed 341
Mean years in trial: control 0.95, Interventions 0.93
% male: 100
Age: unclear
Age range: all 45-54 years
Smokers: 39%-40% current smokers in each arm
Hypertension: unclear
Medications taken by ≥ 50% of those in the control group: not reported
Medications taken by 20%-49% of those in the control group: not reported
Medications taken by some, but < 20% of the control group: not reported
Location: USA
Ethnicity: white 98.2%, non-white 1.8% (not reported by intervention arm)

Interventions

Type: diet provided (bought from a trial shop)
Comparison: ↑ PUFA (n-6) vs usual diet (replacement of SFA and MUFA)
Control aims: total fat 40% E, dietary cholesterol 650-750 mg/d, P/S 0.4 (assume PUFA 6.8% E as at Faribault) (foods bought from a trial shop - normal foods)
Intervention aims: B (C, X) total fat 30% E (40% E, 30% E), SFA < 9% E (< 9% E, < 9% E), dietary cholesterol 350-450 mg/d (350-450 mg/d, 350-450 mg/d), PUFA 15% E (18% E-20% E,

15% E), P/S 1.5 (2.0, 1.5) (foods bought from a trial shop - SFAs removed and replaced by polyunsaturated oils and fats)
Dose aim: increase **B 8.2% E, C 12.2% E, X 8.2% E n-6**
Baseline n-6 (tables IX 1&3): 3.7% LA, 3.9% PUFA
Compliance by biomarkers: serum TC significantly reduced in intervention compared to control (-0.45 mmol/L, 95% CI -0.55 to -0.35). Data on fatty acid composition of red blood cells provided in chapter 10 (table X6: LA rose by 1 in control, by 2-3 in other arms, at the expense of MUFA which did not alter in control, fell by 2-3 in other arms. Palmitic acid remained constant in control and remained constant or fell by 1 in intervention arms, stearic did not alter in control and remained constant or rose by 1 in intervention arms - no statistical significance or variance info provided, units unclear, probably % of LA+oleic+palmitic+stearic).
Compliance by dietary intake: good. Nutritionists' subjective adherence ratings of excellent or good (as compared to fair or poor) intervention B 58%, intervention C 60%, control D 55%.
Dietary intake computed from 7-day food records at 28 weeks (table IX3, no later data found):

- Energy intake, kcal/d: intervention B 2154 (SD432), intervention C 2262 (SD435), intervention X 2117 (SD447), control D 2228 (SD456)
- Total fat intake, % E: intervention B 29.7, intervention C 34.4, intervention X 31.7, control D 34.9 (decrease **B 5.2% E, C 0.5% E, X 3.2 total fat)**
- SFA intake, % E: intervention B 7.1, intervention C 7.4, intervention X 8.9, control D 11.6 (decrease **B 4.5% E, C 4.2% E, X 2.7% E SFA)**
- PUFA intake, % E: intervention B 9.9, intervention C 13.2, intervention X 6.5, control D 4.9 (increase **B 5.0% E, C 8.3% E, X 1.6 PUFA)**
- PUFA n-3 intake: not reported
- PUFA n-6 intake: not reported, probably similar to PUFA
- Trans fat intake: not reported
- MUFA intake, % E (by subtraction of SFA and PUFA from total fat): intervention B 12.7, intervention C 13.8, intervention X 16.3, control D 18.4 (decrease **B 5.7% E, C 4.6% E, X 2.1% E MUFA)**
- CHO intake, % E: intervention B 48.7, intervention C 45.3, intervention X 49.5, control D 44.7 (increase **B 4.0% E, C 0.6% E, X 4.8% E CHO)**
- Sugars intake: not reported
- Protein intake, % E: intervention B 18.6, intervention C 17.6, intervention X 17.1, control D 17.4 (increase **B 1.2% E, C 0.2% E, X -0.3% E protein, little change)**
- Alcohol intake, % E: intervention B 2.1, intervention C 2.1, intervention X 1.7, control D 2.2 (minimal change)

Compliance, other methods: also assessed adherence ratings by nutritionists, subjectively, by recall and by food records. Poor adherence by 17%-29%, others were fair, good or excellent.
Inclusion basis: aimed to increase PUFA intake as well as increase PUFA/SFA, reduce SFA slightly and reduce dietary cholesterol.
PUFA dose: achieved **B 5.0% E, C 8.3% E, X 1.6 PUFA**
Duration of intervention: 1 year

Outcomes

Main trial outcomes: lipid levels and dietary assessment
Dropouts: intervention B 42, C 34, X 5, control D 36
Available outcomes: CV events (MI and PV events), cancer diagnoses, TC (weight, diastolic BP and TG data available but without SDs)
Response to contact: not attempted as trial completed in 1967

Notes

All intervention arms combined for data analysis
Aim was to replace saturates with polyunsaturates, but oils used were omega-6 fats
Dose calculations
Control: assume from Faribault 17% E SFA, P/S 0.4 so PUFA 6.8% E
Interventions: B PUFA 15% E, ↑8.2% E
C PUFA 19% E, ↑12.2% E
X PUFA 15% E, ↑8.2% E Mean for all interventions ↑10% E
Trial funding: National Heart Institute

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Stratified randomisation by the statistical centre
Allocation concealment (selection bias)	Low risk	Stratified randomisation by the statistical centre

Blinding of participants and personnel (performance bias)	Low risk	Participants and trial personnel (aside from the store manager) were blinded to allocation. Blinding of participants was checked using a questionnaire, which found no difference between intervention and control participants in guesses at dietary composition.
Blinding of outcome assessment (detection bias)	Low risk	Outcome assessors were reported as blinded to treatment allocation
Incomplete outcome data (attrition bias)	Low risk	12% dropouts, well described
Selective reporting (reporting bias)	Unclear risk	No protocol or trial registry entry found
Attention	Low risk	Equivalent, both groups bought special foods from trial shop
Compliance	Low risk	TC significantly reduced in intervention compared to control (-0.45 mmol/L, 95% CI -0.55 to -0.35). Data on fatty acid composition of red blood cells shows LA rose by 1 in control, by 2-3 in other arms, at the expense of MUFA, which did not alter in control, fell by 2 or 3 in other arms.
Other bias	Low risk	None noted

NEURAPRO 2017 – ACTRN12608000475347 [362-364]

Methods RCT, parallel, (n3 EPA+DHA vs non-fat), 6 months
Summary risk of bias: Moderate or high

Participants Population: Young people at ultra-high risk for psychotic disorders
N: 153 int., 151 control. (analysed, int: 114 cont: 111)
Level of risk for CVD:
Male: 45.7% for all participants.
Mean age (sd): 19.1 (4.6) for all participants
Age range: NR
Smokers: NR
Hypertension: NR
Medications taken by at least 50% of those in the control group: NR
Medications taken by 20-49% of those in the control group: NR
Medications taken by some, but less than 20% of the control group: NR
Location: Australia, Switzerland, Germany, China, Austria, Singapore, Netherlands
Ethnicity: NR
Depression: Long term condition (high risk)
Anxiety: Long term condition (high risk)

Interventions Type: supplement
Comparison: n-3 capsules vs paraffin & coconut oil
Intervention: 2.8g/d marine fish oil containing ~1.4g n3 (840mg/d EPA, 560mg/d DHA) in 4 X 0.700g capsules/d, administered orally. Plus cognitive behavioural case management (CBCM): A manualised intervention of cognitive-behavioural therapy (CBT) embedded within case management.
Control: The placebo capsule will match the fish oil capsules in size and appearance contain paraffin/coconut oil, tocopherols to match the content in the active ingredient and a small proportion of the fish oil to ensure the placebo capsules have the same odour as the active capsules. Plus CBCM.
Compliance: Patient compliance was assessed by monthly pill counts over the first 6 months of the study, as well as through the measurement of the essential fatty acid content of red blood cells from blood samples collected at baseline and 6 months after study entry (or at the transition assessment if applicable).
There were 66 adherent participants (43.1%) in the ω-3 PUFA group and 62 in the placebo group (41.1%). However, a total of 83 participants had missing data for the capsule counts (ω-3 PUFA, 35; placebo, 48), 9 of whom(10.8%) transitioned to psychosis. To avoid losing participants from the analysis, these 83 individuals were assumed to be nonadherent
Duration of intervention: 6 months

Outcomes Main study outcome: transition to psychosis status at 6 months.
Dropouts: 39 int., 40 control
Available outcomes: general levels of psychopathology and functioning,

BPRS, SANS, YMRS, MADRS, SOFAS, Global functioning (social), Global functioning (role)

Notes Study funding: This work was supported by grant 07TGF-1102 from the Stanley Medical Research Institute, grant 566529 from the NHMRC Australia Program (Drs McGorry, Hickie, and Yung,and Amminger), and a grant from the Colonial Foundation. Dr McGorry was supported by Senior Principal Research Fellowship 1060996 from the National Health and Medical Research Council of Australia (NHMRC); Drs Yung and Amminger were supported by NHMRC Senior Research Fellowships 1080963 and 566593, respectively; and Dr Nelson was supported by NHMRC Career Development Fellowship 1027532.
Role of the Funder/Sponsor: The funding sources of this study have had no input into the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The design is a randomized placebo controlled trial. Subjects will be randomized with a computer generated randomisation code at entry to one of two treatment groups. The randomization will be stratified by site and the Montgomery Asberg Depression Rating Scale (MADRS) (total score <21 or ≥21), as both depression and antidepressants may impact on prodromal symptoms and illness progression.
Allocation concealment (selection bias)	Unclear risk	NR
Blinding of participants and personnel (performance bias)	Low risk	The study medication will be identified by a code linked to the randomization chart. An independent person (typically a pharmacist) at each site will be provided with unblinding envelopes to ensure that unblinding can occur if necessary. Unblinding will only be permitted in the case of a medical emergency and will be documented. Paraffin oil was specifically chosen as placebo because it does not contain PUFAs and has no impact on omega-3 PUFA metabolism. Placebo capsules were carefully matched in appearance and flavour with the active treatment to preserve blinding. The placebo capsules also contained the same amount of vitamin E as the fish oil capsules, and approximately 1% fish oil to mimic taste.
Blinding of outcome assessment (detection bias)	Unclear risk	NR
Incomplete outcome data (attrition bias)	Unclear risk	NR
Selective reporting (reporting bias)	High risk	The trial was registered: ACTRN12608000475347. Date registered: 1/09/2008 date data collection began: 16/03/2010. However a number of secondary outcomes were not reported in the results paper; SPI-A, PAS, structured interview.
Attention	Unclear risk	NR
Compliance	High risk	Patient compliance was assessed by monthly pill counts over the first 6 months of the study, as well as through the measurement of the essential fatty acid content of red blood cells from blood samples collected at baseline and 6 months after study entry (or at the transition assessment if applicable). There were 66 adherent participants (43.1%) in the ω-3 PUFA group and 62 in the placebo group (41.1%).
Other bias	Unclear risk	None noted

Nigam 2014 [365]

Methods RCT, parallel, (n3 ALA vs n6 LA vs MUFA), 6 months
Summary risk of bias: Moderate or high

Participants People with non-alcoholic fatty liver disease
N: 30 n6 int., 33 ALA int, 30 MUFA control. (analysed 30 n6 int., 30 ALA int, 30 MUFA control)
Level of risk for CVD: moderate
Male: 100% n6 int., 100% ALA int, 100% MUFA control
Mean age (sd): 36.2 (7.1) n6 int., 38.0 (6.4) ALA int, 37.2 (6.2) MUFA control
Age range: NR but 20-50years were the inclusion criteria
Smokers: NR
Hypertension: NR
Medications taken by at least 50% of those in the control group: NR
Medications taken by 20-49% of those in the control group: NR
Medications taken by some, but less than 20% of the control group: NR
Location: India
Ethnicity: Asian Indians

Interventions Type: food
Comparisons: n6 vs MUFA, also ALA vs MUFA, also ALA vs n6
n6 Intervention: to use up to 20g/d of soybean or safflower oil for cooking (15-24% MUFA, 50-60% PUFA, n6/n3 7 for soya or >100 for safflower)
ALA Intervention: to use up to 20g/d of canola oil for cooking (61% MUFA, 7% SFA, 21%n6 PUFA, 11% ALA): ALA 2.2g/d
Control: to use up to 20g/d of olive oil for cooking (70% MUFA, 15% SFA, 9%n6 PUFA, 1% ALA)
Dietary counselling was given to all participants.
PUFA Dose: unclear
Compliance: Assessed using FFQ, 24 hour recall and 3 day food diary (unclear how many or how often). Paper states that 1 person was excluded from the canola group for non-compliance but this was not defined. No further compliance details.
Duration of intervention: 6 months

Outcomes Main study outcome: blood glucose control
Dropouts: 0 of 30 n6 int., 3 of 33 ALA int, 0 of 30 MUFA control
Available outcomes: glucose, insulin, HOMA, serum triglycerides, adiposity, (also disposition index, liver span, LFTs provided but not used)
Author contact: not yet

Notes Study funding: Dalmin Continental
Comparisons used: ALA vs MUFA for the effect n3, N6 vs MUFA for the effect of N6, ALA vs LA for n3 vs n6 comparison.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Paper states "randomly allocated by computer-generated number"
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias)	High risk	Appears to be an open study without blinding
Blinding of outcome assessment (detection bias)	High risk	Open label, no further details
Incomplete outcome data (attrition bias)	Low risk	3 of 93 dropped out (3%), reasons given
Selective reporting (reporting bias)	Unclear risk	No protocol or trial register entry found
Attention	Low risk	The study only differed by the content of the oils, but the assessment schedule was not stated to differ between the two arms
Compliance	Unclear risk	Not reported

Other bias	Low risk	None noted

Niki 2016 [366]

Methods	RCT, parallel, (n3 EPA vs nil (both with strong statin)), 6 months Summary risk of bias: Moderate or high
Participants	Patients with angina and hypertension treated with strong statins N: 48 int., 47 control, but only 62 received treatment (?) (analysed, int: 29 cont: 30) Level of risk for CVD: high Male: 72% int., 63% control. Mean age (sd): 68.1 (10.1) int., 69.4 (10.7) control Age range: NR Smokers: 0% both arms Hypertension: 100% both arms Medications taken by at least 50% of those in the control group: statins, aspirin (100%), thienopyridine (anti-platelet, 100%) Medications taken by 20-49% of those in the control group: ACE inhibitors 23%, Angiotensin II receptor blocker 37%, calcium channel blocker 43%, beta-blockers 30% Medications taken by some, but less than 20% of the control group: NR Location: Japan Ethnicity: NR
Interventions	Type: supplement Comparison: EPA ester vs nil Intervention: 1.8g/d EPA ester (brand and form unclear): EPA 1.8g/d Control: nil **PUFA Dose**: (intended) increase 1.8g/d EPA, **0.8%E n-3, 0.8%E PUFA** Compliance: NR Duration of intervention: 6 months
Outcomes	Main study outcome: inflammatory cytokines Dropouts: 2 int., 1 control Available outcomes: HDL and LDL cholesterol, glucose, HbA1c, hs-CRP, TNF alpha, IL-6 (no deaths, MI or revascularisation occurred in either arm, TG reported but too different at baseline, PTX3, MMP-3, MMP-9, MCP-1, BP, lumen, plaque & lipid volume reported but not used)
Notes	Study funding: NR, senior author received lecture fees from 3 pharmaceutical companies

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"allocated to 2 groups using computer assisted permuted-block randomization with random block size of 4–6”
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias)	High risk	Open label (no placebo)
Blinding of outcome assessment (detection bias)	Unclear risk	Unclear, assessors blinded to clinical characteristics, but unclear if blinded to allocation
Incomplete outcome data (attrition bias)	High risk	While 95 were allocated only 62 were treated (unclear what this means in terms of control group who received no placebo)
Selective reporting (reporting bias)	Unclear risk	No protocol or trials registry entry located
Attention	Low risk	There appear to have been similar numbers and duration of appointments
Compliance	Unclear risk	Not reported
Other bias	Low risk	None noted

Nishio 2014 [367]

Methods	RCT, parallel, (n3 EPA vs nil, both with statin), 9 months Summary risk of bias: Moderate or high Aim: "to assess the impact of adding EPA to a standard statin therapy on vulnerable plaques"
Participants	People with untreated dyslipidaemia and thin-cap fibroatheroma N: 16 int., 15 control. (analysed, int: 15 cont: 15) Level of risk for CVD: High (all were at increased risk, and over half had had ACS) Male: 87% int., 87% control. Mean age (sd) yrs: 61 (12.6) int., 63.8 (9.5) control Age range: NR Smokers: 80% int., 60% control Hypertension: 73% int., 67% control Medications taken by at least 50% of those in the control group: aspirin (100%), clopidogrel (100%), ACE-I or ARB (60%) Medications taken by 20-49% of those in the control group: beta-blockers (20%), calcium channel blockers (33%) Medications taken by some, but less than 20% of the control group: antidiabetic agents (13%) Location: Japan Ethnicity: NR
Interventions	Type: supplement Comparison: EPA vs nil Intervention: 1.8g/d EPA plus rosuvastatin (dose adjusted to reach LDL <70mg/dl or <1.8mmol/l): EPA 1.8g/d Control: no placebo, just rosuvastatin (dose adjusted to reach LDL <70mg/dl or <1.8mmol/l) Compliance: assessed using blood lipids, statistically significant difference in EPA/AA ratio in blood lipids at 9 months between arms (p=0.0001) Duration of intervention: 9 months
Outcomes	Main study outcome: stabilisation of thin-cap fibroatheroma Dropouts: 1 of 16 int., 0 of 15 control Available outcomes: hs-CRP at 9 months (lipids, pentraxin-3 and optical coherent tomography data such as cap thickness, lipid length and macrophage accumulation not used, no death or MI occurred, restenosis was noted in 2 intervention and 1 control participants over 18 months of follow up, revascularisation of target plaques in 1 int, 2 cont and revascularisation of non-target plaques in 1 int and 1 control over the 18 months.
Notes	Study funding: Not stated, 3 authors received consulting fees from St Jude Medical Author contact: not yet

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Paper states "randomly assigned", no further details
Allocation concealment (selection bias)	Unclear risk	No further details
Blinding of participants and personnel (performance bias)	High risk	No placebo
Blinding of outcome assessment (detection bias)	Unclear risk	Blinding of assessors not mentioned apart from OCT examination (we did not use this outcome)
Incomplete outcome data (attrition bias)	Low risk	1 dropout only, reason given
Selective reporting (reporting bias)	Unclear risk	No protocol or trials registry entry found
Attention	Unclear risk	Appears similar in appointments periods and dietary counselling for both groups, but few details.
Compliance	Low risk	Statistically significant difference in EPA/AA ratio in blood lipids at 9 months between arms (p=0.0001)
Other bias	Low risk	None noted

Nodari 2009 [368]

Methods RCT, parallel, (n3 EPA+DHA vs MUFA), 6 months
Summary risk of bias: Moderate or high
Aim: "assessed the effects of n-3 PUFAs administration on parameters related to arrhythmic risk... in patients with idiopathic dilated cardiomyopathy (IDC)"

Participants People with cardiomyopathy and frequent or repetitive ventricular arrhythmia
N: 22 int., 22 control. (analysed, int: 21 cont: 20)
Level of risk for CVD: high
Male: 95% int., 86% control.
Mean age (sd) yrs: 61.1 (11.2) int., 64.8 (9.5) control
Age range: NR
Smokers: NR
Hypertension: NR
Medications taken by at least 50% of those in the control group: ACE inhibitors 77%, beta blockers 100%, aldosterone 54%, furosemide 95%, amiodarone 95%
Medications taken by 20-49% of those in the control group: ARBs 23%
Medications taken by some, but less than 20% of the control group: NR
Location: Italy
Ethnicity: NR

Interventions Type: supplement
Comparison: EPA+DHA vs y
Intervention: 5x1g capsules for 1 month then 1 capsule/d for the remaining 5 months (later stable dose 0.87g/d EPA plus 1.44g/d DHA): EPA+DHA 2.31g/d
Control: 5x1g capsules for 1 month then 1 capsule/d of olive oil for the remaining 5 month, of identical appearance to intervention
Compliance: assessed by plasma EPA, DHA and DPA, which increased in the intervention, but not the control, group
Duration of intervention: 6 months

Outcomes Main study outcome: arrhythmic risk
Dropouts: 1 of 22 int., 2 of 22 control
Available outcomes: IL6, TNF alpha (arrhythmia and cancers also reported, but only 6 month intervention)

Notes Study funding: SPA sponsored the cytokines and PUFA assays
Author contact: Not yet

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"randomised"
Allocation concealment (selection bias)	Unclear risk	No further details
Blinding of participants and personnel (performance bias)	Unclear risk	Study reported as double blind, same dose regimen used for both arms, capsules are stated to be of identical appearance. However no information provided as to taste or smell.
Blinding of outcome assessment (detection bias)	Low risk	Stated as double blind, no supporting methodology, but our outcomes are biochemical in nature
Incomplete outcome data (attrition bias)	Low risk	ITT analysis, with last observed assessment used. Few dropouts, similar between arms.
Selective reporting (reporting bias)	Unclear risk	No protocol or trials register entry found
Attention	Low risk	Appeared similar for both arms
Compliance	Low risk	Plasma EPA, DHA and DPA all statistically significantly higher in intervention group than control at 6 months
Other bias	Low risk	None noted

Nodari 2011 AF – NCT01198275 [369]

Methods	RCT, parallel, (DHA + EPA vs MUFA), 12 months Summary risk of bias: moderate or high
Participants	Patients with persistent atrial fibrillation with at least 1 relapse after cardioversion N: 102 intervention, 103 control. (analysed, intervention: 94 control: 94) Level of risk for CVD: high Men: 70% intervention, 63% control Mean age in years (SD): 70 (6) intervention, 69 (9) control Age range: not reported (18-80 inclusion criteria) Smokers: 10% intervention, 9.1% control Hypertension: 47% intervention, 40% control Medications taken by at least 50% of those in the control group: beta-blockers, ACE inhibitors, anticoagulant therapy, amiodarone Medications taken by 20%-49% of those in the control group: diuretics, antiplatelet, statins Medications taken by some, but less than 20% of the control group: calcium channel blockers Location: Italy Ethnicity: not reported
Interventions	Type: supplement (omega-3-acid ethyl esters 90: Omacor) Comparison: EPA + DHA vs MUFA Intervention: 2 × 1 g/d Omacor (total 1.7 g/d EPA + DHA at a ratio of 0.9 to 1.5). Dose: 1.7 g/d EPA + DHA Control: 2 × 1 g/d olive oil (gelatin capsules identical in appearance to Omacor) Compliance: no details Duration of intervention: 12 months
Outcomes	Main study outcome: probability of maintenance of sinus rhythm Dropouts: 6 intervention, 5 control Available outcomes: adverse events, AF recurrence (nil death) Response to contact: no
Notes	Study funding: 'Centro per lo Studio ed il Trattamento dello Scompenso Cardiaco' of the University of Brescia, Brescia, Italy. The work of Dr Campia was supported by National Institutes of Health grant K12 HL083790-01a1

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random assignment followed a computer-generated randomisation list obtained using blocks of size 4
Allocation concealment (selection bias)	Low risk	The randomisation schedule was kept in the research pharmacy area and was available only to unblinded pharmacy personnel until after the database was locked. At that time, the unblinded patient treatment information was made available to the investigators.
Blinding of participants and personnel (performance bias)	Unclear risk	Placebo gelatin capsules identical in appearance to Omacor. However no information provided as to their smell and taste.
Blinding of outcome assessment (detection bias)	Unclear risk	No details
Incomplete outcome data (attrition bias)	Low risk	All randomised were accounted for. ITT analysis for main outcomes
Selective reporting (reporting bias)	Unclear risk	NCT01198275. Registered retrospectively in September 2010, study started January 2006, completed May 2008, main publication 2011
Attention	Low risk	No difference between groups
Compliance	Unclear risk	No details
Other bias	Low risk	None noted

Nodari 2011 HF - NCT01223703 [370-373]

Methods	RCT, parallel, (DHA + EPA vs MUFA), 12 months Summary risk of bias: moderate or high
Participants	People with heart failure (non-ischaemic dilated cardiomyopathy) N: 67 intervention, 66 control. (analysed, intervention: 67 control: 66) Level of risk for CVD: high Men: 95.5% intervention, 84.9% control Mean age in years (SD): 61 (11) intervention, 64 (9) control Age range: not reported (18-75 inclusion criteria) Smokers: not reported Hypertension: not reported Medications taken by at least 50% of those in the control group: beta-blockers, ACE inhibitors, furosemide, amiodarone, aldosterone blockers Medications taken by 20%-49% of those in the control group: not reported Medications taken by some, but less than 20% of the control group: statins, ARB Location: Italy Ethnicity: not reported
Interventions	Type: supplement (Omacor) Comparison: EPA + DHA vs MUFA Intervention: 2 × 1 g/d Omacor (1.7 g/d EPA + DHA at a ratio of 0.9 to 1.5) Control: 2 × 1 g/d olive oil (gelatin capsules identical in appearance to Omacor) Compliance: pill counts – participants were withdrawn if < 80% capsules taken (none were withdrawn). Fatty acid EPA + DHA 0.83% in intervention group, 0.41% in control group. Duration of intervention: 12 months
Outcomes	Main study outcome: left ventricular function and functional capacity Dropouts: 0 intervention, 0 control Available outcomes: mortality (nil death), combined CVD events, AF, BMI, hospitalisation for cardiovascular reasons, hospitalisation for worsening heart failure, lipids, blood glucose (but too different at baseline to use), serum cytokine Response to contact: yes
Notes	Study funding: Centro per lo Studio ed il Trattamento dello Scompenso Cardiaco, one author was a consultant for 8 pharmaceutical companies

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomised"
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias)	High risk	Paper states that placebo and verum were identical and that the study was double blind, but blinding of participants not checked. Author confirmed investigators not blinded
Blinding of outcome assessment (detection bias)	High risk	Author confirmed assessors not blinded
Incomplete outcome data (attrition bias)	Unclear risk	Unclear whether all participants were assessed for all outcomes (e.g. hospitalisation), but some outcomes report no attrition
Selective reporting (reporting bias)	Unclear risk	NCT01223703 – study registration October 2010, recruitment November 2007 to June 2009. Retrospective
Attention	Low risk	No suggestion of this, and investigators appeared blinded (so could not differ in attention provided by allocation)
Compliance	Low risk	See characteristics table

Other bias	Low risk	None noted

Nogueira 2016 – NCT01992809 [374 375]

Methods RCT, parallel, (n3 EPA+DHA vs non-fat), 6 months
Summary risk of bias: Moderate or high

Participants Patients with non-alcoholic steatohepatitis
N: 32 int., 28 control. (analysed, int: 27 cont: 23)
Level of risk for CVD: Low
Male: 14.8% int., 21.7% control
Mean age (sd): 52.5 (7.2) int., 53.9 (6.8) control
Age range: NR
Smokers: NR
Hypertension: NR
Medications taken by at least 50% of those in the control group: NR
Medications taken by 20-49% of those in the control group: NR
Medications taken by some, but less than 20% of the control group: NR
Location: Brazil
Ethnicity: NR

Interventions Type: supplement (capsules with n-3 PUFA or mineral oil)
Comparison: n-3 (EPA+DHA+ALA) vs nil
Intervention: 3 capsules/d omega 3 (including 0.6g/d ALA, 0.194g/d EPA + 0.15g/d DHA, Amway): EPA+DHA 0.345g/d plus ALA 0.6g/d
Control: 3 capsules/d placebo mineral oil capsules
PUFA Dose: (intended) increase 1.0g/d EPA+DHA+ALA, **0.5%E n-3, 0.5%E PUFA**
Compliance: Plasma fatty acid changes
Duration of intervention: 6 months

Outcomes Main study outcome: NAS activity
Dropouts: 5 int., 5 control
All Outcomes collected but unusable due to unclear interpretation about % improvement: Lipids, anthropometrics, glucose, insulin, HbA1c, inflammatory markers

Notes Study funding: University of Sao Paulo. Author contacted (July 2017) but no reply.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated sequence
Allocation concealment (selection bias)	Unclear risk	"Included patients were enrolled in the study by two trained investigators following this randomization sequence"
Blinding of participants and personnel (performance bias)	Unclear risk	Double-blind and "identical" capsules. However no information provided as to their smell and taste.
Blinding of outcome assessment (detection bias)	Unclear risk	With the exception of an independent dietician, staff remained blinded until the end of the statistical analysis of the trial
Incomplete outcome data (attrition bias)	Low risk	8% Drop outs balanced by group, with reasons given
Selective reporting (reporting bias)	Unclear risk	Not all outcomes clearly reported
Attention	Low risk	No suggestion of this
Compliance	Low risk	Significant change in plasma fatty acids
Other bias	Low risk	None noted

Nomura 2009 [376]

Methods	RCT, parallel, (n3 EPA vs nil, both with statins), 6 months Summary risk of bias: Moderate or high
Participants	Hyperlipidaemic type 2 diabetics N: 72 int., 64 control. (analysed, int: 72 cont: 64) Level of risk for CVD: Moderate Male:52.9% in both groups combined Mean age (sd): 65 (3) in both groups combined Age range: NR Smokers: 11% in both groups combined Hypertension: 44% in both groups combined Medications taken by at least 50% of those in the control group: NR Medications taken by 20-49% of those in the control group: NR Medications taken by some, but less than 20% of the control group: Insulin, aspirin, ticlopidine, Ca-antagonists, ARBs, sulfonylureas, alpha-glucoside inhibitors Location: Japan Ethnicity: NR
Interventions	Type: supplement (EPA + Pitavastatin vs Pitavastatin) Comparison: EPA vs none Intervention: Daily capsules (1.8g/d EPA + 2mg/d Pitavastatin): EPA 1.8g/d Control: Daily capsules (2mg/d Pitavastatin) Compliance: NR Duration of intervention: 6 months
Outcomes	Main study outcome: Platelet-derived microparticles and adiponectin Dropouts: NR Available outcomes: Lipids and HbA1c (HbA1c not in useable format- baseline differences)
Notes	A third arm (EPA only) was also included (n=55) Study funding: Grant from the Japan Foundation of Neuropsychiatry and Hematology Research, grant for Advanced Medical Care from the Ministry of Health and Welfare of Japan, and a grant from the Ministry of Education, Science and Culture of Japan

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"randomly selected"
Allocation concealment (selection bias)	Unclear risk	As above
Blinding of participants and personnel (performance bias)	Unclear risk	Not reported
Blinding of outcome assessment (detection bias)	Unclear risk	Not reported
Incomplete outcome data (attrition bias)	Unclear risk	Not reported and blinding not clear
Selective reporting (reporting bias)	Unclear risk	No registry or protocol identified
Attention	Unclear risk	Not reported
Compliance	Unclear risk	Not reported
Other bias	Low risk	None noted

Norouzi 2014 – NCT01311375 [377 378]

Methods	RCT, parallel, (MorDHA capsules vs unclear placebo), 14 months Summary risk of bias: moderate or high
Participants	Patients with chronic traumatic spinal cord injury N: 55 intervention, 55 control. (analysed, intervention: 54 control: 50) Level of risk for CVD: low

Men: 81.5% intervention, 82% control
Mean age in years (SD): 51.15 (13.43) intervention, 54.12 (11.76) control
Age range: 15-74 years intervention, 30-74 years control
Smokers: 0% (exclusion criteria)
Hypertension: not reported
Medications taken by at least 50% of those in the control group: not reported
Medications taken by 20%-49% of those in the control group: not reported
Medications taken by some, but less than 20% of the control group: not reported
Location: Iran
Ethnicity: not reported

Interventions Type: supplement (n-3 capsules)
Comparison: EPA + DHA vs placebo (unclear what)
Intervention: 2 MorDHA capsules (providing 870 mg DHA and 130 mg EPA) per day. Dose: 1 g/d DHA + EPA
Control: 2 placebo capsules per day. Both capsules were similar in colour, shape, and taste. Both groups received one calcium capsules per day consisting of 1000 mg calcium and 400 IU vitamin D.
Compliance: pill counts – compliance averaged 80% in both groups
Duration of intervention: 14 months

Outcomes Main study outcome: professionals evaluation of neurological function
Dropouts: 1 intervention, 5 control
Available outcomes: functional measures (total and sub-scales), BMI, leptin and adiponectin concentration.
Response to contact: no

Notes Study funding: PhD university funding. Omega 3 capsules were provided by Minami Nutrition Co (Aartselaar, Belgium) and placebo capsules were supplied by Zahravi Pharmaceutical Co. (Tabriz, Iran). Calcium capsules were provided by Darou Pakhsh Pharm Co. (Tehran, Iran)
Data were collected at the beginning of the study and after 14 months

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised using permuted balanced block randomisation method
Allocation concealment (selection bias)	Unclear risk	No further detail on allocation
Blinding of participants and personnel (performance bias)	Unclear risk	Stated as double blind but content of placebo not stated and no report of attempt to mask n-3 FA taste.
Blinding of outcome assessment (detection bias)	Low risk	Unclear, few details
Incomplete outcome data (attrition bias)	Low risk	Attrition was 1 in intervention group, 5 in control group, so minor. "the two most common reasons for dropouts were experiencing GI side effects or difficulty to maintain scheduled clinic visits"
Selective reporting (reporting bias)	High risk	Some of the outcomes stated in the trial register are not reported. Registered March 2011, study start November 2010, completion April 2012
Attention	Low risk	No difference between groups
Compliance	Unclear risk	Pill counts – compliance averaged 80% in both groups
Other bias	Low risk	None noted

Norwegian 1968 [379 380]

Methods Norwegian Vegetable Oil Experiment of 1965-6
RCT, parallel, 2 arms (ALA linseed oil vs omega 6 sunflower oil), 1 year
Risk of bias: moderate or high

Participants Men working in Norwegian companies aged 50-59 years

N: 6716 intervention, 6690 control
Level of risk for CVD: low (working men, though a few had had a previous MI or angina)
Men: 100%
Mean age in years (SD): unclear
Age range: 50-59 years
Smokers: unclear (~48% non-smokers)
Hypertension: unclear
Medications taken by at least 50% of those in the control group: not reported
Medications taken by 20%-49% of those in the control group: not reported
Medications taken by some, but less than 20% of the control group: not reported
Location: Norway
Ethnicity: unclear

Interventions Type: supplementary food (oil)
Comparison: ALA vs omega 6
Intervention: linseed oil, 10 mL/d (55% ALA), 5.5 g/d ALA, 1.5 g/d linoleic. Dose: 5.5 g/d ALA
Control: sunflower oil, 10 mL/d (1.4% ALA), 0.1 g/d ALA, 6.3 g/d linoleic. Vitamin E was added to both oils.
Compliance: 73% were still taking the linseed oil at 1 year, 72% were still taking their sunflower oil at 1 year (unclear how this was ascertained)
Duration of intervention: 12 months

Outcomes Main study outcome: morbidity and mortality
Dropouts: survival status was traced for all but 4 included men, health status was missing for about 80 men in total or 0.6%.
Available outcomes: total and CV deaths, MI, angina, stroke, peripheral vascular disease, combined CV events, total cholesterol (subgroup)
Response to contact: no

Notes Study funding: not stated

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Paper states "simple randomisation" without clarification
Allocation concealment (selection bias)	Unclear risk	Few details provided
Blinding of participants and personnel (performance bias)	Low risk	Paper states that the workplace doctors who administered the trial locally were sent bottles for each participant marked only with their trial number, and that "appearance and taste of the products were so similar that most participants were unable to identify the type"
Blinding of outcome assessment (detection bias)	Low risk	Company physicians recorded health status, and were also blinded to intervention (as above)
Incomplete outcome data (attrition bias)	Low risk	Detailed description, and those who left employment during the study were followed up for survival and morbidity via the main health system
Selective reporting (reporting bias)	Unclear risk	No protocol or trials registration found
Attention	Low risk	As company physicians administered oils and assessed outcomes but were blind to treatment arm there could not be attention bias
Compliance	Unclear risk	73% were still taking the linseed oil at 1 year, 72% were still taking their sunflower oil at 1 year (unclear how this was ascertained)
Other bias	Low risk	No further bias noted

Nutristroke 2009 [381]

Methods Nutristroke

RCT, parallel, (diet rich in vitamins and omega 3 plus omega 3 supplement vs diet rich in vitamins and omega 3), 12 months
Summary risk of bias: moderate or high

Participants People in a rehabilitation unit who had survived a stroke
N: 38 intervention, 34 control. (analysed, intervention: 32 control: 20)
Level of risk for CVD: high
Men: 74% intervention, 56% control
Mean age in years (SD): 61.3 (13.6) n-3, 66.3 (11.4) n-3 + antioxidant intervention, 68.4 (12.6) placebo, 65.1 (12.8) antioxidant – control
Age range: not reported
Smokers: not reported
Hypertension: not reported
Medications taken by at least 50% of those in the control group: not reported
Medications taken by 20%-49% of those in the control group: not reported
Medications taken by some, but less than 20% of the control group: not reported
Location: Italy
Ethnicity: not reported

Interventions Type: supplement (capsule)
Comparison: fish oil vs unclear placebo
Intervention: fish oil gelatin capsules including 250 mg DHA + 250 mg EPA. Dose: 0.5 g/d EPA + DHA
Control: "identical to supplement but contained no antioxidants or polyunsaturated fatty acids"
Compliance: appears to have been assessed at meetings or on the phone monthly, but results unclear
Duration of intervention: 12 months

Outcomes Main study outcome: functional status in stroke survivors
Dropouts: 6 intervention, 14 control
Available outcomes: mortality and cardiovascular mortality, lipids (6 months), albumin and lymphocyte counts (6 months), Barthel Index (functional status), neurological impairment (not reported by intervention group), mobility, adiposity (no numerical data presented; quote: "there were no statistically significant differences in body weight, BMI, arm circumference and triceps skin fold at the different time points")
Response to contact: not yet attempted

Notes 2 × 2 study that also had an antioxidant supplementary focus (supplementary vitamins C and E, beta carotene and polyphenols)
Study funding: Italian Ministry of Health, Sigma-Tau Health Science provided omega 3 capsules

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomized by means of a specific list"
Allocation concealment (selection bias)	Unclear risk	Randomisation methodology not mentioned
Blinding of participants and personnel (performance bias)	Unclear risk	Quote: "the placebo was identical to the supplement but contained no antioxidants or polyunsaturated fatty acids; no patient, research assistant, investigator or any other medical or nursing staff could distinguish the placebo from the supplements during the study". However, only one placebo discussed and unclear whether it was a placebo capsule (for omega 3) or pill (for antioxidants)
Blinding of outcome assessment (detection bias)	Low risk	Quote: "assays were quality control checked by internal standard and calibration curve in a random and double blind way"
Incomplete outcome data (attrition bias)	High risk	High rates of dropouts
Selective reporting (reporting bias)	Unclear risk	No protocol or trials registry entry found
Attention	Low risk	All assessments and treatments appear equal across the intervention groups
Compliance	Unclear risk	Appears to have been assessed at meetings or on the phone monthly, but results unclear

Other bias	Low risk	None noted

Nye 1990 [382 383]

Methods	Randomisation: parallel, 3 groups (omega 3 vs olive oil vs aspirin and dipyridamole), 1 year Risk of bias: moderate or high
Participants	People undergoing PTCA N: 36 intervention, 37 control (also 35 allocated to arm 3, aspirin and dipyridamole) Level of risk for CVD: high (people undergoing angioplasty) Men: 78% intervention, 76% control Mean age in years (SD): 54 (8) intervention, 55 (8) control years Age range: unclear Smokers: unclear Hypertension: unclear Medications taken by at least 50% of those in the control group: not reported Medications taken by 20%-49% of those in the control group: not reported Medications taken by some, but less than 20% of the control group: not reported Location: New Zealand Ethnicity: unclear
Interventions	Type: supplement (capsules) Comparison: EPA vs MUFA Intervention: MaxEPA capsules 12/d (2.2 g EPA). Dose: 2.2 g/d EPA Control: olive oil capsules, 12/d, identical to MaxEPA. Both capsules included vitamin E Compliance: no data Length of intervention: 12 months
Outcomes	Main study outcome: angina, restenosis Dropouts: none Available outcomes: angina, interventions, lipids (Nil death) Response to contact: no
Notes	Study funding: Medical Research Council of New Zealand and Scherer Ltd (who supplied MaxEPA and the olive oil capsules)

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomly divided without exclusions into 3 groups"
Allocation concealment (selection bias)	Unclear risk	Unclear, no further info
Blinding of participants and personnel (performance bias)	Unclear risk	States that placebo capsules were identical to the MaxEPA, and "neither the patient nor the attending cardiologist knew which capsules were being used" (but no masking of taste was reported, and participant guesses as to allocation were not reported)
Blinding of outcome assessment (detection bias)	Low risk	Quote: "neither the patient, nor the attending cardiologist knew which capsules were being used" ... "Angioplasty was repeated electively at one year or before where symptoms recurred, and assessed without knowledge of the patient's treatment group."
Incomplete outcome data (attrition bias)	Unclear risk	Some participants were lost to follow-up and reasons for this were unclear
Selective reporting (reporting bias)	Unclear risk	No protocol or trials registration found
Attention	Low risk	No suggestion of attention bias, symptomatic patients were reviewed between scheduled visits, otherwise all on the same schedule
Compliance	Unclear risk	No data

Other bias	Low risk	No further bias noted

OFAMI 2001 – NCT01422317 [384-391]

Methods Omacor Following Acute Myocardial Infarction (OFAMI)
RCT, parallel, 2 arms (omega 3 vs corn oil), 2 years
Summary risk of bias: moderate or high

Participants Patients recruited 4-8 days after confirmed MI
N: 150 intervention, 150 control
Level of risk for CVD: high
Men: 77% intervention, 82% control
Mean age in years (SD): 64.4 intervention, 63.6 control (no SD)
Age range: 28-86 years intervention, 29-87 years control
Smokers: 39% intervention, 38% control
Hypertension: 29% intervention, 23% control
Medications taken by at least 50% of those in the control group: b-blockers, aspirin
Medications taken by 20%-49% of those in the control group: statins, ACE inhibitors
Medications taken by some, but less than 20% of the control group: diuretics, warfarin
Location: Norway
Ethnicity: unclear

Interventions Type: supplement (capsules)
Comparison: EPA + DHA vs omega 6
Intervention: 4 gelatin capsules of omega-3-acid ethyl esters 90 (Omacor, Pronova A/S, Oslo, Norway), each is 1 g containing 850-882 mg EPA and DHA as concentrated ethylesters Dose ~3.4-3.5 g/d EPA + DHA
Control: corn oil capsules, 4/d, each contains 1 g of corn oil
Compliance: assessed by questionnaire and capsule count, 82% intervention group had complete compliance after 6 weeks, 86% of controls
Length of intervention: 24 months

Outcomes Main study outcome: CV events
Dropouts: unclear
Available outcomes: total and CV deaths, MI, unstable angina, interventions, combined CV events, BMI, lipids, BP (authors provided additional data on glucose, AF, stroke)
Response to contact: yes

Notes Study funding: Pharmacia-Upjohn and Pronova

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomly assigned" – Pharmacia was responsible for randomisation. Author response: participants were randomised in blocks of 4
Allocation concealment (selection bias)	Low risk	Author confirmed allocation was concealed
Blinding of participants and personnel (performance bias)	Low risk	Identical capsules containing either Omacor or corn oil. Double blinding stated, but taste not reported as masked and blinding of participants not checked
Blinding of outcome assessment (detection bias)	Low risk	Author stated: all later analyses performed without the knowledge of outcome
Incomplete outcome data (attrition bias)	Unclear risk	Number of dropouts was unclear
Selective reporting (reporting bias)	Unclear risk	Trials registry NCT01422317. Outcomes reported in trials registry appear to have been published, but registration was retrospective.
Attention	Low risk	All participants appear to have been reviewed at the same intervals
Compliance	Unclear risk	Assessed by questionnaire and capsule count, 82% intervention group had complete compliance after 6 weeks, 86% of controls

Other bias	Low risk	No further bias noted

OFAMS 2012 – NCT00360906 [392-394]

Methods RCT, parallel, (n3 EPA & DHA vs n6 LA), 6 months
Summary risk of bias: Moderate to high

Participants Population: Relapsing remitting multiple sclerosis
N: 46 int., 46 control. (analysed, int: 46 cont: 45)
Level of risk for CVD: Low
Male: 34% int., 36% control.
Mean age (sd): 38.8 (8.4) int., 38.3 (8.4) control
Age range: NR
Smokers: NR
Hypertension: NR
Medications taken by at least 50% of those in the control group: NR
Medications taken by 20-49% of those in the control group: NR
Medications taken by some, but less than 20% of the control group: NR
Location: Norway
Ethnicity: NR
Depression: Long term condition (high risk)
Anxiety: Long term condition (high risk)

Interventions Type: supplement
Comparison: EPA & DHA vs corn oil
Intervention: 5 capsules/day 1-g Triomar capsules (Pronova Biocare), containing 60% ω-3 fatty acids: 270 mg of eicosapentaenoic acid (EPA) and 170 mg of docosahexaenoic acid per gram. Four international units of α-tocopherol per gram were added for antioxidative protection
Control: 5 1g capsules/day corn oil
Dose: 1350mg/d EPA, 850mg/d DHA, total 2200mg/d LCn3
Compliance: Sera samples for total monounsaturated and unsaturated fatty acids, saturated fatty acids, and n-3 and n-6 fatty acids were collected at baseline and months 6, 12, and 24
Duration of intervention: 6 months

Outcomes Main study outcome: Expanded Disability Status Scale - EDSS
Dropouts: 3 int., 8 control
Available outcomes: SF36 mental composite, SF26 physical composite, depression incidence (at 12 months), MRI disease activity, MRI brain atrophy, number of relapses, MS Functional Composite Score, changes in immune responses, fatigue, adverse events

Notes Only including results from first 6 months of study as interferon given to all patients after this.
Funding source: Merck Serono provided an unconditional grant. Pronova Biocare provided the study with n-3 fatty acids (Triomar) and placebo. This study was funded by the Western Norway Regional Health Authority, Norwegian Multiple Sclerosis Society, Pronova Biocare, Amersham Health, Norway, and Merck-Serono, Norway.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Patients were randomized by a computer generated procedure, with an assignment ratio of 1:1, with each patient assigned the lowest randomization number available at the study site. The block size of the randomization was 6 and there was no stratification by centres
Allocation concealment (selection bias)	Low risk	The randomization was conducted by an independent research organization (Smerud Medical Research International AS, Oslo, Norway).
Blinding of participants and personnel (performance bias)	Unclear risk	We used independent statistical, packaging, and distribution contractors to maintain the blinding for all other personnel. However, similarity to participants not described.

Blinding of outcome assessment (detection bias)	Low risk	The study drug was not suspected to have any clinical or laboratory adverse effects different from placebo that could disturb the double blind nature of the trial. Therefore, the same neurologist (study neurologist) functioned as both the treating and evaluating physician. Blinding of outcome assessors not described.
Incomplete outcome data (attrition bias)	Low risk	Analysis appears to be intention to treat (Fig 1) – but not described in methods
Selective reporting (reporting bias)	High risk	ClinicalTrials.gov: NCT00360906 First received: August 4, 2006. Patients first recruited December 2004. More outcomes in the results paper than in the protocol in the trial registry – specifically fatigue, SF36
Attention	Low risk	All participants underwent a clinical neurological examination, including EDSS scoring, biochemical tests, and a baseline MRI. Monthly T2-weighted and T1-weighted gadolinium-enhanced MRI scans were performed for the first 9 months and thereafter at months 12 and 24.
Compliance	Low risk	Sera samples for total monounsaturated and unsaturated fatty acids, saturated fatty acids, and n-3 and n-6 fatty acids were collected at baseline and months 6, 12, and 24. As expected, the serum ratio of n-3 fatty acids: total serum phospholipids increased in the group receiving n-3 fatty acids compared with the placebo group, both at month 6 ($P < .001$) and month 24 ($P < .001$). The n-3 fatty acids group had a corresponding decrease in the n-3: n-6 fatty acid ratio in total serum phospholipid level. There were no significant changes in the levels of n-3 or n-6 fatty acids in the placebo group throughout the study period (eTable 2 and eTable 3)
Other bias	Low risk	None noted

OFFER 2015 - NCT02210962 [395 396]

Methods	RCT, parallel, (n3 EPA+DHA vs MUFA), 6 months Summary risk of bias: Low
Participants	Population: people with first episode of schizophrenia aged 16–35 N: 36 int., 35 control. (analysed, int: 32 cont: 33) Level of risk for CVD: Low Male: 52.8% int., 65.7% control. Mean age (sd): 23.2 (4.8) int., 23.3 (4.8) control Age range: NR Smokers: NR Hypertension: NR Medications taken by at least 50% of those in the control group: benzodiazepines (51.4%) Medications taken by 20-49% of those in the control group: NR Medications taken by some, but less than 20% of the control group: antidepressants (17.1%); mood stabilizers (11.4%); anticholinergics (8.6%) Location: Poland Ethnicity: NR Depression: Current / Historical / Long term condition (high risk) / General population (low risk) Anxiety: Current / Historical / Long term condition (high risk) / General population (low risk)
Interventions	Type: supplement Comparison: capsules with EPA & DHA vs olive oil

	Intervention: The active treatment was yellow gel capsules filled with concentrated fish oil containing 0.33 g of EPA and 0.22 g of DHA in each capsule. The daily dose of 4 capsules provided 2.2 g of n-3 PUFA, i.e.: 1.32 g/day of EPA plus 0.88 g/day of DHA. Control: Placebo capsules were prepared to match the active treatment in appearance and flavour. The placebo contained also a scant amount of fish oil to provide a comparable taste and smell of the different capsules. The study medication (concentrated fish oil and placebo) was provided by Marinex International Sp. z o.o. and shipped from Scandinavian Laboratories, Inc. Mt. Bethel, PA, USA Compliance: Adherence to study intervention was monitored through patient/parent self-report and pill count at each medication appointment Duration of intervention: 6 months
Outcomes	Main study outcome: Schizophrenia symptom severity measured by the Positive and Negative Syndrome Scale (PANSS) Dropouts: 4 int., 2 control Available outcomes: Depressive symptoms, patient functioning and the level of insight
Notes	Study funding: Grant from Polish Science National Center.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A computer-generated random sequence based on block randomized design, with three age strata comprising block lengths of four within each.
Allocation concealment (selection bias)	Low risk	A computer-generated random sequence based on block randomized design, with three age strata comprising block lengths of four within each, was kept in a remote secure location and administered by an independent third party until termination of the study and collection of all study data. Patients, parents, stuff involved in administering intervention, assessing the outcomes or entering data were blind to group assignments
Blinding of participants and personnel (performance bias)	Low risk	Patients, parents, stuff involved in administering intervention, assessing the outcomes or entering data were blind to group assignments. Placebo capsules were prepared to match the active treatment in appearance and flavour. The placebo contained also a scant amount of fish oil to provide a comparable taste and smell of the different capsules.
Blinding of outcome assessment (detection bias)	Low risk	Patients, parents, stuff involved in administering intervention, assessing the outcomes or entering data were blind to group assignments. Placebo capsules were prepared to match the active treatment in appearance and flavour. The placebo contained also a scant amount of fish oil to provide a comparable taste and smell of the different capsules.
Incomplete outcome data (attrition bias)	Low risk	Intention to treat analysis
Selective reporting (reporting bias)	Low risk	Protocol registered Aug 2014; NCT02210962. Protocol registered Aug 2014 but the first participant was included in November 2011 and the last participant completed the trial in March 2015 (2016 publication p.35) Secondary outcomes on trials registry not reported in paper (2016) CHANGED TO LOW RISK
Attention	Low risk	No difference between the groups
Compliance	Low risk	Adherence to study intervention was monitored through patient/parent self-report and pill count at each medication appointment (p36 2016) The mean rate for adherence with study intervention, based on pill count and self-report, was 83.2% (SD =

		17.4) in the EPA + DHA group and 78.9% (SD = 16.6) in the placebo group (Student t-test = 1.096; p = 0.277). (p39 2016)
Other bias	Low risk	None noted

OMEGA 2009 - NCT00251134 [397-405]

Methods Effect of Omega 3 fatty acids on reduction of sudden cardiac death after MI (OMEGA)
2 arm, parallel RCT (omega 3 vs olive oil), 12 months
Summary risk of bias: low

Participants People who have had an acute myocardial infarction
N: 1940 intervention,1911 control (analysed for primary endpoints 1919 intervention, 1885 control)
Level of risk for CVD: high
Men: 75.1% intervention, 73.7% control
Age (median): 64.0 years, intervention, 64.0 years control
Age range: unclear (upper and lower quartiles 54-72)
Smokers: 35.9% intervention, 37.5% control
Hypertension: 66.9% intervention, 66.1% control
Medications taken by at least 50% of those in the control group: statins, ACE inhibitors, beta-blockers, clopidogrel, aspirin
Medications taken by 20%-49%: diuretics
Medications taken by some, but < 20%: AT1 receptor blockers, vit K antagonist, calcium channel blockers, digitalis, amiodarone, oral antidiabetics, insulin
Location: Germany
Ethnicity: not reported

Interventions Type: supplement (capsules)
Comparison: EPA + DHA vs MUFA
Intervention: 1 × 1 g/d Pronova BiCare soft gelatin capsule 'zodin' omega-3 acid ethyl esters (460 mg/d EPA and 386 mg/d DHA). Dose: 0.85 g/d EPA + DHA
Control: 1 × 1 g/d olive oil capsule identical to intervention
Compliance: 93.1% of intervention group and 93.2% of control participants took > 70% of capsules
Duration of intervention: 12 months

Outcomes Main study outcome: sudden cardiac death, cardiac arrest
Dropouts: Control: 26 (8-lost to follow-up, 2-withdrew before allocation, 16-excluded.) intervention: 21
Available outcomes: deaths, CV mortality, MACCE, MI, arrhythmias, heart failure, stroke, revascularisation, lipids, authors supplied information on angina, depression, cancers, AF
Response to contact: yes

Notes Study funding: Tromsdorff Arzneimittel commissioned the research

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation code generated by alpha med PHARBIL, done in blocks of 8. Randomisation was stratified by centre.
Allocation concealment (selection bias)	Low risk	Appearance of the drugs or the drug containers did not allow patients and physicians to deduce the study arm. 4-digit number on a concealed container
Blinding of participants and personnel (performance bias)	Low risk	Capsules for placebo and intervention looked the same, randomisation code unknown to investigator (taste and smell not mentioned)
Blinding of outcome assessment (detection bias)	Low risk	Classification of adverse events blinded to allocation, and there was a blinded endpoint committee for all pre-specified outcomes
Incomplete outcome data (attrition bias)	Low risk	All events were documented by the investigators and reported to the assigned clinical research organisation and the sponsor. The data safety

		monitoring board judged any imbalances between the study arms.
Selective reporting (reporting bias)	Low risk	NCT00251134 registered in 2005. Study start date: 2003, Completed: 2008, study design: 2006, Published paper: 2010. All trials registry primary and secondary outcomes reported
Attention	Low risk	Capsules for both arms
Compliance	Low risk	93.1% of intervention group and 93.2% of control participants took > 70% of capsules. EAIC 0.65 intervention, and control
Other bias	Low risk	None noted

OMEGA-Remodel 2016 – NCT00729430 [406-409]

Methods Effect of Fish Oil Supplementation in People who have recently had a heart attack (OMEGA-Remodel)
RCT, parallel, (n3 EPA+DHA vs n6 LA), 6 months
Summary risk of bias: Moderate or high
Aim: assess effects of purified omega-3 fatty acids on reducing left ventricular remodelling after acute myocardial
infarction

Participants People after acute MI
N: 180 int., 178 control. (analysed, int: 180 cont: 178)
Level of risk for CVD: high
Male: 82% int., 79% control.
Mean age (sd) yrs: 60 (10) int., 58 (10) control
Age range: NR
Smokers: 13% int., 20% control
Hypertension: 66% int., 63% control
Medications taken by at least 50% of those in the control group: dual antiplatelet, beta blockers, statins, ACE inhibitors or ARBs
Medications taken by 20-49% of those in the control group: nil
Medications taken by some, but less than 20% of the control group: calcium channel blocker, aldosterone antagonists, insulin, nitroglycerin, diuretics
Location: US
Ethnicity: NR

Interventions Type: supplement
Comparison: EPA+DHA vs corn oil
Intervention: 4x1g/d fish oil capsules with meals (Lovaza including 1.86g/d EPA plus 1.5g/d DHA, GlaxoSmithKline). Encouraged to avoid over the counter fish oil and follow usual post-MI dietary instructions with no specific advice on omega 3 intake: EPA+DHA 3.36g/d
Control: 4x1g/d corn oil capsules with meals (including 2.4g/d LA and no EPA or DHA). Encouraged to avoid over the counter fish oil and follow usual post-MI dietary instructions with no specific advice on omega 3 intake
Compliance: 2-monthly scripted telephone interviews to assess pill counts (also tolerance and adverse events), also red blood cell fatty acids. DPA, DHA and EPA were all significantly higher in intervention than control participants at 6 months.
Duration of intervention: 6 months

Outcomes Main study outcome: left ventricular remodeling
Dropouts: 47 int., 50 control (though ITT analysis)
Available outcomes: CRP, lipids at 6 months (other outcomes included changes to left ventricular end-systolic volume (LVESVI) and change to total infarct size, MECVF volume)

Notes Study funding: NIH, also GlaxoSmithKline provided study medication
Author contact: not yet

Risk of bias table

Bias	Authors' judgement	Support for judgement

Random sequence generation (selection bias)	Low risk	Investigational pharmacies of enrolling centres randomly assigned patients using a 2x2 blocked randomization scheme
Allocation concealment (selection bias)	Low risk	Conducted by the pharmacies
Blinding of participants and personnel (performance bias)	Unclear risk	Described as double blind, but similarity of intervention and placebo not clear
Blinding of outcome assessment (detection bias)	Low risk	Described as double blind, and CRP and lipids are biochemical outcomes
Incomplete outcome data (attrition bias)	Low risk	ITT analyses, 27% drop-out but similar rates between groups
Selective reporting (reporting bias)	Low risk	Trials register entry was Aug 2008, near date of study start. All outcomes mentioned in register were reported, as were many other outcomes
Attention	Low risk	Appeared equivalent
Compliance	Low risk	Significant differences in omega 3 fats in red blood cells between intervention and control
Other bias	Low risk	None noted

OmegAD 2008 – NCT00211159 [410-432]

Methods RCT, cross-over, (n3 EPA+DHA vs n6 LA), 6 months.
Summary risk of bias: Moderate or high

Participants People in Sweden with mild to moderate Alzheimer's disease and stable comorbidities. N: 103 int., 101 control (analysed int: 91 cont: 87).
Level of risk for CVD: Low.
Male: 43% int., 54% control.
Mean age (sd): 72.6 (9.0) int., 72.9 (8.6) control.
Age range: NR.
Smokers: 9% int., 10% control.
Hypertension: NR
Medications taken by at least 50% of those in the control group: ACE inhibitors
Medications taken by 20-49% of those in the control group: acetylsalicylic acid, antidepressants.
Medications taken by some, but less than 20% of the control group: neuroleptic agents, statins herbal medications
Location: Sweden
Ethnicity: NR
Depression: Long term condition (high risk)
Anxiety: Long term condition (high risk)

Interventions Type: Supplement
Comparison: DHA+EPA vs. corn oil
Intervention: Four 1-g capsules daily, each containing 430 mg DHA and 150 mg EPA (daily total = 1.72g/d DHA and 600 mg EPA: EPAX1050TG; Pronova Biocare A/S, Lysaker, Norway)
Control: 4 capsules/d (comprised of mostly corn oil inc 600 mg/d of linoleic acid).
Compliance: Blood samples for analyses of serum fatty acid levels were
obtained to assess compliance with the n-3 fatty acid therapy. The patients in the n-3–treated group showed mean 2.4-and 3.6-fold increases in the ratios of DHA and EPA, respectively, in serum after the first 6 months. Corresponding mean values for the placebo-treated patients were 0.95 and 0.96, respectively.
Duration of intervention: 6 months

Outcomes Main study outcome: Cognitive functions assessed by MMSE and ADAS-COG. Secondary outcomes were safety, tolerability, blood pressure, and global function.
Dropouts: 14 int., 16 control
Available outcomes: cognitive outcomes, functional outcomes, blood pressure, mortality.

Notes Study funding: This study was supported by Pronova Biocare A/S, who was represented in the trial steering committee and provided the EPAX1050TG and placebo preparations; however, the company was not involved in collection, analyses, or interpretation of the data.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Patients were randomized in blocks of four, using sealed envelopes and according to a computerized table of random numbers.
Allocation concealment (selection bias)	Unclear risk	Patients were randomized in blocks of four, using sealed envelopes. However opacity of envelopes not stated.
Blinding of participants and personnel (performance bias)	Unclear risk	Only info is "double blind", no detail how that was achieved.
Blinding of outcome assessment (detection bias)	Unclear risk	Only info is "double blind", no detail how that was achieved.
Incomplete outcome data (attrition bias)	High risk	Due to per-protocol rather than ITT reporting, one extractor felt this should be High risk. Final decision was that total dropouts were 15% in six months (above guidelines threshold of 20% per year). Dropouts were much more likely to be using ACE inhibitor = Donepezil than those who remained in trial; suggests possible drug interaction.
Selective reporting (reporting bias)	High risk	ClinicalTrials.gov: NCT00211159. Study First Received: Sept 13th 2005; date data collection began: Dec 31 2000. Results papers report on more outcomes than specified in register – e.g. lumbar puncture/serum inflammatory markers
Attention	Low risk	Double blind. Design of trial and description of contact suggests no difference between arms.
Compliance	Low risk	Blood samples for analyses of serum fatty acid levels were obtained to assess compliance with the n-3 fatty acid therapy (Fig 2, pg 1403). The patients in the n-3–treated group showed mean 2.4-and 3.6-fold increases in the ratios of DHA and EPA, respectively, in serum after the first 6 months. Corresponding mean values for the placebo-treated patients were 0.95 and 0.96, respectively. (pg 1404)
Other bias	Unclear risk	Note difference in drop outs between Freund Levi et al. 2006 paper (main paper) and Irving 2009 and poster from Freud Levi et al. 2004. Note that data are per protocol not intention to treat (authors said that there were no important differences between results from ITT & PP methods).

OPAL – Dangour 2010 – ISRCTN72331636 [433-437]

Methods
Older People And n-3 Long-chain polyunsaturated fatty acid (OPAL)
2 arm, parallel, RCT, 12 months
Summary risk of bias: low

Participants
Healthy cognitively normal adults aged 70-79 years
N: 434 intervention, 433 control (analysed 376 intervention, 372 control)
Level of risk for CVD: low
Men: 53.4% intervention, 56.6% control
Mean age in years (SD): 74.7 (2.5) intervention, 74.6 (2.7) control
Age range: 70-79 years
Smokers: not reported
Hypertension: 54.9% intervention, 56.9% control
Medications taken by at least 50% of those in the control group: not reported
Medications taken by 20%-49%: not reported
Medications taken by some, but < 20%: not reported

Location: England and Wales
Ethnicity: not reported

Interventions Type: supplement (capsules)
Comparison: EPA + DHA vs MUFA
Intervention: 2 × 650 mg capsule/d Ocean Nutrition vanilla flavoured soft gelatin capsule (total daily dose of 200 mg EPA and 500 mg DHA). Dose: 0.7 g/d EPA + DHA
Control: 2 × 650 mg olive oil capsule identical to intervention
Compliance: count returned capsules.
Capsules not returned:

- Intervention - median: 0.95; IQR: 0.82, 1.00
- Control - median: 0.95; IQR: 0.81, 1.00

Fasting serum fatty acids, mg/L, mean (SD)

- EPA: intervention 49.9, (2.7); control 39.1 (3.1)
- DHA: intervention 95.6 (3.1); control, 70.7 (2.9)
- α-linoleic: intervention 21.5 (0.8); control 22.0 (0.9)

Length of intervention: 24 months

Outcomes Main study outcome: delayed onset of cognitive decline
Dropouts: control: 78 (8 died, 53 withdrew, 17 discontinued intervention but provided data); intervention: 67 (9 died, 49 withdrew, 9 discontinued intervention but provided data)
Available outcomes: deaths, MI, arrhythmias, stroke, diabetes, lipids
Response to contact: yes

Notes Study funding: UK Food Standards Agency, NHS R&D provided support costs
Study website: www.opalstudy.lshtm.ac.uk

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were "selected in random blocks". "Research nurses telephoned a central computerized randomization service to obtain treatment allocation codes".
Allocation concealment (selection bias)	Low risk	Central allocation via telephone
Blinding of participants and personnel (performance bias)	Low risk	Identical capsules (vanilla-flavoured, dark-brown coloured). Supplements packaged into identical pots, each containing 180 capsules, labelled by staff not involved in the study. All project staff were unaware of group assignments until after data analysis.
Blinding of outcome assessment (detection bias)	Low risk	All project staff were unaware of group assignments until after data analysis.
Incomplete outcome data (attrition bias)	Low risk	Participants who discontinued the supplements invited to an interview at 24 months. Dropouts explained and similar in both arms (intervention 49 withdrew, control 53 withdrew)
Selective reporting (reporting bias)	High risk	ISRCTN72331636. Trial registered 2004, before study began. Protocol published 2006. Publication of first results 2010. Many outcomes, such as depression and BP were stated in trials registry entry but not reported.
Attention	Low risk	All participants had the same review schedule, and staff were unaware of assignments
Compliance	Low risk	Count returned capsules. Capsules not returned (intervention - median: 0.95; IQR: 0.82, 1.00; control - median: 0.95; IQR: 0.81, 1.00). Fasting serum fatty acids, mg/L, mean (SD): EPA, intervention 49.9 (2.7); control 39.1 (3.1). DHA, intervention 95.6 (3.1); control 70.7 (2.9). α-linoleic: intervention 21.5 (0.8); control 22.0 (0.9)
Other bias	Low risk	No further bias noted

OPTILIP 2006 [438] [439]

Methods Quantification of the Optimal n6/n3 ratio in the UK Diet (OPTILIP)
RCT, parallel, 5 arms (n3 EPA+DHA vs n3 ALA vs n6 LA), 6 months
Summary risk of bias: Moderate or high

Participants Men and postmenopausal women aged 45-70 years
N: 308 randomised overall (analysed, n-3 int: 61; ALA int: 53; cont: 44)
Level of risk for CVD: Low
Male: 57% n-3 int., 60% ALA int; 68% control.
Mean age (sd): n-3 int., 62; ALA int., 60; control 58 years (sd not reported)
Age range: 45-70 years overall
Smokers: 16% overall
Hypertension: 41% overall
Medications taken by at least 50% of those in the control group: NR
Medications taken by 20-49% of those in the control group: HRT
Medications taken by some, but less than 20% of the control group: BP medication, lipid lowering medication, thyroxine
Location: UK
Ethnicity: NR

Interventions Type: food supplements (spread, oil, canned fish in varying quantities)
Comparison: long chain n-3 vs low long chain n-3; and high ALA vs low ALA
Intervention: **For n-3 group**: Advice to increase oily fish to 2 portions/wk, provided 2 cans tinned salmon and salmon pate/wk (John West and Arctic Fjord), and supplements of 20g/d spread (n-3 EPA & DHA content 2.0g/100g + ALA 5.3g/100g, Unilever) and 16g/d oil (ALA content 0.3g/100g, Anglia Oils) giving overall diet ratio of n-6:n-3 of 3:1: EPA+DHA & ALA unclear
For high linolenate group: No advice to increase oily fish, provided 2 cans tuna/wk (John West), and supplements of 20g/d spread (ALA 5.0g/100g, Unilever) and 16g/d oil (ALA content 8.9g/100g, Anglia Oils) giving overall diet ratio of n-6:n-3 of 3:1: EPA+DHA & ALA unclear
Control: No advice to increase oily fish, provided 2 cans tuna/wk (John West), and supplements of 20g/d spread (ALA 0.5g/100g, Unilever) and 16g/d oil (ALA content 0.3g/100g, Anglia Oils); otherwise habitual diet, giving overall diet ratio of n-6:n-3 of 10:1
Compliance: Dietary record and erythrocyte EPA and DHA
Duration of intervention: 6 months

Outcomes Main study outcome: Lipids, insulin sensitivity and clotting factors
Dropouts: 48 overall
Available outcomes: Insulin, glucose, HOMA, QUICKI, lipids (geometric means- triglycerides not used for ALA comparison and insulin not used for n-3 comparison due to baseline differences)

Notes 5 arms overall- the "moderate linolenate diet" and the "n-3 + linolenate diet" not discussed here
Study funding: Food Standards Agency (with supplemented foods supplied as detailed above)

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"randomly assigned"
Allocation concealment (selection bias)	Unclear risk	As above
Blinding of participants and personnel (performance bias)	High risk	Fish increase requested for n-3 group so participants unblinded
Blinding of outcome assessment (detection bias)	Unclear risk	NR
Incomplete outcome data (attrition bias)	Unclear risk	Numbers randomised to each group and therefore drop outs by group unclear
Selective reporting (reporting bias)	Unclear risk	No registry or protocol identified
Attention	Unclear risk	NR
Compliance	Low risk	Significant increase in EPA/DHA content of erythrocytes in n-3 groups

Other bias	Low risk	None identified

ORIGIN 2012 – NCT00069784 [440-452]

Methods Outcome Reduction With Initial Glargine Intervention (ORIGIN)
RCT, 2 × 2 factorial, (capsule of n-3 fatty acids or placebo), 72 months
Summary risk of bias: low

Participants People at high risk of CV events with impaired fasting glucose, impaired glucose tolerance or diabetes
N: 6319 intervention, 6292 control. (analysed, intervention: 6281 control: 6255)
Level of risk for CVD: moderate
Men: 65.4% intervention, 64.7% control
Mean age in years (SD): 63.5 (7.8) intervention, 63.6 (7.9) control
Age range: unclear, eligible if aged ≥ 50 years
Smokers: current smokers 12.1% intervention, 12.6% control
Hypertension: 78.7% intervention, 80.3% control
Medications taken by at least 50% of those in the control group: ACE inhibitor or ARB, aspirin or other antiplatelet, beta-blocker, statin, glucose-lowering drug
Medications taken by 20%-49%: calcium-channel blocker
Medications taken by some, but less than 20%: thiazide diuretics, anticoagulant
Location: 40 study locations in Europe and the Americas
Ethnicity: unclear

Interventions Type: supplement capsule (Omacor)
Comparison: EPA + DHA vs MUFA
Intervention: 1 gelatin capsule/d Omacor containing at least 900 mg ethyl esters of n-3 fats (465 mg EPA + 375 mg DHA). Dose: 0.84 g/d EPA + DHA
Control: 1 × 1 g gelatin capsule/d olive oil
Compliance: methods of assessment unclear, but reported that "rates of adherence to the study-drug regimen were similar in the two groups with 96% of patients continuing to receive the study drug at 1 year ... and 88% at the end of the study".
Length of intervention: 74 months mean follow-up (median 6.2 years)

Outcomes Main study outcome: composite of the First Occurrence of Cardiovascular (CV) Death, Nonfatal Myocardial Infarction (MI) or Nonfatal Stroke
Dropouts: 38 intervention, 37 control (some of the remainder did not have final outcome status, were lost or withdrew consent, but were included in analysis)
Available outcomes: mortality, CV mortality, fatal arrhythmia, MI, stroke, heart failure, angina, revascularisation, breast cancer, cancer diagnoses and cancer deaths, BP, lipids (HbA1c given as medians only)
Response to contact: yes but no data provided

Notes The other 2 × 2 assignment was to insulin glargine versus standard care, and is not discussed here. Results are reported here for the trial duration and not the follow-up post trial (the ORIGIN and Legacy Effects, ORIGINALE).
Study funding: Sanofi Aventis, Omacor provided by Pronova Biocare

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "randomized by an automated telephone randomization system (using randomly varying block sizes)"
Allocation concealment (selection bias)	Low risk	As above
Blinding of participants and personnel (performance bias)	Low risk	Study described as "double blind" and placebo described as identical. Blinding of patients, investigators, local and central trials personnel described. However, no information provided as to the capsule's smell and taste
Blinding of outcome assessment (detection bias)	Low risk	Quote: "all primary and secondary outcomes were adjudicated with the use of prespecified definitions by

		a committee whose members were unaware of study-group assignments"
Incomplete outcome data (attrition bias)	Low risk	Almost all participants were included in outcomes
Selective reporting (reporting bias)	Low risk	NCT00069784 – registered October 2003, study started August 2003, final data collection December 2011. Most outcomes appear to have been reported in various publications (cardiovascular events only reported by glargine randomisation).
Attention	Low risk	No suggestion of differences between groups
Compliance	Unclear risk	Methods of assessment unclear, but reported that "rates of adherence to the study-drug regimen were similar in the two groups with 96% of patients continuing to receive the study drug at 1 year ... and 88% at the end of the study"
Other bias	Low risk	None noted

ORL 2013 – NCT01350999 [453 454]

Methods	Omega-3 fatty acids randomised long-term (ORL) RCT- parallel, 3 arms (TAK-085 2 g, TAK-085 4 g, and EPA-E 1.8 g), 12 months Summary risk of bias: moderate or high
Participants	Population: Japanese adults with hypertriglyceridaemia N: 171 intervention (4 g TAK), 165 control (2 g TAK) Level of risk for CVD: moderate Men: 70.8% intervention, 71.5% control Mean age in years (SD): 55.9 (10.12) intervention, 56 (10.95) control Age range: 20-74 Smokers (current): 27.5% intervention, 31.5% control Hypertension: 66.7% intervention, 67.3% control Medications taken by at least 50% of those in the control group: HMG-CoA reductase inhibitor Medications taken by 20%-49%: statin Medications taken by some, but less than 20%: not reported Location: Japan Ethnicity: unclear
Interventions	Type: supplement (TAK-085 capsules) Comparison: EPA + DHA higher vs lower dose Intervention: 1 × 2/d capsule each containing 2 g of TAK-085 (1 g of fatty acid in TAK-085 capsules contains approximately 465 mg of EPA-E plus 375 mg of DHA-E). Total dose of 1.86 g/d EPA + 1.5 g/d DHA. Dose: ~3.4 g/d EPA + DHA) (difference of +1.7 g/d from control arm) Control: 1 capsule/d containing 2 g of TAK-085 (1 g of fatty acid in TAK-085 capsules contains approximately 465 mg of EPA-E plus 375 mg of DHA-E). Total dose of 0.93 g/d EPA + 0.75 g/d DHA. Dose: 1.7 g/d EPA + DHA Compliance: monitored every 4 weeks, mean rate of compliance reported as > 96% in each group Length of intervention: 12 months
Outcomes	Main study outcome: safety outcomes and adverse events Dropouts: group 1: 8, group 2: 14, group 3 (not analysed): 21 Available outcomes: adverse events (including CVD events, cancers), CRP, waist circumference, weight, blood pressure (nil death), lipids provided as % change from baseline, but no baseline data available, so not used in meta-analyses Response to contact: no
Notes	A third arm of EPA-E 1.8 g supplementation is not used here. Outcome data used TAK-4 vs TAK-2 Study funding: Takeda Pharmaceutical Company

Risk of bias table

Bias	Authors' judgement	Support for judgement

Random sequence generation (selection bias)	Low risk	Randomisation was stratified according to statin use and performed by an independent registration centre
Allocation concealment (selection bias)	Low risk	As above
Blinding of participants and personnel (performance bias)	High risk	Open label
Blinding of outcome assessment (detection bias)	High risk	Open label
Incomplete outcome data (attrition bias)	Low risk	All participants were accounted for and analysed for main outcomes
Selective reporting (reporting bias)	Low risk	Trials registry entry May 2011, study start date November 2009, completion November 2011, so partially retrospective. However, entry appears to reflect reported outcomes.
Attention	Low risk	Capsules, appears similar
Compliance	Low risk	Monitored every 4 weeks, mean rate of compliance reported as > 96% in each group
Other bias	Low risk	None noted

Palma 2015 [455]

Methods	RCT, parallel, (n-3 capsules plus antipsychotic medication vs antipsychotic medication), 12 months Summary risk of bias: Moderate or high
Participants	Population: People with schizophrenia N: 30 int., 30 control. (analysed, int: 29 cont: 24) Level of risk for CVD: Low Male: NR. Mean age (sd): NR Age range: NR Smokers: NR Hypertension: NR Medications taken by at least 50% of those in the control group: NR Medications taken by 20-49% of those in the control group: NR Medications taken by some, but less than 20% of the control group: NR Location: Spain Ethnicity: NR Depression: Long term condition (high risk) Anxiety: Long term condition (high risk)
Interventions	Type: supplement Comparison: n-3 plus antipsychotics vs antipsychotics Intervention: Omacor capsules with 840mg EPA plus 465mg DHA Control: None stated Compliance: NR Duration of intervention: 12 months
Outcomes	Main study outcome: PANSS and rates of hospitalisation due to worsening schizophrenia symptoms Dropouts: 1 int., 6 control Available outcomes: report reduction in depressive symptoms in those on n3, without significant differences between groups, but without any supporting data. Also assessed but do not report weight, blood pressure.
Notes	Study funding: NR

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	NR

Allocation concealment (selection bias)	Unclear risk	NR
Blinding of participants and personnel (performance bias)	Unclear risk	NR
Blinding of outcome assessment (detection bias)	Unclear risk	NR
Incomplete outcome data (attrition bias)	Unclear risk	NR
Selective reporting (reporting bias)	Unclear risk	NR
Attention	Unclear risk	NR
Compliance	Unclear risk	NR
Other bias	Low risk	None noted

Patch 2005 [456-458]

Methods	RCT, parallel, (n3 EPA+DHA vs nil), 6 months Summary risk of bias: Moderate or high
Participants	Healthy overweight people with mild TG elevation N: 40 int., 45 control. (analysed, int: 38 cont: 37) Level of risk for CVD: Low Male: 48% int., 51% control. Mean age (sd): 50.4 (14.5) int., 50.2 (9.4) control Age range: NR but inclusion criteria were 20-65 years Smokers: NR Hypertension: NR Medications taken by at least 50% of those in the control group: NR Medications taken by 20-49% of those in the control group: NR Medications taken by some, but less than 20% of the control group: NR (Those taking antihypertensives were excluded) Location: Australia Ethnicity: NR
Interventions	Type: supplemented food Comparison: foods supplemented with omega 3 vs non-supplemented foods Intervention: 8 portions/d of foods supplemented with microencapsulated cod fish oil (Maritex), providing 1.0g/d of a mixture of EPA+DHA: EPA+DHA 1.0g/d Control: 8 portions/d of un-supplemented foods **PUFA Dose**: (intended) increase 1.0g/d EPA+DHA, **0.5%E n-3, 0.5%E PUFA** Compliance: assessed by daily logs, 3d weight food intake, erythrocyte fatty acids, and erythrocyte EPA and DHA were higher in intervention than control at 6 months, but statistical significance unclear Duration of intervention: 6 months
Outcomes	Main study outcome: TG Dropouts: 2 of 40 int., 8 of 45 control Available outcomes: weight, TG, glucose, CRP, waist/hip ratio (insulin, total cholesterol, BMI too different at baseline to use, BP reported but only 6 months, urinary thromboxane, creatinine, number and function of leukocytes reported but not used)
Notes	Study funding: Linkage grant from Australian Research Council, Goodman Fielder Ltd (Sydney) provided financial support and product development expertise.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Block randomisation to balance groups according to baseline TG and BMI
Allocation concealment (selection bias)	Unclear risk	No details

Blinding of participants and personnel (performance bias)	Low risk	"Intervention foods (enriched with long-chain n-3 fatty acids) and equivalent control foods (not enriched) were supplied to all subjects in unmarked packages with one of two codes. The content of the study foods was blinded to subjects as well as researchers."
Blinding of outcome assessment (detection bias)	Low risk	As above
Incomplete outcome data (attrition bias)	Unclear risk	Numbers included differ by paper
Selective reporting (reporting bias)	Unclear risk	No protocol or trials register found
Attention	Low risk	Timing and attention appear to be similar by arm
Compliance	Unclear risk	Unclear whether erythrocyte fatty acids differed statistically significantly by arm
Other bias	Low risk	None noted

Paty 1978 [459-461]

Methods RCT, parallel, (n6 LA vs MUFA), 30 months
Summary risk of bias: Moderate or high

Participants pop: Patients with clinically definite multiple sclerosis, ambulatory either on their own or with the use of ambulatory aids.
N: NR int., NR control. but total was 96 (analysed, int: 38 cont: 38)
Level of risk for CVD: low Multiple sclerosis, patients with serious concomitant disease or significant dementia related to MS were excluded
Male: NR% int., NR% control. Overall 47%
Mean age (sd): x (y) int., z (a) control
Age range: NR but mean age for control and intervention was 45 years
Smokers: NR
Hypertension: NR
Medications taken by at least 50% of those in the control group: NR
Medications taken by 20-49% of those in the control group: NR
Medications taken by some, but less than 20% of the control group: NR
Location: Canada
Ethnicity: NR

Interventions Type: supplement n-6 capsules or pills. Emulsion prepared from sunflower seed oil (66.2 % linoleic acid)
Comparison: High LA vs low LA
Intervention: sunflower seed oil (66.2% linoleic acid) 17 g of LA/day
Control: olive oil (83.5% oleic acid and 4% linoleic acid)
Compliance: In the intervention group, oral supplementation with LA raised blood LA levels to a mean of 144% of baseline with some reduction in oleic acid levels (81%). In the control group, oleic acid supplement caused a minor rise in the OA levels (119%).
Duration of intervention: 30 months

Outcomes Main study outcome: Kurtzke Disability Scale (mean), Pyramidal function, Cerebellar function, Brain stem function,
Sensory function, Bowel and bladder function, Visual function, Mental function
Dropouts: NR int., NR control but total was 20
Available outcomes: overall disability scale, pyramidal function, cerebellar function, brain stem function, sensory function, bowel and bladder function, visual function, mental function, total number provided for drop outs, weight gain, depression, gastrointestinal intolerance, rash, death, lost to follow up. Dietary intake of LA, serum levels of LA and oleic acid.
Kurtzke Mental Function scores available at baseline and end of study, no SD provided, no significant difference between groups.

Notes Study funding: NR but different people were acknowledged for their help with planning, administering test, technical aid and statistics analysis.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	All patients were selected from the roles of the Multiple Sclerosis Clinic. Males and females were randomized separately, otherwise there was no matching or stratification
Allocation concealment (selection bias)	Unclear risk	Males and females were randomized separately, otherwise there was no matching or stratification.
Blinding of participants and personnel (performance bias)	Unclear risk	The study was conducted as a double-blind but no further information was provided
Blinding of outcome assessment (detection bias)	Unclear risk	Neurological assessment was performed by the principal investigator (no further information provided)
Incomplete outcome data (attrition bias)	Low risk	20% attrition rate (low attrition rate). Reasons and numbers for attrition were provided
Selective reporting (reporting bias)	Unclear risk	No trials registry or protocol
Attention	Unclear risk	NR
Compliance	Unclear risk	No information on compliance
Other bias	Low risk	None noted.

Pomponi 2014 [462]

Methods RCT, parallel, (n3 DHA+EPA vs n6 LA), 6 months
Summary risk of bias: Moderate or high

Participants Population: Adults with mild to moderate Parkinson's disease
N: 12 int., 12 control. (analysed, int: 12 cont: 12)
Level of risk for CVD: Low
Male: 41.6% int., 50% control.
Mean age (sd): 64.0 (4.9) int., 64.0 (9.8) control
Age range: NR
Smokers: NR
Hypertension: NR
Medications taken by at least 50% of those in the control group: NR
Medications taken by 20-49% of those in the control group: NR
Medications taken by some, but less than 20% of the control group: NR
Location: Italy
Ethnicity: NR
Depression: Long term condition (high risk) (but excluded patients with current and prior depression and current anti-depressant use or psychotherapy)
Anxiety: Long term condition (high risk) and Current (At the beginning of this trial anxiety was present in 83% and 100%, respectively for DHA group and placebo group)

Interventions Type: supplement
Comparison: DHA & EPA vs placebo
Intervention: Daily dose of 800mg DHA and 290mg EPA for 6 months. EPA 150mg/g as triglyceride, 145mg/g as fatty acid and DHA 430mg//g as triglyceride 400mg/g as fatty acid per capsule. Provided by Catalent Italy SpA
Control: Equicaloric amount of corn oils. From Catalent Italy, Spa
Compliance: NR
Duration of intervention: 6 months

Outcomes Main study outcome: Depression (HAM-D)
Dropouts: 0 int., 0 control
Available outcomes: apathy, depression, anxiety, anhedonia, cognitive performance

Notes Study funding: This work is supported by the Italian Ministero dell'Istruzione, dell'Universita, della Ricera (MIUR) research grant. DHA (and placebo_ group capsules were provided by Catalent ItalySpA (formerly Cardinal Health Italy 407 SpA)

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The assignment of the patients to the treatment or placebo group was done using a computer generated blocked randomization list (blocks for gender and age).
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias)	Unclear risk	Patients and clinicians were not aware of the type of treatment administered (double blind) but no details of blinding provided.
Blinding of outcome assessment (detection bias)	Unclear risk	Patients and clinicians were not aware of the type of treatment administered (double blind) but no details of blinding provided.
Incomplete outcome data (attrition bias)	Low risk	No patients lost to follow-up
Selective reporting (reporting bias)	Unclear risk	No protocol published in a trials register
Attention	Low risk	No difference between the two groups except for the capsule
Compliance	Unclear risk	Not stated
Other bias	Low risk	None identified

Pratt 2009 [463 464]

Methods RCT, parallel, (n3 EPA+DHA vs n6 LA), 6 months
Summary risk of bias: Moderate or high

Participants Population: Adults with paroxysmal or persistent atrial fibrillation
N: 332 intervention, 331 control. (analysed, int: 293-322 cont: 291-323)
Level of risk for CVD: High
Male: 60% int., 53% control.
Mean age mean (sd) 59.8 (13.38) int., 61.2 (12.26) control
Age range: NR
Smokers: NR
Hypertension: NR
Medications taken by at least 50% of those in the control group: NR
Medications taken by 20-49% of those in the control group: ACEI (angiotensin converting enzyme inhibitor) or ARB (angiotensin II receptor blocker 37% (HT drugs); Statins 45%
Medications taken by some, but less than 20% of the control group: Antiarrhythmic drug(s)
Location: USA
Ethnicity: 93% white, 4% African American, 3% other int; 90% white, 5% African American, 5% other control.
Depression: General population (low risk)
Anxiety: General population (low risk)

Interventions Type: supplement
Comparison: Omega 3 vs n6 Placebo
Intervention: 4 g/d of prescription omega-3 (Lovaza, GlaxoSmithKline, Research Triangle Park, North Carolina). For the first 7 days of dosing, participants received a loading dose of 8 g/d capsules, followed by 4 g/d through week 24. Each 1-g capsule of prescription omega-3 contained approximately 465 mg of eicosapentaenoic acid and 375 mg of docosahexaenoic acid.
Control: Prescription placebo for the first 7 days; prescription placebo thereafter through week 24. Each placebo capsule contained approximately 1 g of corn oil (n6)
Compliance: No information provided on how this was assessed. 3/332 were excluded for being non-adherent
Duration of intervention: 6 months

Outcomes Main study outcome: Recurrence of AF
Dropouts: 39 int., 40 control
Available outcomes: Depression incidence, HbA1c, adverse events

Notes Study funding: Authors work for GSK

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"The clinical research organization, Kendle International, Cincinnati, Ohio, generated the randomization schedule."
Allocation concealment (selection bias)	Low risk	"Site personnel telephoned into an interactive voice response system to obtain a randomization number and were assigned blinded study medication bottles."
Blinding of participants and personnel (performance bias)	Unclear risk	"Site personnel telephoned into an interactive voice response system to obtain a randomization number and were assigned blinded study medication bottles." ... “Investigators were blinded to the monitoring results.”… “Once a participant experienced the primary end point (first documented symptomatic recurrence of AF or atrial flutter), additional therapies to maintain normal sinus rhythm were allowed, but the participant was encouraged to continue taking the blinded study drug and continue attending the planned follow-up to the study’s completion.” There’s no info about the capsules being identical, or masked in any way
Blinding of outcome assessment (detection bias)	Low risk	"Biweekly transtelephonic monitoring was used to document asymptomatic recurrences of AF and assess symptomatic events. Investigators were blinded to the monitoring results.”
Incomplete outcome data (attrition bias)	High risk	Of the 663 participants randomized, 645 were included in the analysis (97%) (Fig 1, Kowey 2010).
Selective reporting (reporting bias)	Low risk	NCT00402363. Date registered: 20.11.2006 date data collection began: Nov 2006. The protocol outcomes match those in the results paper.
Attention	Low risk	"Biweekly transtelephonic monitoring was used to document asymptomatic recurrences of AF and assess symptomatic events." ...“Visits during the treatment period will occur at weeks 1, 4, 12, and 24 after the week 0 (baseline) visit." Intervention group received the same as control group.
Compliance	Unclear risk	8/331 were excluded for being non-adherent but method of compliance assessment not stated.
Other bias	Low risk	None noted.

PREDIMED 2013 – ISRCTN35739639 [465-542] (and further publications)

Methods PREvención con Dieta MEDiterránea (PREDIMED)
RCT, parallel, 3 arms (high PUFA vs low PUFA, Mediterranean diet with nuts or olive oil), also low-fat arm, 60 months
Summary risk of bias: moderate to high

Participants Men aged 55-80 years and women aged 60-80 years, free of CVD but with diabetes or ≥ 3 CVD risk factors
N: intervention (Med with nuts) 2454, control (Med with olive oil) 2543 - also low-fat arm, not discussed here, 2450
Level of risk for CVD: moderate
Male: intervention 46%, control 41.3%
Mean age (SD): intervention 67 (6), control 67 (6) years
Age range: 55-80 years
Smokers: intervention 14.5%, control 13.9% (current smokers)
Hypertension: intervention 82.4%, control 82.1%
Medications taken by ≥ 50% of those in the control group: nil

Medications taken by 20%-49% of those in the control group: ACEi, diuretics, other antihypertensives, statins, oral hypoglycaemics, antiplatelet therapy
Medications taken by some, but < 20% of the control group: insulin, non-statin lipid-lowering, hormone replacement therapy
Location: Spain
Ethnicity: white from Europe 97%, Hispanic from Central or South America 1%-2%, other 1.5%

Interventions Type: dietary advice and food supplement
Comparison: PUFA vs MUFA
Intervention: Mediterranean dietary advice plus 30 g/d mixed nuts (15 g walnuts, 7.5 g hazelnuts, 7.5 g almonds, provided, rich in ALA and linoleic) - intensive education on diet with individual and up to 20 group sessions with dietitian.
Control: Mediterranean dietary advice plus 1 L/week extra-virgin olive oil (provided) - intensive education on diet with individual and up to 20 group sessions with dietitian.
Dose aim: unclear, food rather than nutrient goals provided, nuts (PUFA) vs olive oil (MUFA)
Baseline PUFA 6.4% E in intervention, 6.1% E in control
Compliance by biomarkers: unclear, no serum TC reported, no tissue fatty acids
Compliance by dietary intake: all assessed at end of trial using a 137-item food frequency questionnaire

- Energy intake, kcal/d: intervention 2229 (SD 477), control 2172 (SD 475)
- Total fat intake, % E: intervention 41.5 (SD 6.1) (MD +0.4% E), control 41.2 (SD 5.4)
- SFA intake, % E: intervention 9.3 (SD 2.0), (MD -0.1% E), control 9.4 (SD 2.0),
- PUFA intake, % E: intervention 7.7 (SD 1.8), (MD +1.6% E), control 6.1 (SD 1.4)
- PUFA n-3 intake (ALA plus marine omega-3), g/d: intervention 2.7 (SD not reported), (MD +0.5 g/d), control 2.2 (SD not reported)
- PUFA n-6 intake, g/d: LA, intervention 16.0 (SD 5.5), (MD +3.8 g/d), control 12.2 (SD 4.6) g
- Trans fat intake: not reported
- MUFA intake, % E: intervention 20.9 (SD 4.1), (MD -1.2% E), control 22.1 (SD 3.7)
- CHO intake, % E: intervention 39.7 (SD 6.3), (MD -0.7% E), control 40.4 (SD 5.9)
- Sugars intake: not reported
- Protein intake, % E: intervention 16.4 (SD 2.5), (MD 0.2% E), control 16.2 (SD 2.4)
- Alcohol intake, % E: not reported

Compliance by other methods: scores on the 14-item Mediterranean-diet screener increased for the participants in both Mediterranean diet groups. Participants assigned to a Mediterranean diet with extra-virgin olive oil and those assigned to a Mediterranean diet with nuts significantly increased their consumption of extra virgin olive oil (to 50 g/d and 32 g/d, respectively) and nuts (to 0.9 and 6 servings/week, respectively).
Inclusion basis: dietary intake data suggested total PUFA intake 1.6% E higher in intervention than control
PUFA dose: 1.6% E
Duration of intervention: 56 months median

Outcomes Main trial outcome: CVD events
Dropouts: intervention 6.3% lost to follow-up for ≥ 2 years, control 3.6% lost to follow-up for ≥ 2 years
Available outcomes: deaths, CV mortality, stroke, MI, CV events
Response to contact: contact established but no additional data provided

Notes All data used were for the Mediterranean diet with nuts vs Mediterranean diet with olive oil, which is higher vs lower PUFA. As nuts were mixed it is not clear whether they were high in ALA or not (probably varied).
Trial funding: mainly governmental funding, but olive oil and nuts were provided by companies

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Tables of random allocation were centrally elaborated. However the main paper (Estruch 2013) was retracted and republished (as Estruch 2018) following a statistical analysis suggesting that baseline variables did not appear consistent with randomisation (Carlisle 2017). The republication states that partners were included in the trial without randomisation (in the same arms as family members) and that some clinics allocated by clinic rather than

		applying the protocol specified individual randomisation. This puts allocation concealment of some participants at high risk.
Allocation concealment (selection bias)	High risk	Trial nurses in charge of the random allocation were independent of the nursing staff, allocation was performed centrally. However, see note on random sequence generation.
Blinding of participants and personnel (performance bias)	High risk	Olive oil and nuts arms could not be blinded to participants
Blinding of outcome assessment (detection bias)	Low risk	Quote: "All medical records related to end points were examined by the end-point adjudication committee, whose members were unaware of the trial-group assignments."
Incomplete outcome data (attrition bias)	Low risk	Quote: "We used four sources of information to identify end points: repeated contacts with participants, contacts with family physicians, a yearly review of medical records, and consultation of the National Death Index." Attrition was < 10% per year, explained and balanced.
Selective reporting (reporting bias)	High risk	Many outcomes in the trials registry entry are not reported by allocated group for the full set of trial participants (for example, cognition)
Attention	Low risk	These appear very similar between the two Mediterranean diet groups
Compliance	Unclear risk	Neither tissue PUFA biomarkers nor TC data reported
Other bias	High risk	Retraction and republication in 2018 due to randomisation problems not reported in the initial publication. However, new outcome data not provided.

Proudman 2015 – ACTRN12613000579796 [543-546]

Methods	RCT, parallel, (EPA + DHA fish oil vs omega 6 sunola oil), 12 months Summary risk of bias: low
Participants	Patients with rheumatoid arthritis < 12 months' duration, DMARD-naive N: 87 intervention, 53 control. (analysed, intervention: 75 control: 47) Level of risk for CVD: low Men: 29% intervention, 25% control Mean age in years (SD): 56.1 (15.9) intervention, 55.5 (14.1) control Age range: unclear Smokers: 65.1% intervention, 54.7% control (includes current and previous smokers) Hypertension: not reported Medications taken by at least 50% of those in the control group: triple DMARD therapy (SSZ 0.5 g/d, HCQ 200 mg twice/day and MTX 10 mg once per week) Medications taken by 20%-49% of those in the control group: NSAIDS Medications taken by some, but less than 20% of the control group: oral or parenteral steroids Location: Australia Ethnicity: not reported
Interventions	Type: supplement (fish oil) Comparison: high EPA + DHA vs omega 6 (low EPA + DHA with sunola oil) Intervention: 10 mL/d fish oil concentrate (BLT Incromega TG3525) providing 5.5 g/day (3.2 EPA + 2.3 DHA). Dose: 5.5 g/d EPA + DHA Control: 10 mL/d sunola oil: capelin oil (2:1) providing 0.21 g EPA + 0.19 g DHA/d as TAG (0.40 g/day EPA + DHA). Compliance: consumption checked at each visit. 100% compliance would be consumption of 3650 mL oil at 12 months. The fish oil group was less compliant than the control group with median intakes

of 2482 mL and 3248 mL, respectively (P = 0.015, Mann-Whitney U test). This provided an average daily intake of EPA + DHA of 3.7 g and 0.36 g in the fish oil and control groups, respectively.
Duration of intervention: 12 months

Outcomes Main study outcome: disease-modifying anti-rheumatic drugs (DMARD) failure and remission
Dropouts: 11 intervention, 6 control
Available outcomes: mortality (nil death), adverse events including CVD, DAS score, diabetes, authors supplied methodology data plus BMI change
Response to contact: yes

Notes DAS scores are reported as median and IQR in Proudman 2012 abstract
Study funding: National Health Medical Research Council of Australia and Royal Adelaide Hospital Research Committee. Melrose Health provided support for ongoing studies. The oil was made by the Royal Adelaide Hospital Pharmacy

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The randomisation schedule was prepared using an online random number generator and involved randomly permuted blocks of size six."
Allocation concealment (selection bias)	Low risk	Quote: "Randomisation was performed by the RAH pharmacy, which also prepared and provided the study oils in 500 mL identical dark brown bottles labelled with consecutive study numbers"
Blinding of participants and personnel (performance bias)	Low risk	Quote: "Both participants and investigators/assessors were blinded to the group allocation. Although the control oil was paler in colour than the fish oil, this was not evident in the brown bottles. The 'fishy' odour of each oil was similar."
Blinding of outcome assessment (detection bias)	Low risk	Both participants and investigators/assessors were blinded to the group allocation. Quote: "Investigators and subjects remained blinded for all withdrawals."
Incomplete outcome data (attrition bias)	Low risk	The flow of all study participants shown in FIGURE 2
Selective reporting (reporting bias)	Unclear risk	Outcomes reported in trial register matched with the outcomes reported in publications. However, the study was retrospectively registered – registered in 2013, recruitment began in 2001
Attention	Low risk	No difference between groups
Compliance	High risk	Consumption checked at each visit. 100% compliance would be consumption of 3650 mL oil at 12 months. The fish oil group was less compliant than the control group with median intakes of 2482 mL (68%) and 3248 mL (89%), respectively (P = 0.015, Mann-Whitney U test). This provided an average daily intake of EPA + DHA of 3.7 g and 0.36 g in the fish oil and control groups, respectively
Other bias	Low risk	None noted

Puri 2005 – ISRCTN79170611 [547 548]

Methods RCT, parallel (ethyl-EPA vs paraffin), 2 arm, 12 months
Summary risk of bias: low

Participants People with Huntington's Disease
N: 67 intervention, 68 control (analysed, intervention: 39 control: 44)
Level of risk for CVD: low
Men: 57% intervention, 44% control
Mean age in years (SD): 50 (9.3) intervention, 49 (9.0) control

Age range: not reported
Smokers: not reported
Hypertension: not reported
Medications taken by at least 50% of those in the control group: not reported
Medications taken by 20%-49% of those in the control group: antidepressants
Medications taken by some, but < 20%: neuroleptics
Location: UK, USA, Canada, Australia
Ethnicity: intervention: 94% white, 4% black, 1% Asian; control: 97%, 3%, 0%, respectively

Interventions Type: supplement (ethyl-EPA)
Comparison: EPA vs paraffin (non-fat)
Intervention: 2 × 2 × 500 mg capsules/d, total dose of 2 g/day ethyl-EPA (code name LAX-101, purity 95%). Dose: 1.9 g/d EPA
Control: 2 × 2 × 500 mg capsules/d liquid paraffin
Compliance: 38 were excluded for protocol violations, 4 intervention and 16 control were non-compliant with capsules
Duration of intervention: 12 months

Outcomes Main study outcome: functional status in Huntington's Disease
Dropouts: 7 intervention, 7 control
Available outcomes: measures of functional capacity, CV events, cancers (nil deaths)
Response to contact: yes (no additional data provided)

Notes Study funding: Amarin Neuroscience Ltd. (formerly known as Laxdale Ltd.), provided organisation, funding and salaries

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "After screening and acceptance... patients were assigned to treatment by receiving a numbered pack supplied by a clinical trials packaging organization ... independent of all other aspects of the trial. Randomization was stratified in a block size of four, with the appropriate number of blocks allocated to each center. PCI Clinical Services held the randomization code until the database had been closed and all patients had been assigned"
Allocation concealment (selection bias)	Low risk	As above
Blinding of participants and personnel (performance bias)	Low risk	Quote: "[p]lacebo and ethyl-EPA capsules were of identical appearance" (though taste and smell not reported).
Blinding of outcome assessment (detection bias)	Low risk	Randomisation described as "double-blind", "neither the patients nor the participating medical staff had access to this code during the course of the study"
Incomplete outcome data (attrition bias)	High risk	Clearly reported and complete, however > 20% attrition
Selective reporting (reporting bias)	Unclear risk	No protocol or trials registry entry identified
Attention	Low risk	Unlikely
Compliance	Unclear risk	38 were excluded for protocol violations, 4 intervention and 16 control were non-compliant with capsules
Other bias	Low risk	None noted

Raitt 2005 – NCT00004558 [549]

Methods RCT, parallel, (fish oil or olive oil), 24 months
Summary risk of bias: moderate or high

Participants People with implantable cardioverter defibrillators and recent sustained ventricular tachycardia or ventricular fibrillation (VT/VF)
N: 100 intervention, 100 control
Level of risk for CVD: high
Men: 86% intervention, 86% control
Mean age in years (SD): 63 (13) intervention, 62 (13) control
Age range: not reported but 18-75 inclusion criteria
Smokers: not reported
Hypertension: 46% intervention, 55% control
Medications taken by at least 50% of those in the control group: diuretic, beta blockers, ACE inhibitors
Medications taken by 20%-49% of those in the control group: digoxin, statins
Medications taken by some, but less than 20% of the control group: calcium channel blocker
Location: USA
Ethnicity: 94% white in intervention group, 97% in control group

Interventions Type: supplement (fish oil capsules vs olive oil capsules)
Comparison: EPA + DHA vs MUFA
Intervention: 1.8 g/d fish oil capsules (Hoffman LaRoche, including ethyl esters of EPA and DHA, 0.76 g/d EPA, 0.54 g/d DHA). Dose: 1.3 g/d EPA + DHA
Control: 1.8 g/d olive oil capsules (Hoffman LaRoche, 73% oleic acid)
Compliance: while control group plasma and platelet DHA and EPA did not change, there were increases of 2%-8.3% in the intervention group
Duration of intervention: 24 months (median 718 days)

Outcomes Main study outcome: time to first episode of VT/VF
Dropouts: 17 intervention, 26 control
Available outcomes: deaths, CV death, MI, angina, revascularisation, arrhythmias, sudden cardiac death, cancer
Response to contact: yes but no data provided

Notes Study funding: NIH and Hoffman LaRoche

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "computer generated block randomisation scheme"
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias)	Unclear risk	Participant blinding unclear
Blinding of outcome assessment (detection bias)	Low risk	ICD traces were viewed by researchers blinded to allocation, "double blind placebo-controlled"
Incomplete outcome data (attrition bias)	Low risk	Almost all participants were included in outcome assessment, well described
Selective reporting (reporting bias)	High risk	NCT registered in February 2000, study carried out from February 1999 to January 2004. Most outcomes stated in registry entry reported, but quality of life missing
Attention	Low risk	Capsules were the only different interventions between arms, little opportunity for attention bias
Compliance	Low risk	While control group plasma and platelet DHA and EPA did not change, there were increases of 2%-8.3% in the intervention group
Other bias	Low risk	None noted

Ramirez-Ramirez 2013 [550 551]

Methods RCT, parallel, (fish oil vs sunflower oil), 12 months
Summary risk of bias: moderate or high

Participants People with relapsing remitting multiple sclerosis

N: 25 intervention, 25 control. (analysed, intervention: 20 control: 19)
Level of risk for CVD: low
Men: 83% intervention, 82% control (but these appear unlikely)
Mean age (SD) years: 35.1 (7.6) intervention, 34.9 (7.8) control
Age range: not reported but 18-55 years were inclusion criteria
Smokers: not reported
Hypertension: not reported
Medications taken by at least 50% of those in the control group: 100% treated with interferon beta1b for at least 1 year before the trial began
Medications taken by 20%-49% of those in the control group: not reported
Medications taken by some, but less than 20% of the control group: not reported
Location: Mexico
Ethnicity: not reported

Interventions Type: supplement
Comparison: DHA + EPA vs sunflower oil
Intervention: 4 g/d omega Rx capsules (Dr Sears zone diet, with excipient of glycerin, water, tocopherol, sunflower oil, titanium dioxide, includes 0.8 g/d EPA plus 1.6 g/d DHA). Dose: 2.4 g/d EPA + DHA
Control: excipient only (Perfect Source Natural Products, glycerin, water, tocopherol, sunflower oil, titanium dioxide)
Compliance: consumption diary plus pills returned at each visit, adherence calculated (correct formula?? pills consumed × 100/pills returned), optimal adherence was considered to be > 80%, 1 intervention and 3 control were excluded due to compliance < 80%. Blood DHA and EPA were significantly different at 12 months.
Duration of intervention: 12 months

Outcomes Main study outcome: TNF-alpha
Dropouts: 5 of 25 intervention, 6 of 25 control
Available outcomes: TNF-alpha, IL-6, IL-1 beta, nitric oxide catabolites, MS relapse, disability EDSS, liver and renal function tests, haemoglobin, leucocytes, platelets, oxidative outcomes (glucose and lipids data collected but not reported, for BMI and BP paper reports "no difference through study")
Response to contact: not yet attempted

Notes Study funding: not reported

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation sequence (blocks of 4)
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias)	Low risk	Quote: "capsules were identical in appearance, packaging and labelling", "physicians and patients were blind to the intervention", and there was a rosemary flavour to mask.
Blinding of outcome assessment (detection bias)	Low risk	Quote: "an independent physician evaluated the EDSS score and collected samples at each clinic visit"
Incomplete outcome data (attrition bias)	High risk	Loss of 11/50 over 1 year, 22% loss
Selective reporting (reporting bias)	High risk	Paper reports analysis of glucose and lipids but these are not reported
Attention	Low risk	Appeared similar, reviewed every 3 months
Compliance	Low risk	Blood DHA and EPA were significantly different at 12 months
Other bias	Low risk	None noted

Rebello 2015 – NCT01669200 [552]

Methods	RCT, parallel, (n3 ALA vs mixed fat), 24 wks. Summary risk of bias: Moderate or high
Participants	Healthy older people from USA N: 3 int., 3 control. (analysed, int: 2 cont: 2) Level of risk for CVD: Low Male: 50% int., 50% control. Mean age (sd): NR Age range: 58-78 years Smokers: NR Hypertension: NR Medications taken by at least 50% of those in the control group: NR Medications taken by 20-49% of those in the control group: NR Medications taken by some, but less than 20% of the control group: NR Location: USA Ethnicity: Not reported
Interventions	Type: food supplement (Yoghurt with added canola oil or added Medium Chain Triglyceride Oil (MCT oil, Nestle™)) Comparison: PUFA vs. SFA Intervention: Yogurt with added 56g canola oil (about 65% MUFA, & 28% PUFA, typically): ALA unclear Control: Yogurt with added 56 g/d MCTs (type of saturated fat) Compliance: Measured but Not reported; one participant dropped due to non-compliance Duration of intervention: 24 wks
Outcomes	Main study outcome: cognitive decline Dropouts: 1 int., 1 control Available outcomes: ADAS-Cog, body ketones, trail-making test, digit-symbol test
Notes	Study funding: Sponsor: Pennington Biomedical Research Centre (register). Product was a Nestle one.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was conducted by the study pharmacist using a random-number table and was revealed to study staff and investigators only at the conclusion of the study
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias)	Unclear risk	Insufficient detail. "blinded" and mentions capsules were colour matched.
Blinding of outcome assessment (detection bias)	Unclear risk	Insufficient description. Randomisation ...was revealed to study staff and investigators only at the conclusion of the study
Incomplete outcome data (attrition bias)	High risk	Explains both drop outs, but doesn't explicitly say that is one from each arm. Exceeds 20% drop outs.
Selective reporting (reporting bias)	High risk	MMSE is primary outcome in register but not reported in article.
Attention	Low risk	Blood was drawn at randomisation Each subject's diet was assessed by a registered dietician. At baseline blood was drawn for ApoE4 status, serum BHB, blood glucose and insulin and ADAS- Cog, Trail making and Digit symbol tests. Post baseline visits were at weeks 4, 8, 12, 16 & 20 & included dispensation of study products, compliance assessment, instruction by a registered dietician. At 4 week, baseline blood testing for glucose, insulin and pre/post praindial BHB were repeated. At week 24 clinical tests and psychological tests were repeated. Weight & vital signs measured at all visits. This is the same for intervention and control

Compliance	Unclear risk	Data collected but not reported in article.
Other bias	Low risk	None noted

REDUCE-IT 2011 - NCT01492361 [553]

Methods
Reduction of Cardiovascular Events with EPA - Intervention Trial (REDUCE-IT)
RCT, parallel, (LCn3 vs paraffin oil), median 4.9 years
Summary risk of bias: moderate or high

Participants
Patients (45 years+) with hypertriglyceridaemia, and with cardiovascular disease or with DM and another risk factor, and on statin
N: intervention 4089 randomised, control 4090 randomised (analysed, intervention: 4083 control: 4077)
Level of risk for CVD: moderate (w DM) and high (with CVD)
Men: 71.6% intervention, 70.8% control
Age median (IQ range) years: median 64 (57-69) intervention, 64 (57-69) control
Age range: not reported those with CVD included if at least 45 years, those with DM if at least 50 years old
Smokers: not reported
Hypertension: not reported
Medications taken by at least 50% of those in the control group: 100% treated with statins to be randomised
Medications taken by 20%-49% of those in the control group: not reported
Medications taken by some, but less than 20% of the control group: ezetimbe
Location: 11 countries including USA, Netherlands, Ukraine, Russia, South Africa, Poland, India, Romania, Australia, New Zealand
Ethnicity: white 90.3% intervention, 90.2% control

Interventions
Type: supplement
Comparison: EPA vs paraffin
Intervention: EPA ethyl ester derived from fish oil (AMR101 4 g/d, Amarin), 3.99g/d EPA plus 8mg/d vitamin E (2 capsules twice a day)
Control: 3.73g/d light liquid paraffin oil in 4 capsules (2 capsules twice a day)
Compliance: serum EPA assessed, expressed as medians, ~26µg/ml at baseline, at 1 year rose to 144 in intervention group, 23.3 in control.
Duration of intervention: median 4.9 years (max 6.2 years)

Outcomes
Main study outcome: composite of cardiovascular death, MI, stroke, coronary revascularisation and hospitalisation for unstable angina
Dropouts: 6 intervention, 13 control
Available outcomes: deaths, CVD deaths, CVD events, MACCEs, stroke, MI, sudden cardiac death, new angina, heart failure, amputations due to PVD, atrial fibrillation, revascularisation, DM, TIA, HT, (lipid levels and CRP provided as medians)
Response to contact: not yet attempted

Notes
NCT01492361
Study funding: study designed, run and funded by Amarin (who produce the intervention capsules)

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	stratified randomisation
Allocation concealment (selection bias)	Unclear risk	No details provided
Blinding of participants and personnel (performance bias)	Low risk	Participants and personnel stated to be blinded, not clearly stated that containers were identical but capsular content was identical
Blinding of outcome assessment (detection bias)	Low risk	Adjudication was by independant clinical endpoint committee unaware of assignment

Incomplete outcome data (attrition bias)	Low risk	Low levels of participant loss
Selective reporting (reporting bias)	Low risk	Only 2 outcomes mentioned in trials register, both reported plus many more. Registered Nov 2011, recruitment Nov 2011 to Aug 2016.
Attention	Low risk	Appeared similar
Compliance	Low risk	Median serum EPA rose in intervention but not in control
Other bias	Unclear risk	Some changes in inclusion criteria (levels of TG included) during trial

Reed 2014 – NCT00072982 [554 555]

Methods RCT, parallel, 3 arms (fish oil or borage oil), 18 months
Summary risk of bias: low

Participants Adults with rheumatoid arthritis
N: 53 intervention, 52 control (28 intervention, 24 control analysed)
Level of risk for CVD: low
Men: 13.2% intervention, 23.1% control
Mean age in years (SD): 57.3 (12.3) intervention, 60.3 (9.2) control
Age range: not reported but 18-85 inclusion criteria
Smokers: not reported
Hypertension: not reported
Medications taken by at least 50% of those in the control group: methotrexate, DMARDs, and TNF blockers
Medications taken by 20%-49% of those in the control group: corticosteroids and TNF blockers
Medications taken by some, but less than 20% of the control group: not reported
Location: USA
Ethnicity: black/African-American: intervention (fish oil): 7.8% control (borage oil): 7.8%

Interventions Type: supplement (fish oil vs borage oil)
Comparison: EPA + DHA vs Omega 6
Intervention: 7 fish oil (2.1 gm EPA:1.4 gm DHA) capsules and 6 sunflower seed oil capsules daily = 13 capsules divided doses. Dose: 3.5 g/d EPA + DHA
Control: 6 borage seed oil (1.8 g GLA) capsules plus 7 sunflower seed oil capsules daily
Compliance: assessed by capsule counts and patient report. Patient report, indicates that 45% of patients reported ever missing a dose (borage: 42%, fish 48%). Median total capsules missed (excluding those with 0) were 182 (borage: 164, fish 169)
Duration of intervention: 18 months

Outcomes Main study outcome: RA modified disease activity score
Dropouts: 25 intervention, 28 control
Available outcomes: mortality (nil death), CVD events (nil), DAS score, CDAI score. Authors suggested that LDL and total cholesterol were reduced in the intervention group at 18 months, and HDL was increased in both intervention and control at 18 months, while diastolic BP was reduced in the intervention group at 18 months, but no numbers provided. CRP and ESR data were provided combined for the intervention and control arms in the author response, so not useable
Response to contact: yes, authors supplied details of methodology but no usable outcome data

Notes A third arm (45 participants) were given a combination of both oils but not discussed here.
Study funding: National Institutes of Health Grant RO1-AT000309 from the National Center for Complementary and Alternative Medicine

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Author stated "stratified random block, stratified by site using random blocks of 3 & 6"
Allocation concealment (selection bias)	Low risk	No methodology provided in the paper, but the author suggested concealment

Blinding of participants and personnel (performance bias)	Low risk	Double-blind, all capsules were identical in appearance and colour, they were shipped in opaque plastic bottles to the University of Massachusetts University Hospital pharmacy, from where they were distributed to participating centres. However no information provided as to their smell and taste.
Blinding of outcome assessment (detection bias)	Low risk	Author confirmed outcome assessors were blinded.
Incomplete outcome data (attrition bias)	High risk	Authors mention intention-to-treat analysis but shows completers analysis. Numbers of participants are not provided for all outcomes measured. Provide results for the overall group (69 participants table 3a) while the flow diagram states there are 74 completers. 51% dropped out.
Selective reporting (reporting bias)	Low risk	Study prospectively registered in 2003, estimated study completion November 2008, published in 2014. Both outcomes reported in registry are reported in the publication.
Attention	Low risk	All patients were evaluated at 3-month intervals, by the same examiner.
Compliance	Unclear risk	Assessed by capsule counts and patient report. Patient report, indicates that 45% of patients reported ever missing a dose (borage: 42%, fish 48%). Median total capsules missed (excluding those with 0) were 182 (borage: 164, fish 169)
Other bias	Low risk	None noted

Risk & Prevention 2013 – NCT00317707 [556-559]

Methods
RCT, parallel, (n-3 vs olive oil), 60 months
Summary risk of bias: moderate or high

Participants
Patients with multiple cardiovascular risk factors
N: 6244 intervention, 6269 control (analysed, intervention: 6239 control: 6266)
Level of risk for CVD: high
Men: 62.3% intervention, 60.6% control
Mean age in years (SD): 63.9 (9.3) intervention, 64.0 (9.6) control
Age range: not reported
Smokers: 22.1% intervention, 21.4% control.
Hypertension: 84.6% intervention, 84.5% control
Medications taken by at least 50% of those in the control group: not reported
Medications taken by 20%-49% of those in the control group: ACE inhibitor; ARB; diuretic agent; calcium-channel blocker; beta-blocker; oral hypoglycaemic drug; statin; antiplatelet agent
Medications taken by some, but less than 20% of the control group: insulin
Location: Italy
Ethnicity: not reported

Interventions
Type: supplement (n-3 capsules)
Comparison: EPA + DHA vs MUFA
Intervention: 1 g/d n-3 capsules polyunsaturated fatty acid ethyl esters (EPA and DHA content 850-882 mg with an average ratio of 1.0 to 1.2). Dose: ~0.87 g/d EPA + DHA
Control: 1 g/d olive oil capsules
Compliance: measured by self-report during follow-up visits but no results reported
Duration of intervention: 60 months

Outcomes
Main study outcome: composite of time to death from cardiovascular causes or hospital admission for cardiovascular causes
Dropouts: intervention: 5 withdrew consent before baseline, 43 lost to follow-up, 1115 stopped treatment. 6239 analysed.
Control: 3 (withdrew consent before baseline), 39 lost to follow-up, 1218 stopped treatment. 6266 analysed

Available outcomes: mortality, CV mortality, CV events, coronary related events and mortality, MI, AF, heart failure, side effects, stroke, cancer diagnosis, cancer death. Authors provided data on diabetes diagnosis, glucose and HbA1c.
Response to contact: yes

Notes All continuous outcomes change data are reported as least squares mean hence not used.
Study funding, quote: "The steering committee had the full and sole responsibility for planning and coordinating the study, analyzing and interpreting the data, and preparing the manuscript and submitting it for publication. Società Prodotti Antibiotici, Pfizer, and Sigma Tau funded the trial but had no role in the study design, planning, conduct, or analysis or in the interpretation or reporting of the results"

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Treatment was centrally assigned by means of telephone on the basis of a concealed, computer-generated randomization list, stratified according to general practitioner."
Allocation concealment (selection bias)	Low risk	As above
Blinding of participants and personnel (performance bias)	Unclear risk	Quote: "Patients, general practitioners, coordination and statistical staff, and outcome assessors were unaware of the study assignments until the final analyses were completed." However, there was no mention of placebo appearance or other methods of blinding, so unclear.
Blinding of outcome assessment (detection bias)	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." Quote: "All events included in the primary efficacy end point were documented with the use of a narrative summary and supporting documentation and were adjudicated on the basis of prespecified criteria by an ad hoc committee consisting of a cardiologist, an internist, and a neurologist who were unaware of the study assignments"
Incomplete outcome data (attrition bias)	Low risk	Quote: "Analyses were performed in the intention-to-treat population, except for a prespecified per protocol analysis of the primary end point in patients with no major protocol violations who did not permanently stop treatment." Figures differ in Visentin 2008: (p. i73) ″At the end of March 2006, 12 521 patients have been Randomized"; "After 1-year of follow-up, 2.5% of the patients withdrawn from the trial and 5% of the patients discontinued treatment. The reasons for drug discontinuation were 1.7% for side effects (mainly gastrointestinal) and 3.3% others (clinical or patient's refusal)… After 1-year of follow-up, 1.0% had CV death and 3.4% hospitalisation for CV events (primary end point)"
Selective reporting (reporting bias)	High risk	Primary endpoint was amended part way through study. Differences in groupings of cardiovascular events in tables 2; S4 and S5. For hospital admissions notes each patient could have more than one cardiovascular cause
Attention	Unclear risk	Does not state attention differs or is the same between groups- regularly see GP for follow-up and blinding not clear
Compliance	Unclear risk	No results

Other bias	Low risk	None noted

Romero 2013 [560]

Methods	RCT, parallel, (n3 EPA+DHA vs nil), 6 months Summary risk of bias: Moderate or high
Participants	Population: patients with mild cognitive impairment N: 15 int., 15 control. (analysed, int: 13 cont: 13) Level of risk for CVD: low Male: NR int., NR control. Mean age (sd): NR int., NR control, but mean age for total population given as 72.5 years Age range: NR Smokers: NR Hypertension: NR Medications taken by at least 50% of those in the control group: NR Medications taken by 20-49% of those in the control group: NR Medications taken by some, but less than 20% of the control group: NR Location: Spain Ethnicity: NR
Interventions	Type: Omega-3 food supplement Comparison: omega-3 supplement vs no omega-3 Intervention: 2 ACUTIL capsules per day: 500 mg DHA + 80 EPA per day: EPA+DHA 0.58g/d Control: no omega-3 Compliance: NR Duration of intervention: 6 months
Outcomes	Main study outcome: cognition Dropouts: 2 int., 2 control (based on report implying that 15 started the study in each group and report that 13 finished the study) Available outcomes: cognition assessed by PHOTOTEST
Notes	Only an abstract was available for this study. Cognition was assessed by the PHOTOTEST method (regarded as a simple, easy and very brief test with theoretical advantages over available dementia screening tests in Spain. Reported to detect mild dementia or MCI, with good accuracy and good correlation with tests measuring overall cognitive impairment [Russo MJ et al 2014. Diagnostic accuracy of the Phototest for cognitive impairment and dementia in Argentina. Clin Neuropsychol 28(5)826-40)] PHOTOTEST results cannot be added as it is not in usable form: – Positive but not significant trend (p=0.15) in the Omega-3 group at 3 months. – Significant difference (p=0.003) between the groups at 6 months in favour of the Omega-3 group. After 6 months with the Omega-3 supplement, the PHOTOTEST results show a significant cognitive improvement in the group that received the Omega-3 supplement compared to the group not receiving any supplement. Omega-3 tolerance was good.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	'patients diagnosed with mild cognitive impairment were randomly divided into two groups'
Allocation concealment (selection bias)	Unclear risk	Insufficient detail to assess this
Blinding of participants and personnel (performance bias)	High risk	Control group received normal treatment without Omega-3 (no omega-3) while treatment group received Omega-3 food supplement plus normal treatment. It appeared that placebo was not given and so it is possible that participants will know if they are part of the intervention or not.

Blinding of outcome assessment (detection bias)	Unclear risk	Insufficient detail to assess this
Incomplete outcome data (attrition bias)	Unclear risk	Insufficient detail to assess this
Selective reporting (reporting bias)	Unclear risk	Insufficient detail to assess this
Attention	Low risk	'Assessment of cognitive function was done by means of the PHOTOTEST at visit 0 (day 0), visit 1 (3 months) and visit 2 (6 months)'. It appears that participants were given the same attention.
Compliance	Unclear risk	Insufficient detail to assess this
Other bias	Unclear risk	Insufficient detail to assess this

Rose 1965 [561]

Methods RCT, 2 arms, parallel (n6 LA vs MUFA), 24 months
Summary risk of bias: moderate to high

Participants People with ischaemic heart disease
CVD risk: high
N: 28 intervention, 26 control (analysed 15 intervention, 12 control)
% male: not reported
Mean age: 52.6 intervention, 55 control (no SDs)
Age range: not reported
Smokers: not reported
Hypertension: not reported
Medications taken by ≥ 50% of those in the control group: not reported
Medications taken by 20%-49% of those in the control group: not reported
Medications taken by some, but < 20% of the control group: not reported
Location: UK
Ethnicity: not reported

Interventions Type: test oil provided (equivalent advice to both arms)
Comparison: n-6 vs MUFA
Intervention: 80 g/day corn oil to be taken in 3 equal doses at meal-times plus participants were instructed to avoid fried foods. Fatty meat, sausages, pastry, ice-cream, cheese, cakes, milk, eggs, butter were restricted: assuming 80% LA in corn oil, 64 g/d LA or 576 kcal/d or 28.8% E from LA
Control: 80 g/day olive oil plus participants were instructed to avoid fried foods, fatty meat, sausages, pastry, ice-cream, cheese, cakes, milk, eggs, butter were restricted. assuming 12% LA and 69% MUFA in olive oil, 9.6 g/d LA or 4.3% E LA and 55.2 g/d MUFA or 24.8% E
Dose aim: **+24.5% E from LA, -24.8% E MUFA**
Baseline PUFA: unclear
Compliance using biomarkers: serum TC reduced, but not statistically significantly reduced in intervention compared to control (-0.49 mmol/L, 95% CI -1.34 to 0.36). No fatty acid biomarkers reported.
Compliance using dietary assessment: poor. Measured using questionnaire. Mean intake of oil in intervention was 595 kcal/d or 476 kcal/d LA or 23.8% E, in control 540 kcal/d or 3.2% E LA and 18.6% E MUFA, achieved: +20.6% E from LA, -18.6% E MUFA within the oils, unclear how diet altered

- Energy intake: intervention 2070 kcal/d control 2045 kcal/d
- Total fat intake: intervention 50 g/d + 595 kcal from oil or 1045 kcal/d or 52% E, control 45 g/d + 540 kcal from oil or 945 kcal/d or 47.3% E
- SFA intake: not reported
- PUFA intake: not reported
- PUFA n-3 intake: not reported
- PUFA n-6 intake: +20.6% E (higher in intervention than control)
- Trans fat intake: not reported (oils provided so not likely to be a problem)
- MUFA intake: -18.6% E (lower in intervention than control)
- CHO intake: intervention 189 g/d or 756 kcal/d or 37.8% E, control 216 g/d or 864 kcal/d or 43.2% E
- Sugars intake: not reported

- Protein intake: intervention 57 g/d or 228 kcal/d or 11.4% E, control 49 g/d or 196 kcal/d or 9.8% E
- Alcohol intake: not reported

Compliance by other methods: no others reported
Inclusion basis: aim was to increase omega-6 fats, not total PUFA. Total PUFA not reported but LA dose so big that total PUFA must have been increased in intervention compared to control. Best estimate 20.6% E total PUFA dose, > 10% increase from baseline
PUFA dose: according to questionnaire 20.6% E from LA, assume equivalent to 20.6% E from total PUFA
Duration of intervention: 2 years

Outcomes Main trial outcome: occurrence of infraction
Dropouts: 6 intervention, 11 control?, details provided in table but unclear how many dropped out.
Available outcomes: major CVD events, MI (fatal and non-fatal), sudden death, serum cholesterol
Response to contact: not attempted as published in the 1960s

Notes Trial funding: no details
The trial had a 3rd control arm (no intervention), which has not been used here.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	When a new participant was accepted for the trial a sealed envelope was opened containing the allocation instructions. In the case of participants allocated to an oil group the instructions referred only to a code number.
Allocation concealment (selection bias)	Unclear risk	Unclear
Blinding of participants and personnel (performance bias)	Low risk	The physicians in charge knew which participants were receiving oil, but they did not know until the end of the trial the kind of oil that they were receiving.
Blinding of outcome assessment (detection bias)	Low risk	The electrocardiograms were assessed without the knowledge of the participant's treatment group
Incomplete outcome data (attrition bias)	Low risk	52% intervention, and 57% control remained in the trial after 24 months. However, the list of reasons and complications is provided.
Selective reporting (reporting bias)	Unclear risk	No trial registry record or protocol found
Attention	Low risk	Oil provided to both groups, appeared similar
Compliance	Low risk	TC somewhat reduced in intervention compared to control (-0.49 mmol/L, 95% CI -1.34 to 0.36). No fatty acid biomarkers reported
Other bias	Low risk	None noted

Rossing 1996 [562 563]

Methods RCT, parallel, (fish oil vs olive oil), 12 months
Summary risk of bias: moderate or high

Participants Adults with insulin-dependent diabetes mellitus, diabetic nephropathy and normal BP
N: 18 intervention, 18 control (analysed, 17 intervention, 15 control)
Level of risk for CVD: moderate
Men: 64% intervention, 67% control
Mean age (SD) years: 32 (7) intervention, 34 (10) control
Age range: 18-55 years
Smokers: 50% intervention, 47% control
Hypertension: not reported
Medications taken by at least 50% of those in the control group: insulin
Medications taken by 20%-49% of those in the control group: not reported
Medications taken by some, but less than 20% of the control group: not reported

Location: Denmark
Ethnicity: not reported

Interventions Type: supplement
Comparison: EPA + DHA vs MUFA
Intervention: cod-liver oil emulsion (Pharma-Vinci A/S Denmark). EPA 2 g, DHA 2.6 g, total PUFA 4.6 g/day. Dose: 4.6 g/d EPA + DHA
Control: olive oil emulsion (Pharma-Vinci A/S Denmark)
Compliance: assessed through omega 3 incorporation in platelets, and the paper reports significantly higher omega 3 levels in platelets at 12 months
Duration of intervention: 12 months

Outcomes Main study outcome: diabetic nephropathy
Dropouts: 1 intervention, 3 control (though 3 further intervention participants are not included in all data)
Available outcomes: mortality (nil), breast cancer, total and LDL cholesterol, sBP (TGs reported as medians so not used, albuminurea, fractional albumin clearance, transcapillary escape rate of albumin, prothrombin fragment reported as geometric means or medians, HbA1c, HDL and diastolic BP too different at baseline to include, GFR, PAI1, TPA, fibrinogen, etc. not relevant)
Response to contact: yes

Notes Study funding: the Danish Heart Association. Eskisol Fish oil and placebo oil emulsions were provided by Pharma-Vinci A/S, Frederiksvaerk, Denmark

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Patients were randomised using concealed randomisation to receive either fish oil or olive oil in blocks of 4 according to their glomerular filtration rate."
Allocation concealment (selection bias)	Unclear risk	No further details
Blinding of participants and personnel (performance bias)	Low risk	"Active and placebo (olive oil) were given as emulsions with orange flavour. At the end patients were allowed to guess about treatment and ~50% were right"
Blinding of outcome assessment (detection bias)	Unclear risk	No details
Incomplete outcome data (attrition bias)	Low risk	Dropouts similar between groups although relatively high for small sample size. 3 dropouts from fish oil and 1 from control due to side effects. Intention-to-treat analysis appears to have been given for albuminuria only
Selective reporting (reporting bias)	Unclear risk	No trials registry entry or protocol found
Attention	Low risk	Time and attention appear to be the same. All patients were given dietary advice.
Compliance	Low risk	Reports significantly higher omega 3 levels in platelets at 12 months for the intervention group
Other bias	Low risk	None noted

Salari 2010 [564]

Methods 2 arm, parallel RCT (omega 3 vs unclear placebo), 6mo
Summary risk of bias: Moderate or high

Participants Osteoporotic postmenopausal women
N: 13 int.,12 control (analysed 10 int., 8 control)
Level of risk for CVD: Low
Male: 0%
Age (Mean): 60.0 (5.6), int., 63 (8.9) control

Age range: Unclear
Smokers: 0% (exclusion criteria)
Hypertension: NR
Medications taken by at least 50% of those in the control group: NR
Medications taken by 20-49%: NR
Medications taken by some, but <20%: NR
Location: Iran
Ethnicity: Iranians

Interventions Type: supplement (capsules)
Comparison: Omega 3 fats vs unclear
Intervention: 3 Omega 3 capsules/ day Zahravi Pharmaceutical Co. (Iran). (900mg/d total n3 fats)
Control: 3 placebo capsules Zahravi Pharmaceutical Co. (Iran) similar in taste, texture, and appearance to intervention capsules. Content is unclear.
Compliance: Measured through visits and phone calls but no results reported
Duration of intervention: 6 months

Outcomes Main study outcome: Bone biomarkers
Dropouts: Control: 4 Int: 3
Available outcomes: osteocalcin, bone alkaline phosphatase, serum creatinine, calcium, vitamin D, parathormone, urinary pyridinoline, calcium, and creatinine.
Response to contact: yes

Notes Study funding: This study was supported by a grant from Endocrinology and Metabolism Research Center, Tehran University of Medical Sciences. Zahravi Pharmaceutical Company provided the drug and placebo.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Just randomised
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias)	Low risk	Capsules were similar in colour, taste and texture.
Blinding of outcome assessment (detection bias)	Unclear risk	No details
Incomplete outcome data (attrition bias)	High risk	28% attrition rate in 6 months. Reasons not provided by group.
Selective reporting (reporting bias)	Unclear risk	No protocol or trial registration found.
Attention	Low risk	Appears to be similar
Compliance	Unclear risk	No results provided on compliance
Other bias	Low risk	None detected

Sandhu 2016 – NCT00723398 [565 566]

Methods RCT, parallel 5 arms (combined groups 4 and 5 omega-3-acid ethyl esters (Lovaza) n-3 ± raloxifene vs control groups 1 and 3 ± raloxifene), 24 months
Summary risk of bias: moderate or high

Participants Healthy postmenopausal women (50% normal weight, 30% overweight, 20% obese) with high breast density detected on their routine screening mammograms
N: 54 + 53 intervention, 53 + 53 control
Level of risk for CVD: low
Men: 0% intervention, 0% control
Mean age in years (SD): 56.56 (6.9) + 57.85 (5.1) intervention, 57.11 (5.9) + 57.68 (5.1) control
Age range: not reported
Smokers: 0% intervention, 0% control
Hypertension: not reported

Medications taken by at least 50% of those in the control group: not reported
Medications taken by 20%-49% of those in the control group: not reported
Medications taken by some, but less than 20% of the control group: not reported
Location: USA
Ethnicity: not reported

Interventions Type: supplement (n-3 capsules)
Comparison: EPA + DHA vs nil
Intervention: group 4, Lovaza 4 g per day. Lovaza is the FDA-approved n-3 FA formulation containing 465 mg of EPA + 375 mg of DHA per gram, total dose; 1860 mg/d EPA, 1500 mg/d DHA. Group 5 as group 4 plus 30 mg raloxifene/d. Dose: 3.36 g/d EPA + DHA
Control: group 1, no treatment; group 3, 30 mg raloxifene/d
Compliance: measured by pill count, recorded at follow-up visits and further verified by serum fatty acids monitoring. Compliance was 94% (SE 2%) at 6 months and 97% (SE 2%) at 12 months. Only 2 participants had a compliance < 85% (84% and 81%).
Duration of intervention: 24 months

Outcomes Main study outcome: change in breast density
Dropouts: 5 intervention, 6 control
Available outcomes: cardiovascular events, breast cancer, lipids, dietary intake, plasma FAs, adverse events (including one incidence of hyperglycaemia)
Response to contact: yes

Notes The study had 5 arms: group 1, no treatment, control; group 2, raloxifene 60 mg orally daily; group 3, raloxifene 30 mg orally daily; group 4, Lovaza 4 g orally daily; and group 5, Lovaza 4 g/d plus raloxifene 30 mg orally daily. Data here is combined for groups 4 and 5 vs 1 and 3 for binary outcomes and group 1 vs 4 used for continuous outcomes
Study funding: GlaxoSmith Kline and Eli Lilly provided Lovaza and raloxifene, respectively. Funded by Susan G Komen for the Cure, KG081632 (A Manni) and pilot funds from the Penn State Hershey Cancer Institute (K El-Bayoumy)

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Sandhu 2016 pg 276: "each study participant was randomly assigned with equal probability to one of the following five groups. A block randomization scheme was used to ensure balance treatment allocation during the course of enrolment."
Allocation concealment (selection bias)	Unclear risk	No description of concealment of allocation
Blinding of participants and personnel (performance bias)	High risk	Open label
Blinding of outcome assessment (detection bias)	High risk	Open label
Incomplete outcome data (attrition bias)	Low risk	< 20% lost over 2 years, detailed reasons provided, no suggestion these are unbalanced
Selective reporting (reporting bias)	High risk	Biomarkers of oxidative stress (Urinary 8-(isoprostane) F-2α and 8OHdG, Lymphocyte 8-OHdG, DNA etheno adducts), Urinary 2-OHE1, 4-OHE1, and 16α-OHE1, Serum level of C-reactive protein and IL-6, Serum level of IGF-I and IGFBP-3, complete blood count mentioned in trial registry but not reported in Sandhu 2016. (More outcomes reported than in registry – diet, physical activity levels, adverse events)
Attention	Low risk	Participants assessed at baseline, 1-year and 2-year follow-up
Compliance	Unclear risk	Measured by pill count, recorded at follow-up visits and further verified by serum fatty acids monitoring. Compliance was 94% (SE 2%) at 6 months and 97% (SE 2%) at 12 months. Only 2 participants had a compliance < 85% (84% and 81%)

Other bias	Low risk	None noted

Sasaki 2012 – UMIN000005783 [567]

Methods	RCT, parallel, (n3 EPA vs nil, both arms had statins), 6 months Summary risk of bias: Moderate or high
Participants	Type 2 diabetic patients with dyslipidaemia and statin treated N: 15 int., 14 control. (analysed, int: 15 cont: 13) Level of risk for CVD: Moderate Male: 54% int., 46% control Mean age (sd): 65.5 (5.4) int., 69.2 (7.7) control Age range: NR Smokers: 13% int., 21% control Hypertension: NR Medications taken by at least 50% of those in the control group: Statin Medications taken by 20-49% of those in the control group: Sulfonylurea, metformin, insulin, ACE inhibitor or ARB, aspirin Medications taken by some, but less than 20% of the control group: Calcium channel blocker Location: Japan Ethnicity: NR
Interventions	Type: supplement (EPA + statin or statin alone) Comparison: EPA vs nil Intervention: 1.8g/d purified EPA preparation (Epadel, Mochida Pharmaceutical Co. Ltd) + statin: EPA 1.8g/d Control: Statin alone **PUFA Dose**: (intended) increase 1.8g/d EPA+DHA, **0.8%E n-3, 0.8%E PUFA** Compliance: NR Duration of intervention: 6 months
Outcomes	Main study outcome: Endothelial outcome Dropouts: 0 int., 1 control? Available outcomes: BMI, glucose, HbA1c, lipids (LDL used)
Notes	Data for triglycerides and HDL cholesterol not used due to baseline differences Study funding: Self-funded

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"randomly assigned"
Allocation concealment (selection bias)	Unclear risk	As above
Blinding of participants and personnel (performance bias)	Unclear risk	NR
Blinding of outcome assessment (detection bias)	Unclear risk	NR
Incomplete outcome data (attrition bias)	Low risk	Low drop out with reason provided
Selective reporting (reporting bias)	High risk	Appears secondary outcomes not reported and retrospectively registered
Attention	Unclear risk	NR and blinding unclear
Compliance	Unclear risk	NR
Other bias	Low risk	None noted

Sawada 2016 – UMIN000011265 [568]

Methods RCT, parallel, (n3 EPA vs nil), 6 months
Summary risk of bias: Moderate or high

Participants Newly-diagnosed impaired glucose metabolism patients with coronary artery disease
N: 59 int., 59 control. (analysed, int: 54 cont: 53)
Level of risk for CVD: High
Male: 81.5% int., 81.1% control.
Mean age (sd): 67.8 (9.1) int., 68.9 (8.8) control
Age range: NR
Smokers: 9.3% int., 7.5% control
Hypertension: 88.9% int., 92.5% control
Medications taken by at least 50% of those in the control group: Statin, calcium channel blocker, ACEI/ARB; no anti-diabetics were allowed.
Medications taken by 20-49% of those in the control group: NR
Medications taken by some, but less than 20% of the control group: NR
Location: Japan
Ethnicity: NR

Interventions Type: supplement (EPA capsules or nil)
Comparison: EPA vs nil
Intervention: 2x capsules/d (including 1.8g/d EPA, EPADEL, Mochida Pharmaceutical Co Ltd): EPA 1.8g/d
Control: "no EPA"
PUFA Dose: (intended) increase 1.8g/d EPA, **0.8%E n-3, 0.8%E PUFA**
Compliance: NR
Duration of intervention: 6 months

Outcomes Main study outcome: Hyperglycaemia, hyperlipaemia and endothelial dysfunction
Dropouts: 5 int., 6 control
Available outcomes: Type 2 diabetes and impaired glucose tolerance, glucose, HbA1c, HOMA, CRP, lipids, weight, BMI, (HOMA medians only, FPG not used due to baseline differences, bp 6 months not used)

Notes Study funding: No grant support for the present study but all authors declare that they have no competing interests

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was performed by means of random, permuted blocks of four in sealed envelopes
Allocation concealment (selection bias)	High risk	This study was open-label, single-blinded
Blinding of participants and personnel (performance bias)	High risk	Patients knew whether they were intervention or control and no placebo capsule mentioned for the control group
Blinding of outcome assessment (detection bias)	Unclear risk	NR
Incomplete outcome data (attrition bias)	Low risk	Drop outs balanced and less than 10% over 6 months
Selective reporting (reporting bias)	Low risk	Registry outcomes reported
Attention	Low risk	All patients saw a dietitian and treatment only differs by capsule
Compliance	Low risk	EPA/AA ratio significantly increased in intervention group at 6 months
Other bias	Low risk	None noted

Schattin 2016 – ISRCTN12084831 [569] [570]

Methods RCT, 2 arms, parallel, (LCn3 vs MUFA), 6 months
Summary risk of bias: Low

Participants Older adults (>65 years)
N: 29 int., 29 control. (analysed, int: 22 cont: 20)
Level of risk for CVD: low
Male: 55% int., 35% control.
Mean age (sd): median 67 years for both groups
Age range: NR
Smokers: NR
Hypertension: NR
Medications taken by at least 50% of those in the control group: NR
Medications taken by 20-49% of those in the control group: NR
Medications taken by some, but less than 20% of the control group: NR
Location: Italy
Ethnicity: NR

Interventions Type: supplement (capsules)
Comparison: LCn3 vs MUFA
Intervention: 2.9g/d n3 in 13.5ml fish oil
Control: 13.5ml/d olive oil
PUFA Dose: (intended) increase 2.9g/d LCn3, 1.3**%E LCn-3, 1.3%E PUFA**
Compliance: int 98%, cont 96%
Duration of intervention: 26 weeks

Outcomes Main study outcome: neuronal structure and function
Dropouts: 7 int., 8 control
Available outcomes: excitability of neuronal system, neuronal activity, cognitive function, motor function & gait, concern about falling, MMSE, depression, blood fatty acids in protocol

Notes ISRCTN12084831
Study funding: ETH Foundation, San Omega AS provided supplements, Swiss Medical Plus

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	block randomisation, generating number used on tablet packets
Allocation concealment (selection bias)	Low risk	capsules were labelled by external body, enabling blinding of allocation and study
Blinding of participants and personnel (performance bias)	Low risk	Capsules were similar in looks, double blinding stated
Blinding of outcome assessment (detection bias)	Low risk	all study personnel blinded
Incomplete outcome data (attrition bias)	High risk	Dropouts specified, equivalent but high proportions
Selective reporting (reporting bias)	High risk	Not all protocol outcomes reported in trials registry outcome data
Attention	Low risk	No difference suggested
Compliance	Low risk	Compliance high by capsule counts, and statistically significant differences for EPA and DHA blood fatty acids between intervention and control at 6 months
Other bias	Low risk	None noted

Schirmer 2007 [571]

Methods RCT, 2 arm, parallel (n-6 GLA vs MUFA), 1 year
Summary risk of bias: moderate to high

Participants Formerly obese adults with a recent minimum weight loss of 12 kg, a current BMI of < 34 kg/m^2, otherwise healthy
CVD risk: low
N: 23 intervention, 22 control (analysed only completers 13 intervention, 17 control)
% male: 8% intervention, 6% control

Mean age (SD) in years: 44.2 (10.1) intervention, 52.6 (8.1) control
Age range: not reported
Smokers: not reported
Hypertension: 0%
Medications taken by at least 50% of those in the control group: anorexigenic agent
Medications taken by 20%-49% of those in the control group: not reported
Medications taken by some, but less than 20% of the control group: not reported
Location: USA
Ethnicity: not reported

Interventions

Type: supplement (capsule)
Comparison: n-6 (GLA) vs MUFA
Intervention: 5 g/d of 500 mg borage oil capsules providing 0.89 g/d GLA
Control: 5 g/d of identical 500 mg olive oil capsules
Subjects in both groups were required to take a balanced multivitamin-mineral supplement daily, which included 80 mg of d-alpha-tocopherol
Dose aim: increase 0.89 g/d GLA or 8 kcal or **0.4% E GLA,** plus approx 0.9 g/d LA or **0.4% E LA, 0.8% E n-6**
Baseline n-6: unclear
Compliance by biomarkers: good. Measurement of adipose GLA showed increased GLA in intervention (2.16 µmol/g of adipose TG at baseline to 5.39 µmol/g at 1 year) but not in control (2.51 µmol/g of adipose TG at baseline to 2.87 µmol/g at 1 year, statistically significant difference suggested). DGLA increased in intervention group, but fell in control
Compliance by dietary intake: unclear, participants maintained daily food intake and exercise records

- Energy intake: not reported
- Total fat intake: not reported
- Saturated fat intake: not reported
- PUFA intake: not reported
- PUFA n-3 intake: not reported
- PUFA n-6 intake: not reported
- Trans fat intake: not reported
- MUFA intake: not reported
- CHO intake: not reported
- Sugars intake: not reported
- Protein intake: not reported
- Alcohol intake: not reported

Duration of intervention: 1 year (results reported only for participants completing a minimum of 50 weeks)

Outcomes

Main study outcome: measures of adiposity
Dropouts: unclear, only one withdrew after randomisation but trial was terminated and only reported on 30/45 completers
Available outcomes: weight, fat weight (fasting blood glucose and blood pressure measured but not reported)

Notes

Study funding: supported in part by a gift from Shaklee Technica
Response to contact: Prof Phinney replied "I am sorry to inform you that I cannot provide meaningful feedback within the parameters of your survey"

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomly assigned"
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias)	Low risk	Quote: "Both oil supplements were administered in a double-blind protocol as identical 500 mg capsules"
Blinding of outcome assessment (detection bias)	Low risk	Quote: "The initial study was terminated, and all remaining subjects were assessed over a 6-wk period. Unblinding revealed" …"the monitoring of their weights (simple ANOVA of group means while

		investigators and subjects remained unaware of treatment)"
Incomplete outcome data (attrition bias)	High risk	Quote: "At the termination of the randomized placebo-controlled trial, 45 subjects remained in the study". Mentions one dropped out between randomisation and treatment commencement but no details/explanation of remaining dropouts/non-completers
Selective reporting (reporting bias)	Unclear risk	No protocol or trial register entry
Attention	Unclear risk	
Compliance	Low risk	Adipose GLA was significantly higher in intervention group compared to control (P < 0.0001)
Other bias	Low risk	None noted

SCIMO 1999 [572-574]

Methods Study on prevention of Coronary atherosclerosis with Marine Omega 3 fatty acids (SCIMO)
RCT, parallel (omega 3 vs average European fats), 2 years
Summary risk of bias: low

Participants People with angiographically proven coronary artery disease
N: 112 intervention, 111 control (analysed 82 intervention, 80 control)
Level of risk for CVD: high
Men: 82% intervention, 78.6% control
Mean age in years (SD): 57.8 (9.7) intervention, 58.9 (8.1) control
Age range: unclear (18-75 inclusion criteria)
Smokers: 16.2% intervention, 22.3% control
Hypertension: 53.1% intervention, 45.5% control (history of high blood pressure)
Medications taken by at least 50% of those in the control group: platelet inhibitors, beta-blockers
Medications taken by 20%-49% of those in the control group: long-term nitrate therapy, lipid-lowering agents, ACE inhibitors, diuretics, calcium antagonists, other antihypertensive agents and digitalis.
Medications taken by some, but less than 20% of the control group: nitrates only on demand
Location: Germany
Ethnicity: not reported

Interventions Type: supplement (capsule)
Comparison: EPA + DHA vs SFA + MUFA (average European fat composition)
Intervention: concentrated fish oil capsules, 6x 1 g capsules/d for first 3 months, 3 × 1 g/d for rest of study (4 g/d EPA +DHA + DPA + ALA for first 3 months, then 2 g/d). Dose: ~2 g/d LCn3
Control: capsules containing fat which replicated the fat composition of the average European diet, 6/d for first 3 months, 3/d for rest of study, opaque soft gelatin capsules identical to fish capsules in identical screw-top containers
Compliance: capsule count, overall 2284 (SD 313) capsules taken of 2460 prescribed for each person, erythrocyte phospholipids rose from 4.6% to 11.8% at 24 months in intervention, and didn't alter from baseline in controls
Length of intervention: 24 months

Outcomes Main study outcome: changes in stenosis on angiography
Dropouts: unclear
Available outcomes: mortality, MI, CV events, revascularisation, angina, stroke, cancer diagnosis, weight, lipids, BP, side effects
Response to contact: yes

Notes Asked participants to guess treatment allocation, of those in intervention 63/90 were unsure, 5/90 guessed placebo and 22/90 guessed fish oil; of those in control 66/85 were unsure, 9/85 guessed placebo and 10/85 guessed fish oil
Study funding: Pronova provided capsules and funds for study monitoring but it was stated that the funders played no part in analysis or publication

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Stratified, and for the resulting 9 strata "a random sequence of study group assignments was computer generated by the trial monitor"
Allocation concealment (selection bias)	Low risk	Sealed, sequential numbered envelopes used (opaque not stated, but provided only a random number which linked to a specific container of capsules).
Blinding of participants and personnel (performance bias)	Low risk	Placebo and fish oil capsules "looked identical and were made of soft opaque gelatin and each contained 1 g of a fatty acid mixture". These were provided in identical containers with identical labels with a randomisation number. Patients were told that capsules differed in composition but not in taste.
Blinding of outcome assessment (detection bias)	Low risk	Blinding is described and is very strong for angiographic outcomes, but there is no description of how cardiovascular events were assessed or recorded. However outcomes assessors were probably the same assessors and so blinded
Incomplete outcome data (attrition bias)	Unclear risk	Unclear for how many participants clinical events were assessed (though described in detail for angiographic outcomes), so trial flow unclear
Selective reporting (reporting bias)	Unclear risk	No study trials register entry or protocol was found
Attention	Low risk	As study personnel were unaware of assignments bias in attention was not possible
Compliance	Low risk	Capsule count, overall 2284 (SD 313) capsules taken of 2460 prescribed for each person, erythrocyte phospholipids rose from 4.6% to 11.8% at 24 months in intervention and didn't alter from baseline in controls
Other bias	Low risk	No further bias noted

seAFOod Hull 2018 - ISRCTN05926847 [575-577]

Methods
Systematic Evaluation of Aspirin and Fish Oil (seAFOod) polyp prevention trial
RCT, parallel, 2x2 (n3 EPA vs MCT), 12 months (also randomised to aspirin arm)
Summary risk of bias: Low

Participants
NHS Bowel Cancer Screening Programme patients (55-73 years) identified as "high risk" (five or more small adenomas; or three or more adenomas with at least one being 10mm or more in diameter) after their 1st screening colonoscopy
N: 356 int., 353 control (analysed 314 int., 326 control)
Level of risk for CVD: Low
Male: 80% int., 80% control
Mean age (sd): 65 or 66 years int., 65 years control (IQR 62-69)
Age range: Unclear (55-73 inclusion criteria)
Smokers: 12% int., 17% control
Hypertension: NR
Medications taken by at least 50% of those in the control group: nil
Medications taken by 20-49% of those in the control group: statins (28%)
Medications taken by some, but less than 20% of the control group: metformin (8%), PPI (11%), others 1% or less
Location: England
Ethnicity: NR

Interventions
Type: supplement (capsule)
Comparison: EPA vs capric and capryllic acid MCTs
Intervention:
Arm 1: EPA (ALFA capsules: 2x500mg bd= 2g/d EPA) and aspirin placebo (1/d)

Arm 2: EPA placebo (capric and capryllic acid triglycerides: 2/d) and aspirin EC (1/d= 300mg/d)
Control:
Arm 3: EPA (ALFA capsules: 2x500mg bd= 2g/d) and aspirin EC (1/d= 300mg/d)
Arm 4: EPA placebo (cparic and capryllic acid triglycerides: 2/d) and aspirin placebo (1/d)
Identical looking capsules and pills.
Compliance: capsule count, 95% capsules taken by all arms, red blood cell EPA at 12 months was ~1.5% fatty acids in intervention, ~0.5% in control (as at baseline).
Oily fish intake: 42% of int and 40% control ate 1 or more portions of oily fish/week at 12 months.
Length of intervention: 12 mo

Outcomes Main study outcome: Number of patients with one or more adenomas at 12 months
Dropouts: 40 int, 27 control
Available outcomes: Mortality, colorectal adenoma counts (and various types of severity eg number of "advanced" adenomas per patients, number of "high risk" pateints re-classified as "intermediate risk", number patients with one or more advanced adenomas, adenoma region in the colorectum, total number of adenomas per patient, number of patients with colorectal cancer, levels of bioactive lipid mediators e.g. omega 3), adverse events (red blood cell lipids, oily fish intake)
Response to contact: Not yet attempted

Notes ISRCTN05926847
EudraCT 2010-020943-10
www.seafood-trial.co.uk

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation used a secure web-based system with treatment assignment established by pseudorandom code, using random permuted blocks of randomly varying size
Allocation concealment (selection bias)	Low risk	As above, allocation of participants not revealed to anyone until data lock.
Blinding of participants and personnel (performance bias)	Low risk	Idential looking placebos were used for both interventions.
Blinding of outcome assessment (detection bias)	Low risk	Participants and outcome assessors blinded to allocation.
Incomplete outcome data (attrition bias)	Low risk	Few drop-outs, ITT analysis
Selective reporting (reporting bias)	Low risk	Outcomes in registry entry appear in paper
Attention	Low risk	All capsules, no scope for attention bias.
Compliance	Low risk	Good compliance by all counts.
Other bias	Low risk	None noted

Shimizu 1995 [578]

Methods RCT, parallel, (n3 EPA vs nil), 12 months
Summary risk of bias: Moderate or high

Participants Non-insulin dependent diabetic patients
N: 29 int., 16 control. (analysed, NR)
Level of risk for CVD: Moderate
Male: 34.5% int., 75% control
Mean age (sd): 66.3 (13.5) int., 58.6 (7.2) control
Age range: NR
Smokers: NR
Hypertension: 37.9% int., 43.8% control
Medications taken by at least 50% of those in the control group: Sulfonylurea
Medications taken by 20-49% of those in the control group: Insulin, antihypertensives
Medications taken by some, but less than 20% of the control group: NR

Location: Japan
Ethnicity: NR

Interventions Type: supplement (EPA-E capsules or nil)
Comparison: EPA vs nil
Intervention: 3 capsules/d (total 0.9g/d EPA, Mochida Pharmaceuticals): EPA 0.9g/d
Control: Unclear
Compliance: Capsule count (no data provided)
Duration of intervention: 12 months

Outcomes Main study outcome: Albuminuria
Dropouts: Unclear
Available outcomes: deaths (nil), CV events (nil), side effects (nil overall), bp, lipids, glucose, HbA1c (treated as not useable due to baseline differences)
Response to contact: Yes

Notes Data for lipids, glucose, HbA1c not used due to baseline differences, dropouts unclear
Study funding: NR

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Each doctor picked up an envelope which contained a treatment group allocation
Allocation concealment (selection bias)	High risk	Author response: Recruiters were aware of treatment allocation
Blinding of participants and personnel (performance bias)	High risk	Author response: recipients and providers aware of treatment
Blinding of outcome assessment (detection bias)	Unclear risk	No details
Incomplete outcome data (attrition bias)	Unclear risk	NR
Selective reporting (reporting bias)	Unclear risk	No registry or protocol identified
Attention	Unclear risk	NR and no blinding
Compliance	Unclear risk	NR
Other bias	Low risk	None noted

Shinto 2014 – NCT00090402 [579 580]

Methods RCT, parallel (fish oil capsule vs soybean oil capsule), 12 months
Summary risk of bias: moderate to high

Participants Patients aged 55 or more with probable Alzheimer dementia diagnosis
N: 13 intervention, 13 control
Level of risk for CVD: low
Men: 61% intervention 46% control
Mean age in years (SD): 75.9 (8.1) intervention, 75.2 (10.8) control
Age range: 55+ (inclusion criteria)
Smokers: not reported
Hypertension: not reported
Medications taken by at least 50% of those in the control group: anti-cholinesterases or memantine
Medications taken by 20%-49% of those in the control group: not reported
Medications taken by some, but less than 20% of the control group: not reported
Lipid-lowering medications and many other drugs were not allowed
Location: USA
Ethnicity: 100% white

Interventions Type: fish oil capsules
Comparison: EPA + DHA vs n-6
Intervention: 3 × 1 g capsules/day of fish oils (975 mg EPA, 675 mg DHA per day). Dose: 1.65 g/d EPA + DHA

	Control: 3 × 1 g capsules/day soybean oil (which contains 5% fish oil) Both groups had a placebo lipoic acid tablet and lemon-flavoured capsules Compliance: assessed by pill counts and FA in red blood cell membranes. Results showed increased EPA + DHA levels in the intervention group. Length of intervention: 12 months
Outcomes	Main study outcome: F2-isoprostane levels (oxidative stress measure) Dropouts: 2 intervention, 2 control Available outcomes: mortality, CVD events, adverse events, serum fatty acids, measures of cognition (ADAS Cog and MMSE), ADL, IADL (also F2 isoprostane) Response to contact: not attempted
Notes	Study funding: National Institutes of Health/National Institute of Aging (NIH/NIA) and NIH General Clinical Research

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomised by a computer-generated scheme that was stratified by smoking status
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias)	Low risk	Capsules matched for taste and flavour. Blinding assessed at the end and majority of staff and participants were unaware of treatment
Blinding of outcome assessment (detection bias)	Low risk	As above
Incomplete outcome data (attrition bias)	Low risk	15% dropouts explained and included
Selective reporting (reporting bias)	Low risk	NCT00090402 first received: 25 August 2004, study start date April 2004. More secondary outcomes reported than included in the trial register entry
Attention	Low risk	Both arms seem to have had the same contact
Compliance	Low risk	Compliance measured and FAs levels reported. Results showed increased EPA + DHA levels in the intervention group
Other bias	Low risk	None noted

SHOT 1996 [581-590]

Methods	SHunt Occlusion Trial (SHOT) RCT, parallel (omega 3 vs nil), 4 arms, 1 year Summary risk of bias: moderate or high
Participants	People admitted for coronary bypass grafting N: 317 intervention, 293 control Level of risk for CVD: high Men: 86% intervention, 88% control Mean age in years (SD): 59.9 (8.7) intervention, 59.4 (8.8) control Age range: unclear Smokers: 19% intervention, 20% control Hypertension: 20% intervention, 25% control Medications taken by at least 50% of those in the control group: not reported Medications taken by 20%-49% of those in the control group: antihypertensives Medications taken by some, but less than 20% of the control group: not reported Location: Norway Ethnicity: not reported
Interventions	Type: supplement (capsule) Comparison: EPA + DHA vs nil

Intervention: 4 fish-oil concentrate soft gelatin capsules/d (Omacor; Pronova AS, Oslo, Norway) containing 51% EPA and 32% DHA ethyl esters and 3.7 mg
vitamin E as an antioxidant. Dose: 3.3 g/d EPA + DHA
Control: no treatment
Compliance: capsule count, 88% taken, serum EPA + DHA rose in the intervention group (176 to 257 mg/L at 9 months) and fell in the control group (170 to 169 mg/L at 9 months)
Length of intervention: 12 months

Outcomes Main study outcome: CABG graft patency
Dropouts: 15 intervention, 14 control
Available outcomes: deaths, CV deaths, MI, stroke, repeat CABG, combined CV events, lipids, side effects
Response to contact: yes

Notes The study had 4 arms; aspirin; warfarin; fish oil + aspirin; and warfarin + fish oil. The first 2 groups are combined as the control and the last two combined as intervention.
Dietary assessment suggested total diet plus supplement intakes as follows: 2.7 g/d EPA + DHA at baseline, 5.5 g/d at 9 months intervention, 2.5 g/d at baseline, 2.2 g/d at 9 months control group
Study funding: in part by Pronova and Nycomed Pharma

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random numbers were provided in consecutively sealed envelopes generated centrally
Allocation concealment (selection bias)	Unclear risk	Envelopes not reported as opaque
Blinding of participants and personnel (performance bias)	High risk	Open trial, no blinding apart from outcome assessors so participants and study personnel were aware of assignments. However, author suggested in personal communication that participants were not aware of their assignments.
Blinding of outcome assessment (detection bias)	Low risk	Outcome assessors (radiologists) reported as blinded
Incomplete outcome data (attrition bias)	Low risk	Reasons for attrition and exclusions stated, numbers clear, dropouts < 20% per year
Selective reporting (reporting bias)	Unclear risk	No study protocol or trials register entry was found
Attention	Low risk	Appeared equivalent between arms
Compliance	Low risk	Capsule count, 88% taken, serum EPA + DHA rose in the intervention group (176 to 257 mg/L at 9 months) and fell in the control group (170 to 169 mg/L at 9 months)
Other bias	Low risk	No further bias noted

Sianni 2013 [591]

Methods RCT, parallel, (fish oil vs placebo), 12 months
Summary risk of bias: moderate or high

Participants Patients with hypertension and paroxysmal or persistent atrial fibrillation (AF)
N: 268 intervention, 60 control
Level of risk for CVD: moderate
Men: not reported
Mean age (SD) years: 62 (6), not reported by arm
Age range: not reported
Smokers: not reported
Hypertension: 100%
Medications taken by at least 50% of those in the control group: not reported
Medications taken by 20%-49% of those in the control group: not reported
Medications taken by some, but less than 20% of the control group: not reported

Location: Greece
Ethnicity: not reported

Interventions Type: supplement
Comparison: fish oil vs unclear placebo
Intervention: omega-3 fatty acids with no further details. Dose: 4 g/d omega
Control: placebo, no further details
Compliance: no details
Duration of intervention: 12 months

Outcomes Main study outcome: AF recurrence and BP
Dropouts: no details
Available outcomes: new AF episodes, BP (not in a usable format)
Response to contact: no

Notes Study funding: unclear
The study's only publication was a conference abstract.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details, probably randomised but unclear
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias)	Unclear risk	No details
Blinding of outcome assessment (detection bias)	Unclear risk	No details
Incomplete outcome data (attrition bias)	Unclear risk	No details
Selective reporting (reporting bias)	Unclear risk	No protocol or trial register record found
Attention	Unclear risk	No details
Compliance	Unclear risk	No details
Other bias	Unclear risk	No details

Simon 1997 [592-596]

Methods RCT, parallel, (low fat with low PUFA vs usual diet), 24 months
Summary risk of bias: moderate or high

Participants Women with a high risk of breast cancer
N: 98 intervention, 96 control (analysed 72 intervention: 75 control)
Level of risk for CVD: low
Male: 0% intervention, 0% control
Mean age (SD): 46 (not reported) intervention, 46 (not reported) control
Age range: not reported
Smokers: not reported
Hypertension: not reported
Medications taken by ≥ 50% of those in the control group: not reported
Medications taken by 20%-49% of those in the control group: not reported
Medications taken by some, but < 20% of the control group: not reported (those on statins excluded)
Location: USA
Ethnicity: white 89%, African American 9%, Hispanic 2%

Interventions Type: dietary advice
Comparison: reduced fat including PUFA (intervention) vs usual diet
Intervention: aims total fat 15% E; methods biweekly individual dietetic appointments over 3 months followed by monthly individual or group appointments, including education, goal setting, evaluation, feedback and self-monitoring. Intervention delivered face to face by a dietitian
Control: aim usual diet, no stated intervention(s)

Dose aim: unclear PUFA
Baseline 7.7% E PUFA
Compliance by biomarkers: no fatty acid biomarkers reported, TC reported in a subgroup and fell by 0.34 mmol/L in intervention and fell by 0.08 mmol/L in control over 1 year
Compliance by dietary intake: assessed using 3-day 24-h recalls every 3 months, 1 year data reported

- Energy intake, kcal/d: intervention 1570 (SE 47.0), control 1594 (SE 63.6)
- Total fat intake, % E: intervention 17.6 (SD 5.8), control 33.8 (SD 7.4)
- SFA intake, % E: intervention 6.0 (SD 3.0), control 12.1 (SD 5.2)
- PUFA intake, % E: intervention 3.8 (SD 1.7), control 7.3 (SD 4.1)
- PUFA n-3 intake: not reported
- PUFA n-6 intake: not reported
- Trans fat intake: not reported
- MUFA intake, % E: intervention 6.1 (SD 3.0), control 12.8 (SD 6.3)
- CHO intake: not reported
- Sugars intake: not reported
- Protein intake, not reported
- Alcohol intake: not reported

Compliance, other methods: not reported
Inclusion basis: no intention to increase total PUFA stated. Achieved total PUFA reduction of 6.7% E in intervention compared to control at 1 year, > 10% higher than baseline 7.7% E from total PUFA
PUFA dose: -6.7% E PUFA
Compliance: dietary assessment
Duration of intervention: 24 months (mean years in trial: control 1.8, intervention 1.7)

Outcomes Main trial outcome: intervention feasibility
Dropouts: unclear intervention, unclear control
Available outcomes: TC, TG, LDL and HDL (2 deaths, but unclear in which arms, 8 cancer diagnosis but not clear in which arms), (weight, BMI, % body fat and waist-hip ratio reported but all too unbalanced at baseline to use)
Trial author contact: Dr Simon confirmed that some deaths occurred (but not in which arms) and sent a further reference.

Notes Trial funding: Marilyn J Smith Fund, Harper-Grace Hospitals, the Wesley Foundation, National Cancer Institute, Karmanos Cancer Institute Core Grant, the United Foundation of Detroit
Trial **aim** was to reduce total fat to 15% E (SFA not mentioned), but PUFA fat intake in the intervention group was significantly lower than in the control group.
Note: PUFA lower in intervention arm, so higher PUFA arm is the control

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Stratified by age and randomised (block size 2)
Allocation concealment (selection bias)	Unclear risk	Allocation method not clearly enough described
Blinding of participants and personnel (performance bias)	High risk	Participants not blinded (as given dietary advice or not), personnel unclear
Blinding of outcome assessment (detection bias)	Unclear risk	Not reported
Incomplete outcome data (attrition bias)	Unclear risk	Unclear, deaths, cancer and CV events are dropouts - unclear if any data missing
Selective reporting (reporting bias)	Unclear risk	No protocol or trials registry entry found
Attention	High risk	Time and attention in the intervention group not mirrored in control
Compliance	High risk	No fatty acid biomarkers reported, TC reported in a subgroup and fell by 0.34 mmol/L in intervention and fell by 0.08 mmol/L in control over 1 year (but control group should have been higher in PUFA in this trial)
Other bias	Low risk	None noted

Sinn 2012 – ACTRN12609000167268 [597-599]

Methods	RCT, 3 arms in parallel, (supplements rich in EPA with some DHA vs. supplements rich in DHA with some EPA vs. safflower oil rich in Linoleic acid), 6 months. Summary risk of bias: Low
Participants	Older Australian people with few comorbidities and mild cognitive impairment N: 18 Int EPA, 18 Int DHA, 18 control. (analysed, Int EPA: 13, Int DHA: 16, cont=LA group: 11) Level of risk for CVD: Low Male: 82% IntEPA, 72% IntDHA, 47% = LAgroup Mean age (sd): 74.88 (5.06) intEPA, 74.22 (7.00) IntDHA, 73 (3.96) = LAgroup Age range: NR, but eligibility criteria > 65 yrs Smokers: 12% IntEPA, 0% IntDHA, 0% = LAgroup Hypertension: NR Medications taken by at least 50% of those in the control group = LAgroup: NR Medications taken by 20-49% of those in the control group = LAgroup: NR Medications taken by some, but less than 20% of the control group = LAgroup: NR Location: Australia Ethnicity: NR Depression: General population (low risk) Anxiety: General population (low risk)
Interventions	Type: supplement capsules (EPA rich, DHA rich or LA rich) Comparison: EPA rich vs. DHA vs rich (both n-3 rich) vs. safflower oil (linoleic acid rich, n-6 rich) InterventionEPA: 4 capsules/d (total dose = 1.67g/d EPA + 160 mg/d DHA) InterventionDHA: 4 capsules/d (total dose = 1.55g/d DHA + 400 mg/d EPA) Control=LAgroup: 4 capsules/d (total dose = 2.2g/d LA). How identical supplements in each arm were to each other is not reported; but ability participants had poor ability to correctly guess which supplement they had. Compliance: Capsule count and comparisons of FA levels in erythrocytes. No p-values reported for erythrocyte data, but capsule consumption was 93% on average (range = 82-97%). Duration of intervention: 6 months
Outcomes	Main study outcome: cognitive decline and depression Dropouts: 4 IntEPA, 2 IntDHA, 4 LAgroup. Available outcomes: cognitive and depression
Notes	Difference in EPA and DHA supplements in protocol versus the published paper Study funding: This study was funded by an Australian Research Council Linkage grant in partnership with Novasel Australia

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	randomised on age, gender and GDS scores by an independent researcher who has the coding sequence for pre-allocated supplement numbers. (protocol)
Allocation concealment (selection bias)	Low risk	Allocations are concealed from investigators and participants by numbered containers, for which the treatment codes are held by an independent researcher (protocol)
Blinding of participants and personnel (performance bias)	Low risk	All researchers involved with participants, data entry or analysis, and participants were blinded to treatment conditions. Supplements were coded and labelled independently. Also, participants had poor ability to correctly guess which supplement they had taken.
Blinding of outcome assessment (detection bias)	Low risk	All researchers involved with participants, data entry or analysis, and participants were blinded to treatment conditions. Supplements were coded and labelled independently

Incomplete outcome data (attrition bias)	High risk	Per-protocol analysis. Only 40 completed/50 assessed at baseline, so attrition also > 20% per year.
Selective reporting (reporting bias)	Low risk	Protocol and results paper match ACTRN12609000167268 Date registered 3/04/2009. Started 18/02/2009. Completed 14/08/2009.
Attention	Low risk	
Compliance	Low risk	Lack of between group comparison for FA levels in erythrocytes; however capsule % compliance was > 80% in all arms.
Other bias	Low risk	No further bias noted

Skoldstam 1992 [600]

Methods RCT, parallel, (n3 EPA+DHA vs n6), 6 months
Summary risk of bias: Moderate or high
Aim: "clinical and biochemical effects of fish oil ... over 6 months in" patients with rheumatoid arthritis

Participants People with stable rheumatoid arthritis
N: 23 int., 23 control. (analysed, int: 22 cont: 21)
Level of risk for CVD: low
Male: 18% int., 33% control.
Mean age (sd) yrs: 58 (NR) int., 55 (NR) control
Age range: 40-73yrs int., 28-70yrs control
Smokers: NR
Hypertension: NR
Medications taken by at least 50% of those in the control group: NSAID (86% of whole group),
Medications taken by 20-49% of those in the control group: DMARDS (42% of whole group)
Medications taken by some, but less than 20% of the control group: NR
Location: Sweden
Ethnicity: NR

Interventions Type: supplement
Comparison: fish oil (n3) vs vegetable oil capsules (n6 and MUFA)
Intervention: 10x1g MaxEPA capsules/d (1.8g/d EPA plus 1.2g/d DHA plus 10mg alpha tocopherol) and asked to maintain usual diet: EPA+DHA 3.0g/d
Control: 10x1g vegetable oil capsules/d (maize, corn and peppermint oils, <2.5% n3) and asked to maintain usual diet
Compliance: blood fatty acids were measured, with significant differences between arms for EPA, DHA and DPA at 6 months.
Duration of intervention: 6 months

Outcomes Main study outcome: clinical effects on RhA
Dropouts: 1 of 23 int., 2 of 23 control
Available outcomes: functional outcomes for arthritis, medication use, ESR, CRP

Notes Study funding: Swedish Council for Planning and Coordination of Research
Author contact: established, reported that no deaths occurred.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"randomly allocated"
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias)	Unclear risk	States that patients and investigators were all unaware of assignment through the study, but unclear if this is possible given fish taste in intervention and peppermint taste in control
Blinding of outcome assessment (detection bias)	Unclear risk	As above

Incomplete outcome data (attrition bias)	Low risk	3 of 46 lost in 6 months, similar in both arms
Selective reporting (reporting bias)	Unclear risk	No protocol or trials register entry found
Attention	Low risk	Patients were all seen at baseline, 3 and 6 months, appear similar
Compliance	Low risk	Significant differences in blood lipids at 6 months between arms
Other bias	Low risk	None noted

SMART 2013 – ACTRN12608000425392 [601-606]

Methods SMART trial (from the Smart Foods Centre)
RCT, 3-arm parallel, (Fish + S: hypocaloric diet plus fish plus fish oil capsules vs Fish: hypocaloric diet plus fish plus olive oil capsules vs control: hypocaloric diet plus olive oil capsules), 12 months
Summary risk of bias: moderate or high

Participants Overweight adults
N: fish + S intervention 41, fish 43, control 42. (analysed, fish + S intervention 21, fish 25, control 18)
Level of risk for CVD: low
Men: 27% fish + S intervention, 23% fish intervention, 28% control
Mean age (SD) years: unclear by arm, overall 45.1 (8.4)
Age range: not reported but 18-60 years eligible
Smokers: not reported but 5.9% overall
Hypertension: not reported
Medications taken by at least 50% of those in the control group: not reported
Medications taken by 20%-49% of those in the control group: not reported
Medications taken by some, but less than 20% of the control group: not reported
Location: Australia
Ethnicity: not reported

Interventions Type: supplement and food
Comparison: EPA + DHA vs MUFA (Fish plus fish oil supplements vs Fish plus olive oil supplements vs olive oil supplements)
Intervention, Fish + S: hypocaloric diet aiming at 30% E from fat, 25% E from protein, 45% E from CHO, plus 180 g fish/week plus capsules including 420 mg/d EPA + 210 mg/d DHA (Blackmores Promega Heart). Dose: 0.63 g/d EPA + DHA
Intervention, fish: hypocaloric diet aiming at 30% E from fat, 25% E from protein, 45% E from CHO, plus 180 g fish/week plus capsules including 1 g olive oil/d
Control: hypocaloric diet aiming at 30% E from fat, 25% E from protein, 45% E from CHO, plus capsules including 1 g olive oil/d
Compliance: assessed through diet histories (fish) and erythrocyte fatty acid supplements (capsules), but results not reported
Duration of intervention: 12 months

Outcomes Main study outcome: total % body fat
Dropouts: fish + supplement intervention 20, fish intervention 18, control 24
Available outcomes: weight, BMI, lipids, BP, fasting glucose, fasting insulin, % body fat (leptin also reported), no deaths or cardiovascular events occurred (authors report)
Response to contact: authors provided data on CVD events (none) and mean/SD data for TGs and fasting insulin

Notes To assess effects of omega 3 fats the best comparison in this study is fish + S vs fish, so numerical data reflect this comparison.
Study funding: Australian National Health and Medical Research Council, fish and olive oil capsules were provided free by Blackmores Australia

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "A researcher independent of the subject interface undertook the randomisation of participants

		into diet groups (stratified by sex and block randomised...)"
Allocation concealment (selection bias)	Low risk	Quote: "Randomisation was performed centrally, off-site and the holder of the allocation schedule provided the codes to a single researcher who was independent to the subject interface. The placebo and active ingredient capsules were coded off-site . The codes were kept from the researchers collecting dietary data and delivering treatment. Allocation concealment was maintained as the persons responsible for screening eligible participants for inclusion in the trial was unaware to which supplement group the subject would be allocated. Different dietitians collected the dietary data and provided dietary advice"
Blinding of participants and personnel (performance bias)	High risk	As above, but impossible to blind participants to the fish advice
Blinding of outcome assessment (detection bias)	Unclear risk	As above
Incomplete outcome data (attrition bias)	Low risk	Very high levels of attrition, though intention-to-treat analyses carried out
Selective reporting (reporting bias)	High risk	We were unable to find data on 24 hour energy expenditure, oxidation or heart rate which were stated as primary and secondary outcomes in the trials registry.
Attention	Unclear risk	While dietary education was for 1 hour then 6 further half hour follow-ups plus written materials and monthly newsletters plus dietary interviews it is not clear whether this was in all arms or only some of them.
Compliance	High risk	Quote: "Of the 12 months completers, 57% were judged to be compliant, 39% (n = 7) for the control group who reported < 180 g fish/week, 48% (n = 12) for the Fish group who reported ≥180 g fish/week, and 85% (n = 17) for the Fish + S group who reported ≥180 g fish/week or ≥90% supplements". However, erythrocyte (EPA + DHA)/total fatty acids × 100 was significantly different for the fish oil supplemented group compared to the two others – but it was only measured in around half of the participants as the others dropped out, so presumably were non-compliant.
Other bias	Low risk	None noted

Smith 2015 – NCT01308957 [607 608]

Methods RCT, parallel, (n3 EPA+DHA vs n6 LA), 6 months
Summary risk of bias: Moderate or high

Participants Healthy older adults
N: 40 int., 20 control. (analysed, int: 29 cont: 15)
Level of risk for CVD: low
Male: 34% int., 33% control.
Mean age (sd) yrs: 68 (5) int., 69 (7) control
Age range: NR
Smokers: NR
Hypertension: NR
Medications taken by at least 50% of those in the control group: NR
Medications taken by 20-49% of those in the control group: NR
Medications taken by some, but less than 20% of the control group: NR

Location: USA
Ethnicity: NR

Interventions Type: supplement
Comparison: LCn3 vs n6
Intervention: 4x1g/d capsules of n3 acid ethyl esters (Lovaza, GlaxoSmithKline, 1.86g/d EPA + 1.5g/d DHA, equivalent to 200-400g/d freshwater fish): EPA+DHA 3.36g/d
Control: 4x1g/d capsules of corn oil (capsules looked identical to Lovaza capsules)
Compliance: Assessed using pill count, participants were given excess pills and asked to return the remainder at study end. Mean compliance according to pills returned was 94% in intervention, 92% in control.
Duration of intervention: 6 months

Outcomes Main study outcome: Muscle mass and function
Dropouts: 11 of 40 int., 5 of 20 control
Available outcomes: weight, body fat, intermuscular fat content, TG, HDL & LDL cholesterol, fasting glucose (glucose 2 hours post GTT, LFTs, BP not used)

Notes Study funding: NIH, Clinical Translational Science Award, study drugs were a gift from GlaxoSmithKline
Author contact: not yet

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"randomly assigned" - no further details
Allocation concealment (selection bias)	Unclear risk	As above
Blinding of participants and personnel (performance bias)	Unclear risk	Stated "double blind" and that capsules appeared identical. However no information provided as to their smell and taste.
Blinding of outcome assessment (detection bias)	Unclear risk	Stated "double blind" but no details as to method
Incomplete outcome data (attrition bias)	High risk	14 of 60 (27%) lost over 24 weeks
Selective reporting (reporting bias)	Low risk	Trials register entry made Feb 2011, study started June 2011 so prospective. Outcomes stated in trials register were all stated in paper.
Attention	Unclear risk	Follow up schedule unclear
Compliance	Unclear risk	Pill count suggests compliance with intervention and control capsules was greater than 90%
Other bias	Low risk	None noted

SO927 Hershman 2015 – NCT01385137 [609-611]

Methods RCT, parallel, (n3 EPA+DHA vs n6 LA), 6 months
Summary risk of bias: Moderate or high
Aim: "test the hypothesis that n3-FAs reduce pain and stiffness in women undergoing adjuvant aromatase inhibitor therapy for early-stage breast cancer"

Participants Women with early stage breast cancer receiving an aromatase inhibitor with musculoskeletal pain
N: 131 int., 131 control. (analysed, int: 102 cont: 107)
Level of risk for CVD: low
Male: 0% int., 0% control.
Mean age (sd) yrs: 59.5 (NR) int., 59.1 (NR) control
Age range: NR
Smokers: NR
Hypertension: NR
Medications taken by at least 50% of those in the control group: all an aromatase inhibitors
Medications taken by 20-49% of those in the control group: NR
Medications taken by some, but less than 20% of the control group: NR

Location: Canada
Ethnicity: int 93% white of whom 6% reported Hispanic ethnicity, 4% black, 1% Asian. Control 82% white of whom 7% reported Hispanic ethnicity, 12% black, 2% Asian.

Interventions Type: supplement
Comparison: EPA+DHA vs soy and corn oil
Intervention: 6 fish oil capsules/d (Ocean Nutrition, 3.36g/d EPA plus 1.68g/d DHA) coloured with carob and flavoured with lemon/lime: EPA+DHA 5.04g/d
Control: 6 capsules/d of soybean and corn oil blend, coloured with carob and flavoured with lemon/lime
Compliance: Assessed by researcher review of intake calendar and capsule count. 2 control and one intervention participants were excluded due to non-compliance but it is not clear what level of compliance was required.
Duration of intervention: 6 months

Outcomes Main study outcome: Joint pain and stiffness, quality of life
Dropouts: 29 int., 24 control
Available outcomes: pain, lipids, CRP

Notes Study funding: Roche/ Genetech, Novartis, Amgen
Author contact: Not yet

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random assignment stratified
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias)	Low risk	Placebo described as matching, same administration details, same colouring and flavouring, study described as double blind
Blinding of outcome assessment (detection bias)	Low risk	Unclear, but our outcomes are biochemical, and study described as double blind
Incomplete outcome data (attrition bias)	High risk	Only 169 participants (of 262 randomised) included in CRP analysis
Selective reporting (reporting bias)	Low risk	Trials register entry several months before study start date so prospective, and all primary and secondary outcomes reported in trials register (a couple in published paper)
Attention	Low risk	Schedule appears similar for both groups
Compliance	Unclear risk	Unclear
Other bias	Low risk	None noted

SOFA 2006 – NCT00110838 [612-616]

Methods Study on Omega-3 Fatty Acids and Ventricular Arrhythmia (SOFA)
2 arm, parallel RCT (n-3 EPA + DHA vs MUFA), 12 months
Summary risk of bias: low

Participants People with previous ventricular arrhythmias and implantable cardioverter defibrillators
N: 273 intervention, 273 control (273 intervention, 273 control analysed)
Level of risk for CVD: high
Men: 84% intervention, 85 % control
Mean age in years (SD): 60.5 (12.8) intervention, 62.4 (11.4) control
Age range: unclear (18 years and older)
Smokers: 16% intervention, 8% control
Hypertension: 53% intervention, 49% control
Medications taken by at least 50% of those in the control group: beta-blockers
Medications taken by 20%-49% of those in the control group: lipid lowering, antiarrhythmic medications (combined)

	Medications taken by some, but less than 20% of the control group: amiodarone, sotalol Location: 8 countries in Europe Ethnicity: not reported
Interventions	Type: supplement (capsule) Comparison: EPA + DHA vs MUFA + omega 6 Intervention: 2 g/d (4 capsules) purified fish oil. 961 mg n-3 PUFAS (464 mg EPA + 335 mg DHA and 162 mg other n-3 PUFAs) daily. 3000 ppm vitamin E (Loders Croklann, Wormeveer). Dose: 0.8 g/d EPA + DHA Control: 2 g/d high-oleic acid sunflower oil. 3000 ppm vitamin E (Loders Croklann, Wormeveer) Compliance: daily diary, checked by research nurses every 4 months. Judging by capsule count, 207 patients in the fish oil group and 218 in the placebo took more than 80% of their capsules. N-3 fatty acid composition in serum cholesterol levels was measured at baseline and the end of the trial. The EPA concentration in serum cholesterol esters increased in the expected range. No data provided Length of intervention: 12 months
Outcomes	Main study outcome: spontaneous ventricular tachyarrhythmias and all-cause mortality Dropouts: 33 intervention (23 partial follow-up), 33 control (14 partial follow-up) Available outcomes: deaths, MI, new angina, new heart failure, no fatal arrhythmias, cancer, cardiovascular events, side effects Response to contact: yes but no data provided
Notes	Study funding: Wageningen Centre for Food Sciences (alliance of major Dutch food industries and others)

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Patients using beta-blockers were separately randomised in blocks of 2. A computer randomisation programme randomly took the first treatment of a block. The second patient in a block of 2 always received the opposite treatment.
Allocation concealment (selection bias)	Low risk	Treatments (blinded medication numbers) were centrally assigned by a telephone allocation service.
Blinding of participants and personnel (performance bias)	Low risk	Double blinding. Bottles containing capsules labelled with medication numbers that are unidentifiable for patients as well as investigators. Fish oil and placebo capsules have identical appearance. Difference can't be tasted if swallowed with water (as suggested)
Blinding of outcome assessment (detection bias)	Low risk	Quote: "blinded endpoint adjudication committee"
Incomplete outcome data (attrition bias)	Low risk	ITT analysis. Did a partial follow-up on some patients who dropped out due to non-compliance.
Selective reporting (reporting bias)	Low risk	NCT00110838, trial registered in May 2005, end of trial January 2005, trial results published in 2006. However, rationale and design paper (stating outcomes) published in 2003. Outcomes in the 2006 paper appear to be the same as in Rationale paper.
Attention	Low risk	Unlikely as intervention blinded to investigators and only intervention was capsules
Compliance	Unclear risk	Daily diary, checked by research nurses every 4 months. Judging by capsule count, 207 patients in the fish oil group and 218 in the placebo took more than 80% of their capsules. N-3 fatty acid composition in serum cholesterol levels was measured at baseline and the end of the trial. The EPA concentration in serum cholesterol esters increased in the expected range. No data provided
Other bias	Low risk	No further bias noted

Sofi 2010 [617]

Methods 2-arm, parallel RCT (enriched olive oil vs olive oil), 12 months
Summary risk of bias: moderate or high

Participants Non-alcoholic fatty liver disease patients
N: 6 intervention, 5 control
Level of risk for CVD: low
Men: 66.7% intervention, 100% control
Median age: 55 intervention, 54 control
Age range: 30-41 intervention, 42-70 control
Smokers: not reported
Hypertension: not reported
Medications taken by at least 50% of those in the control group: not reported
Medications taken by 20%-49% of those in the control group: not reported
Medications taken by some, but less than 20% of the control group: not reported
Location: Italy
Ethnicity: not reported

Interventions Type: supplement (oil)
Comparison: EPA + DHA vs MUFA
Intervention: 6.5 mL/d olive oil enriched with n-3 (t-Omega 3, tFarma srl, Italy) containing 0.47 g EPA, 0.24 g DHA plus dietary recommendations. Dose: 0.83 g/d EPA + DHA
Control: 6.5 mL/d olive oil plus dietary recommendations
Compliance: was verified by counting the empty boxes on return but no data reported
Length of intervention: 12 months

Outcomes Main study outcome: fatty liver status
Dropouts: unclear
Available outcomes: lipids, glucose, insulin, HOMA, (BMI not in usable format, also LFTs, oxidative markers, adiponectin, fatty liver and steatosis outcomes)
Response to contact: not yet attempted

Notes Study funding: oil supplied by tFarma and funding not stated

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "The patients were randomized into two groups"
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias)	Unclear risk	No details
Blinding of outcome assessment (detection bias)	Unclear risk	No details
Incomplete outcome data (attrition bias)	Unclear risk	Numbers analysed for liver health are for those randomised. Numbers analysed for other outcomes not stated. No mention of dropouts
Selective reporting (reporting bias)	Unclear risk	No protocol or trial registration
Attention	Low risk	Both groups received same contact
Compliance	Unclear risk	Measured but no results reported
Other bias	Low risk	None noted

Spadaro 2008 [618]

Methods RCT, parallel, (high LCn3s vs low LCn3s, not specific which LCn3s), 6 months
Summary risk of bias: Moderate or high

Participants People with non-alcoholic fatty liver disease (NAFLD)
N: 20 int., 20 control. (analysed, int: 18 cont: 18)

Level of risk for CVD: moderate
Male: 61% int., 44% control.
Mean age (sd) yrs: 50.2 (12.9) int., 51.3 (9.8) control
Age range: NR
Smokers: NR
Hypertension: NR
Medications taken by at least 50% of those in the control group: NR
Medications taken by 20-49% of those in the control group: NR
Medications taken by some, but less than 20% of the control group: NR
Location: Italy
Ethnicity: NR

Interventions Type: supplement
Comparison: PUFA vs nil
Intervention: 2g/d PUFA (in capsule form), plus American Heart Association dietary advice (50%E CHO, 20%E protein, 30%E fats), overweight and obese participants were encouraged to lose weight by reducing total energy intake
Control: American Heart Association dietary advice (50%E CHO, 20%E protein, 30%E fats), overweight and obese participants were encouraged to lose weight by reducing total energy intake
n3 Dose: (intended) increase 2.0g/d**, 0.9%E n3**
Compliance: Evaluated using a questionnaire, no results presented
Duration of intervention: 6 months

Outcomes Main study outcome: fatty liver status
Dropouts: 2 int., 2 control
Available outcomes: lipids, TNF alpha, BMI, HOMA-IR (LFTs, degree of steatosis presented but not used)

Notes Study funding: NS
Author contact: Not yet

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"randomly assigned into two study groups using random sampling numbers"
Allocation concealment (selection bias)	Unclear risk	No further data
Blinding of participants and personnel (performance bias)	High risk	No placebo, open study
Blinding of outcome assessment (detection bias)	Unclear risk	Unclear, not stated, though mostly biochemical outcomes
Incomplete outcome data (attrition bias)	Low risk	2 lost of 20 from each arm, 10% lost in 6 months. Reasons given, balanced.
Selective reporting (reporting bias)	Unclear risk	No protocol or trials register entry found
Attention	Low risk	The study only differed by the additional capsules, but the assessment schedule was not stated to differ between the two arms
Compliance	Unclear risk	Not stated
Other bias	Low risk	None noted

Stammers 1992 [619]

Methods RCT, parallel, (EPA+DHA vs olive oil), 24 weeks
Summary risk of bias: moderate to high

Participants Patients with clinical diagnosis of osteoarthritis
N: 44 int., 42 control (31 int., 33 control analysed)
Level of risk for CVD: low
Male: 34% int., 21% control.
Mean age (sd) yrs: 67 (NR) int., 69 (NR) control.

Age range: 49-87
Smokers: NR BMI: NR
Hypertension: NR
Medications taken by at least 50% of those in the control group: NSAID
Medications taken by 20-49% of those in the control group: NR
Medications taken by some, but less than 20% of the control group: NR
Location: UK
Ethnicity: NR

Interventions Type: supplement
Comparison: EPA+DHA vs MUFA
Intervention: 10 ml Cod liver oil/day (Seven Seas) containing 786mg EPA.
Control: 10 ml olive oil/ day
Compliance: Seems to have been measured but no details reported.
Duration of intervention: 24 weeks

Outcomes Main study outcome: Scores of pain and disability
Dropouts: 13 int., 9 control
Available outcomes: changes in VAL score of pain and disability
Author contact: not yet attempted

Notes Study funding: supported by Seven Seas

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Just stated, no details
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias)	Unclear risk	No details
Blinding of outcome assessment (detection bias)	Unclear risk	No details
Incomplete outcome data (attrition bias)	High risk	High attrition rate (~30% int., and 21% control excluded from analysis)
Selective reporting (reporting bias)	Unclear risk	No protocol found.
Attention	Low risk	Appears similar
Compliance	Unclear risk	5 int., & 3 control excluded as non-compliant but no details on compliance threshold or results.
Other bias	Low risk	None noted

Stonehouse 2013 – ACTRN12610000212055 [620]

Methods RCT, parallel, (n3 DHA vs MUFA), 6 months
Summary risk of bias: Moderate or high

Participants pop: Healthy men and women 18-45 years
N: 115 int., 113 control. (analysed, int: 85 cont: 91)
Level of risk for CVD: Low
Male: 37.4% int., 35.4% control.
Mean age 33.4 (7.8) int., 33.2 (7.9) control
Age range: 18-45 allowed.
Smokers: 0% (exclusion criterion)
Hypertension: NR
Medications taken by at least 50% of those in the control group: NR
Medications taken by 20-49% of those in the control group: NR
Medications taken by some, but less than 20% of the control group: NR
Location: New Zealand
Ethnicity: European 78.2% int, 80.9% control.

Interventions Type: supplement

	Comparison: DHA (n3) vs high oleic sunflower oil Intervention: 3 capsules/d. In total 2.25 g/d, comprised of 1.16 g DHA/d, 60 mg/d DPA and 0.17 g EPA/d: EPA+DHA 1.39g/d Control: 3 capsules/d with total dose = 2.25 g/d, comprised of 1.61 g/d oleic acid, at least 160 mg/d PUFA and at least 150 mg/d SFA. Compliance: Treatment compliance was determined with combination of weekly diary records, pill-counting of leftover capsules, and analysis of erythrocyte LC n23 PUFA levels. P-values < 0.001 for erythrocyte level differences of active FAs in supplements. Duration of intervention: 6 months
Outcomes	Main study outcome: Cognitive performance Dropouts: 30 int., 22 control Available outcomes: Changes in memory measures, reaction times and processing speed.
Notes	Study funding: "DK has previously received funding from Efamol, Martek, and Ginsana SA for DHA research." DK registered trial but was not lead or corresponding of main publication. "Supported by grants from the Massey University Research Fund, Neurological Foundation of New Zealand, and Oakley Mental Health Research Fund. The DHA and placebo supplements were supplied by Efamol Ltd (Surrey, United Kingdom) and Health & Herbs International Ltd (Albany, New Zealand)." In addition to revision of manuscript DK "designed the computerized cognitive test battery."

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The randomization scheme was generated by using the website Randomization.com (http://www.randomization.com)'.
Allocation concealment (selection bias)	Low risk	**"**Allocation will be done by central randomisation by computer.**"** "The person who will determine if a subject is eligible for inclusion in the trial will be unaware, when this decision is made, to which group the subjects will be allocated."
Blinding of participants and personnel (performance bias)	Unclear risk	Placebo and treatment capsules were identical in size and shape. Capsules were provided in identical opaque drug containers."..."Both research staff and participants were blind as to which participants received DHA or placebo treatments until after data analysis." However no information provided as to the capsule's smell and taste.
Blinding of outcome assessment (detection bias)	Low risk	"Who is / are masked / blinded? The people receiving the treatment/s The people administering the treatment/s The people assessing the outcomes The people analysing the results/data" "Both research staff and participants were blind as to which participants received DHA or placebo treatments until after data analysis."
Incomplete outcome data (attrition bias)	High risk	113 control became 91 analysed (20% loss), 115 int became 85 analysed (26% loss), over 6 months. Attempt to give good reasons, but unclear what were "personal reasons".
Selective reporting (reporting bias)	Low risk	Outcomes in protocol are all in output publication(s). ACTRN12610000212055 registered 16/03/2010. First participant enrolled 30/03/2010.
Attention	Low risk	Identical attention for each arm was described.
Compliance	Low risk	p-values < 0.001 for target FAs in erythrocytes
Other bias	Low risk	None noted

SU.FOL.OM3 2010 – ISRCTN41926726 [621-640]

Methods Supplementation en Folates et Omega 3 (SU.FOL.OM3)
RCT, 2 × 2 factorial (LCn3 omega 3 vs placebo, also B vitamin comparison), 4 years
Summary risk of bias: low

Participants People with a history of MI, unstable angina or ischemic stroke
N: control: 1248, intervention: 1253
Level of risk for CVD: high
Men: 80.85% intervention, 78.25% control
Mean age in years (SD): 61.1 (8.8) intervention, 60.8 (8.7) control
Age range: 53-68 years intervention, 54-68 years control
Smokers: 11.1% intervention, 10.4% control
Hypertension: not reported
Medications taken by at least 50% of those in the control group: beta-blockers, aspirin or antiplatelets, lipid lowering, ACE inhibitors
Medications taken by 20%-49%: not reported
Medications taken by some, but < 20%: calcium channel blocker, angiotensin II receptor blockers
Location: France
Ethnicity: not reported

Interventions Type: supplement (capsule)
Comparison: EPA + DHA vs non-fat placebo
Intervention: 2 gelatin capsules Pierre Fabre omega 3 (400 mg/d EPA and 200 mg/d DHA)
Control: 2 gelatin capsules/d placebo (liquid paraffin with fish flavour)
Compliance: tested by questionnaire, response rate was on average 96%. Out of this, 86% complied
Duration of intervention: 4 years

Outcomes Main study outcome: composite of myocardial infarction, cerebral vascular ischemic accident or cardiovascular deaths
Dropouts: control: 145 (66 withdrew, 11 lost to follow-up, 68 deaths), intervention: 134 (61 withdrew, 7 lost to follow-up, 66 deaths)
Available outcomes: deaths, cardiovascular death, non-fatal MI, stroke, CV events, coronary events, cancer events, Geriatric Depression Scale score, authors provided additional information on outcomes and methodology
Response to contact: yes (data provided)

Notes The other factorial intervention was B-vitamins (560 µg methyl-tetrahydrofolate, 3 mg B-6, 20 µg B12) vs placebo
Study funding: French Ministry of Research, Ministry of Health, Sodexo, Candia, Unilever, Danone, Roche, Merck

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Used computerized block randomisation with stratification by sex, age, prior CVD, and city of residence". "Permuted block randomisation (with a block size randomly selected as 8) was used".
Allocation concealment (selection bias)	Low risk	Allocation of participants was programmed by the statistical coordinating centre, who sent participants sufficient treatment capsules for 1 year in an appropriately labelled package
Blinding of participants and personnel (performance bias)	Low risk	Quote: "All subjects and investigators were blinded to treatment allocation", and placebo capsules looked and tasted "identical to the active supplementation". Fish oil flavour was used in placebos.
Blinding of outcome assessment (detection bias)	Low risk	Outcome investigators were blinded to allocation
Incomplete outcome data (attrition bias)	Low risk	Attritions and exclusions were well described. Only 10% loss over 4 years, well balanced
Selective reporting (reporting bias)	Low risk	ISRCTN41926726 registered 2005, 2003 publication on background and rationale, recruitment started April 2003, 2008 protocol, recruitment ended June

		2009, 2010 results published. Outcomes in registry entry appear to have been published.
Attention	Low risk	Not likely as capsules used
Compliance	Low risk	Quote: "Allocation to omega 3 fatty acids increased plasma concentrations of omega 3 fatty acids by 37% compared with placebo" (appears statistically significantly different, though not explicitly stated) … "The overall response rate for return of completed questionnaires was 99%, 96%, 94%, and 95% at 6, 12, and 24 months and at the end of the trial, respectively. About 86% of those who returned a questionnaire reported that they were compliant with the study treatment and compliance was similar in all four groups"
Other bias	Low risk	No further bias noted

Sydney Diet-Heart 1978 - NCT01621087 [641-643]

Methods
Sydney Diet-Heart Study
RCT, 2 arm, parallel (n6 LA vs SFA), 4.3 years
Summary risk of bias: low (as diet advice trial)

Participants
Men with previous MI
CVD risk: high
Control: randomised 237, analysed 221 at 2 years
Intervention: randomised 221, analysed 205 at 2 years
Mean years in trial: control 4.3, intervention 4.3
% male: 100
Age: mean intervention 48.7 (SD 6.8), control 49.1 (SD 6.5)
Age range: 30-59 years
Smokers: intervention 71.5%, control 68.8%
Hypertension: unclear
Medications taken by ≥ 50% of those in the control group: not reported
Medications taken by 20%-49% of those in the control group: not reported
Medications taken by some, but < 20% of the control group: not reported
Location: Australia
Ethnicity: not reported

Interventions
Type: diet advice and supplemental foods
Comparison: ↑ safflower oil and safflower oil-based margarine (n-6) vs usual diet (reduced SFA and MUFA)
Control aims: reduction in energy if overweight, no other specific dietary advice, allowed to use PUFA margarine instead of butter (no specific dietary instruction, except re weight)
Intervention aims: SFA 10% E, PUFA 15% E, reduction in energy if overweight, dietary cholesterol < 300 mg/day through provision of safflower oil and safflower margarine (advised and tutored individually, diet assessed 3 times in first year, twice annually thereafter)
Dose aim: increase **6.6% E PUFA, most of which n6**
Baseline n-6: unclear, 6.1% E PUFA, mostly n6
Compliance by biomarkers: serum TC significantly reduced in intervention compared to control (-0.30 mmol/L, 95% CI -0.51 to -0.09). No body fatty acid markers reported
Compliance by dietary intake: good. From diet records, medians provided

- Energy intake, kcal/d: intervention 2256, control 2194
- Total fat intake, % E: intervention -1.9, control -1.1 (reduction of **0.8% E total fat**, not statistically significant)
- SFA intake, % E: intervention -6.9, control -2.1 (reduction of **4.8% E SFA**, statistically significant)
- PUFA intake, % E: intervention +9.3, control +2.2 (increase of **7.1% E PUFA**, statistically significant)
- PUFA n-3 intake: not reported
- PUFA n-6 intake: not reported
- Trans fat intake: not reported

- MUFA intake, % E: intervention -3.4, control -0.7 (reduction of **2.7% E MUFA**, statistically significant)
- CHO intake, % E: intervention +1.4, control +0.1 (increase of **1.3% E CHO**, not statistically significant)
- Sugars intake: not reported
- Protein intake, % E: intervention +0.4, control +1.2 (decrease of **0.8% E protein,** not statistically significant)
- Alcohol intake, % E: intervention +0.7, control +1.7 (decrease of **1.0% E alcohol**, not statistically significant)

Compliance, other methods: not reported
Inclusion basis: aimed to increase total PUFA intake as well as reduce SFA
PUFA dose: 7.1% E PUFA (from dietary intake data)
Duration of intervention: 2-7 years

Outcomes Main trial outcomes: CV mortality and morbidity
Dropouts: unclear, probably 16 dropouts in each arm, but participants were included from 2-7 years
Available outcomes: mortality, TC, TG
Response to contact: yes, further data provided

Notes Trial funding: Life Insurance Medical Research Fund of Australia and New Zealand

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "table of random numbers ... generated by a research assistant and was concealed until after medical evaluations and testing at baseline were completed"
Allocation concealment (selection bias)	Low risk	As above
Blinding of participants and personnel (performance bias)	High risk	Very difficult to blind trials where participants need to make their own dietary changes
Blinding of outcome assessment (detection bias)	Low risk	Initially masked to group assignment (though success of blinding not checked)
Incomplete outcome data (attrition bias)	Low risk	Survival analysis used
Selective reporting (reporting bias)	Unclear risk	No protocol or trials registry entry located
Attention	High risk	Different levels of dietary support (non-dietary aspects were equivalent)
Compliance	Low risk	TC significantly reduced in intervention compared to control (-0.30 mmol/L, 95% CI -0.51 to -0.09). No body fatty acid markers reported.
Other bias	Low risk	None noted

Tajalizadekhoob 2011 [644]

Methods RCT, parallel, (fish oil capsule vs placebo capsule), 6 months
Summary risk of bias: Moderate or high

Participants Population: Elderly residents of the Kahrizak Charity Foundation with mild or moderate depression (physically handicapped or elderly individuals with no financial resources are cared for free of charge).
N: 33 int., 33 control. (analysed, int: 32 cont: 29)
Level of risk for CVD: Low
Male: 30.3% int., 30.3% control.
Mean age 79.64 (sd 7.39) int: 79.73 (sd 7.01) control
Age range: NR
Smokers: NR
Hypertension: NR
Medications taken by at least 50% of those in the control group: NR
Medications taken by 20-49% of those in the control group: NR
Medications taken by some, but less than 20% of the control group: SSRIs, TCAs

Location: Iran
Ethnicity: NR
Depression: Long term condition (high risk) and general population (low risk)
Anxiety: Long term condition (high risk) and general population (low risk)

Interventions Type: supplement
Comparison: fish oil capsule vs placebo capsule
Intervention: One hard gelatin capsule containing one gram of fish oil was used daily for the drug group. Each capsule contained cod liver oil, glycerol, water, and fish oil and was comprised of 180 mg eicosapentaenoic acid (EPA) and 120 mg DHA. The cod liver oil and fish oil were obtained from cold water fish.
Control: The placebo was a hard gelatin capsule containing medium-chain triglycerides (MCTs) derivate from coconut oil, glycerol, and water, which appeared similar to the fish oil capsules of the drug group.
Compliance: The drugs were given to the participants daily. Participants took the drugs under the supervision of the individual responsible for the administration of the drugs. The individual reported the drug intake of each participant. She was responsible to report whether any of the participants did not agree to take the drug and returned the drug to the research office. The participants were not coerced into taking the drugs and had a choice of not accepting the treatment. The staff were strictly responsible to report non-adherence to the drug treatment.
Duration of intervention: 6 months

Outcomes Main study outcome: depression (Geriatric Depression Scale)
Dropouts: 1 int., 4 control
Available outcomes: dietary intake, adverse events (depression reported as the number of participants that had clinically improved, remained unchanged or worsened for depression, so no data could be used in meta-analysis).

Notes Funding: This research was supported by a grant from the Endocrinology and Metabolism Research Institute, Tehran University of Medical Science. We also thank Zahravi Pharmaceutical Company for preparation of the drugs and the placebos.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The 66 participants were divided into the placebo and the drug groups using Random Number Generation Method (33 participants in each group).
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias)	Low risk	We used hard gelatin capsules to eliminate the odour and taste of the fish oil in order to keep our study blind. The fish oil and the placebo capsules were contained in identical packaging. The capsules were coded with the letters A and B on the back of the packages, respectively. An individual with limited medical knowledge was designated to administer the drugs to the participants based on each participant's code and the drug codes. This individual was blind to the contents of the capsules. In addition, the participants had no knowledge of the contents of the capsules and their designated codes. The 66 participants did not live in one single dormitory. Rather, they lived separately among the other 1,050 residents. This condition helped to keep the study blind.
Blinding of outcome assessment (detection bias)	Low risk	Double blind (details above).
Incomplete outcome data (attrition bias)	Low risk	Only 5 withdrawals from 66 (7.5%)
Selective reporting (reporting bias)	Unclear risk	No protocol identified.
Attention	Low risk	No difference between the groups except for the capsules.

Compliance	Low risk	Participants took the drugs under the supervision of the individual responsible for the administration of the drugs. The individual reported the drug intake of each participant.
Other bias	Low risk	None identified

Tande 2016 [645]

Methods	2 arm, parallel RCT (calanus (marine) oil vs olive oil), 12 months Summary risk of bias: moderate to high
Participants	Healthy male and female volunteers with BMI 25-35 kg/m^2 N: 64 intervention, 63 control (50 intervention, 50 control analysed) Level of risk for CVD: low Men: 42% intervention, 43 % control Mean age in years (SD): 50.7 (7.7) intervention, 49 (9.4) control Age range: unclear (18 years and older) Smokers: not reported Hypertension: not reported Medications taken by at least 50% of those in the control group: not reported Medications taken by 20%-49% of those in the control group: not reported Medications taken by some, but less than 20% of the control group: not reported Location: Norway Ethnicity: not reported
Interventions	Type: supplement (capsule) Comparison: EPA + DHA vs MUFA Intervention: 2 × 500 mg Calanus oil capsules twice daily to provide a daily dose of 2 g. Supplements were provided by Ayanda AS (Norway) as blister packs of 60 capsules each. The Calanus oil contained approximately 85% wax ester with a sum of neutral lipids > 90%. Dose: 2 g/d EPA + DHA Control: identical capsules of olive oil. Compositional analysis indicated that the fatty acid content of the olive oil was primarily oleic acid (76.9%), palmitic acid (10.2%), and linoleic acid (7.7%). Compliance: assessed through the return of unused capsules. Compliance rate reported for both intervention and placebo groups was good (86-88%) Length of intervention: 12 months
Outcomes	Main study outcome: safety of Calanus oil consumption Dropouts: 14 intervention, 13 control Available outcomes: BMI, waist-hip ratio, BP, pulse, HbA1c, ESR, CRP, lipids, glucose tolerance, insulin, clinical chemistry parameters, adverse events (no CVD events, deaths or other major health outcomes occurred according to author reply) Response to contact: author replied with methodological and event information
Notes	Study funding: Calanus AS

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomization of the study subjects into the intervention group or the placebo group was performed by the University Hospital of North Norway clinical research unit and was stratified by gender." Author reply stated that "[r]andomization was performed by competent people at the drugstore affiliated to the University Hospital, with no interconnection, formally or materially with the research department from where the study was managed. Randomization was performed prior to recruiting subjects."
Allocation concealment (selection bias)	Unclear risk	As above, unclear.

Blinding of participants and personnel (performance bias)	Low risk	Participants in the placebo group received identical capsules at similar daily doses as the intervention group. However, no information provided as to their smell and taste. Also unclear if investigators were blinded. Author reply stated "Each study subject was given a randomization number, which carried the name of the person, date of birth and treatment information (intervention or control). The randomization number was the only information made available to the study personnel, and the code was managed by personnel outside the research department. This code was broken after the completion of all analysis with all primary data processed." Blinding of participants only possible for fish plus supplementation vs fish plus placebo.
Blinding of outcome assessment (detection bias)	Low risk	As above
Incomplete outcome data (attrition bias)	Low risk	All dropouts (~20%) are explained
Selective reporting (reporting bias)	Unclear risk	No trials registry entry or protocol found
Attention	Low risk	Appear to be similar in both groups
Compliance	Unclear risk	Quote: "levels of DHA and EPA in the blood were generally higher in the Calanus oil group over baseline values relative to the placebo controls" but no data provided
Other bias	Low risk	None noted

Tani 2017 – UMIN000010452 [646-648]

Methods Single-centre, prospective, open-label RCT (n3 EPA+DHA vs nil), 6 months
Summary risk of bias: Moderate or high
Aim: "to investigate the effect of additional administration of EPA on the plasma PTX3 [pentraxin 3] levels in statin-treated stable CAD patients"

Participants People with stable coronary artery disease on statin therapy
N: 55 int., 55 control. (analysed, int: 53 cont: 53)
Level of risk for CVD: High
Male: 92% int., 83% control.
Mean age (sd): 68 (11) int., 66 (11) control
Age range: 35-80y eligible
Smokers: 8% int., 11% control
Hypertension: 81% int., 68% control
Medications taken by at least 50% of those in the control group: Antiplatelets (98%), Ca channel blockers (62%), Strong statins (72%)
Medications taken by 20-49% of those in the control group: ACE inhibitor/ Angiotensin receptor blocker (49%), β blocker (38%), Moderate statin (26%)
Medications taken by some, but less than 20% of the control group:
Location: Japan
Ethnicity: NR

Interventions Type: supplement (capsules containing EPA or no treatment)
Comparison: Higher EPA Vs lower EPA
Intervention: 1800mg/d capsules (2x900mg) containing 1.8g/d EPA (total n3 PUFA 1.8g/d) manufactured by Mochida Pharmaceuticals, Tokyo, Japan: EPA+DHA 1.8g/d
Control: No treatment.
Compliance: Serum fatty acid status data
Duration of intervention: 6 months

Outcomes Main study outcome: percentage change of plasma PTX3 levels
Dropouts: 2 int., 1 control
Available outcomes: changes in serum non-high-density lipoprotein cholesterol (non-HDL-C) levels and triglyceride-rich lipoproteins (TRLs) as residual risk factors of CAD in patients receiving additional

administration of EPA to ongoing statin therapy. Serum fatty acid status data (EPA/AA), serum hs-CRP, Amyloid A.
Contact with authors: not yet

Notes Study funding: Authors state no conflicts of interest; publically funded

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomised using simple sealed envelope method - no further detail provided
Allocation concealment (selection bias)	Unclear risk	Unclear, no details provided.
Blinding of participants and personnel (performance bias)	High risk	Unblinded study
Blinding of outcome assessment (detection bias)	Unclear risk	Process of outcome assessment not described
Incomplete outcome data (attrition bias)	Low risk	Findings reported for 106/110 (96.4%)
Selective reporting (reporting bias)	Low risk	Primary outcome reported matches trials register. UMIN000010452 Registered 2013/04/11 Participants recruited 1/4/2013- 31/3/2014
Attention	Unclear risk	Unclear follow up
Compliance	Low risk	Measured by serum fatty acid status data – C-RoB calculated as low
Other bias	Low risk	None noted

Tapsell 2004 [649-652]

Methods RCT, parallel, (n3 ALA vs nil), 6 months
Summary risk of bias: Moderate or high

Participants Patients with type 2 diabetes
N: 17 int., 20 control. (analysed, int: 16 cont: 19)
Level of risk for CVD: Moderate
Male: 29.4% int., 64.7% control.
Mean age (sd): 57.7 (9.0) int., 59.3 (7.1) control
Age range: 35-75 years overall
Smokers: NR
Hypertension: NR
Medications taken by at least 50% of those in the control group: NR
Medications taken by 20-49% of those in the control group: NR
Medications taken by some, but less than 20% of the control group: NR
Location: Australia
Ethnicity: NR

Interventions Type: supplemented food (walnuts + advice for modified low fat diet, or advice for modified low fat diet alone)
Comparison: ALA vs nil
Intervention: 30g/d walnuts + advice for modified low fat diet: ALA dose unclear
Control: Advice for modified low fat diet only
PUFA Dose: (intended) increase unclear
Compliance: Diet history and 3-d food record
Duration of intervention: 6 months

Outcomes Main study outcome: Cholesterol
Dropouts: 1 int., 1 control
Available outcomes: Mortality and cardiovascular events (nil), anthropometrics (not useable), lipids, HbA1c
Response to contact: Yes

Notes Author confirmed no deaths or cardiovascular events

Data for anthropometrics, total and LDL cholesterol not used due to baseline differences
3 arm trial: Low fat (unmodified) arm not discussed here
Study funding: California Walnut Commission

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"randomly allocated"
Allocation concealment (selection bias)	Unclear risk	"randomly allocated"
Blinding of participants and personnel (performance bias)	High risk	Open label
Blinding of outcome assessment (detection bias)	Unclear risk	NR
Incomplete outcome data (attrition bias)	Low risk	Low drop out and balanced across arms
Selective reporting (reporting bias)	Unclear risk	No registry or protocol identified
Attention	Unclear risk	Unclear since open label (in low fat arm not discussed fully here, participants received fewer phone calls)
Compliance	High risk	Majority of p values for differences in fatty acid status >0.05
Other bias	Low risk	None noted

Tardivo 2015 – RBR-5668v4 [653 654]

Methods
RCT, parallel, (n3 EPA+DHA vs nil), 6 months
Summary risk of bias: Moderate or high

Participants
Postmenopausal women with metabolic syndrome
N: 44 int., 43 control. (analysed, int: 44 cont: 43 - paper states ITT analysis, but there were dropouts, below)
Level of risk for CVD: moderate
Male: 0% int., 0% control.
Mean age (sd) years: 55.1 (6.6) int., 55.0 (7.3) control
Age range: NR but inclusion criteria were 45-70 years
Smokers: 21% overall (not reported by arm)
Hypertension: NR
Medications taken by at least 50% of those in the control group: NR
Medications taken by 20-49% of those in the control group: NR
Medications taken by some, but less than 20% of the control group: NR
Location: Brazil
Ethnicity: NR

Interventions
Type: supplement
Comparison: EPA+DHA vs nil
Intervention: 3 capsules/d EPA+DHA (Proepa, Ache, providing 0.54g/d EPA plus 0.36g/d DHA with 6mg/d alpha-tocopherol) plus dietary advice on energy intake (encouraging weight loss for those overweight), with 5-6 meals/d, 45-60%E CHO, 10-35%E protein, 20-35%E fat, SFA<7%E, MUFA 10-15%E, individualised to usual dietary intake: EPA+DHA 0.9g/d
Control: dietary advice on energy intake (encouraging weight loss for those overweight), with 5-6 meals/d, 45-60%E CHO, 10-35%E protein, 20-35%E fat, SFA<7%E, MUFA 10-15%E, individualised to usual dietary intake.
PUFA Dose: (intended) increase 0.9g/d EPA+DHA, **0.4%E n-3, 0.4%E PUFA**
Compliance: Assessed in intervention with count of returned capsule containers at each visit, but no results of this mentioned, not in control as no placebo used.
Duration of intervention: 6 months

Outcomes
Main study outcome: metabolic and inflammatory markers
Dropouts: 11 of 44 int., 13 of 43 control

Available outcomes: waist circumference, body fat%, BMI, lipids, glucose, insulin, HOMA-IR, CRP, IL-6, TNF alpha (also IL-1beta, BP not used)

Notes Funding: FAPESP - Fundação de Amparo a Pesquisa do Estado de São Paulo, Faculdade de Medicina de Botucatu da Universidade Estadual Paulista UNESP, Julio de Mesquita Filho
Author contact: not yet

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	All given a number from 1 to 87, and randomised using a centralised computer (SAS)
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias)	High risk	Open trial, no placebo
Blinding of outcome assessment (detection bias)	Unclear risk	Not stated, biochemistry outcomes primarily
Incomplete outcome data (attrition bias)	High risk	11 of 44 in int, and 13 of 43 in control lost over 6 months (28%)
Selective reporting (reporting bias)	Unclear risk	RBR-5668v4 Registration Date: Feb, 3, 2013, Enrolment between 1/2/2011-22/12/2011. All outcomes reported.
Attention	Low risk	Appointments were 2 monthly to review and encourage dietary changes
Compliance	Unclear risk	Not reported
Other bias	Low risk	None noted

Tartibian 2011 [655]

Methods RCT, 2x2 design, parallel, (n3 EPA+DHA vs nil), 6 months (the other intervention is aerobic exercise)
Summary risk of bias: Moderate or high
Aim: "to examine the effects of long-term aerobic exercise and omega-3 (N-3) supplementation on serum inflammatory markers, bone mineral density (BMD), and bone biomarkers in post-menopausal women"

Participants Sedentary postmenopausal women
N: 21 int with exercise, 20 int alone, 20 exercise alone, 18 no intervention (analysed NR)
Level of risk for CVD: low
Male: 0% int., 0% control.
Mean age (sd) yrs: 59.7 (2.3) int with exercise, 63.1 (7.5) int alone, 61.4 (6.9) exercise alone, 58.9 (8.1) no int
Age range: NR
Smokers: NR
Hypertension: NR
Medications taken by at least 50% of those in the control group: Nil, inclusion criteria were that that participants took no medications
Medications taken by 20-49% of those in the control group: nil
Medications taken by some, but less than 20% of the control group: nil
Location: Iran
Ethnicity: NR

Interventions Type: supplement
Comparison: EPA+DHA vs nil (plus or minus aerobic exercise)
Intervention: omega 3 capsules (Viva omega 3 fish oil, each containing 180mgEPA plus 120mg DHA): EPA+DHA 0.9g/d
Control: Nil
2x2 study, plus or minus an aerobic exercise programme
Compliance: assessed by pill counts was 96%, neutrophil cell membrane EPA and DHA appear to be significantly higher at 6 months in the intervention groups

Duration of intervention: 6 months

Outcomes Main study outcome: osteoporosis
Dropouts: NR
Available outcomes: IL-6, TNFalpha, (hormones, bone mineral density, osteoporosis biomarkers also reported)

Notes Study funding: "No specific funding"
Author contact: not yet

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"randomly assigned"
Allocation concealment (selection bias)	Unclear risk	No further details
Blinding of participants and personnel (performance bias)	High risk	Open study (no placebo)
Blinding of outcome assessment (detection bias)	Unclear risk	Not mentioned, though mainly laboratory analysed outcomes
Incomplete outcome data (attrition bias)	Unclear risk	Numbers analysed unclear
Selective reporting (reporting bias)	Unclear risk	No protocol or trial register entry found
Attention	Unclear risk	No details
Compliance	Low risk	Neutrophil cell membrane EPA and DHA appear to be significantly higher at 6 months in the intervention groups
Other bias	Low risk	None noted

Terano 1999 [656]

Methods RCT, parallel, (n3 EPA+DHA vs nil), 12 months.
Summary risk of bias: Moderate or high.

Participants Older adults living in a care home with mild to moderate dementia
N: 10 int., 10 control. (analysed, int: 10 cont: 10)
Level of risk for CVD: High: all had "dementia of CVD".
Male: 10% int., 10% control.
Mean age (sd): 82.7 (6.4) int., 83.3 (5.3) control
Age range: NR
Smokers: 0% (not allowed at residence)
Hypertension: NR
Medications taken by at least 50% of those in the control group: NR
Medications taken by 20-49% of those in the control group: NR
Medications taken by some, but less than 20% of the control group: NR
Location: Japan
Ethnicity: NR

Interventions Type: supplement
Comparison: more DHA vs no supplement (open label)
Intervention: 6 capsules to create daily dose = 720 mg/d: DHA 0.72g/d
Control: no capsules
PUFA Dose: (intended) increase 0.72g/d, **0.3%E n-3, 0.3%E PUFA**
Compliance: Nurses who gave capsules made sure they were swallowed; strictly controlled intake of all participants so unlikely any "always takers".
Duration of intervention: 12 months

Outcomes Main study outcome: Change of scores of HDS-R and MMSE
Dropouts: 0 int., 0 control
Available outcomes: HDS-R, MMSE

Notes Study Funding: NR

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomised by age, but no details on how the sequence was random.
Allocation concealment (selection bias)	Low risk	Those recruiting participants in the trial were not aware of treatment allocation before inclusion was finally decided, allocation was not able to be altered after treatment group had been assigned. (Additional information from Terano 1999- author response)
Blinding of participants and personnel (performance bias)	High risk	Open-label
Blinding of outcome assessment (detection bias)	Low risk	2 doctors came from University hospitals only for psychiatric testing, they were not aware of the recipients assigned treatment
Incomplete outcome data (attrition bias)	Low risk	No participants lost.
Selective reporting (reporting bias)	Unclear risk	No protocol or register found.
Attention	Unclear risk	Only the intervention arm was hand-fed these capsules; but most participants probably hand-fed many daily medications.
Compliance	Low risk	Intervention arm hand-fed, nurses checked they swallowed. Living circumstances made it very unlikely any participant could be an "always taker".
Other bias	Low risk	None noted

THIS DIET 2008 – NCT00269425 [657]

Methods
The Heart Institute of Spokane Diet Study (THIS-DIET)
RCT- parallel, 24 months
Summary risk of bias: moderate or high

Participants
Recent survivors of first myocardial infarction (within < 6 weeks)
N: 51 intervention, 50 control
Level of CVD risk: high
Men: 80% intervention, 68% control
Mean age in years (SD): 58 (10) intervention, 58 (9) control
Age range: unclear
Smokers: 25% intervention, 30% control
Hypertension: 43% intervention, 50% control (uncontrolled or secondary hypertension excluded)
Medications taken by at least 50% of those in the control group: aspirin, statins, beta-blockers, and ACE inhibitors or angiotensin receptor blockers.
Medications taken by 20%-49%: not reported
Medications taken by some, but < 20%: not reported
Location: USA
Ethnicity: intervention 98% white; control 94% white

Interventions
Type: dietary advice (to follow a Mediterranean style diet high in n-3)
Comparison: EPA + DHA vs MUFA (biggest dietary change)
Intervention: Mediterranean style diet high in n-3. Dietary counselling group sessions; two in first month then at months 3, 6, 12 and 24. Sessions focused on behaviour modification and practical aspects of assigned diet including recipes, shopping and dining out. Aim to increase omega 3 fat intake to > 0.75% kcal. Dose: ~1.5 g/d omega 3 fat, or 0.31% E by intake assessment.
Control: dietary advice (to follow the American Heart Association Step II diet). Same number of group sessions as intervention.
The 2 diets were low in saturated fat (< 7% kcal) and cholesterol (< 200 mg/day); the Mediterranean-style diet was distinguished by greater omega-3 fat intake (> 0.75% kcal).
Compliance: participants were required to attend six sessions and only invited but not required to attend extra sessions. 3-day food diaries were reviewed with dietitians. Compliance results not stated.

Dietary achievements:
Total fat intake, % E (at 24 months): control 29.7 (SD 9.3), intervention 29.1 (SD 8.6)
Saturated fat intake, % E (at 24 months): control 8.0 (SD 2.9), intervention 7.9 (SD 3.2)
PUFA intake, % E (at 24 months): control 5.7 (SD 3.1), intervention 5.7 (SD 2.4)
PUFA n-3 intake, % E: control 0.46 (SD 0.38), intervention 0.67 (SD 0.35) g/week
PUFA n-6 intake: not reported
MUFA intake, % E (at 24 months): control 10.3 (SD 5.1), intervention 9.7 (SD 3.6)
CHO intake, % E (at 24 months): control 54 (SD 11), intervention 54 (SD 10)
Protein intake, % E (at 24 months): control 17 (SD 2), intervention 18 (SD 3)
Trans fat intake: not reported
Length of intervention: 24 months

Outcomes Main study outcome: a composite of endpoints including all-cause and cardiac death, MI, hospital admissions for heart failure, unstable angina, or stroke
Dropouts: none for primary outcomes
Available outcomes: total and CVD deaths (nil deaths), CV events, stroke, MI, diagnosis of diabetes mellitus, BMI and weight (different at baseline hence not used), waist circum, lipids, blood pressure, albuminuria, CRP, creatinine and dietary intake (authors supplied further data on newly diagnosed DM, glucose and insulin data, cancers, depression, atrial fibrillation)
Response to contact: yes further data supplied as above

Notes The study compared the 2 intervention groups to a non-randomised usual care control group (not reported here)
Study funding: no funding details is provided but some reported conflict of interests for an author.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Sealed envelopes concealing the allocation sequence were prepared by a research coordinator. Assignment was stratified by diabetes mellitus status using 10-envelope blocks. Envelopes were selected in the prepared order from a locked drawer by a study dietitian to assign interventions
Allocation concealment (selection bias)	Unclear risk	As above but opacity of envelopes is not stated.
Blinding of participants and personnel (performance bias)	High risk	Neither the intervention team nor participants could be blinded to dietary assignment.
Blinding of outcome assessment (detection bias)	Low risk	The PI was blinded for the purpose of adjudicating clinical end points and adverse events by the removal of identifiers from records used for review.
Incomplete outcome data (attrition bias)	Low risk	Primary outcomes data provided for all randomised
Selective reporting (reporting bias)	High risk	NCT00269425. Trial was registered in 2005, data collection started in October 2000, January 2008 (final data collection date for primary outcome measure), publication 2008. A number of the outcomes from the registration were not reported e.g. cardiovascular revascularisation, peripheral revascularisation or amputation, doubling of serum creatinine, dialysis, or kidney transplant, new hypertension. Also numerous secondary measures were reported that were not in the original registration.
Attention	Low risk	Both arms had the same contact and attention
Compliance	Unclear risk	No details
Other bias	Low risk	None noted

TREND-HD 2008 – NCT00146211 [658]

Methods	RCT, parallel, (n3 EPA vs non-fat), 6 months Summary risk of bias: Moderate or high
Participants	People with Huntington's disease N: 158 int., 158 control. (analysed, int: 152 cont: 156) Level of risk for CVD: Low Male: 56% int., 43% control. Mean age (sd): 52.3 (9.8) int., 53.3 (10.2) control Age range: NR Smokers: NR Hypertension: NR Medications taken by at least 50% of those in the control group: NR Medications taken by 20-49% of those in the control group: NR Medications taken by some, but less than 20% of the control group: NR Location: United States and Canada Ethnicity: white 145 int, 149 control. Depression: Long term condition (high risk) Anxiety: Long term condition (high risk)
Interventions	Type: supplement Comparison: Ethyl-EPA vs placebo Intervention: 2 x 500mg capsules ethyl-EPA (>95% purity, 0.2% DL-α-tocopherol) /day Control: 2 x 500mg light paraffin oil (0.2% DL-α-tocopherol) / day **PUFA Dose**: (intended) increase 0.95g/d, **0.4%E EPA, 0.4%E PUFA** Compliance: Not measured Duration of intervention: 6 months
Outcomes	Main study outcome: Total Motor Score component of the Unified Huntington's Disease Rating Scale Dropouts: 12 int., 7 control Available outcomes: Depression incidence, adverse events, cognitive outcomes (Stroop colour naming, Symbol digit modalities, Chorea score of UHDRS, CGI, total dustonia score), bradykinesia, total functional capacity, independence assessment (depression measured using Beck Depression Index, and MMSE to assess cognition but change scores were provided with no variance data, so could not be used in meta-analysis).
Notes	Results presented in review for first 6 months of study only - open label after this time point. Study funding: This study was funded by a grant from Amarin Neuroscience to the University of Rochester

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	At baseline participants were randomized according to a block-balanced computer-generated randomization plan (generated by the Biostatistics Center, University of Rochester, Rochester, New York) that was stratified by site. Treatment packets were pre-numbered with randomization codes. Pg 1583
Allocation concealment (selection bias)	Low risk	Treatment packets were pre-numbered with randomization codes. Pg 1583
Blinding of participants and personnel (performance bias)	Unclear risk	Initial treatment assignments were not disclosed to study participants or investigators. Details of blinding not provided.
Blinding of outcome assessment (detection bias)	Unclear risk	Double-blind for first 6 months of study. Details of blinding not provided.
Incomplete outcome data (attrition bias)	Low risk	Per protocol analysis. 6% drop outs.
Selective reporting (reporting bias)	Low risk	The protocol reported in the trial registration had fewer outcomes than were reported in the results paper. Trials register: ClinicalTrials.gov registry number: NCT00146211 Date registered: First received: September 2, 2005 date data collection began: September 2005.

Attention	Low risk	After screening and baseline visits, study participants received a telephone call at month 1, 7, and 13 and underwent clinical assessment at month 3, 6, 9, and 12.
Compliance	Unclear risk	Not measured.
Other bias	Low risk	None

Vanlint 2012 ACTRN12609000238279 [659]

Methods RCT, parallel, (n3 DHA vs corn oil), 12 months
Summary risk of bias: Low

Participants Sedentary postmenopausal women
N: 20 int, 20 control (analysed 19 int, 18 control)
Level of risk for CVD: low
Male: 10% int. overall, not reported by arm.
Mean age (sd) yrs: 59.2 (NR) overall, not reported by arm.
Age range: NR BMI: 25.4(3.3) int., 25.5(3.9) control
Smokers: NR
Hypertension: NR
Medications taken by at least 50% of those in the control group: Calcium, vitamin D
Medications taken by 20-49% of those in the control group: NR
Medications taken by some, but less than 20% of the control group: NR
Location: Australia
Ethnicity: NR

Interventions Type: supplement
Comparison: DHA vs n6
Intervention: 2 capsules/day containing DHA, 'Life'sDHA©. Each capsule contained 200 mg DHA derived from algal oil, in a sunflower oil medium. Dose: 400mg DHA/d
Control: 2 placebo capsules/day containing corn oil.
All participants were asked to take two tablets/d 'Ostelin Vitamin D plus Calcium©', equivalent to calcium carbonate 1200 mg & vitamin D3 1000 IU daily.
Compliance: Participants were reviewed at 3-monthly intervals and were asked to keep a diary with detailed medication compliance. Mean number of missed doses over 12 month was 12.4 dose/participant.
Duration of intervention: 12 months

Outcomes Main study outcome: BMD
Dropouts: 1 int., 2 control
Available outcomes: Bone mineral density (lumbar, proximal femur & neck of femur), CTx, dietary calcium, side effects.

Notes Study funding: supported by the 2007 Vicki Kotsirilos Integrative Medicine Grant, administered by the Royal Australian College of General Practitioners. DHA and placebo capsules donated by Martek Biosciences Corporation (Columbia, USA) and calcium/vitamin D tablets donated by Reckitt-Benckiser (Australia) Pty Ltd (Sydney, Australia).
Author contact: not yet attempted

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	participants were randomly allocated to two groups using a random number table
Allocation concealment (selection bias)	Low risk	Randomisation was done by a third party.
Blinding of participants and personnel (performance bias)	Low risk	Both investigators and participants remained blinded with regard to all participants' group allocation until after all participant visits were completed
Blinding of outcome assessment (detection bias)	Low risk	As above

Incomplete outcome data (attrition bias)	Low risk	Very few dropouts, all explained and balanced between groups.
Selective reporting (reporting bias)	Low risk	Outcomes reported match prospectively registered protocol (ACTRN 12609000238279)
Attention	Low risk	Both arms were given the same attention
Compliance	Low risk	Mean number of missed doses over 12 month was 12.4 dose/participant.
Other bias	Low risk	None noted

Varghese 2000 [660]

Methods RCT, parallel, (n3 vs n6), 6 months
Summary risk of bias: Moderate to high

Participants People with active and extensive ulcerative colitis
N: NR (~25) int, NR (~25) control (51 randomised, unclear how many analysed)
Level of risk for CVD: low
Male: NR
Mean age (sd) yrs: NR
Age range: NR
Smokers: NR
Hypertension: NR
Medications taken by at least 50% of those in the control group: NR
Medications taken by 20-49% of those in the control group: NR
Medications taken by some, but less than 20% of the control group: NR
Location: UK
Ethnicity: NR

Interventions Type: supplement (probably capsules)
Comparison: n3 vs n6
Intervention: 5.6mg/d (sic) n3 (unclear whether ALA or LCn3)
Control: sunflower oil (quantity unclear)
Compliance: NR
Duration of intervention: 6 months

Outcomes Main study outcome: degree of UC
Dropouts: NR
Available outcomes: (assessed extent of disease, colonoscopy and clinical scores, as well as side effects, but only p-values reported). Suggested improvement in n3 group for clinical and colonoscopic scores.

Notes Study funding: NR
Author contact: not yet attempted

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"randomized"
Allocation concealment (selection bias)	Unclear risk	no information
Blinding of participants and personnel (performance bias)	Unclear risk	stated "double blind" but no further information
Blinding of outcome assessment (detection bias)	Unclear risk	no information
Incomplete outcome data (attrition bias)	Unclear risk	No information
Selective reporting (reporting bias)	Unclear risk	No protocol or trials registry entry found
Attention	Unclear risk	unclear

Compliance	Unclear risk	No information
Other bias	Low risk	None noted

Veleba 2015 – EudraCT 2009-011106-42 [661 662]

Methods RCT, parallel, 2x2 (n3 EPA+DHA vs n6 LA, plus or minus pioglitazone), 6 months
Summary risk of bias: Moderate or high

Participants Overweight/obese type 2 diabetic patients treated with metformin
N: 17 n-3; 17 n-3 + Pio; 18 Pio; 17 control. (analysed, n-3: 16; n-3+Pio 14; Pio 17; cont: 13)
Level of risk for CVD: Moderate
Male: 66% in all groups combined
Age median: 59.5 n-3; 60.5 n-3+Pio: 62.0 Pio; 62.0 control
Smokers: NR
Hypertension: NR
Medications taken by at least 50% of those in the control group: Metformin
Medications taken by 20-49% of those in the control group: NR
Medications taken by some, but less than 20% of the control group: NR
Location: Czech Republic
Ethnicity: NR

Interventions Type: supplement (capsules with EPA+DHA; Pio+EPA+DHA; Pio alone; or corn oil)
Comparison: EPA+DHA vs low EPA+DHA
Intervention: **n-3 arm:** 5g/d omega-3 concentrate (including 0.75g/d EPA + 2g/d DHA, EPAX, Aalesund): EPA+DHA 2.75g/d
n-3+ pioglitazone arm: as for n-3 + 15mg/d pioglitazone (Pio, Takeda): EPA+DHA 2.75g/d
Pio arm: 15mg/d pioglitazone alone
Control: 5g/d corn oil capsules (EPAX, Aalesund)
PUFA Dose: (intended) increase 2.75g/d EPA+DHA, **1.2%E n-3, 1.2%E PUFA**
Compliance: Serum omega-3 PhL index
Duration of intervention: 24 weeks

Outcomes Main study outcome: Insulin sensitivity (not in measures we use) and triacylglycerol
Dropouts: 1 n-3; 3 n-3+Pio; 1 Pio; 4 control
Available outcomes: Insulin, weight, BMI, lipids, glucose, HbA1c, inflammatory markers (as medians and interquartile range)

Notes 4 arm trial, 2x2, omega 3 and pioglitazone interventions
Study funding: Ministry of Health of the Czech Republic

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomization was performed using a computer-based algorithm arranging experimental units in blocks of four"
Allocation concealment (selection bias)	Unclear risk	"The randomization code was kept secret and revealed after the clean-file procedure had been completed when all data had been filled in the case report forms"
Blinding of participants and personnel (performance bias)	Unclear risk	"double blind"
Blinding of outcome assessment (detection bias)	Unclear risk	"double blind"
Incomplete outcome data (attrition bias)	High risk	Drop out >20% in the control arm
Selective reporting (reporting bias)	High risk	EudraCT 2009-011106-42. Unclear if prospectively registered. Registered on 26/05/2009. Some outcomes not reported e.g. liver and muscle (musculus tibialis) fat content, body fat distribution: fat quantity in different departments (subcutaneous, visceral)

Attention	Unclear risk	No specific statement and blinding unclear (open for pioglitazine arm)
Compliance	Low risk	Serum omega-3 PhL index significantly increased in response to omega-3
Other bias	Low risk	None noted

Veterans Admin 1969 [349 350 663-678]

Methods
Veterans Administration Trial
RCT, 2 arms, parallel (n6 LA vs SFA), up to 8 years
Summary risk of bias: moderate to high

Participants
Men living at the Veterans Administration Centre
CVD risk: low
Control: randomised 422, analysed 422
Intervention: randomised 424, analysed 424
Mean years in trial: control 3.7, intervention 3.7
% male: 100
Age: mean control 65.6, intervention 65.4
Age range: all 54-88 years
Smokers: intervention 283, control 279 (unknown intervention 41, control 58)
Hypertension: unclear
Medications taken by ≥ 50% of those in the control group: not reported
Medications taken by 20%-49% of those in the control group: not reported
Medications taken by some, but < 20% of the control group: digitalis, diuretics, oestrogens, corticoids, androgens, coumarins, nicotinic acid
Location: USA
Ethnicity: white 90%, black 7%, Asian 1%, Hispanic 1%, other 1%

Interventions
Type: diet provided (residential institution)
Comparison: ↑ corn, soybean, safflower and cottonseed oils (n-6) vs usual institutional diet
Control aims: provided, total fat 40% E (whole diet provided)
Intervention aims: total fat 40% E, 2/3 of SFA replaced by unsaturated fats (from corn, soybean, safflower and cottonseed oils), dietary cholesterol reduced (whole diet provided)
Dose aim: 2/3 of baseline SFA is increase of **~12%E PUFA**
Baseline n-6: 4% E LA, control arm 4.8% E PUFA
Compliance by biomarkers: subcutaneous 18:2 + 18:3 11.7% fat at baseline, rising to 12.8% fat in control and 34.8% fat in intervention (after "prolonged" adherence to diet). Serum TC reduced, but not statistically significantly in intervention compared to control (-0.37 mmol/L, 95% CI -0.77 to 0.03).
Compliance by dietary intake: unclear, **c**hecked using coloured tickets to assess dining room attendance - described as 49% in intervention and 56% in controls. Laboratory analysis of the mean of over 400 weekly collections of diet provided:

- Energy intake, kcal/d: intervention 2496, control 2496
- Total fat intake, % E: intervention 38.9 (SD 1.9), control 40.1 (SD 2.2)
- SFA intake, % E: intervention 8.3, control 18.5 (decrease **10.2% E SFA**)
- PUFA intake: not reported but shown in graph as 18:2 + 18:3 ~12% of dietary fat (4.8% E) in control and 43% in intervention (17.2% E), increase 12.4% E
- PUFA n-3 intake, % E: not reported
- PUFA n-6 intake, % E: intervention 16.1, control 4.4 (increase **11.7% E LA**)
- Trans fat intake: not reported
- MUFA intake, % E: intervention 14.6, control 17.1 (decrease **2.5% E MUFA**s)
- CHO intake: not reported
- Sugars intake: not reported
- Protein intake, % E: intervention 15.6 (SD not reported), control 15.4 (SD not reported)
- Alcohol intake: not reported

Compliance by other methods: no others reported
Inclusion basis: aim was to increase unsaturated fats, not total PUFA. Total PUFA not reported but LA dose 11.7% E (best estimate), > 10% increase from baseline of ~5% E
PUFA dose: 11.7% E from total PUFA (best estimate from food composition data)
Duration of intervention: up to 8-9 years

Outcomes
Main trial outcomes: mortality, heart disease

Dropouts: intervention 117, control 58 withdrawals over whole trial, a few participants were involved for up to 8-9 years
Available outcomes: mortality, CV mortality (sudden death, definite MI, definite stroke, angina, PV events), cancer deaths, cancer diagnoses, stroke, non-fatal MI, total MI, CHD deaths (fatal MI and sudden death due to CHD), CHD events (any MI or sudden death due to CHD), some data on TC, but no variance info
Response to contact: attempted but no author contact established (trial published in 1969)

Notes Dayton S et al, J Lab & Clin Med 1965;65(%):739-747
Trial dates: recruitment 1959-1967
Trial funding: mainly US Public Health Service, Los Angeles County Heart Assoc, Arthur Dodd Fuller Assoc, but Corn Products Co (provided Corn oil and margarine), National Soybean Processors Assoc (provided soybean oil), Pitman-Moore Co (provided margarine), Frozen Desserts Co (imitation ice cream). All trial authors worked for academic or health institutions

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "table of random numbers used"
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias)	Low risk	Institution provided diet in a masked fashion
Blinding of outcome assessment (detection bias)	Low risk	Physician knowledge of allocation was assessed and found not much better than random
Incomplete outcome data (attrition bias)	Low risk	All followed up via Veterans Admin system
Selective reporting (reporting bias)	Unclear risk	No protocol or trials registry entry located
Attention	Low risk	Appeared equivalent, diet provided to both arms
Compliance	Low risk	Subcutaneous 18:2 + 18:3 11.7% fat at baseline, rising to 12.8% fat in control and 34.8% fat in intervention (after "prolonged" adherence to diet). TC reduced, but not statistically significantly in intervention compared to control (-0.37 mmol/L, 95% CI -0.77 to 0.03).
Other bias	Low risk	None found

Vijayakumar 2014 [679-681]

Methods RCT, 2 arms, parallel (n6 LA vs SFA), 2 years
Summary risk of bias: moderate to high

Participants People with stable coronary artery disease
CVD risk: high
N: intervention (sunflower oil): 100 randomised, analysed at 2 years 94; control (coconut oil): 100 randomised, analysed at 2 years 96
Mean years in trial: 2
% male: intervention 92.9%, control 93.9%
Age, mean (SD) years: intervention 59.0 (8.9), control 59.0 (8.4)
Age range: unclear
Smokers, ex: intervention 57.1%, control 54.1%
Hypertension: intervention 55.1%, control 58.2%
Medications taken by ≥ 50% of those in the control group: statins
Medications taken by 20%-49% of those in the control group: not reported
Medications taken by some, but < 20% of the control group: fibrates, nicotinic acid
Location: India
Ethnicity: not reported

Interventions Type: food (cooking oil) provided

Comparison: sunflower oil (n6) vs coconut oil (SFA)
Intervention aims: whole family to use branded sunflower oil for cooking (15% E provided in form of sunflower oil, ~66% PUFA)
Control aims: whole family to use branded coconut oil for cooking (15% E provided in form of coconut oil, ~5% PUFA)
Dose aim: increase **9.2% E PUFA**
Baseline PUFA: unclear
Compliance by biomarkers: Serum TC reduced but not significantly reduced in intervention compared to control (-0.06 mmol/L, 95% CI -0.22 to 0.34) though rose slightly in control, fell slightly in intervention. No biomarker data reported
Compliance by dietary intake: unclear. Reports that 7-day recall and diet diaries were used to monitor intake, but results not provided.

- Energy intake: not reported
- Total fat intake: not reported
- SFA intake: not reported
- PUFA intake: not reported
- PUFA n-3 intake: not reported
- PUFA n-6 intake: not reported
- Trans fat intake: not reported
- MUFA intake: not reported
- CHO intake: not reported
- Sugars intake: not reported
- Protein intake: not reported
- Alcohol intake: not reported

Compliance, other methods: oils were provided for family members to encourage compliance
Inclusion basis: did not aim to increase total PUFA intake. Quantity and standard compositions suggest dose ~9.2% E total PUFA, > 10% more than assumed baseline of 6% E PUFA
PUFA dose: 9.2% E PUFA
Duration of intervention: 2 years

Outcomes Main trial outcome: CV risk factors
Dropouts: intervention 6 lost, control 4 lost
Available outcomes: lipids, death, revascularisation, (glycaemic control, weight, BMI available but unbalanced at baseline)
Response to contact: author replied and provided additional outcome data

Notes Trial funding: coconut development board, Amrita Institute of Medical Science and Research. Sponsors had no role in trial design or analysis

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Block randomisation with 5 blocks of 40
Allocation concealment (selection bias)	Unclear risk	Unclear
Blinding of participants and personnel (performance bias)	Unclear risk	Unlikely as participants and their families used branded oils
Blinding of outcome assessment (detection bias)	Unclear risk	Unclear
Incomplete outcome data (attrition bias)	Low risk	5% withdrawals. Clear, with reasons
Selective reporting (reporting bias)	Unclear risk	Unclear, no protocol or trials register entry found
Attention	Low risk	Appeared equivalent
Compliance	Low risk	TC reduced in intervention compared to control (-0.06 mmol/L, 95% CI -0.22 to 0.34, rose slightly in control, fell slightly in intervention). No biomarker data reported
Other bias	Low risk	None noted

VITAL 2018 - NCT01169259 [682-689]

Methods	VITamin D and OmegA 3 TriaL (VITAL) RCT- parallel 2x2 (LCn3 vs MUFA), median 5.3 years Summary risk of bias: low
Participants	Multi-ethnic population of > 25,000 apparently healthy adults (men 50+ years, women 55+ years) without cancer or CVD at baseline N: 12933 intervention, 12938 control (analysed int 12933, control 12938) Level of CVD risk: low Men: 49.4% intervention, 49.5% control Mean age in years (SD): 67.2 (7.1) intervention, 67.1 (7.1) control Age range: unclear Smokers: 7.2% intervention, 7.2% control Hypertension: 49.3% intervention, 50.22% control Medications taken by at least 50% of those in the control group: antihypertensives Medications taken by 20%-49%: cholesterol-lowering medication, aspirin, multivitamins Medications taken by some, but < 20%: post-menopausal hormones Location: USA Ethnicity: intervention 71.5% white, 20.1% black, 3.9% hispanic, 1.6% asian; control 71.2% white, 20.2% black, 4.1% hispanic, 1.5% asian
Interventions	Type: supplement Comparison: LCn3 vs MUFA Intervention: Arm 1: omega-3, 1 capsule/d, Omacor fish oil, ProNova. EPA + DHA 840mg/d: 465 mg EPA; 375 mg DHA provided in calendar packs and placebo D3 Arm 3: omega-3 as in Arm 1 and vitamin D3 (1/d, 2000 IU) Control: Arm 2: placebo omega-3 and vitamin D3 (1/d, 2,000IU) Arm 4: placebo omega-3 and placebo D3 Dose: 840mg/d LCn3, or 0.38% E Compliance: % of participants who reported taking at least 2/3 of capsules - int 75.8%, control 75.7% at 5 years. N3 index was measured in ~10% who volunteered - unclear if representative. Dietary achievements: not mentioned Duration of intervention: median 5.3 years, range 3.8 to 6.1 years
Outcomes	Main study outcome: reduction in risk for total cancer and CVD events (a composite of MI, stroke, and cardiovascular mortality) Dropouts: none for primary outcomes (ITT) Available outcomes: death, CVD death, total stroke (also ischaemic and haemorrhagic stroke, stroke death), total MI, fatal MI, revascularisation (PCI and CABG), any cancer diagnosis, breast cancer diagnosis, prostate and colorectal cancer diagnoses, cancer deaths, CVD events (CV death, MI and stroke), side effects (various trial registry entries also suggest diabetes, hypertension, cognitive decline, autoimmune conditions, infections, chronic respiratory disease, depression, bone health, fractures, chronic knee pain, body composition, physical disability, falls, plasma biomarker measures) Response to contact: not yet attempted
Notes	NCT01169259 www.vitalstudy.org Study funding: NIH with some additional funding eg Quest Diagnostics analysed vitamin D, Omacor donated by Pronova BioPharma and matching placebos

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was computer generated within sex, race and 5-year age groups in blocks of 8
Allocation concealment (selection bias)	Low risk	Computer randomisation and lack of direct contact with trial staff probably ensured adequate allocation concealment
Blinding of participants and personnel (performance bias)	Low risk	Placebo described as "matching", no contact with study personnel except via mailed questionnaire

Blinding of outcome assessment (detection bias)	Low risk	Endpoints committee were unaware of trial-group assignments
Incomplete outcome data (attrition bias)	Low risk	ITT analysis
Selective reporting (reporting bias)	Low risk	All outcomes of the main trial are reported. Other sub-trials have not yet reported.
Attention	Low risk	No contact with study personnel, little opportunity for attention bias
Compliance	Low risk	Compliance appears acceptable though lipid data were in a small self-selected sample
Other bias	Low risk	None noted

WAHA 2016 – NCT01634841 [690-695]

Methods The Walnut and Healthy Aging Study (WAHA)
2-arm, parallel RCT (usual diet plus walnuts vs usual diet), 2 years
Summary risk of bias: moderate to high

Participants Middle-aged healthy adults
N: 362 intervention, 346 control (only preliminary data on 312 participants from one of the two centres is available)
Level of risk for CVD: low
Men: 32.6% intervention, 31.5% control
Mean age in years (SD): 69.4 (3.8) intervention, 68.9 (3.5) control
Age range: 63-79 (inclusion criteria)
Smokers: 4.4% intervention, 1.2% control
Hypertension: 52.8% intervention, 52.9% control
Medications taken by at least 50% of those in the control group: not reported
Medications taken by 20%-49% of those in the control group: not reported
Medications taken by some, but less than 20% of the control group: not reported
Location: Spain and USA
Ethnicity: not reported

Interventions Type: supplement (food)
Comparison: ALA vs unclear
Intervention: 15% of daily energy intake as walnuts. The estimated amount of walnuts ranged from about 30–60 g/day (1-2 ounces). Sachets for daily consumption containing 30 g, 45 g, or 60 g of raw, pieced walnuts were provided as 8-week allotments to be eaten daily, preferably as the raw product, either as a snack or by incorporating them into shakes, yogurts, cereals, or salads. To improve participants' compliance, 1-kg extra walnut allowances were provided every 2 months to take into account family needs. Dose: ~5 g/d ALA
Control: usual diet without walnut
Compliance: assessed by dietitians through FFQs, recount of empty packages, and changes in FAs concentrations. 95% consumed at least 30 g/d. The proportion of α-linolenic acid in red blood cells increased in the walnut group by 0.16% (95% CI 0.14 to 0.18) and in the control group by 0.02% (95% CI −0.01 to 0.04; P < 0.001). No data on dietary intake provided.
Length of intervention: 2 years (only 1 year results have partly been published)

Outcomes Main study outcome: change in cognitive decline (results not yet published)
Dropouts: 36 intervention, 21 control (after 1 year)
Available outcomes: lipids (for TG and HDL only data states "no between diet differences were observed"), weight (waist circumference was provided but without variance, abstract stated that "there were no significant changes in body fat and waist-to-hip ratio over time and between the two groups"). Authors provided data on mortality, CVD events, cancer deaths and diagnoses, IBD diagnosis (no CVD deaths). Cognitive, ophthalmological, inflammatory markers, glycaemic status and other outcomes are not yet available.
Response to contact: authors provided additional outcome and methodology data.

Notes Study funding: California Walnut Commission
The 2-year results as well the full 1-year results are yet to be published. Outcome data reported are for only for participants from one centre (USA)

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "randomized to either the control or walnut group using a computerized random number table with stratification by center, sex, and age range. Couples entering the study were treated as one number and were randomized into the same group".
Allocation concealment (selection bias)	Low risk	Author reply states, "Baseline subject data was collected before randomization. Randomization was done by the clinician, pressing the key on the computer. Since this was a dual center (Barcelona and Loma Linda) trial, a single computer software randomized participants for both the centers."
Blinding of participants and personnel (performance bias)	High risk	Single blind. "An unavoidable limitation of the study is not being able to blind participants to the intervention since it consists of a whole food" Rajaram 2017.
Blinding of outcome assessment (detection bias)	High risk	Author reply states "Study personnel not in contact with the subjects were blind to the treatment assignment. So (lab technicians, ophthalmology technician, neuro cognitive testers) were not aware of the treatment assignment. Of course clinicians who were visited by subjects every two months, knew the treatment assignment". This suggests that allocation was known by physicians, so high risk for event data
Incomplete outcome data (attrition bias)	Low risk	38/362 dropouts in intervention group = 10.5%. 34/346 dropouts in control group = 9.8%. Similar dropout in groups over 2 years.
Selective reporting (reporting bias)	Unclear risk	Although prospectively registered, no full results paper published – results from conference abstracts only report some secondary outcomes
Attention	Unclear risk	Not enough details
Compliance	Low risk	ALA levels were significantly higher in the intervention group
Other bias	Low risk	None noted

Wang 2016 – ChiCTR-TRC-14005084 [696]

Methods RCT, parallel, (n3 EPA+DHA vs n6 LA), 6 months
Summary risk of bias: Moderate or high

Participants Type 2 diabetic patients with abdominal obesity
N: 50 int., 50 control. (analysed, int: 49 cont: 50)
Level of risk for CVD: Moderate
Male: 30.6% int., 40% control.
Mean age (sd): 64.6 (5.5) int., 66.3 (5.1) control
Age range: 60 years plus
Smokers: NR
Hypertension: NR
Medications taken by at least 50% of those in the control group: Oral agents
Medications taken by 20-49% of those in the control group: Insulin, antihypertensives
Medications taken by some, but less than 20% of the control group: NR
Location: China
Ethnicity: Chinese

Interventions Type: supplement (capsules with EPA+DHA or corn oil)
Comparison: Fish oil vs corn oil
Intervention: 4x1g fish oil capsules/d (containing 1.34g EPA + 1.07g DHA, By-Health Co. China): EPA+DHA 2.41g/d
Control: 4x1g corn oil capsules/d

Compliance: Monthly check-ins and returning empty bottles. Serum fatty acid composition at baseline and trial end
Duration of intervention: 6 months

Outcomes Main study outcome: Glycaemic control and dyslipidaemia
Dropouts: 1 int., 0 control
Available outcomes: Anthropometrics, lipids, glucose, HbA1c, insulin, HOMA-IR (insulin and HOMA not used due to baseline differences; BP 6mths only)

Notes Study funding: Grant from the National Natural Science Foundation of China, the nutrition research foundation from the Chinese Nutrition Society, the Fundamental Research Funds for the Central Universities, and the Graduate Research and Innovation Projects of Colleges in Jiangsu Province.
Commercial supply of capsules

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random numbers were generated through the statistics software of SAS PROC PLAN procedure programming
Allocation concealment (selection bias)	Unclear risk	Both participants and investigators were blinded for treatment allocation until the completion of the final data analysis
Blinding of participants and personnel (performance bias)	Low risk	Identical-looking capsules and participants were asked to swallow the whole capsules before their main meals to avoid unmasking
Blinding of outcome assessment (detection bias)	Unclear risk	Both participants and investigators were blinded for treatment allocation until the completion of the final data analysis
Incomplete outcome data (attrition bias)	Low risk	Low drop out (1 participant with reason)
Selective reporting (reporting bias)	High risk	C-reactive protein not reported
Attention	Low risk	Participant seen at the same points and asked to maintain stable diet, medications and physical activity
Compliance	Low risk	Significant increase in serum EPA and DHA in the intervention group
Other bias	Low risk	None noted

Weinstock-Guttman 2005 [697]

Methods RCT, parallel, (low fat diet (15% fat) with n-3 fish oils vs AHA Step I diet (fat ≤ 30%) with olive oil supplements), 12 months
Summary risk of bias: moderate or high

Participants Population: adults with multiple sclerosis
N: 15 intervention, 16 control (analysed, intervention: 13, control: 14)
Level of risk for CVD: low
Men: 15.4% intervention, 14.3% control
Mean age in years (SD): 39.9 (10.0) intervention, 45.1 (7.7) control
Age range: not reported
Smokers: not reported
Hypertension: not reported
Medications taken by at least 50% of those in the control group: all patients received 400 units of vitamin E, one multivitamin tablet (not containing any PUFA) and at least 500 mg calcium per day
Medications taken by 20%-49% of those in the control group: not reported
Medications taken by some, but less than 20% of the control group: not reported
Location: USA
Ethnicity: not reported

Interventions Type: dietary advice plus supplement

Comparison: EPA + DHA vs MUFA (low fat diet (15% fat) with n-3 fish oils vs AHA Step I diet (fat ≤ 30%) with olive oil supplements)
Intervention: 1.98 g/d EPA, 1.32 g/d DHA supplements (EPAX 5500 EE, Tishcon Corp) + low fat diet (< 15% total calories). Dose: 3.3 g/d EPA + DHA
Control: one 1 g olive oil placebo capsules 6 times daily, moderate fat diet (< 30% total calories) (American Heart Association Step 1 diet)
Compliance: assessed by individual food records; intervention 69.2% control 66.7% compliance; also at 12 months there was a significant difference between the fatty acid status of the intervention and control groups in terms of EPA (P = 0.027), as described in table 3 of the main paper
Duration of intervention: 12 months

Outcomes Main study outcome: physical component scale (PCS)
Dropouts: 3 intervention, 7 control
Available outcomes: Mental Health Inventory, Modified Fatigue Impact Scale, weight change, HDL and LDL cholesterol, adverse events (MS relapse, TNF-alpha, ICAM-1, VCAM-1 and other inflammatory markers, SF-36 not used)
Response to contact: no

Notes Study funding: National Multiple Sclerosis Society (PP0620T), Mellen Center Foundation and "The Jog for the Jake" grant

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	States "randomly assigned", no further details
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias)	High risk	Quote: "Patients knew the percentage of dietary fat but did not know the assignment of capsules oil supplementation."
Blinding of outcome assessment (detection bias)	Unclear risk	Not reported
Incomplete outcome data (attrition bias)	High risk	Discrepancy in numbers of participants discontinued and numbers analysed. Per protocol analysis
Selective reporting (reporting bias)	Unclear risk	No protocol or trials register entry found
Attention	Low risk	Treated equally
Compliance	Low risk	Assessed by individual food records; intervention 69.2% control 66.7% compliance. At 12 months there was a significant difference between the EPA status of the intervention and control groups (P = 0.027).
Other bias	Low risk	None noted

WELCOME 2015 – NCT00760513 [698-711]

Methods Wessex Evaluation of Fatty Liver and Cardiovascular Markers in NAFLD with Omacor Therapy (WELCOME)
RCT, parallel, (Omacor or placebo), 15-18 months
Summary risk of bias: low

Participants Patients with NAFLD
N: 51 intervention, 52 control (analysed, 47 intervention, 48 control)
Level of risk for CVD: moderate
Men: 49% intervention, 67% control
Mean age in years (SD): 48.6 (11.1) intervention, 54 (9.6) control
Age range: not reported (18-75 years inclusion criteria)
Smokers: 14.3% intervention, 11.8% control
Hypertension: not reported
Medications taken by at least 50% of those in the control group: lipid lowering drugs

Medications taken by 20%-49% of those in the control group: antihypertensives, metformin (data not provided by group)
Medications taken by some, but less than 20% of the control group: none reported
Location: UK
Ethnicity: not reported

Interventions Type: supplement (Omacor capsules)
Comparison: DHA + EPA vs MUFA
Intervention: 4 g OMACOR per day (providing 1.84 g EPA, 1.52 g DHA as ethyl esters)]. Dose: 3.36 g/d EPA + DHA
Control: 4 g olive oil capsules/ day (providing; ALA1%, oleic acid 67%, palmitic acid 15%, stearic acid 2%, n-6 fat: 15%)
Compliance: was assessed by recording the returned unused capsules and quantification of erythrocyte EPA + DHA enrichment (a prespecified threshold of 2% for DHA & threshold of 0.7% for EPA enrichment)
Duration of intervention: 15-18 months

Outcomes Main study outcome: changes in mean liver fat %, changes in 2 liver fibrosis scores, change in serum biomarkers
Dropouts: 4 intervention, 4 control
Available outcomes: weight, BMI, lipids, blood pressure, glucose, insulin sensitivity, body fat measures, liver enzymes, HbA1c, serum n-3 FAs, authors provided details of diabetes diagnoses, % body fat, BP and carotid intima media thickness
Response to contact: yes

Notes Study funding: National Institute for Health Research (NIHR) Southampton Biomedical Research Unit grant and by a Diabetes UK allied health research training fellowship awarded to KGM (Diabetes UK. BDA 09/ 0003937). CDB, PCC and ES are supported in part by the NIHR Southampton Biomedical Research Centre. Omacor and placebo were provided by Pronova Biopharma through Abbott Laboratories, Southampton, UK

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were block randomised by an independent clinical trials pharmacist to treatment with identical capsules by mouth of either n-3 fatty acid ethyl esters (4 g/d Omacor; Pronova, Sandefjord, Norway) or placebo (4 g/d olive oil) for a minimum of 15 months and a maximum of 18 months (McCormick-2015, p2). Patients were randomised according to standardised procedures (computerised block randomisation) by a research pharmacist at University Hospital Southampton NHS Foundation Trust. Simple randomisation in blocks of 4, either to trial medication or placebo was used. (Scorletti-2014, p 2)
Allocation concealment (selection bias)	Low risk	Participants were block randomised by an independent clinical trials pharmacist to treatment with identical capsules by mouth of either n-3 fatty acid ethyl esters (4 g/d Omacor; Pronova, Sandefjord, Norway) or placebo (4 g/d olive oil) for a minimum of 15 months and a maximum of 18 months (McCormick-2015, p2). Only the clinical trials pharmacist was unblinded, and randomisation group allocation was concealed from all study members throughout the trial. (McCormick-2015, p 2).
Blinding of participants and personnel (performance bias)	Low risk	Paper states that only the clinical trials pharmacist was unblinded, and randomisation group allocation was concealed from all study members throughout the trial. However, the trial register record states "single blind (investigator)". Although the capsules were identical, no information provided as to their smell and taste

Blinding of outcome assessment (detection bias)	Low risk	As above
Incomplete outcome data (attrition bias)	Low risk	The ITT analysis included all patients randomised who had complete data (baseline and end-of-study measurements), regardless of whether they were later found to be ineligible, a protocol violator, given the wrong treatment allocation, or never treated) (Scorletti 2014, p 4)
Selective reporting (reporting bias)	Unclear risk	Prospectively registered September 2008, study start September 2009, end February 2017. Outcome data for cardiac function not yet published, though other cardiovascular measures reported – take as ongoing as recent end date
Attention	Low risk	Both groups had the same attention
Compliance	Low risk	Assessed by recording the returned unused capsules and quantification of erythrocyte EPA + DHA enrichment (a prespecified threshold of 2% for DHA and threshold of 0.7% for EPA enrichment). Quote: "Enrichment was highly variable in the DHA+EPA group and 5 and 6 participants in the DHA+EPA group did not reach the prespecified threshold for EPA and DHA enrichment, respectively. In the placebo group, we expected no enrichment between baseline and end of study in all participants in this group, but 3 and 4 participants reached the thresholds set for the DHA+EPA group, for EPA and DHA, respectively. One participant in the placebo group admitted to taking cod liver oil during the study and another markedly increased consumption of fish." 10 of 95 non-compliant
Other bias	Low risk	None noted

Westberg 1990 [712 713]

Methods Double blind, crossover, placebo controlled RCT (n3 EPA vs MUFA), 6 months
Summary risk of bias: Moderate or high
Aim: "effects of dietary supplementation with EPA in patients with [systemic lupus erythematosus] SLE"

Participants Individuals with a long-term diagnosis of systemic lupus erythematosus
N: 20 int., 20 control (analysed – int: 17 cont: 17)
Level of risk for CVD: Low
Male: 12% int., 12% control.
Mean age (sd): 44.2 (6.6) int.; 44.2 (6.6) cont.
Age range: 31-64 int., 31-64 cont.
Smokers: NR
Hypertension: NR
Medications taken by at least 50% of those in the control group: prednisolone (65%)
Medications taken by 20-49% of those in the control group: azathioprine (29.4%)
Medications taken by some, but less than 20% of the control group: cyclophosphamide (6%)
Location: Sweden
Ethnicity: NR

Interventions Type: supplement (capsules of fish oil or olive oil)
Comparison: EPA+DHA vs MUFA/n6 FA
Intervention: 10-15 capsules MaxEPA per day calculated as 0.2g/kg body weight (including 18.6% EPA + 12.1% DHA, 5.3% n6FA [LA/AA]; supplied by Seven Seas Healthcare Ltd, Kingston-upon-Hull, Yorkshire, England): EPA+DHA ~3.5g/d
Control: 10-15 capsules olive oil per day calculated as 0.2g/kg body weight (including 68.6% oleic acid and 12.4% n6FA; supplied by Seven Seas Healthcare Ltd, Kingston-upon-Hull, Yorkshire, England)
Compliance: NR

Duration of intervention: 6 months

Outcomes Main study outcome: Clinical and serological activity (clinical and sigmoidoscopic scores)
Dropouts: 0 int., 0 control
Available outcomes: blood pressure (ESR collected but data not provided)

Notes Capsules supplied by Seven Seas Ltd; no indication of study funding; no conflict of interest statement

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method described (numbered cards in an envelope) but not clear if this was truly random
Allocation concealment (selection bias)	Low risk	Key to randomisation numbers kept in pharmacy; code not broken until all data obtained and tabulated.
Blinding of participants and personnel (performance bias)	Unclear risk	"Identical capsules" but no information provided about attempt to mask/match smell or taste.
Blinding of outcome assessment (detection bias)	Unclear risk	Two patients said they knew which arm they were allocated to as they bit through a capsule. Physicians remained blind.
Incomplete outcome data (attrition bias)	Unclear risk	Numbers analysed were numbers who completed the trial – drop outs not included
Selective reporting (reporting bias)	Unclear risk	No study registration or protocol found
Attention	Low risk	Identical follow-up described for participants in each arm.
Compliance	Unclear risk	No compliance data provided.
Other bias	Low risk	None noted

WINS 2006 [714-723]

Methods Women's Intervention Nutrition Study (WINS)
RCT, parallel, (reduced fat with reduced PUFA vs usual diet), 60 months
Summary risk of bias: low (as diet advice trial)

Participants Women with localised resected breast cancer
N: 975 intervention, 1462 control (analysed 975 int, 1462 cont)
Level of risk for CVD: low
Male: 0% intervention, 0% control
Mean age (95% CI): 58.6 (44.4-72.8) intervention, 58.5 (43.6-73.4) control
Age range: not reported, all postmenopausal
Smokers: 49.9% intervention, 48.7% control never smokers
Hypertension: not reported
Medications taken by ≥ 50% of those in the control group: menopausal hormone therapy (65.3% intervention, 64.0% control), tamoxifen (47.7% tamoxifen alone, 38.5% tamoxifen plus chemotherapy in intervention, 47.4% and 38.0% respectively in control), all were on chemotherapy, most on radiotherapy
Medications taken by 20%-49% of those in the control group: not reported
Medications taken by some, but < 20% of the control group: not reported
Location: USA
Ethnicity: 85% white, 5% black, 4% Hispanic, 5% Asian or Pacific Islander, < 1% American Indian or unknown (no outcome data based on ethnicity)

Interventions Type: dietary advice
Comparison: reduced fat intake (with reduced PUFA) vs usual diet
Intervention: aims total fat 15%-20% E; methods 8 biweekly individual dietetic sessions plus 3-monthly contact and optional monthly group sessions, incorporating individual fat gram goals, social cognitive theory, self-monitoring, goal setting, modelling, social support and relapse prevention and management. Intervention was delivered face to face individually by trained dietitian
Control: aims minimal nutritional counselling focused on nutritional adequacy; methods one baseline dietetic session plus 3-monthly sessions

Dose aim: unclear **PUFA**
Baseline 5.4% E PUFA
Compliance by biomarkers: no fatty acid biomarkers reported, TC reported but only in a subgroup (N = 18 at 2 years) and unbalanced at baseline so not used in analyses, little change but TC fell by 6 mg/dL in intervention and increased by 0.8 mg/dL in control over 2 years
Compliance by dietary intake: assessed using unannounced phone calls over several days, 1-year data reported apart from protein and carbohydrate which were 6-month data

- Energy intake, MJ/d: intervention 7.3 (SD 1.8), control 7.7 (SD 1.9)
- Total fat intake, % E: intervention 20.3 (SD 8.1), control 29.2 (SD 7.4)
- SFA intake: intervention 6.4 (SD 0.14 (4.4)), control 9.8 (SD 0.15 (5.7))
- PUFA intake: intervention 4.5 (SD 0.09 (2.8)), control 6.4 (SD 0.10 (3.8))
- PUFA n-3 intake: not reported
- PUFA n-6 intake: not reported
- Trans fat intake: not reported
- MUFA intake: intervention 7.6 (SD 0.14 (4.4)), control 11.5 (SD 0.16 (6.1))
- CHO intake: intervention 60.8 (SD 19.6), control 50.5 (SD 14.8)
- Sugars intake: not reported
- Protein intake, % E: intervention 19.1 (SD 5.2), control 17.6 (SD 4.1)
- Alcohol intake: intervention 5% E (SD 6), control 4% E (SD 6)

Compliance, other methods: not reported
Inclusion basis: no intention to increase total PUFA stated. Achieved total PUFA reduction of 1.9% E in intervention compared to control at 1 year, > 10% higher than baseline 5.4% E from total PUFA
PUFA dose: -1.9% E PUFA
Duration of intervention: 60 months

Outcomes Main trial outcome: dietary fat intake, TC, weight and waist
Dropouts: 45 lost to follow-up, 170 discontinued intervention, 66 lost and 106 discontinued control
Available outcomes: all-cause mortality, cancer diagnoses (including recurrences), new breast cancer diagnoses, weight, BMI (TC, TG, HDL, insulin provided in tiny subgroup - 9 participants in each group at 2 years - and unbalanced at baseline, not useable)
Author contact: limited information received

Notes Trial funding: National Cancer Institute, Breast Cancer Research Foundation, American Institute for Cancer Research
*SDs appear incorrect, probably SEs?
NOTE: control arm is the arm higher in PUFA, intervention arm lower in PUFA

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random stratified permuted block design, carried out at the statistical co-ordinating centre of WINS
Allocation concealment (selection bias)	Low risk	Random stratified permuted block design, carried out at the statistical co-ordinating centre of WINS
Blinding of participants and personnel (performance bias)	High risk	Not for dietary advice and participants
Blinding of outcome assessment (detection bias)	Low risk	All outcomes assessed by the blinded outcome committee
Incomplete outcome data (attrition bias)	Low risk	All assessed
Selective reporting (reporting bias)	Low risk	Outcomes stated in protocol all appear to have been published
Attention	High risk	Intervention group appear to have received more time and attention
Compliance	Unclear risk	No fatty acid biomarkers reported, TC reported but only in a subgroup (n = 18 at 2 years) and unbalanced at baseline so not used in analyses, little change but TC fell by 6 mg/dL in intervention and increased by 0.8 mg/dL in control over 2 years (note, control group should be higher in PUFA in this trial). Overall changes not reported

Other bias	Low risk	None noted

Witte 2012 – NCT00996229 [724-726]

Methods RCT, parallel, (n3 EPA+DHA vs n6 LA), 6 months
Summary risk of bias: Moderate or high

Participants Healthy older adults (aged 50 to 80 years)
N: 40 int., 40 control. (analysed, int: 32 cont: 33)
Level of risk for CVD: low
Male: 53% int., 55% control.
Mean age (sd): 65 (6.3) int., 62.9 (6.8) control
Age range: int 51-75 yrs, cont 50-75 yrs
Smokers: NR
Hypertension: NR
Medications taken by at least 50% of those in the control group: NR
Medications taken by 20-49% of those in the control group: NR
Medications taken by some, but less than 20% of the control group: NR
Location: Germany
Ethnicity: NR

Interventions Type: supplement
Comparison: fish oil capsules vs sunflower oil capsules
Intervention: fish oil capsules, 4 capsules/d (including 1.32g/d EPA plus 0.88g/d DHA, provided by Via Vitamine), and advised not to change usual dietary habits: EPA+DHA 2.2g/d
Control: sunflower oil capsules, 4 capsules/d (provided by Via Vitamine), identical in shape and colour, and advised not to change usual dietary habits
Compliance: compliance assessed by capsule counts, questionnaire, and omega 3 index in erythrocyte membrane, capsule count suggested missed capsules were <5%
Duration of intervention: 6 months

Outcomes Main study outcome: brain function
Dropouts: 7 of 40 int., 6 of 40 control
Available outcomes: glucose, HbA1c, hsCRP, TNF alpha, IL-6, BMI, TG, cognition including executive function, memory, sensorimotor speed, attention and mood (there were no deaths in either arm, weight, % body fat, insulin and serum total cholesterol were too different at baseline to use, BP data not used as only 6 mo, MRI imaging data, carotid intima media thickness not used)

Notes There was a 3rd arm to this study, testing calorie restriction - we have not used these data.
Study funding: Deutsche Forschungsgemeinschaft, Else-Kroner Fresenius Stiftung, Bundesministerium fur Bildung und Forschung. Capsules provided by Via Vitamine.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"block randomisation"
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias)	Unclear risk	"subjects and investigators were blinded to the treatment group" and capsules described as identical in shape and colour but no information provided as to taste or smell
Blinding of outcome assessment (detection bias)	Low risk	As above
Incomplete outcome data (attrition bias)	Low risk	Less than 20% lost to follow up, loss similar in each arm and described
Selective reporting (reporting bias)	Low risk	Trials register entry Oct 2009, data collection started Nov 2009. All outcomes mentioned in trials register, and many more, reported in publications.
Attention	Low risk	No suggestion of difference between arms

Compliance	Low risk	Appears to be a statistically significant difference between arms in omega 3 index at study end
Other bias	Low risk	None noted

Wright 2008 [727]

Methods RCT, parallel, (n3 EPA+DHA vs MUFA), 6 months
Summary risk of bias: Moderate or high
Aim: "To determine the clinical effect of dietary supplementation with low-dose n3-polyunsaturated fatty acids on disease activity and endothelial function in patients with systemic lupus erythematosus"

Participants People with systemic lupus erythematosus (SLE)
N: 30 int., 30 control. (analysed, int: 27 cont: 29)
Level of risk for CVD: low
Male: 3% int., 10% control.
Mean age (sd) yrs: 48.5 (9.1) int., 47.6 (9.6) control
Age range: NR
Smokers: 17% int., 13% control
Hypertension: NR
Medications taken by at least 50% of those in the control group: hydroxychloroquine or chloroquine (63%)
Medications taken by 20-49% of those in the control group: prednisolone (33%), NSAIDs (27%), aspirin (27%)
Medications taken by some, but less than 20% of the control group: NR
Location: UK
Ethnicity: NR

Interventions Type: supplement
Comparison: EPA+DHA vs MUFA
Intervention: 4 capsules/d Omacor (Solvay, 1.8g/d EPA plus 1.2g/d DHA): EPA+DHA 3.0g/d
Control: 4 identical capsules/d olive oil (MUFA, exact content unclear)
Compliance: assessed by capsule return and change in platelet membrane fatty acid composition, EPA and DHA composition was significantly higher at 24 weeks than baseline in the intervention group, but no data comparing intervention with control groups (control group stated not to have altered significantly).
Duration of intervention: 6 months

Outcomes Main study outcome: disease activity (of SLE) and endothelial function
Dropouts: 3 of 30 int., 1 of 30 control
Available outcomes: CRP & ESR measured and reported but too different at baseline to use in meta-analyses (also BP and lipids but only at 6 months, homocysteine, heart rate, SLE activity (SLAM-R and BILAG), FMD, 8-isoprostanes which were not used).

Notes Study funding: Wellcome Trust, Lupus UK
Author contact: none yet

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was off-site by an independent body (Victoria Pharmaceuticals)
Allocation concealment (selection bias)	Low risk	As above
Blinding of participants and personnel (performance bias)	Unclear risk	Described as double blind, capsules appeared identical. However no information provided as to taste or smell.
Blinding of outcome assessment (detection bias)	Low risk	Paper states "all clinical assessments and vascular measures were performed by the same researcher (SW) who was blinded to study medication", and our outcomes were measured in a laboratory.
Incomplete outcome data (attrition bias)	Low risk	Of 60 randomised 4 failed to complete (7%) over 6 months, reasons described (1 dropout from control

		due to personal issues, 3 from intervention due to gastrointestinal disturbance).
Selective reporting (reporting bias)	Unclear risk	No protocol or trials registry entry found.
Attention	Low risk	Appeared similar with assessments at baseline, weeks 12 and 24.
Compliance	Unclear risk	Of the 56 who completed the study 38% took all of their capsules, and the remaining participants took more than 90%. Platelet membrane fatty acid composition EPA and DHA were significantly higher at 24 weeks than baseline in the intervention group, but no data comparing intervention with control groups (control group stated not to have altered significantly).
Other bias	Low risk	None noted

Zhang 2017 – ChiCTR-IOR-15006058 [728]

Methods	RCT, parallel, (n-3 DHA vs n-6 LA), 12 months Summary risk of bias: moderate to high
Participants	Otherwise healthy elderly people with mild cognitive impairment. N: 120 intervention, 120 control (analysed, intervention: 110 control: 109) Level of risk for CVD: low Men: 35.8% intervention, 34.2% control Mean age in years (SD): 74.5 (2.65) intervention, 74.6 (3.31) control Age range: eligibility criteria were age 65-85 years at trial start Smokers: 59.17% intervention, 61.67% control Hypertension: 9.17% intervention, 7.50% control Medications taken by at least 50% of those in the control group: not reported Medications taken by 20%-49% of those in the control group: not reported Medications taken by some, but less than 20% of the control group: not reported Location: China Ethnicity: assumed Chinese
Interventions	Type: supplement (capsule) Comparison: DHA vs corn oil (n-6) Intervention: 1 capsule twice a day, with meals, including 2 g algal DHA (45-55% DHA by weight). Martek Biosciences, Columbia, MD. Dose: ~1 g/d DHA Control: corn oil, orange-flavoured and orange colour to protect the study blind Compliance: participants were asked to return any remaining tablets. Compliance was defined as a ratio (actually taken/should have taken). Achieved 97% for intervention, 95% for control. Serum levels of DHA also measured, DHA at 6 months barely higher in intervention than in controls Duration of intervention: 12 months
Outcomes	Main study outcome: cognitive function and hippocampal volume Dropouts: 10 intervention, 11 control Available outcomes: mortality, cognitive outcomes and cerebral volume measurements Response to contact: no reply to date
Notes	Study funding: Chinese Nutrition Society (CNS) Nutrition Research Foundation- DSM Research Fund

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated, also statistics analyst ignorant to this study used random number table
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding of participants and personnel (performance bias)	Low risk	Placebo capsules … identical in appearance. All capsules were orange-flavoured and orange colour to protect the study blind. Packaged into identical pots,

		each containing 180 capsules, and labelled by staff who were not involved in the study. A blinding key linked each participant to his or her assigned treatment. This key was kept by an investigator not involved in any data collection or analyses, in a secure electronic file. The code was revealed at the completion of the trial following analyses of the main study aims.
Blinding of outcome assessment (detection bias)	Low risk	All project staff were unaware of group assignments until the completion of the trial and after data analysis
Incomplete outcome data (attrition bias)	Unclear risk	They did not describe how they imputed missing data (lost contact with patients, but called this an ITT analysis). Overall well matched and not high attrition.
Selective reporting (reporting bias)	Low risk	Registered trial prospectively. Outcomes match protocol
Attention	Low risk	"Adherence was encouraged and monitored throughout the trial by telephone assessment at 15 time points, and by blood assay at baseline" 6 months and 12 months. This and assessments were described as same for both arms.
Compliance	Unclear risk	Quote: "participants were requested to return any remaining tablets in order to measure compliance, together with the replenishment of capsules for the following month." Compliance … defined "as a ratio = actually taken/should have taken". "Adherence was encouraged and monitored throughout the trial by telephone assessment at 15 time points, and by blood assay at baseline" 6 months and 12 months On compliance tree, leads to "No, because no P values were supplied" therefore risk of compliance bias unclear
Other bias	Unclear risk	Although the register says single blind, the publication very clearly describes a double-blind RCT

Zheng 2016 – NCT01857167 [729-731]

Methods RCT, parallel, (n3 EPA+DHA vs n3 ALA vs n6 LA), 6 months
Summary risk of bias: Moderate or high

Participants People with type 2 diabetes mellitus
N: 63 fish oil int., 61 flaxseed oil int, 61 control. (analysed, 58 fish oil int., 53 flaxseed oil int, 55 control)
Level of risk for CVD: moderate
Male: 33% fish oil int., 60% flaxseed oil int, 48% control
Mean age (sd) yrs: 59.7 (8.8) fish oil int., 59.7 (11.1) flaxseed oil int, 59.1 (10.0) control
Age range: men 35-80 years, women menopause to 80 years (inclusion criteria)
Smokers: NR
Hypertension: NR
Medications taken by at least 50% of those in the control group: diabetic medication
Medications taken by 20-49% of those in the control group: NR
Medications taken by some, but less than 20% of the control group: NR
Location: China
Ethnicity: NR

Interventions Type: supplement
Comparison: fish oil (LCn3) vs flaxseed oil (ALA) vs corn oil (n6)
Fish oil Intervention: 4 capsules/d fish oil (1.2g/d EPA, 0.8g/d DHA), Neptunus Bioengineering: EPA+DHA 2.0g/d
Flaxseed oil Intervention: 4 capsules/d flaxseed oil (2.5g/d ALA), Neptunus Bioengineering: ALA 2.5g/d
Control: 4 capsules/d corn oil (2.1g/d LA), Neptunus Bioengineering
Compliance: evaluated by measurement of erythrocyte phospholipid fatty acid compositions at baseline and end, counting empty bottles returned to study centres at days 90 and 180, and monthly

phone contact. Sig diff of EPA and DHA between fish oil and corn oil groups at 6 months, and of ALA between flaxseed oil and corn oil at 6 months.
Duration of intervention: 6 months

Outcomes Main study outcome: insulin resistance
Dropouts: 5 of 63 fish oil int., 8 of 61 flaxseed oil int, 6 of 61 control
Available outcomes: glucose, insulin, HbA1c, HOMA, lipids (some unbalanced at baseline so not used, liver and renal function markers not used)

Notes Study funding: National Basic Research Program of China, National Natural Science Foundation of China, Ph.D. Programs Foundation of Ministry of Education of China, Cambridge Initiative – Nutrition.
Author contact: not yet

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**"**randomly allocated to one of the three treatments by computer-generated random numbers with a block size of six, allocation sequence generated by J.S.Z."
Allocation concealment (selection bias)	Unclear risk	"Doctors/nurses at each study centre enrolled and assigned participants to the intervention groups"
Blinding of participants and personnel (performance bias)	Unclear risk	Capsules had "identical appearance", standardised to 1g each, study reported as **"**double blind". "All the patients were given four bottles of capsules at baseline, and given another four bottles at 90 days"… "None of the participants or the nurses/physicians in the study centers knew the oil types during the intervention."… "capsules were kept in white bottles (90 capsules/bottle), which were labelled as Oil A, Oil B, and Oil C for the three types of capsules." No attempt mentioned to mask flavour or smell of fish oil.
Blinding of outcome assessment (detection bias)	Low risk	"None of the participants or the nurses/physicians in the study centers knew the oil types during the intervention" and outcomes biochemical.
Incomplete outcome data (attrition bias)	Unclear risk	Clear about numbers and time of dropout, but no reasons. Attrition <20% each arm.
Selective reporting (reporting bias)	Low risk	Only insulin resistance mentioned in trials register entry (registered before participant recruitment), but many other outcomes reported.
Attention	Low risk	Appears similar across groups
Compliance	Low risk	Sig diff of EPA and DHA between fish oil and corn oil groups at 6 months, and of ALA between flaxseed oil and corn oil at 6 months.
Other bias	Low risk	None noted.

Özaydin 2011 [732]

Methods RCT, parallel, (n-3 fish oil + amiodarone vs amiodarone), 12 months
Summary risk of bias: moderate or high

Participants Patients with persistent atrial fibrillation (AF) referred to cardioversion
N: 23 intervention, 24 control
Level of risk for CVD: high
Men: 47.8% intervention, 37.5% control
Mean age in years (SD): 62 (12) intervention, 61 (11) control
Age range: 37-81
Smokers: not reported
Hypertension: 56.5% intervention, 50% control
Medications taken by at least 50% of those in the control group: all patients received amiodarone (an antiarrhythmic medication)

	Medications taken by 20%-49% of those in the control group: beta-blockers, statins, ACE inhibitors and ARBs Medications taken by some, but less than 20% of the control group: calcium antagonists Location: Turkey Ethnicity: not reported
Interventions	Type: supplement (capsule) Comparison: LCn3 vs nil Intervention: 2 g/d n-3 PUFA (Marincap, Kocak, Turkey). 4 × 500 mg capsules providing EPA 18% (360 mg/d); DHA 12% (240 mg/d). Dose: 0.6 g/d EPA + DHA Control: no placebo. Amiodarone was given to both groups. Compliance: no details Duration of intervention: 12 months or AF recurrence
Outcomes	Main study outcome: AF recurrence(endpoint) Dropouts: no details Available outcomes: all-cause mortality (nil death), stroke, TIA, AF recurrence (hyperthyroidism diagnosis, hospitalisation) Response to contact: not yet attempted
Notes	Study funding: unclear

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details
Allocation concealment (selection bias)	Unclear risk	Quote: "randomised"; no further details
Blinding of participants and personnel (performance bias)	High risk	No placebo
Blinding of outcome assessment (detection bias)	Unclear risk	No details
Incomplete outcome data (attrition bias)	Low risk	All were accounted for
Selective reporting (reporting bias)	Unclear risk	No trial registry entry or protocol found
Attention	Low risk	Both groups seem to have the same care
Compliance	Unclear risk	No information
Other bias	Low risk	None noted

Footnotes

ACE: angiotensin-converting enzyme; **ADAS**: Alzheimer's Disease Assessment Scale; **ADL**: activities of daily living; **AF**: atrial fibrillation; **AHA**: American Heart Association; **BMI**: body mass index; **ALT**: alanine transaminase; **ARB**: angiotensin-receptor blocker; **BMD**: bone mineral density; **BMI**: body mass index; **BP**: blood pressure; **CABG**: coronary artery bypass grafting; **CDAI**: Clinical Disease Activity Index; **CHD**: coronary heart disease; **CHO**: carbohydrate; **CV**: cardiovascular; **CRP**: C-reactive protein; **CVD**: cardiovascular disease; **DAS**: Disease Activity Score; **DBP**: diastolic blood pressure; **DHA**: docosahexaenoic acid; **DM**: diabetes mellitus; **DMARD**: disease-modifying anti-rheumatic drugs; **DPA**: docosapentaenoic acid; **E**: dietary energy; **ECG**: electrocardiogram; **EDSS**: Expanded Disability Status Scale; **EPA**: eicosapentaenoic acid; **ESR**: erythrocyte sedimentation rate; **FA**: fatty acid; **FFQ**: food frequency questionnaire; **FH**: family history; **FMD**: flow-mediated dilatation; **GFR**: glomerular filtration rate; **GLA**: gamma linolenic acid; **HbA1c**: glycated haemoglobin; **HCQ**: hydroxychloroquine; **HDL**: high-density lipoprotein; **H/O**: personal history of; **HOMA-IR**: homeostatic model assessment of insulin resistance; **HRT**: hormone replacement therapy; **HT**: hypertension; **IBD**: inflammatory bowel disease; **IADL**: instrumental activities of daily living; **ICAM-1**: intercellular adhesion molecule 1; **IL**: interleukin; **IMT**: immune-mediated thrombocytopenia; **IQR**: interquartile range; **LCn3**: long-chain omega-3 fatty acids; **LDL**: low-density lipoprotein; **MD**: mean difference; **MDA**: malondialdehyde; **MI**: myocardial infarction; **MMSE**: Mini–Mental State Examination; **MS**: multiple sclerosis; **MUFA**: mono-unsaturated fatty acids; **MXT**: methotrexate; **n-3**: omega-3; **NASH**: non-alcoholic steatohepatitis; **NSAID**: non-steroidal anti-inflammatory drug; **PAI1**: plasminogen activator inhibitor-1; **PI**: principal investigator; **PUFA**: poly-unsaturated fatty acids; **PTCA**: percutaneous transluminal coronary angioplasty; **P/S**: poly-unsaturated/saturated fat ratio; **QoL**: quality of life; **QUICKI**: quantitative insulin sensitivity check index; **RA**: rheumatoid arthritis; **RCT**: randomised controlled trial; **SBP**: systolic blood pressure; **SD**: standard deviation; **SE**: standard error; **RCT**: randomised controlled trial; **SFA**:

saturated fatty acids; **SSZ**: sulfasalazine; **TAG**: triacylglycerol; **TG**: serum triglycerides; **TIA**: transient ischaemic attack; **TNF**: tumour necrosis factor; **VCAM-1**: vascular cell adhesion molecule 1; **WHO**: World Health Organization.

References

1. Quinn J, Shinto L, Yurko-Mauro K, et al. Biomarkers of fattyacid oxidation in a clinical trial of dha for Alzheimer's disease. *Alzheimer's dement* 2012;1):585.
2. Quinn JF, Raman R, Thomas RG, et al. Docosahexaenoic acid supplementation and cognitive decline in Alzheimer disease: a randomized trial. *Jama* 2010;304(17):1903-11.
3. Quinn JF, Raman R, Thomas R, et al. Omega 3 fatty acids and alzheimer's disease: trial design and baseline study population characteristics in a clinical trial of docosahexaenoic acid for alzheimer's disease. *Alzheimer's & dementia : the journal of the Alzheimer's Association* 2008;4(Suppl 1):T773.
4. Nigam A, Talajic M, Roy D, et al. Multicentre trial of fish oil for the reduction of atrial fibrillation recurrence, inflammation and oxidative stress: the atrial fibrillation fish oil research study. *Can J Cardiol* 2013;1:S383-S83.
5. Nigam A, Talajic M, Roy D, et al. Fish oil for the reduction of atrial fibrillation recurrence, inflammation, and oxidative stress. *J Am Coll Cardiol* 2014;64(14):1441-48.
6. Ahn J, Park SK, Park TS, et al. Effect of n-3 polyunsaturated fatty acids on regression of coronary atherosclerosis in statin treated patients undergoing percutaneous coronary intervention. *Korean Circulation Journal* 2016;46(4):481-89.
7. Almallah YZ, El-Tahir A, Heys SD, et al. Distal procto-colitis and n-3 polyunsaturated fatty acids: the mechanism(s) of natural cytotoxicity inhibition. *Eur J Clin Invest* 2000;30(1):58-65.
8. Almallah YZ, Ewen SW, El Tahir A, et al. Distal proctocolitis and n-3 polyunsaturated fatty acids (n-3 PUFAs): the mucosal effect in situ. *J Clin Immunol* 2000;20(1):68-76.
9. Almallah YZ, Ewen SW, Mowat NA, et al. Immunohistological modulation after nutritional supplementation with omega-3 essential fatty acids in patients with inflammatory bowel disease [abstract]. *Br J Surg* 1998;85:690-91.
10. Almallah YZ, O'Hanrahan T, Richardson S, et al. Eicosapentaenoic acid and docosahexaenoic acid in the treatment of patients with distal procto-colitis [abstract]. *Br J Surg* 1996;83 Suppl 1:2-2.
11. Almallah YZ, O'Hanrahan T, Richardson S, et al. Inhibition of natural cytotoxicity with eicosapentaenoic and docosahexaenoic acids: possible mechanisms [abstract]. *Br J Surg* 1996;83:685-85.
12. Almallah YZ, Richardson S, O'Hanrahan T, et al. Distal procto-colitis, natural cytotoxicity, and essential fatty acids. *Am J Gastroenterol* 1998;93(5):804-09.
13. Brouwer IA, Geleijnse JM, Klaasen VM, et al. Effect of alpha linolenic acid supplementation on serum prostate specific antigen (PSA): results from the alpha omega trial. *PLoS ONE* 2013;8(12):e81519-e19.
14. Eussen SR, Geleijnse JM, Giltay EJ, et al. Effects of n-3 fatty acids on major cardiovascular events in statin users and non-users with a history of myocardial infarction. *Eur Heart J* 2012;33(13):1582-88.
15. Geleijnse J, Giltay E, Kromhout D. Effects of n-3 fattyacids on cognitive decline: A randomized double-blind, placebo-controlled trial in stable myocardial infarction patients. *Alzheimer's dement* 2011;1):S512.
16. Geleijnse JM, Giltay EJ, Kromhout D. Effects of n-3 fatty acids on cognitive decline: a randomized, double-blind, placebo-controlled trial in stable myocardial infarction patients. *Alzheimer's dement* 2012;8(4):278-87.
17. Geleijnse JM, Giltay EJ, Schouten EG, et al. Effect of low doses of n-3 fatty acids on cardiovascular diseases in 4,837 post-myocardial infarction patients: Design and baseline characteristics of the Alpha Omega Trial. *Am Heart J* 2010;159(4):539-46.
18. Giltay EJ, Geleijnse JM, Heijboer AC, et al. No effects of n-3 fatty acid supplementation on serum total testosterone levels in older men: the Alpha Omega Trial. *Int J Androl* 2012;35(5):680-87.
19. Giltay EJ, Geleijnse JM, Kromhout D. Effects of n-3 fatty acids on depressive symptoms and dispositional optimism after myocardial infarction. *Am J Clin Nutr* 2011;94(6):1442-50.
20. Hoogeveen E, Gemen E, Geleijnse M, et al. Effects of N-3 fatty acids on decline of kidney function after myocardial infarction: Alpha omega trial. *Nephrol Dial Transplant* 2012;27:ii64.
21. Hoogeveen EK, Geleijnse JM, Kromhout D, et al. No effect of n-3 fatty acids on high-sensitivity C-reactive protein after myocardial infarction: the Alpha Omega Trial. *European Journal of Preventive Cardiology* 2014;21(11):1429-36.
22. Hoogeveen EK, Geleijnse JM, Kromhout D, et al. Effect of omega-3 fatty acids on kidney function after myocardial infarction: the Alpha Omega Trial. *Clin J Am Soc Nephrol* 2014;9(10):1676-83.
23. Hoogeveen EK, Geleijnse JM, Kromhout D, et al. No effect of n-3 fatty acids supplementation on NT-proBNP after myocardial infarction: The Alpha Omega Trial. *European Journal of Preventive Cardiology* 2015;22(5):648-55.

24. Kromhout D, Geleijnse JM, de Goede J, et al. n-3 fatty acids, ventricular arrhythmia-related events, and fatal myocardial infarction in postmyocardial infarction patients with diabetes. *Diabetes Care* 2011;34(12):2515-20.
25. Kromhout D, Giltay EJ, Geleijnse JM. N-3 fatty acids and cardiovascular events after myocardial infarction. *N Engl J Med* 2010;363(18):2015-26.
26. Van De Rest O, de Goede J, Sytsma F, et al. Association of n-3 long-chain PUFA and fish intake with depressive symptoms and low dispositional optimism in older subjects with a history of myocardial infarction. *Br J Nutr* 2010;103(9):1381-87.
27. Kromhout D. Alpha-Omega Trial Research Plan https://www.alphaomegacohort.org/trial/2008 [accessed 27/01/2019 2019.
28. Araujo CA, Moraes-Fontes MF, Santos L, et al. Omega-3 fatty acids and Mediterranean diet as complimentary therapies for rheumatoid arthritis. *Arthritis and Rheumatology* 2014;66:S1050.
29. Age-Related Eye Disease S. Lutein + zeaxanthin and omega-3 fatty acids for age-related macular degeneration: the Age-Related Eye Disease Study 2 (AREDS2) randomized clinical trial.[Erratum appears in JAMA. 2013 Jul 10;310(2):208]. *Jama* 2013;309(19):2005-15.
30. Age-Related Eye Disease Study, Chew EY, Clemons TE, et al. Secondary analyses of the effects of lutein/zeaxanthin on age-related macular degeneration progression: AREDS2 report No. 3. *JAMA Ophthalmology* 2014;132(2):142-49.
31. Age-Related Eye Disease Study, Chew EY, SanGiovanni JP, et al. Lutein/zeaxanthin for the treatment of age-related cataract: AREDS2 randomized trial report no. 4. *JAMA Ophthalmology* 2013;131(7):843-50.
32. AREDS Research Group, Chew EY, Clemons T, et al. The Age-Related Eye Disease Study 2 (AREDS2): study design and baseline characteristics (AREDS2 report number 1). *Ophthalmology* 2012;119(11):2282-89.
33. Bonds DE, Harrington M, Worrall BB, et al. Effect of long-chain omega-3 fatty acids and lutein + zeaxanthin supplements on cardiovascular outcomes: results of the Age-Related Eye Disease Study 2 (AREDS2) randomized clinical trial. *JAMA Intern Med* 2014;174(5):763-71.
34. Chew EY, Clemons TE, Agron E, et al. Effect of Omega-3 Fatty Acids, Lutein/Zeaxanthin, or Other Nutrient Supplementation on Cognitive Function: The AREDS2 Randomized Clinical Trial. *Jama* 2015;314(8):791-801.
35. Group A-REDSR. Age-related Eye Disease Study 2 Protocol https://web.emmes.com/study/areds22010 [accessed 27/01/2019 2019.
36. Bowman L, Aung T, Haynes R, et al. ASCEND: Design and baseline characteristics of a large randomised trial in diabetes. *Diabetes* 2012;61:A556-A57.
37. ASCEND Study Collaborative Group. Effects of n−3 Fatty Acid Supplements in Diabetes Mellitus. *N Engl J Med* 2018;379(16):1540-50. doi: 10.1056/NEJMoa1804989
38. Baldassarre D, Amato M, Eligini S, et al. Effect of n-3 fatty acids on carotid atherosclerosis and haemostasis in patients with combined hyperlipoproteinemia: a double-blind pilot study in primary prevention. *Ann Med* 2006;38(5):367-75.
39. Baleztena Gurrea J, Ruiz-Canela M, Pardo M, et al. Utility of heavy food supplement in omega-3 fatty acids in the prevention of dementia, in relation to the basal nutritional level, in people of advanced age: randomized multicenter study. *Revista Española de Geriatría y Gerontología* 2015;50:1-49.
40. Bes-Rastrollo M, Baleztena J, Aguirre I, et al. Utility of a rich food supplement Omega-3 fatty acids in the prevention of dementia, in relation to baseline nutritional level, in people with advanced age: multicentre randomised study. *Nutrición Clínica en Medicina* 2015;9(1):38-38.
41. Balfego M, Canivell S, Hanzu F, et al. Effects of sardine-enriched diet on metabolic control, inflammation and gut microbiota in drug-naive patients wtih type 2 diabetes: a pilot randomized trial. *Lipids Health Dis* 2016;15:78. doi: DOI 10.1186/s12944-DOI 10.1016-0245-0
42. Bassey EJ, Littlewood JJ, Rothwell MC, et al. Lack of effect of supplementation with essential fatty acids on bone mineral density in healthy pre- and postmenopausal women: two randomized controlled trials of Efacal v. calcium alone. *Br J Nutr* 2000;83(6):629-35.
43. Bates D, Fawcett PR, Shaw DA, et al. Trial of polyunsaturated fatty acids in non-relapsing multiple sclerosis. *Br Med J* 1977;2(6092):932-33.
44. Dworkin RH, Bates D, Millar JH, et al. Linoleic acid and multiple sclerosis: a reanalysis of three double-blind trials. *Neurology* 1984;34(11):1441-45.
45. Bates D, Fawcett PR, Shaw DA, et al. Polyunsaturated fatty acids in treatment of acute remitting multiple sclerosis. *Br Med J* 1978;2(6149):1390-91.

46. Bates D, Fawcett PR, Shaw DA, et al. Polunsaturated fatty acids in multiple sclerosis. *Br Med J* 1979;1(6164):683-83.
47. Bates D, Cartlidge NE, French JM, et al. A double-blind controlled trial of long chain n-3 polyunsaturated fatty acids in the treatment of multiple sclerosis. *J Neurol Neurosurg Psychiatry* 1989;52(1):18-22.
48. Bates D, Cartlidge NEF, French JM. Results of a trial of N-3 polyunsaturated fatty acids in the treatment of multiple sclerosis [abstract]. *Ir J Med Sci* 1988;157(8):277.
49. Baxheinrich A, Stratmann B, Lee-Barkey Y, et al. Effects of a rapeseed oil-enriched hypoenergetic diet with a high content of alpha-linolenic acid on body weight and cardiovascular risk profile in patients with the metabolic syndrome. *Br J Nutr* 2012;108:682-91.
50. Belch JJ, Ansell D, Madhok R, et al. Effects of altering dietary essential fatty acids on requirements for non-steroidal anti-inflammatory drugs in patients with rheumatoid arthritis: a double blind placebo controlled study. *Ann Rheum Dis* 1988;47(2):96-104.
51. Belluzzi, A, Brignola, et al. Effect of an enteric-coated fish-oil preparation on relapses in Crohn's Disease. *N Engl J Med* 1996;334(24):1557-60.
52. Belluzzi A, Campieri M, Belloli C, et al. A new enteric coated preparation of omega-3 fatty acids for preventing post-surgical recurrence in Crohn's disease. *Gastroenterology* 1997;112(4 (AGA Abstracts)):A930.
53. Berbert AA, Kondo, Crm, et al. Supplementation of fish oil and olive oil in patients with rheumatoid arthritis. *Nutrition* 2005;21:131-36.
54. Berson EL, Rosner B, Sandberg MA, et al. Clinical trial of docosahexaenoic acid in patients with retinitis pigmentosa receiving vitamin A treatment. *Arch Ophthalmol* 2004;122(9):1297-305.
55. Berson EL, Rosner B, Sandberg MA, et al. Further evaluation of docosahexaenoic acid in patients with retinitis pigmentosa receiving vitamin A treatment: subgroup analyses. *Arch Ophthalmol* 2004;122(9):1306-14.
56. Black HS, Herd JA, Goldberg LH, et al. Effect of a low-fat diet on the incidence of actinic keratosis. *N Engl J Med* 1994;330(18):1272-75.
57. Black HS, Thornby JI, Wolf-Je J, et al. Evidence that a low-fat diet reduces the occurrence of non-melanoma skin cancer. *Int J Cancer* 1995;62(2):165-69.
58. Jaax S, Scott LW, Wolf-Je J, et al. General guidelines for a low-fat diet effective in the management and prevention of nonmelanoma skin cancer. *Nutr Cancer* 1997;27(2):150-56.
59. Bo Y, Zhang X, Wang Y, et al. The n-3 Polyunsaturated Fatty Acids Supplementation Improved the Cognitive Function in the Chinese Elderly with Mild Cognitive Impairment: A Double-Blind Randomized Controlled Trial. *Nutrients* 2017;9(1):E54-E54.
60. Boespflug EL, McNamara RK, Eliassen JC, et al. Fish Oil Supplementation Increases Event-Related Posterior Cingulate Activation in Older Adults with Subjective Memory Impairment. *J Nutr Health Aging* 2016;20(2):161-69.
61. Bonnema SJ, Jespersen LT, Marving J, et al. Supplementation with olive oil rather than fish oil increases small arterial compliance in diabetic patients. *Diabet Nutr Metab* 1995;8(2):81-87.
62. Brox J, Olaussen K, Osterud B, et al. A long-term seal- and cod-liver-oil supplementation in hypercholesterolemic subjects. *Lipids* 2001;36(1):7-13.
63. Brzeski M, Madhok R, Capell HA. Evening primrose oil in patients with rheumatoid arthritis and side-effects of non-steroidal anti-inflammatory drugs. *Br J Rheumatol* 1991;30(5):370-72.
64. Caldwell SH, Argo CK, Henry TD, et al. Dissociated histological and metabolic effects of omega-3 (3000 mg/d) versus placebo with both exercise and diet in a double-blind randomized controlled trial of NASH. *J Hepatol* 2011;54:S8.
65. Argo CK, Northup PG, Jayakumar S, et al. Serological markers of cytoskeletal injury and insulin metabolism collectively predict histological activity in NASH. *Hepatology* 2011;54:1133A.
66. Argo CK, Patrie JT, Lackner C, et al. Effects of n-3 fish oil on metabolic and histological parameters in NASH: a double-blind, randomized, placebo-controlled trial. *J Hepatol* 2015;62(1):190-97.
67. Moulder G, Smith EZ, Caldwell SH, et al. RBC lipid composition is favorably altered in NASH patients treated with omega-3 fish oil versus placebo. *Hepatology* 2013;1):499A.
68. Chiu CC, Su KP, Cheng TC, et al. The effects of omega-3 fatty acids monotherapy in Alzheimer's disease and mild cognitive impairment: a preliminary randomized double-blind placebo-controlled study. *Prog Neuropsychopharmacol Biol Psychiatry* 2008;32(6):1538-44.
69. Clark LF, Thivierge MC, Kidd CA, et al. Fish oil supplemented for 9 months does not improve glycaemic control or insulin sensitivity in subjects with impaired glucose regulation: a parallel randomised controlled trial. *Br J Nutr* 2016;115(1):75-86.

70. Clark LF, Thivierge M, McGeoch SC, et al. Long term high dose fish oil supplementation does not alter glucose disposal in older subjects with impaired glucose regulation. *Diabetologia* 2011;54:S137.
71. Connor WE, Prince MJ, Ullmann D, et al. The hypotriglyceridemic effect of fish oil in adult-onset diabetes without adverse glucose control. *Ann N Y Acad Sci* 1993;683:337-40.
72. Ullmann D, Prince MJ, Riddle M, et al. The effects of dietary fish oil versus olive oil in diabetic patients [abstract]. *Arteriosclerosis* 1990;10:881a.
73. Darghosian L, Free M, Li J, et al. Effect of omega-three polyunsaturated fatty acids on inflammation, oxidative stress, and recurrence of atrial fibrillation. *Am J Cardiol* 2015;115(2):196-201.
74. Burr ML, Fehily AM. Fatty fish and heart disease: a randomized controlled trial. *World Rev Nutr Diet* 1991;66:306-12.
75. Burr ML, Fehily AM. Fish and the heart [letter]. *Lancet* 1989;ii:1451-52.
76. Burr ML, Fehily AM, Gilbert JF, et al. Effects of changes in fat, fish, and fibre intakes on death and myocardial reinfarction: diet and reinfarction trial (DART). *Lancet* 1989;2(8666):757-61.
77. Burr ML, Fehily AM, Rogers S, et al. Diet and reinfarction trial (DART): design, recruitment, and compliance. *Eur Heart J* 1989;10(6):558-67.
78. Burr ML, Holliday RM, Fehily AM, et al. Haematological prognostic indices after myocardial infarction: evidence from the diet and reinfarction trial (DART). *Eur Heart J* 1992;13(2):166-70.
79. Fehily AM, Vaughan-Williams E, Shiels K, et al. The effect of dietary advice on nutrient intakes: Evidence from the diet and reinfarction trial (DART). *J Hum Nutr Diet* 1989;2(4):225-35.
80. Fehily AM, Vaughan-Williams E, Shiels K, et al. Factors influencing compliance with dietary advice: the Diet and Reinfarction Trial (DART). *J Hum Nutr Diet* 1991;4:33-42.
81. Ness AR, Hughes J, Elwood PC, et al. The long-term effect of dietary advice in men with coronary disease: follow-up of the Diet and Reinfarction Trial (DART). *Eur J Clin Nutr* 2002;56(6):512-18.
82. Ness AR, Whitley E, Burr ML, et al. The long-term effect of advice to eat more fish on blood pressure in men with coronary disease: results from the diet and reinfarction trial. *Journal of human hypertension* 1999;13(11):729-33.
83. Burr ML, Sweetham PM, Fehily AM. Diet and reinfarction [letter]. *Eur Heart J* 1994;15(8):1152-53.
84. Burr ML. Secondary prevention of CHD in UK men: the Diet and Reinfarction Trial and its sequel. *Proc Nutr Soc* 2007;66(1):9-15.
85. Burr ML, Ashfield-Watt PA, Dunstan FD, et al. Lack of benefit of dietary advice to men with angina: results of a controlled trial. *Eur J Clin Nutr* 2003;57(2):193-200.
86. Burr ML, Dunstan FD, George CH. Is fish oil good or bad for heart disease? Two trials with apparently conflicting results. *J Membr Biol* 2005;206(2):155-63.
87. Ness AR, Ashfield-Watt PA, Whiting JM, et al. The long-term effect of dietary advice on the diet of men with angina: the diet and angina randomized trial. *J Hum Nutr Diet* 2004;17(2):117-19.
88. Ness AR, Gallacher JE, Bennett PD, et al. Advice to eat fish and mood: a randomised controlled trial in men with angina. *Nutritional Neuroscience* 2003;6(1):63-65.
89. Dasarathy S, Dasarathy J, Khiyami A, et al. Double blind randomized placebo controlled clinical trial of omega 3 fatty acids for the treatment of diabetic patients with nonalcoholic steatohepatitis. *J Clin Gastroenterol* 2015;49(2):137-44.
90. Dasarathy S, Dasarathy J, Khiyami A, et al. Randomized controlled trial of omega 3 fatty acids in the treatment of non alcoholic steatohepatitis in type 2 diabetes mellitus. *Hepatology* 2013;1):518A.
91. de Luis D, Domingo J, Izaola O, et al. Effect of DHA supplementation in a very low-calorie ketogenic diet in the treatment of obesity: a randomized clinical trial. *Endocrine* 2016;54:111-22.
92. DeFina L, Marcoux L, Devers S, et al. Effects of omega-3 supplementation in combination with diet and exercise on weight loss and body composition. *Am J Clin Nutr* 2010:doi: 10.3945/ajcn.110.002741-doi: 10.3945/ajcn.110.41.
93. Delamaire M, Durand F, Bouillaux M, et al. Influence of polyunsaturated fatty acid (MaxEPA) treatment on the haemorheological parameters of 28 IDD patients. *Diabetologia* 1991;34:A74-A74.
94. Derosa G, Maffioli P, D'Angelo A, et al. Effects of long chain omega-3 fatty acids on metalloproteinases and their inhibitors in combined dyslipidemia patients. *Expert Opin Pharmacother* 2009;10(8):1239-47.
95. Derosa G, Cicero AFG, Fogari E, et al. Effects of n-3 PUFA on insulin resistance after an oral fat load. *Eur J Lipid Sci Technol* 2011;113:950-60.

96. Derosa G, Cicero AFG, Fogari E, et al. Effects of n-3 PUFAs on postprandial variation of metalloproteinases, and inflammatory and insulin resistance parameters in dyslipidemic patients: evaluation with euglycemic clamp and oral fat load. *J Clin Lipidol* 2012;6:553-64.
97. Derosa G, Cicero AF, D'Angelo A, et al. Effects of n-3 PUFAs on fasting plasma glucose and insulin resistance in patients with impaired fasting glucose or impaired glucose tolerance. *BioFactors* 2016;42(3):316-22.
98. Blok WL, Deslypere JP, Demacker PM, et al. Pro- and anti-inflammatory cytokines in healthy volunteers fed various doses of fish oil for 1 year. *Eur J Clin Invest* 1997;27(12):1003-08.
99. Deslypere JP. Influence of supplementation with N-3 fatty acids on different coronary risk factors in men--a placebo controlled study. *Verh K Acad Geneeskd Belg* 1992;54(3):189-216.
100. Katan MB, Deslypere JP, van BA, et al. Kinetics of the incorporation of dietary fatty acids into serum cholesteryl esters, erythrocyte membranes, and adipose tissue: an 18-month controlled study. *J Lipid Res* 1997;38(10):2012-22.
101. Tokudome S, Kuriki K, Yokoyama Y, et al. Dietary n-3/long-chain n-3 polyunsaturated fatty acids for prevention of sporadic colorectal tumors: a randomized controlled trial in polypectomized participants. *Prostaglandins Leukot Essent Fatty Acids* 2015;94:1-11.
102. Tokudome S, Yokoyama Y, Kamiya T, et al. Rationale and study design of dietary intervention in patients polypectomized for tumors of the colorectum. *Jpn J Clin Oncol* 2002;32(12):550-53.
103. Harrison RA. Dietary Intervention for Maintaining Sinus Rhythm Following Cardioversion for Atrial Fibrillation: a Randomised Controlled Trial [PhD thesis]. Manchester (UK): Faculty of Medicine, Dentistry, Nursing and Pharmacy 2005.
104. Harrison RA, Elton PJ. Can an oil-rich fish diet improve treatment outcomes following cardioversion for atrial fibrillation? A randomised controlled trial. Study design and compliance [poster]. *International Society for the Study of Fatty Acids and Lipids (ISSFAL) Montreal, Canada* 2003
105. Harrison RA, Elton PJ. Is there a role for long-chain omega3 or oil-rich fish in the treatment of atrial fibrillation? *Medical Hypotheses* 2005;64(1):59-63.
106. Can an oil-rich fish diet improve treatment outcomes following cardioversion for atrial fibrillation? A randomised controlled trial. Study design and compliance. International Society for the Study of Fatty Acids and Lipids (ISSFAL); 2002 May; Montreal, Canada 2002.
107. Harrison RA, Purnell P, Elton PJ. Using community-based dietary assistants to increase the intake of oil-rich fish among older people [Abstract]. *European journal of public health* 2003;13(Suppl 1):105.
108. Harrison RA, Sagara M, Rajpura A, et al. Can foods with added soya-protein or fish-oil reduce risk factors for coronary disease? A factorial randomised controlled trial. *Nutr Metab Cardiovasc Dis* 2004;14(6):344-50.
109. Berstad P, Seljeflot I, Veierod MB, et al. Supplementation with fish oil affects the association between very long-chain n-3 polyunsaturated fatty acids in serum non-esterified fatty acids and soluble vascular cell adhesion molecule-1. *Clinical Science* 2003;105(1):13-20.
110. Eid HM, Arnesen H, Hjerkinn EM, et al. Effect of diet and omega-3 fatty acid intervention on asymmetric dimethylarginine. *Nutr Metab* 2006;3:4.
111. Einvik G, Ekeberg O, Klemsdal TO, et al. Physical distress is associated with cardiovascular events in a high risk population of elderly men. *BMC Cardiovasc Disord* 2009;9:14-14.
112. Einvik G, Ekeberg O, Lavik JG, et al. The influence of long-term awareness of hyperlipidemia and of 3 years of dietary counseling on depression, anxiety, and quality of life. *J Psychosom Res* 2010;68(6):567-72.
113. Einvik G, Klemsdal TO, Sandvik L, et al. A randomized clinical trial on n-3 polyunsaturated fatty acids supplementation and all-cause mortality in elderly men at high cardiovascular risk. *Eur J Cardiovasc Prev Rehabil* 2010;17(5):588-92.
114. Ellingsen I, Hjerkinn EM, Arnesen H, et al. Follow-up of diet and cardiovascular risk factors 20 years after cessation of intervention in the Oslo Diet and Antismoking study. *Eur J Clin Nutr* 2006;60(3):378-85.
115. Furenes EB, Seljeflot I, Solheim S, et al. Long-term influence of diet and/or omega-3 fatty acids on matrix metalloproteinase-9 and pregnancy-associated plasma protein-A in men at high risk of coronary heart disease. *Scand J Clin Lab Invest* 2008;68(3):177-84.
116. Hjerkinn EM, Abdelnoor M, Breivik L, et al. Effect of diet or very long chain omega-3 fatty acids on progression of atherosclerosis, evaluated by carotid plaques, intima-media thickness and by pulse wave propagation in elderly men with hypercholesterolaemia. *Eur J Cardiovasc Prev Rehabil* 2006;13(3):325-33.
117. Hjerkinn EM, Seljeflot I, Ellingsen I, et al. Influence of long-term intervention with dietary counseling, long-chain n-3 fatty acid supplements, or both on circulating markers of endothelial activation in men with long-standing hyperlipidemia. *Am J Clin Nutr* 2005;81(3):583-89.

118. Lindman AS, Pedersen JI, Hjerkinn EM, et al. The effects of long-term diet and omega-3 fatty acid supplementation on coagulation factor VII and serum phospholipids with special emphasis on the R353Q polymorphism of the FVII gene. *Thromb Haemost* 2004;91(6):1097-104.
119. Troseid M, Arnesen H, Hjerkinn EM, et al. Serum levels of interleukin-18 are reduced by diet and n-3 fatty acid intervention in elderly high-risk men. *Metabolism* 2009;58(11):1543-49.
120. Troseid M, Seljeflot I, Weiss TW, et al. Arterial stiffness is independently associated with interleukin-18 and components of the metabolic syndrome. *Atherosclerosis* 2010;209(2):337-39.
121. Ellingsen I, Hjerkinn EM, Seljeflot I, et al. Consumption of fruit and berries is inversely associated with carotid atherosclerosis in elderly men. *Br J Nutr* 2008;99(3):674-81 (Erratum in: British Journal of Nutrition 2008;99(3):697).
122. Ellingsen I, Seljeflot I, Arnesen H, et al. Vitamin C consumption is associated with less progression in carotid intima media thickness in elderly men: A 3-year intervention study. *Nutr Metab Cardiovasc Dis* 2009;19(1):8-14.
123. Laake K, Seljeflot I, Fagerland MW, et al. Effects on serum fractalkine by diet and omega-3 fatty acid intervention: relation to clinical outcome. *Mediators of Inflammation* 2015;2015:373070.
124. Neubronner J, Schuchardt JP, Kressel G, et al. Enhanced increase of omega-3 index in response to long-term n-3 fatty acid supplementation from triacylglycerides versus ethyl esters. *Eur J Clin Nutr* 2011;65(2):247-54.
125. Andric T, Weiss TW, Huber K, et al. Effects of diet and/or n-3 fatty acid supplementation on components of the interleukin-6 trans-signalling system in elderly men AU - Andric, Tijana. *Scand J Clin Lab Invest* 2015;75(8):646-51. doi: 10.3109/00365513.2015.1063002
126. Troseid M, Seljeflot I, Arnesen H. Serum levels of interleukin-18 are reduced by diet and N-3 fatty acid intervention in elderly high-risk men. *Atherosclerosis Supplements Conference: 15th International Symposium on Atherosclerosis Boston, MA United States Conference Start* 2009;10(2)
127. Dodin S, Cunnane SC, Masse B, et al. Flaxseed on cardiovascular disease markers in healthy menopausal women: a randomized, double-blind, placebo-controlled trial. *Nutrition* 2008;24(1):23-30.
128. Dodin S, Lemay A, Jacques H, et al. The effects of flaxseed dietary supplement on lipid profile, bone mineral density, and symptoms in menopausal women: a randomized, double-blind, wheat germ placebo-controlled clinical trial. *J Clin Endocrinol Metab* 2005;90(3):1390-97.
129. Doi M, Nosaka K, Miyoshi T, et al. Clinical outcomes of early initiation of pure eicosapentaenoic acid supplement after percutaneous coronary intervention in patients with acute coronary syndrome. *Eur Heart J* 2014;35(Abstract Suppl):1156-56.
130. Doi M, Nosaka K, Miyoshi T, et al. Early eicosapentaenoic acid treatment after percutaneous coronary intervention reduces acute inflammatory responses and ventricular arrhythmias in patients with acute myocardial infarction: a randomized, controlled study. *Int J Cardiol* 2014;176(3):577-82.
131. Nosaka K, Doi M, Miyoshi T, et al. Early loading of omega-3 fatty AC IDS decreases inflammation and in-hospital events in patients with acute myocardial infarction undergoing percutaneous coronary intervention. *J Am Coll Cardiol* 2014;1):A38.
132. Nosaka K, Miyoshi T, Iwamoto M, et al. Early initiation of eicosapentaenoic acid and statin treatment is associated with better clinical outcomes than statin alone in patients with acute coronary syndromes: 1-year outcomes of a randomized controlled study. *Int J Cardiol* 2017;228:173-79.
133. Dullaart RP, Beusekamp BJ, Meijer S, et al. Long-term effects of linoleic-acid-enriched diet on albuminuria and lipid levels in type 1 (insulin-dependent) diabetic patients with elevated urinary albumin excretion. *Diabetologia* 1992;35(2):165-72.
134. Ebrahimi M, Ghayour-Mobarhan M, Azimi-Nezhad M, et al. Dietary supplementation of omega-3 reduced antibody titers to heat shock protein 27 in metabolic syndrome subjects. *77th Congress of the European Atherosclerosis Society, April 26–29, 2008, Istanbul, Turkey* 2008;PO29-494:138-38.
135. Ebrahimi M, Ghayour-Mobarhan M, Rezaiean S, et al. Omega-3 fatty acid supplements improve the cardiovascular risk profile of subjects with metabolic syndrome, including markers of inflammation and auto-immunity. *Acta Cardiologica* 2009;64(3):321-27.
136. Takaki A, Umemoto S, Ono K, et al. Add-on therapy of EPA reduces oxidative stress and inhibits the progression of aortic stiffness in patients with coronary artery disease and statin therapy: a randomized controlled study. *J Atheroscler Thromb* 2011;18(10):857-66.
137. Sanyal AJ, Abdelmalek MF, Suzuki A, et al. No significant effects of ethyl-eicosapentanoic acid on histologic features of nonalcoholic steatohepatitis in a phase 2 trial. *Gastroenterology* 2014;147(2):377-84.e1.

138. Feagan BG, Sandborn WJ, Mittmann U, et al. Omega-3 free fatty acids for the maintenance of remission in Crohn disease: the EPIC Randomized Controlled Trials. *Jama* 2008;299(14):1690-97.
139. Danthiir V, Burns NR, Nettelbeck T, et al. The older people, omega-3, and cognitive health (EPOCH) trial design and methodology: a randomised, double-blind, controlled trial investigating the effect of long-chain omega-3 fatty acids on cognitive ageing and wellbeing in cognitively healthy older adults. *Nutr J* 2011;10:117.
140. Danthiir V, Hosking D, Burns NR, et al. Cognitive performance in older adults is inversely associated with fish consumption but not erythrocyte membrane n-3 fatty acids. *J Nutr* 2014;144(3):311-20.
141. Erdogan A, Bayer M, Kollath D, et al. Omega AF study: polyunsaturated fatty acids (PUFA) for prevention of atrial fibrillation relapse after successful external cardioversion. *Heart Rhythm* 2007;4(5):S185-S86.
142. Heidt MC, Vician M, Stracke SK, et al. Beneficial effects of intravenously administered N-3 fatty acids for the prevention of atrial fibrillation after coronary artery bypass surgery: a prospective randomized study. *Thorac Cardiovasc Surg* 2009;57(5):276-80.
143. Mariani J, Doval HC, Nul D, et al. N-3 polyunsaturated fatty acids to prevent atrial fibrillation: updated systematic review and meta-analysis of randomized controlled trials. *J Am Heart Assoc* 2013;2(1):e005033-e33.
144. Eschen O, Christensen JH, Mt LAR, et al. Effects of marine n-3 fatty acids on circulating levels of soluble adhesion molecules in patients with chronic heart failure. *Cell Mol Biol (Noisy-le-grand)* 2010;56(1):45-51.
145. Leaf A, Albert CM, Josephson M, et al. Prevention of fatal arrhythmias in high-risk subjects by fish oil n-3 fatty acid intake. *Circulation* 2005;112(18):2762-68.
146. Fakhrzadeh H, Ghaderpanahi M, Sharifi F, et al. Fatty acids on serum lipid profiles and insulin resistance of the elderly: a randomized controlled clinical trial. *Int J Vit Nutr Res* 2010;80(2):107-16.
147. Ghaderpanahi M, Fakhrzadeh H, Sharifi F, et al. The effects of fish oil supplementation on hematologic pattern of the elderly "Kahrizak elderly study". *Iran J Diabet Lipid Disord* 2010;9:21-27.
148. Ferrara L, Raimondi A, d'Episcopo L, et al. Olive oil and reduced need for antihypertensive medications. *Arch Intern Med* 2000;160:837-42.
149. Ferreira JJ, Rosser A, Craufurd D, et al. Ethyl-eicosapentaenoic acid treatment in Huntington's disease: A placebo-controlled clinical trial. *Mov Disord* 2015;30(10):1426-29.
150. Childs CE, Kew S, Finnegan YE, et al. Increased dietary alpha-linolenic acid has sex-specific effects upon eicosapentaenoic acid status in humans: re-examination of data from a randomised, placebo-controlled, parallel study. *Nutr J* 2014;13(1):113.
151. Finnegan YE, Howarth D, Minihane AM, et al. Plant and marine derived (n-3) polyunsaturated fatty acids do not affect blood coagulation and fibrinolytic factors in moderately hyperlipidemic humans. *J Nutr* 2003;133(7):2210-13.
152. Kew S, Banerjee T, Minihane AM, et al. Lack of effect of foods enriched with plant- or marine-derived n-3 fatty acids on human immune function. *Am J Clin Nutr* 2003;77(5):1287-95.
153. Kew S, Banerjee T, Minihane AM, et al. Relation between the fatty acid composition of peripheral blood mononuclear cells and measures of immune cell function in healthy, free-living subjects aged 25-72y. *Am J Clin Nutr* 2003;77:1278-86.
154. Pot GK, Brouwer IA, Enneman A, et al. No effect of fish oil supplementation on serum inflammatory markers and their interrelationships: a randomized controlled trial in healthy, middle-aged individuals. *Eur J Clin Nutr* 2009;63(11):1353-59.
155. Pot GK, Geelen A, Majsak-Newman G, et al. Increased consumption of fatty and lean fish reduces serum C-reactive protein concentrations but not inflammation markers in feces and in colonic biopsies. *J Nutr* 2010;140(2):371-76.
156. Pot GK, Habermann N, Majsak-Newman G, et al. Increasing fish consumption does not affect genotoxicity markers in the colon in an intervention study. *Carcinogenesis* 2009;31(6):1087-91.
157. Pot GK, Majsak-Newman G, Geelen A, et al. Fish consumption and markers of colorectal cancer risk: a multicenter randomized controlled trial. *Am J Clin Nutr* 2009;90(2):354-61.
158. Caligiuri SP, Aukema HM, Ravandi A, et al. Flaxseed consumption reduces blood pressure in patients with hypertension by altering circulating oxylipins via an alpha-linolenic acid-induced inhibition of soluble epoxide hydrolase. *Hypertension* 2014;64(1):53-59.
159. Caligiuri SP, Penner B, Pierce GN. The HYPERFlax trial for determining the anti-HYPERtensive effects of dietary flaxseed in newly diagnosed stage 1 hypertensive patients: study protocol for a randomized, double-blinded, controlled clinical trial. *Trials* 2014;15:232.

160. Caligiuri SP, Rodriguez-Leyva D, Aukema HM, et al. Dietary flaxseed reduces central aortic blood pressure without cardiac involvement but through changes in plasma oxylipins. *Hypertension* 2016;68(4):1031-38.
161. Edel AL, Rodriguez-Leyva D, Maddaford TG, et al. Dietary flaxseed independently lowers circulating cholesterol and lowers it beyond the effects of cholesterol-lowering medications alone in patients with peripheral artery disease. *J Nutr* 2015;145(4):749-57.
162. Pierce GN, Edel AL, LaVallee R, et al. The use of dietary flaxseed to promote cardiovascular health. *Acta Physiologica* 2014;211:15-15.
163. Edel A, Rodriguez-Leyva D, Weighell W, et al. Flaxseed lignan metabolites elicit antihypertensive effects in pad patients in the flax-pad trial. *Ann Nutr Metab* 2013;63:1339.
164. Leyva DR, Zahradka P, Ramjiawan B, et al. The effect of dietary flaxseed on improving symptoms of cardiovascular disease in patients with peripheral artery disease: rationale and design of the FLAX-PAD randomized controlled trial. *Contemp Clin Trials* 2011;32(5):724-30.
165. Pierce GN, Rodriguez-Leyva D, Edel A, et al. The clinical use of flaxseed as a powerful nutritional intervention to treat cardiovascular disease. *Cardiology* 2013;126:201.
166. Rodriguez-Leyva D, Weighell W, Edel AL, et al. Potent antihypertensive action of dietary flaxseed in hypertensive patients. *Hypertension* 2013;62(6):1081-89.
167. Edel A, Rodriguez-Leyva D, Weighell W, et al. Flaxseed lignan metabolites elicit antihypertensive effects in pad patients in the flax-pad trial. *Ann Nutr Metab* 2013;63:1339-39.
168. Rodriguez D, Weighell W, Edel A, et al. Potent anti-hypertensive actions of dietary flaxseed in patients with peripheral arterial disease in the flaxpad trial. *Circulation Conference: American Heart Association* 2012;126(21 SUPPL. 1)
169. Rodriguez-Leyva D, Weighell W, Edel AL, et al. Potent antihypertensive action of dietary flaxseed in hypertensive patients. *Hypertension* 2013;62(6):1081-89.
170. MacChia A, Grancelli H, Varini S, et al. Omega-3 fatty acids for the prevention of recurrent symptomatic atrial fibrillation: Results of a double-blind randomized clinical trial (FORWARD) (NCT00597220). *Circulation* 2012;126 (23):2780-81.
171. Macchia A, Grancelli H, Varini S, et al. Omega-3 fatty acids for the prevention of recurrent symptomatic atrial fibrillation: results of the FORWARD (randomized trial to assess efficacy of PUFA for the maintenance of sinus rhythm in persistent atrial fibrillation) trial. *J Am Coll Cardiol* 2013;61(4):463-68.
172. Macchia A, Varini S, Grancelli H, et al. The rationale and design of the FORomegaARD trial: a randomized, double-blind, placebo-controlled, independent study to test the efficacy of n-3 PUFA for the maintenance of normal sinus rhythm in patients with previous atrial fibrillation. *Am Heart J* 2009;157(3):423-27.
173. Chen JS, Hill CL, Lester S, et al. Supplementation with omega-3 fish oil has no effect on bone mineral density in adults with knee osteoarthritis: a 2-year randomized controlled trial. *Osteoporos Int* 2016;27(5):1897-905.
174. Hill C, Lester SE, Jones G. Response to 'Low-dose versus high-dose fish oil for pain reduction and function improvement in patients with knee osteoarthritis' by Chen et al. Ann Rheum Dis, 2016:e8-e8.
175. Hill CL, Jones G, Lester S, et al. Effect of fish oil on structural progression in knee osteoarthritis: A two year randomized, double-blind clinical trial comparing high dose with low dose. *Arthritis Rheum* 2013;65:S914.
176. Hill CL, March LM, Aitken D, et al. Fish oil in knee osteoarthritis: a randomised clinical trial of low dose versus high dose. *Ann Rheum Dis* 2016;75(1):23-29.
177. Murthy S, Lester S, March L, et al. Serum cartilage oligomeric matrix protein (comp) in knee osteoarthritis and the effect of high and low dose fish oil on compl levels in FOSTAR study group. *Intern Med J* 2015;45(Supp 2):1-46.
178. Franzen D. A prospective, randomized, and double-blind trial on the effect of fish oil on the incidence of restenosis following ptca. *Cathet Cardiovasc Diagn* 1993;28(4):301-10.
179. Franzen D, Geisel J, Hopp HW, et al. Long-term effects of low dosage fish oil on serum lipids and lipoproteins. *Medizinische Klinik* 1993;88(3):134-38.
180. Franzen D, Geisel J, Hopp HW, et al. [Long-term effects of low dosage fish oil on serum lipids and lipoproteins]. *Medizinische Klinik* 1993;88(3):134-38.
181. Gill EA, Chen MA, Paramsothy P, et al. Omega-3 fatty acids effects on carotid IMT in metabolic syndrome. *Circulation* 2014;130:A1269. Abstract no. 12697-A1269. Abstract no. 97.
182. Gill EA, Chen MA, Thirumalai A, et al. Omega-3 fatty acids improve dyslipidemia but not inflammatory markers in metabolic syndrome. *J Clin Lipidol* 2012;6 (3):278-79.
183. Aleksova A, Masson S, Maggioni AP, et al. N-3 polyunsaturated fatty acids and atrial fibrillation in patients with chronic heart failure: the GISSI-HF trial. *Eur J Heart Fail* 2013;15(11):1289-95.

184. Canepa M, Temporelli PL, Rossi A, et al. Prevalence and prognostic impact of chronic obstructive pulmonary disease in patients with chronic heart failure. Data from the GISSI-Heart Failure trial. *Eur J Heart Fail* 2016;18:442-43.
185. Cowie MR, Cure S, Bianic F, et al. Cost-effectiveness of highly purified omega-3 polyunsaturated fatty acid ethyl esters in the treatment of chronic heart failure: results of Markov modelling in a UK setting. *Eur J Heart Fail* 2011;13(6):681-89.
186. Eleuteri E, Palvarini M, Vriz O, et al. Effect of N-3 polyunsaturated fatty acids and rosuvastatin on left ventricular function in patients with chronic heart failure. A substudy of the GISSI-HF trial Stefano Ghio Laura Scelsi. *J Am Coll Cardiol* 2010;55 (10 SUPPL 1):A16.
187. Finzi A, Barlera S, Serra DM, et al. Antiarrhythmic effects of n-3 PUFA in patients with heart failure and an implantable cardioverter defibrillator in the GISSI-HF trial. *Eur Heart J* 2009;30:279.
188. Finzi AA, Latini R, Barlera S, et al. Effects of n-3 polyunsaturated fatty acids on malignant ventricular arrhythmias in patients with chronic heart failure and implantable cardioverter-defibrillators: A substudy of the Gruppo Italiano per lo Studio della Sopravvivenza nell'Insufficienza Cardiaca (GISSI-HF) trial. *Am Heart J* 2011;161(2):338-43.
189. Ghio S, Scelsi L, Latini R, et al. Effects of n-3 polyunsaturated fatty acids and of rosuvastatin on left ventricular function in chronic heart failure: a substudy of GISSI-HF trial. *Eur J Heart Fail* 2010;12(12):1345-53.
190. Gissi-Hf Investigators, Tavazzi L, Maggioni AP, et al. Effect of n-3 polyunsaturated fatty acids in patients with chronic heart failure (the GISSI-HF trial): a randomised, double-blind, placebo-controlled trial. *Lancet* 2008;372(9645):1223-30.
191. La Rovere MT, Barlera S, Staszewsky L, et al. Effect of n-3PUFA on heart rate variability. Data from the GISSI-HF holter substudy. *Circulation Conference: American Heart Association's Scientific Sessions* 2011;124(21 SUPPL. 1)
192. La Rovere MT, Pinna GD, Maestri R, et al. Autonomic markers and cardiovascular and arrhythmic events in heart failure patients: still a place in prognostication? Data from the GISSI-HF trial. *Eur J Heart Fail* 2012;14(12):1410-19.
193. La Rovere MT, Staszewsky L, Barlera S, et al. n-3PUFA and Holter-derived autonomic variables in patients with heart failure: data from the Gruppo Italiano per lo Studio della Sopravvivenza nell'Insufficienza Cardiaca (GISSI-HF) Holter substudy. *Heart Rhythm* 2013;10(2):226-32.
194. Latini R, Masson S, Tacconi M, et al. Circulating levels of n-3 polyunsaturated fatty acids in patients with chronic heart failure. Data from the GISSI-HF trial. *Eur Heart J* 2011;32:919.
195. Maggioni AP, Fabbri G, Lucci D, et al. Effects of rosuvastatin on atrial fibrillation occurrence: ancillary results of the GISSI-HF trial. *Eur Heart J* 2009;30(19):232736-36.
196. Marchioli R, Aldegheri MP, Borghese L, et al. Time course analysis of the effect of n-3 PUFA on fatal and non fatal arrhythmias in heart failure: Secondary results of the GISSI-HF trial. *Eur Heart J* 2009;30:165.
197. Marchioli R, Franzosi MG, Latini R, et al. Prognostic ability of a Mediterranean dietary score in heart failure: Preliminary analysis of the GISSI-Heart failure Trial. *Eur Heart J* 2009;30:1026.
198. Marchioli R, Franzosi MG, Latini R, et al. Effect of n-3 PUFA in heart failure patients with different dietary habits: Preliminary results of the GISSI-heart failure trial. *Eur Heart J* 2009;30:426.
199. Marchioli R, Franzosi MG, Levantesi G, et al. Effect of n-3 PUFA according to fish intake: Preliminary results of GISSI-Heart Failure. *Eur Heart J* 2009;30:707.
200. Marchioli R, Levantesi G, Silletta MG, et al. Effect of n-3 polyunsaturated fatty acids and rosuvastatin in patients with heart failure: Results of the GISSI-HF trial. *Expert Rev Cardiovasc Ther* 2009;7(7):735-48.
201. Masson S, Anand I, Favero C, et al. Serial measurement of cardiac troponin T using a highly sensitive assay in patients with chronic heart failure: Data from 2 large randomized clinical trials. *Circulation* 2012;125(2):280-88.
202. Masson S, Latini R, Milani V, et al. Prevalence and prognostic value of elevated urinary albumin excretion in patients with chronic heart failure: data from the GISSI-Heart Failure trial. *Circ* 2010;3(1):65-72.
203. Masson S, Marchioli R, Mozaffarian D, et al. Plasma n-3 polyunsaturated fatty acids in chronic heart failure in the GISSI-Heart Failure Trial: relation with fish intake, circulating biomarkers, and mortality. *Am Heart J* 2013;165(2):208-15.
204. Røysland R, Masson S, Omland T, et al. Prognostic value of osteoprotegerin in chronic heart failure: The GISSI-HF trial. *Am Heart J* 2010;160(2):286-93.
205. Tavazzi L. Gruppo Italiano per Io Studio della Sopravvivenza nell'Infarto Miocardico Heart Failure (GISSI-HF): effect of n-3 polyunsaturated fatty acids in patients with chronic heart failure. *Clin* 2008;97(12):860-61.

206. Tavazzi L, Maggioni AP, Marchioli R, et al. Effect of n-3 polyunsaturated fatty acids in patients with chronic heart failure (the GISSI-HF trial): a randomised, double-blind, placebo-controlled trial. *Lancet* 2008;372(9645):1223-30.
207. Tavazzi L, Tognoni G, Franzosi MG, et al. Rationale and design of the GISSI heart failure trial: a large trial to assess the effects of n-3 polyunsaturated fatty acids and rosuvastatin in symptomatic congestive heart failure. *Eur J Heart Fail* 2004;6(5):635-41.
208. Wu JH, Marchioli R, Silletta MG, et al. Oxidative Stress Biomarkers and Incidence of Postoperative Atrial Fibrillation in the Omega-3 Fatty Acids for Prevention of Postoperative Atrial Fibrillation (OPERA) Trial. *J Am Heart Assoc* 2015;4(5)
209. Marchioli R, Levantesi G. n-3 PUFAs and heart failure. *Int J Cardiol* 2013;170(2 Suppl 1):S28-S32.
210. Marchioli R. Omega-3 fatty acids and arrhythmia. *Atherosclerosis Supplements Conference: 15th International Symposium on Atherosclerosis Boston, MA United States Conference Start* 2009;10(2)
211. Franzosi MG, Brunetti M, Marchioli R, et al. Cost-effectiveness analysis of n-3 polyunsaturated fatty acids (PUFA) after myocardial infarction: results from Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto (GISSI)-Prevenzione trial. *Pharmacoeconomics* 2001;19(4):411-20.
212. Franzosi MG, Brunetti M, Marchioli R, et al. Cost-effectiveness analysis of n-3 polyunsaturated fatty acids (PUFA) after myocardial infarction: results from Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto (GISSI)-Prevenzione Trial. *Pharmacoeconomics* 2001;19(4):411-20.
213. Marchioli R. Results of GISSI Prevenzione: diet, drugs, and cardiovascular risk. Researchers of GISSI Prevenzione. [Italian]. *Cardiologia (Rome, Italy)* 1999;44 Suppl 1(Pt 2):745-46.
214. Marchioli R. n-3 Polyunsaturated fatty acids reduced mortality and morbidity after recent myocardial infarction: Commentary. *Evidence-Based Medicine* 2000;5(1):13.
215. Marchioli R. Treatment with n-3 polyunsaturated fatty acids after myocardial infarction: results of GISSI-Prevenzione Trial. *European heart journal supplements* 2001;3(Supplement D):D85-d97.
216. Marchioli R. [Omega-3 polyunsaturated fatty acids and cardiovascular diseases]. *Minerva Cardioangiologica* 2003;51(5):561-76.
217. Marchioli R, Barzi F, Bomba E, et al. Early protection against sudden death by n-3 polyunsaturated fatty acids after myocardial infarction: time-course analysis of the results of the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI)-Prevenzione. *Circulation* 2002;105(16):1897-903.
218. Marchioli R, Di Pasquale A. [The biochemical, pharmacological and epidemiological reference picture of the GISSI-Prevention. The Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico]. *Giornale Italiano di Cardiologia* 1993;23(9):933-64.
219. Marchioli R, Levantesi G, MacChia A, et al. Antiarrhythmic mechanisms of n-3 PUFA and the results of the GISSI-Prevenzione trial. *J Membr Biol* 2005;206(2):117-28.
220. Marchioli R, Levantesi G, MacChia A, et al. Vitamin E increases the risk of developing heart failure after myocardial infarction: Results from the GISSI-Prevenzione trial. *J Cardiovasc Med (Hagerstown)* 2006;7(5):347-50.
221. Marchioli R, Schweiger C, Tavazzi L, et al. Efficacy of n-3 polyunsaturated fatty acids after myocardial infarction: results of GISSI-Prevenzione trial. Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico. *Lipids* 2001;36 Suppl:S119-S26.
222. Marchioli R, Valagussa F. The results of the GISSI-Prevenzione trial in the general framework of secondary prevention. *Eur Heart J* 2000;21(12):949-52.
223. Dietary supplementation with n-3 polyunsaturated fatty acids and vitamin E after myocardial infarction: results of the GISSI-Prevenzione trial. Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico.[Erratum appears in Lancet 2001 Feb 24;357(9256):642], [Erratum appears in Lancet. 2007 Jan 13;369(9556):106]. *Lancet* 1999;354(9177):447-55.
224. Marchioli R, Avanzini F, Barzi F, et al. Assessment of absolute risk of death after myocardial infarction by use of multiple-risk-factor assessment equations: GISSI-Prevenzione mortality risk chart. *Eur Heart J* 2001;22:2085-103.
225. Marchioli R, Marfisi RM, Borrelli G, et al. Efficacy of n-3 polyunsaturated fatty acids according to clinical characteristics of patients with recent myocardial infarction: insights from the GISSI-Prevenzione trial. *J Cardiovasc Med (Hagerstown)* 2007;8 Suppl 1:S34-S37.
226. Barzi F, Woodward M, Marfisi RM, et al. Mediterranean diet and all-causes mortality after myocardial infarction: results from the GISSI-Prevenzione trial.[Erratum appears in Eur J Clin Nutr. 2003 Aug;57(8):1034]. *Eur J Clin Nutr* 2003;57(4):604-11.

227. MacChia A, Levantesi G, Marfisi RM, et al. [Determinants of late-onset heart failure in myocardial infarction survivors: GISSI Prevenzione trial results]. *Rev Esp Cardiol* 2005;58(11):1266-72.
228. Keen H, Payan J, Allawi J, et al. Treatment of diabetic neuropathy with gamma-linolenic acid. The gamma-Linolenic Acid Multicenter Trial Group. *Diabetes Care* 1993;16(1):8-15.
229. Greenfield SM, Green AT, Teare JP, et al. A randomized controlled study of evening primrose oil and fish oil in ulcerative colitis. *Aliment Pharmacol Ther* 1993;7(2):159-66.
230. Gruenwald J, Petzold E, Busch R, et al. Effect of glucosamine sulfate with or without omega-3 fatty acids in patients with osteoarthritis. *Adv Ther* 2009;26(9):858-71.
231. Pasternak RC, Brown LE, Stone PH, et al. Effect of combination therapy with lipid-reducing drugs in patients with coronary heart disease and "normal" cholesterol levels. A randomized, placebo-controlled trial. *Ann Intern Med* 1996;125(7):529-40.
232. Sacks FM, Pasternak RC, Gibson CM, et al. Effect on coronary atherosclerosis of decrease in plasma cholesterol concentrations in normocholesterolaemic patients. *Lancet* 1994;344(8931):1182-86.
233. Sacks FM, Stone PH, Gibson CM, et al. Controlled trial of fish oil for regression of human coronary atherosclerosis. HARP Research Group. *J Am Coll Cardiol* 1995;25(7):1492-98.
234. Hashimoto M, Yamashita K, Kato S, et al. Beneficial effects of dietary docosahexaenoic acid intervention on cognitive function in elderly people with very mild dementia in Japan. *Alzheimer's dement* 2011;1):S610-S11.
235. Hashimoto M, Yamashita K, Kato S, et al. Beneficial effects of daily dietary omega-3 polyunsaturated fatty acid supplementation on age related cognitive decline in elderly Japanese with very mild dementia: a 2-year randomized,double-blind, placebo-controlled trial. *J Aging Res Clin Pract* 2012;1(3):193-201.
236. Hashimoto M, Kato S, Tanabe Y, et al. Beneficial effects of dietary docosahexaenoic acid intervention on cognitive function and mental health of the oldest elderly in Japanese care facilities and nursing homes. *Geriatrics & Gerontology International* 2016;17(2):330-37.
237. Kato S, Hashimoto M, Ohno M, et al. Effects of dietary N-3 PUFA intervention on cognitive function and mental health in Japanese oldest-elderly with dementia. *Alzheimer's dement* 2015;1):721.
238. Mitarai M, Tamai T, Kato S, et al. The effects of 2-years' daily dietary fish sausages containing DHA and EPA on cognitive functions in elderly Japanese - A randomized, double-blind, placebo-controlled trial. [Japanese]. *Japanese Pharmacology and Therapeutics* 2015;43(5):667-77.
239. Hawthorne AB, Daneshmend TK, Hawkey CJ, et al. Treatment of ulcerative colitis with fish oil supplementation: a prospective 12 month randomised controlled trial. *Gut* 1992;33(7):922-28.
240. Heine R, Mulder C, Popp-Snijders C, et al. Linoleic-acid-enriched diet: long-term effects on serum lipoprotein and apolipoprotein concentrations and insulin sensitivity in noninsulin-dependent diabetic patients. *Am J Clin Nutr* 1989;49:448-56.
241. Tan SY. Dietary Manipulation and Weight Management [PhD thesis]. Wollongong, Australia: University of Wollonong 2010.
242. Tapsell LC, Batterham MJ, Teuss G, et al. Long-term effects of increased dietary polyunsaturated fat from walnuts on metabolic parameters in type II diabetes. *Eur J Clin Nutr* 2009;63(8):1008-15.
243. Higashihara E, Itomura M, Terachi T, et al. Effects of eicosapentaenoic acid on biochemical failure after radical prostatectomy for prostate cancer. *In Vivo* 2010;24(4):561-65.
244. Houtsmuller AJ, Van Hal-Ferwerda J, Zahn KJ, et al. Favourable influences of linoleic acid on the progression of diabetic micro-and macroangiopathy. *Nutr Metab* 1980;24(SUPPL. 1):105-18.
245. Houtsmuller AJ, van Hal-Ferwerda J, Zahn KJ, et al. Influence of different diets on the progression of diabetic retinopathy. *Prog Food Nutr Science* 1980;4(5):41-46.
246. Houtsmuller AJ, Zahn KJ, Henkes HE. Unsaturated fats and progression of diabetic retinopathy. *Documenta Ophthalmologia* 1979;48(2):363-71.
247. Huang YC, Jessup JM, Forse RA, et al. N-3 fatty acids decrease colonic epithelial cell proliferation in high-risk bowel mucosa. *Lipids* 1996;31:S313-S17.
248. Dong H, Hutchins-Wiese H, Kleppinger A, et al. Effects of Omega-3 Polyunsaturated Fatty Acid Supplementation on Bone Turnover in Older Women. *Int J Vit Nutr Res* 2014;84(3-4):124-32.
249. Hutchins-Wiese HL, Feinn R, Kerstetter JE, et al. Effect of fish oil supplementation on bone turnover markers in women on aromatase inhibitors: A pilot study. *FASEB Journal Conference: Experimental Biology* 2012;26(no pagination)
250. Hutchins-Wiese HL, Kleppinger A, Annis K, et al. The impact of supplemental n-3 long chain polyunsaturated fatty acids and dietary antioxidants on physical performance in postmenopausal women. *J Nutr Health Aging* 2013;17(1):76-80.

251. Hutchins-Wiese HL, Picho K, Watkins BA, et al. High-dose eicosapentaenoic acid and docosahexaenoic acid supplementation reduces bone resorption in postmenopausal breast cancer survivors on aromatase inhibitors: a pilot study. *Nutr Cancer* 2014;66(1):68-76.
252. Patti L, Maffettone A, Iovine C, et al. Long-term effects of fish oil on lipoprotein subfractions and low density lipoprotein size in non-insulin-dependent diabetic patients with hypertriglyderidemia. *Atherosclerosis* 1999;146:361-67.
253. Rivellese A, Maffettone A, Iovine C, et al. Long-term effects of fish oil on insuin resistance and plasma lipoproteins in NIDDM patients with hypertriglyceridemia. *Diabetes Care* 1996;19(11):1207-2013.
254. Sirtori C, Crepaldi G, Manzato E, et al. One-year treatment with ethyl esters of n-3 fatty acids in patients withhypertriglyceridemia and glucose intoleranceReduced triglyceridemia, total cholesterol and increased HDL-Cwithout glycemic alterations. *Atherosclerosis* 1998;137:419-27.
255. Sirtori C, Paoletti R, Mancini M, et al. n-3 Fatty acids do not lead to an increased diabetic risk in patients with hyperlipidemia and abnormal glucose tolerance. *Am J Clin Nutr* 1997;65:1974-881.
256. Maffettone A. Long-term effects (six months) of omega-3 polyunsaturated fatty acids on insulin sensitivity and lipid metabolism in patients with type 2 diabetes and hypertriglycaeridemia. *G Ital Diabetol* 1996;16(4):185-93.
257. Jackson PA, Forster JS, Bell JG, et al. DHA Supplementation Alone or in Combination with Other Nutrients Does not Modulate Cerebral Hemodynamics or Cognitive Function in Healthy Older Adults. *Nutrients* 2016;8:86-86.
258. Ishikawa Y, Yokoyama M, Saito Y, et al. Preventive effects of eicosapentaenoic acid on coronary artery disease in patients with peripheral artery disease. *Circ J* 2010;74(7):1451-57.
259. Itakura H, Yokoyama M, Matsuzaki M, et al. Relationships between plasma fatty acid composition and coronary artery disease. *J Atheroscler Thromb* 2011;18(2):99-107.
260. Itakura H, Yokoyama M, Matsuzaki M, et al. The change in low-density lipoprotein cholesterol concentration is positively related to plasma docosahexaenoic acid but not eicosapentaenoic acid. *J Atheroscler Thromb* 2012;19(7):673-79.
261. Matsuzaki M, Yokoyama M, Saito Y, et al. Incremental effects of eicosapentaenoic acid on cardiovascular events in statin-treated patients with coronary artery disease. Secondary prevention analysis from JELIS. *Circ J* 2009;73(7):1283-90.
262. Oikawa S, Yokoyama M, Origasa H, et al. Suppressive effect of EPA on the incidence of coronary events in hypercholesterolemia with impaired glucose metabolism: sub-analysis of the Japan EPA Lipid Intervention Study (JELIS). *Atherosclerosis* 2009;206(2):535-39.
263. Origasa H, Yokoyama M, Matsuzaki M, et al. Clinical importance of adherence to treatment with eicosapentaenoic acid by patients with hypercholesterolemia. *Circ J* 2010;74(3):510-17.
264. Saito Y, Yokoyama M, Origasa H, et al. Effects of EPA on coronary artery disease in hypercholesterolemic patients with multiple risk factors: sub-analysis of primary prevention cases from the Japan EPA Lipid Intervention Study (JELIS). *Atherosclerosis* 2008;200(1):135-40.
265. Tanaka K, Ishikawa Y, Yokoyama M, et al. Relationship of ischemic stroke with serum lipid levels, and influence of plasma eicosapentanoic acid (EPA) concentration in patients with hypercholesterolemia. *Int J Stroke* 2008;3(Suppl 1):65-66.
266. Tanaka K, Ishikawa Y, Yokoyama M, et al. Reduction in the recurrence of stroke by eicosapentaenoic acid for hypercholesterolemic patients: subanalysis of the JELIS trial. *Stroke* 2008;39(8):2052-58.
267. Yokoyama M. [Japan EPA Lipid Intervention Study (JELIS). Randomized clinical trial involving primary and secondary prevention of cardiovascular events with EPA in hypercholesterolemia]. *Nippon Ronen Igakkai Zasshi* 2009;46(1):22-25.
268. Yokoyama M, Origasa H, for the Jelis Investigators. Effects of eicosapentaenoic acid on cardiovascular events in Japanese patients with hypercholesterolaemia: Rationale, design, and baseline characteristics of the Japan EPA Lipid Intervention Study (JELIS). *Am Heart J* 2003;146:613-20.
269. Yokoyama M, Origasa H, Matsuzaki M, et al. Effects of eicosapentaenoic acid on major coronary events in hypercholesterolaemic patients (JELIS): a randomised open-label, blinded endpoint analysis. *Lancet* 2007;369(9567):1090-98.
270. Yamanouchi D, Komori K. Eicosapentaenoic acid as the gold standard for patients with peripheral artery disease? - subanalysis of the JELIS trial. *Circ J* 2010;74(7):1298-99.
271. Sasaki J, Yokoyama M, Matsuzaki M, et al. Relationship between coronary artery disease and non-HDL-C, and effect of highly purified EPA on the risk of coronary artery disease in hypercholesterolemic patients treated

with statins: sub-analysis of the Japan EPA Lipid Intervention Study (JELIS). *J Atheroscler Thromb* 2012;19(2):194-204.
272. Maysuzaki M, Yokoyama M, Saito Y. Eicosapentaenoic acid and heart disease risk reduction: Secondary prevention strata from jelis. *Atherosclerosis Supplements Conference: 15th International Symposium on Atherosclerosis Boston, MA United States Conference Start* 2009;10(2)
273. Kanorskii SG, Bodrikova VV, Kanorskaia Iu S. [Influence of perindopril, rosuvastatin, or omega-3 polyunsaturated fatty acids on efficacy of antirecurrence therapy with sotalol in patients with persistent atrial fibrillation]. *Kardiologiia* 2007;47(12):39-44.
274. Krebs J, Browning L, McLean N, et al. Additive benefits of long-chain n-3 polyunsaturated fatty acids and weight-loss in the mangement of cardiovascular disease risk in overweight hyperinsulinaemic women. *Int J Obes (Lond)* 2006;30:1535-44.
275. Kremer JM, Lawrence DA, Petrillo GF, et al. Effects of high-dose fish oil on rheumatoid arthritis after stopping nonsteroidal antiinflammatory drugs. Clinical and immune correlates. *Arthritis Rheum* 1995;38(8):1107-14.
276. Kristensen S, Schmidt EB, Schlemmer A, et al. Beneficial effect of n-3 polyunsaturated fatty acids on inflammation and analgesic use in psoriatic arthritis: a randomized, double blind, placebo-controlled trial. *Scand J Rheumatol* 2018;47(1):27-36. doi: 10.1080/03009742.2017.1287304
277. Kristensen S, Schmidt EB, Schlemmer A, et al. Beneficial effect of n-3 polyunsaturated fatty acids on inflammation and analgesic use in psoriatic arthritis - a randomised, double-blind, placebo-controlled trial. 2016 ACR/ARHP Annual Meeting, 2016.
278. Kristensen S, Schmidt EB, Schlemmer A, et al. The effect of marine n-3 polyunsaturated fatty acids on cardiac autonomic and hemodynamic function in patients with psoriatic arthritis: a randomised, double-blind, placebo-controlled trial. *Lipids Health Dis* 2016;15:216. doi: 10.1186/s12944-016-0382-5
279. Kruger MC, Coetzer H, de Winter R, et al. Calcium, gamma-linolenic acid and eicosapentaenoic acid supplementation in senile osteoporosis. *Aging Clin* 1998;10(5):385-94.
280. Kumar P, Strang A, Ho M, et al. The effects of borage oil supplementation on non-steroidal anti-inflammatory drug requirements in patients with rheumatoid arthritis. *Journal of Complementary and Integrative Medicine* 2008;5 (1) (no pagination)(23)
281. Kumar S, Sutherland F, Morton JB, et al. Long-term omega-3 polyunsaturated fatty acid supplementation reduces the recurrence of persistent atrial fibrillation after electrical cardioversion. *Heart Rhythm* 2012;9(4):483-91.
282. Kumar S, Sutherland F, Heck P, et al. Mechanisms and effects of chronic omega-3 polyunsaturated fatty acid supplementation on human atrial electrical and mechanical function. *Heart Lung and Circulation* 2011;20:S101.
283. Kumar S, Sutherland F, Rosso R, et al. Effects of chronic omega-3 polyunsaturated fatty acid supplementation on human atrial electrophysiology. *Heart Rhythm* 2011;8(4):562-68.
284. Kumar S, Sutherland F, Sparks PB. Chronic fish oil supplementation in humans reduces the recurrence of persistent atrial fibrillation after cardioversion. *Circulation Conference: American Heart Association's Scientific Sessions* 2011;124(21 SUPPL. 1)
285. Kumar S, Sutherland F, Sparks P. Fish oil supplementation for the prevention of persistent AF recurrence after cardioversion: Who benefits most? *Heart Lung and Circulation* 2012;21:S124-S25.
286. Kumar S, Sutherland F, Sparks P. Fish oil supplementation when commenced >one month pre-cardioversion increases rates of pharmacological reversion and reduces rates of persistent AF recurrence after electrical cardioversion over one year: Results from a prospective randomised study. *Heart Lung and Circulation* 2012;21:S125.
287. Kumar S, Sutherland F, Stevenson I, et al. Effects of long-term omega-3 polyunsaturated fatty acid supplementation on paroxysmal atrial tachyarrhythmia burden in patients with implanted pacemakers: results from a prospective randomised study. *Int J Cardiol* 2013;168(4):3812-17.
288. Lalia AZ, Johnson ML, Jensen MD, et al. Effects of Dietary n-3 Fatty Acids on Hepatic and Peripheral Insulin Sensitivity in Insulin-Resistant Humans. *Diabetes Care* 2015;38(7):1228-37.
289. Lau CS, McLaren M, Belch JJ. Effects of fish oil on plasma fibrinolysis in patients with mild rheumatoid arthritis. *Clin Exp Rheumatol* 1995;13(1):87-90.
290. Lau CS, Morley KD, Belch JJ. Effects of fish oil supplementation on non-steroidal anti-inflammatory drug requirement in patients with mild rheumatoid arthritis: a double-blind placebo controlled study. *Br J Rheumatol* 1993;32(11):982-89.

291. Lau CS, McMahon H, Morley KD, et al. Effects of Maxepa on non-steroidal anti-inflammatory drug useage in patients with mild rheumatoid arthritis. *Br J Rheumatol* 1991;30:137-37.
292. Lee KL, Shahar S, Chin A, et al. Docosahexaenoic acid-concentrated fish oil supplementation in subjects with mild cognitive impairment (MCI): a 12-month randomised, double-blind, placebo-controlled trial. *Psychopharmacology* 2013;225:605-12.
293. Lee LK, Shahar S, Chin A, et al. Prevalence of gender disparities and predictors affecting the occurrence of mild cognitive impairment (MCI). *Archives of Gerontology and Geriatrics* 2012;54:185-91.
294. Leventhal LJ, Boyce EG, Zurier RB. Treatment of rheumatoid arthritis with gammalinolenic acid. *Ann Intern Med* 1993;119(9):867-73.
295. Leventhal LJ, Boyce EG, Zurier RB. Treatment of rheumatoid arthritis with blackcurrant seed oil. *Br J Rheumatol* 1994;33(9):847-52.
296. Ley SJ, Metcalf PA, Scragg RKR, et al. Long-term effects of a reduced fat diet intervention on cardiovascular disease risk factors in individuals with glucose intolerance. *Diabetes Research and Clinical Practice* 2004;63:103-12.
297. Swinburn BA, Metcalf PA, Ley SJ. Long-term (5-year) effects of a reduced-fat diet intervention in individuals with glucose intolerance. *Diabetes Care* 2001;24(4):619-24.
298. Swinburn BA, Woollard GA, Chang EC, et al. Effects of reduced-fat diets consumed ad libitum on intake of nutrients particularly antioxidant vitamins. *J Am Diet Assoc* 1999;99(11):1400-05.
299. Li YH, Yang LH, Sha KH, et al. Efficacy of poly-unsaturated fatty acid therapy on patients with nonalcoholic steatohepatitis. *World Journal of Gastroenterology* 2015;21(22):7008-13.
300. Loeschke K, Ueberschaer B, Pietsch A, et al. N-3 fatty acids only delay early relapse of ulcerative colitis in remission. *Digestive Diseases and Sciences* 1996;41(10):2087-94.
301. Lorenz-Meyer H, Bauer P, Nicolay C, et al. Omega-3 fatty acids and low carbohydrate diet for maintenance of remission in Crohn's disease. A randomized controlled multicenter trial. *Scandinavian Journal of Gastroenterology* 1996;31(8):778-85.
302. Macsai MS. The role of omega-3 dietary supplementation in blepharitis and meibomian gland dysfunction (an AOS thesis). *Trans Am Ophthalmol Soc* 2008;106:336-56.
303. Mansel RE, Gateley CA, Harrison BJ, et al. Effects and tolerability of n-6 essential fatty acid supplementation in patients with recurrent breast cysts -- a randomized double-blind placebo-controlled trial. *Journal of Nutritional Medicine* 1990;1(3):195-95.
304. Mansel RE, Harrison BJ, Melhuish J, et al. A randomized trial of dietary intervention with essential fatty acids in patients with categorized cysts. *Ann N Y Acad Sci* 1990;586:288-94.
305. Mansel RE, Pye JK, Hughes LE. Effects of essential fatty acids on cyclical mastalgia and noncyclical breat disorders. *Omega-6 Essential Fatty Acids: Pathophysiology and Roles in Clinical Medicine* 1990:557-66.
306. Mantzaris GJ, Archavlis E, Zografos C, et al. A prospective, randomized, placebo-controlled study of fish oil in ulcerative colitis. *Hellenic Journal of Gastroenterology* 1996;9(2):138-41.
307. Carrie I, van Kan GA, Gillette-Guyonnet S, et al. Recruitment strategies for preventive trials. The MAPT study (MultiDomain Alzheimer Preventive Trial). *J Nutr Health Aging* 2012;16(4):355-59.
308. Delrieu J, Andrieu S, Pahor M, et al. Neuropsychological Profile of “Cognitive Frailty” Subjects in MAPT Study. *J Prev Alzheimers Dis* 2016;3(3):151-59.
309. Delrieu J, Payoux P, Hitzel A, et al. Multidomain alzheimer's disease preventive trial: Florbetapir ancillary study. *Alzheimer's dement* 2011;1):S419.
310. Fougere B, Barreto PD, Goisser S, et al. Red blood cell membrane omega-3 fatty acid levels and physical performance: Cross-sectional data from the MAPT study. *Clinical Nutrition* 2017:1-4.
311. Gillette-Guyonnet S, Andrieu S, Dantoine T, et al. Commentary on "A roadmap for the prevention of dementia II. Leon Thal Symposium 2008." The Multidomain Alzheimer Preventive Trial (MAPT): a new approach to the prevention of Alzheimer's disease. *Alzheimer's dement* 2009;5(2):114-21.
312. Gillette-Guyonnet S, Vellas B, Andrieu S, et al. MAPT study: a 3-year randomized trial of omega 3 and/or multidomain intervention for the prevention of cognitive decline in frail elderly subjects-rationale, design and baseline data. *Alzheimer's dement* 2011;1:S97-S98.
313. Vellas B, Carrie I, Gillette-Guyonnet S, et al. MAPT Study: a multidomain approach for preventing ALzheimer's disease: design and baseline data. *Journal of Prevention of Alzheimers Disease* 2014;1(1):13-22.
314. Vellas B, Carrie I, Guyonnet S, et al. MAPT (multi-domain Alzheimer's prevention trial): Results at 36 months. *Alzheimer's dement* 2015;1):331.

315. Vellas B, Touchon J, Weiner M. MAPT (multidomain Alzheimer preventive trial) imaging (MRI, FDG-PET, amyloid-PET) data. *J Nutr Health Aging* 2012;16 (9):812-15.
316. Andrieu S, Guyonnet S, Coley N, et al. Effect of long-term omega 3 polyunsaturated fatty acid supplementation with or without multidomain intervention on cognitive function in elderly adults with memory complaints (MAPT): a randomised, placebo-controlled trial. *Lancet Neurology* 2017;16:377-89.
317. Gillette S. The multidomain Alzheimer preventive trial (MAPT): A new approach for the prevention of Alzheimer's disease. *Alzheimer's dement* 2009;1):145.
318. Tabue-Teguo M, Barreto de Souza P, Cantet C, et al. Effect of Multidomain Intervention, Omega-3 Polyunsaturated Fatty Acids Supplementation or their Combinaison on Cognitive Function in Non-Demented Older Adults According to Frail Status: Results from the MAPT Study. *J Nutr Health Aging* 2018;22(2):923-27. doi: 10.1007/s12603-018-1024-6.
319. Bemelmans WJ, Broer J, de Vries JH, et al. Impact of Mediterramean diet education versus posted leaflet on dietary habits and serum cholesterol in a high risk population for cardiovascular disease. *Public Health Nutr* 2000;3(3):273-83.
320. Bemelmans WJ, Broer J, Feskens EJ, et al. Effect of an increased intake of alpha-linolenic acid and group nutritional education on cardiovascular risk factors: the Mediterranean alpha-linolenic enriched Groningen dietary intervention (MARGARIN) study. *Am J Clin Nutr* 2002;75:221-27.
321. Bemelmans WJ, Lefrandt JD, Feskens EJ, et al. Change in saturated fat intake is associated with progression of carotid and femoral intima-media thickness, and with levels of soluble intercellular adhesion molecule-1. *Atherosclerosis* 2002;163(1):113-20.
322. Bemelmans WJ, Lefrandt JD, Feskens EJ, et al. Increased alpha-linolenic acid intake lowers C-reactive protein, but has no effect on markers of atherosclerosis. *Eur J Clin Nutr* 2004;58(7):1083-89.
323. Bemelmans WJ, Muskiet FA, Feskens EJ, et al. Associations of alpha-linolenic acid and linoleic acid with risk factors for coronary heart disease. *Eur J Clin Nutr* 2000;54(12):865-71.
324. Siero FW, Broer J, Bemelmans WJ, et al. Impact of group nutrition education and surplus value of Prochaska based stage-matched information on health-related cognitions and on Mediterranean nutrition behaviour. *Health Education Research* 2000;15(5):635-47.
325. Bemelmans WJ, Broer J, Smit AJ, et al. Reply to D Lanzmann-Petithory et al. *Am J Clin Nutr* 2002;76(6):1456-57. doi: 10.1093/ajcn/76.6.1456a
326. Al-Hilal M, Alsaleh A, Maniou Z, et al. Genetic variation at the FADS1-FADS2 gene locus influences delta-5 desaturase activity and LC-PUFA proportions after fish oil supplement. *J Lipid Res* 2013;54(2):542-51.
327. Alsaleh A, Crepostnaia D, Maniou Z, et al. Adiponectin gene variant interacts with fish oil supplementation to influence serum adiponectin in older individuals. *J Nutr* 2013;143(7):1021-27.
328. AlSaleh A, Maniou Z, Lewis FJ, et al. Interaction between a CSK gene variant and fish oil intake influences blood pressure in healthy adults. *J Nutr* 2014;144(3):267-72.
329. Hall WL, Hay G, Maniou Z, et al. Effect of low doses of long chain n-3 polyunsaturated fatty acids on sleep-time heart rate variability: a randomized, controlled trial. *Int J Cardiol* 2013;168(4):4439-42.
330. Pinto AM, Hall WL, Sanders TAB. Effect of low doses of long chain n-3 PUFA intake on daytime heart rate variability: results from the MARINA study. *European Journal of Preventive Cardiology* 2015;1:S146-S46.
331. Sanders TA, Hall WL, Maniou Z, et al. Effect of low doses of long-chain n-3 PUFAs on endothelial function and arterial stiffness: a randomized controlled trial. *Am J Clin Nutr* 2011;94(4):973-80.
332. Sanders TAB, Chowienczyk PJ, Hall W, et al. The influences of increasing intakes of EPA and DHA on vascular function and risk factors for cardiovascular disease. Food Standards Agency Project N02041 Final Report, 2011.
333. Alsaleh A, Maniou Z, Lewis FJ, et al. Genetic predisposition scores for dyslipidaemia influence plasma lipid concentrations at baseline, but not the changes after controlled intake of n-3 polyunsaturated fatty acids. *Genes nutr* 2014;9(4):412.
334. Martinez GL, Koury JC, Martins MA, et al. Serum level changes of long chain-polyunsaturated fatty acids in patients undergoing periodontal therapy combined with one year of omega-3 supplementation: a pilot randomized clinical trial. *J Periodontal Implant Sci* 2014;44(4):169-77.
335. Mate J, Castanos R, Garcia-Samaniego J, et al. Does dietary fish oil maintain the remission of Crohn's Disease (CD): a study case control. *Gastroenterology* 1991;100(5, part 2):A228-A28.
336. McIllmurray MB, Turkie W. Controlled trial of gamma linolenic acid in Duke's C colorectal cancer.[Erratum appears in Br Med J (Clin Res Ed) 1987 Aug 22;295(6596):475]. *Br Med J (Clin Res Ed)* 1987;294(6582):1260.

337. Bouwens M, Van De Rest O, Dellschaft N, et al. Fish-oil supplementation induces antiinflammatory gene expression profiles in human blood mononuclear cells. *Am J Clin Nutr* 2009;90(2):415-24.
338. Van De Rest O, Geleijnse JM, Kok FJ, et al. Effect of fish oil on cognitive performance in older subjects: a randomized, controlled trial. *Neurology* 2008;71(6):430-38.
339. Van De Rest O, Geleijnse JM, Kok FJ, et al. Effect of fish-oil supplementation on mental well-being in older subjects: a randomized, double-blind, placebo-controlled trial. *Am J Clin Nutr* 2008;88(3):706-13.
340. Van De Rest O, Geleijnse JM, Kok FJ, et al. Effect of fish oil supplementation on quality of life in a general population of older Dutch subjects: a randomized, double-blind, placebo-controlled trial. *J Am Geriatr Soc* 2009;57(8):1481-86.
341. Mendis S, Samarajeewa U, Thattil RO. Coconut fat and serum lipoproteins: effects of partial replacement with unsaturated fats. *Br J Nutr* 2001;85(5):583-89.
342. Tran Le BA, Flatt SW, Natarajan L, et al. Effects of diet composition and insulin resistance status on plasma lipid levels in a weight loss intervention in women. *J Am Heart Assoc* 2016;5(1):e002771-e71.
343. Rock CL, Flatt SW, Pakiz B, et al. Effects of diet composition on weight loss, metabolic factors and biomarkers in a 1-year weight loss intervention in obese women examined by baseline insulin resistance status. *Metabolism* 2016;65(11):1605-13.
344. Yurko-Mauro K, McCarthy D, Bailey-Hall E, et al. Results of the MIDAS Trial: Effects of Docosahexaenoic acid on physiologica and safety parameters in age-related cognitive decline. 2009:P84-P84.
345. Yurko-Mauro K, McCarthy D, Rom D, et al. Beneficial effects of docosahexaenoic acid on cognition in age-related cognitive decline. *Alzheimer's dement* 2010;6(6):456-64.
346. Yurko-Mauro K. Cognitive and cardiovascular benefits of docosahexaenoic acid in aging and cognitive decline. *Curr Alzheimer Res* 2010;7(3):190-96.
347. Mita T, Watada H, Ogihara T, et al. Eicosapentaenoic acid reduces the progression of carotid intima-media thickness in patients with type 2 diabetes. *Atherosclerosis* 2007;191(1):162-67.
348. Moore CS, Bryant SP, Mishra GD, et al. Oily fish reduces plasma triacylglycerols: a primary prevention study in overweight men and women. *Nutrition* 2006;22(10):1012-24.
349. Ederer F, Leren P, Turpeinen O, et al. Cancer among men on cholesterol lowering diets: experience of five clinical trials. *Lancet* 1971;2:203-06.
350. Heady JA. Are PUFA harmful? *BMJ (Clinical Research Ed)* 1974;1:115-16.
351. MRC. Controlled trial of soya-bean oil in myocardial infarction. *Lancet* 1968;2(570):693-99.
352. Miller M, Sorkin J, Mastella L, et al. Poly is more effective than monounsaturated fat for dietary management in the metabolic syndrome: The muffin study. *J Clin Lipidol* 2016;10:996-1003.
353. Merle BM, Benlian P, Puche N, et al. Circulating omega-3 fatty acids and neovascular age-related macular degeneration. *Invest Ophthalmol Vis Sci* 2014;55(3):2010-19.
354. Merle BM, Richard F, Benlian P, et al. CFH Y402H and ARMS2 A69S Polymorphisms and Oral Supplementation with Docosahexaenoic Acid in Neovascular Age-Related Macular Degeneration Patients: The NAT2 Study. *PLoS ONE* 2015;10(7):e0130816.
355. Querques G, Merle BM, Pumariega NM, et al. Dynamic drusen remodelling in participants of the nutritional AMD treatment-2 (NAT-2) randomized trial. *PLOS ONE* 2016;11(2):e0149219-e19.
356. Souied EH, Delcourt C, Querques G, et al. Oral docosahexaenoic acid in the prevention of exudative age-related macular degeneration: the nutritional AMD treatment 2 study. *Ophthalmology* 2013;120(8):1619-31.
357. Page IH, Brown HB. Some observations on the National Diet-Heart Study. *Circulation* 1968;37:313-15.
358. Brown HB. The National Diet Heart Study - implications for dietitians and nutritionists. *J Am Diet Assoc* 1968;52:279-87.
359. Baker BM, Frantz Id Jr, Keys A, et al. The National Diet-Heart Study: an initial report. *Jama* 1963;185:105-06.
360. The National Diet-Heart Study. Nutr Rev, 1968:133-36.
361. NDHS Research Group. The National Diet-Heart Study final report. *Circulation* 1968;37(II):1-428.
362. Markulev C, McGorry PD, Nelson B, et al. NEURAPRO-E study protocol: a multicentre randomized controlled trial of omega-3 fatty acids and cognitive-behavioural case management for patients at ultra high risk of schizophrenia and other psychotic disorders. *Early Intervention in Psychiatry* 2015:1-11.
363. McGorry P, et al. The neurapro-E study: A multicenter RCT of omega-3 fatty acids and cognitive-behavioural case management for patients at ultra high risk of schizophrenia and other psychotic disorders. *Schizophrenia Bulletin* 2015;41:S322-S23.
364. McGorry PD, Nelson B, Markulev C, et al. Effect of ω-3 Polyunsaturated Fatty Acids in Young Peopleat Ultrahigh Risk for Psychotic DisordersThe NEURAPRO Randomized Clinical Trial. *JAMA Psychiatry* 2017;74(1):19-27.

365. Nigam P, Bhatt S, Misra A, et al. Effect of a 6-month intervention with cooking oils containing a high concentration of monounsaturated fatty acids (olive and canola oils) compared with control oil in male Asian Indians with nonalcoholic fatty liver disease. *Diabetes Technol Ther* 2014;16(4):255-61.
366. Niki T, Wakatsuki T, Yamaguchi K, et al. Effects of the addition of eicosapentaenoic acid to strong statin therapy on inflammatory cytokines and coronary plaque components assessed by integrated backscatter intravascular ultrasound. *Circ J* 2016;80(2):450-60.
367. Nishio R, Shinke T, Otake H, et al. Stabilizing effect of combined eicosapentaenoic acid and statin therapy on coronary thin-cap fibroatheroma. *Atherosclerosis* 2014;234(1):114-19.
368. Nodari S, Metra M, Milesi G, et al. The role of n-3 PUFAs in preventing the arrhythmic risk in patients with idiopathic dilated cardiomyopathy. *Cardiovasc Drugs Ther* 2009;23(1):5-15.
369. Nodari S, Triggiani M, Campia U, et al. N-3 polyunsaturated fatty acids in the prevention of atrial fibrillation recurrences after electrical cardioversion: a prospective, randomized study. *Circulation* 2011;124(10):1100-06.
370. Nodari S, Triggiani M, Berlinghieri N, et al. Effects of n-3 polyunsaturated fatty acids on left ventricular function and functional capacity in heart failure patients. *Eur Heart J* 2010;31:850.
371. Nodari S, Triggiani M, Campia U, et al. Effects of n-3 polyunsaturated fatty acids on left ventricular function and functional capacity in patients with dilated cardiomyopathy. *J Am Coll Cardiol* 2011;57(7):870-79.
372. Nodari S, Triggiani M, Campia U, et al. Plasma levels of n-3 polyunsaturated fatty acids and risk of hospitalization in patients with non-ischemic cardiomyopathy. *Circulation Conference: American Heart Association* 2012;126(21 SUPPL. 1)
373. Nodari S, Triggiani M, Foresti A, et al. Use of N-3 polyunsaturated fatty acids to maintain sinus rhythm after conversion from persistent atrial fibrillation. A prospective randomized study. *J Am Coll Cardiol* 2010;55 (10 SUPPL 1):A2.
374. Nogueira M, Alves V, Stefano J, et al. Effects of omega-3 polyunsaturated fatty acids(PUFA) from fish and flaxseed oils on nonalcoholic steatohepatitis (NASH). *J Hepatol* 2013;58:S544.
375. Nogueira M, Oliveira C, Alves V, et al. Omega-3 polyunsaturated fatty acids in treating non-alcoholic steatohepatitis: A randomized, double-blind, placebo-controlled trial. *Clinical Nutrition* 2016;35:578-86.
376. Nomura S, Inami N, Shouzu A, et al. The effects of pitavastatin, eicosapentaenoic acid and combined therapy on platelet-derived microparticles and adiponectin in hyperlipidemic, diabetic patients. *Platelets* 2009;20(1):16-22.
377. Norouzi Javidan A, Sabour H, Latifi S, et al. Does consumption of polyunsaturated fatty acids influence on neurorehabilitation in traumatic spinal cord-injured individuals? A double-blinded clinical trial. *Spinal Cord* 2014;52(5):378-82.
378. Sabour H, Norouzi Javidan A, Latifi S, et al. Omega-3 fatty acids' effect on leptin and adiponectin concentrations in patients with spinal cord injury: a double-blinded randomized clinical trial. *J Spinal Cord Med* 2015;38(5):599-606.
379. Natvig H. [The effect of unsaturated fatty acids on the incidence of coronary infarction, etc]. *Tidsskr Nor Laegeforen* 1967;87(11):1033-41.
380. Natvig H, Borchgrevink CF, Dedichen J, et al. A controlled trial of the effect of linolenic acid on incidence of coronary heart disease. The Norwegian vegetable oil experiment of 1965-66. *Scandinavian Journal of Clinical and Laboratory Investigation Supplement* 1968;105:1-20.
381. Garbagnati F, Cairella G, De Martino A, et al. Is antioxidant and n-3 supplementation able to improve functional status in poststroke patients? Results from the Nutristroke Trial. *Cerebrovasc Dis* 2009;27(4):375-83.
382. Ilsey CDJ, Nye ER, Sutherland W, et al. Randomised placebo controlled trial of MAXEPA and aspirin/persantin after successful coronary angioplasty. *Aust N Z J Med* 1987;17:559-59.
383. Nye ER, Ablett MB, Robertson MC, et al. Effect of eicosapentaenoic acid on restenosis rate, clinical course and blood lipids in patients after percutaneous transluminal coronary angioplasty. *Australian and New Zealand Journal of Medicine* 1990;20(4):549-52.
384. Aarsetoy H, Brugger-Andersen T, Hetland O, et al. Long term influence of regular intake of high dose n-3 fatty acids on CD40-ligand, pregnancy-associated plasma protein A and matrix metalloproteinase-9 following acute myocardial infarction. *Thromb Haemost* 2006;95(2):329-36.
385. Grundt H, Hetland O, Nilsen DW. Changes in tissue factor and activated factor XII following an acute myocardial infarction were uninfluenced by high doses of n-3 polyunsaturated fatty acids. *Thromb Haemost* 2003;89(4):752-59.

386. Grundt H, Nilsen DW, Hetland O, et al. Clinical outcome and atherothrombogenic risk profile after prolonged wash-out following long-term treatment with high doses of n-3 PUFAs in patients with an acute myocardial infarction. *Clinical Nutrition* 2004;23(4):491-500.
387. Grundt H, Nilsen DW, Mansoor MA, et al. Reduction in homocysteine by n-3 polyunsaturated fatty acids after 1 year in a randomised double-blind study following an acute myocardial infarction: no effect on endothelial adhesion properties. *Pathophysiol Haemost Thromb* 2003;33(2):88-95.
388. Grundt H, Nilsen DW, Mansoor MA, et al. Increased lipid peroxidation during long-term intervention with high doses of n-3 fatty acids (PUFAs) following an acute myocardial infarction. *Eur J Clin Nutr* 2003;57(6):793-800.
389. Naesgaard PA, Grundt H, Brede C, et al. The effect on vitamin D levels of long-term high-dose treatment with a concentrated omega-3 compound (omacor/lovaza) in patients hospitalized with a myocardial infarction. *Circulation Conference: American Heart Association's* 2014;130(no pagination)
390. Nilsen DW, Albrektsen G, Landmark K, et al. Effects of a high-dose concentrate of n-3 fatty acids or corn oil introduced early after an acute myocardial infarction on serum triacylglycerol and HDL cholesterol. *Am J Clin Nutr* 2001;74(1):50-56.
391. Poenitz V, Grundt H, Bottazzi B, et al. Pentraxin 3 is uninfluenced by high doses of concentrated omega-3 fatty acids administered for 12 months following an acute myocardial infarction. *Circulation Conference: American Heart Association* 2012;126(21 SUPPL. 1)
392. Torkildsen O, Wergeland S, Bakke S, et al. Omega-3 fatty acid treatment in multiple sclerosis (OFAMS Study): a randomized, double-blind, placebo-controlled trial. *Arch Neurol* 2012;69(8):1044-51.
393. Beiske A, Hovdal H, Midgard R, et al. Effect of omega-3 fatty acid treatment in multiple sclerosis (OFAMS study): Results from a randomised, double-blind, placebo-controlled trial O. Torkildsen. *Multiple Sclerosis* 2011;1):S412.
394. Torkildsen O, Myhr K, Beiske A, et al. α-Linolenic acid (ALA) serum levels are associated with reduced MRI activity in a prospective cohort of MS patients. *Multiple Sclerosis* 2017;23(S1):15.
395. Pawelczyk T, Grancow M, Kotlicka-Antczak M, et al. Omega-3 polyunsaturated fatty acids can prevent relapse in first-episode schizophrenia: The results of offer trial. *European Psychiatry* 2015;30:1751.
396. Pawelczyk T, Grancow-Grabka M, Kotlicka-Antczak M, et al. A randomized controlled study of the efficacy of six-month supplementation with concentrated fish oil rich in omega-3 polyunsaturated fatty acids in first episode schizophrenia. *Journal of Psychiatric Research* 2016;73:34-44.
397. Rauch B, Riemer T, Schwaab B, et al. Short-term comprehensive cardiac rehabilitation after AMI is associated with reduced 1-year mortality: results from the OMEGA study. *European Journal of Preventive Cardiology* 2014;21(9):1060-69.
398. Rauch B, Schiele R, Schneider S, et al. OMEGA, a randomized, placebo-controlled trial to test the effect of highly purified omega-3 fatty acids on top of modern guideline-adjusted therapy after myocardial infarction. *Circulation* 2010;122(21):2152-59.
399. Rauch B, Schiele R, Schneider S, et al. Response to letters regarding article, "oMEGA, a randomized, placebo-controlled trial to test the effect of highly purified omega-3 fatty acids on top of modern guideline-adjusted therapy after myocardial infarction". *Circulation* 2011;124(1):e24-e25.
400. Rauch B, Schiele R, Schneider S, et al. Highly purified omega-3 fatty acids for secondary prevention of sudden cardiac death after myocardial infarction-aims and methods of the OMEGA-study. *Cardiovasc Drugs Ther* 2006;20(5):365-75.
401. Rauch B, Schiele R, Schneider S, et al. Prognostic effect of omega-3 fatty acid supplementation on top of current guideline adjusted therapy of acute myocardial infarction - The OMEGA trial. *European Journal of Cardiovascular Prevention and Rehabilitation* 2010;17:S1.
402. Rauch B, Schneider S, Schiele R, et al. Prognostic effect of cardiac rehabilitation after acute myocardial infarction - Results of the OMEGA-study. *European Journal of Cardiovascular Prevention and Rehabilitation* 2010;17:S106.
403. Rauch B, Senges J. The effects of supplementation with omega-3 polyunsaturated Fatty acids on cardiac rhythm: anti-arrhythmic, pro-arrhythmic, both or neither? It depends. *Front Physiol* 2012;3:57.
404. Zimmer R, Riemer T, Rauch B, et al. Effects of 1-year treatment with highly purified omega-3 fatty acids on depression after myocardial infarction: results from the OMEGA trial. *Journal of Clinical Psychiatry* 2013;74(11):e1037-e45.
405. Bauer T, Schiele R, Zahn R, et al. Predictors of 1-year mortality in patients with contemporary opimised guideline-adherent secondary prevention therapy after acute myocardial infarction: Results from the OMEGA Study. *Eur Heart J* 2012;33:346.

406. Heydari B, Abbasi S, Shah R, et al. Effect of purified omega-3 fatty acids on reducing left ventricular remodeling after acute my ocardial infarction (omega-remodel study: A double-blind randomized clinical trial). *J Am Coll Cardiol* 2015;1):A1083.
407. Heydari B, Abdullah S, Pottala JV, et al. Effect of Omega-3 Acid Ethyl Esters on Left Ventricular Remodeling After Acute Myocardial Infarction: The OMEGA-REMODEL Randomized Clinical Trial. *Circulation* 2016;134:378-91.
408. Heydari B, Abdullah S, Pottala JV, et al. ST2 is reduced by high-dose omega-3 fatty acid treatment following acute MI and is correlated with reduction of the extracellular volume fraction of non-infarcted myocardium. *Journal of Cardiovascular Magnetic Resonance Conference: 19th Annual SCMR Scientific Sessions Los Angeles, CA United States Conference Start* 2016;18(no pagination)
409. Heydari B, Harris WS, Kwong RY. Response by Heydari et al to Letter Regarding Article, "Effect of Omega-3 Acid Ethyl Esters on Left Ventricular Remodeling After Acute Myocardial Infarction: The OMEGA-REMODEL Randomized Clinical Trial". *Circulation* 2017;135(2):e13-e14.
410. Eriksdotter M, Falahati F, Vedin I, et al. Effects of omega-3 fattyacid supplementation on plasma fattyacids, gender effects, and effects on cognition in Alzheimer's patients: The omegAD study. *Alzheimer's dement* 2014;10:455.
411. Eriksdotter M, Vedin I, Falahati F, et al. Plasma Fatty Acid Profiles in Relation to Cognition and Gender in Alzheimer's Disease Patients During Oral Omega-3 Fatty Acid Supplementation: The OmegAD Study. *J Alzheimers Dis* 2015;48(3):805-12.
412. Faxén Irving G, Freund-Levi Y, Eriksdotter-Jönhagen M, et al. N-3 fatty acid supplementation effects on weight and appetite in patients with Alzheimer's disease: The OmegAD Study. *J Am Geriatr Soc* 2009;57:11-17.
413. Faxén Irving G, Freund-Levi Y, Eriksdotter-Jönhagen M, et al. Effects on transthyretin in plasma and cerebrospinal fluid by DHA-rich n-3 fatty acid supplementation in patients with Alzheimer's Disease: The OmegAD study. *J Alzheimers Dis* 2013;36:1-6.
414. Faxen-Irving G, Falahati F, Basun H, et al. Does fatty acid composition in subcutaneous fat differ between patients with alzheimer's disease and their cohabiting relatives? *Clinical Nutrition* 2015;34:S245-S46.
415. Freund Levi Y, Eriksdotter-Jönhagen M, Cederholm T, et al. Omega-3 fatty acid treatment of 174 patients with mild to moderate Alzheimer's disease (OmegAD): a randomized double-blind trial. *Arch Neurol* 2006;63:1402-08.
416. Freund Levi Y, Vedin I, Cederholm, et al. Transfer of n-3 fatty acids over the blood-brain barrier after dietary supplementation with a DHA rich n-3 fatty acid oil to Alzheimer disease patients. The OmegAD study. *Journal of Internal Medicine* 2014;275:428-36.
417. Freund Levi Y, Vedin I, Cederholm T, et al. Effects of a DHA rich omega-3 fatty acid supplementation for Alzheimer disease patients on fatty acid composition in cerebrospinal fluid, disease biomarkers and cognition: The OmegAD study. *Journal of Molecular Neuroscience* 2012;48:S36.
418. Freund Levi Y, Vedin I, Cederholm T, et al. Transfer of omega-3 fatty acids across the blood-brain barrier after dietary supplementation with a docosahexaenoic acid-rich omega-3 fatty acid preparation in patients with Alzheimer's disease: the OmegAD study. *Journal of Internal Medicine* 2014;275(4):428-36.
419. Freund-Levi Y, Basun H, Cederholm T, et al. Omega-3 supplementation in mild to moderate Alzheimer's disease: effects on neuropsychiatric symptoms. *International Journal of Geriatric Psychiatry* 2008;23(2):161-69.
420. Freund-Levi Y, Hjorth E, Lindberg C, et al. Effects of omega-3 fatty acids on inflammatory markers in cerebrospinal fluid and plasma in Alzheimer's disease: the OmegAD study. *Dement Geriatr Cogn Disord* 2009;27(5):481-90.
421. Freund-Levi Y, Vedin I, Hjorth E, et al. Effects of supplementation with omega-3 fatty acids on oxidative stress and inflammation in patients with Alzheimer's disease: The OmegAD Study. *J Alzheimers Dis* 2014;42:823-31.
422. Hjorth E, Zhu M, Cortés Toro V, et al. Omega-3 fatty acids enhance phagocytosis of Alzheimer-related Ab42 by human microglia and decrease inflammatory markers. *J Alzheimers Dis* 2013;35:697-713.
423. Irving GF, Freund-Levi Y, Eriksdotter-Jonhagen M, et al. Omega-3 fatty acid supplementation effects on weight and appetite in patients with Alzheimer's disease: the omega-3 Alzheimer's disease study.[Erratum appears in J Am Geriatr Soc. 2009 Mar;57(3):579]. *J Am Geriatr Soc* 2009;57(1):11-17.
424. Irving GF, Freund-Levi Y, Eriksdotter-Jonhagen M, et al. N-3 fatty acid treatment and plasma transthyretin in patients with Alzheimer's disease. *The FASEB Journal* 2009;23(S1)
425. Vedin I, Cederholm T, Freund Levi Y, et al. Effects of DHA rich n-3 fatty acid supplementation on cytokine release from blood mononuclear leukocytes. The OmegAD Study. *Am J Clin Nutr* 2008;87:1616-22.

426. Vedin I, Cederholm T, Freund Levi Y, et al. Effects of docosahexaenoic acid-rich n-3 fatty acid supplementation on cytokine release from blood mononuclear leukocytes: the OmegAD study. *Am J Clin Nutr* 2008;87(6):1616-22.
427. Vedin I, Cederholm T, Freund-Levi Y, et al. Effects of DHA- rich n-3 fatty acid supplementation on gene expression changes in blood mononuclear leukocytes: the OmegAD study. *PLOS One* 2012;7:e35425-e25.
428. Vedin I, Cederholm T, Freund-Levi Y, et al. Reduced prostaglandin F2 alpha release from blood mononuclear leukocytes after oral supplementation of omega3 fatty acids: the OmegAD study. *J Lipid Res* 2010;51(5):1179-85.
429. Vedin I, Levi YF, Cederholm T, et al. Effects of a DHA rich n-3 fatty acid supplementation on fatty acid composition in cerebrospinal fluid in Alzheimer disease. The OmegAD study. *FASEB Journal Conference: Experimental Biology* 2013;27(no pagination)
430. Wang X, Hjorth E, Vedin I, et al. Effects of n-3 FA supplementation on the release of proresolving lipid mediators by blood mononuclear cells: the OmegAD study. *J Lipid Res* 2015;56(3):674-81.
431. Freund-Levi Y, Cederholm T, Basu S. Oxidative stress and cox-mediated inflammation in patients with alzheimer's disease and effects of N-3 fatty acid supplementation the omegad study. *Clinical Nutrition, Supplement* 2011;6 (1):9.
432. Freund-Levi Y, Jonhagen ME, Wahlund LO, et al. Safety and tolerability of omega-3 fatty acids in patients with Alzheimers disease. *Neurobiol Aging* 2004;25(S2):471.
433. Dangour AD, Allen E, Elbourne D, et al. Effect of 2-y n-3 long-chain polyunsaturated fatty acid supplementation on cognitive function in older people: a randomized, double-blind, controlled trial. *Am J Clin Nutr* 2010;91(6):1725-32.
434. Dangour AD, Allen E, Elbourne D, et al. Fish consumption and cognitive function among older people in the UK: baseline data from the OPAL study. *J Nutr Health Aging* 2009;13(3):198-202.
435. Dangour AD, Allen E, Elbourne D, et al. N-3 fatty acids and retinal function. *Ophthalmology* 2013;120(3):643-43.
436. Dangour AD, Clemens F, Elbourne D, et al. A randomised controlled trial investigating the effect of n-3 long-chain polyunsaturated fatty acid supplementation on cognitive and retinal function in cognitively healthy older people: the Older People And n-3 Long-chain polyunsaturated fatty acids (OPAL) study protocol [ISRCTN72331636]. *Nutr J* 2006;5:20-20.
437. Neveu MM, Dangour A, Allen E, et al. Electroretinogram measures in a septuagenarian population. *Documenta Ophthalmologica* 2011;123(2):75. doi: 10.1007/s10633-011-9282-1
438. Sanders T, Lewis F, Slaughter S, et al. Effect of varying the ratio of n6 to n3 fatty acids by increasing the dietary intake of -linolenic acid, eicosapentaenoic and docosahexaenoic acid, or both on fibrinogen and clotting factors VII and XII in persons aged 45–70 y: the OPTILIP Study. *Am J Clin Nutr* 2006;84:513-22.
439. Griffin M, Sanders T, Davies I, et al. Effects of altering the ratio of dietary n6 to n3 fatty acids on insulin sensitivity, lipoprotein size, and postprandial lipemia in men and postmenopausal women aged 45–70 y: the OPTILIP Study. *Am J Clin Nutr* 2006;84:1290-98.
440. Bordeleau L, Dagenais G, Yakubovich N, et al. Incident cancers in people with dysglycemia and other cardiovascular risk factors: Cohort study of the ORIGIN trial. *Journal of Clinical Oncology Conference: ASCO Annual Meeting* 2011;29(15 SUPPL. 1)
441. Bordeleau L, Yakubovich N, Dagenais G, et al. Cancer outcomes in patients with dysglycemia on basal insulin: results of the origin trial. *Diabetes* 2013;62:A98.
442. Bordeleau L, Yakubovich N, Dagenais GR, et al. The association of basal insulin glargine and/or n-3 fatty acids with incident cancers in patients with dysglycemia. *Diabetes Care* 2014;37(5):1360-66.
443. Cukierman-Yaffe T, Bosch J, Diaz R, et al. Effects of basal insulin glargine and omega-3 fatty acid on cognitive decline and probable cognitive impairment in people with dysglycaemia: a substudy of the ORIGIN trial. *The Lancet Diabetes & Endocrinology* 2014;2(7):562-72.
444. Lonn EM, Bosch J, Diaz R, et al. Effect of insulin glargine and n-3FA on carotid intima-media thickness in people with dysglycemia at high risk for cardiovascular events: the glucose reduction and atherosclerosis continuing evaluation study (ORIGIN-GRACE). *Diabetes Care* 2013;36(9):2466-74.
445. Maggioni AP, Fabbri G, Bosch J, et al. Effects of n-3 fatty acids on long-term outcomes of high risk patients with type 2 diabetes mellitus or IGF/IGT with a recent myocardial infarction. *Eur Heart J* 2013;34:352.
446. Origin Trial Investigators, Bosch J, Gerstein HC, et al. n-3 fatty acids and cardiovascular outcomes in patients with dysglycemia. *N Engl J Med* 2012;367(4):309-18.
447. Origin Trial Investigators, Gerstein HC, Bosch J, et al. Basal insulin and cardiovascular and other outcomes in dysglycemia. *N Engl J Med* 2012;367(4):319-28.

448. Origin Trial Investigators, Gerstein H, Yusuf S, et al. Rationale, design, and baseline characteristics for a large international trial of cardiovascular disease prevention in people with dysglycemia: the ORIGIN Trial (Outcome Reduction with an Initial Glargine Intervention). *Am Heart J* 2008;155(1):26-32, 32.
449. Punthakee Z, Gerstein HC, Bosch J, et al. Cardiovascular and other outcomes postintervention with insulin glargine and omega-3 fatty acids (ORIGINALE). *Diabetes Care* 2016;39(5):709-16.
450. Punthakee Z, Tyrwhitt J, Bosch J, et al. Outcome reduction with an initial glargine intervention and legacy effects (ORIGINALE). *Diabetologia* 2014;1):S516.
451. Gilbert RE, Mann JFE, Hanefeld M, et al. Basal insulin glargine and microvascular outcomes in dysglycaemic individuals: Results of the Outcome Reduction with an Initial Glargine Intervention (ORIGIN) trial. *Diabetologia* 2014;57(7):1325-31.
452. Hanefeld M, Koehler C, Hoffmann C, et al. Effect of targeting normal fasting glucose levels with basal insulin glargine on glycaemic variability and risk of hypoglycaemia: a randomized, controlled study in patients with early Type 2 diabetes. *Diabet Med* 2010;27(2):175-80. doi: doi:10.1111/j.1464-5491.2009.02915.x
453. Tatsuno I, Saito Y, Kudou K, et al. Long-term safety and efficacy of TAK-085 in Japanese subjects with hypertriglyceridemia undergoing lifestyle modification: the omega-3 fatty acids randomized long-term (ORL) study. *J Clin Lipidol* 2013;7(6):615-25.
454. Tatsuno IT, Saito YS, Kudou KK, et al. Effects of long-term treatment with omega-3 polyunsaturated fatty acids (Lotriga) on atherogenic lipoproteins in hypertriglyceridemia: Results from a phase 3 randomized, open-label, 1-year study. *Eur Heart J* 2013;34:768.
455. Palma C. Omega 3 fatty acids supplementation in Schizophrenia. *European Archives of Psychiatry and Clinical Neuroscience* 2015;265(Supplement 1):S122-S22.
456. Murphy KJ, Meyer BJ, Mori TA, et al. Impact of foods enriched with n-3 long chain polyunsaturated fatty acids on erythrocyte n-3 levels and cardiovascualar risk factors. *Br J Nutr* 2007;97(4):749-57.
457. Patch CS, Tapsell LC, Mori TA, et al. The use of novel foods enriched with long-chain n-3 fatty acids to increase dietary intake: a comparison of methodologies assessing nutrient intake. *J Am Diet Assoc* 2005;105(12):1918-26.
458. Mukaro VR, Costabile M, Murphy KJ, et al. Leukocyte numbers and function in subjects eating n-3 enriched foods: selective depression of natural killer cell levels. *Arthritis Research and Therapy* 2008;10(3)
459. Paty, D.W, Cousin, et al. Linoleic acid in multiple sclerosis: failure to show any therapeutic benefit. *Acta Neurologica Scandinavica* 1978;58(1):53-58.
460. Paty DW. Double-blind trial of linoleic acid in multiple sclerosis. *Arch Neurol* 1983;40(11):693-94.
461. Paty DW, Cousin HK, McDonald LE. Letter: Linoleic acid in multiple sclerosis. *Lancet* 1975;1(7917):1197-98.
462. Pomponi M, Loria G, Salvati S, et al. DHA effects in Parkinson disease depression. *Basal Ganglia* 2014;4(2):61-66.
463. Kowey PR, Reiffel JA, Ellenbogen KA, et al. Efficacy and safety of prescription omega-3 fatty acids for the prevention of recurrent symptomatic atrial fibrillation: a randomized controlled trial. *Jama* 2010;304(21):2363-72.
464. Pratt CM, Reiffel JA, Ellenbogen KA, et al. Efficacy and safety of prescription omega-3-acid ethyl esters for the prevention of recurrent symptomatic atrial fibrillation: a prospective study. *Am Heart J* 2009;158(2):163-69.
465. Alvarez-Perez J, Sanchez-Villegas A, Diaz-Benitez EM, et al. Influence of a Mediterranean Dietary Pattern on Body Fat Distribution: Results of the PREDIMED-Canarias Intervention Randomized Trial. *J Am Coll Nutr* 2016:1-13.
466. Babio N, Toledo E, Estruch R, et al. Mediterranean diets and metabolic syndrome status in the PREDIMED randomized trial. *Cmaj* 2014;186(17):E649-E57.
467. Barcelo F, Perona JS, Prades J, et al. Mediterranean-style diet effect on the structural properties of the erythrocyte cell membrane of hypertensive patients: the Prevencion con Dieta Mediterranea Study. *Hypertension* 2009;54(5):1143-50.
468. Bullo M, Amigo-Correig P, Marquez-Sandoval F, et al. Mediterranean diet and high dietary acid load associated with mixed nuts: effect on bone metabolism in elderly subjects. *J Am Geriatr Soc* 2009;57(10):1789-98.
469. Casas R, Sacanella E, Romero E, et al. Inhibition of activation NF-kappaB Related to atherogenesis after one year of intervention with a Mediterranean diet. *Ann Nutr Metab* 2011;58:318.
470. Casas R, Sacanella E, Urpi-Sarda M, et al. The effects of the mediterranean diet on biomarkers of vascular wall inflammation and plaque vulnerability in subjects with high risk for cardiovascular disease. A randomized trial. *PLoS ONE* 2014;9(6):e100084.

471. Casas RM, Urpi-Sarda M, Chiva-Blanch G, et al. Inhibition of circulating immune cells related to atherogenesis intervention after 1, 3 and 5 years with mediterranean diet. *Ann Nutr Metab* 2013;62:43-44.
472. Cohen J, Rimm EB, Martinez-Gonzalez MA, et al. The association between obesity status and long-term adherence to mediterranean diet in the predimed trial. *Circulation Conference: American Heart Association's Epidemiology and Prevention/Physical Activity, Nutrition and Metabolism* 2013;127(12 Meeting Abstracts)
473. Damasceno NR, Sala-Vila A, Cofan M, et al. Mediterranean diet supplemented with nuts reduces waist circumference and shifts lipoprotein subfractions to a less atherogenic pattern in subjects at high cardiovascular risk. *Atherosclerosis* 2013;230(2):347-53.
474. Domenech M, Estruch R, Ros E, et al. Effect of the mediterranean diet on blood pressure: The ambulatory blood pressure substudy (Predimed-ABPM). *J Hypertens* 2010;28:e373.
475. Domenech M, Roman P, Lapetra J, et al. Mediterranean diet reduces 24-hour ambulatory blood pressure, blood glucose, and lipids: one-year randomized, clinical trial. *Hypertension* 2014;64(1):69-76.
476. Downer MK, Gea A, Stampfer M, et al. Predictors of short- and long-term adherence with a Mediterranean-type diet intervention: the PREDIMED randomized trial. *Int* 2016;13(1):67.
477. Escurriol V, Cofan M, Serra M, et al. Serum sterol responses to increasing plant sterol intake from natural foods in the Mediterranean diet. *Eur J Nutr* 2009;48(6):373-82.
478. Estruch R. Lessons from predimed: The Spanish multicenter study. *Obesity Facts* 2014;7:13.
479. Estruch R, Casas R, Sacanella E, et al. Mediterranean diet and inflammatory biomarkers. *Ann Nutr Metab* 2015;67:41-42.
480. Estruch R, Martinez-Gonzalez MA, Corella D, et al. Effect of a high-fat Mediterranean diet on bodyweight and waist circumference: a prespecified secondary outcomes analysis of the PREDIMED randomised controlled trial. *The Lancet Diabetes & Endocrinology* 2016;6:6.
481. Estruch R, Ros E. Eat a healthy diet and drink wisely to postpone dying if you survived a myocardial infarction?: Yes, but randomized clinical trials are needed. *JAMA Intern Med* 2013;173(19):1819-20.
482. Estruch R, Ros E, Salas-Salvadó J, et al. Retraction and republication: Primary prevention of cardiovascular disease with a Mediterranean diet. N Engl J Med 2013; 368:1279-90. *N Engl J Med* 2018;378:25-25.
483. Estruch R, Ros E, Salas-Salvado J, et al. Primary prevention of cardiovascular disease with a Mediterranean diet.[RETRACTED and republished as Estruch 2018, Erratum appears in N Engl J Med. 2014 Feb 27;370(9):886]. *N Engl J Med* 2013;368(14):1279-90.
484. Estruch R, Ros E, Salas-Salvado J, et al. Clinical trials in nutrition: The predimed study. *Ann Nutr Metab* 2013;62:4.
485. Fernandez-Real JM, Bullo M, Moreno-Navarrete JM, et al. A Mediterranean diet enriched with olive oil is associated with higher serum total osteocalcin levels in elderly men at high cardiovascular risk. *J Clin Endocrinol Metab* 2012;97(10):3792-98.
486. Fito M, Estruch R, Salas-Salvado J, et al. Effect of the Mediterranean diet on heart failure biomarkers: a randomized sample from the PREDIMED trial. *Eur J Heart Fail* 2014;16(5):543-50.
487. Fito M, Guxens M, Corella D, et al. Effect of a traditional Mediterranean diet on lipoprotein oxidation: a randomized controlled trial. *Arch Intern Med* 2007;167(11):1195-203.
488. Garcia-Arellano A, Ramallal R, Ruiz-Canela M, et al. Dietary Inflammatory Index and Incidence of Cardiovascular Disease in the PREDIMED Study. *Nutrients* 2015;7(6):4124-38.
489. Garcia-Lopez M, Toledo E, Beunza JJ, et al. Mediterranean diet and heart rate: The PREDIMED randomised trial. *Int J Cardiol* 2014;171(2):299-301.
490. Guasch-Ferre M, Babio N, Martinez-Gonzalez MA, et al. Dietary fat intake and risk of cardiovascular disease and all-cause mortality in a population at high risk of cardiovascular disease. *Am J Clin Nutr* 2015;102(6):1563-73.
491. Guasch-Ferre M, Bullo M, Babio N, et al. Mediterranean diet and risk of hyperuricemia in elderly participants at high cardiovascular risk. *J Gerontol A Biol Sci Med Sci* 2013;68(10):1263-70.
492. Guasch-Ferre M, Bullo M, Estruch R, et al. Dietary magnesium intake is inversely associated with mortality in adults at high cardiovascular disease risk. *J Nutr* 2014;144(1):55-60.
493. Guasch-Ferre M, Bullo M, Martinez-Gonzalez MA, et al. Frequency of nut consumption and risk of total mortality in the predimed study. *Ann Nutr Metab* 2013;62:17-18.
494. Guasch-Ferre M, Hu FB, Martinez-Gonzalez MA, et al. Olive oil intake and risk of cardiovascular disease and mortality in the PREDIMED Study. *BMC Medicine* 2014;12:78.
495. Juanola-Falgarona M, Salas-Salvado J, Estruch R, et al. Association between dietary phylloquinone intake and peripheral metabolic risk markers related to insulin resistance and diabetes in elderly subjects at high cardiovascular risk. *Cardiovasc Diabetol* 2013;12 (1) (no pagination)(7)

496. Lamuela-Raventos R, Tulipani S, Martinez Huelamo M, et al. Olive oil matrix of tomato sauce affects plasma phenolic concentrations and systemic inflammatory biomarkers related to atherosclerosis. *Ann Nutr Metab* 2011;58:251-52.
497. Lasa A, Miranda J, Bullo M, et al. Comparative effect of two Mediterranean diets versus a low-fat diet on glycaemic control in individuals with type 2 diabetes. *Eur J Clin Nutr* 2014;68(7):767-72.
498. Llorente-Cortes V, Estruch R, Mena MP, et al. Effect of Mediterranean diet on the expression of pro-atherogenic genes in a population at high cardiovascular risk. *Atherosclerosis* 2010;208(2):442-50.
499. Martínez-González MÁ, Corella D, Salas-Salvadó J, et al. Cohort profile: design and methods of the PREDIMED study. *Int J Epidemiol* 2012;41(2):377-85.
500. Martinez-Gonzalez MA, Garcia-Arellano A, Toledo E, et al. Association between adherence to the Mediterranean diet and waist-to-height ratio among high-risk subjects: The PREDIMED trial. *European Journal of Epidemiology* 2012;1):S63.
501. Martinez-Gonzalez MA, Salas-Salvado J, Estruch R, et al. Benefits of the Mediterranean Diet: Insights From the PREDIMED Study. *Progress in Cardiovascular Diseases* 2015;58(1):50-60.
502. Martinez-Gonzalez MA, Sanchez-Tainta A, Corella D, et al. A provegetarian food pattern and reduction in total mortality in the Prevencion con Dieta Mediterranea (PREDIMED) study.[Erratum appears in Am J Clin Nutr. 2014 Dec;100(6):1605]. *Am J Clin Nutr* 2014;100 Suppl 1:320S-28S.
503. Martinez-Gonzalez MA, Toledo E, Aros F, et al. Extravirgin olive oil consumption reduces risk of atrial fibrillation: the PREDIMED (Prevencion con Dieta Mediterranea) trial. *Circulation* 2014;130(1):18-26.
504. Martinez-Huelamo M, Tulipani S, Estruch R, et al. The tomato sauce making process affects the bioaccessibility and bioavailability of tomato phenolics: a pharmacokinetic study. *Food Chemistry* 2015;173:864-72.
505. Martinez-Huelamo M, Vallverdu-Queralt A, Di Lecce G, et al. Bioavailability of tomato polyphenols is enhanced by processing and fat addition: Evidence from a randomized feeding trial. *Mol Nutr Food Res* 2016;60(7):1578-89.
506. Martinez-Lapiscina EH, Clavero P, Toledo E, et al. Mediterranean diet improves cognition: the PREDIMED-NAVARRA randomised trial. *J Neurol Neurosurg Psychiatry* 2013;84(12):1318-25.
507. Mayneris-Perxachs J, Sala-Vila A, Chisaguano M, et al. Effects of 1-year intervention with a Mediterranean diet on plasma fatty acid composition and metabolic syndrome in a population at high cardiovascular risk. *PLoS ONE* 2014;9(3):e85202.
508. Medina-Remon A, Casas R, Tressserra-Rimbau A, et al. Polyphenol intake from a Mediterranean diet decreases inflammatory biomarkers related to atherosclerosis: A sub-study of The PREDIMED trial. *British Journal of Clinical Pharmacology* 2016;21:21.
509. Medina-Remon A, Tresserra-Rimbau A, Pons A, et al. Effects of total dietary polyphenols on plasma nitric oxide and blood pressure in a high cardiovascular risk cohort. The PREDIMED randomized trial. *Nutr Metab Cardiovasc Dis* 2015;25(1):60-67.
510. Mena MP, Sacanella E, Vazquez-Agell M, et al. Inhibition of circulating immune cell activation: a molecular antiinflammatory effect of the Mediterranean diet. *Am J Clin Nutr* 2009;89(1):248-56.
511. Mitjavila MT, Fandos M, Salas-Salvado J, et al. The Mediterranean diet improves the systemic lipid and DNA oxidative damage in metabolic syndrome individuals. A randomized, controlled, trial. *Clinical Nutrition* 2013;32(2):172-78.
512. Murie M, Buil P, Irimia P, et al. Effect of mediterranean diet on carotid intima-media thickness progression in patients with high vascular risk. *Cerebrovasc Dis* 2010;29:21.
513. Murie-Fernandez M, Irimia P, Toledo E, et al. Carotid intima-media thickness changes with Mediterranean diet: a randomized trial (PREDIMED-Navarra). *Atherosclerosis* 2011;219(1):158-62.
514. Perona JS, Covas MI, Fito M, et al. Reduction in systemic and VLDL triacylglycerol concentration after a 3-month Mediterranean-style diet in high-cardiovascular-risk subjects. *J Nutr Biochem* 2010;21(9):892-98.
515. Razquin C, Martinez JA, Martinez-Gonzalez MA, et al. A 3 years follow-up of a Mediterranean diet rich in virgin olive oil is associated with high plasma antioxidant capacity and reduced body weight gain. *Eur J Clin Nutr* 2009;63(12):1387-93.
516. Razquin C, Martinez JA, Martinez-Gonzalez MA, et al. A 3-year Mediterranean-style dietary intervention may modulate the association between adiponectin gene variants and body weight change. *Eur J Nutr* 2010;49(5):311-19.
517. Ros E, Martinez-Gonzalez MA, Estruch R, et al. Mediterranean diet and cardiovascular health: Teachings of the PREDIMED study. *Adv Nutr* 2014;5(3):330S-36S.

518. Ruiz-Canela M, Estruch R, Corella D, et al. Association of Mediterranean diet with peripheral artery disease: the PREDIMED randomized trial. *Jama* 2014;311(4):415-17.
519. Salas-Salvado J, Bullo M, Babio N, et al. Reduction in the incidence of type 2 diabetes with the Mediterranean diet: results of the PREDIMED-Reus nutrition intervention randomized trial. *Diabetes Care* 2011;34(1):14-19.
520. Salas-Salvado J, Bullo M, Estruch R, et al. Prevention of diabetes with Mediterranean diets: a subgroup analysis of a randomized trial. *Ann Intern Med* 2014;160(1):1-10.
521. Salas-Salvado J, Fernandez-Ballart J, Ros E, et al. Effect of a Mediterranean diet supplemented with nuts on metabolic syndrome status: one-year results of the PREDIMED randomized trial. *Arch Intern Med* 2008;168(22):2449-58.
522. Sala-Vila A, Romero-Mamani ES, Gilabert R, et al. Changes in ultrasound-assessed carotid intima-media thickness and plaque with a Mediterranean diet: a substudy of the PREDIMED trial. *Arterioscler Thromb Vasc Biol* 2014;34(2):439-45.
523. Sanchez-Villegas A, Galbete C, Martinez-Gonzalez MA, et al. The effect of the Mediterranean diet on plasma brain-derived neurotrophic factor (BDNF) levels: the PREDIMED-NAVARRA randomized trial. *Nutritional Neuroscience* 2011;14(5):195-201.
524. Sanchez-Villegas A, Martinez-Gonzalez MA, Estruch R, et al. Mediterranean dietary pattern and depression: the PREDIMED randomized trial. *BMC Medicine* 2013;11:208.
525. Sola R, Fito M, Estruch R, et al. Effect of a traditional Mediterranean diet on apolipoproteins B, A-I, and their ratio: a randomized, controlled trial. *Atherosclerosis* 2011;218(1):174-80.
526. Storniolo CE, Bullo M, Fito M, et al. Mediterranean diet with virgin olive oil or nuts modulate nitric oxide, endothelin-1 and blood pressure in hypertensive women. *Ann Nutr Metab* 2013;62:35.
527. Toledo E, Hu FB, Estruch R, et al. Effect of the Mediterranean diet on blood pressure in the PREDIMED trial: results from a randomized controlled trial. *BMC Medicine* 2013;11:207.
528. Toledo E, Hu FB, Estruch R, et al. Association between adherence to the Mediterranean diet and blood pressure: 4-year follow-up in the PREDIMED trial. *European Journal of Epidemiology* 2012;1):S46-S47.
529. Toledo E, Salas-Salvado J, Donat-Vargas C, et al. Mediterranean Diet and Invasive Breast Cancer Risk Among Women at High Cardiovascular Risk in the PREDIMED Trial: A Randomized Clinical Trial. *JAMA Intern Med* 2015;175(11):1752-60.
530. Tresserra-Rimbau A, Guasch-Ferre M, Salas-Salvado J, et al. Intake of Total Polyphenols and Some Classes of Polyphenols Is Inversely Associated with Diabetes in Elderly People at High Cardiovascular Disease Risk. *J Nutr* 2016;9:9.
531. Tresserra-Rimbau A, Medina-Remon A, Perez-Jimenez J, et al. Dietary intake and major food sources of polyphenols in a Spanish population at high cardiovascular risk: the PREDIMED study. *Nutr Metab Cardiovasc Dis* 2013;23(10):953-59.
532. Tresserra-Rimbau A, Rimm EB, Medina-Remon A, et al. Inverse association between habitual polyphenol intake and incidence of cardiovascular events in the PREDIMED study. *Nutr Metab Cardiovasc Dis* 2014;24(6):639-47.
533. Tulipani S, Martinez Huelamo M, Rotches Ribalta M, et al. Oil matrix effects on plasma exposure and urinary excretion of phenolic compounds from tomato sauces: Evidence from a human pilot study. *Food Chemistry* 2012;130(3):581-90.
534. Urpi-Sarda M, Casas R, Chiva-Blanch G, et al. The Mediterranean diet pattern and its main components are associated with lower plasma concentrations of tumor necrosis factor receptor 60 in patients at high risk for cardiovascular disease. *J Nutr* 2012;142(6):1019-25.
535. Valderas-Martinez P, Casas R, Arranz S, et al. Changes in cellular inflammatory biomarkers related to Atherosclerosis after consumption of tomato sauces. *Ann Nutr Metab* 2011;58:320-21.
536. Valderas-Martinez P, Chiva-Blanch G, Casas R, et al. Tomato Sauce Enriched with Olive Oil Exerts Greater Effects on Cardiovascular Disease Risk Factors than Raw Tomato and Tomato Sauce: A Randomized Trial. *Nutrients* 2016;8(3):170.
537. Valls-Pedret C, Sala-Vila A, Serra-Mir M, et al. Mediterranean Diet and Age-Related Cognitive Decline: A Randomized Clinical Trial. *JAMA Intern Med* 2015;175(7):1094-103.
538. Vazquez C, Botella-Carretero JI, Corella D, et al. White fish reduces cardiovascular risk factors in patients with metabolic syndrome: The WISH-CARE study, a multicenter randomized clinical trial. *Nutrition, Metabolism and Cardiovascular Diseases* 2014;24(3):328-35.

539. Vazquez-Fresno R, Llorach R, Urpi-Sarda M, et al. Metabolomic pattern analysis after mediterranean diet intervention in a nondiabetic population: a 1- and 3-year follow-up in the PREDIMED study. *Journal of Proteome Research* 2015;14(1):531-40.
540. Zamora-Ros R, Serafini M, Estruch R, et al. Mediterranean diet and non enzymatic antioxidant capacity in the PREDIMED study: evidence for a mechanism of antioxidant tuning. *Nutr Metab Cardiovasc Dis* 2013;23(12):1167-74.
541. Zazpe I, Estruch R, Toledo E, et al. Predictors of adherence to a Mediterranean-type diet in the PREDIMED trial. *Eur J Nutr* 2010;49(2):91-99.
542. Zazpe I, Sanchez-Tainta A, Estruch R, et al. A large randomized individual and group intervention conducted by registered dietitians increased adherence to Mediterranean-type diets: the PREDIMED study. *J Am Diet Assoc* 2008;108(7):1134-44.
543. Proudman S, Spargo L, Hall C, et al. Fish oil in rheumatoid arthritis: a randomised, double blind trial comparing high dose with low dose. *Intern Med J* 2012;42(Suppl 1):2-3.
544. Proudman SM, Cleland LG, Metcalf RG, et al. Plasma n-3 fatty acids and clinical outcomes in recent-onset rheumatoid arthritis. *Br J Nutr* 2015;114(6):885-90.
545. Proudman SM, James MJ, Spargo LD, et al. Fish oil in recent onset rheumatoid arthritis: a randomised, double-blind controlled trial within algorithm-based drug use. *Ann Rheum Dis* 2015;74(1):89-95.
546. Proudman S, Cleland L, Wechalekar MD, et al. Relationship between plasma omega-3 fatty acids and clinical outcomes in recent onset rheumatoid arthritis. *Intern Med J* 2014;44(suppl 2):24.
547. Puri BK, Leavitt BR, Hayden MR, et al. Ethyl-EPA in Huntington disease: a double-blind, randomized, placebo-controlled trial. *Neurology* 2005;65(2):286-92.
548. Puri BK, Bydder GM, Manku MS, et al. Reduction in cerebral atrophy associated with ethyl-eicosapentaenoic acid treatment in patients with Huntington's disease. *Journal of International Medical Research* 2008;36(5):896-905.
549. Raitt MH, Connor WE, Morris C, et al. Fish oil supplementation and risk of ventricular tachycardia and ventricular fibrillation in patients with implantable defibrillators: a randomized controlled trial. *Jama* 2005;293(23):2884-91.
550. Ramirez-Ramirez V, Macias-Islas MA, Ortiz GG, et al. Efficacy of fish oil on serum of TNF alpha , IL-1 beta , and IL-6 oxidative stress markers in multiple sclerosis treated with interferon beta-1b. *Oxid Med Cell Longev* 2013;2013:709493.
551. Sorto-Gomez TE, Ortiz GG, Pacheco-Moises FP, et al. Effect of fish oil on glutathione redox system in multiple sclerosis. *American Journal of Neurodegenerative Diseases* 2016;5(2):145-51.
552. Rebello CJ, Keller JN, Liu AG, et al. Pilot feasibility and safety study examining the effect of medium chain triglyceride supplementation in subjects with mild cognitive impairment: A randomized controlled trial. *BBA Clinical* 2015;3:123-25.
553. Bhatt DL, Steg PG, Miller M, et al. Cardiovascular Risk Reduction with Icosapent Ethyl for Hypertriglyceridemia. *N Engl J Med* 2018 doi: 10.1056/NEJMoa1812792
554. Olendzki BC, Leung K, Van Buskirk S, et al. Treatment of rheumatoid arthritis with marine and botanical oils: influence on serum lipids. *Evid Based Complement Alternat Med* 2011;2011:827286.
555. Reed GW, Leung K, Rossetti RG, et al. Treatment of rheumatoid arthritis with marine and botanical oils: an 18-month, randomized, and double-blind trial. *Evid Based Complement Alternat Med* 2014;2014:857456.
556. Rischio, Prevenzione I. Efficacy of n-3 polyunsaturated fatty acids and feasibility of optimizing preventive strategies in patients at high cardiovascular risk: rationale, design and baseline characteristics of the Rischio and Prevenzione study, a large randomised trial in general practice. *Trials* 2010;11:68.
557. Roncaglioni MC, Tombesi M, Avanzini F, et al. N-3 fatty acids in patients with multiple cardiovascular risk factors. *N Engl J Med* 2013;368(19):1800-08. doi: 10.1056/NEJMoa1205409
558. Visentin G, Risk, Prevention Study G. Towards evidence-based practice via practice-based evidence: the Italian experience. *Family Practice* 2008;25 Suppl 1:i71-i74.
559. Marchioli R. Omega 3 fatty acids and heart disease risk reduction. *Atherosclerosis Supplements Conference: 15th International Symposium on Atherosclerosis Boston, MA United States Conference Start* 2009;10(2)
560. Romero Imbroda J. The role of Omega-3 fatty acids in patients with mild cognitive impairment by means of the PHOTOTEST. *Journal of the Neurological Sciences* 2013;333:e610.
561. Rose GA, Thomson WB, Williams RT. Corn oil in treatment of ischaemic heart disease. *Br Med J* 1965;1857(5449):1531-33.

562. Myrup B, Rossing P, Jensen T, et al. Lack of effect of fish oil supplementation on coagulation and transcapillary escape rate of albumin in insulin-dependent diabetic patients with diabetic nephropathy. *Scand J Clin Lab Invest* 2001;61(5):349-56.
563. Rossing P, Hansen BV, Nielsen FS, et al. Fish oil in diabetic nephropathy. *Diabetes Care* 1996;19(11):1214-19.
564. Salari Sharif P, Asalforoush M, Ameri F, et al. The effect of n-3 fatty acids on bone biomarkers in Iranian postmenopausal osteoporotic women: a randomized clinical trial. *Age* 2010;32(2):179-86.
565. Sandhu N, Schetter SE, Liao J, et al. Influence of Obesity on Breast Density Reduction by Omega-3 Fatty Acids: Evidence from a Randomized Clinical Trial. *Cancer Prev Res* 2016;9(4):275-82.
566. Signori C, DuBrock C, Richie JP, et al. Administration of omega-3 fatty acids and Raloxifene to women at high risk of breast cancer: interim feasibility and biomarkers analysis from a clinical trial. *Eur J Clin Nutr* 2012;66(8):878-84.
567. Sasaki J, Miwa T, Odawara M. Administration of highly purified eicosapentaenoic acid to statin-treated diabetic patients further improves vascular function. *Endocr J* 2012;59(4):297-304.
568. Sawada T, Tsubata H, Hashimoto N, et al. Effects of 6-month eicosapentaenoicacid treatment on postprandial hyperglycemia,hyperlipidemia, insulin secretion ability, and concomitant endothelial dysfunction among newly-diagnosed impaired glucose metabolism patients with coronary artery disease. An open label, single blinded,prospective randomized controlled trial. *Cardiovasc Diabetol* 2016;15(1):121. doi: DOI 10.1186/s12933-DOI 10.1016-0437-y
569. Schättin A. Influence of exergame training and its combination with omega-3 fatty acids on the elderly brain. ET Zurich, 2017.
570. Schattin A, de Bruin ED. Combining Exergame training with omega-3 fatty acid supplementation: protocol for a randomized controlled study assessing the effect of neuronal structure/ function in the elderly brain. *Front Aging Neurosci* 2016;8:283.
571. Schirmer MA, Phinney SD. Gamma-linolenate reduces weight regain in formerly obese humans. *J Nutr* 2007;137(6):1430-35.
572. Angerer P, Kothny W, Stork S, et al. Effect of dietary supplementation with omega-3 fatty acids on progression of atherosclerosis in carotid arteries. *Cardiovascular Research* 2002;54(1):183-90.
573. von Schacky C, Angerer P, Kothny W, et al. The effect of dietary omega-3 fatty acids on coronary atherosclerosis. A randomized, double-blind, placebo-controlled trial. *Ann Intern Med* 1999;130(7):554-62.
574. von Schacky C, Baumann K, Angerer P. The effect of n-3 fatty acids on coronary atherosclerosis: results from SCIMO, an angiographic study, background and implications. *Lipids* 2001;36 Suppl:S99-102.
575. Hull MA, Sandell AC, Montgomery AA, et al. A randomized controlled trial of eicosapentaenoic acid and/or aspirin for colorectal adenoma prevention during colonoscopic surveillance in the NHS Bowel Cancer Screening Programme (The seAFOod Polyp Prevention Trial): study protocol for a randomized controlled trial. *Trials* 2013;14:237-37.
576. Hull MA, Sprange K, Hepburn T, et al. Eicosapentaenoic acid and aspirin, alone and in combination, for the prevention of colorectal adenomas (seAFOod Polyp Prevention trial): a multicentre, randomised, double-blind, placebo-controlled, 2 × 2 factorial trial. *The Lancet* 2018;392(10164):2583-94. doi: 10.1016/S0140-6736(18)31775-6
577. Sprange K, Mitchell EA, Hull M, et al. No drug, no trial? Think again!. Trials. *Trials* 2015;16(Suppl 2):P201.
578. Shimizu H, Ohtani K, Tanaka Y, et al. Long-term effect of eicosapentaenoic acid ethyl (EPA-E) on albuminuria of non-insulin dependent diabetic patients. *Diabetes Res Clin Pract* 1995;28(1):35-40.
579. Shinto L, Quinn J, Montine T, et al. A randomized placebo-controlled pilot trial of omega-3 fatty acids and alpha lipoic acid in Alzheimer's disease. *Journal of Alzheimer's Disease: JAD* 2014;38(1):111-20.
580. Shinto L, Silbert LC, Dodge HH, et al. Omega 3 fatty acids for the prevention of vascular cognitive aging: Methods and rationale for a phase ii trial. *Alzheimer's dement* 2015;1):610.
581. Eritsland J, Arnesen H, Berg K, et al. Serum Lp(a) lipoprotein levels in patients with coronary artery disease and the influence of long-term n-3 fatty acid supplementation. *Scand J Clin Lab Invest* 1995;55(4):295-300.
582. Eritsland J, Arnesen H, Gronseth K, et al. Effect of dietary supplementation with n-3 fatty acids on coronary artery bypass graft patency. *Am J Cardiol* 1996;77(1):31-36.
583. Eritsland J, Arnesen H, Gronseth K, et al. Effect of supplementation with n-3 fatty acids on graft patency in patients undergoing coronary artery bypass operation. Results from SHOT study [abstract]. *Eur Heart J* 1994;15:29-29.
584. Eritsland J, Arnesen H, Seljeflot I, et al. Long-term metabolic effects of n-3 polyunsaturated fatty acids in patients with coronary artery disease. *Am J Clin Nutr* 1995;61(4):831-36.

585. Eritsland J, Arnesen H, Seljeflot I, et al. Long-term effects of n-3 polyunsaturated fatty acids on haemostatic variables and bleeding episodes in patients with coronary artery disease. *Blood Coagul Fibrinolysis* 1995;6(1):17-22.
586. Eritsland J, Seljeflot I, Abdelnoor M, et al. Long-term influence of omega-3 fatty acids on fibrinolysis, fibrinogen, and serum lipids. *Fibrinolysis* 1994;8(2):120-25.
587. Eritsland J, Seljeflot I, Abdelnoor M, et al. Long-term effects of n-3 fatty acids on serum lipids and glycaemic control. *Scand J Clin Lab Invest* 1994;54(4):273-80.
588. Eritsland J, Seljeflot I, Arnesen H, et al. Long-term effects of fish oil supplementation in patients with coronary artery disease: influence on lipoproteins, coagulation and fibrinolysis [abstract]. *Thromb Res* 1992;65:75.
589. Eritsland J, Seljeflot I, Arnesen H, et al. Long-term influence of omega-3 fatty acids on fibrinolysis, fibrinogen, and serum lipids [abstract]. *Thromb Haemost* 1993;69:1065-65.
590. Eritsland J, Seljeflot I, Arnesen H, et al. Effect of long-term, moderate-dose supplementation with omega-3 fatty acids on monocyte procoagulant activity and release of interleukin-6 in patients with coronary artery disease. *Thromb Res* 1995;77(4):337-46.
591. Sianni A, Matsoukis I, Ganotopoulou A, et al. Effect of omega 3 fatty acids in patients with hypertension and atrial fibrillation. *Clinical Nutrition* 2013;32:S70-S71. doi: 10.1016/S0261-5614(13)60173-9
592. Djuric Z, Heilbrun LK, Reading BA, et al. Effects of a low fat diet on levels of oxidative damage to DNA in human peripheral nucleated blood cells. *Journal of the National Cancer Institute* 1991;83(11):766-69.
593. Djuric Z, Martino S, Heilbrun LK, et al. Dietary modulation of oxidative DNA damage. *Advances In Experimental Medicine and Biology* 1994;354:71-83.
594. Kasim SE, Martino S, Kim PN, et al. Dietary and anthropometric determinants of plasma lipoproteins during a long-term low-fat diet in healthy women. *Am J Clin Nutr* 1993;57:146-53.
595. Simon MS, Heilbrun LK, Boomer A, et al. A randomised trial of a low-fat dietary intervention in women at high risk for breast cancer. *Nutr Cancer* 1997;27(2):136-42.
596. Simon MS, Lababidi S, Djuric Z, et al. Comparison of dietary assessment methods in a low-fat dietary intervention program. *Nutr Cancer* 2001;40(2):108-17.
597. Sinn N, Milte CM, Street SJ, et al. Effects of n-3 fatty acids, EPA v. DHA, on depressive symptoms, quality of life, memory and executive function in older adults with mild cognitive impairment: a 6-month randomised controlled trial. *Br J Nutr* 2012;107(11):1682-93.
598. O'Callaghan N, Parletta N, Milte CM, et al. Telomere shortening in elderly individuals with mild cognitive impairment may be attenuated with omega-3 fatty acid supplementation: a randomized controlled pilot study. *Nutrition* 2014;30(4):489-91.
599. Milte CM, Sinn N, Street SJ, et al. Erythrocyte polyunsaturated fatty acid status, memory, cognition and mood in older adults with mild cognitive impairment and healthy controls. *Prostaglandins, Leukotrienes and Essential Fatty Acids (PLEFA)* 2011;84(5):153-61. doi: https://doi.org/10.1016/j.plefa.2011.02.002
600. Skoldstam L, Borjesson O, Kjallman A, et al. Effect of six months of fish oil supplementation in stable rheumatoid arthritis. A double-blind, controlled study. *Scandinavian journal of rheumatology* 1992;21(4):178-85.
601. Anil S, Charlton KE, Tapsell LC, et al. Identification of dietary patterns associated with blood pressure in a sample of overweight Australians. *J Hum Hypertens* 2016;30(11):672-78.
602. Tapsell LC, Batterham MJ, Charlton KE. Effect of dietary restriction and n-3PUFA supplementation on insulin resistance in obese adults. *FASEB Journal Conference: Experimental Biology* 2010;24(no pagination)
603. Tapsell LC, Batterham MJ, Charlton KE, et al. Foods, nutrients or whole diets: effects of targeting fish and LCn3PUFA consumption in a 12mo weight loss trial. *BMC Public Health* 2013;13:1231-31.
604. Zhang Q, O'Shea JE, Thorne RL, et al. Baseline characteristics of volunteers in the smart clinical trial: associations between habitual physical activity and lifestyle disease risk factors. *Nutrition and Dietetics* 2010;67(Suppl 1):67-68.
605. Tapsell LC, Batterham MJ, Charlton KE. Effects of n-3 fatty acids on weight loss: A 1 year randomized controlled trial. *FASEB Journal Conference: Experimental Biology* 2011;25(no pagination)
606. Thorne RL, O'Shea JE, Zhang Q, et al. Fibre: male participants not getting enough [abstract]. *Nutrition and Dietetics* 2010;67(S1):12-13.
607. Smith GI, Julliand S, Reeds DN, et al. Fish oil-derived n-3 PUFA therapy increases muscle mass and function in healthy older adults. *Am J Clin Nutr* 2015;102(1):115-22.
608. Yoshino J, Smith GI, Kelly SC, et al. Effect of dietary n-3 PUFA supplementation on the muscle transcriptome in older adults. *Physiol Rep* 2016;4(11)

609. Hershman DL, Unger JM, Crew KD, et al. Randomized Multicenter Placebo-Controlled Trial of Omega-3 Fatty Acids for the Control of Aromatase Inhibitor-Induced Musculoskeletal Pain: SWOG S0927. *Journal of Clinical Oncology* 2015;33(17):1910-17.
610. Hershman DL, Unger JM, Crew KD, et al. Omega-3 fatty acids for aromatase inhibitor-induced musculoskeletal symptoms in women with early-stage breast cancer (SWOG S0927). *Journal of Clinical Oncology Conference* 2014;32(15 SUPPL. 1)
611. Hershman DL, Unger JM, Crew KD, et al. SWOG S0927: A randomized double blind placebo-controlled trial of omega-3-fatty acid for the control of aromatase inhibitor (AI)-induced musculoskeletal pain in women with early stage breast cancer. *Cancer Research Conference: 34th Annual CTRC AACR San Antonio Breast Cancer Symposium San Antonio, TX United States Conference Start* 2011;71(24 SUPPL. 3)
612. Brouwer IA, Katan MB, Schouten EG, et al. Rationale and design of a clinical trial on n-3 fatty acids and cardiac arrhythmia (SOFA). *Ann Nutr Metab* 2001;45(Suppl 1):79-79.
613. Brouwer IA, Katan MB, Zock PL. Effects of n-3 fatty acids on arrhythmic events and mortality in the SOFA implantable cardioverter defibrillator trial. *Am J Clin Nutr* 2006;84(6):1554.
614. Brouwer IA, Raitt MH, Dullemeijer C, et al. Effect of fish oil on ventricular tachyarrhythmia in three studies in patients with implantable cardioverter defibrillators. *Eur Heart J* 2009;30(7):820-26.
615. Brouwer IA, Zock PL, Camm AJ, et al. Effect of fish oil on ventricular tachyarrhythmia and death in patients with implantable cardioverter defibrillators: the Study on Omega-3 Fatty Acids and Ventricular Arrhythmia (SOFA) randomized trial. *Jama* 2006;295(22):2613-19.
616. Brouwer IA, Zock PL, Wever EF, et al. Rationale and design of a randomised controlled clinical trial on supplemental intake of n-3 fatty acids and incidence of cardiac arrhythmia: SOFA. *Eur J Clin Nutr* 2003;57(10):1323-30.
617. Sofi F, Giangrandi I, Cesari F, et al. Effects of a 1-year dietary intervention with n-3 polyunsaturated fatty acid-enriched olive oil on non-alcoholic fatty liver disease patients: a preliminary study. *Int J Food Sci Nutr* 2010;61(8):792-802.
618. Spadaro L, Magliocco O, Spampinato D, et al. Effects of n-3 polyunsaturated fatty acids in subjects with nonalcoholic fatty liver disease. *Dig Liver Dis* 2008;40(3):194-99.
619. Stammers T, Sibbald B, Freeling P. Efficacy of cod liver oil as an adjunct to non-steroidal anti-inflammatory drug treatment in the management of osteoarthritis in general practice. *Ann Rheum Dis* 1992;51(1):128-29.
620. Stonehouse et al. DHA supplementation improved both memory and reaction time in healthy young adults: a randomized controlled trial. *Am J Clin Nutr* 2013;97(5):1134-43.
621. Ahluwalia N, Blacher J, Szabo De Edelenyi F, et al. Prognostic value of multiple emerging biomarkers in cardiovascular risk prediction in patients with stable cardiovascular disease. *Atherosclerosis* 2013;228(2):478-84.
622. Andreeva VA, Galan P, Torres M, et al. Supplementation with B vitamins or n-3 fatty acids and depressive symptoms in cardiovascular disease survivors: ancillary findings from the SUpplementation with FOLate, vitamins B-6 and B-12 and/or OMega-3 fatty acids (SU.FOL.OM3) randomized trial. *Am J Clin Nutr* 2012;96(1):208-14.
623. Andreeva VA, Kesse-Guyot E, Barberger-Gateau P, et al. Cognitive function after supplementation with B vitamins and long-chain omega-3 fatty acids: ancillary findings from the SU.FOL.OM3 randomized trial. *Am J Clin Nutr* 2011;94(1):278-86.
624. Andreeva VA, Latarche C, Hercberg S, et al. B vitamin and/or n-3 fatty acid supplementation and health-related quality of life: ancillary findings from the SU.FOL.OM3 randomized trial. *PLoS ONE* 2014;9(1):e84844.
625. Andreeva VA, Touvier M, Kesse-Guyot E, et al. B vitamin and/or omega-3 fatty acid supplementation and cancer: ancillary findings from the supplementation with folate, vitamins B6 and B12, and/or omega-3 fatty acids (SU.FOL.OM3) randomized trial. *Arch Intern Med* 2012;172(7):540-47.
626. Arnaud J, Bost M, Vitoux D, et al. Effect of low dose antioxidant vitamin and trace element supplementation on the urinary concentrations of thromboxane and prostacyclin metabolites. *J Am Coll Nutr* 2007;26(5):405-11.
627. Astorg P, Bertrais S, Alessandri JM, et al. Long-chain n-3 fatty acid levels in baseline serum phospholipids do not predict later occurrence of depressive episodes: a nested case-control study within a cohort of middle-aged French men and women. *Prostaglandins Leukot Essent Fatty Acids* 2009;81(4):265-71.
628. Astorg P, Couthouis A, Bertrais S, et al. Association of fish and long-chain n-3 polyunsaturated fatty acid intakes with the occurrence of depressive episodes in middle-aged French men and women. *Prostaglandins Leukot Essent Fatty Acids* 2008;78(3):171-82.

629. Blacher J, Czernichow S, Paillard F, et al. Cardiovascular effects of B-vitamins and/or n-3 fatty acids: the SU.FOL.OM3 trial. *Int J Cardiol* 2013;167(2):508-13.
630. Blacher J, Safar ME, Ly C, et al. Blood pressure variability: Cardiovascular risk integrator or independent risk factor. *Journal of Human Hypertension* 2015;29(2):122-26.
631. Czernichow S, Bruckert E, Oppert JM, et al. Intake of added oils and fats among middle-aged French adults: relationships with educational level and region of residence. *J Am Diet Assoc* 2005;105(12):1889-94.
632. de Bree A, Mennen LI, Hercberg S, et al. Evidence for a protective (synergistic?) effect of B-vitamins and omega-3 fatty acids on cardiovascular diseases. *Eur J Clin Nutr* 2004;58(5):732-44.
633. Fezeu LK, Laporte F, Kesse-Guyot E, et al. Baseline plasma fatty acids profile and incident cardiovascular events in the SU.FOL.OM3 trial: the evidence revisited. *PLOS ONE* 2014;9(4):e92548-e48.
634. Galan P, Briancon S, Blacher J, et al. The SU.FOL.OM3 Study: a secondary prevention trial testing the impact of supplementation with folate and B-vitamins and/or Omega-3 PUFA on fatal and non fatal cardiovascular events, design, methods and participants characteristics. *Trials* 2008;9:35.
635. Galan P, Briancon S, Blacher J, et al. The scientific basis of the SU.FOL.OM3 study: A secondary intervention trial of folate, B6 and B12 vitamins and/or omega3 falty acid supplements in the prevention of recurrent ischemic events. [French]. *Sang Thrombose Vaisseaux* 2009;21(4):207-13.
636. Galan P, de Bree A, Mennen L, et al. Background and rationale of the SU.FOL.OM3 study: double-blind randomized placebo-controlled secondary prevention trial to test the impact of supplementation with folate, vitamin B6 and B12 and/or omega-3 fatty acids on the prevention of recurrent ischemic events in subjects with atherosclerosis in the coronary or cerebral arteries. *J Nutr Health Aging* 2003;7(6):428-35.
637. Galan P, Kesse-Guyot E, Czernichow S, et al. Effects of B vitamins and omega 3 fatty acids on cardiovascular diseases: A randomised placebo controlled trial. *Br Med J* 2011;342(7787):36.
638. Kesse-Guyot E, Peneau S, Hercberg S, et al. Thirteen-year prospective study between fish consumption, long-chain N-3 fatty acids intakes and cognitive function. *J Nutr Health Aging* 2011;15(2):115-20.
639. Szabo De Edelenyi F, Vergnaud AC, Ahluwalia N, et al. Effect of B-vitamins and n-3 PUFA supplementation for 5 years on blood pressure in patients with CVD. *Br J Nutr* 2012;107(6):921-27.
640. Vesin C, Galan P, Gautier B, et al. Control of baseline cardiovascular risk factors in the SU-FOL-OM3 study cohort: does the localization of the arterial event matter? *Eur J Cardiovasc Prev Rehabil* 2010;17(5):541-48.
641. Blacket RB, Leelarthaepin B, McGilchrist C, et al. The synergistic effect of weight loss and changes in dietary lipids on the serum cholesterol of obese men with hypercholesterolaemia: implications for prevention of coronary heart disease. *Australian and New Zealand Journal of Medicine* 1979;9:521-29.
642. Ramsden CE, Zamora D, Leelarthaepin B, et al. Use of dietary linoleic acid for secondary prevention of coronary heart disease and death: evaluation of recovered data from the Sydney Diet Heart Study and updated meta-analysis. (Erratum appears in BMJ. 2013;346:f903). *Br Med J* 2013;346:e8707-e07.
643. Woodhill JM, Palmer AJ, Leelarthaepin B, et al. Low fat, low cholesterol diet in secondary prevention of coronary heart disease. *Advances in Experimental Medicine and Biology* 1978;109:317-30.
644. Tajalizadekhoob Y, Sharifi F, Fakhrzadeh H, et al. The effect of low-dose omega 3 fatty acids on the treatment of mild to moderate depression in the elderly: a double-blind, randomized, placebo-controlled study. *Eur Arch Psychiatry Clin Neurosci* 2011;261(8):539-49.
645. Tande KS, Vo TD, Lynch BS. Clinical safety evaluation of marine oil derived from Calanus finmarchicus. *Regul Toxicol Pharmacol* 2016;80:25-31.
646. Tani S, Hirayama A, Atsumi W, et al. Impact of adding eicosapentaenoic acid to strong statin therapy on serum pentraxin X3 level: A six-month, randomized control study. *Eur Heart J* 2015;36:180.
647. Tani S, Nagao K, Matsumoto M, et al. Highly purified eicosapentaenoic acid may increase low-density lipoprotein particle size by improving triglyceride metabolism in patients with hypertriglyceridemia. *Circ J* 2013;77(9):2349-57.
648. Tani S, Nagao K, Yagi T, et al. impact of accing eicosapentaenoic acid to statin therapy on plasma pentraxin 3 level in patients with stable coronary artery disease: a 6-month, randomized controlled study. *Am J Cardiovasc Drugs* 2017;17:49-59.
649. Gillen LJ, Tapsell LC, Patch CS, et al. Structured dietary advice incorporating walnuts achieves optimal fat and energy balance in patients with type 2 diabetes mellitus. *J Am Diet Assoc* 2005;105(7):1087-96.
650. Tapsell LC, Gillen LJ, Patch CS, et al. Including walnuts in a low-fat/modified-fat diet improves HDL cholesterol-to-total cholesterol ratios in patients with type 2 diabetes. *Diabetes Care* 2004;27(12):2777-83.

651. Tapsell LC, Hokman A, Sebastiao A, et al. The impact of usual dietary patterns, selection of significant foods and cuisine choices on changing dietary fat under 'free living' conditions. *Asia Pacific Journal of Clinical Nutrition* 2004;13(1):86-91.
652. Martin GS, Tapsell LC, Denmeade S, et al. Relative validity of a diet history interview in an intervention trial manipulating dietary fat in the management of Type II diabetes mellitus☆. *Preventive Medicine* 2003;36(4):420-28. doi: https://doi.org/10.1016/S0091-7435(02)00054-3
653. Tardivo AP, Nahas-Neto J, Orsatti CL, et al. Effects of omega-3 on metabolic markers in postmenopausal women with metabolic syndrome. *Climacteric* 2015;18(2):290-98.
654. Tardivo AP, Nahas-Neto J, Orsatti CL, et al. Effect of diet and omega 3 supplementation on the metabolic and inflammatory markers in postmenopausal women with metabolic syndrome. *Menopause* 2013;20 (12):1345.
655. Tartibian B, Hajizadeh Maleki B, Kanaley J, et al. Long-term aerobic exercise and omega-3 supplementation modulate osteoporosis through inflammatory mechanisms in post-menopausal women: a randomized, repeated measures study. *Nutr Metab* 2011;8:71.
656. Terano T, Fujishiro S, Ban K. Yamamoto K, et al. Docosahexaenoic acid supplementation improves the moderately severe dementia from thrombotic cerebrovascular diseases. *Lipids* 1999;34:S345-S46.
657. Tuttle KR, Shuler LA, Packard DP, et al. Comparison of low-fat versus Mediterranean-style dietary intervention after first myocardial infarction (from The Heart Institute of Spokane Diet Intervention and Evaluation Trial). *Am J Cardiol* 2008;101(11):1523-30.
658. Dorsey ER. Randomized controlled trial of ethyl-eicosapentaenoic acid in huntington disease the trend-hd study. *Arch Neurol* 2008;65(12):1582-89.
659. Vanlint SJ, Ried K. Efficacy and tolerability of calcium, vitamin D and a plant-based omega-3 oil for osteopenia: a pilot RCT. *Maturitas* 2012;71(1):44-48.
660. Varghese TJ, Coomansingh D, Richardson S, et al. Clinical response of ulcerative colitis with dietary omega-3 fatty acids: a double-blind randomized study [abstract]. *Br J Surg* 2000;87(1):73-73.
661. Kopecky J, Veleba J, Janovska P, et al. Combined intervention with pioglitazone and n-3 fatty acids in metformin-treated diabetic patients. *Diabetologia* 2015;1):S342-S43.
662. Veleba J, Kopecky J, Jr., Janovska P, et al. Combined intervention with pioglitazone and n-3 fatty acids in metformin-treated type 2 diabetic patients: improvement of lipid metabolism. *Nutr Metab* 2015;12:52.
663. Dayton S, Hashimoto S, Dixon W, et al. Composition of lipids in human serum and adipose tissue during prolonged feeding of a diet high in unsaturated fat. *J Lipid Res* 1966;7:103-11.
664. Dayton S, Hashimoto S, Pearce ML. Adipose tissue linoleic acid as a criterion of adherence to a modified diet. *J Lipid Res* 1967;8:508-10.
665. Dayton S, Hashimoto S, Pearce ML. Influence of a diet high in unsaturated fat upon composition of arterial tissue and atheromata in man. *Circulation* 1965;32:911-24.
666. Dayton S, Hashimoto S, Rosenblum D, et al. Vitamin E status of humans during prolonged feeding of unsaturated fats. *Journal of Laboratory and Clinical Medicine* 1965;65(5):739-47.
667. Dayton S, Pearce ML. Diet high in unsaturated fat: a controlled clinical trial. *Minnesota Medicine* 1969;1969:1237-42.
668. Dayton S, Pearce ML. Diet and cardiovascular diseases. *Lancet* 1969;1(584):51-52.
669. Dayton S, Pearce ML. Trial of unsaturated-fat diet. *Lancet* 1968;2(581):1296-97.
670. Dayton S, Pearce ML. Prevention of coronary heart disease and other complications of atherosclerosis by modified diet. *American Journal of Medicine* 1969;46:751-62.
671. Dayton S, Pearce ML, Goldman H, et al. Controlled trial of a diet high in unsaturated fat for prevention of atherosclerotic complications. *Lancet* 1968;2(577):1060-62.
672. Dayton S, Pearce ML, Hashimoto S, et al. A controlled clinical trial of a diet high in unsaturated fat in preventing complications of atherosclerosis. *Circulation* 1969;15(1, Suppl 2):II-1-63.
673. Dayton S, Pearce ML, Hashimoto S, et al. A controlled clinical trial of a diet high in unsaturated fat. Preliminary observations. *NEJM* 1962;266(20):1017-23.
674. Hiscock E, Dayton S, Pearce ML, et al. A palatable diet high in unsaturated fat. *J Am Diet Assoc* 1962;40:427-31.
675. Pearce ML, Dayton S. Incidence of cancer in men on a diet high in polyunsaturated fat. *Lancet* 1971;1(7697):464-67.
676. Sturdevant RA, Pearce ML, Dayton S. Increased prevalence of cholelithiasis in men ingesting a serum-cholesterol-lowering diet. *N Engl J Med* 1973;288(1):24-27.
677. Tompkins MJ, Dayton S, Pearce ML. Effect of long-term feeding of various fats on whole blood clotting times in men. *Journal of Laboratory and Clinical Medicine* 1964;64(5):763-72.

678. Dayton S, Pearce ML. Diet and atherosclerosis. *Lancet* 1970;1(644):473-74.
679. Nandakumar S, Vijayakumar M, Krishnan S. Coconut oil Vs Sunfloweroil in atherosclerosis-Challenges in dietary intervention. *Indian Heart J* 2014;66:S11.
680. Vijayakumar M, Krishnaan S, Sundram KR, et al. What oil in patients with established coronory artery disease: outcomes of two year dietary intervention with coconut oil & sunflower oil. *Indian Heart J* 2014;66:S12.
681. Vijayakumar M, Vasudevan DM, Sundaram KR, et al. A randomized study of coconut oil versus sunflower oil on cardiovascular risk factors in patients with stable coronary heart disease. *Indian Heart J* 2016;68:498-506.
682. Manson JE, Bassuk SS, Lee IM, et al. The VITamin D and OmegA-3 TriaL (VITAL): rationale and design of a large randomized controlled trial of vitamin D and marine omega-3 fatty acid supplements for the primary prevention of cancer and cardiovascular disease. *Contemp Clin Trials* 2012;33(1):159-71.
683. Manson JE, Cook NR, Lee IM, et al. Marine n−3 Fatty Acids and Prevention of Cardiovascular Disease and Cancer. *N Engl J Med* 2018 doi: 10.1056/NEJMoa1811403
684. Bassuk SS, Manson JE, Lee IM, et al. Baseline characteristics of participants in the VITamin D and OmegA-3 TriaL (VITAL). *Contemp Clin Trials* 2016;47:235-43.
685. Gold DR, Litonjua AA, Carey VJ, et al. Lung VITAL: Rationale, design, and baseline characteristics of an ancillary study evaluating the effects of vitamin D and/or marine omega-3 fatty acid supplements on acute exacerbations of chronic respiratory disease, asthma control, pneumonia and lung function in adults. *Contemp Clin Trials* 2016;47:185-95.
686. Gold DR, Luttmann-Gibson H, Litonjua AA, et al. Baseline chronic obstructive pulmonary disease in the lung vitamin D and omega-3 trial. *American Journal of Respiratory and Critical Care Medicine Conference: American Thoracic Society International Conference, ATS* 2014;189(no pagination)
687. Kang JH, Grodstein F, Manson JAE. Cognitive substudy of the vitamin d and omega-3 trial (vital-cog): Design of a large randomized trial of omega-3 and vitamin d supplements in relation to cognitive change. *Alzheimer's dement* 2015;1):608.
688. LeBoff MS, Yue AY, Copeland T, et al. VITAL-Bone Health: rationale and design of two ancillary studies evaluating the effects of vitamin D and/or omega-3 fatty acid supplements on incident fractures and bone health outcomes in the VITamin D and OmegA-3 TriaL (VITAL). *Contemp Clin Trials* 2015;41:259-68.
689. Pradhan AD, Manson JE. Update on the Vitamin D and OmegA-3 trial (VITAL). *J Steroid Biochem Mol Biol* 2016;155(Pt B):252-56.
690. Bitok, Edward, Rajaram, et al. Does a Daily Walnut Supplement Given for a Year Result in Body Weight Gain? Faseb J, 2016:1157.5-57.5.
691. Bitok E, Jaceldo-Siegl K, Rajaram S, et al. Favourable nutrient intake and displacement with long-term walnut supplementation among elderly: results of a randomised trial. *Br J Nutr* 2017;118(3):201-09.
692. Bitok E, Rajaram S, Ros E. Does a daily walnut supplement given for a year result in body weight gain? FASEB Journal, 2016:1157.5-57.5.
693. Huey, Lynnley, Bitok, et al. Dietary compliance of walnut or no walnut intake in a 1-year randomized intervention trial among free-living elderly in the Walnuts and Healthy Aging Study (WAHA). Faseb J, 2016:1157.10-57.10.
694. Rajaram S, Valls-Pedret C, Cofan M, et al. The Walnuts and Healthy Aging Study (WAHA): Protocol for a Nutritional Intervention Trial with Walnuts on Brain Aging. *Front Aging Neurosci* 2016;8:333-33.
695. Ros, Emilio, Rajaram, et al. Effect of a 1-Year Walnut Supplementation on Blood Lipids among Older Individuals: Findings from the Walnuts and Healthy Aging (WAHA) study. Faseb J, 2016:293.4-93.4.
696. Wang F, Wang Y, Zhu Y, et al. Treatment for 6 months with fish oil-derived n-3 polyunsaturated fatty acids has neutral effects on glycemic control but improves dyslipidemia in type 2 diabetic patients with abdominal obesity: a randomized, double-blind, placebo-controlled trial. *Eur J Nutr* 2016;DOI 10.1007/s00394-016-1352-4
697. Weinstock-Guttman B, Baier M, Park Y, et al. Low fat dietary intervention with n-3 fatty acid supplementation in multiple sclerosis patients. *Prostaglandins Leukot Essent Fatty Acids* 2005;73:397-404.
698. Bhatia L, Scorletti E, Curzen N, et al. Improvement in non-alcoholic fatty liver disease severity is associated with a reduction in carotid intima-media thickness progression. *Atherosclerosis* 2016;246:13-20.
699. Byrne CD, Scorletti E, Bhatia L, et al. Benefits of docosahexanoic acid tissue enrichment in nonalcoholic fatty liver disease: Results from a randomised, double-blind, placebo-controlled study testing the effects of omega-3 fatty acid treatment. *Diabetes* 2014;63:A468.
700. Byrne CD, Targher G. Time to Replace Assessment of Liver Histology With MR-Based Imaging Tests to Assess Efficacy of Interventions for Nonalcoholic Fatty Liver Disease. Gastroenterology, 2016:7-10.

701. Clough GF, McCormick KG, Scorletti E, et al. Higher body fat percentage is associated with enhanced temperature perception in NAFLD: results from the randomised Wessex Evaluation of fatty Liver and Cardiovascular markers in NAFLD with OMacor thErapy trial (WELCOME) trial. *Diabetologia* 2016;59(7):1422-29.
702. McCormick KG, Scorletti E, Bhatia L, et al. Impact of high dose n-3 polyunsaturated fatty acid treatment on measures of microvascular function and vibration perception in non-alcoholic fatty liver disease: results from the randomised WELCOME trial. *Diabetologia* 2015;58(8):1916-25.
703. McCormick KG, Scorletti ES, Bhatia L, et al. Peripheral sensory nerve function is independently associated with microvascular function, but neither are improved by n-3 fatty acids. *Diabet Med* 2015;32:99.
704. Scorletti E, Bhatia B, McCormick KG, et al. Potential benefits of purified long chain omega-3 fatty acid treatment in non-alcoholic fatty liver disease (NAFLD): A potential treatment for early NAFLD in metabolic syndrome and Type 2 diabetes. Results from the WELCOME study. *Diabet Med* 2014;31:1.
705. Scorletti E, Bhatia L, McCormick KG, et al. 'Corrigendum to Design and rationale of the WELCOME trial: A randomised, placebo controlled study to test the efficacy of purified long chain omega-3 fatty treatment in non-alcoholic fatty liver disease [Contemp Clin Trials 37 (2) (2014) 301-311]'. *Contemp Clin Trials* 2014;38(1):156.
706. Scorletti E, Bhatia L, McCormick KG, et al. Design and rationale of the WELCOME trial: A randomised, placebo controlled study to test the efficacy of purified long chain omega-3 fatty acid treatment in non-alcoholic fatty liver disease. *Contemp Clin Trials* 2014;37(2):301-11.
707. Scorletti E, Bhatia L, McCormick KG, et al. Effects of purified eicosapentaenoic and docosahexaenoic acids in nonalcoholic fatty liver disease: results from the WELCOME study. *Hepatology* 2014;60(4):1211-21.
708. Scorletti E, West AL, Bhatia L, et al. Treating liver fat and serum triglyceride levels in NAFLD, effects of PNPLA3 and TM6SF2 genotypes: Results from the WELCOME trial. *J Hepatol* 2015;63(6):1476-83.
709. Targher G, Byrne CD. Clinical Review: Nonalcoholic fatty liver disease: a novel cardiometabolic risk factor for type 2 diabetes and its complications. *J Clin Endocrinol Metab* 2013;98(2):483-95.
710. Hodson L, Bhatia L, Scorletti E, et al. Docosahexaenoic acid enrichment in NAFLD is associated with improvements in hepatic metabolism and hepatic insulin sensitivity: a pilot study. *Eur J Clin Nutr* 2017;71(8):973-79.
711. Bhatia LS, Scorletti E, Shojaee-Moradie F, et al. High-dose n-3 fatty acid treatment in non-alcoholic fatty liver disease is independently associated with reduced hepatic steatosis and improved hepatic insulin sensitivity. *Diabet Med* 2014;31:53.
712. Westberg G, Tarkowski A. Effect of MaxEPA in patients with SLE. A double-blind, crossover study. *Scandinavian Journal of Rheumatology* 1990;19(2):137-43.
713. Westberg G, Tarkowski A. Effect of MaxEPA in patients with SLE: a double blind crossover study [abstract]. *Kidney International* 1989;35:235-35.
714. Chlebowski RT, Blackburn GL, Buzzard IM, et al. Adherence to a dietary fat intake reduction program in postmenopausal women receiving therapy for early breast cancer. The Women's Intervention Nutrition Study. *Journal of Clinical Oncology* 1993;11(11):2072-80.
715. Chlebowski RT, Blackburn GL, Thomson CA, et al. Dietary fat reduction and breast cancer outcome: interim efficacy results from the women's intervention nutrition study. *JNCI Journal of the National Cancer Institute* 2006;98(24):1767-76.
716. Chlebowski RT, Rose DP, Buzzard IM, et al. Dietary fat reduction in adjuvant breast cancer therapy: current rationale and feasibility issues. *Adjuvant The Cancer Journal* 1990;6:357-63.
717. Hoy MK, Winters BL, Chlebowski RT, et al. Implementing a low-fat eating plan in the Women's Intervention Nutrition Study. *J Am Diet Assoc* 2009;109(4):688-96.
718. Rose DP, Chlebowski RT, Connolly JM, et al. Effects of tamoxifen adjuvant therapy and a low-fat diet on serum binding proteins and estradiol bioavailability in postmenopausal breast cancer patients. *Cancer Research* 1992;52:5386-90.
719. Rose DP, Connolly JM, Chlebowski RT, et al. The effects of a low-fat dietary intervention and tamoxifen adjuvant therapy on the serum estrogen and sex hormone-binding globulin concentrations of postmenopausal breast cancer patients. *Breast Cancer Res Treat* 1993;27(3):253-62.
720. Wynder EL, Cohen LA, Winters BL. The challenges of assessing fat intake in cancer research investigations. *J Am Diet Assoc* 1997;97(7 Suppl):S5-S8.

721. Chlebowski RT, Rose DP, Buzzard IM, et al. Adjuvant dietary fat intake reduction in postmenopausal breast cancer patient management. The Women's Intervention Nutrition Study (WINS). *Breast Cancer Res Treat* 1992;20(2):73-84.
722. Buzzard IM, Faucett CL, Jeffery RW, et al. Monitoring Dietary Change in a Low-Fat Diet Intervention Study: Advantages of Using 24-Hour Dietary Recalls vs Food Records. *J Am Diet Assoc* 1996;96(6):574-79. doi: https://doi.org/10.1016/S0002-8223(96)00158-7
723. Winters BL, Mitchell DC, Smiciklas-Wright H, et al. Dietary patterns in women treated for breast cancer who successfully reduce fat intake: The Women's Intervention Nutrition Study (WINS). *J Am Diet Assoc* 2004;104(4):551-59. doi: https://doi.org/10.1016/j.jada.2004.01.012
724. Kulzow N, Witte AV, Kerti L, et al. Impact of Omega-3 Fatty Acid Supplementation on Memory Functions in Healthy Older Adults. *J Alzheimers Dis* 2016;51(3):713-25.
725. Witte AV, Kerti L, Hermannstadter HM, et al. Long-chain omega-3 fatty acids improve brain function and structure in older adults. *Cereb Cortex* 2014;24(11):3059-68.
726. Witte V, Kerti L, Floel A. Effects of omega-3 supplementation on brain structure and function in healthy elderly subjects. *Alzheimer's dement* 2012;1):441.
727. Wright SA, O'Prey FM, McHenry MT, et al. A randomised interventional trial of omega-3-polyunsaturated fatty acids on endothelial function and disease activity in systemic lupus erythematosus. *Ann Rheum Dis* 2008;67(6):841-48.
728. Zhang, Yan P, Rujuan Miao, et al. Effects of DHA supplementation on hippocampal volume and cognitive function in older adults with mild cognitive impairment: A 12-month randomized, double-blind, placebo-controlled trial. *J Alzheimers Dis* 2016;55(2):497-507.
729. Li D, Zheng JS, Lin M, et al. Change of plasma metabolites in response to omega-3 fatty acids in Chinese patients with type 2 diabetes: A double-blinded randomized controlled trial. *FASEB Journal Conference: Experimental Biology* 2015;29(1 Meeting Abstracts)
730. Zheng JS, Lin M, Fang L, et al. Effects of n-3 fatty acid supplements on glycemic traits in Chinese type 2 diabetic patients: A double-blind randomized controlled trial. *Mol Nutr Food Res* 2016;9:9-9.
731. Zheng JS, Lin M, Imamura F, et al. Serum metabolomics profiles in response to n-3 fatty acids in Chinese patients with type 2 diabetes: a double-blind randomised controlled trial. *Sci* 2016;6:29522-22.
732. Özaydin M, Erdoğan D, Tayyar S, et al. N-3 polyunsaturated fatty acids administration does not reduce the recurrence rates of atrial fibrillation and inflammation after electrical cardioversion: a prospective randomized study. *Anadolu Kardiyoloji Dergisi* 2011;11(4):305-09.