Supplementary File 2, Dataset 2.
Omega-3, omega-6 and total PUFA long-term RCT Database

(Supplementary File 2 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 96 included studies without relevant outcome data for our review set

Annuzzi 2014 - NCT01154478 [1-3]

Methods	RCT 2x2, (diet rich in LCn3 vs diet low in LCn3), 48 months (other intervention increases polyphenols) Summary risk of bias: not yet assessed
Participants	Overweight/ obese adults with a large waist circumference and another component of the metabolic syndrome N: 38 high LCn3 int., 40 low LCn3 control (of whom 39 were on high polyphenols, 39 on low polyphenols) Level of risk for CVD: moderate Location: Italy
Interventions	Type: Diet provided for 8 weeks, unclear how it worked for remaining 46 months Comparison: diet rich in LCn3 vs diet low in LCn3 Intervention: 1.5%E from n3 (0.46%E EPA, 0.59%E DHA) high LCn3 & high polyphenol, 1.4%E from n3 (0.40%E EPA, 0.53%E DHA) high LCn3 & low polyphenol. Control: 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**: (achieved) increase **1%E n-3, 1%E LCn3, -0.3% n-6, 0.7%E PUFA** Duration of intervention: 48 months according to ClinicalTrials.gov entry.
Outcomes	Main study outcome: incremental AUC (unclear of what) after TG test meal Available outcomes: outcomes only reported at up to 8 weeks of intervention (body weight, lipids, oxidative measures, glucose, insulin, QUICKI, HOMA-B)
Notes	Trials registry reports this to be a 48 month trial (was this incorrect?), but only 8 week data located

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	
Allocation concealment (selection bias)	Unclear risk	
Blinding of participants and personnel (performance bias)	Unclear risk	
Blinding of outcome assessment (detection bias)	Unclear risk	
Incomplete outcome data (attrition bias)	Unclear risk	

Selective reporting (reporting bias)	Unclear risk
Other bias	Unclear risk

AREDS2 Pilot - Huang 2008 – NCT00121589 [4 5]

Methods	RCT 2x2, (LCn3 vs unclear placebo), 6 months (other intervention increases lutein and zeaxanthin) Summary risk of bias: not yet assessed
Participants	Adults with age-related macular degeneration (AMD) N: 20 LCn3 int., 20 control Level of risk for CVD: low Location: USA
Interventions	Type: Supplements (capsules) Comparison: LCn3 vs unclear placebo Intervention: 1g/d LCn3 (650mg/d EPA, 350mg/d DHA) Control: unclear placebo **PUFA Dose**: (intended) increase 0.5**%E n-3, 0.5%E LCn3, 0.5%E PUFA** Duration of intervention: 6 months
Outcomes	Main study outcome: serum levels of lutein, zeaxanthin and LC3 Available outcomes: visual acuity, adverse events (authors report no deaths occurred) Response to contact: yes
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	
Allocation concealment (selection bias)	Unclear risk	
Blinding of participants and personnel (performance bias)	Unclear risk	
Blinding of outcome assessment (detection bias)	Unclear risk	
Incomplete outcome data (attrition bias)	Unclear risk	
Selective reporting (reporting bias)	Unclear risk	
Other bias	Unclear risk	

Bairati 1992 [6-11]

Methods	RCT, (EPA vs MUFA), 7 months Summary risk of bias: partially assessed
Participants	Patients undergoing first percutaneous transluminal coronary angioplasty (PTCA) N: 59 int., 60 control Level of risk for CVD: high Location: Canada
Interventions	Type: supplementary capsules

	Comparison: EPA vs MUFA Intervention: 15g/d MaxEPA, including 2.7g/d EPA plus 1.8g/d DHA Control: 15g/d olive oil **PUFA Dose**: (intended) increase **2%E n-3, 2%E LCn3, 2%E PUFA** Duration of intervention: 7 months
Outcomes	Main study outcome: restenosis Dropouts: 48 int, 38 control Available outcomes: recurrent angina, BMI, lipids, BP, heart rate, side effects Response to contact: yes
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation: randomised using a randomisation table by an epidemiologist
Allocation concealment (selection bias)	Low risk	Allocation concealment: Done
Blinding of participants and personnel (performance bias)	Low risk	Participants masked: yes Providers masked: yes
Blinding of outcome assessment (detection bias)	Low risk	Outcome assessors masked: yes
Incomplete outcome data (attrition bias)	Unclear risk	
Selective reporting (reporting bias)	Unclear risk	
Other bias	Unclear risk	

Bellamy 1992 [12]

Methods	RCT (EPA vs nil), 7 months Summary risk of bias: partially assessed
Participants	Patients undergoing coronary angioplasty N: 60 int., 53 control Level of risk for CVD: high Location: UK
Interventions	Type: supplementary capsules Comparison: EPA vs nil Intervention: MaxEPA, including 1.8g/d EPA plus 1.2g/d DHA Control: nil **PUFA Dose**: (intended) increase **1.4%E n-3, 1.4%E LCn3, 1.4%E PUFA** Duration of intervention: 7 months
Outcomes	Main study outcome: restenosis Dropouts: 3 int., 7 control Available outcomes: recurrent angina, repeat CABG or angioplasty, side effects Response to contact: No
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation: by random number allocation

Allocation concealment (selection bias)	Unclear risk	Allocation concealment: Unclear
Blinding of participants and personnel (performance bias)	Unclear risk	Participants masked: Unclear Providers masked: Unclear
Blinding of outcome assessment (detection bias)	Unclear risk	Outcome assessors masked: Unclear
Incomplete outcome data (attrition bias)	Unclear risk	
Selective reporting (reporting bias)	Unclear risk	
Other bias	Unclear risk	

Bhargava 2015 [13]

Methods	RCT (LCn3 vs n6), 6 months Summary risk of bias: not yet assessed
Participants	Contact lens wearers N: 240 LCn3 int., 256 control Level of risk for CVD: low Location: India
Interventions	Type: Supplement (capsules) Comparison: LCn3 vs n6 Intervention: 4x300mg capsules/d including 720mgEPA + 480mgDHA (1.2mg/d LCn3) Control: 4 capsules/d corn oil **PUFA Dose**: (intended) increase **0.5%E n-3, 0.5%E LCn3, unclear% n-6, unclear %E PUFA** Duration of intervention: 6 months
Outcomes	Main study outcome: dry eye symptoms Available outcomes: dry eye symptoms Response to contact: not yet attempted
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	
Allocation concealment (selection bias)	Unclear risk	
Blinding of participants and personnel (performance bias)	Unclear risk	
Blinding of outcome assessment (detection bias)	Unclear risk	
Incomplete outcome data (attrition bias)	Unclear risk	
Selective reporting (reporting bias)	Unclear risk	
Other bias	Unclear risk	

Bhargava 2016 [14]

Methods	RCT (LCn3 vs MUFA), 6 months Summary risk of bias: not yet assessed

Participants People with rosacea and dry eye symptoms
N: 65 LCn3 int., 65 MUFA control
Level of risk for CVD: low
Location: India

Interventions Type: Supplement (capsules)
Comparison: LCn3 vs MUFA
Intervention: 4x300mg capsules/d including 720mgEPA + 480mgDHA (1.2mg/d LCn3)
Control: 4 capsules/d olive oil
PUFA Dose: (intended) increase **0.5%E n-3, 0.5%E LCn3, unclear% n-6, 0.5%E PUFA**
Duration of intervention: 6 months

Outcomes Main study outcome: eye outcomes
Available outcomes: dry eye symptoms, tearfilm breakup time, meibomian gland score, Schirmer test
Response to contact: not yet attempted

Notes

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	
Allocation concealment (selection bias)	Unclear risk	
Blinding of participants and personnel (performance bias)	Unclear risk	
Blinding of outcome assessment (detection bias)	Unclear risk	
Incomplete outcome data (attrition bias)	Unclear risk	
Selective reporting (reporting bias)	Unclear risk	
Other bias	Unclear risk	

Bianconi 2011 [15]

Methods 2 arm, parallel, RCT, 6mo
Summary risk of bias: Medium to high

Participants People with persistent Atrial Fibrillation
N: control: 103, int: 111
Level of risk for CVD: High
Male: 70.5% int., 67.4% control
Mean age, sd: 69.3, 8.0. int., 69.2, 7.8 control
Age range: no data available
Smokers: no data available
Hypertension: 73.7% int., 69.6% control
Location: Italy

Interventions Type: supplement (capsule) Intervention: Societá Prodotti Antibiotici, Milan, 3 x 1g capsule/day until ECV (7 days) and 2 x 1g capsule thereafter (9.27mg/d EPA and 7.73mg/d DHA).
Control: 3 x 1g capsule/day olive oil until ECV and 2 x 1g thereafter.
Compliance: Capsule count. >80% of capsules taken by 93.7% int., 93.5% control. Plasma EPA int., 1.05 (0.44) 1 month, 1.18 (0.56) 3 months; control, 0.42 (0.2) 1 month, 0.42 (0.21) 3 months. Plasma DHA int., 0.69 (0.20) 1 month, 0.81 (0.25) 3 months; control, 1.31 (0.63) 1 month, 1.287 (0.62) 3 months.
Duration of intervention: 6mo

Outcomes Main study outcome: Atrial fibrillation reoccurrence
Dropouts: Control: 11 (3-discontinued before ECV, 4-discontinued after ECV, 4-failed second ECV), Int., 16 (7-discontinued before ECV, 6-discontinued after ECV, 3-failed second ECV).
Available outcomes: heart failure, non-fatal arrhythmias, cardiovascular events.
Response to contact: not yet attempted

Notes

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated randomization list, using blocks of six. Double blind.
Allocation concealment (selection bias)	Unclear risk	Method of allocation unclear.
Blinding of participants and personnel (performance bias)	Low risk	"assignment fully blinded", placebo capsules of identical size, colour and weight.
Blinding of outcome assessment (detection bias)	Unclear risk	unclear
Incomplete outcome data (attrition bias)	Low risk	Attritions and exclusions were well described.
Selective reporting (reporting bias)	Unclear risk	Trial not registered. Recruitment began in July 2006.
Other bias	Low risk	No further bias noted

Bierenbaum 1963 [16]

Methods RCT (total PUFA vs usual fat), 11.5 months
Summary risk of bias: not yet assessed

Participants Men who had had a myocardial infarction
N: 53 int., 46 control
Level of risk for CVD: high
Location: USA

Interventions Type: Dietary advice
Comparison: total PUFA vs usual fat
Intervention: 14.1%E PUFA, 27.8%E total fat, 5.5% SFA, 9.3%E MUFA, 20.4% protein, 51.8%E CHO
Control: 3.3%E PUFA, 28.2%E total fat, 9.6% SFA, 13.2%E MUFA, 20.7% protein, 51.1%E CHO
PUFA Dose: (intended) increase **10.8%E PUFA**
Duration of intervention: 50 weeks

Outcomes Main study outcome: cholesterol
Available outcomes: lipids, adiposity
Response to contact: not yet attempted

Notes

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	
Allocation concealment (selection bias)	Unclear risk	

Blinding of participants and personnel (performance bias)	Unclear risk
Blinding of outcome assessment (detection bias)	Unclear risk
Incomplete outcome data (attrition bias)	Unclear risk
Selective reporting (reporting bias)	Unclear risk
Other bias	Unclear risk

Blommers 2002 [17 18]

Methods RCT, 4 arms, 2x2 (total PUFA [LCn3 + n6] vs LCn3 vs n6), 6 months
Summary risk of bias: not yet assessed

Participants Women with severe chronic mastalgia
N: 30 total PUFA int, 30 LCn3 int., 60 n6 (including 30 GLA, 30 n6 corn oil)
Level of risk for CVD: low
Location: the Netherlands

Interventions Type: Supplement (capsules)
Comparison: total PUFA vs LCn3 vs n6
Intervention: LCn3 FC: 3g/d fish oil (38% EPA or 1.14g/d EPA, 24%DHA or 0.72g/d DHA), 1.86g/d LCn3, **0.8%E LCn3** plus 3g/d corn oil (60%LA), 1.8g/d n6 or **0.8%E n6**
total PUFA EF: 3g/d fish oil (1.86g/d LCn3) and 3g/d evening primrose oil (9.6% GLA or 0.29g/d GLA + 71.2% LA or 2.14g/d LA, total 2.43g/d n6), total 4.3g/d total PUFA, **1.9%E total PUFA**
Control EC: EPO: 3g/d evening primrose oil (9.6% GLA or 0.29g/d GLA + 71.2% LA or 2.14g/d LA, total 2.43g/d n6) and total 4.14g/d n6, **1.9%E n6**
Control CC: 3g/d corn oil (60%LA), 1.8g/d n6 or 0.8%E n6 and 3g/d wheat germ oil (57%LA), 1.7g/d n6, total 3.5g/d n6, **1.6%E n6**
PUFA Dose: (intended) increase as above
Duration of intervention: 6 months

Outcomes Main study outcome: % of days with breast pain
Available outcomes: side effects (gastric, abdominal, skin) and body weight, % of pain days, severity of pain (authors reported no deaths or CVD events)
Response to contact: yes

Notes

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	
Allocation concealment (selection bias)	Unclear risk	
Blinding of participants and personnel (performance bias)	Unclear risk	
Blinding of outcome assessment (detection bias)	Unclear risk	
Incomplete outcome data (attrition bias)	Unclear risk	
Selective reporting (reporting bias)	Unclear risk	
Other bias	Unclear risk	

Borchgrevink 1966 [19-21]

Methods RCT (ALA vs omega-6), 10 months
Summary risk of bias: low

Participants Men with impending or recent myocardial infarction (MI)
N: 100 int., 100 control
Level of risk for CVD: High (men with impending or recent myocardial infarction)
Male: 100%
Mean age, sd: 57.3 int., 57.4 control
Age range: all <70 yrs
Smokers: 77% int., 85% control
Hypertension: 7% int., 10% control
Location: Norway

Interventions Type: supplement (oil)
Intervention: linseed oil 10 ml/d initially, later raised to 20 or 30 ml/d (4.5g/d a-lin, later 9 or 13.5 g/d)
Control: corn oil, 10 ml/d initially, later raised to 20 or 30 ml/d
Compliance: bottle counts, no data presented
Length of intervention: mean 10 (range 3-16) mo

Outcomes Main study outcome: CV events
Dropouts: unclear
Available outcomes: total and cardiovascular deaths, MI, stroke, heart failure, combined CV events, lipids, adverse events
Response to contact: Yes

Notes Both groups were advised to cut out fried foods and other oils, and avoid margarine containing linolenic acids

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Statistical office at the hospital performed block randomisation on a pre-constructed list. Randomisation was carried out by the statistical office from a list with block randomisation (blocks of 20)
Allocation concealment (selection bias)	Low risk	As above
Blinding of participants and personnel (performance bias)	Low risk	Participants masked: Yes. Providers masked: Yes
Blinding of outcome assessment (detection bias)	Low risk	Outcome assessors masked: Yes
Incomplete outcome data (attrition bias)	Unclear risk	Mortality is well described, but unclear how many participants dropped out overall
Selective reporting (reporting bias)	Unclear risk	No study protocol was found
Other bias	Low risk	No further bias noted

CART - Johansen 1999 [22-24]

Methods RCT (LCn3 vs n6), 6.5 months
Summary risk of bias: medium or high

Participants Patients having elective PTCA
N: 250 int., 250 control
Level of risk for CVD: High (people about to undergo elective coronary angioplasty)
Male: 74.5% int., 80.7 % control

	Mean age, sd: 60.3, 9.3 int., 59.1, 9.3 control Age range: Unclear Smokers: 16.3% int., 22.4% control Hypertension: 34.2% int., 33.9% control Location: Norway
Interventions	Type: supplement (capsule) Intervention: Omacor capsules, 6/d (5g EPA + DHA daily) Control: corn oil capsules, 6/d Compliance: capsule count (results not reported), serum EPA + DHA rose in the intervention group (185 to 267 mg/L at 6 mo) and fell in the control group (172 to 155 mg/L at 6 mo) Length of intervention: 6.5 mo
Outcomes	Main study outcome: restenosis Dropouts: 54 int., 58 control Available outcomes: total and CV deaths, lipids, side effects Response to contact: No
Notes	Those using fish oil capsules at baseline were asked to stop.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Consecutively numbered sealed envelopes mentioned, but not method of including allocations in the envelopes
Allocation concealment (selection bias)	Unclear risk	Envelopes not stated as opaque
Blinding of participants and personnel (performance bias)	Low risk	Participants masked: Yes Providers masked: Yes
Blinding of outcome assessment (detection bias)	Low risk	Outcome assessors masked: Yes
Incomplete outcome data (attrition bias)	Low risk	Well described
Selective reporting (reporting bias)	Unclear risk	No study protocol was found
Other bias	Low risk	No further bias noted

Chen 2008 [25]

Methods	RCT (high dose n3 vs low dose LCn3 vs unspecified placebo), 6 months Summary risk of bias: not yet assessed
Participants	People with non-alcoholic fatty liver disease (NAFLD) N: 15 high n3 int., 15 low dose n3, 16 control Level of risk for CVD: low Location: China
Interventions	Type: Supplement (capsules) Comparison: high dose n3 vs low dose LCn3 vs unspecified placebo Intervention: high dose n3 (no further details of dose or n3 type) vs low dose n3 Control: unspecified placebo **PUFA Dose**: (intended) increase unclear**%E n-3, unclear %E LCn3, unclear %E PUFA** Duration of intervention: 24 weeks
Outcomes	Main study outcome: extent of NAFLD Available outcomes: ultrasound assessment, lipids, liver function tests Response to contact: not yet attempted
Notes	Notes: paper in Chinese, information only taken from the abstract and figures

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	
Allocation concealment (selection bias)	Unclear risk	
Blinding of participants and personnel (performance bias)	Unclear risk	
Blinding of outcome assessment (detection bias)	Unclear risk	
Incomplete outcome data (attrition bias)	Unclear risk	
Selective reporting (reporting bias)	Unclear risk	
Other bias	Unclear risk	

CHOICE - Peters 2014 [26]

Methods	RCT, 3 arms (ALA vs nil), 12 months Summary risk of bias: not yet assessed
Participants	Healthy postmenopausal women N: 37 ALA int., 39 control (also 40 in another arm) Level of risk for CVD: low Location: USA
Interventions	Type: Supplement of ground flax seed Comparison: ALA vs nil Intervention: Flax Plus - moderate fat diet (as in control) plus 10g/d ground flax seed Control: Food Power - moderate fat diet. AHA type diet where foods high in saturated fat were replaced by lower fat foods **PUFA Dose**: (intended) increase unclear **%E n-3, 0%E LCn3, unclear %E PUFA** Duration of intervention: 12 months
Outcomes	Main study outcome: adherence to dietary plans Available outcomes: body weight, attitudes Response to contact: not yet attempted
Notes	Note: 3rd arm was called Whole Foods - macrobiotic whole food diet, predominantly vegetarian, high in phytoestrogens. In the published paper Whole Foods were compared with both moderate fat arms (combined), so no useful outcome data were reported.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	
Allocation concealment (selection bias)	Unclear risk	
Blinding of participants and personnel (performance bias)	Unclear risk	
Blinding of outcome assessment (detection bias)	Unclear risk	
Incomplete outcome data (attrition bias)	Unclear risk	

Selective reporting (reporting bias)	Unclear risk
Other bias	Unclear risk

Chrysohoou 2016 [27 28]

Methods	RCT (n3 vs nil), 6 months Summary risk of bias: moderate to high
Participants	People with chronic compensated heart failure N: 101 or 104 n3 int., 104 or 101 control Level of risk for CVD: high Location: Greece
Interventions	Type: Supplement (capsules) Comparison: n3 vs nil Intervention: 1g/d n3 (no type or source given) Control: nil (no placebo) **PUFA Dose**: (intended) increase unclear **%E n-3, unclear %E LCn3, unclear %E PUFA** Duration of intervention: 6 months
Outcomes	Main study outcome: ventricular function Available outcomes: BNP, weight, BMI, heart rate, white blood cell count, uric acid, proteins, albumin, U&Es, lipids, CRP, platelet count, echiographic assessments (including ejection fractions, atrial volume, etc), depression (Zung's Depression Rating Scale, ZDRS), adverse events Response to contact: yes (confirmed 6 month duration of supplementation, but did not provide further data)
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	
Allocation concealment (selection bias)	Unclear risk	
Blinding of participants and personnel (performance bias)	High risk	No placebo used, so unblinded
Blinding of outcome assessment (detection bias)	Unclear risk	
Incomplete outcome data (attrition bias)	Unclear risk	
Selective reporting (reporting bias)	Unclear risk	
Other bias	Unclear risk	

Cod-Fish - Thomashow 2014 [29]

Methods	RCT (unclear n3 vs unclear placebo), 6 months Summary risk of bias: not yet assessed
Participants	People with chronic obstructive pulmonary disease (COPD) N: ~20 n3 int., ~20 control Level of risk for CVD: low Location: USA
Interventions	Type: Supplement (capsules?)

	Comparison: unclear n3 vs unclear placebo Intervention: 3g/d n3 Control: unclear placebo **PUFA Dose**: (intended) increase **1%.4E n-3, unclear %E LCn3, unclear %E PUFA** Duration of intervention: 6 months
Outcomes	Main study outcome: flow-mediated dilatation of brachial artery Available outcomes: peripheral arterial tonometry, CD31+, CD62E+, endothelial microparticles, pulmonary function, 6 minute walk test, oxygen saturation, respiratory questionnaire Response to contact: not yet attempted
Notes	Note: abstract only

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	
Allocation concealment (selection bias)	Unclear risk	
Blinding of participants and personnel (performance bias)	Unclear risk	
Blinding of outcome assessment (detection bias)	Unclear risk	
Incomplete outcome data (attrition bias)	Unclear risk	
Selective reporting (reporting bias)	Unclear risk	
Other bias	Unclear risk	

Colli 2012 [30]

Methods	RCT (ALA vs protein placebo), 6 months Summary risk of bias: not yet assessed
Participants	Women with menopausal symptoms N: 28 flaxseed extract int., 22 flaxseed meal int, 25 collagen placebo Level of risk for CVD: low Location: Brazil
Interventions	Type: Supplement (capsules) for flaxseed extract and collagen placebo, flaxseed meal is food supplement Comparison: ALA vs protein Intervention: extract - 1g/d flaxseed extract (2x500mg capsules) meal - 90g/d flaxseed meal, 2x45g, Control: 1g/d collagen (2x500mg capsules) **PUFA Dose**: (intended) increase unclear **%E n-3, 0 %E LCn3, unclear %E PUFA** Duration of intervention: 6 months
Outcomes	Main study outcome: menopausal symptoms (Kupperman index) Available outcomes: intensity of hot flashes, menopausal symptoms, vaginal epithelial maturation value, endometrial thickness, estradiol, FSH, body weight Response to contact: not yet attempted
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement

Random sequence generation (selection bias)	Unclear risk
Allocation concealment (selection bias)	Unclear risk
Blinding of participants and personnel (performance bias)	Unclear risk
Blinding of outcome assessment (detection bias)	Unclear risk
Incomplete outcome data (attrition bias)	Unclear risk
Selective reporting (reporting bias)	Unclear risk
Other bias	Unclear risk

DREAM 2018 - NCT02128763 [31 32]

Methods	RCT 2 arms, (LCn3 vs MUFA), 12 months Summary risk of bias: not yet assessed
Participants	People with moderate to severe dry eye disease N: 349 LCn3 int., 186 control (of whom 329 and 170 were analysed) Level of risk for CVD: low Location: USA
Interventions	Type: Supplements (capsules) Comparison: LCn3 vs MUFA Intervention: 3g/d LCn3 from 5 soft gel capsules/d, 2g/d EPA plus 1g/d DHA, TG form Control: 5mg/d olive oil placebo from 5 soft gel capsules/d, 68% oleic acid (3.4g/d oleic acid), 11% LA, 0.55mg/d LA (both types of capsule contained 3mg vit E/capsule plus lemon and masking flavour). Access Business Group manufactured and donated all capsules. **PUFA Dose**: (planned) increase **1.4%E n-3, 1.4%E LCn3, unclear % n-6, 1.4%E PUFA** Duration of intervention: 12 months
Outcomes	Main study outcome: Occular surface disease index (OSDI) Available outcomes: variety of eye outcomes, physical and mental health subscales of SF-36, adverse events, red cell fatty acids
Notes	NCT02128763

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	
Allocation concealment (selection bias)	Unclear risk	
Blinding of participants and personnel (performance bias)	Unclear risk	
Blinding of outcome assessment (detection bias)	Unclear risk	
Incomplete outcome data (attrition bias)	Unclear risk	
Selective reporting (reporting bias)	Unclear risk	
Other bias	Unclear risk	

Dry 1991 [33 34]

Methods RCT (LCn3 vs unclear placebo) 12 months
Summary risk of bias: low

Participants People with asthma
N: 6 int., 6 control
Level of risk for CVD: Low
Male: Unclear
Mean age, sd: Unclear
Age range: Unclear
Smokers: Unclear
Hypertension: Unclear
Location: France

Interventions Type: supplement (capsule?)
Intervention: Liparmonyl (1g/d EPA + DHA)
Control: 'placebo', no further details
Compliance: capsule count (results not reported)
Length of intervention: 12 mo

Outcomes Main study outcome: pulmonary function
Dropouts: none
Available outcomes: deaths
Response to contact: Yes

Notes

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	randomised in blocks of 4
Allocation concealment (selection bias)	Low risk	Adequate
Blinding of participants and personnel (performance bias)	Low risk	Participants masked: Yes Providers masked: Yes
Blinding of outcome assessment (detection bias)	Low risk	Outcome assessors masked: Yes
Incomplete outcome data (attrition bias)	Unclear risk	
Selective reporting (reporting bias)	Unclear risk	
Other bias	Unclear risk	

Duffy 2004 [35]

Methods RCT 2x2 (LCn3 vs MUFA), 6 months (also copper vs not)
Summary risk of bias: not yet assessed

Participants People with systemic lupus erythematosus (SLE)
N: 27 LCn3 int., 25 placebo
Level of risk for CVD: low
Location: UK

Interventions Type: Supplement (capsules)
Comparison: LCn3 vs MUFA
Intervention: 3g/d fish oil (MaxEPA), 3x1g capsules, (18% EPA or 0.54g/d, 12% DHA or

0.36g/d DHA), 0.9g/d LCn3, 0.4%E LCn3
Control: 3g/d olive oil, 3x1g capsules with peppermint oil
PUFA Dose: (intended) increase 0.4**%E n-3, 0.4 %E LCn3, 0.4 %E PUFA**
Duration of intervention: 6 months

Outcomes Main study outcome: disease activity in SLE
Available outcomes: disease activity, blood pressure, BMI, antibodies (dsDNA, IgG, IgM, complement factors 3 & 4), haemoglobin, white cell count, platelets, ESR, U&Es, total protein, patient reported outcomes
Response to contact: not yet attempted

Notes

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	
Allocation concealment (selection bias)	Unclear risk	
Blinding of participants and personnel (performance bias)	Unclear risk	
Blinding of outcome assessment (detection bias)	Unclear risk	
Incomplete outcome data (attrition bias)	Unclear risk	
Selective reporting (reporting bias)	Unclear risk	
Other bias	Unclear risk	

El Khouli 2014 [36]

Methods RCT (LCn3 vs unspecified placebo), 6 months
Summary risk of bias: not yet assessed

Participants People with recurrent aphthous stomatitis
N: 25 n3 int., 25 control
Level of risk for CVD: low
Location: Egypt

Interventions Type: Supplement (capsules)
Comparison: LCn3 vs unspecified placebo
Intervention: 3x n3 soft gelatine capsules/d (including 300mg EPA and 200mg DHA per capsule), 0.9g/d EPA plus 0.6g/d DHA, 1.5g/d LCn3
Control: 3x soft gelatine capsules/d of unspecified placebo
PUFA Dose: (intended) increase **0.7%E n-3, 0.7 %E LCn3, 0.7%E PUFA**
Duration of intervention: 6 months

Outcomes Main study outcome: stomatitis symptoms
Available outcomes: number of ulcers, ulcer duration, pain, adverse events, oral-health related quality of life
Response to contact: not yet attempted

Notes

Risk of bias table

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

Allocation concealment (selection bias)	Unclear risk
Blinding of participants and personnel (performance bias)	Unclear risk
Blinding of outcome assessment (detection bias)	Unclear risk
Incomplete outcome data (attrition bias)	Unclear risk
Selective reporting (reporting bias)	Unclear risk
Other bias	Unclear risk

ESPRIT - Maresta 2002 [37 38]

Methods RCT (LCn3 vs MUFA), 7 months
Summary risk of bias: low

Participants Italians needing PTCA
N:169 int., 170 control
Level of risk for CVD: high (undergoing planned PTCA)
Male: 86% int., 83% control
Mean age, sd: 58.9, 9.5 int, 58.6, 8.7 control
Age range: Unclear
Smokers: 23% int., 21% control
Hypertension: 47% int., 34% control
Location: Italy

Interventions Type: supplement (capsule)
Intervention: Esapent capsules, 6/d for 2 mo, then 3/d (5.1g/d EPA + DHA initially, later 2.6g/d)
Control: identical olive oil capsules, 6/d for 2 mo, then 3/d
Compliance: plasma fatty acids used to assess, 13.7% of int. group did not adhere strictly to Esapent (no info on controls)
Length of intervention: 7 mo

Outcomes Main study outcome: restenosis
Dropouts: 44 int, 38 control
Available outcomes: total MI, significant angina, combined CV events, thrombo-embolism, TGs, side effects
Response to contact: yes

Notes Study states that 3 participants experienced a sudden death, but numbers were not provided by study arm

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"central randomisation stratified by center, performed by Pharmacia Upjohn"
Allocation concealment (selection bias)	Unclear risk	Unclear whether the randomisation list was produced and used before or after recruitment
Blinding of participants and personnel (performance bias)	Unclear risk	unclear
Blinding of outcome assessment (detection bias)	Unclear risk	unclear
Incomplete outcome data (attrition bias)	Unclear risk	Numbers of dropouts and reasons provided, but not by study arm
Selective reporting (reporting bias)	Unclear risk	No protocol found

Other bias	Low risk	No further bias noted

FORCE - Harper 2006 [39 40]

Methods RCT (ALA vs MUFA), 6 months
Summary risk of bias: not yet assessed

Participants People with coronary heart disease
N: 31 ALA int., 25 MUFA control
Level of risk for CVD: high
Location: USA

Interventions Type: Supplement (capsules)
Comparison: ALA vs MUFA
Intervention: Flaxseed oil 5.2g/d, 3g/d ALA as capsules (RxVitamins)
Control: Olive oil 5.2g/d
PUFA Dose: (intended) increase **1.4%E n-3, 0%E LCn3, 1.4%E PUFA**
Duration of intervention: 26 weeks

Outcomes Main study outcome: lipids
Available outcomes: lipoproteins and lipoprotein subfractions
Response to contact: no reply

Notes

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	
Allocation concealment (selection bias)	Unclear risk	
Blinding of participants and personnel (performance bias)	Unclear risk	
Blinding of outcome assessment (detection bias)	Unclear risk	
Incomplete outcome data (attrition bias)	Unclear risk	
Selective reporting (reporting bias)	Unclear risk	
Other bias	Unclear risk	

FORT - Leaf 1994 – NCT00000473 [41-43]

Methods RCT (LCn3 vs n6), 6 months
Summary risk of bias: low

Participants People undergoing angioplasty
N: 275 int., 276 control
Level of risk for CVD: High
Male: 77% int., 81% control
Mean age, sd: Unclear
Age range: 30->70 int., 30->70 control
Smokers: 14% int., 19% control
Hypertension: 47% int., 37% control
Location: USA

Interventions Type: supplement (capsule)
Intervention: fish oil concentrate capsules 10x1 g/d (6.9g/d EPA + DHA)
Control: corn oil capsules 10x1 g/d with 0.4% fish oil to maintain blinding (0.003g/d EPA +

DHA)
Compliance: plasma EPA + DHA rose by 8.5% total fatty acids to 6 mo in int., by 0.6% in controls
Length of intervention: 6 mo

Outcomes Main study outcome: restenosis
Dropouts: 69 int., 69 control
Available outcomes: deaths, combined cardiovascular events, weight, lipids, BP, side effects
Response to contact: Yes

Notes All on step 1 AHA diet.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was by study statistician and distribution by a pharmacist - only the research pharmacist was blinded at each centre
Allocation concealment (selection bias)	Low risk	As above
Blinding of participants and personnel (performance bias)	Low risk	Participants blinded by adding small amount of fish oil to placebo capsules. Only statistician and PI were unblinded at the coordinating center
Blinding of outcome assessment (detection bias)	Low risk	as above
Incomplete outcome data (attrition bias)	Unclear risk	Data fully reported
Selective reporting (reporting bias)	Unclear risk	Study protocol found (NCT00000473) BUT submitted in 1999 (study published in 1994)
Other bias	Low risk	No further bias noted

Galarraga 2008 [44]

Methods RCT (LCn3 vs air filled placebo), 9 months
Summary risk of bias: moderate to high

Participants People with rheumatoid arthritis
N: 49 LCn3 int., 48 control
Level of risk for CVD: low
Location: UK

Interventions Type: supplementary capsules
Comparison: diet rich in seven seas marine oil, LCn3 vs air-filled placebo capsules
Intervention: 10g/d seven seas marine oil (cod liver oil and fish oil), 1.5g/d EPA + 0.7g/d DHA (2.2g/d LCn3).
Control: 10 air-filled capsules/d
PUFA Dose: (intended) increase **1%E n-3, 1%E LCn3, 1%E PUFA**
Duration of intervention: 9 months

Outcomes Main study outcome: reduction in NSAID intake
Available outcomes: pain, grip strength, early morning stiffness, HAQ, CRP
Response to contact: not yet attempted

Notes

Risk of bias table

Bias	Authors' judgement	Support for judgement

Random sequence generation (selection bias)	Low risk	randomisation generated manually in blocks of 10
Allocation concealment (selection bias)	Unclear risk	unclear
Blinding of participants and personnel (performance bias)	High risk	stated as double blind, but some withdrawals were due to fishy taste or awareness that capsules were empty
Blinding of outcome assessment (detection bias)	Unclear risk	unclear
Incomplete outcome data (attrition bias)	Low risk	all participants assessed for adverse events
Selective reporting (reporting bias)	Unclear risk	No protocol or trials registry entry found
Other bias	Unclear risk	

Garcia-Medina 2011 [45 46]

Methods	RCT, 3 arms (LCn3 vs nil), 24 months Summary risk of bias: not yet assessed
Participants	People with primary open-angle glaucoma N: 26 LCn3 int., 28 control Level of risk for CVD: low Location: Spain
Interventions	Type: Supplement (capsules) Comparison: LCn3 vs nil Intervention: 1 capsule/d oral antioxidants plus LCn3 (ICAPS, Alcon Labs, 85mg EPA, 95mg DHA per capsule), 0.18g/d LCn3 (antioxidants include Vits A, B, D, E, lutein, Zeaxanthin, zinc, copper, selenium & manganese) Control: 1 capsule/d oral antioxidants without LCn3 (OFTAN MACULA, Esteve Labs, 0mg EPA, 0mg DHA per capsule), 0g/d LCn3 (antioxidants include Vits A, B, D, E, lutein, Zeaxanthin, zinc, copper, selenium & manganese, some at slightly different doses than ICAPS) **PUFA Dose**: (intended) increase **0.08%E n-3, 0.08 %E LCn3, 0.08 %E PUFA** Duration of intervention: 24 months
Outcomes	Main study outcome: eye outcomes Available outcomes: visual field, peripapillary retinal nerve fibre layer thickness, macular ganglion cell complex thickness, fast MD deterioration (no deaths occurred) Response to contact: not yet attempted
Notes	Note: additional arm gave neither antioxidants nor n3

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	
Allocation concealment (selection bias)	Unclear risk	
Blinding of participants and personnel (performance bias)	Unclear risk	
Blinding of outcome assessment (detection bias)	Unclear risk	
Incomplete outcome data (attrition bias)	Unclear risk	

Selective reporting (reporting bias)	Unclear risk
Other bias	Unclear risk

Geusens 1994 [47]

Methods	RCT, 3 arms (LCn3 higher dose vs LCn3 lower dose vs MUFA) 12 months Summary risk of bias: medium or high
Participants	People with active rheumatoid arthritis on NSAIDs or DMARDs N: 30 low dose, 30 high dose, 30 control Level of risk for CVD: Low Male: 23.8% low dose, 21.0% high dose, 20.0% control Mean age, sd: 57, 9.2 low dose, 59, 8.7 high dose, 56, 8.9 control Age range: Unclear Smokers: Unclear Hypertension: Unclear Location: Belgium
Interventions	Type: supplement (capsule) Intervention: fish oil capsules, 3/d plus 3 olive oil capsules (1.3g EPA + DHA daily) low dose, fish oil capsules, 6/d (2.6g EPA + DHA daily) high dose Control: olive oil capsules, 6/d Compliance: capsule count (results not reported) Length of intervention: 12 mo
Outcomes	Main study outcome: arthritic symptoms Dropouts: 9 low dose, 11 high dose, 10 control Available outcomes: deaths, side effects Response to contact: No
Notes	All 3 groups had a stable diet with 30% fat and fish eaten once a week prescribed.

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	Unclear
Blinding of participants and personnel (performance bias)	Low risk	Participants masked: Yes Providers masked: Yes
Blinding of outcome assessment (detection bias)	Low risk	Outcome assessors masked: Yes
Incomplete outcome data (attrition bias)	Unclear risk	
Selective reporting (reporting bias)	Unclear risk	
Other bias	Unclear risk	

Ghadian 2017 [48]

Methods	RCT (n3 vs nil), 6 months Summary risk of bias: not yet assessed
Participants	Men with lower urinary tract symptoms and benign prostatic hyperplasia N: 50 n3 int., 50 control Level of risk for CVD: low Location: Iran

Interventions Type: Supplement (capsules)
Comparison: n3 vs nil (both)
Intervention: 3x300mg omega 3/d, 0.9g/d n3 (as Natural Wealth Omega-3 softgels) with finasteride 5mg/d and tamsulocin 0.4mg/d
Control: nil with finasteride 5mg/d and tamsulocin 0.4mg/d
PUFA Dose: (intended) increase 0.4**%E n-3, unclear %E LCn3, unclear %E PUFA**
Duration of intervention: 6 months

Outcomes Main study outcome: prostate outcomes
Available outcomes: prostate outcomes (volume, symptoms), adverse events (no deaths or CVD events, or abnormal bleeding, one GI event in control group, none in intervention, others are sexual health outcomes
Response to contact: not yet attempted

Notes

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	
Allocation concealment (selection bias)	Unclear risk	
Blinding of participants and personnel (performance bias)	Unclear risk	
Blinding of outcome assessment (detection bias)	Unclear risk	
Incomplete outcome data (attrition bias)	Unclear risk	
Selective reporting (reporting bias)	Unclear risk	
Other bias	Unclear risk	

Hamazaki 2006 [49]

Methods RCT (ALA vs n6), 8 months
Summary risk of bias: not yet assessed

Participants People with recurrent aphthous stomatitis
N: 15 LCn3 int., 15 control
Level of risk for CVD: low
Location: Japan

Interventions Type: Supplement (capsules)
Comparison: ALA vs n6
Intervention: perilla oil used for cooking, ~60% ALA
Control: soybean oil used for cooking
PUFA Dose: (intended) increase unclear **%E n-3, 0%E LCn3, unclear % n-6, unclear %E PUFA**
Duration of intervention: 8 months

Outcomes Main study outcome: occurrences of recurrent aphthous stomatitis
Available outcomes: recurrent aphthous stomatitis
Response to contact: none

Notes

Risk of bias table

Bias	Authors' judgement	Support for judgement

Random sequence generation (selection bias)	Unclear risk
Allocation concealment (selection bias)	Unclear risk
Blinding of participants and personnel (performance bias)	Unclear risk
Blinding of outcome assessment (detection bias)	Unclear risk
Incomplete outcome data (attrition bias)	Unclear risk
Selective reporting (reporting bias)	Unclear risk
Other bias	Unclear risk

Hansen 2010 [50 51]

Methods	RCT (diet rich in LCn3 vs diet low in LCn3), 6 months Summary risk of bias: not yet assessed
Participants	Prisoners N: 38 high LCn3 int., 40 low LCn3 control Level of risk for CVD: moderate Location: Norway
Interventions	Type: Provided diet (to prisoners) Comparison: diet rich in LCn3 vs diet low in LCn3 Intervention: Diet provided included 3 seafood dinners (including mostly fatty fish)/week, 69 fatty fish main courses over 23 weeks Control: usual prison diet, 6 fatty fish main courses over 23 weeks **PUFA Dose**: (intended) increase unclear **%E n-3, unclear %E LCn3, unclear %E PUFA** Duration of intervention: 23 weeks
Outcomes	Main study outcome: heart rate variability Available outcomes: heart rate variability components, vitamin D Response to contact: replied but did not provide any useful information
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	
Allocation concealment (selection bias)	Unclear risk	
Blinding of participants and personnel (performance bias)	Unclear risk	
Blinding of outcome assessment (detection bias)	Unclear risk	
Incomplete outcome data (attrition bias)	Unclear risk	
Selective reporting (reporting bias)	Unclear risk	
Other bias	Unclear risk	

Harbige 2007 [52]

Methods	RCT 3 arms (high GLA n6 vs low GLA n6 vs polyethylene glycol 400), 18 months Summary risk of bias: not yet assessed
Participants	People with active multiple sclerosis N: 11 high n6 int., 7 low dose n6, 10 control Level of risk for CVD: low Location: UK
Interventions	Type: supplementary oil (in capsules?) Comparison: borage oil rich in GLA n6 high and low dose vs PEG Intervention: high dose 14g/d borage oil (n6 dose unclear), vs low dose 5g/d borage oil Control: polyethylene glycol 400 **PUFA Dose**: (intended) increase unclear **% n-6, unclear %E PUFA** Duration of intervention: 18 months
Outcomes	Main study outcome: MS relapse rate Available outcomes: Expanded disability status scale, PBMC cytokine levels, TNF alpha, TGF beta, IL-1, DGLA Response to contact: yes
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	
Allocation concealment (selection bias)	Unclear risk	
Blinding of participants and personnel (performance bias)	Unclear risk	
Blinding of outcome assessment (detection bias)	Unclear risk	
Incomplete outcome data (attrition bias)	Unclear risk	
Selective reporting (reporting bias)	Unclear risk	
Other bias	Unclear risk	

Harris 1991 [53]

Methods	RCT 4 arms (various doses of LCn3 vs lower dose LCn3), 6 months Summary risk of bias: not yet assessed
Participants	People with hyperlipidaemia N: 8 high LCn3 int., 5 moderate, 9 low, 6 very low LCn3 Level of risk for CVD: moderate Location: USA
Interventions	Type: supplementary capsules Comparison: different doses of LCn3 Intervention: 12x1g/d fish oil capsules, 5g/d LCn3, 9x1g/d fish oil capsules, 3.8g/d LCn3, 6x1g/d fish oil capsules, 2.5g/d LCn3 Control: 3x1g/d fish oil capsules, 1.3g/d LCn3 **PUFA Dose**: (intended) increase **2.3%E LCn3, 1.7%E LCn3, 1.2%E LCn3, 0.6%E LCn3** Duration of intervention: 6 months
Outcomes	Main study outcome: lipids Available outcomes: RBC deformability, bleeding time Response to contact: not yet attempted
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	
Allocation concealment (selection bias)	Unclear risk	
Blinding of participants and personnel (performance bias)	Unclear risk	
Blinding of outcome assessment (detection bias)	Unclear risk	
Incomplete outcome data (attrition bias)	Unclear risk	
Selective reporting (reporting bias)	Unclear risk	
Other bias	Unclear risk	

Henz 1999 [54]

Methods	RCT (n6 vs other fat), 6 months Summary risk of bias: not yet assessed
Participants	People with atopic eczema N: 80 n6 int., 80 control Level of risk for CVD: low Location: several European countries
Interventions	Type: Supplement (capsules) Comparison: n6 vs other fat Intervention: 6x500mg capsules/d borage oil, 23% GLA or 0.69g/d GLA Control: 6x500mg capsules/d bland oil (miglyol) **PUFA Dose**: (intended) increase 0**%E n-3, 0%E LCn3, 0.3% n-6, 0.3%E PUFA** Duration of intervention: 26 weeks
Outcomes	Main study outcome: eczema outcomes Available outcomes: Costa score, corticosteroid use, serum IgE, %responders Response to contact: not yet attempted
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	
Allocation concealment (selection bias)	Unclear risk	
Blinding of participants and personnel (performance bias)	Unclear risk	
Blinding of outcome assessment (detection bias)	Unclear risk	
Incomplete outcome data (attrition bias)	Unclear risk	
Selective reporting (reporting bias)	Unclear risk	
Other bias	Unclear risk	

Holguin 2005 [55]

Methods RCT (LCn3 vs n6), 6 months
Summary risk of bias: not yet assessed

Participants Elderly nursing home residents
N: 26 LCn3 int., 26 control
Level of risk for CVD: low
Location: USA

Interventions Type: Supplement capsules
Comparison: fish oil LCn3 vs soy oil
Intervention: 2g/d fish oil capsules, 83% LCn3, 1.7g/d LCn3
Control: 2g/d soy oil capsules
PUFA Dose: (intended) increase **0.7%E n-3, 0.7%E LCn3, unclear %E PUFA**
Duration of intervention: 6 months

Outcomes Main study outcome: heart rate variability
Available outcomes: heart rate
Response to contact: not yet attempted

Notes

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	
Allocation concealment (selection bias)	Unclear risk	
Blinding of participants and personnel (performance bias)	Unclear risk	
Blinding of outcome assessment (detection bias)	Unclear risk	
Incomplete outcome data (attrition bias)	Unclear risk	
Selective reporting (reporting bias)	Unclear risk	
Other bias	Unclear risk	

Horrobin 1997 [56]

Methods RCT (GLA n6 vs unclear placebo), 12 months
Summary risk of bias: not yet assessed

Participants People with mild to moderate diabetic neuropathy
N: 202 n6 int., 202 control
Level of risk for CVD: moderate
Location: UK, Sweden, Finland, Germany plus

Interventions Type: Supplement capsules
Comparison: GLA n6 vs unclear placebo
Intervention: 0.48g/d GLA
Control: unclear placebo
PUFA Dose: (intended) increase **0%E n-3, 0%E LCn3, 0.2%E n6, unclear %E PUFA**
Duration of intervention: 12 months

Outcomes Main study outcome: symptoms of diabetic neuropathy
Available outcomes: thermal threshold, clinical sensory assessments, electrophysiological measures

	Response to contact: Horrobin has died, no other contacts could be established
Notes	Caution: may be some shared participants with GLAMT

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	
Allocation concealment (selection bias)	Unclear risk	
Blinding of participants and personnel (performance bias)	Unclear risk	
Blinding of outcome assessment (detection bias)	Unclear risk	
Incomplete outcome data (attrition bias)	Unclear risk	
Selective reporting (reporting bias)	Unclear risk	
Other bias	Unclear risk	

J-EACH - Domei 2013 [57]

Methods	RCT (LCn3 vs nil), 6 months Summary risk of bias: moderate to high
Participants	Patients having an elective PCI N: 20 LCn3 int., 17 control Level of risk for CVD: high Location: Japan
Interventions	Type: Supplement (capsules) Comparison: LCn3 vs nil Intervention: EPA (dose unclear) plus statin Control: statin alone (no placebo) **PUFA Dose**: (intended) increase unclear **%E n-3, unclear %E LCn3, unclear %E PUFA** Duration of intervention: 6 months
Outcomes	Main study outcome: atherosclerosis progression Available outcomes: diameter of stenosis, EPA to AA ratio, lipids Response to contact: not yet attempted
Notes	Note: only abstract located

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	
Allocation concealment (selection bias)	Unclear risk	
Blinding of participants and personnel (performance bias)	High risk	No placebo, participants were not blinded.
Blinding of outcome assessment (detection bias)	Unclear risk	

Incomplete outcome data (attrition bias)	Unclear risk
Selective reporting (reporting bias)	Unclear risk
Other bias	Unclear risk

Jamal 1986 [58 59]

Methods	RCT (GLA n6 vs unclear placebo), 6 months Summary risk of bias: moderate to high
Participants	Patients with diabetic neuropathy N: 12 int., 10 control Level of risk for CVD: moderate Location: UK
Interventions	Type: Supplementary capsules Comparison: GLA in evening primrose oil vs identical placebo Intervention: 8x 500mg capsules/d providing 8x360mg GLA, 2.9g/d GLA Control: unclear placebo **PUFA Dose**: (intended) increase **1.3% n-6, 1.3%E PUFA** Duration of intervention: 6 months
Outcomes	Main study outcome: measures of diabetic neuropathy Available outcomes: motor nerve conduction velocity, amplitude of sensory nerve action potentials, heat threshold, cold threshold Response to contact: yes
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	
Allocation concealment (selection bias)	Unclear risk	
Blinding of participants and personnel (performance bias)	Unclear risk	
Blinding of outcome assessment (detection bias)	Unclear risk	
Incomplete outcome data (attrition bias)	Unclear risk	
Selective reporting (reporting bias)	Unclear risk	
Other bias	Unclear risk	Accusation of research fraud by GMC

Jenkins 1996 [60]

Methods	RCT (GLA vs non-fat), 12 months Summary risk of bias: not yet assessed
Participants	People with chronic hepatitis B N: ~12 GLA int., ~12 control (24 total) Level of risk for CVD: low Location: UK
Interventions	Type: Supplement (capsules) Comparison: GLA vs non-fat Intervention: 4g/d evening primrose oil (8x500mg capsules with 10mg vit E), 9% GLA or

0.36g/d, 75% LA or 3g/d, 3.36g/d n6
Control: liquid paraffin similarly administered in identical gelatin capsules (no vitamin E)
PUFA Dose: (intended) increase 0**%E n-3, 0%E LCn3, 1.5% n-6, 1.5%E PUFA**
Duration of intervention: 12 months

Outcomes Main study outcome: liver disease
Available outcomes: hepatitis B antigens, serum alanine transferase (biochemical and histological indices of liver damage)
Response to contact: not yet attempted

Notes

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	
Allocation concealment (selection bias)	Unclear risk	
Blinding of participants and personnel (performance bias)	Unclear risk	
Blinding of outcome assessment (detection bias)	Unclear risk	
Incomplete outcome data (attrition bias)	Unclear risk	
Selective reporting (reporting bias)	Unclear risk	
Other bias	Unclear risk	

Khan 2003 [61]

Methods RCT, 6 arms (n6 vs n3 vs total PUFA vs MUFA), 8 months
Summary risk of bias: not yet assessed

Participants Healthy non-smoking adults
N: 31 EPO n6 int., 28 soya oil n6 int, 28 LCn3 tuna int, 28 total PUFA (tuna & EPO) int, 30 MUFA int, 28 usual Scottish fat control
Level of risk for CVD: low
Location: UK

Interventions Type: Supplement (emulsions)
Comparison: n6 vs n3 vs total PUFA vs MUFA
Interventions: all 50ml daily doses of 20% oil-water emulsion, peppermint flavoured, inc tocopherol
EPO n6: 400mg/d GLA + 3.3g/d LA - (intended) increase 0**%E n-3, 0%E LCn3, 1.7% n-6, 1.7%E PUFA**
soya n6: 3.2g/d LA - (intended) increase 0**%E n-3, 0%E LCn3, 1.4% n-6, 1.4%E PUFA**
tuna LCn3: 1.1g/d LCn3 (of which 0.9g/d DHA, 0.2g/d EPA) - (intended) increase **0.5%E n-3, 0.5%E LCn3, 0% n-6, 0.5%E PUFA**
total PUFA: 3.8g/d PUFA (including EPA, DHA, GLA, LA, ALA and AA) - (intended) increase 0.5**%E n-3, 0.5%E LCn3, 1.7% n-6, 2.2%E PUFA**
MUFA: 1.6g/d PUFA - control
placebo: 1.3g/d PUFA - control
Duration of intervention: 8 months

Outcomes Main study outcome: endothelial function and vascular tone
Available outcomes: peak vasodilator responses,
Response to contact: not yet attempted

Notes

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	
Allocation concealment (selection bias)	Unclear risk	
Blinding of participants and personnel (performance bias)	Unclear risk	
Blinding of outcome assessment (detection bias)	Unclear risk	
Incomplete outcome data (attrition bias)	Unclear risk	
Selective reporting (reporting bias)	Unclear risk	
Other bias	Unclear risk	

Kojuri 2013 – NCT01227837 [62]

Methods	RCT (n3 (unclear if ALA or LCn3) vs water), 6 months Summary risk of bias: not yet assessed
Participants	People with congestive heart failure N: 38 n3 int., 32 control Level of risk for CVD: high Location: Iran
Interventions	Type: Supplementary capsules Comparison: n3 vs water Intervention: 2x1g/d n3 Control: capsules of water **PUFA Dose**: (intended) increase **1%E n-3** Duration of intervention: 6 months
Outcomes	Main study outcome: BNP Available outcomes: 6-min walk test, echocardiographic findings Response to contact: not yet attempted

Notes

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	
Allocation concealment (selection bias)	Unclear risk	
Blinding of participants and personnel (performance bias)	Unclear risk	
Blinding of outcome assessment (detection bias)	Unclear risk	
Incomplete outcome data (attrition bias)	Unclear risk	
Selective reporting (reporting bias)	Unclear risk	

Other bias	Unclear risk

Kokke 2008 [63]

Methods	RCT (GLA vs MUFA), 6 months Summary risk of bias: not yet assessed
Participants	People with contact lens associated dry eye N: ~38 GLA int., ~38 control Level of risk for CVD: low Location: UK
Interventions	Type: Supplement (capsules) Comparison: GLA vs MUFA Intervention: evening primrose oil rich in GLA (10.5% GLA, 72.6% LA), 50mg GLA/capsule but unclear how many capsules/d Control: olive oil, 78% MUFA, quantity unclear **PUFA Dose**: (intended) increase **unclear % n-6, unclear %E PUFA** Duration of intervention: 6 months
Outcomes	Main study outcome: eye dryness Available outcomes: eye dryness, contact lens comfort, tear film characteristics, meibomian gland function, ocular surface perameters Response to contact: not yet attempted
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	
Allocation concealment (selection bias)	Unclear risk	
Blinding of participants and personnel (performance bias)	Unclear risk	
Blinding of outcome assessment (detection bias)	Unclear risk	
Incomplete outcome data (attrition bias)	Unclear risk	
Selective reporting (reporting bias)	Unclear risk	
Other bias	Unclear risk	

Koziolova 2015 [64]

Methods	RCT (n3 vs nil), 6 months Summary risk of bias: not yet assessed
Participants	People with chronic heart failure and permanent atrial fibrillation N: 30 LCn3 int., 30 control Level of risk for CVD: high Location: Russia
Interventions	Type: Supplement (capsules) Comparison: n3 vs nil Intervention: omega-3 PUFA (no further details) with basic treatment Control: nil with basic treatment **PUFA Dose**: (intended) increase unclear **%E n-3, unclear %E LCn3, unclear %E PUFA** Duration of intervention: 6 months

Outcomes Main study outcome: arterial wall structure & function
Available outcomes: arterial wall structure and function
Response to contact: not yet attempted

Notes

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	
Allocation concealment (selection bias)	Unclear risk	
Blinding of participants and personnel (performance bias)	Unclear risk	
Blinding of outcome assessment (detection bias)	Unclear risk	
Incomplete outcome data (attrition bias)	Unclear risk	
Selective reporting (reporting bias)	Unclear risk	
Other bias	Unclear risk	

Kurabayashi 2000 [65 66]

Methods RCT (LCn3 vs nil), 11 months
Summary risk of bias: moderate to high

Participants hyperlipidaemic menopausal women
N: 69 LCn3 int., 72 control
Level of risk for CVD: moderate
Location: Japan

Interventions Type: supplementary capsules
Comparison: EPA vs nil
Intervention: EPAdel capsules (Mochida pharmaceuticals), 1.8g/d (plus 3.5mg/d vit E) plus estriol (HRT, 2mg/d))
Control: Estriol only (2mg/d)
PUFA Dose: (intended) increase **0.8%E n-3, 0.8%E LCn3, 0.8%E PUFA**
Duration of intervention: 48 weeks

Outcomes Main study outcome: lipids
Available outcomes: (no deaths or CV events)
Response to contact: not attempted

Notes

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	opaque sealed envelopes prepared by staff not directly involved in subject care, using computer generated random numbers
Allocation concealment (selection bias)	Unclear risk	unclear
Blinding of participants and personnel (performance bias)	High risk	recipients were aware of assigned treatments (no placebo)

Blinding of outcome assessment (detection bias)	Unclear risk	unclear
Incomplete outcome data (attrition bias)	Unclear risk	
Selective reporting (reporting bias)	Unclear risk	
Other bias	Unclear risk	

Lau 1995 [67 68]

Methods RCT (LCn3 vs air filled capsules) 6 months
Summary risk of bias: low

Participants People with rheumatoid arthritis
N: 25 int., 20 control
Level of risk for CVD: Low
Male: 28% int., 30% control
Mean age, sd: median 50 int, median 52 control
Age range: 27-69 int., 28-69 control
Smokers: Unclear
Hypertension: Unclear
Location: Hong Kong, China

Interventions Type: supplement (capsule)
Intervention: MaxEPA 10x 1g capsules daily (2.8g/d EPA + DHA)
Control: air-filled capsules, 10/d
Compliance: capsule counts, no data provided; red cell membrane phospholipids show rise in int. from 2.4% to 5.4% fatty acids and a fall in the control from 2.9 to 2.5% fatty acids
Length of intervention: 6 mo

Outcomes Main study outcome: fibrinolytic parameters
Dropouts: None
Available outcomes: deaths, MI, cardiovascular events, grip strength, pain, joint stiffness
Response to contact: Yes

Notes

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer software system, blocks of 10
Allocation concealment (selection bias)	Low risk	Adequate
Blinding of participants and personnel (performance bias)	Low risk	Participants masked: Yes Providers masked: Yes
Blinding of outcome assessment (detection bias)	Low risk	Outcome assessors masked: Yes
Incomplete outcome data (attrition bias)	Unclear risk	
Selective reporting (reporting bias)	Unclear risk	
Other bias	Unclear risk	

Malaguarnera 1999 [69]

Methods RCT (LCn3 vs nil) 6 months
Summary risk of bias: moderate to high

Participants	People with chronic hepatitis C N: 26 int., 26 control Level of risk for CVD: moderate Male: 46% int., 42% control Mean age, sd: 48.7, 6.5 int, 56.9, 7.2 control Age range: Unclear Smokers: Unclear Hypertension: Unclear Location: Italy
Interventions	Type: supplement (capsule) Intervention: EPA + DHA daily (3g/d EPA + DHA) plus IFNa subcutaneously Control: nil, only IFNa subcutaneously Compliance: unused capsules returned after 2 mo, no-one returned >3 capsules Length of intervention: 6 mo
Outcomes	Main study outcome: liver enzymes Dropouts: Unclear Available outcomes: combined cardiovascular events, psychiatric disorders, lipids, ALT, side effects Response to contact: No
Notes	

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	Unclear
Blinding of participants and personnel (performance bias)	High risk	Participants masked: No Providers masked: Unclear
Blinding of outcome assessment (detection bias)	Unclear risk	Outcome assessors masked: Unclear
Incomplete outcome data (attrition bias)	Unclear risk	
Selective reporting (reporting bias)	Unclear risk	
Other bias	Unclear risk	

Masterton 2015 [70]

Methods	RCT (n3 (unclear if ALA or LCn3) vs placebo), 6 months Summary risk of bias: not yet assessed
Participants	Non-alcoholic fatty liver disease N: ~25 n3 int., ~25 control Level of risk for CVD: low Location: UK
Interventions	Type: Unclear, probably supplementary capsules Comparison: n3 vs placebo Intervention: 4g/d n3 (no details of type) Control: placebo (no details) **PUFA Dose**: (intended) increase **1.8%E n-3** Duration of intervention: 6 months
Outcomes	Main study outcome: steatosis (ultrasound grade) Available outcomes: liver function tests, QoL (WHOQOL-BREF)

Response to contact: not yet attempted

Notes

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	
Allocation concealment (selection bias)	Unclear risk	
Blinding of participants and personnel (performance bias)	Unclear risk	
Blinding of outcome assessment (detection bias)	Unclear risk	
Incomplete outcome data (attrition bias)	Unclear risk	
Selective reporting (reporting bias)	Unclear risk	
Other bias	Unclear risk	

McKew 2012 [71]

Methods	RCT (LCn3 vs placebo), 6 months Summary risk of bias: not yet assessed
Participants	People with systemic lupus erythematosus N: ~30 LCn3 int., ~30 control Level of risk for CVD: low Location: UK
Interventions	Type: Supplements (probably capsules) Comparison: LCn3 vs placebp Intervention: 3g/d Omacor (1.8g/d EPA + 1.2g/d DHA) Control: placebo (unclear) **PUFA Dose**: (intended) increase **1.4%E n-3, 1.4%E LCn3** Duration of intervention: 6 months
Outcomes	Main study outcome: QoL (SF-36) Available outcomes: QoL re emotional, pain, general health Response to contact: not yet attempted

Notes

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	
Allocation concealment (selection bias)	Unclear risk	
Blinding of participants and personnel (performance bias)	Unclear risk	
Blinding of outcome assessment (detection bias)	Unclear risk	
Incomplete outcome data (attrition bias)	Unclear risk	

Selective reporting (reporting bias)	Unclear risk
Other bias	Unclear risk

Mehta 2008 [72 73]

Methods	RCT (LCn3 vs nil), 6 months Summary risk of bias: moderate to high
Participants	People with Barrett's oesophagus N: 33 LCn3 int., 19 control Level of risk for CVD: low Location: UK
Interventions	Type: Supplement (capsules) Comparison: LCn3 vs nil Intervention: 1.5g/d unesterified EPA (99% pure, in 500mg capsules) Control: no supplementation **PUFA Dose**: (intended) increase **0.7%E n-3, 0.7%E LCn3, 0.7%E PUFA** Duration of intervention: 26 weeks
Outcomes	Main study outcome: inflammatory markers Available outcomes: inflammatory markers including COX2 protein, prostaglandin E2, leukotriene B4, RNA. Authors reported that no deaths, CVD events, cancer or diabetes diagnoses occurred. Response to contact: yes
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Authors stated "random allocation of sealed envelopes containing random numbers (generated by random-number software) prepared prior to recruitment. Cards were allocated by the principal investigator"
Allocation concealment (selection bias)	Unclear risk	no details
Blinding of participants and personnel (performance bias)	High risk	no placebo
Blinding of outcome assessment (detection bias)	Unclear risk	
Incomplete outcome data (attrition bias)	Unclear risk	
Selective reporting (reporting bias)	Unclear risk	
Other bias	Unclear risk	

Meyer 2007 [74-76]

Methods	RCT (LCn3 at 2 doses vs MUFA), 6 months Summary risk of bias: not yet assessed
Participants	People on statins with hyperlipidaemia and persistent raised TGs N: 15 high LCn3 int., 15 low LC3 int, 15 MUFA control Level of risk for CVD: moderate Location: Australia
Interventions	Type: Supplement (capsules)

	Comparison: LCn3 at 2 doses vs MUFA Intervention: 8g/d tuna oil (HiDHA) including 2.16g/d DHA plus 0.56g/d EPA. 4g/d tuna oil including 1.08g/d DHA plus 0.28g/d EPA Control: 4 or 8g/d olive oil **PUFA Dose**: (intended) increase high dose **1.2%E n-3, 1.2%E LCn3, 1.2%E PUFA low dose: 0.6%E n-3, 0.6%E LCn3, 0.6%E PUFA** Duration of intervention: 6 months
Outcomes	Main study outcome: lipids Available outcomes: lipids (authors reported no SAEs occurred - so no deaths, CVD events) Response to contact: yes
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	
Allocation concealment (selection bias)	Unclear risk	
Blinding of participants and personnel (performance bias)	Unclear risk	
Blinding of outcome assessment (detection bias)	Unclear risk	
Incomplete outcome data (attrition bias)	Unclear risk	
Selective reporting (reporting bias)	Unclear risk	
Other bias	Unclear risk	

Millar 1973 [77]

Methods	RCT (n6 vs MUFA), 24 months Summary risk of bias: not yet assessed
Participants	People with multiple sclerosis N: 72 n6 int., 78 MUFA control Level of risk for CVD: low Location: UK
Interventions	Type: oil emulsion Comparison: n6 vs MUFA Intervention: 2x30ml/d sunflower oil emulsion (17.2g/d LA) Control: 2x30ml olive oil emulsion (7.6g/d oleic acid) **PUFA Dose**: (intended) increase **7.7% n-6, 07.7%E PUFA** Duration of intervention: 24 months
Outcomes	Main study outcome: MS relapses Available outcomes: neurological assessment, disability, relapses Response to contact: not yet attempted
Notes	

Risk of bias table

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

Allocation concealment (selection bias)	Unclear risk
Blinding of participants and personnel (performance bias)	Unclear risk
Blinding of outcome assessment (detection bias)	Unclear risk
Incomplete outcome data (attrition bias)	Unclear risk
Selective reporting (reporting bias)	Unclear risk
Other bias	Unclear risk

Milner 1989 [78 79]

Methods	RCT (LCn3 vs nil) 6 months Summary risk of bias: medium or high
Participants	People about to undergo angioplasty N:100 int., 100 control Level of risk for CVD: High Male: 74% int., 71% control Mean age, sd: 59 int., 59 control Age range: Unclear Smokers: 23% int., 28% control Hypertension: 43% int., 47% control Location: USA
Interventions	Type: supplement (capsules) Intervention: Promega 9 capsules/d (4.5g EPA + DHA) Control: nil Compliance: 77% took 5-9 capsules/d, 11% took none (int. group) Length of intervention: 6 mo
Outcomes	Main study outcome: restenosis Dropouts: all followed for outcomes Available outcomes: deaths, angina, side effects Response to contact: Yes
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated list of random numbers
Allocation concealment (selection bias)	Low risk	Method of allocation unclear, though author has stated that allocation was after consent and that the researcher was not able to alter allocation
Blinding of participants and personnel (performance bias)	High risk	Participants masked: No Providers masked: Unclear
Blinding of outcome assessment (detection bias)	Low risk	Outcome assessors masked: Yes
Incomplete outcome data (attrition bias)	Low risk	Full data set provided
Selective reporting (reporting bias)	Unclear risk	No protocol found
Other bias	Low risk	No further bias noted

NAT-1 Querques 2009 [80 81]

Methods RCT (LCn3 vs nil), 6 months
Summary risk of bias: moderate to high

Participants People with age-related macular degeneration
N: 22 LCn3 int., 16 control
Level of risk for CVD: low
Location: France

Interventions Type: Supplement (capsules)
Comparison: LCn3 vs nil
Intervention: fish oil including EPA 720mg/d plus DHA 480mg/d, LCn3 overall 1.2g/d LCn3
Control: nil (no placebo)
PUFA Dose: (intended) increase 0.5**%E n-3, 0.5%E LCn3, 0% n-6, 0.5%E PUFA**
Duration of intervention: 27 weeks

Outcomes Main study outcome: eye outcomes
Available outcomes: no side effects of drop-outs were observed, eye outcomes, authors reported no deaths, CVD events, diabetes or cancer diagnoses.
Response to contact: yes

Notes

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	
Allocation concealment (selection bias)	Unclear risk	
Blinding of participants and personnel (performance bias)	High risk	No placebo
Blinding of outcome assessment (detection bias)	Unclear risk	
Incomplete outcome data (attrition bias)	Unclear risk	
Selective reporting (reporting bias)	Unclear risk	
Other bias	Unclear risk	

Neubronner 2011 [82-84]

Methods RCT, 3 arms (LCn3 ethyl esters vs LCn3 triglycerides vs n6), 6 months
Summary risk of bias: not yet assessed

Participants People with hyperlipidaemia treated with statins
N: 49 ethyl ester LCn3 int., 52 triglyceride LCn3, 49 n6 control
Level of risk for CVD: moderate
Location: Germany

Interventions Type: Supplement (capsules)
Comparison: LCn3 ethyl esters vs LCn3 triglycerides vs n6
Intervention: 4 gelatine coated soft capsules/d including 2.02g/d n6, 1.01 g/d EPA, 0.67g/d DHA (for both ethyl esters and triglycerides)
Control: 4 gelatine coated soft capsules/d of corn oil, n6
PUFA Dose: (intended) increase **0.9%E n-3, 0.76%E LCn3, 0.9%E PUFA**
Duration of intervention: 6 months

Outcomes Main study outcome: omega 3 index
Available outcomes: RBC membrane fatty acid composition, omega 3 index, lipids (authors state that no deaths or CVD events, no cancer or diabetes diagnoses occurred during the trial except 1 fatal arrhythmia in the triglyceride LCn3 arm, and reported adverse effects).
Response to contact: yes

Notes

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	
Allocation concealment (selection bias)	Unclear risk	
Blinding of participants and personnel (performance bias)	Unclear risk	
Blinding of outcome assessment (detection bias)	Unclear risk	
Incomplete outcome data (attrition bias)	Unclear risk	
Selective reporting (reporting bias)	Unclear risk	
Other bias	Unclear risk	

Njike 2016 [85]

Methods RCT, 2x2 (ALA from walnuts vs nil), 6 months (other arm was assessing effects of reducing energy intake)
Summary risk of bias: not yet assessed

Participants Adults at risk of diabetes mellitus
N: ~66 ALA int., ~66 control
Level of risk for CVD: moderate
Location: USA

Interventions Type: Supplement (walnuts)
Comparison: ALA from walnuts vs nil
Intervention: 56g walnuts/d
Control: no walnuts
PUFA Dose: (intended) increase unclear **%E n-3, 0%E LCn3, unclear %E PUFA**
Duration of intervention: 6 months

Outcomes Main study outcome: dietary patterns
Available outcomes: foods displaced by walnuts
Response to contact: not yet attempted

Notes

Risk of bias table

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

Blinding of outcome assessment (detection bias)	Unclear risk
Incomplete outcome data (attrition bias)	Unclear risk
Selective reporting (reporting bias)	Unclear risk
Other bias	Unclear risk

Nostratzehi 2016 – IRCT 2015041620377N2 [86]

Methods RCT (n3 vs unclear placebo), 6 months
Summary risk of bias: not yet assessed

Participants People with recurrent aphthous stomatitis
N: 25 n3 int., 25 control
Level of risk for CVD: low
Location: Iran

Interventions Type: Supplement (capsules)
Comparison: n3 vs unclear placebo
Intervention: 3x1g omega 3 capsules/d
Control: unclear placebo
PUFA Dose: (intended) increase unclear **%E n-3, unclear %E LCn3, unclear %E PUFA**
Duration of intervention: 6 months

Outcomes Main study outcome: ulcer recurrence and pain
Available outcomes: ulcer recurrence and pain
Response to contact: not yet attempted

Notes

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	
Allocation concealment (selection bias)	Unclear risk	
Blinding of participants and personnel (performance bias)	Unclear risk	
Blinding of outcome assessment (detection bias)	Unclear risk	
Incomplete outcome data (attrition bias)	Unclear risk	
Selective reporting (reporting bias)	Unclear risk	
Other bias	Unclear risk	

Oliwiecki 1994 [87]

Methods RCT (total PUFA - LCn3 & n6 vs non-fat), 6 months
Summary risk of bias: not yet assessed

Participants People with chronic stable plaque psoriasis
N: ~18 int., ~18 control (37 in total)
Level of risk for CVD: low
Location: UK

Interventions Type: Supplement (capsules)

	Comparison: total PUFA vs non-fat Intervention: 12 capsules/d with each capsule including 430mg evening primrose oil plus 107mg fish oil Control: 12 capsules/d liquid paraffin **PUFA Dose**: (intended) increase unclear **%E n-3, unclear %E LCn3, unclear % n-6, unclear %E PUFA** Duration of intervention: 24 weeks
Outcomes	Main study outcome: clinical assessment of psoriasis Available outcomes: observer and patient clinical assessment (including itch, redness, anxiety and depression), plaque thickness, trans-epidermal water loss, Response to contact: not yet attempted
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	
Allocation concealment (selection bias)	Unclear risk	
Blinding of participants and personnel (performance bias)	Unclear risk	
Blinding of outcome assessment (detection bias)	Unclear risk	
Incomplete outcome data (attrition bias)	Unclear risk	
Selective reporting (reporting bias)	Unclear risk	
Other bias	Unclear risk	

Palozza 1996 [88]

Methods	RCT, 4 arms (EPA + DHA at 3 doses vs usual fat), 6 months Summary risk of bias: moderate to high
Participants	Healthy adults N: 10 high LCn3 int., 10 moderate, 10 low LCn3 intake, 10 control Level of risk for CVD: low Location: Italy
Interventions	Type: supplementary capsules Comparison: LCn3 vs usual fat Intervention: high dose 9 capsules/d of 455mg EPA + 395mg DHA (4.1g/d EPA, 3.6g/d DHA), moderate dose 6 capsules/d of 455mg EPA + 395mg DHA (2.7g/d EPA, 2.4g/d DHA) + 3 usual fat capsules, low dose 3 capsules/d of 455mg EPA + 395mg DHA (1.4g/d EPA, 1.2g/d DHA) + 6 usual fat capsules. Control: fats similar in balance to usual Italian diet, 9/day **PUFA Dose**: (intended) increase high dose **3.5%E n-3, 3.5%E LCn3, unclear %E PUFA, moderate** dose 2.3**%E n-3, 2.3%E LCn3, unclear %E PUFA, low** dose 1.2**%E n-3, 1.2%E LCn3, unclear %E PUFA,** Duration of intervention: 180 days
Outcomes	Main study outcome: lipid peroxidation Available outcomes: malondialdehyde Response to contact: not yet attempted
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"subjects were randomly assigned" - no methods provided
Allocation concealment (selection bias)	Unclear risk	no methods described
Blinding of participants and personnel (performance bias)	Low risk	"double blind" stated and all participants took 9 capsules
Blinding of outcome assessment (detection bias)	Unclear risk	unclear
Incomplete outcome data (attrition bias)	Unclear risk	
Selective reporting (reporting bias)	Unclear risk	
Other bias	Unclear risk	

Parulkar 2009 [89]

Methods	RCT (n3 vs placebo), 6.5 months (other intervention increases polyphenols) Summary risk of bias: not yet assessed
Participants	People with chronic periodontitis N: ~32 n3 int., ~32 control (65 in total) Level of risk for CVD: low Location: unclear
Interventions	Type: Supplement (capsules) Comparison: n3 vs placebo Intervention: 3g/d n3 (no further details) Control: placebo (no further details) **PUFA Dose**: (intended) increase unclear **%E n-3, unclear %E LCn3, unclear %E PUFA** Duration of intervention: 28 weeks
Outcomes	Main study outcome: measures of periodontitis Available outcomes: pocket depth, bleeding, attachment loss, plaque index Response to contact: not yet attempted
Notes	Note: abstract only

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	
Allocation concealment (selection bias)	Unclear risk	
Blinding of participants and personnel (performance bias)	Unclear risk	
Blinding of outcome assessment (detection bias)	Unclear risk	
Incomplete outcome data (attrition bias)	Unclear risk	
Selective reporting (reporting bias)	Unclear risk	
Other bias	Unclear risk	

PEACH - Urakawa 2014 [90]

Methods	RCT (LCn3 vs nil, both with pitavastatin), 12 months (also higher dose statin arm) Summary risk of bias: not yet assessed
Participants	People with no atherosclerotic cardiovascular disease, but needing statin N: 68 LCn3 int., 64 control Level of risk for CVD: moderate Location: Japan
Interventions	Type: Supplement assumed Comparison: LCn3 vs nil Intervention: 1.8g/d EPA with 2mg/d pitavastatin Control: nil with 2mg/d pitavastatin **PUFA Dose**: (intended) increase **1%E n-3, 1%E LCn3, -0.3% n-6, 0.7%E PUFA** Duration of intervention: 12 months
Outcomes	Main study outcome: coronary artery calcification Available outcomes: calcification, lipids Response to contact: not yet attempted
Notes	Note: abstract only

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	
Allocation concealment (selection bias)	Unclear risk	
Blinding of participants and personnel (performance bias)	Unclear risk	
Blinding of outcome assessment (detection bias)	Unclear risk	
Incomplete outcome data (attrition bias)	Unclear risk	
Selective reporting (reporting bias)	Unclear risk	
Other bias	Unclear risk	

Pinheiro 2007 [91 92]

Methods	RCT, 3 arms (ALA at 2 doses vs placebo), 6 months Summary risk of bias: not yet assessed
Participants	People with rheumatoid arthritis or lupus and keratocunjunctivitis sicca and Sjogren's syndrome N: 12 high ALA int., 13 low ALA int, 13 control Level of risk for CVD: low Location: Brazil
Interventions	Type: Supplement (capsules) Comparison: ALA at 2 doses vs placebo Intervention: 2g/d flaxseed oil capsules, or 1g/d flaxseed oil capsules Control: unclear placebo **PUFA Dose**: (intended) increase unclear **%E n-3, 0%E LCn3, unclear % n-6, unclear %E PUFA** Duration of intervention: 180 days

Outcomes Main study outcome: eye outcomes
Available outcomes: symptoms, ocular surface inflammation, fluorescein break-up time, Schirmer test (authors stated that no participants experienced any CVD events)
Response to contact: yes

Notes

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	
Allocation concealment (selection bias)	Unclear risk	
Blinding of participants and personnel (performance bias)	Unclear risk	
Blinding of outcome assessment (detection bias)	Unclear risk	
Incomplete outcome data (attrition bias)	Unclear risk	
Selective reporting (reporting bias)	Unclear risk	
Other bias	Unclear risk	

Pinna 2007 [93]

Methods RCT, 3 groups (n6 vs nil), 6 months (final group was n6 alone, n6 + eyelid hygeine was used for this comparison)
Summary risk of bias: not yet assessed

Participants People with meibomian gland dysfunction
N: 19 n6 int., 19 control
Level of risk for CVD: low
Location: Italy

Interventions Type: Supplement (capsules)
Comparison: n6 vs nil
Intervention: group C, 15mg GLA + 28.5mg LA with eyelid hygiene
Control: eyelid hygiene alone
PUFA Dose: (intended) increase 0**%E n-3, 0%E LCn3, 0.2% n-6, 0.2%E PUFA**
Duration of intervention: 180 days

Outcomes Main study outcome: ocular surface disorder
Available outcomes: eyelid oedema, self evaluation questionnaire, slit-lamp examination (and many other eye assessments)
Response to contact: not yet attempted

Notes

Risk of bias table

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

Blinding of outcome assessment (detection bias)	Unclear risk
Incomplete outcome data (attrition bias)	Unclear risk
Selective reporting (reporting bias)	Unclear risk
Other bias	Unclear risk

Purewal 1997 [94]

Methods RCT, parallel, (n6 GLA vs unclear placebo), 12 months
Summary risk of bias: Moderate or high

Participants People with diabetes and painful neuropathy
N: 26 int., 25 control. (analysed unclear)
Level of risk for CVD: moderate
Male: NR% int., NR% control.
Mean age (sd): 64.6 (7.8) int., 60.5 (10.1) 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 (probably capsules)
Comparison: GLA vs unclear placebo
Intervention: 480mg/d GLA
Control: "placebo", no dose or type described
PUFA Dose: (intended) increase 0**%E n-3, 0.2%E n6, 0.2%E PUFA**
Compliance: no details provided
Duration of intervention: states trial is 24 months duration, results provided for 12 months

Outcomes Main study outcome: measures neuropathic pain
Dropouts: unclear int., unclear control
Available outcomes: progression of neuropathy including vibration perception threshold, Valsalva ratio, RR interval, heart rate change on standing, postural hypotension
Response to contact: not yet attempted

Notes Study funding: not stated
Note: abstract only found

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)	Unclear risk	Paper states "double blind", no further details
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

Puri 2002 [95 96]

Methods	RCT, parallel (ethyl-EPA vs non-fat), 2 arm, 6 months Summary risk of bias: not yet assessed
Participants	People with Huntington's Disease N: 4 intervention, 4 control Level of risk for CVD: low Location: UK
Interventions	Type: supplement (capsules of ethyl-EPA) Comparison: EPA vs non-fat Intervention: 2g/d ethyl-EPA, 1.9 g/d EPA Control: capsules of liquid paraffin **PUFA Dose**: (intended) increase 0.86**%E n-3, 0.86%E LCn3, 0.86%E PUFA** Duration of intervention: 6 months
Outcomes	Main study outcome: Huntington's disease severity Available outcomes: Unified Huntington's Disease Rating Scale, MRI brain scans (1 death in control group before intervention began) Response to contact: yes, no additional data provided
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	
Allocation concealment (selection bias)	Unclear risk	
Blinding of participants and personnel (performance bias)	Unclear risk	
Blinding of outcome assessment (detection bias)	Unclear risk	
Incomplete outcome data (attrition bias)	Unclear risk	
Selective reporting (reporting bias)	Unclear risk	
Other bias	Unclear risk	

Reis 1991 [97-102]

Methods	RCT (LCn3 vs MUFA) 6 months Summary risk of bias: low
Participants	People undergoing angioplasty N: 146 int., 72 control Level of risk for CVD: High Male: 73% int., 76% control Mean age, sd: 60 int., 57 control Age range: Unclear Smokers: 31% int., 27% control

Hypertension: Unclear
Location: USA

Interventions Type: supplement (capsules)
Intervention: Super EPA capsules 12x1 g/d (7.0g EPA + DHA + ALA) OR Promega capsules 12x1 g/d (6.0g EPA + DHA + ALA)
Control: olive oil capsules, 12x1 g/d, appearance identical to fish oil capsules
Compliance: capsule counts, >75% of capsules taken by 66% int., 65% controls, plasma EPA rose from 0.7% total fatty acids to 4.5% at 6 mo in the int. group, 0.7% in controls
Length of intervention: 6 mo

Outcomes Main study outcome: restenosis, angina
Dropouts: 22 int, 10 control
Available outcomes: deaths, MI, CV events, weight, lipids, side effects
Response to contact: Yes

Notes

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random numbers were produced and stratified by an independent statistician
Allocation concealment (selection bias)	Low risk	Co-ordinator enrolled patients and then called statistician for allocation number
Blinding of participants and personnel (performance bias)	Low risk	Participants masked: Yes Providers masked: Yes
Blinding of outcome assessment (detection bias)	Low risk	Outcome assessors masked: Yes
Incomplete outcome data (attrition bias)	Low risk	All drop-outs left the study in the first week
Selective reporting (reporting bias)	Unclear risk	No study protocol found
Other bias	Low risk	No further bias noted

Rezapour-Firouzi 2013 [103-107]

Methods RCT, 3 arms (total PUFA - ALA & GLA vs MUFA), 6 months (other intervention arm delivers "hot diet")
Summary risk of bias: not yet assessed

Participants People with multiple sclerosis (MS)
N: 33 total PUFA int., 33 MUFA control
Level of risk for CVD: low
Location: Iran

Interventions Type: supplementary (capsules or oils?)
Comparison: total PUFA inc ALA & GLA vs MUFA
Intervention: 18-21g/d hemp seed and evening primrose oil. Hemp seed oil is approx 55% LA, 22% ALA, 1-4% GLA. EPO is high in GLA.
Control: 18-21g/d olive oil.
PUFA Dose: (intended) increase unclear**%E n-3, 0%E LCn3, unclear% n-6, 9%E PUFA**
Duration of intervention: 6 months

Outcomes Main study outcome: MS progression and relapse
Available outcomes: disability (EDSS) and function, immunology (IL-4, IL-17 and IFN-gamma), delta-6-desaturase, serum phospholipase A2, liver function tests (AST, ALT, GGT)
Response to contact: not yet attempted

Notes

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	
Allocation concealment (selection bias)	Unclear risk	
Blinding of participants and personnel (performance bias)	Unclear risk	
Blinding of outcome assessment (detection bias)	Unclear risk	
Incomplete outcome data (attrition bias)	Unclear risk	
Selective reporting (reporting bias)	Unclear risk	
Other bias	Unclear risk	

Rocha Filho 2011 [108]

Methods	RCT, 3 arms (n6 at 2 doses vs non-fat), 6 months Summary risk of bias: not yet assessed
Participants	Women experiencing pre-menstrual syndrome N: 40 high n6 int., 40 low n6 int, 40 control Level of risk for CVD: low Location: Brazil
Interventions	Type: Supplement (capsules) Comparison: n6 higher dose vs n6 lower dose vs non-fat placebo Intervention: high dose: 30x 1g capsules/d each including 0.21g GLA, 0.35gLA, 0.25g other PUFA, total 16.65g/d n6, total 24.15g/d PUFA low dose: 15x 1g capsules/d each including 0.21g GLA, 0.35gLA, 0.25g other PUFA, total 8.3g/d n6, total 12.1g/d PUFA (plus 15 capsules of placebo) Control: 30x1g capsules/d mineral oil **PUFA Dose**: (intended) increase high dose 0**%E n-3, 0%E LCn3, 7.5% n-6, 10.9%E PUFA, low** dose 0**%E n-3, 0%E LCn3, 3.8% n-6, 5.4%E PUFA** Duration of intervention: 180 days
Outcomes	Main study outcome: impact and severity of premenstrual symptoms Available outcomes: cholesterol, prolactin, Response to contact: not yet attempted

Notes

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	
Allocation concealment (selection bias)	Unclear risk	
Blinding of participants and personnel (performance bias)	Unclear risk	
Blinding of outcome assessment (detection bias)	Unclear risk	

Incomplete outcome data (attrition bias)	Unclear risk
Selective reporting (reporting bias)	Unclear risk
Other bias	Unclear risk

Rodrigues 2015 [109]

Methods	RCT (ALA & LCn3 vs unclear placebo), 6 months Summary risk of bias: not yet assessed
Participants	People with non-alcoholic steatohepatitis N: 32 n3 int., 28 control Level of risk for CVD: low Location: Brazil
Interventions	Type: Supplements (capsules) Comparison: ALA & LCn3 vs unclear placebo Intervention: 945mg/d n3 (of which 64% 605mg/d ALA, 16% 151mg/d EPA, 21% 198mg/d DHA) within 3 capsules/d Control: matching placebo **PUFA Dose**: (intended) increase **0.4%E n-3, 0.2%E LCn3, 0.4%E PUFA** Duration of intervention: 6 months
Outcomes	Main study outcome: endoplasmic reticulum stress and mitochondrial dysfunction Available outcomes: endoplasmic reticulum stress and mitochondrial dysfunction Response to contact: not yet attempted
Notes	Note: abstract only

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	
Allocation concealment (selection bias)	Unclear risk	
Blinding of participants and personnel (performance bias)	Unclear risk	
Blinding of outcome assessment (detection bias)	Unclear risk	
Incomplete outcome data (attrition bias)	Unclear risk	
Selective reporting (reporting bias)	Unclear risk	
Other bias	Unclear risk	

Sabaté 2005 [110-113]

Methods	RCT crossover (diet with walnuts ALA vs usual diet), 6 months crossover periods Summary risk of bias: not yet assessed
Participants	Healthy adults N: 90 int., 90 control Level of risk for CVD: low Location: USA
Interventions	Type: supplementary walnuts

	Comparison: usual diet plus walnuts vs usual diet Intervention: usual diet plus walnuts to make up 12% E Control: usual diet **PUFA Dose**: (intended) increase unclear **%E n-3, 0%E LCn3, unclear %E PUFA** Duration of intervention: 6 months
Outcomes	Main study outcome: weight gain Available outcomes: weight, BMI, body fat, fat free mass, Prostate specific antigen (PSA), nutrient intake. Authors report no deaths of CVD events, no diabetes or cancer diagnoses, but 1 hypothyroidism diagnosis in control arm Response to contact: yes
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	
Allocation concealment (selection bias)	Unclear risk	
Blinding of participants and personnel (performance bias)	Unclear risk	
Blinding of outcome assessment (detection bias)	Unclear risk	
Incomplete outcome data (attrition bias)	Unclear risk	
Selective reporting (reporting bias)	Unclear risk	
Other bias	Unclear risk	

Safarinajad 2009 [114-116]

Methods	RCT (LCn3 vs n6), 7.5 months Summary risk of bias: moderate to high
Participants	Infertile men N: 119 LCn3 int., 119 control Level of risk for CVD: low Location: Iran
Interventions	Type: Supplementation (capsules) Comparison: LCn3 vs n6 Intervention: 1.84g/d EPA & DHA (EPAX 5500TG), in 4 capsules/d Control: corn oil, 4 capsules/d **PUFA Dose**: (intended) increase **0.8%E n-3, 0.8%E LCn3, -0.8% n-6, unclear %E PUFA** Duration of intervention: 7.5 months
Outcomes	Main study outcome: sperm quality Available outcomes: sperm motility, sexual satisfaction (authors report no deaths or CVD events, diabetes or cancer diagnoses, also adverse events in both arms) Response to contact: yes
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement

Random sequence generation (selection bias)	Low risk	"randomised" - random permuted blocks
Allocation concealment (selection bias)	Low risk	randomisation carried out by staff member blind to pre-assessments
Blinding of participants and personnel (performance bias)	Unclear risk	placebo provided, details unclear
Blinding of outcome assessment (detection bias)	Unclear risk	unclear
Incomplete outcome data (attrition bias)	Unclear risk	
Selective reporting (reporting bias)	Unclear risk	
Other bias	Unclear risk	

Sarkkinen 1998 [117-122]

Methods	RCT (ALA vs low fat) 6 months Summary risk of bias: medium or high
Participants	People with moderate hypercholesterolaemia N: 41 int., 37 control Level of risk for CVD: Moderate Male: 46% int., 46% control Mean age, sd: 46.4, 7.4 int., 43.2, 8.2 control Age range: Unclear Smokers: Unclear Hypertension: Unclear Location: Finland
Interventions	Type: dietary advice and supplement (foods) Intervention: Advised on diet providing 38% of energy as fat, 18% as MUFA, with rapeseed oil, rapeseed margarine and skimmed milk provided (achieved 42% E from fat, 12% from MUFA) Control: Advised on diet providing 38% of energy as fat, 15% E from MUFA, with rapeseed oil, butter and semi-skimmed milk provided (achieved 36% E from fat, 10% from MUFA) Compliance: weighed dietary intakes, omega-3 fats in plasma fatty acids rose from 3.5 to 3.8% at 6 mo int., from 3.3 to 3.6% control. Length of intervention: 6 mo
Outcomes	Main study outcome: lipids, diet, BP Dropouts: None Available outcomes: deaths, BMI, lipids Response to contact: Yes
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Stratified in blocks of 4, the order in blocks was from random number tables
Allocation concealment (selection bias)	Unclear risk	Unclear
Blinding of participants and personnel (performance bias)	High risk	Participants masked: No Providers masked: No
Blinding of outcome assessment (detection bias)	Low risk	Outcome assessors masked: Yes

Incomplete outcome data (attrition bias)	Unclear risk
Selective reporting (reporting bias)	Unclear risk
Other bias	Unclear risk

Schaefer 1996 [123]

Methods	RCT (diet rich in LCn3 vs diet low in LCn3), 6 months Summary risk of bias: not yet assessed
Participants	Middle aged and older adults N: 11 high LCn3 int., 11 low LCn3 control Level of risk for CVD: low Location: USA
Interventions	Type: food provided by study to eat at home Comparison: Step 2 diet rich in LCn3 vs step 2 diet low in LCn3 Intervention: NCEP step 2 diet with 8 weekly fish portions (including sole, tuna, salmon) Control: NCEP step 2 diet with with 2 weekly fish portions **PUFA Dose**: (achieved) increase **0.5%E n-3, 0.6%E LCn3, 0% n-6, -0.2%E PUFA** Duration of intervention: 24 weeks
Outcomes	Main study outcome: lipids Available outcomes: lipids including VLDL, apoB, Lp(a), LDL particle size Response to contact: not attempted
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	
Allocation concealment (selection bias)	Unclear risk	
Blinding of participants and personnel (performance bias)	Unclear risk	
Blinding of outcome assessment (detection bias)	Unclear risk	
Incomplete outcome data (attrition bias)	Unclear risk	
Selective reporting (reporting bias)	Unclear risk	
Other bias	Unclear risk	

Selvais 1995 [124-126]

Methods	RCT (LCn3 vs unclear placebo) 9 months Summary risk of bias: low
Participants	People with insulin dependant diabetes and micro-albuminurea N: 12 int., 12 control Level of risk for CVD: Moderate Male: 'comparable' between 2 groups Mean age, sd: 'comparable' Age range: Unclear Smokers: Unclear

Hypertension: Unclear
Location: Belgium

Interventions Type: supplement (capsules) Intervention: omega-3 fatty acids (2.4g/d EPA + DHA)
Control: 'inert placebo'
Compliance: diet history, capsule count and fatty acid data (none provided)
Length of intervention: 9 mo

Outcomes Main study outcome: immunoreactivity
Dropouts: 4 int., 2 control
Available outcomes: deaths, MI, CV events
Response to contact: Yes

Notes

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	'toss' by Sanofi, Belgium
Allocation concealment (selection bias)	Low risk	Authors report that those recruiting participants were not aware of assignment, and that they could not alter allocation but no methods provided
Blinding of participants and personnel (performance bias)	Low risk	Authors reported that participants and providers were masked
Blinding of outcome assessment (detection bias)	Low risk	Outcome assessors masked: Yes
Incomplete outcome data (attrition bias)	Unclear risk	
Selective reporting (reporting bias)	Unclear risk	
Other bias	Unclear risk	

Sheppard 2013 – NCT00883649 [127]

Methods RCT (n3 - ALA & LCn3 vs n6), 6 months
Summary risk of bias: not yet assessed

Participants People with keratoconjunctivitis Sicca
N: 19 n3 int., 19 control
Level of risk for CVD: low
Location: USA

Interventions Type: Supplement (capsules)
Comparison: n3 vs n6
Intervention: 4 softgel capsules/d, including 196mg/d ALA, 126mg/d EPA, 99mg/d DHA, 264mg/d LCn3, 710mg/d LA, 240mg/d GLA, 950mg/d n6
Control: 4 softgel capsules, of sunflower oil
PUFA Dose: (intended) increase **0.2%E n-3, 0.1%E LCn3, unclear E PUFA**
Duration of intervention: 6 months

Outcomes Main study outcome: eye symptoms
Available outcomes: Ocular Surface Disease Index (OSDI), symptom severity, tear flow, corneal staining, conjunctival impression cytology, artificial tear usage, facial expression discomfort, surface regularity and asymmetry, inflammation, intraoccular pressure
Response to contact: not yet attempted

Notes

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	
Allocation concealment (selection bias)	Unclear risk	
Blinding of participants and personnel (performance bias)	Unclear risk	
Blinding of outcome assessment (detection bias)	Unclear risk	
Incomplete outcome data (attrition bias)	Unclear risk	
Selective reporting (reporting bias)	Unclear risk	
Other bias	Unclear risk	

Shevelyok 2013 [128]

Methods	RCT (unclear n3 vs unclear control), 6 months Summary risk of bias: not yet assessed
Participants	People with paroxsymal atrial fibrillation (AF) N: 30 n3 int., 41 control Level of risk for CVD: high Location: unclear
Interventions	Type: Supplements (capsules?) Comparison: n3 vs unclear control Intervention: omega-3, type and dose unclear Control: unclear control **PUFA Dose**: (intended) increase **unclear %E n-3, unclear %E LCn3, unclear % n-6, unclear %E PUFA** Duration of intervention: 6 months
Outcomes	Main study outcome: atrial late potentials Available outcomes: AF recurrence Response to contact: not yet attempted
Notes	Note: abstract only

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	
Allocation concealment (selection bias)	Unclear risk	
Blinding of participants and personnel (performance bias)	Unclear risk	
Blinding of outcome assessment (detection bias)	Unclear risk	
Incomplete outcome data (attrition bias)	Unclear risk	
Selective reporting (reporting bias)	Unclear risk	
Other bias	Unclear risk	

Singer 2004 [129]

Methods RCT (LCn3 vs MUFA), 6 months
Summary risk of bias: not yet assessed

Participants People with cardiac arrhythmia but without CHD or heart failure
N: 33 LCn3 int., 32 control
Level of risk for CVD: high
Location: Germany

Interventions Type: Supplemental capsules
Comparison: fish oil LCn3 vs olive oil
Intervention: 3g/d fish oil including 1g/d LCn3
Control: 3g/d olive oil
PUFA Dose: (intended) increase **0.5%E n-3, 0.5%E LCn3, unclear %E PUFA**
Duration of intervention: 6 months

Outcomes Main study outcome: cardiac arrhythmia
Available outcomes: lipids, blood pressure, body weight, TXB2
Response to contact: not yet attempted

Notes

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	
Allocation concealment (selection bias)	Unclear risk	
Blinding of participants and personnel (performance bias)	Unclear risk	
Blinding of outcome assessment (detection bias)	Unclear risk	
Incomplete outcome data (attrition bias)	Unclear risk	
Selective reporting (reporting bias)	Unclear risk	
Other bias	Unclear risk	

Slack 1987 [130]

Methods RCT (LCn3 vs nil), 6 months
Summary risk of bias: moderate to high

Participants Adults undergoing PTCA
N: 80 LCn3 int., 82 control
Level of risk for CVD: moderatehigh
Location: USA

Interventions Type: supplementary capsules
Comparison: EPA capsules vs nil
Intervention: 6-9 capsules/d MaxEPA
Control: nil
PUFA Dose: (intended) increase of **%E n-3, %E LCn3, % n-6, %E PUFA not stated**
Duration of intervention: 6 months

Outcomes Main study outcome: restenosis
Available outcomes: none (cholesterol, TG, HDL reported for intervention but not control)
Response to contact: not attempted

Notes

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"randomly assigned" - no method provided
Allocation concealment (selection bias)	Unclear risk	unclear, no method provided
Blinding of participants and personnel (performance bias)	High risk	no placebo
Blinding of outcome assessment (detection bias)	Unclear risk	unclear
Incomplete outcome data (attrition bias)	Unclear risk	
Selective reporting (reporting bias)	Unclear risk	
Other bias	Unclear risk	

Stainforth 1996 [131]

Methods RCT (total PUFA - GLA & LCn3 vs n6), 6 months
Summary risk of bias: not yet assessed

Participants People with systemic sclerosis
N: 13 int., 12 control
Level of risk for CVD: low
Location: UK

Interventions Type: Supplements (capsules)
Comparison: total PUFA (GLA & LCn3) vs n6
Intervention: evening primrose oil and fish oil, 6 capsules/d including 1.62g/d GLA plus LCn3 (dose unclear)
Control: 500mg/capsule sunflower oil, 6 capsules/d, 3g/d sunflower oil
PUFA Dose: (intended) increase unclear **%E n-3, unclear %E LCn3, -0.45% n-6, unclear %E PUFA**
Duration of intervention: 6 months

Outcomes Main study outcome: unclear
Available outcomes: blood flow, ulcers, subjective assessment
Response to contact: not yet attempted

Notes

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	
Allocation concealment (selection bias)	Unclear risk	
Blinding of participants and personnel (performance bias)	Unclear risk	
Blinding of outcome assessment (detection bias)	Unclear risk	
Incomplete outcome data (attrition bias)	Unclear risk	
Selective reporting (reporting bias)	Unclear risk	

Other bias	Unclear risk

Tani 2013 [132]

Methods	RCT (LCn3 vs nil), 6 months Summary risk of bias: moderate to high
Participants	People with raised triglycerides (TG) N: 72 LCn3 int., 72 control Level of risk for CVD: moderate Location: Japan
Interventions	Type: Supplement (capsules) Comparison: LCn3 vs nil Intervention: 1.8g/d EPA (highly purified, Mochida) Control: nil **PUFA Dose**: (intended) increase 0.8**%E n-3, 0.8%E LCn3, 0.8%E PUFA** Duration of intervention: 6 months
Outcomes	Main study outcome: LDL particle size Available outcomes: lipids Response to contact: not yet attempted
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	
Allocation concealment (selection bias)	Unclear risk	
Blinding of participants and personnel (performance bias)	High risk	no placebo
Blinding of outcome assessment (detection bias)	Unclear risk	
Incomplete outcome data (attrition bias)	Unclear risk	
Selective reporting (reporting bias)	Unclear risk	
Other bias	Unclear risk	

Theander 2002 [133]

Methods	RCT, 3 arms (GLA high dose vs GLA low dose), 6 months (3rd arm increased corn oil n6, not included here) Summary risk of bias: not yet assessed
Participants	People with Sjogren's syndrome N: 30 high GLA int., 30 low GLA, 30 control Level of risk for CVD: low Location: Sweden
Interventions	Type: Supplemental (emulsions?) Comparison: high GLA vs low GLA vs n6 Intervention: 1.6g/d GLA vs 0.8g/d GLA Control: corn oil emulsion, mainly n6 **PUFA Dose**: (intended) increase **0.7%E GLA high, 0.4%E GLA low (increase 0.3%E GLA)** Duration of intervention: 6 months

Outcomes Main study outcome: fatigue
Available outcomes: fatigue, sleeping time, eyesight (Shirmer), eye and mouth dryness, muscle pain, hand and finger pain, depression, medication, blood cell count, platelet count, creatinin, ESR, CRP, immunoglobulin, lymphocyte subpopulations
Response to contact: not yet attempted

Notes

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	
Allocation concealment (selection bias)	Unclear risk	
Blinding of participants and personnel (performance bias)	Unclear risk	
Blinding of outcome assessment (detection bias)	Unclear risk	
Incomplete outcome data (attrition bias)	Unclear risk	
Selective reporting (reporting bias)	Unclear risk	
Other bias	Unclear risk	

Thien 1993 [134 135]

Methods RCT (LCn3 vs MUFA) 6 months
Summary risk of bias: low

Participants People with hayfever and asthma
N: 21 int., 16 control
Level of risk for CVD: Low
Male: 60% int., 40% control
Mean age, sd: Unclear
Age range: 22-42 int., 19-39 control
Smokers: None
Hypertension: Unclear
Location: Australia

Interventions Type: supplement (capsule)
Intervention: MaxEPA capsules, 18/d (5.4g/d EPA + DHA)
Control: olive oil capsules 18/d, appeared identical to MaxEPA
Compliance: plasma fatty acids, EPA rose from 1.4 to 5.4% fatty acids at 6 mo in int group, and fell from 1.1 to 0.8% in control group
Length of intervention: 6 mo

Outcomes Main study outcome: hayfever and asthma symptoms
Dropouts: 6 int, 6 control
Available outcomes: deaths, side effects
Response to contact: Yes

Notes

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation: After screening a list was given to a non-clinical investigator who randomly

		allocated subjects, treatment was blinded to clinical investigators
Allocation concealment (selection bias)	Low risk	As above
Blinding of participants and personnel (performance bias)	Low risk	Participants masked: Yes Providers masked: Yes
Blinding of outcome assessment (detection bias)	Low risk	Outcome assessors masked: Yes
Incomplete outcome data (attrition bias)	Unclear risk	
Selective reporting (reporting bias)	Unclear risk	
Other bias	Unclear risk	

Tobin 1988 [136]

Methods	RCT, 3 arms (LCn3 vs more fish vs MUFA), 6 months Summary risk of bias: not yet assessed
Participants	Adults with serum cholesterol >7mmol/L on 3 occasions N: ~15 LCn3 int., ~15 control Level of risk for CVD: moderate Location: Ireland
Interventions	Type: supplementary capsules Comparison: fish oil vs olive oil Intervention 1: fish oil including 6g/d n3 Intervention 2: dietary regimen including 4 fish meals each week Control: olive oil capsules **PUFA Dose**: (intended) increase **2.7%E n-3, unclear for %E LCn3, % n-6, %E PUFA** Duration of intervention: 6 months
Outcomes	Main study outcome: oxidative metabolism and neutrophil superoxide Available outcomes: insufficient data (abstract only), but cholesterol and TG were measured Response to contact: no
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	
Allocation concealment (selection bias)	Unclear risk	
Blinding of participants and personnel (performance bias)	Unclear risk	
Blinding of outcome assessment (detection bias)	Unclear risk	
Incomplete outcome data (attrition bias)	Unclear risk	
Selective reporting (reporting bias)	Unclear risk	
Other bias	Unclear risk	

TOHP 1 - Sacks 1994 [137-145]

Methods	RCT (LCn3 vs MUFA) 6 months Summary risk of bias: low
Participants	People with high normal blood pressure (BP) N: 175 int., 175 control Level of risk for CVD: Low Male: 70.9% int., 69.7% control Mean age, sd: 42.6, 6.3 int., 43.1, 6.6 control Age range: Unclear Smokers: Unclear Hypertension: None Location: USA
Interventions	Type: supplement (capsules) Intervention: Promega, purified sardine oil, capsules 6x1 g/d (3.0g EPA + DHA + DPA) Control: olive oil capsules, 6x1 g/d, appearance identical to Promega capsules OR cellulose tablets, 3/d (identical to potassium supplements used in another arm of the trial) Compliance: capsule counts, 72% took at least 95% capsules at 6 mo in int., 80% in control Length of intervention: 6 mo
Outcomes	Main study outcome: blood pressure Dropouts: 1 int, 1 control Available outcomes: deaths, weight, lipids, BP, side effects Response to contact: No
Notes	Note: there were also a variety of other intervention arms. No dietary, weight or smoking advice was provided to any group in this comparison

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	treatment assignments obtained by phone from coordinating centre or (when phone contact not possible) from written instructions contained in sealed opaque envelopes
Allocation concealment (selection bias)	Low risk	Adequate
Blinding of participants and personnel (performance bias)	Low risk	Participants masked: Yes Providers masked: Yes
Blinding of outcome assessment (detection bias)	Low risk	Outcome assessors masked: Yes
Incomplete outcome data (attrition bias)	Unclear risk	
Selective reporting (reporting bias)	Unclear risk	
Other bias	Unclear risk	

Tomer 2001 [146 147]

Methods	RCT (LCn3 vs MUFA), 12 months Summary risk of bias: not yet assessed
Participants	People with sickle cell disease N: 5 LCn3 int., 10 control Level of risk for CVD: low Location: USA
Interventions	Type: supplementary capsules Comparison: LCn3 vs MUFA Intervention: Menhaden oil, 0.25g/kg/d as 1g capsules (assume 70kg participants, so

17.5g/d, including 7g/d n3
Control: olive oil, 17.5g/d as 1g capsules
PUFA Dose: (achieved) increase 3**%E n-3, 3%E LCn3, 3%E PUFA**
Duration of intervention: 12 months

Outcomes Main study outcome: pain
Available outcomes: pain, adverse events, blood parameters including bleeding time, thrombin time, white-cell count, haemoglobin, etc, plus urea, creatinine, albumin, bilirubin, cholesterol, lactate dehydrogenase, aspartate aminotransferase, PF4, betaTG, D-dimer, PAP. Author correspondence reported no deaths, CVD events, diabetes diagnoses, cancer diagnoses.
Response to contact: yes

Notes

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	
Allocation concealment (selection bias)	Unclear risk	
Blinding of participants and personnel (performance bias)	Unclear risk	Author correspondence reported that doctor and patient were blinded, without detail of mechanisms
Blinding of outcome assessment (detection bias)	Unclear risk	Author correspondence reported that doctor and patient were blinded, without detail of mechanisms
Incomplete outcome data (attrition bias)	Unclear risk	
Selective reporting (reporting bias)	Unclear risk	
Other bias	Unclear risk	

Tremoli 1994 [148]

Methods RCT (n3 vs MUFA), 6 months
Summary risk of bias: not yet assessed

Participants People with hypertriglyceridaemia
N: ~15 int., ~15 control
Level of risk for CVD: Moderate
Location: Italy

Interventions Type: supplement (capsules?)
Intervention: 3g/d n3
Control: 3g/d olive oil
PUFA Dose: (intended) increase **1.4%E n-3, unclear %E LCn3, 1.4%E PUFA**
Length of intervention: 24 weeks

Outcomes Main study outcome: tissue factor activity
Available outcomes: haematocrit, erythrocyte, leukcoyte, platelet counts, renal and liver function tests, lipids
Response to contact: not yet attempted

Notes

Risk of bias table

Bias	Authors' judgement	Support for judgement

Random sequence generation (selection bias)	Unclear risk	
Allocation concealment (selection bias)	Low risk	A - Adequate
Blinding of participants and personnel (performance bias)	Unclear risk	
Blinding of outcome assessment (detection bias)	Unclear risk	
Incomplete outcome data (attrition bias)	Unclear risk	
Selective reporting (reporting bias)	Unclear risk	
Other bias	Unclear risk	

Uehara 2013 [149]

Methods	RCT (LCn3 vs unclear control), 9 months Summary risk of bias: not yet assessed
Participants	People on statins for at least 6 months N: 9 LCn3 int., 5 control Level of risk for CVD: moderate Location: Japan
Interventions	Type: Supplement (capsules?) Comparison: LCn3 vs unclear Intervention: 1.8mg/d EPA Control: unclear control **PUFA Dose**: (intended) increase 0.8**%E n-3, 0.8%E LCn3, unclear %E PUFA** Duration of intervention: 9 months
Outcomes	Main study outcome: plaque stability Available outcomes: fibrous cap thickness Response to contact: not attempted
Notes	Note: abstract only

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	
Allocation concealment (selection bias)	Unclear risk	
Blinding of participants and personnel (performance bias)	Unclear risk	
Blinding of outcome assessment (detection bias)	Unclear risk	
Incomplete outcome data (attrition bias)	Unclear risk	
Selective reporting (reporting bias)	Unclear risk	
Other bias	Unclear risk	

Vaddadi 2002 [150]

Methods	RCT (total PUFA - GLA & LCn3 vs saturated fats), 24 months

Summary risk of bias: not yet assessed

Participants Peple with Huntingdon's disease
N: 9 int., 8 control (of whom 39 were on high polyphenols, 39 on low polyphenols)
Level of risk for CVD: low
Location: Australia

Interventions Type: Supplementation (capsules)
Comparison: total PUFA (GLA & LCn3) vs saturated fat
Intervention: 8 capsules or 8g/d including 560mg/d GLA, 280mg/d EPA, 160mg/d DHA with LA as carrier
Control: 8 capsules of coconut oil (including no PUFA)
PUFA Dose: (intended) increase **0.2%E LCn3, 0.3% n-6, 3.6%E PUFA**
Duration of intervention: 24 months

Outcomes Main study outcome: progression of Hungtingdon's disease
Available outcomes: dyskinesia (RSDRS), motor symptoms (UHDRS, including functional and capacity, behaviour, verbal fluency, symbol digit, cognitive.
Response to contact: not yet attempted

Notes

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	
Allocation concealment (selection bias)	Unclear risk	
Blinding of participants and personnel (performance bias)	Unclear risk	
Blinding of outcome assessment (detection bias)	Unclear risk	
Incomplete outcome data (attrition bias)	Unclear risk	
Selective reporting (reporting bias)	Unclear risk	
Other bias	Unclear risk	

Veale 1994 [151 152]

Methods RCT (total PUFA - LCn3 + GLA vs non-fat) 9 months
Summary risk of bias: low

Participants People with chronic stable plaque psoriasis and inflammatory arthritis
N: 19 int., 19 control
Level of risk for CVD: Low
Male: 37% int., 37% control
Mean age, sd: median 40 in both groups
Age range: 18-76 int., 25-58 control
Smokers: Unclear
Hypertension: Unclear
Location: UK

Interventions Type: supplement (capsule)
Intervention: Efamol marine capsules, 12/d (0.4g/d EPA + DHA plus 0.5g/d gamma-linoleic acid (not omega-3))
Control: capsules containing liquid paraffin and vitamin E, 12/d, appeared identical
Compliance: no data
Length of intervention: 9 mo

Outcomes	Main study outcome: skin and joint symptoms, use of NSAIDs Dropouts: 4 int, 0 control Available outcomes: deaths, MI, stroke, side effects Response to contact: Yes
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Pharmaceutical company randomised in groups of 4 using random numbers
Allocation concealment (selection bias)	Low risk	Done, as above
Blinding of participants and personnel (performance bias)	Low risk	Participants masked: Yes Providers masked: Yes
Blinding of outcome assessment (detection bias)	Low risk	Outcome assessors masked: Yes
Incomplete outcome data (attrition bias)	Unclear risk	
Selective reporting (reporting bias)	Unclear risk	
Other bias	Unclear risk	

Wakita 2013 [153]

Methods	RCT (LCn3 vs unclear control), 8 months Summary risk of bias: not yet assessed
Participants	People with asymptomatic cerebral infarction and coronary artery disease N: 20 LCn3 int., 20 control Level of risk for CVD: high Location: Japan
Interventions	Type: Supplement (capsules?) Comparison: LCn3 vs unclear control Intervention: 1.8g/d EPA with 2g/d pitavastatin Control: unclear with 2g/d pitavastatin **PUFA Dose**: (intended) increase **0.8%E n-3, 0.8%E LCn3, 0.8%E PUFA** Duration of intervention: 8 months
Outcomes	Main study outcome: intima media thickness Available outcomes: pulsatility index Response to contact: not yet attempted
Notes	Note: abstract only

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	
Allocation concealment (selection bias)	Unclear risk	
Blinding of participants and personnel (performance bias)	Unclear risk	
Blinding of outcome assessment (detection bias)	Unclear risk	

Incomplete outcome data (attrition bias)	Unclear risk
Selective reporting (reporting bias)	Unclear risk
Other bias	Unclear risk

Weisman 2011 [154]

Methods	RCT crossover (LCn3 vs unclear placebo), 6 months first phase Summary risk of bias: moderate to high
Participants	People post-MI with implantable cardioverter defibrillator N: 105 LCn3 int., 105 control Level of risk for CVD: high Location: Israel
Interventions	Type: Supplement (capsules?) Comparison: LCn3 vs unclear placebo Intervention: 3.6g/d EPA + DHA (fish oil) Control: placebo, unclear composition **PUFA Dose**: (intended) increase **1.6%E n-3, 1.6%E LCn3, 1.6%E PUFA** Duration of intervention: 6 months
Outcomes	Main study outcome: arrhythmia Available outcomes: arrhythmic events Response to contact: not yet attempted
Notes	Note: abstract only

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"random order"
Allocation concealment (selection bias)	Unclear risk	unclear, no details
Blinding of participants and personnel (performance bias)	Unclear risk	none mentioned
Blinding of outcome assessment (detection bias)	Unclear risk	none mentioned
Incomplete outcome data (attrition bias)	Unclear risk	attrition not discussed
Selective reporting (reporting bias)	Unclear risk	no information
Other bias	Low risk	no other issues

West 2010 – NCT00510692 [155-158]

Methods	RCT (LCn3 vs MCT), 6 months Summary risk of bias: low
Participants	People with familial adenomatous polyposis, post-colectomy N: 28 LCn3 int., 27 control Level of risk for CVD: low Location: UK
Interventions	Type: Supplementary capsules

Comparison: LCn3 vs MCT
Intervention: 2 x 500mg enteric coated capsules of EPA, 1g/d EPA
Control: 2x 500mg enteric coated capric and caprylic acid
PUFA Dose: (intended) increase 0.5**%E n-3, 0.5%E LCn3, 0.5%E PUFA**
Duration of intervention: 6 months

Outcomes Main study outcome: polyp number and size
Available outcomes: adverse events (in trials registry in some detail). Authors report no CVD events, no deaths, and no diabetes diagnoses, but 1 cancer diagnosis in intervention arm, none in control.
Response to contact: yes

Notes

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	computer-generated randomisation schedule was used to assign sequentially numbered treatment packs which were supplied randomised in blocks of 4
Allocation concealment (selection bias)	Low risk	As above
Blinding of participants and personnel (performance bias)	Low risk	identical capsules
Blinding of outcome assessment (detection bias)	Low risk	blinded
Incomplete outcome data (attrition bias)	Unclear risk	
Selective reporting (reporting bias)	Unclear risk	
Other bias	Unclear risk	

Wolf-Schnurrbusch 2015 – NCT00563979 [159]

Methods RCT (LCn3 vs nil), 12 months
Summary risk of bias: not yet assessed

Participants People with age-related macular degeneration
N: 39 LCn3 int., 40 control
Level of risk for CVD: low
Location: Switzerland

Interventions Type: Supplement (capsules)
Comparison: supplement including LCn3 vs supplement without LCn3
Intervention: Lutein, zeaxanthin, vitamins and minerals plus omega-3. 160mg/d omega3, 130mg/d LCn3.
Control: Lutein, zeaxanthin, vitamins and minerals
PUFA Dose: (intended) increase <0.**1%E n-3, <0.1%E LCn3, <0.1%E PUFA**
Duration of intervention: 12 months

Outcomes Main study outcome: macular pigment density, contrast sensitivity
Available outcomes: eye outcomes
Response to contact: not yet attempted

Notes

Risk of bias table

Bias	Authors' judgement	Support for judgement

Random sequence generation (selection bias)	Unclear risk
Allocation concealment (selection bias)	Unclear risk
Blinding of participants and personnel (performance bias)	Unclear risk
Blinding of outcome assessment (detection bias)	Unclear risk
Incomplete outcome data (attrition bias)	Unclear risk
Selective reporting (reporting bias)	Unclear risk
Other bias	Unclear risk

Yamano 2012 [160]

Methods RCT (LCn3 vs unclear control), 9 months
Summary risk of bias: not yet assessed

Participants People with acute coronary syndrome
N: 15 LCn3 int., 15 control
Level of risk for CVD: high
Location: Japan

Interventions Type: Supplement (capsules)
Comparison: LCn3 vs unclear control
Intervention: EPA
Control: unclear
PUFA Dose: (intended) increase unclear **%E n-3, unclear %E LCn3, unclear %E PUFA**
Duration of intervention: 9 months

Outcomes Main study outcome: fibrous cap thickness
Available outcomes: lipids, fibrous cap thickness
Response to contact: not yet attempted

Notes Note: abstract only

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	
Allocation concealment (selection bias)	Unclear risk	
Blinding of participants and personnel (performance bias)	Unclear risk	
Blinding of outcome assessment (detection bias)	Unclear risk	
Incomplete outcome data (attrition bias)	Unclear risk	
Selective reporting (reporting bias)	Unclear risk	
Other bias	Unclear risk	

Yee 2010 [161]

Methods RCT (high LCn3 vs low LCn3), 6 months

Summary risk of bias: not yet assessed

Participants Women at increased breast cancer risk
N: 12 high LCn3 int., 12 moderate LCn3, 12 low-mod LCn3, 12 low LCn3 control
Level of risk for CVD: low
Location: USA

Interventions Type: Supplement (capsules)
Comparison: high LCn3 vs low LCn3
Intervention: 7.56g/d LCn3 (EPA+DHA), 9 capsules/d, also 6 capsules/d or 5.04g/d LCn3 and 3 capsules/d or 2.52g/d LCn3
Control: 1 capsule/d or 0.84g/d LCn3
PUFA Dose: (intended) increase **3.0%E, 1.9%E, 0.7%E LCn3 compared with 1 capsule/d**
Duration of intervention: 6 months

Outcomes Main study outcome: dose effects in breast adipose tissue
Available outcomes: lipids, platelet function, closure time, ALT
Response to contact: not yet attempted

Notes

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	
Allocation concealment (selection bias)	Unclear risk	
Blinding of participants and personnel (performance bias)	Unclear risk	
Blinding of outcome assessment (detection bias)	Unclear risk	
Incomplete outcome data (attrition bias)	Unclear risk	
Selective reporting (reporting bias)	Unclear risk	
Other bias	Unclear risk	

Yoon 2015 [162]

Methods RCT, 3 arms (n3 with metformin vs metformin alone), 6 months (further arm is n3 alone)
Summary risk of bias: not yet assessed

Participants Women with polycystic ovary syndrome
N: ~27 n3 int., ~27 control
Level of risk for CVD: low
Location: Korea

Interventions Type: Supplement (capsules?)
Comparison: n3 with metformin vs metformin alone
Intervention: n3 with metformin, dose and composition unclear
Control: metformin alone
PUFA Dose: (intended) increase **unclear %E n-3, unclear %E LCn3**
Duration of intervention: 6 months

Outcomes Main study outcome: ovarian morphology and blood flow
Available outcomes: hormones and follicle count (others unclear)
Response to contact: not yet attempted

Notes Note: abstract only

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	
Allocation concealment (selection bias)	Unclear risk	
Blinding of participants and personnel (performance bias)	Unclear risk	
Blinding of outcome assessment (detection bias)	Unclear risk	
Incomplete outcome data (attrition bias)	Unclear risk	
Selective reporting (reporting bias)	Unclear risk	
Other bias	Unclear risk	

Zhu 2008 [163]

Methods RCT (seal oil LCn3 vs unclear placebo), 6 months
Summary risk of bias: not yet assessed

Participants People with non-alcoholic fatty liver disease (NAFLD)
N: 72 LCn3 int., 72 control
Level of risk for CVD: low
Location: China

Interventions Type: Supplement (capsules)
Comparison: seal oil LCn3 vs unclear placebo
Intervention: 2g of omega-3 PUFA from seal oil 3x/d or 6g/d LCn3, plus recommended diet (50% CHO, 20% protein, 30% fat, those overweight to lose weight)
Control: 2g of placebo 3x/d or 6g/d placebo, plus recommended diet (50% CHO, 20% protein, 30% fat, those overweight to lose weight)
PUFA Dose: (intended) increase **2.7%E n-3, 2.7%E LCn3, unclear %E PUFA**
Duration of intervention: 24 weeks

Outcomes Main study outcome: fatty liver
Available outcomes: fatty liver progression, lipids, liver function tests, adverse events, body weight, fasting blood glucose, blood cells
Response to contact: not yet attempted

Notes

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	
Allocation concealment (selection bias)	Unclear risk	
Blinding of participants and personnel (performance bias)	Unclear risk	
Blinding of outcome assessment (detection bias)	Unclear risk	
Incomplete outcome data (attrition bias)	Unclear risk	

Selective reporting (reporting bias)	Unclear risk
Other bias	Unclear risk

Total 91 studies, 8 Trials registry entries, 159 published papers, abstracts and author contacts.

References

1. Annuzzi G, Bozzetto L, Pacini G, et al. Effects of dietary polyphenols and/or long-chain N-3 pufa on glucose metabolism in people at high cardiovascular risk: A controlled, randomized intervention. *Diabetes* 2014;63:A15-A16.
2. Bozzetto L, Alderisio A, Giorgini M, et al. Extra-Virgin Olive Oil Reduces Glycemic Response to a High-Glycemic Index Meal in Patients With Type 1 Diabetes: A Randomized Controlled Trial. *Diabetes Care* 2016;39(4):518-24.
3. Bozzetto L, Annuzzi G, Pacini G, et al. Polyphenol-rich diets improve glucose metabolism in people at high cardiometabolic risk: a controlled randomised intervention trial. *Diabetologia* 2015;58(7):1551-60.
4. Huang LL, Coleman HR, Kim J, et al. Oral supplementation of lutein/zeaxanthin and omega-3 long chain polyunsaturated fatty acids in persons aged 60 years or older, with or without AMD. *Invest Ophthalmol Vis Sci* 2008;49(9):3864-69.
5. Chew E. Personal communication, 2011.
6. Bairati I. Personal communication. 2011
7. Bairati I, Roy L, Meyer F. Double-blind, randomized, controlled trial of fish oil supplements in prevention of recurrence of stenosis after coronary angioplasty. *Circulation* 1992;85(3):950-56.
8. Bairati I, Roy L, Meyer F. Effects of a fish oil supplement on blood pressure and serum lipids in patients treated for coronary artery disease. *Can J Cardiol* 1992;8(1):41-46.
9. Bairati I, Roy L, Meyer F. Measurement errors in standard visual analysis of coronary angiograms: consequences on clinical trials. *Can J Cardiol* 1993;9(3):225-30.
10. Meyer F, Bairati I, Roy L. Preventing restenosis after angioplasty with fish oil supplements. *Cardiology Board Review* 1993;10(1):16+23-16+25.
11. Roy L, Bairati I, Meyer F. Double blind randomised controlled trial of fish oil supplements in the prevention of restenoses after coronary angioplasty. *Circulation* 1991;84 (supplement II):365.
12. Bellamy CM, Schofield PM, Faragher EB, et al. Can supplementation of diet with omega-3 polyunsaturated fatty acids reduce coronary angioplasty restenosis rate? *Eur Heart J* 1992;13(12):1626-31.
13. Bhargava R, Kumar P. Oral omega-3 fatty acid treatment for dry eye in contact lens wearers. *Cornea* 2015;34(4):413-20.
14. Bhargava R, Chandra M, Bansal U, et al. A Randomized Controlled Trial of Omega 3 Fatty Acids in Rosacea Patients with Dry Eye Symptoms. *Curr Eye Res* 2016:1-7.
15. Bianconi L, Calo L, Mennuni M, et al. n-3 polyunsaturated fatty acids for the prevention of arrhythmia recurrence after electrical cardioversion of chronic persistent atrial fibrillation: a randomized, double-blind, multicentre study. *Europace* 2011;13(2):174-81.
16. Bierenbaum ML, Green DP, Gherman C, et al. The effects of two low fat dietary patterns on the blood cholesterol level of young male coronary patients. *Journal of Chronic Diseases* 1963;16(10):1073-83.
17. Blommers J, de Lange-De Klerk ES, Kuik DJ, et al. Evening primrose oil and fish oil for severe chronic mastalgia: a randomized, double-blind, controlled trial. *Am J Obstet Gynecol* 2002;187(5):1389-94.
18. de Lange de Klerk ESM. Personal communication. 2011
19. Borchgrevink CF. Personal communication. 2001
20. Borchgrevink CF, Berg KJ, Skaga E, et al. Effect of linseed oil on platelet adhesiveness and bleeding time in patients with coronary heart disease. *Lancet* 1965;ii:980-82.
21. Borchgrevink CF, Skaga E, Berg KJ, et al. Absence of prophylactic effect of linolenic acid in patients with coronary heart-disease. *Lancet* 1966;2(7456):187-89.

22. Johansen O, Seljeflot I, Hostmark AT, et al. The effect of supplementation with omega-3 fatty acids on soluble markers of endothelial function in patients with coronary heart disease. *Arterioscler Thromb Vasc Biol* 1999;19(7):1681-86.
23. Johansen O, Brekke M, Seljeflot I, et al. N-3 fatty acids do not prevent restenosis after coronary angioplasty: results from the CART study. Coronary Angioplasty Restenosis Trial. *J Am Coll Cardiol* 1999;33(6):1619-26.
24. Seljeflot I, Johansen O, Arnesen H, et al. Procoagulant activity and cytokine expression in whole blood cultures from patients with atherosclerosis supplemented with omega-3 fatty acids. *Thromb Haemost* 1999;81(4):566-70.
25. Chen R, Guo Q, Zhu WJ, et al. Therapeutic efficacy of omega-3 polyunsaturated fatty acid capsule in treatment of patients with non-alcoholic fatty liver disease. [Chinese]. *World Chinese Journal of Digestology* 2008;16(18):2002-06.
26. Peters NC, Contento IR, Kronenberg F, et al. Adherence in a 1-year whole foods eating pattern intervention with healthy postmenopausal women. *Public Health Nutr* 2014;17(12):2806-15.
27. Chrysohoou C, Metallinos G, Georgiopoulos G, et al. Short term omega-3 polyunsaturated fatty acid supplementation induces favorable changes in right ventricle function and diastolic filling pressure in patients with chronic heart failure; A randomized clinical trial. *Vascul Pharmacol* 2016;79:43-50.
28. Chrysohoou C. Personal communication. 2016
29. Thomashow MA, Yip NH, Parikh M, et al. Randomization to omega-3 polyunsaturated fatty acid supplementation and endothelial function in chronic obstructive pulmonary disease: the COD-Fish pilot randomized controlled trial (Abstract). *Am J Respir Crit Care Med* 2014;189:A6016.
30. Colli MC, Bracht A, Soares AA, et al. Evaluation of the efficacy of flaxseed meal and flaxseed extract in reducing menopausal symptoms. *J med food* 2012;15(9):840-45.
31. DREAM Study Research Group. *New England Journal of Medicine* 2018;378(18):1681-90.
32. Nct. Dry eye assessment and management study (DREAM). clinicaltrialsgov/ct2/show/NCT02128763, 2014.
33. Dry J, Vincent D. Effect of a fish oil diet on asthma: results of a 1-year double-blind study. *Int Arch Allergy Applied Immunol* 1991;95(2-3):156-57.
34. Vincent D. Personal communication, 2001.
35. Duffy EM, Meenagh GK, McMillan SA, et al. The clinical effect of dietary supplementation with omega-3 fish oils and/or copper in systemic lupus erythematosus. *J Rheumatol* 2004;31(8):1551-56.
36. El Khouli AM, El-Gendy EA. Efficacy of omega-3 in treatment of recurrent aphthous stomatitis and improvement of quality of life: a randomized, double-blind, placebo-controlled study. *Oral Surg Oral Med Oral Pathol Oral Radiol* 2014;117(2):191-96.
37. Maresta A, Balduccelli M, Varani E, et al. Prevention of postcoronary angioplasty restenosis by omega-3 fatty acids: main results of the Esapent for Prevention of Restenosis ITalian Study (ESPRIT). *Am Heart J* 2002;143(6):E5.
38. Maresta A. Personal communication, 2003.
39. DeFilippis AP, Harper CR, Cotsonis GA, et al. Effect of baseline plasma fatty acids on eicosapentaenoic acid levels in individuals supplemented with alpha-linolenic acid. *Int J Food Sci Nutr* 2009;60 Suppl 5:28-37.
40. Harper CR, Edwards MC, Jacobson TA. Flaxseed oil supplementation does not affect plasma lipoprotein concentration or particle size in human subjects. *J Nutr* 2006;136(11):2844-48.
41. Leaf A, Jorgensen MB, Jacobs AK, et al. Do fish oils prevent restenosis after coronary angioplasty? *Circulation* 1994;90(5):2248-57.
42. Mehta VY, Jorgensen MB, Raizner AE, et al. Spontaneous regression of restenosis: an angiographic study. *J Am Coll Cardiol* 1995;26(3):696-702.
43. Leaf A. Personal communication, 2000.
44. Galarraga B, Ho M, Youssef HM, et al. Cod liver oil (n-3 fatty acids) as an non-steroidal anti-inflammatory drug sparing agent in rheumatoid arthritis. *Rheumatology (Oxford)* 2008;47(5):665-69.
45. Garcia-Medina JJ, Garcia-Medina M, Garrido-Fernandez P, et al. A 2-year follow-up of antioxidant supplementation in primary open-angle glaucoma. *Ophthalmic Research* 2011;46 (4):238.
46. Garcia-Medina JJ, Garcia-Medina M, Garrido-Fernandez P, et al. A two-year follow-up of oral antioxidant supplementation in primary open-angle glaucoma: an open-label, randomized, controlled trial. *Acta Ophthalmol (Oxf)* 2015;93(6):546-54.
47. Geusens P, Wouters C, Nijs J, et al. Long-term effect of omega-3 fatty acid supplementation in active rheumatoid arthritis. A 12-month, double-blind, controlled study. *Arthritis Rheum* 1994;37(6):824-29.

48. Ghadian AR, M. Combination therapy with omega-3 fatty acids plus tamsulocin and finasteride in the treatment of men with lower urinary tract symptoms (LUTS) and benign prostatic hyperplasia (BPH). *Inflammopharmacology* 2017;25(4):451-58. doi: 10.1007/s10787-017-0343-2
49. Hamazaki K, Itomura M, Hamazaki T, et al. Effects of cooking plant oils on recurrent aphthous stomatitis: a randomized, placebo-controlled, double-blind trial. *Nutrition* 2006;22(5):534-38.
50. Hansen AL, Dahl L, Bakke L, et al. Fish consumption and heart rate variability: Preliminary results. *J Psychophysiol* 2010;24(1):41-47.
51. Hansen A. Personal communication, 2011.
52. Harbige LS, Sharief MK. Polyunsaturated fatty acids in the pathogenesis and treatment of multiple sclerosis. *Br J Nutr* 2007;98 Suppl 1:S46-S53.
53. Harris WS, Windsor SL. N-3 fatty acid supplements reduce chylomicron levels in healthy volunteers. *Journal of applied nutrition* 1991;43(1):5-15.
54. Henz BM, Jablonska S, van de Kerkhof PC, et al. Double-blind, multicentre analysis of the efficacy of borage oil in patients with atopic eczema. *Br J Dermatol* 1999;140(4):685-88.
55. Holguin F, Tellez-Rojo MM, Lazo M, et al. Cardiac autonomic changes associated with fish oil vs soy oil supplementation in the elderly. *Chest* 2005;127(4):1102-07.
56. Horrobin DF. Essential fatty acids in the management of impaired nerve function in diabetes. *Diabetes* 1997;46 Suppl 2:S90-S93.
57. Domei T, Amemiya K, Enomoto S, et al. Eicosapentaenoic acid reduced the progression of the coronary atherosclerosis in the patients with optimal LDL cholesterol lowering therapy. *Eur Heart J* 2013;34:137.
58. Jamal GA, Carmichael H, Weir AI. Gamma-linolenic acid in diabetic neuropathy. *Lancet* 1986;1(8489):1098.
59. Dyer O. Doctor accused of giving false information to drug trial. *Br Med J* 2002;325(7365):618.
60. Jenkins AP, Green AT, Thompson RP. Essential fatty acid supplementation in chronic hepatitis B. *Aliment Pharmacol Ther* 1996;10(4):665-68.
61. Khan F, Elherik K, Bolton-Smith C, et al. The effects of dietary fatty acid supplementation on endothelial function and vascular tone in healthy subjects. *Cardiovascular Research* 2003;59(4):955-62.
62. Kojuri J, Ostovan MA, Rezaian GR, et al. Effect of omega-3 on brain natriuretic peptide and echocardiographic findings in heart failure: Double-blind placebo-controlled randomized trial. *J Cardiovasc Dis Res* 2013;4(1):20-24.
63. Kokke KH, Morris JA, Lawrenson JG. Oral omega-6 essential fatty acid treatment in contact lens associated dry eye. *Contact lens anterior eye* 2008;31(3):141-46.
64. Koziolova N, Polyanskaya E, Shilova Y, et al. Dynamics of structure and function of arterial wall in patients with permanent atrial fibrillation after treatment with omega-3 unsaturated fatty acids. *Atherosclerosis* 2015;241 (1):e228.
65. Kurabayashi T, Okada M, Tanaka K. Eicosapentaenoic acid effect on hyperlipidemia in menopausal Japanese women. The Niigata Epadel Study Group. *Obstet Gynecol* 2000;96(4):521-28.
66. Tanaka K. Personal communication, 2011.
67. 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.
68. Lau CS. Personal communication, 2001.
69. Malaguarnera M, Restuccia N, Di Fazio I, et al. Fish oil treatment of interferon-alpha-induced dyslipidaemia: Study in patients with chronic hepatitis C. *BioDrugs* 1999;11(4):285-91.
70. Masterton G, Shams A, Walsh J, et al. A clinical trial investigating the effect of omega-3 fatty acids on non-alcoholic fatty liver disease. *Gut* 2015;64:A256.
71. McKew JR, Millar AM, Wright SA, et al. Beneficial effects of omega-3-polyunsaturated fatty acids on SF-36 scores in systemic lupus erythematosus. *Rheumatology (United Kingdom)* 2012;51:iii158.
72. Mehta SP, Boddy AP, Cook J, et al. Effect of n-3 polyunsaturated fatty acids on Barrett's epithelium in the human lower esophagus. *Am J Clin Nutr* 2008;87(4):949-56.
73. Johnson IT. Personal communication, 2011.
74. Meyer BJ, Hammervold T, Rustan AC, et al. Dose-dependent effects of docosahexaenoic acid supplementation on blood lipids in statin-treated hyperlipidaemic subjects. *Lipids* 2007;42(2):109-15.
75. Meyer BJ, Lane AE, Mann NJ. Comparison of seal oil to tuna oil on plasma lipid levels and blood pressure in hypertriglyceridaemic subjects. *Lipids* 2009;44(9):827-35.
76. Howe P. Personal communication, 2011.

77. Millar JH, Zilkha KJ, Langman MJ, et al. Double-blind trial of linoleate supplementation of the diet in multiple sclerosis. *Br Med J* 1973;1(5856):765-68.
78. Milner MR, Gallino RA, Leffingwell A, et al. Usefulness of fish oil supplements in preventing clinical evidence of restenosis after percutaneous transluminal coronary angioplasty. *Am J Cardiol* 1989;64(5):294-99.
79. Milner MR, Gallino RA, Leffingwell A, et al. High dose omega-3 fatty acid supplementation reduces clinical restenosis after coronary angioplasty [abstract]. *Circulation* 1988;78:II634-II34.
80. Querques G, Benlian P, Chanu B, et al. Nutritional AMD treatment phase I (NAT-1): Feasibility of oral DHA supplementation in age-related macular degeneration. *Eur J Ophthalmol* 2009;19(1):100-06.
81. Querques G. Personal communication, 2011.
82. 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.
83. Schuchardt JP, Neubronner J, Block RC, et al. Associations between Omega-3 Index increase and triacylglyceride decrease in subjects with hypertriglyceridemia in response to six month of EPA and DHA supplementation. *Prostaglandins Leukot Essent Fatty Acids* 2014;91(4):129-34.
84. Neubronner J. Personal communication, 2011.
85. Njike VYY, N.; Petraro, P.; Ayettey, R.G.; Treu, J.A.; Katz, D.L. Inclusion of walnut in the diets of adults at risk for type 2 diabetes and their dietary pattern changes: a randomized, controlled, cross-over trial. *BMJ Open Diabetes Res* 2016;4:e000293.
86. Nosratzehi TA, A. Efficacy of omega-3 in treatment of recurrent aphthous stomatitis: a randomised, double-blind, placebo-controlled study. *Chinese Journal of Dental Research* 2016;19(3):159-64. doi: 10.3290/j.cjdr.a36681
87. Oliwiecki S, Burton JL. Evening primrose oil and marine oil in the treatment of psoriasis. *Clin Exp Dermatol* 1994;19(2):127-29.
88. Palozza P, Sgarlata E, Luberto C, et al. n-3 fatty acids induce oxidative modifications in human erythrocytes depending on dose and duration of dietary supplementation. *Am J Clin Nutr* 1996;64(3):297-304.
89. Parulkar M, Dawson DR, Kryscio R, et al. Lack of effect of omega-3 fatty acid (PUFA) dietary supplement on clinical measures of periodontitis in humans. *The FASEB Journal Conference: Experimental Biology* 2009;23(S1)
90. Urakawa S, Kohno K, Miyoshi T, et al. Effect of pitavastatin and eicosapentaenoic acid on coronary artery calcification detected by multi detector-row computed tomography. *Eur Heart J* 2014;35:452.
91. Pinheiro MN, dos Santos PM, dos Santos RCR, et al. Oral flaxseed oil (Linum usitatissimum) in the treatment for dry-eye Sjögren's syndrome patients. *Arq Bras Oftalmol* 2007;70(4):649-55.
92. Pinheiro MN. Personal communication, 2011.
93. Pinna A, Piccinini P, Carta F. Effect of oral linoleic and gamma-linolenic acid on meibomian gland dysfunction. *Cornea* 2007;26(3):260-64.
94. Purewal TS, Evans PMS, Harvard F, et al. Lack of effect of evening primrose oil on autonomic function tests after 12 months of treatment [abstract]. *Diabetologia* 1997;40(Suppl):2186.
95. Puri BK, Bydder GM, Counsell SJ, et al. MRI and neuropsychological improvement in Huntington disease following ethyl-EPA treatment. *Neuroreport* 2002;13(1):123-26.
96. Puri BK. Personal communication, 2011.
97. Reis GJ. Fish oil supplements raise LDL cholesterol: results of a blinded, placebo-controlled trial in patients with coronary disease [abstract]. *Circulation (Supp)* 1988;78(4):Ii385.
98. Reis GJ, Boucher TM, McCabe CH. Results of a randomised, double blind placebo controlled trial of fish oil for prevention of restenosis after PTCA [abstract]. *Circulation* 1988;78 (supplement 2):291-91.
99. Reis GJ, Boucher TM, Sipperly ME, et al. Randomised trial of fish oil for prevention of restenosis after coronary angioplasty. *Lancet* 1989;2(8656):177-81.
100. Reis GJ, Kuntz RE, Silverman DI, et al. Effects of serum lipid levels on restenosis after coronary angioplasty. *Am J Cardiol* 1991;68(15):1431-35.
101. Reis GJ, Silverman DI, Boucher TM, et al. Effects of two types of fish oil supplements on serum lipids and plasma phospholipid fatty acids in coronary artery disease. *Am J Cardiol* 1990;66(17):1171-75.
102. Sipperly ME, Reis GJ, Boucher TM, et al. Predictors of patient compliance in a placebo-controlled trial of fish oil [abstract]. *Circulation* 1988;78:II614-II14.
103. Rezapour-Firouzi S, Arefhosseini SR, Ebrahimi-Mamaghani M, et al. Alteration of delta-6-desaturase (FADS2), secretory phospholipase-A2 (sPLA2) enzymes by Hot-nature diet with co-supplemented hemp seed, evening primrose oils intervention in multiple sclerosis patients. *Complementary Therapies in Medicine* 2015;23(5):652-57.

104. Rezapour-Firouzi S, Arefhosseini SR, Ebrahimi-Mamaghani M, et al. Activity of liver enzymes in multiple sclerosis patients with Hot-nature diet and co-supplemented hemp seed, evening primrose oils intervention. *Complementary Therapies in Medicine* 2014;22(6):986-93.
105. Rezapour-Firouzi S, Arefhosseini SR, Ebrahimi-Mamaghani M, et al. Erythrocyte membrane fatty acids in multiple sclerosis patients and hot-nature dietary intervention with co-supplemented hemp-seed and evening-primrose oils. *Afr J Tradit Complement Altern Med* 2013;10(6):519-27.
106. Rezapour-Firouzi S, Arefhosseini SR, Mehdi F, et al. Immunomodulatory and therapeutic effects of Hot-nature diet and co-supplemented hemp seed, evening primrose oils intervention in multiple sclerosis patients. *Complementary Therapies in Medicine* 2013;21(5):473-80.
107. Rezapour-Firouzi S, Rafie S, Farhoudi M, et al. Regulation of lipid-dependent membrane enzymes by Hot nature diet with co-supplemented hemp seed, evening primrose oils intervention in multiple sclerosis patients. *Journal of Pure and Applied Microbiology* 2013;7(4):2891-901.
108. Rocha Filho EA, Lima JC, Pinho Neto JS, et al. Essential fatty acids for premenstrual syndrome and their effect on prolactin and total cholesterol levels: a randomized, double blind, placebo-controlled study. *Reproductive Health* 2011;8:2.
109. Rodrigues L, Oliveira CP, Stefano JT, et al. Omega-3 fatty acids improve proteomic and lipidomic markers of endoplasmic reticulum (ER) stress and mitochondrial dysfunction in a randomized controlled trial in subjects with Nonalcoholic Steatohepatitis. *Hepatology* 2015;62:333A.
110. Sabate J, Cordero-Macintyre Z, Siapco G, et al. Does regular walnut consumption lead to weight gain? *Br J Nutr* 2005;94(5):859-64.
111. Segovia-Siapco G, Singh P, Jaceldo-Siegl K, et al. Validation of a food-frequency questionnaire for measurement of nutrient intake in a dietary intervention study. *Public Health Nutr* 2007;10(2):177-84.
112. Simon JA, Tanzman JS, Sabate J. Lack of effect of walnuts on serum levels of prostate specific antigen: a brief report. *J Am Coll Nutr* 2007;26(4):317-20.
113. Segovia-Siapco G. Personal communication, 2011.
114. Safarinejad M. Effect of omega-3 polyunsaturated fatty acid supplementation on semen profile and enzymatic antioxidant capacity of seminal plasma in infertile men with idiopathic oligoasthenoteratospermia: A double blind, placebocontrolled, randomized study. *Urology* 2009;74 (4 SUPPL S):S96.
115. Safarinejad M. Efficacy and safety of omega-3 for treatment of early stage peyronie's disease: A prospective, randomized, doubleblind placebocontrolled study. *Urology* 2009;74 (4 SUPPL S):S328.
116. Safarinejad M. Personal communication, 2011.
117. Sarkkinen ES, Agren JJ, Ahola I, et al. Fatty acid composition of serum cholesterol esters, and erythrocyte and platelet membranes as indicators of long-term adherence to fat-modified diets. *Am J Clin Nutr* 1994;59(2):364-70.
118. Sarkkinen ES, Uusitupa MI, Gylling H, et al. Fat-modified diets influence serum concentrations of cholesterol precursors and plant sterols in hypercholesterolemic subjects. *Metabolism* 1998;47(6):744-50.
119. Sarkkinen ES, Uusitupa MI, Pietinen P, et al. Long-term effects of three fat-modified diets in hypercholesterolemic subjects. *Atherosclerosis* 1994;105:9-23.
120. Makinen E, Uusitupa MI, Pietinen P, et al. Long term effects of three fat modified diets on serum lipids in free living hypercholesterolemic subjects [abstract]. *Eur Heart J* 1991;12:168-68.
121. Sarkkinen E. Personal communication, 2000.
122. Sarkkinen ES, Uusitupa MI, Nyyssonen K, et al. Effects of two low-fat diets, high and low in polyunsaturated fatty acids, on plasma lipid peroxides and serum vitamin E levels in free-living hypercholesterolaemic men. *Eur J Clin Nutr* 1993;47(9):623-30.
123. Schaefer EJ, Lichtenstein AH, Lamon FS, et al. Effects of National Cholesterol Education Program Step 2 diets relatively high or relatively low in fish-derived fatty acids on plasma lipoproteins in middle-aged and elderly subjects. *Am J Clin Nutr* 1996;63(2):234-41.
124. Selvais PL, Ketelslegers JM, Buysschaert M, et al. Plasma endothelin-1 immunoreactivity is increased following long-term dietary supplementation with omega-3 fatty acids in microalbuminuric IDDM patients. *Diabetologia* 1995;38:253-53.
125. Hermans MP. Personal communication. 2000
126. Selvais PL. Personal communication, 2000.
127. Sheppard JD, Jr., Singh R, McClellan AJ, et al. Long-term Supplementation With n-6 and n-3 PUFAs Improves Moderate-to-Severe Keratoconjunctivitis Sicca: A Randomized Double-Blind Clinical Trial. *Cornea* 2013;32(10):1297-304.

128. Shevelyok A, Vatutin N, Kalinkina N, et al. Omega-3 polyunsaturated fatty acids reduce the atrial late potentials rate in patients with paroxysmal atrial fibrillation. *European Journal of Preventive Cardiology* 2013;1):S62.
129. Singer P, Wirth M. Can n-3 PUFA reduce cardiac arrhythmias? Results of a clinical trial. *Prostaglandins Leukot Essent Fatty Acids* 2004;71(3):153-59.
130. Slack JD, Pinkerton CA, Van Tassel J, et al. Can oral fish oil supplement minimise restenosis after percutaneous transluminal coronary angioplasty? [abstract]. *J Am Coll Cardiol* 1987;9:64-64.
131. Stainforth JM, Layton AM, Goodfield MJ. Clinical aspects of the use of gamma linolenic acid in systemic sclerosis. *Acta Dermato-Venereologica* 1996;76(2):144-46.
132. 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.
133. Theander E, Horrobin DF, Jacobsson LT, et al. Gammalinolenic acid treatment of fatigue associated with primary Sjogren's syndrome. *Scandinavian Journal of Rheumatology* 2002;31(2):72-79.
134. Thien FC, Mencia HJ, Lee TH. Dietary fish oil effects on seasonal hay fever and asthma in pollen-sensitive subjects. *Am Rev Respir Dis* 1993;147(5):1138-43.
135. Thien FC. Personal communication, 2000.
136. Tobin A, Clarke R. Therapeutic effects of fish oil supplementation in hyperlipidaemia [abstract]. *Ir J Med Sci* 1988;157(9):301-01.
137. Sacks FM, Hebert P, Appel LJ, et al. The effect of fish oil on blood pressure and high-density lipoprotein-cholesterol levels in phase I of the Trials of Hypertension Prevention. Trials of Hypertension Prevention Collaborative Research Group. *J Hypertens Suppl* 1994;12(7):S23-S31.
138. Sacks FM, Hebert P, Appel LJ, et al. Short report: the effect of fish oil on blood pressure and high-density lipoprotein-cholesterol levels in phase I of the Trials of Hypertension Prevention. *J Hypertens* 1994;12(2):209-13.
139. Meilahn EN, Kuller LH, Kiss JE, et al. Coagulation parameters among healthy adults taking fish oil versus placebo. *Arteriosclerosis* 1990;10:916A-16A.
140. He J, Klag MJ, Appel LJ, et al. Seven-year incidence of hypertension in a cohort of middle-aged African Americans and whites. *Hypertension* 1998;31(5):1130-35.
141. Satterfield S, Borhani NO, Whelton P, et al. Recruitment for phase I of the Trials of Hypertension Prevention. *Am J Prev Med* 1993;9(4):237-43.
142. Whelton PK, Kumanyika SK, Cook NR, et al. Efficacy of nonpharmacologic interventions in adults with high-normal blood pressure: results from phase 1 of the Trials of Hypertension Prevention. *Am J Clin Nutr* 1997;65(2 Suppl):652S-60S.
143. Trials of Hypertension Prevention Collaborative Research Group. The effects of nonpharmacologic interventions on blood pressure of persons with high normal levels. Results of the Trials of Hypertension Prevention, phase I. *Jama* 1992;267(9):1213-20.
144. Sacks FM. Personal communication, 2000.
145. Satterfield S, Cutler JA, Langford HG, et al. Trials of hypertension prevention. Phase I design. *Annals of epidemiology* 1991;1(5):455-71.
146. Tomer A, Kasey S, Connor WE, et al. Reduction of pain episodes and prothrombotic activity in sickle cell disease by dietary n-3 fatty acids. *Thromb Haemost* 2001;85(6):966-74.
147. Tomer A. Personal communication, 2011.
148. Tremoli E, Eligini S, Colli S, et al. n-3 Fatty acid ethyl ester administration to healthy subjects and to hypertriglyceridemic patients reduces tissue factor activity in adherent monocytes. *Arteriosclerosis and Thrombosis* 1994;14(10):1600-08.
149. Uehara H, Miyagi N, Shimajiri M, et al. The additional effect of Eicosapentanoic acid on coronary plaque stability in stable angina patients with statin use by Optical Coherence Tomography analysis. *Eur Heart J* 2013;34:1011.
150. Vaddadi KS, Soosai E, Chiu E, et al. A randomised, placebo-controlled, double blind study of treatment of Huntington's disease with unsaturated fatty acids.[Erratum appears in Neuroreport 2002 Feb;13(2):inside back cover]. *Neuroreport* 2002;13(1):29-33.
151. Veale DJ, Torley HI, Richards IM, et al. A double-blind placebo controlled trial of Efamol Marine on skin and joint symptoms of psoriatic arthritis. *Br J Rheumatol* 1994;33(10):954-58.
152. Belch JJF. Personal communication, 2001.

153. Wakita Y, Wakida Y, Itou T, et al. High purity eicosapentaenoic acid in addition to a strong statin makes regression of intima-media thickness in patients with asymptomatic cerebral infarction. *Stroke Conference* 2013;44(2 MeetingAbstract)
154. Weisman D, Glikson M, Goldbourt U, et al. Effect of supplemented intake of docosahexaenoic and eicosapentaenoic fatty acids on ventricular arrhythmias in coronary heart disease patient's with implantable cardioverter defibrillator. *J Am Coll Cardiol* 2011;1):E139.
155. West NJ, Clark SK, Belluzzi A, et al. Eicosapentaenoic acid (EPA) free fatty acid reduces polyp burden in familial adenomatous polyposis (FAP): Results of a randomised, placebo-controlled trial. *Gastroenterology* 2010;1):S79.
156. West NJ. Personal communication, 2011.
157. West NJ, Clark SK, Belluzzi A, et al. Eicosapentaenoic acid free fatty acid (EPA-FFA) reduces the number of rectal polyps in familial adenomatous polyposis (FAP). *Familial Cancer* 2011;10:S15-S16.
158. West NJ, Clark SK, Phillips RK, et al. Eicosapentaenoic acid reduces rectal polyp number and size in familial adenomatous polyposis. *Gut* 2010;59(7):918-25.
159. Wolf-Schnurrbusch UE, Zinkernagel MS, Munk MR, et al. Oral Lutein Supplementation Enhances Macular Pigment Density and Contrast Sensitivity but Not in Combination With Polyunsaturated Fatty Acids. *Invest Ophthalmol Vis Sci* 2015;56(13):8069-74.
160. Yamano T, Wada T, Nishiguchi T, et al. The impact of ethyl icosapentate therapy on coronary fibrous-cap thickness in acute coronary syndrome patients without hyperlipidemia: Assessment by optical coherence tomography study. *Eur Heart J* 2013;34:706.
161. Yee LD, Lester JL, Cole RM, et al. Omega-3 fatty acid supplements in women at high risk of breast cancer have dose-dependent effects on breast adipose tissue fatty acid composition. *Am J Clin Nutr* 2010;91(5):1185-94.
162. Yoon JW, Kim CH, Ahn JW, et al. Effect of omega-3-polyunsaturated fatty acids and metformin on ovarian morphology and intraovarian blood flow in patients with polycystic ovary syndrome. *Fertility and Sterility* 2010;1):S194.
163. Zhu FS, Liu S, Chen XM, et al. Effects of n-3 polyunsaturated fatty acids from seal oils on nonalcoholic fatty liver disease associated with hyperlipidemia. *World Journal of Gastroenterology* 2008;14(41):6395-400.