

# Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease (Review)

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[Intervention Review]

# Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

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# ABSTRACT

#### Background

Evidence on the health effects of total polyunsaturated fatty acids (PUFA) is equivocal. Fish oils are rich in omega-3 PUFA and plant oils in omega-6 PUFA. Evidence suggests that increasing PUFA-rich foods, supplements or supplemented foods can reduce serum cholesterol, but may increase body weight, so overall cardiovascular effects are unclear.

#### Objectives

To assess effects of increasing total PUFA intake on cardiovascular disease and all-cause mortality, lipids and adiposity in adults.

#### Search methods

We searched CENTRAL, MEDLINE and Embase to April 2017 and clinicaltrials.gov and the World Health Organization International Clinical Trials Registry Platform to September 2016, without language restrictions. We checked trials included in relevant systematic reviews.

#### Selection criteria

We included randomised controlled trials (RCTs) comparing higher with lower PUFA intakes in adults with or without cardiovascular disease that assessed effects over 12 months or longer. We included full texts, abstracts, trials registry entries and unpublished data. Outcomes were all-cause mortality, cardiovascular disease mortality and events, risk factors (blood lipids, adiposity, blood pressure), and adverse events. We excluded trials where we could not separate effects of PUFA intake from other dietary, lifestyle or medication interventions.

#### Data collection and analysis

Two review authors independently screened titles and abstracts, assessed trials for inclusion, extracted data, and assessed risk of bias. We wrote to authors of included trials for further data. Meta-analyses used random-effects analysis, sensitivity analyses included fixedeffects and limiting to low summary risk of bias. We assessed GRADE quality of evidence.

## Main results

We included 49 RCTs randomising 24,272 participants, with duration of one to eight years. Eleven included trials were at low summary risk of bias, 33 recruited participants without cardiovascular disease. Baseline PUFA intake was unclear in most trials, but 3.9% to 8% of total energy intake where reported. Most trials gave supplemental capsules, but eight gave dietary advice, eight gave supplemental foods such as nuts or margarine, and three used a combination of methods to increase PUFA.

Increasing PUFA intake probably has **little or no effect on all-cause mortality** (risk 7.8% vs 7.6%, risk ratio (RR) 0.98, 95% confidence interval (CI) 0.89 to 1.07, 19,290 participants in 24 trials), but **probably slightly reduces risk of coronary heart disease events** from 14.2% to 12.3% (RR 0.87, 95% CI 0.72 to 1.06, 15 trials, 10,076 participants) and **cardiovascular disease events** from 14.6% to 13.0% (RR 0.89, 95% CI 0.79 to 1.01, 17,799 participants in 21 trials), all moderate-quality evidence. Increasing PUFA **may slightly reduce risk of coronary heart disease death** (6.6% to 6.1%, RR 0.91, 95% CI 0.78 to 1.06, 9 trials, 8810 participants) and**stroke** (1.2% to 1.1%, RR 0.91, 95% CI 0.58 to 1.44, 11 trials, 14,742 participants, though confidence intervals include important harms), but has **little or no effect on cardiovascular mortality** (RR 1.02, 95% CI 0.82 to 1.26, 16 trials, 15,107 participants) all low-quality evidence. Effects of increasing PUFA on **major adverse cardiac and cerebrovascular events** and **atrial fibrillation** are unclear as evidence is of very low quality.

Increasing PUFA intake slightly **reduces total cholesterol** (mean difference (MD) -0.12 mmol/L, 95% CI -0.23 to -0.02, 26 trials, 8072 participants) and **probably slightly decreases triglycerides** (MD -0.12 mmol/L, 95% CI -0.20 to -0.04, 20 trials, 3905 participants), but has little or no effect on high-density lipoprotein (**HDL**) (MD -0.01 mmol/L, 95% CI -0.02 to 0.01, 18 trials, 4674 participants) or low-density lipoprotein (**LDL**) (MD -0.01 mmol/L, 95% CI -0.02 to 0.01, 18 trials, 4674 participants) causes slight **weight gain** (MD 0.76 kg, 95% CI 0.34 to 1.19, 12 trials, 7100 participants).

Effects of increasing PUFA on **serious adverse events** such as pulmonary embolism and bleeding are unclear as the evidence is of very low quality.

#### Authors' conclusions

This is the most extensive systematic review of RCTs conducted to date to assess effects of increasing PUFA on cardiovascular disease, mortality, lipids or adiposity. Increasing PUFA intake probably slightly reduces risk of coronary heart disease and cardiovascular disease events, may slightly reduce risk of coronary heart disease mortality and stroke (though not ruling out harms), but has little or no effect on all-cause or cardiovascular disease mortality. The mechanism may be via lipid reduction, but increasing PUFA probably slightly increases weight.

# PLAIN LANGUAGE SUMMARY

#### Polyunsaturated fatty acids for prevention and treatment of diseases of the heart and circulation

#### **Review question**

We reviewed randomised trials (participants have an equal chance to be assigned to either treatment) examining effects of increasing intake of polyunsaturated fatty acids (PUFA) on deaths and diseases of the heart and circulation (cardiovascular diseases), including heart attacks and stroke.

#### Background

We eat PUFA in our usual food, but quantities of PUFA eaten vary. There is some evidence that increasing the amount of PUFA we eat can reduce our blood cholesterol and make us less likely to develop cardiovascular disease, particularly if PUFAs are eaten instead of saturated fats (fats from animal sources such as meat and cheese). But eating more PUFA may increase our body weight, and omega-6 fats (one component of PUFA) may worsen cardiovascular risk by increasing inflammation. Evidence on the benefits or harms of increasing PUFA intake on diseases of the heart and circulation, or on other health outcomes, is inconclusive.

#### **Trial characteristics**

Evidence in this Cochrane Review is current to 27 April 2017. We included 49 trials randomising 24,272 participants, for one to eight years. These trials assessed effects of eating more, compared to less PUFA, on diseases of the heart and circulation, and deaths. Twelve trials were very trustworthy (had low risk of bias overall). Participants were men and women, some with existing illnesses and some not. Trials took place in North America, Asia, Europe and Australia, and sixteen were funded only by national or charitable agencies.

#### Key results

Increasing PUFA probably makes little or no difference (neither benefit nor harm) to our risk of death (moderate-quality evidence), and may make little or no difference to our risk of dying from cardiovascular disease (low-quality evidence). However, increasing PUFA probably slightly reduces our risk of heart disease events and of combined heart and stroke events (moderate-quality evidence). Fifty three people would need to eat more PUFA to prevent one person experiencing a heart disease event, and 63 people to prevent one person experiencing a heart or stroke event. Increasing PUFA may very slightly reduce risk of death due to heart disease, as well as stroke, but harm is possible (low-quality evidence). PUFA probably slightly reduces fats circulating in the blood (cholesterol, high-quality evidence and triglycerides, moderate-quality evidence). Increasing PUFA probably slightly increases body weight (moderate-quality evidence). The evidence mainly comes from trials of men living in high-income countries.

# SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

# Higher PUFA compared to lower PUFA for CVD

Patient or population: people with or without existing CVD, men and women

Setting: includes free-living participants and those living in institutions. Includes participants from all continents but most events occurred in trials carried out in Europe or North America.

Intervention: higher PUFA intake

Comparison: lower PUFA intake

Eligible trials compared higher with lower total PUFA intakes. The intervention had to be dietary supplementation, or a provided diet, or advice on diet. The advice, foodstuffs or supplements had to aim to increase or decrease total PUFA intake, or a dietary component high in total PUFA intake such as vegetable oil, or, if no clear aim was stated (but implied, such as aiming to provide a 'heart health', 'reduced fat' or 'Mediterranean' diet) then the intervention had to achieve an increase or decrease of at least 10% of the baseline total PUFA level

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% Cl)	∾ of participants (trials)	Certainty of the evi- dence	Comments
	Risk with lower PUFA	Risk with higher PUFA			(GRADE)	
All-cause mortality Follow-up: range 12 months to 96 months	No CVD at baseline (primary prevention)		RR 0.98 (0.89 to 1.07)	19,290 (24 RCTs)	$\oplus \oplus \oplus \bigcirc$ Moderate <sup>a</sup>	Increasing PUFA intake probably has little or no
	34 per 1000	33 per 1000 (27 to 41)				effect on all-cause mor- tality (risk alters from 7. 8% to 7.6% in the overall
	CVD at baseline (secondary prevention)					study population), mod- erate-quality evidence
	117 per 1000	115 per 1000 (101 to 131)				
Coronary heart disease events Follow-up: range 12 months to 96 months	No CVD at baseline (pri	mary prevention)	RR 0.87 (0.72 to 1.06)	10,076 (15 RCTs)	⊕⊕⊕⊖ Moderate <sup>b</sup>	Increasing PUFA intake may reduce risk of CHD events (from 14.2% to 12.3% in the study pop- ulation,NNT = 53),mod- erate-quality evidence

	134 per 1000	71 per 1000 (34 to 149)				
	CVD at baseline (s	econdary prevention)				
	143 per 1000	137 per 1000 (122 to 156)				
<b>Stroke</b> Follow-up: range 12	No CVD at baseline (primary prevention)		RR 0.91 (0.58 to 1.44)	14,742 (11 RCTs)	$\oplus \oplus \bigcirc \bigcirc$ Low <sup>c</sup>	Increasing PUFA intake may reduce risk of
months to 96 months	21 per 1000	15 per 1000 (10 to 24)				stroke (from 1.2% to 1. 1% in the study popula- tion, NNT= 1000), low-
	CVD at baseline (secondary prevention)					quality evidence. How- ever, the 95% confi-
	5 per 1000	6 per 1000 (3 to 13)				dence intervals include important harms as well as benefit
diac and cerebrovascu-	- No CVD at baseline (primary prevention) -		RR 0.84 (0.59 to 1.20)	2879 (2 RCTs)	$\oplus \bigcirc \bigcirc \bigcirc$ Very low <sup>d</sup>	Effects of increasing PUFA on MACCEs are
lar events Follow-up: range 24 months to 96 months	206 per 1000	142 per 1000 (105 to 192)				unclear as the evidence is of very low quality
	CVD at baseline (secondary prevention)					
	332 per 1000	329 per 1000 (289 to 372)				

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

CI: Confidence interval; CVD: cardiovascular disease; OR: odds ratio; PUFA: polyunsaturated fatty acids; RR: risk ratio

# **GRADE Working Group grades of evidence**

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

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

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

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

# <sup>a</sup>All-cause mortality

1. **Risk of bias**: effect size did not alter when restricted to trials at low summary risk of bias, low risk of bias from allocation, attention or compliance. Not downgraded.

2. Inconsistency: consistent effects,  $I^2$  statistic less than 50%. Not downgraded.

3. Indirectness: most data came from trials of men, but some were from trials of women or men and women combined.

Most events occurred in older participants, but events also occurred in younger and middle-aged participants. Included trials were from all continents but most events occurred in trials carried out in Europe or North America. Not downgraded.

4. Imprecision: over 1400 events occurred in trials including over 19,000 participants over at least 12 months. However, 95% Cl included important benefits. Downgraded once.

5. **Publication bias**: funnel plot did not suggest small study bias, we are aware of few events that could not be added to the meta-analysis. Not downgraded.

# <sup>b</sup>Coronary heart disease events

1. **Risk of bias**: sensitivity analyses restricting trials to low risk of bias for attention and compliance give similar results to the main analysis, as do restricting to trials without industry funding or pre-2010 and trials on trials registries, and larger trials all confirmed a small beneficial effect on coronary heart disease (CHD) events. However, limiting to trials at low risk of bias from allocation concealment and to trials of low summary risk of bias suggest increased CHD risk with more PUFA, making us less certain of the effect of increasing PUFA on this outcome. It was further noted by the WHO NUGAG Subgroup on Diet and Health that although limiting to trials at low risk of bias from allocation concealment and to trials of low summary risk of bias suggest increased CHD risk with more PUFA, results of the most heavily weighted trial are consistent with results of the main analysis, while the next largest trial differs from the main result; therefore, confidence in the results of these analyses is low and the outcome was not downgraded. Not downgraded, but part of the downgrading for imprecision was for risk of bias.

2. Inconsistency: consistent effects, I<sup>2</sup> statistic less than 50%. Not downgraded.

3. Indirectness: most events occurred in men, and in high-income countries. Not downgraded.

4. Imprecision: the 95% confidence intervals did not exclude harm from increased PUFA. Downgraded once (with risk of bias).

5. **Publication bias**: funnel plot did not suggest small study bias, we are aware of few events that could not be added to the meta-analysis. Not downgraded.

<sup>c</sup>Stroke

1. **Risk of bias**: some sensitivity analyses suggested benefit of increased PUFA, some suggested harm or little effect. It was further noted by the WHO NUGAG Subgroup on Diet and Health that in most analyses, the most heavily weighted trials

- were consistent with the main results, and the outcome was therefore not downgraded. Not downgraded, but part of the downgrading for imprecision was for risk of bias.
  - 2. Inconsistency: consistent effects, I<sup>2</sup> statistic less than 50%. Not downgraded.
  - 3. Indirectness: most events occurred in men, and in high-income countries. Not downgraded.
- 4. **Imprecision**: with only 166 participants experiencing a stroke imprecision was high, the 95% confidence intervals did not exclude important harm from increased PUFA. Downgraded twice (with risk of bias).
- 5. **Publication bias**: funnel plot did not suggest small study bias, we are aware of few events that could not be added to the meta-analysis. Not downgraded.

# <sup>d</sup>Major adverse cardiac and cerebrovascular events (MACCEs)

- 1. **Risk of bias**: neither of the included trials were at low risk from allocation concealment, or at low summary risk of bias. Downgraded once.
- 2. Inconsistency: I<sup>2</sup> statistic = 79%. Downgraded once.
- 3. Indirectness: all participants of the included trials were men, and trials were conducted in Europe and North America.
- Not downgraded.
- 4. Imprecision: 817 people experienced MACCEs, although harm was not excluded by the 95% Cl. Downgraded once.
- 5. Publication bias: not possible to assess with only 2 trials. Not downgraded.

# BACKGROUND

#### **Description of the condition**

The World Health Organization (WHO) reports cardiovascular diseases as the primary cause of death in the world (WHO 2016). In 2012 they estimated that 17.5 million people died from cardiovascular diseases, three-quarters of whom were in low- to middle-income countries. Cardiovascular diseases are disorders of the heart and blood vessels and include a range of conditions. Some are diseases of blood vessels supplying the heart (coronary heart disease), brain (cerebrovascular disease), or arms or legs (peripheral arterial disease). Others are due to infection (rheumatic heart disease, where damage to the heart muscle and valves is due to rheumatic fever), are present at birth (congenital heart disease), or are due to blood clots (deep vein thrombosis and pulmonary embolism) (WHO 2016). This review is concerned with the forms of cardiovascular disease that are potentially modifiable by dietary means, particularly coronary heart disease and cerebrovascular disease.

#### **Description of the intervention**

Polyunsaturated fatty acids (PUFAs) are fats that include at least two double carbon-to-carbon bonds (unsaturated carbon bonds) in their long hydrocarbon chain. This makes the fats pack less well, so they tend to be liquid at room temperature, rather than solid like many saturated fats. PUFAs can be omega-3 (where the first double bond is three carbons away from the methyl-carbon end of the molecule), omega-6 or omega-9 (although most omega-9 fats do not have at least two double bonds, so are not included). Fish and plant oils are often rich in PUFAs, with fish being rich in omega-3 and plant oils rich in omega-6. Two PUFAs, alphalinolenic acid (omega-3) and linoleic acid (omega-6), are essential nutrients in humans.

Dietary fats have been implicated in cardiovascular health since Keys published his groundbreaking study linking plasma cholesterol and dietary saturated fat (Keys 1950), and Oliver reported higher levels of low density lipoprotein (LDL) in those surviving myocardial infarction compared to controls without myocardial infarction (Oliver 1953). In 1965 Hegsted published an equation that quantified the relationship between dietary fat and serum total cholesterol, suggesting that increasing saturated fats increased serum cholesterol, while increasing PUFA reduced serum cholesterol (Hegsted 1965). More recently there has been debate about what type of PUFA may be protective, with interest in omega-3 PUFAs following randomised controlled trials (RCTs) with dietary fish and fish oil supplementation interventions in the 1980s and 1990s (Burr 1989; GISSI-P 1999), although subsequent trials have been equivocal (Abdelhamid 2018; Hooper 2006). Similarly, while there are good theoretical grounds for suggesting that omega-6 fats may be protective against cardiovascular diseases, the RCT evidence is limited (Hooper 2018). However, there is evidence that replacing saturated fats with PUFAs does protect against cardiovascular disease, and that PUFAs appear to be more protective than reducing saturated fats and replacing them with carbohydrates (Hooper 2015a). On the other hand, reducing dietary fat (including PUFAs) appears to result in lower weight in adults, suggesting that lower PUFA intake would tend to protect against cardiovascular disease (Hooper 2015b).

#### How the intervention might work

PUFAs are generally thought to work by producing a reduction in serum total cholesterol and LDL, which slows the progress of atherosclerosis (a complex syndrome in which plaque builds up inside the arteries over time, reducing blood flow and leading to an increased risk of blood clots), and so delays or prevents the onset of cardiovascular and cerebrovascular disease. This theory is reinforced by evidence that replacing saturated fats with polyunsaturated fats is associated with greater reductions in cardiovascular events and with greater reduction of serum total cholesterol (Hooper 2015a). Additional modes of action have been proposed for omega-3 PUFAs (particularly EPA (eicosapentaenoic acid) and DHA (docosahexaenoic acid) both fish-based omega-3 polyunsaturated fatty acids. These modes of action include: lowering of blood pressure; reducing thrombotic tendency; anti-inflammatory and antiarrhythmic effects; improving vascular endothelial function; increasing plaque stability (through increased plaque calcification); and improving insulin sensitivity (Calder 2012; Ohwada 2016). Omega-6 PUFAs may reflect the general lipid-lowering effects of PUFAs, but there has been concern that high levels of omega-6 intake can increase production of 2-series prostaglandins and 4-series leukotrienes compared with the 3-series prostaglandins and 5-series leukotrienes associated with omega-3 intake. As the 2-series prostaglandins and 4-series leukotrienes exert a more potent pro-inflammatory effect, omega-6 could increase the risk of cardiovascular disease by promoting inflammation (Russo 2009).

#### Why it is important to do this review

The evidence on the health effects of total PUFA intake, which is the combination of omega-3 and omega-6 fats, is equivocal. As cardiovascular diseases are important determinants of health, that particularly burden the poorest people (WHO 2016), we need to understand the role of PUFAs to provide the best advice for individuals and populations about how to eat to reduce the risk of ill health. This assessment of health effects of total PUFA intake is needed alongside updated assessment of the effects of omega-3 and omega-6 fats (Hooper 2018; Abdelhamid 2018).

The World Health Organization (WHO) is currently updating its guidance on polyunsaturated fatty acid intake in adults and children. This new review was commissioned by WHO Nutrition Guidance Expert Advisory Group (NUGAG) Subgroup on Diet and Health in order to inform and contribute to the development of updated WHO recommendations. The results of this review including GRADE assessments were discussed and reviewed by the WHO NUGAG Subgroup on Diet and Health as part of their guideline development process. This is a new review and forms a set with Abdelhamid 2018 (assessing effects of omega-3 fats), Hooper 2018 (assessing effects of omega-6 fats), reviews of diabetes and glucose tolerance (Brown 2017), inflammatory bowel disease (IBD) (Thorpe 2017), cognition (Jimoh 2017), depression (Hanson 2017a), bone and muscle health (Abdelhamid 2017), and cancers (Hanson 2017b).

# OBJECTIVES

To assess effects of increasing total PUFA intake on cardiovascular disease and all-cause mortality, lipids and adiposity in adults.

# METHODS

#### Criteria for considering studies for this review

#### **Types of studies**

We included randomised controlled trials (RCTs) that compared higher with lower polyunsaturated fatty acid intakes and assessed effects over at least 12 months (12 months' continuous involvement). We included trials reported as full text, those published as abstracts only, as trials registry entries and unpublished data. We did not include cross-over trials (unless we could use data from the first part of the cross-over only), as this design is inappropriate for outcomes such as cardiovascular disease events or mortality, but included cluster-randomised trials, as long as there were at least six clusters (to facilitate equivalence of the arms at baseline).

#### **Types of participants**

We included trials of adults (18 years of age and above). Included participants could be adults who were well, or with increased risk of cancer, those undergoing - or who had undergone - coronary artery bypass grafting or angioplasty, and those with current or previous cardiovascular disease, diabetes mellitus, rheumatoid arthritis, depression, cognitive impairment, or multiple sclerosis. We were interested in both primary and secondary prevention, so included people with or without a history of cardiovascular disease. We excluded participants who were pregnant or acutely ill, and defined acute illness as including people with diagnosed current cancer, undergoing heart or renal transplantation, with HIV or AIDS, on haemodialysis, with immunoglobulin A (IgA) glomerulonephritis, or any other renal problem except diabetic nephropathy. Our reasoning was to exclude people with conditions that may affect the relationship between polyunsaturated fatty acids and cardiovascular disease events.

Where trials included some adults and some people under 18 years of age, then we included the trial if at least 90% of participants were aged 18 years or over at baseline, or where outcomes for adults could be separated from those for younger people.

#### **Types of interventions**

Eligible trials compared higher with lower total polyunsaturated fatty acid (PUFA) intakes. The intervention had to be dietary supplementation, or a provided diet, or advice on diet. The advice, foodstuffs or supplements had to aim to increase or decrease total PUFA intake, or a dietary component high in total PUFA intake such as vegetable oil, or, if no clear aim was stated (but implied, such as aiming to provide a 'heart health', 'reduced fat' or 'Mediterranean' diet), then the intervention had to achieve an increase or decrease of at least 10% of the baseline total PUFA level.

Supplementation had to be in oil or capsule form, or as foodstuffs provided, to be consumed by mouth (we excluded enteral and parenteral feeds, and enemas). Trials were included if they compared the effect of this intervention with usual diet, no advice, no supplementation or placebo (as appropriate) or with a lower PUFA intake.

We did not include trials if they included multiple risk factor intervention on lifestyle factors such as weight reduction, smoking or physical activity goals, or differential dietary interventions not involving dietary fats (such as advice to eat more fruit and vegetables, increase fibre, or take a vitamin supplement), except where that other intervention was a direct replacement for polyunsaturated fatty acids or the effect of the fat intervention could be separated out from the other interventions. Where a single intervention that increased PUFA intake (such as increasing walnuts, sunflower oil or a margarine) included additional nutrients (they all do) we included it, regardless of what nutrients were displaced. We interpreted this consistently across the review.

We made decisions on inclusion using the following decision tree: 1. Include if the trial aimed to increase total PUFA regardless of dose (or aimed to increase a combination of omega-3 and omega-6). If not then assess point 2.

2. Include if the trial provided within-trial intervention and control group total PUFA intake data, and the difference was 10% or more of the control group total PUFA intake OR the difference was 10% or more of baseline total PUFA intake or an assumed baseline intake of 6% of energy (6% E) from total PUFA. The assumed baseline intake of 6% E from total PUFA was an average from the trials for which there were data, so we

included trials that provided 0.6% E or above (or  $\geq 1.33$  g/d) more or less total PUFA to the intervention arm compared to control. If not then assess point 3.

3. Include if the trial provided within-trial intervention and control group total PUFA intake aims, and the difference was 10% or more of the control group total PUFA intake OR the difference was 10% or more of baseline total PUFA intake or an assumed baseline intake of 6% E from total PUFA. Where intake information came from trial aims we looked for corroboration that there was a higher total PUFA intake in one arm than the other, using information on control group supplements or advice, body fat markers of total PUFA or serum total cholesterol. Where a suggested higher intake of PUFA in one arm by trial aims was contradicted by biomarker or total cholesterol data (assuming lower total cholesterol with higher PUFA) we excluded. We included trials that provided an additional total PUFA of 0.6% E or more, or 1.33 g/d or more to the intervention arm compared to control (taking into account PUFA content of placebo and excluding if placebo content was unclear). If no inclusion from point 3 then we excluded the trial. We documented our reasoning over inclusion decisions in Characteristics of included studies (see 'Inclusion basis') and reasons for exclusion in Characteristics of excluded studies. We also ran sensitivity analyses on risk of bias from compliance (see Sensitivity analysis).

#### Types of outcome measures

#### **Primary outcomes**

Primary outcomes were:

1. all-cause mortality;

2. coronary heart disease events: number of participants experiencing at least one myocardial infarction (fatal or nonfatal) or angina;

3. stroke (number of participants experiencing an ischaemic and/or haemorrhagic stroke); and

4. major adverse cardiac and cerebrovascular events (MACCEs, used where we could assess the numbers of participants experiencing fatal or non-fatal myocardial infarction, unstable angina or stroke).

#### Secondary outcomes

Secondary outcomes were all systematically reviewed. If any trial fulfilled the other inclusion criteria and reported a secondary outcome (even if no primary outcomes were reported) we included it. Secondary outcomes included:

1. cardiovascular mortality (deaths due to cardiovascular causes including myocardial infarction and stroke)

2. cardiovascular events (all available data on number of participants experiencing any of fatal and non-fatal myocardial infarction, angina and/or stroke);

- 3. coronary heart disease mortality;
- 4. myocardial infarction;
- 5. sudden cardiac death;

6. atrial fibrillation (arrhythmias including atrial fibrillation, ventricular fibrillation and ventricular tachycardia);

- 7. angina;
- 8. heart failure;
- 9. Peripheral arterial disease (PAD);

10. revascularisation (participants experiencing angioplasty or coronary artery bypass grafting);

11. measures of adiposity (including body weight, body mass index (BMI), waist circumference, percentage body fat);

12. serum lipids (including total cholesterol, fasting

triglycerides, high-density lipoprotein (HDL) and low density lipoprotein (LDL)).

#### **Tertiary outcomes**

Tertiary outcomes (not formally systematically reviewed) included:

1. blood pressure (systolic and diastolic);

2. quality-of-life measures (such as feelings of health and time off work);

3. economic costs;

4. serious adverse events (all serious adverse events presented were collated but cancers, inflammatory bowel disease,

neurocognitive outcomes such as dementia, diabetes, functional outcomes and depression are not reported here);

5. dropouts.

We included trials where data on any primary or secondary outcome were available in published reports or based on contact with trial authors. We collated data on tertiary outcomes where they were present in included trials. Data on cancers (Hanson 2017b), inflammatory bowel disease (Thorpe 2017), neurocognitive outcomes including dementia (Jimoh 2017), diabetes (Brown 2017), bone and muscle outcomes (Abdelhamid 2017) and depression (Hanson 2017a) are reported fully and systematically in associated reviews within this series, rather than a subset being presented within this review.

Where it was clear that no participants experienced a particular primary or secondary outcome (and the study had not collected data on other primary or secondary outcomes) we excluded the trial. For example, on exploration, a number of trial authors confirmed that no participants had died or experienced heart attacks in their trials; in the absence of other primary or secondary outcomes being recorded we excluded these from this review and noted them in the exclusion list. Their inclusion into the review would have swollen the size of the review without adding any useful data.

**Key outcomes** 

When the WHO NUGAG Subgroup on Diet and Health requested this review they named the following as key outcomes to inform their planned dietary guidance:

- 1. all-cause mortality;
- 2. cardiovascular disease mortality;
- 3. cardiovascular disease events
- 4. coronary heart disease mortality
- 5. coronary heart disease events
- 6. stroke
- 7. atrial fibrillation (arrhythmia)

8. serum lipids including total cholesterol, fasting triglycerides, HDL and LDL; and

9. measures of adiposity (body weight and BMI)

We were not able make all of these primary outcomes. However, because WHO NUGAG Subgroup on Diet and Health will use these outcomes to underpin guidance, we carried out sensitivity analyses, subgroup analyses and GRADE assessment of quality of evidence for them, even when they were not primary outcomes. All of these outcomes were formally systematically reviewed.

# Search methods for identification of studies

#### **Electronic searches**

We searched the following electronic databases on 27 April 2017 to identify reports of relevant randomised controlled trials:

- Cochrane Central Register of Controlled Trials
- (CENTRAL; 2017, Issue 4) in the Cochrane Library;

• Epub Ahead of Print, In-Process & Other Non-Indexed Citations, MEDLINE Daily and MEDLINE (Ovid, 1946 to 27 April 2017);

• Embase Classic and Embase (Ovid, 1947 to 27 April 2017).

We adapted the search strategy for MEDLINE (Ovid) from the search strategy in Hooper 2018 and also used it to locate trials to update Hooper 2018. This complex strategy was adapted for use in the other databases (Appendix 1). We applied the Cochrane sensitivity and precision-maximising RCT filter to MEDLINE (Ovid), and for Embase, we applied terms recommended in the Cochrane Handbook for Systematic Reviews of Interventions (Lefebvre 2011). As we were also running searches for, updating and extending, another existing Cochrane Review of the effects of omega-3 fats on health outcomes (Abdelhamid 2018), and there was a great deal of overlap between the searches, the omega-3 searches were also run to May 2017, using the same RCT filters (Appendix 2). The results of these searches were de-duplicated with the results from the searches for this review and all the titles and abstracts assessed as a single set. We created a dataset of RCTs that compared higher versus lower omega-6 fats, omega-3 fats or total PUFA in adults with a duration of at least 6 months. We used this dataset as the wider trial pool from which to select included trials for all the systematic reviews in this series (Abdelhamid 2016; Abdelhamid

2017; Abdelhamid 2018; Brown 2017; Hanson 2017a; Hanson 2017b; Jimoh 2017; Hooper 2018; Thorpe 2017).

We searched two clinical trials registers, ClinicalTrials.gov ( www.ClinicalTrials.gov) and the WHO International Clinical Trials Registry Platform (ICTRP, www.who.int/ictrp/en/) during September 2016 for registry entries for relevant completed and ongoing trials.

#### Searching other resources

We checked included trials of relevant systematic reviews, and wrote to authors of included studies for additional trials and trial data (including unpublished outcome data).

We attempted to obtain full-text translations or evaluations of all relevant non-English articles. Where these were not available we translated papers ourselves using our existing language skills and language translation software.

#### Data collection and analysis

#### Selection of studies

Two review authors independently screened titles and abstracts identified by the searches and coded them as 'retrieve' (eligible or potentially eligible/unclear) or 'do not retrieve'. All review authors carried out screening. All articles coded for retrieval by either reviewer were collected in full text. We retrieved full-text study reports/publications and two review authors independently screened the full text, assessed studies for inclusion, and identified and recorded reasons for exclusion of ineligible trials (LH and AA). We resolved any disagreement through discussion. Where a trial met our inclusion criteria with the exception that they did not report any relevant outcome, we wrote to the trial author to ask whether any relevant outcomes occurred. We excluded trials when no relevant primary or secondary outcome events had occurred and the trial had not collected any data on our primary or secondary continuous outcomes.

We identified and collated multiple reports of the same trial (as each trial, rather than each report, was the unit of interest in the review). We recorded the selection process in sufficient detail to complete a PRISMA flow diagram and Characteristics of excluded studies table (Moher 2009).

#### Data extraction and management

We developed a draft data collection form for collating study characteristics and outcome data, then all review authors piloted the form on a single included trial to standardise data extraction and improve the data extraction form. All review authors took part in data extraction. Two review authors each extracted the following characteristics from included trials, independently in duplicate:

1. bibliographic details;

2. trial registration database and number;

3. methods: trial design, total trial duration, details of any 'run in' period, number of study centres and location, trial setting, withdrawals, and trial dates;

4. participants: number randomised in each arm, number analysed in each arm, mean age, age range, gender, health status, cardiovascular disease risk and a brief description of participants. We categorised baseline cardiovascular risk as primary prevention (participants not included on the basis of having existing cardiovascular disease) and secondary prevention (participants included on the basis of existing cardiovascular disease, such as angina or a previous stroke or myocardial infarction);

5. interventions: intervention (including composition and dose of PUFA intake advised or supplement used), comparison, concomitant medications, and excluded medications;

6. outcomes: primary, secondary and tertiary outcomes specified in trial registry, data on outcomes reported in publications and by contact with authors, time points reported. We assessed dichotomous outcomes at the latest point of available follow-up within the trial, while we assessed continuous outcomes at the latest point available in the trial (and after at least 12 months);

7. process data: intake data (mean and standard deviation (SD) of total PUFA, omega-3, omega-6, total fat, saturated fat, monounsaturated fat (MUFA), carbohydrate, protein, energy, alcohol and trans fat intake), biomarker data (erythrocyte, serum or adipose tissue fatty acid status data) and serum total cholesterol in intervention and control groups at latest point available during RCT;

8. study funding and notable conflicts of interest of trial authors.

We resolved disagreements between data extractions by consensus or by involving a third person (LH or AA). One review author (AA or LH) transferred data into the Review Manager 5 (RevMan 5) file (RevMan 2014). We double-checked that data had been entered correctly from the agreed data extraction by comparing the data presented in the systematic review with data extraction (AA, JB, TJB or LH).

## Assessment of risk of bias in included studies

Two review authors independently assessed risk of bias for each trial, alongside data extraction, using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a). All review authors carried out data extraction and assessment of risk of bias. We resolved disagreements by discussion or by involving another author (LH or AA). We assessed the risk of bias according to the following domains:

- 1. random sequence generation (selection bias);
- 2. allocation concealment (selection bias);
- 3. blinding of participants and personnel (performance bias);
- 4. blinding of outcome assessment (detection bias);
- 5. incomplete outcome data (attrition bias);

6. selective outcome reporting (reporting bias);

7. attention bias (another aspect of performance bias, where the intervention or control groups receive more time and/or attention from trial or health personnel during the trial); and

8. compliance (to be assessed as at low risk of bias regarding compliance, the higher PUFA arm had to demonstrate an increase in PUFA over control in a body biomarker (total PUFA had to be assessed by at least linoleic acid plus one or more further components of PUFA), or greater reduction in total cholesterol in the higher PUFA arm. Where lipid biomarker and total cholesterol contradicted each other we chose unclear.

9. other risk of bias

These are the domains of the Cochrane 'Risk of bias' tool, with the exceptions of attention bias and compliance, which were specific to our review and added after discussion with the WHO NUGAG Subgroup on Diet and Health. We followed recommendations in Higgins 2011a, recording funding data in the Characteristics of included studies but not using them as a separate issue for assessing risk of bias.

We graded each potential source of bias as high, low or unclear risk and provided trial details, a quote from the trial report, or both, together with a justification for our judgment in the 'Risk of bias' tables. We assessed summary risk of bias for each trial. Where information on risk of bias related to unpublished data or correspondence with a trial author, we noted it in the 'Risk of bias' tables. Further details of how we interpreted the risk of bias elements across trials are found in Table 1.

#### Summary risk of bias

Schultz 1995 found that poorly concealed allocation was associated with a 40% greater effect size and so randomisation and allocation concealment are core issues for all trials. Lack of blinding is associated with bias, though smaller levels of bias than lack of allocation concealment (Savovic 2012), especially in trials with objectively measured outcomes (Wood 2008). Most of our outcomes were objectively measured. Although we originally planned to assess summary risk of bias in the same way across all trials in this Cochrane Review, the omega-3 Cochrane Review and the omega-6 Cochrane Review (Abdelhamid 2016; Abdelhamid 2018; Hooper 2018) we adopted a different approach after discussing the different nature of supplement trials compared to dietary advice or food provision trials with the NUGAG Subgroup on Diet and Health. We considered a supplement or capsule-type trial to be at low summary risk of bias, where we judged randomisation, allocation concealment, blinding of participants and personnel, and blinding of outcome assessors adequate. We considered all other trials at moderate or high risk of bias (a single category).

We considered a dietary-advice or all-food-provided-type trial to be at low summary risk of bias, where we judged randomisation, allocation concealment, and blinding of outcome assessors adequate. We considered all other trials at moderate or high risk of bias (a single category).

# Assessment of bias in conducting the systematic review

We conducted this Cochrane Review according to the published Cochrane protocol and reported any deviations from it in the 'Differences between protocol and review' section of the systematic review.

#### Measures of treatment effect

We analysed dichotomous data as risk ratios (RRs) with 95% confidence intervals (CIs) and continuous data as mean difference (MD) with 95% CIs. We presented continuous data with a consistent direction of effect (as a smaller reading is generally positive), with the exception of HDL, where an increase is positive.

We used change data (change from baseline to latest point in trial in each arm) for continuous data where available with appropriate variance data. When change data were not available we used absolute data from the latest point in each trial arm, unless baseline data were too different between arms. (We considered baseline data too different to use when the change in both arms, from baseline to end data, was smaller than the baseline difference between arms). Where continuous data were too different to use this we noted it in the outcome section of Characteristics of included studies but we did not add data to meta-analyses.

We intended narrative description of skewed data reported as medians (without variance data or with interquartile ranges). We added these data to forest plots so that there could be visual comparison of findings (though we did not include these data in meta-analyses). We intended to use standardised mean differences (SMD) to combine data where included trials had used different scales to measure the same factor (such as quality of life). We did not find any such data, so did not use SMD. We converted data on different scales to the same scale, such as mg/dL and mmol/L for lipids.

#### Unit of analysis issues

## Trials with multiple intervention groups

Where trials included more than two arms we assessed all arms for inclusion. Where there were more than one intervention arm and a single control arm we combined dichotomous and continuous data for the intervention arms and compared them to the single control arm. This meant there were no problems with trial participants appearing more than once in any forest plot.

# Cluster-RCTs

Where cluster-RCTs were included we planned to account for unit of analysis issues by data extracting a direct estimate of the required effect measure (for example, a RR with its CI) from an analysis that accounted for the cluster design properly (for example, an analysis based on a 'multilevel model', a 'variance components analysis' or that used 'generalised estimating equations (GEEs)'). Where these data were available we planned to use them in metaanalysis using the generic inverse-variance method (Deeks 2011). Where no such correct analysis of the cluster-randomised data were available, we planned to use approximate analyses using intracluster correlation co-efficient (ICC) analysis as outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011b, section 16.3.4). We did not identify any such clusterrandomised trials, so we did not need this methodology.

#### Dealing with missing data

We contacted (or attempted to contact) the authors of all potentially included RCTs to better assess inclusion. We contacted authors of all included trials that had randomised at least 100 participants (and some smaller trials) to request available data on all of the trial outcomes relevant to our set of reviews and key information on risk of bias. Due to limited resources, we focused on contacting authors of larger trials, who we thought were most likely to provide substantial quantities of useful data. We sent an email and a posted letter to the corresponding author at the latest address we were able to obtain (tracking latest publications in Medline). Where data on at least one review outcome were available (and at least one person had experienced a relevant outcome), we included the RCT, and asked the authors to provide any additional data about trial methodology or risk of bias.

Where papers reported continuous results as change from baseline we used these data, otherwise we used data at the latest point available. We did not impute change data.

#### Assessment of heterogeneity

We used the I<sup>2</sup> statistic (Higgins 2003) to measure heterogeneity among the trials in each analysis. Where we identified substantial heterogeneity (assumed when I<sup>2</sup> was greater than 50%, as 30% to 60% represents moderate heterogeneity and we were allowing for the varied dietary interventions included as well as potential dose effects) we reported it and explored possible causes by prespecified subgroup analysis.

#### Assessment of reporting biases

Where we were able to pool at least 10 trials, we created and examined a funnel plot to explore possible reporting biases for the primary outcomes (Sterne 2011).

We noted where we were aware of missing data. This occurred where trial methods noted that an outcome had been measured but those data had not been presented or had been presented but not by trial arm, where continuous data were unbalanced at baseline, or presented as medians or as means but without variance information.

## Data synthesis

We undertook meta-analyses only where we considered it to be meaningful, that is, where the treatments, participants and the underlying clinical question were similar enough for pooling to make sense. We carried out statistical analysis using RevMan 5 (RevMan 2014). We used a random-effects model, as dietary interventions are complex and somewhat heterogeneous by their nature (more so than most medical treatments), but we compared the results of random-effects and fixed-effect meta-analysis in sensitivity analyses. As the random-effects model assigns more weight to smaller trials, it is more conservative and may lead to imprecise estimates of effect. We also carried out sensitivity analyses to assess the effects of methodological rigour (see Sensitivity analysis).

#### 'Summary of findings' table

We created a 'Summary of findings' table for the primary outcomes:

- 1. all-cause mortality;
- 2. coronary heart disease events;
- 3. stroke; and
- 4. MACCEs.

As WHO NUGAG Subgroup on Diet and Health required a specific set of key outcomes for their guidance, we created a second 'Summary of findings' table for the key outcomes not represented in the main 'Summary of findings' table:

- 1. cardiovascular mortality;
- 2. cardiovascular events;
- 3. coronary heart disease mortality;
- 4. atrial fibrillation;
- 5. measures of adiposity body weight;
- 6. measures of adiposity BMI; and
- 7. serum lipids (including total cholesterol, fasting
- triglycerides, HDL and LDL).

We used the five GRADE considerations (trial limitations, consistency of effect, imprecision, indirectness and publication bias) to assess the quality of a body of evidence as it related to the trials that contributed data to the meta-analyses for the prespecified outcomes. We used methods and recommendations described in Section 8.5 (Higgins 2011a) and Chapter 12 (Schünemann 2011) of the *Cochrane Handbook for Systematic Reviews of Interventions*, and used GRADEpro GDT software (GRADEpro GDT 2015). We justified all decisions to downgrade the quality of trials using footnotes and made comments to aid reader's understanding of the review where necessary.

#### Subgroup analysis and investigation of heterogeneity

We explored the effects of PUFA intake on primary outcomes and key outcomes by performing exploratory subgroup analyses on:

1. total PUFA dose (and dose response: total PUFA dose < 1% E, 1% E to < 2% E; 2% E to < 5% E and  $\geq$  5% E where dose is

the difference in total PUFA intake between intervention and control arms);

2. trial duration: trials with medium follow-up (12 to 23 months), medium to long follow-up (24 to 47 months), and long follow-up (48 months or more);

3. baseline risk of cardiovascular disease (primary prevention, or secondary prevention);

4. baseline total PUFA intake (< 6% E from total PUFA, 6% E to < 11% E, and  $\geq$  11% E from total PUFA);

5. replacement of saturated fat, MUFA, carbohydrate and protein with total PUFA;

6. participants' sex (> 70% of the control group were men, > 70% of the control group were women, and mixed men and women);

7. participants' age (mean age in control group < 50 years, 50 to < 65 years and  $\geq$  65 years);

8. statin use (at least 50% of control group on statins versus fewer than 50% on statins); and

9. intervention type (dietary advice, supplements (capsules), supplemental foods and all foods provided, or any combination) We also planned to subgroup by change in the omega-3/omega-6 fat ratio (assessing whether the intervention primarily increased omega-3 fats (putting up the ratio) or omega-6 fats (lowering the ratio)). However, in almost no trials did we have information allowing us to calculate the omega-3/omega-6 fat ratio, so we did not carry out this subgrouping.

The 6% E and 11% E cut-offs for total PUFA were prespecified by WHO NUGAG Subgroup on Diet and Health, as their existing recommendations for PUFA intake were 6% E to 11% E in adults (WHO/FAO 2008).

We have not discussed differential effects of omega-3 and omega-6 PUFAs in this review, as separate reviews address the effects of omega-3 and omega-6 fats on cardiovascular disease in more detail (Hooper 2018; Abdelhamid 2018).

We used the formal test for subgroup interactions in RevMan 5 (RevMan 2014). These subgroupings were requested by WHO NUGAG Subgroup on Diet and Health to better help them understand the data. The danger of having so many subgroup analyses is that they may be over-interpreted, increasing the risk of a type one error.

#### **Meta-regression**

We planned meta-regression to further explore effects of total PUFA dose (looking for evidence of dose response), baseline total PUFA intake and duration on dichotomous primary and secondary outcomes with at least seven included trials and for which subgrouping was undertaken. However baseline total PUFA intake was only clear in a handful of trials, so we did not run metaregression by baseline PUFA intake. Random-effects meta-regression (Berkley 1995) was performed using the STATA command metareg (Sharp 1998): log(e) relative risk versus [dose or primary/ secondary prevention or type of intervention or risk of bias or du-

ration], weighted by the standard error of the log(e) relative risk. Where there were no events in one arm we added 0.1 to the numbers for both groups (so a trial with 10 people experiencing stroke in one arm but none in the other arm would be entered as 10.1 and 0.1).

#### Sensitivity analysis

We planned to carry out the following sensitivity analyses on all primary outcomes, and key outcomes:

1. only including trials with a low risk of bias for allocation concealment;

2. only including trials with a low risk of attention bias;

3. only including trials with a low risk of bias from compliance;

4. only including trials at low summary risk of bias;

5. only including all trials up to 2010, plus trials post-2010 that were registered in a trials register (Roberts 2015, regardless of the date of registration);

6. only including trials with no industry funding reported (trials with funding or support from partial bodies such as government boards to support specific foods or where funding was not mentioned were also excluded);

7. only including trials with less than 10% difference in intake of trans fats between trial arms during the intervention;

8. only including trials that randomised at least 100 participants;

9. only including trials that randomised at least 250 participants;

10. using fixed-effect meta-analysis.

Unfortunately almost no data on trans fats were available, so we did not carry out sensitivity analysis around trans fats.

#### **Reaching conclusions**

We based our conclusions only on findings from the quantitative or narrative synthesis of included trials for this review. Outcome data were interpreted as follows:

1. Is there an effect? (Options were 'increased risk', 'decreased risk', or 'little or no effect'). Our main outcome measures were RR and MD so we decided on existence of an effect using RR. RR >8% (RR <0.92 or >1.08) for the highest quality evidence suggested increased or decreased risk (otherwise little or no effect). The presence or not of an effect was decided on the RR for the main analysis and sensitivity analyses.

2. Quality of evidence was assessed using GRADE assessment (GRADE Working Group 2004) for key outcomes. We used the

five GRADE considerations (risk of bias, consistency of effect, imprecision, indirectness and publication bias) to assess the quality of the body of evidence as it related to the trials that contributed data to the meta-analyses for the prespecified outcomes. We used methods and recommendations described in Section 8.5 and Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), plus GRADEpro GDT software (GRADEpro GDT 2015). We justified all decisions to downgrade the quality of trials using footnotes and made comments to aid reader's understanding of the review.

3. Where there was a suggested effect the size of effect was assessed using the MD, NNT or ARR.

We avoided making recommendations for practice and our implications for research suggest priorities for future research and outline the remaining uncertainties in the area.

## RESULTS

# **Description of studies**

#### **Results of the search**

The electronic searches for the full set of reviews (populating the dataset of all trials that assessed effects of higher versus lower omega-6, omega-3 or PUFA over at least 6 months) generated 37,810 titles and abstracts, which we de-duplicated to 19,772 hits. We assessed these along with 53 studies previously included from Hooper 2018 and Abdelhamid 2018, to reassess for inclusion; 986 potentially relevant trials registry entries; and 35 new references gained from systematic review reference lists. In total, we assessed 20,846 titles and abstracts in duplicate to decide whether to retrieve full texts. We ultimately assessed 2155 full-text reports, of which 226 were systematic reviews. Two review authors independently assessed the remaining 1929 papers for inclusion and grouped them into studies. Of these, we included 208 RCTs in a wider set of trials that underpinned the full set of reviews (this review and several others including Abdelhamid 2018; Abdelhamid 2017; Hooper 2018; Brown 2017; Hanson 2017a; Hanson 2017b; Jimoh 2017; Thorpe 2017). This wider set of trials included RCTs of omega-3, omega-6 or total polyunsaturated fatty acids (PUFA) interventions with a duration of at least six months (Figure 1) and comprised 730 reports.

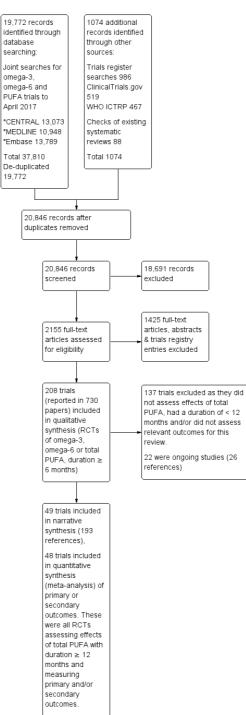


Figure I. Study flow diagram

Of these 208 RCTs:

• 22 RCTs (26 documents) assessed effects of PUFA over at least one year but were ongoing (without published outcome data);

• 137 RCTs (361 documents) did not assess effects of a high enough dose of PUFA or had a duration of less than one year, so we excluded them; and

• 49 RCTs (183 documents) were eligible for inclusion in this review.

Of these 49 RCTs, 48 were included in meta-analyses.

Details of the flow of trials are in Figure 1.

The 22 potential ongoing trials are described in the table of Characteristics of ongoing studies. These trials are very difficult to assess for inclusion in terms of total PUFA dose until further details are published. We will formally assess these trials for inclusion when we update this review.

## **Included studies**

The details of the methods, participants, intervention, comparison group, and outcome measures for each of the included trials are shown in the Characteristics of included studies table. Forty-nine trials, including 24,272 randomised participants, met the inclusion criteria. Trials ranged in size from 36 randomised participants (Rossing 1996) to 4997 randomised participants (PREDIMED 2013), with 15 trials randomising at least 250 participants (AlphaOmega - ALA; Bates 1989; DART fat 1989; EPIC-1 2008; EPIC-2 2008; EPOCH 2011; FAAT - Leaf 2005; MRC 1968; NDHS Open 1st 1968; ORL 2013; PREDIMED 2013; Sydney Diet-Heart 1978; Veterans Admin 1969; WAHA -Ros 2016; WINS 2006).

Twenty-two trials recruited mostly men (at least 70% men in the control group, Ahn 2016; AlphaOmega - ALA; DART fat 1989; DIPP-Tokudome 2015; Doi 2014; Dullaart 1992; FAAT - Leaf 2005; GLAMT 1993; HARP- Sacks 1995; Kumar 2012; Ley 2004; Mendis 2001; MRC 1968; NDHS Faribault 1968; NDHS Open 1st 1968; Nodari 2011 HF; Nye 1990; ORL 2013; Raitt 2005; Sydney Diet-Heart 1978; Veterans Admin 1969; Vijayakumar 2014), six trials recruited mostly women (at least 70% women in the control group, Bassey 2000-Post; Bassey 2000-Pre; Dodin 2005; Proudman 2015; Simon 1997; WINS 2006), 16 recruited similar numbers of men and women while five trials did not state the sex or participants (Bates 1977; EPOCH 2011; HERO-Tapsell 2009; McIllmurray 1987; Rose 1965).

Almost half of the trials (24 trials) recruited participants with a mean age between 50 and 65 years, but 12 trials recruited younger participants (mean age < 50 years, Bassey 2000-Pre; Bates 1978; Bates 1989; Dullaart 1992; EPIC-1 2008; EPIC-2 2008; NDHS Faribault 1968; NDHS Open 1st 1968; Puri 2005; Rossing 1996; Simon 1997; Sydney Diet-Heart 1978), eight trials recruited older

participants (mean age 65 years or more, AlphaOmega - ALA; Doi 2014; FAAT - Leaf 2005; Kumar 2013; Nodari 2011 AF; PREDIMED 2013; Veterans Admin 1969; WAHA - Ros 2016), and five trials did not give a mean age or range that could be classified (Ahn 2016; Bates 1977; EPOCH 2011; Houtsmuller 1979; Mendis 2001).

Twenty trials were conducted in Europe (AlphaOmega - ALA; Bassey 2000-Post; Bassey 2000-Pre; Bates 1977; Bates 1978; Bates 1989; Brox 2001; DART fat 1989; Dullaart 1992; GLAMT 1993; Houtsmuller 1979; MARINA - Sanders 2011; McIllmurray 1987; MRC 1968; Nodari 2011 AF; Nodari 2011 HF; PREDIMED 2013; Rose 1965; Rossing 1996; WELCOME 2015), 10 in North America (Black 1994; Dodin 2005; FAAT - Leaf 2005; HARP-Sacks 1995; NDHS Faribault 1968; NDHS Open 1st 1968; Raitt 2005; Simon 1997; Veterans Admin 1969; WINS 2006), seven in Asia (Ahn 2016; DIPP-Tokudome 2015; Doi 2014; Mendis 2001; Mita 2007; ORL 2013; Vijayakumar 2014), eight in Australia or New Zealand (EPOCH 2011; HERO-Tapsell 2009; Kumar 2012; Kumar 2013; Ley 2004; Nye 1990; Proudman 2015; Sydney Diet-Heart 1978), while four trials were conducted across several continents (EPIC-1 2008; EPIC-2 2008; Puri 2005; WAHA - Ros 2016).

The trials varied in the types of participants recruited and their level of cardiovascular risk. Most trials recruited participants without a personal history of cardiovascular disease (primary prevention), but 16 recruited participants with existing cardiovascular disease of some sort (secondary prevention of cardiovascular disease, Ahn 2016; AlphaOmega - ALA; DART fat 1989; Doi 2014; FAAT - Leaf 2005; HARP- Sacks 1995; Kumar 2012; Kumar 2013; MRC 1968; Nodari 2011 AF; Nodari 2011 HF; Nye 1990; Raitt 2005; Rose 1965; Sydney Diet-Heart 1978; Vijayakumar 2014).

Total PUFA dose (the difference in total PUFA between intervention and control arms) was between 0.6% E and less than 1% E for 13 trials (Doi 2014; EPOCH 2011; FAAT - Leaf 2005; Kumar 2012; Kumar 2013; Ley 2004; MARINA - Sanders 2011; Mita 2007; Nodari 2011 AF; Nodari 2011 HF; ORL 2013; Puri 2005; Raitt 2005), 1% E to less than 2% E total PUFA in 17 trials (Ahn 2016; AlphaOmega - ALA; Bassey 2000-Post; Bassey 2000-Pre; Bates 1977; Bates 1978; Bates 1989; Brox 2001; DIPP-Tokudome 2015; Dodin 2005; EPIC-1 2008; EPIC-2 2008; Nye 1990; PREDIMED 2013; Proudman 2015; WELCOME 2015; WINS 2006), 2% E to less than 5% E in eight trials (Black 1994; DART fat 1989; Dullaart 1992; GLAMT 1993; HARP- Sacks 1995; McIllmurray 1987; Mendis 2001; Rossing 1996), and at least 5% E from total PUFA in 11 trials (HERO-Tapsell 2009; Houtsmuller 1979; MRC 1968; NDHS Faribault 1968; NDHS Open 1st 1968; Rose 1965; Simon 1997; Sydney Diet-Heart 1978; Veterans Admin 1969; Vijayakumar 2014; WAHA - Ros 2016).

Increases in total PUFA were delivered to participants in various

ways. Most trials gave supplemental capsules or foods taken as supplements (supplemental oil drunk with meals in Rose 1965, seal or cod liver oil drunk in Brox 2001 and flax seed incorporated into foods in Dodin 2005), while eight trials gave dietary advice resulting in increased PUFA (Black 1994; DART fat 1989; Dullaart 1992; Houtsmuller 1979; Ley 2004; Simon 1997; Sydney Diet-Heart 1978; WINS 2006), eight trials gave supplemental foods such as margarines or nuts (AlphaOmega - ALA; HERO-Tapsell 2009; NDHS Faribault 1968; NDHS Open 1st 1968; PREDIMED 2013; Veterans Admin 1969; Vijayakumar 2014; WAHA - Ros 2016), and three trials used a combination of methods (DIPP-Tokudome 2015; Mendis 2001; MRC 1968).

Baseline total PUFA intake was unclear in most trials, but where information was provided it ranged from 3.9% E (NDHS Open 1st 1968) to 8% E (Black 1994) in control groups. Seven trials had baseline total PUFA intake less than 6% E (Dodin 2005; HERO-Tapsell 2009; Ley 2004; NDHS Faribault 1968; NDHS Open 1st 1968; Veterans Admin 1969; WINS 2006), while nine had baselines of at least 6% E PUFA (Black 1994; DART fat 1989; DIPP-Tokudome 2015; Dullaart 1992; MARINA - Sanders 2011; PREDIMED 2013; Simon 1997; Sydney Diet-Heart 1978; WAHA - Ros 2016). PUFA replaced saturated fat at least partially in nine trials (DART fat 1989; Dullaart 1992; HARP- Sacks 1995; MRC 1968; NDHS Faribault 1968; NDHS Open 1st 1968; Sydney Diet-Heart 1978; Veterans Admin 1969; Vijayakumar 2014), replaced monounsaturated fats in 21 trials (AlphaOmega -ALA; Bates 1977; Bates 1978; Bates 1989; EPOCH 2011; FAAT - Leaf 2005; HARP- Sacks 1995; MARINA - Sanders 2011; NDHS Faribault 1968; NDHS Open 1st 1968; Nodari 2011 AF; Nodari 2011 HF; Nye 1990; PREDIMED 2013; Proudman 2015; Raitt 2005; Rose 1965; Rossing 1996; Sydney Diet-Heart 1978; Veterans Admin 1969; WELCOME 2015), replaced carbohydrate in 11 trials (Black 1994; DIPP-Tokudome 2015; Dodin 2005; Houtsmuller 1979; Ley 2004; MARINA - Sanders 2011; Mendis 2001; Rose 1965; Simon 1997; WAHA - Ros 2016; WINS 2006), and replaced protein at least partially in four trials (HERO-Tapsell 2009; Ley 2004; MRC 1968; WAHA - Ros 2016). In some trials PUFA replaced several dietary components, in others there was one main replacement, but replacements were unclear for 14 trials (Ahn 2016; Bassey 2000-Post; Bassey 2000-Pre; Brox 2001; Doi 2014; GLAMT 1993; Kumar 2012; Kumar 2013; EPIC-1 2008; EPIC-2 2008; McIllmurray 1987; Mita 2007; ORL 2013; Puri 2005).

In most trials fewer than 50% of participants in the control group were taking statins (assumed in trials published before 1994 when the 4S Trial 1994 was published showing overall benefits from statins in higher-risk populations and statin use began to rise, and in populations not at particular cardiovascular disease risk), but in seven trials at least 50% of participants were taking statins (Ahn 2016; AlphaOmega - ALA; Doi 2014; HERO-Tapsell 2009; Kumar 2013; Vijayakumar 2014; WELCOME 2015), and three trials were unclear (FAAT - Leaf 2005; Ley 2004; WAHA - Ros 2016).

The duration of the intervention was one to less than two years in most trials, but was two to less than four years in 16 trials (AlphaOmega - ALA; Bates 1977; Bates 1978; Bates 1989; Black 1994; DART fat 1989; DIPP-Tokudome 2015; Dullaart 1992; HARP- Sacks 1995; McIllmurray 1987; Mita 2007; Raitt 2005; Rose 1965; Simon 1997; Vijayakumar 2014; WAHA - Ros 2016), and four years or more in duration in six trials (Houtsmuller 1979; MRC 1968; PREDIMED 2013; Sydney Diet-Heart 1978; Veterans Admin 1969; WINS 2006).

Included trials were published over half a century between the 1960s (Rose 1965; MRC 1968; NDHS Faribault 1968; NDHS Open 1st 1968; Veterans Admin 1969) and the 2010s (Ahn 2016; AlphaOmega - ALA; DIPP-Tokudome 2015; Doi 2014; EPOCH 2011; Kumar 2012; Kumar 2013; MARINA - Sanders 2011; Nodari 2011 AF; Nodari 2011 HF; ORL 2013; PREDIMED 2013; Proudman 2015; Vijayakumar 2014; WAHA - Ros 2016; WELCOME 2015), with some trials published in each decade.

Funding sources were reported and appeared to be purely from national or charitable agencies in 17 trials (Ahn 2016; Black 1994; Brox 2001; DIPP-Tokudome 2015; Dullaart 1992; FAAT - Leaf 2005; Houtsmuller 1979; Ley 2004; MARINA - Sanders 2011; Mendis 2001; MRC 1968; NDHS Faribault 1968; NDHS Open 1st 1968; Nodari 2011 AF; Sydney Diet-Heart 1978; Vijayakumar 2014; WINS 2006). Seven trials appeared to be directly funded by industrial sources (Bassey 2000-Post; Bassey 2000-Pre; EPIC-1 2008; EPIC-2 2008; GLAMT 1993; ORL 2013; Puri 2005), two funded by bodies set up to promote specific foods (HERO-Tapsell 2009; WAHA - Ros 2016), 16 trials funded by some governmental or charity sources with additional funding or support from commercial sources (AlphaOmega - ALA; Bates 1977; Bates 1978; Bates 1989; DART fat 1989; EPOCH 2011; HARP- Sacks 1995; Kumar 2012; Nye 1990; PREDIMED 2013; Proudman 2015; Raitt 2005; Rossing 1996; Simon 1997; Veterans Admin 1969; WELCOME 2015), two trials that included authors on industry honoraria (Doi 2014; Nodari 2011 HF), and five trials where funding was not reported (Dodin 2005; Kumar 2013; McIllmurray 1987; Mita 2007; Rose 1965).

Most included trials had a single intervention arm and a single control arm, but some trials were more complex.

1. Bates 1977 had four arms, two intervention arms each had their own control arm, so were dealt with as separate trials. Both were included, as deaths appear to have occurred, but it is no longer clear how many or which arms they occurred in.

2. Bates 1978 also had two intervention arms each with their own control arm, but comparison C versus D did not have any relevant outcome data so we excluded it. We only included A versus B.

3. Brox 2001 had two intervention arms and one control arm. For all outcomes, we combined the two intervention groups and compared to the single control group.

4. DART fat 1989 was a factorial trial, but we have included

only one of the three factorial interventions in this review, so all participants have been included only once.

5. MARINA - Sanders 2011 had three intervention arms of different doses and one control arm. Only one intervention arm was included in this review (D2) and compared to the control arm.

6. NDHS Faribault 1968 and NDHS Open 1st 1968 each had three intervention arms and a single control. We combined data for the three arms and compared them to the single control arm in each trial.

7. Nye 1990 had three arms, but one was irrelevant to this review so not included.

8. ORL 2013 had three arms, but we only included two arms (higher vs lower dose omega-3)

9. PREDIMED 2013 had three arms, a Mediterranean diet with nuts, a Mediterranean diet with olive oil and a low-fat arm. For this review we compared the Mediterranean diet with nuts (high PUFA) with the Mediterranean diet with olive oil (low PUFA) as these two arms were very similar but with different PUFA intakes. For many outcomes data were reported in publications by trial centre (or combination of trial centres), so we checked for overlap of participants then reported the

outcome centre by centre where we were sure that no participants were included more than once.

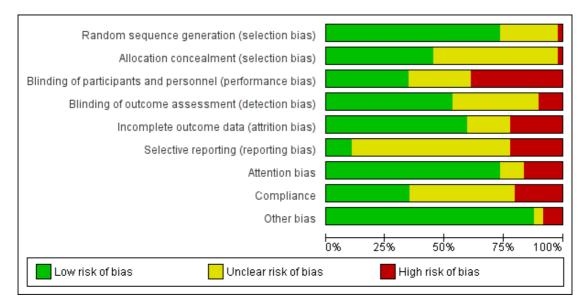
#### **Excluded studies**

We have presented details and reasons for exclusion of the trials that most closely missed the inclusion criteria in the Characteristics of excluded studies table.

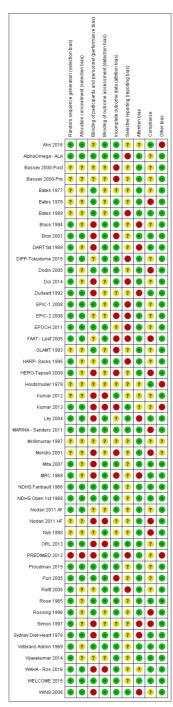
#### **Risk of bias in included studies**

Our assessment of risk of bias of included trials is summarised in Figure 2 and detailed by trial in Figure 3. We assessed eleven of the 49 included trials as being at low summary risk of bias; eight trials as being at low risk of bias from randomisation, allocation concealment, performance and detection biases (AlphaOmega - ALA; EPOCH 2011; MARINA - Sanders 2011; NDHS Faribault 1968; NDHS Open 1st 1968; Proudman 2015; Puri 2005; WELCOME 2015), and three trials, which were dietary advice or provision trials, as being at low risk of bias from randomisation, allocation concealment and detection bias (Ley 2004; Sydney Diet-Heart 1978; WINS 2006). We assessed the remaining 37 trials as being at moderate or high risk of bias.

# Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included trials



# Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included trial



#### Allocation

Randomisation was adequate in 36 of the 49 trials, not well described in 12 trials and at high risk in one trial (PREDIMED 2013). Allocation concealment was appropriate in 22 included trials, unclear in 26, and at high risk of bias in one (PREDIMED 2013). Twenty-two trials were at low risk of selection bias, with low risk of bias from both randomisation and allocation concealment (see Figure 3).

#### Blinding

Blinding of participants and personnel appeared at low risk of bias for 17 trials, unclear for 13 and at high risk of bias for the remaining 19 trials. Blinding of outcome assessors was at low risk of bias in 26 trials, unclear in 18 and at high risk of bias in five trials. Eleven trials were well blinded, at low risk of bias from both blinding of participants, personnel and outcome assessors.

#### Incomplete outcome data

Twenty-nine trials appeared to be at low risk of attrition bias, 11 were at high risk and the remainder unclear.

#### Selective reporting

We found five trials that had a trials registry entry or protocol published before data collection was completed, and reported all outcomes suggested in the entry or protocol. Thirty-three were unclear, generally because no trials registry entry or protocol was identified, or because they were published after the end of data collection. We found 11 trials were at high risk of selective reporting, as at least one outcome suggested in the trials registry entry or protocol was not reported in full.

We attempted to access additional outcome data as well as methodological data from most included trials. We established contact with most trial authors, and received data on outcomes that had not been fully published from many (noted in Characteristics of included studies for relevant trials), although some trial authors were unable to provide additional information or repeated phrases from their published papers. We tried to contact, but did not receive any reply from, authors of 10 trials (Ahn 2016; Doi 2014; GLAMT 1993; Houtsmuller 1979; Kumar 2012; Kumar 2013; Mendis 2001; Nodari 2011 AF; ORL 2013; Raitt 2005). We did not attempt to contact authors of some of the oldest trials, as the trials were conducted in the 1960s and their authors were unlikely to be accessible (NDHS Faribault 1968; NDHS Open 1st 1968; Rose 1965; Veterans Admin 1969), although we had made contact with the retired statistician of another older trial when including that trial in an earlier systematic review (MRC 1968). We did not

attempt to contact authors of five trials (Bassey 2000-Post; Bassey 2000-Pre; HERO-Tapsell 2009; Mita 2007; Nye 1990).

#### Other potential sources of bias

We assessed attention bias, where intervention participants appeared to receive more time or attention from health professionals than those in the control group. Thirty-six trials appeared to be at low risk of attention bias, eight were at high risk, and the remaining five were unclear.

We assessed compliance, to ensure that PUFA truly appeared to have been higher in one arm than the other, by looking for evidence of changes or differences in a body biomarker (total PUFA had to be assessed by at least linoleic acid (LA) plus one or more further components of PUFA), or greater reduction in total cholesterol in the higher PUFA arm. Where lipid biomarker and total cholesterol contradicted each other we chose unclear. We found that 17 trials demonstrated appropriate compliance, 10 suggested poor compliance while 22 trials were unclear.

Four trials were found to be at high risk from other potential bias. Ahn 2016 was unclear about whether the control arm received a placebo or not, and some SDs appeared to be incorrectly reported. When we looked for additional data on Houtsmuller 1979 we found that concerns had been raised over potential research fraud of the first author in later trials (assessing effects of diet on cancer). While no concerns were found about the included research we felt that this did potentially reflect a risk of fraud in the included trial. In Kumar 2013, 21 of the 39 participants randomised to the intervention were inexplicably crossed over to the control condition at six months, so that 12-month outcomes were only reported for 17 of the 39 randomised participants. The main publication of PREDIMED 2013 was retracted and republished in 2018 due to randomisation and allocation concealment problems not mentioned in the initial publication that resulted in a distribution of baseline variables inconsistent with randomisation (Carlisle 2017). We found McIllmurray 1987 and Mendis 2001 to be at unclear risk of other bias, as neither described their control group interventions. The remaining trials were considered to be at low risk of other potential bias.

#### **Effects of interventions**

See: Summary of findings for the main comparison Higher polyunsaturated fatty acid (PUFA) compared to lower PUFA for cardiovascular disease - primary outcomes; Summary of findings 2 Higher polyunsaturated fatty acid (PUFA) compared to lower PUFA for cardiovascular disease - additional key outcomes

#### **Primary outcomes**

For 'Summary of findings' table on primary outcomes see Summary of findings for the main comparison.

#### All-cause mortality

PUFA intake probably has little or no effect on all-cause mortality (moderate-quality evidence).

Twenty-four trials including 19,290 participants reported at least one death and could be added to the meta-analysis. There was no clear effect of more PUFA compared to less PUFA intake on allcause mortality (RR 0.98, 95% CI 0.89 to 1.07, I<sup>2</sup> = 0%, 1443 deaths; Analysis 1.1). This lack of effect did not differ in fixedeffect analysis (RR 0.98, 95% CI 0.89 to 1.07; Analysis 1.3), or sensitivity analysis restricting to trials at low risk of bias for allocation concealment (RR 1.03, 95% CI 0.87 to 1.22), low risk of attention bias (RR 0.96, 95% CI 0.87 to 1.07), compliance bias (RR 1.01, 95% CI 0.89 to 1.14), low summary risk of bias (RR 1.04, 95% CI 0.87 to 1.26), trials registry or pre-2010 publication (RR 0.99, 95% CI 0.90 to 1.08), trials without any industry funding (RR 1.09, 95% CI 0.84 to 1.42), that randomised at least 100 participants (RR 0.98, 95% CI 0.89 to 1.08) or at least 250 participants (RR 1.00, 95% CI 0.91 to 1.10; Analysis 1.2). The funnel plot did not suggest any publication bias, though we are aware of two trials with deaths that we were not able to add to the analyses (Bates 1977; Simon 1997).

Subgrouping did not suggest differential effects by total PUFA dose (Analysis 1.4), duration (Analysis 1.5), primary or secondary prevention (Analysis 1.6), baseline PUFA intake (Analysis 1.7), dietary component displaced by the increase in PUFA (Analysis 1.8), participant sex (Analysis 1.9), participant age (Analysis 1.10), statin use (Analysis 1.11), or type of intervention (Analysis 1.12). There was no suggestion of important effects in any of the four trials each taking more than 10% of the weight in meta-analysis (AlphaOmega - ALA; DART fat 1989; PREDIMED 2013; Veterans Admin 1969).

Meta-regression did not suggest any relationships between total PUFA dose (P = 0.94) or trial duration (P = 0.81) and all-cause mortality. We did not run meta-regression of baseline PUFA dose and all-cause mortality as few trials provided this information.

We downgraded the GRADE evidence level for imprecision as the 95% CI included important benefits (moderate-quality evidence), Summary of findings for the main comparison.

#### Coronary heart disease events

PUFA intake probably reduces risk of coronary heart disease events slightly (NNT 53, moderate-quality evidence).

Fifteen trials including 10,076 participants were included and 1351 participants reported at least one coronary heart disease event. Meta-analysis suggested that higher PUFA intake resulted in 13% fewer participants having coronary heart disease events

(RR 0.87, 95% CI 0.72 to 1.06,  $I^2 = 45\%$ ; Analysis 1.13). None of the four trials that carried at least 10% of the weight of the meta-analyses suggested statistically significant effects in their own right (AlphaOmega - ALA; DART fat 1989; MRC 1968; Veterans Admin 1969). The funnel plot did not suggest any serious publication bias (not shown).

Sensitivity analyses using fixed-effects analysis suggested a 10% reduction in risk of coronary heart disease with increased PUFA (RR 0.90, 95% CI 0.82 to 0.99; Analysis 1.15), but other sensitivity analyses suggested varying results both sides of no effect (RR 1.00). These included restricting to trials at low risk of bias for allocation concealment (RR 1.14, 95% CI 0.73 to 1.78), low risk of attention bias (RR 0.86, 95% CI 0.72 to 1.02), compliance bias (RR 0.87, 95% CI 0.65 to 1.17), low summary risk of bias (RR 1.18, 95% CI 0.76 to 1.81), trials registry or pre-2010 publication (RR 0.87, 95% CI 0.72 to 1.06), trials without any industry funding (RR 0.72, 95% CI 0.31 to 1.63), that randomised at least 100 participants (RR 0.87, 95% CI 0.82 to 1.09; Analysis 1.14).

Subgrouping by PUFA dose and trial duration did not suggest important differences between subgroups, or dose or duration effects. There were only six events in trials with doses of less than 1% E (Analysis 1.16) and 21 events in trials of less than two years (Analysis 1.17). Meta-regression did not suggest any relationship between PUFA dose (P = 0.69) or trial duration (P = 0.51) and coronary heart disease events.

Subgrouping did not suggest differential effects by primary or secondary prevention (P = 0.12; Analysis 1.18), baseline PUFA intake (Analysis 1.19), replacement of saturated fat or MUFA with PUFA (Analysis 1.20), age (Analysis 1.22), statin use or intervention type (Analysis 1.23; Analysis 1.24). Most coronary heart disease events occurred in trials of men, there is insufficient information to understand effects in other subgroups, though rather surprisingly there was a significant difference between subgroups of men and women combined and trials of mostly men or mostly women (Analysis 1.21).

We downgraded the GRADE evidence level for imprecision and risk of bias combined (as despite over 10,000 participants the 95% confidence intervals included harm from increasing PUFA as well as benefit). PUFA intake probably reduces risk of coronary heart disease events, from 14.2% to 12.3% in the study populations, NNT 53 (moderate-quality evidence), Summary of findings for the main comparison.

#### Stroke

PUFA intake may very slightly reduce risk of stroke (NNT 1000, low-quality evidence). However, the 95% confidence intervals include important harms as well as benefit.

Eleven trials including 14,742 participants of whom 166 experienced at least one fatal or non-fatal stroke. Meta-analysis suggested some reduction in risk of stroke with increased PUFA, but

confidence intervals were wide (RR 0.91, 95% CI 0.58 to 1.44, I<sup>2</sup> = 24%; Analysis 1.25). The funnel plot did not suggest any small study bias (not shown).

This suggestion of benefit from PUFA was also seen in the fixedeffect sensitivity analysis (RR 0.82, 95% CI 0.61 to 1.11, Analysis 1.27). While sensitivity analyses retaining only trials at low risk of bias from allocation concealment, attention and low summary risk of bias all suggested reduced stroke risk with increased PUFA, as did those on trials registers or pre-2010, and trials of at least 100 participants, this was not the case for sensitivity analyses of trials at low risk of bias from compliance (RR 1.36, 95% CI 0.45 to 4.11, I<sup>2</sup> = 56%), trials without industry funding or of at least 250 participants (RR 0.98, 95% CI 0.60 to 1.60, I<sup>2</sup> = 33%), Analysis 1.26.

Subgrouping did not suggest greater effects with higher doses of PUFA (Analysis 1.28), or longer duration (Analysis 1.29), without significant differences between subgroups. Meta-regression did not suggest relationships between PUFA dose and stroke (P = 0.69), but there was limited non-statistically significant suggestion of greater benefit in longer trials (P = 0.11).

There were no significant differences between subgroups by primary or secondary prevention (P = 0.20; Analysis 1.30), baseline PUFA dose (Analysis 1.31), sex (Analysis 1.33), statin use (Analysis 1.35), fatal or non-fatal stroke (Analysis 1.37), replacement (Analysis 1.32), or intervention type (Analysis 1.36). There were differences when subgrouping was by age (Analysis 1.34), but greater protection at older age was balanced by harm in midlife - a confusing picture. Where data on ischaemic or haemorrhagic stroke could be separated out, both subgroups suggested harm from increased PUFA, while data on combined ischaemic and haemorrhagic events suggested benefit from increased PUFA, again a non-intuitive pattern (Analysis 1.38).

We downgraded the GRADE quality assessment twice for imprecision (even though over 14,000 participants were included only 166 people experienced stroke so we were underpowered to assess effects). PUFA intake may reduce risk of stroke, from 1.2% to 1.1% in the study populations, NNT 1000 (low-quality evidence), but harms are not ruled out, Summary of findings for the main comparison.

#### Major adverse cardiac and cardiovascular events (MACCEs)

Effects of PUFA on risk of MACCEs are unclear as data are of very low quality.

Two trials recruited 1879 participants, and 817 people experienced at least one MACCE. The trials suggested a 16% decrease in MACCE risk with increased PUFA, but were highly heterogeneous (RR 0.84, 95% CI 0.59 to 1.20,  $I^2 = 79\%$ ; Analysis 1.39). With only two included trials assessment of small study bias was not possible, and fixed-effect analysis also suggested some benefit of PUFA (RR 0.92, 95% CI 0.82 to 1.04,  $I^2 = 79\%$ ; Analysis 1.41). Most sensitivity analyses preserved the suggested reduction of risk of MACCEs with increased PUFA but no trials were at low summary risk of bias and none were at low risk of bias from allocation concealment (Analysis 1.40).

With only two trials, subgrouping was generally uninformative ( Analysis 1.42; Analysis 1.43; Analysis 1.44; Analysis 1.45; Analysis 1.46; Analysis 1.47; Analysis 1.48; Analysis 1.49; Analysis 1.50). Whenever the two trials were in separate subgroups there was a statistically significant difference between subgroups. We did not attempt meta-regression.

We downgraded GRADE assessment for risk of bias, inconsistency and imprecision. Effects of PUFA on risk of MACCEs was unclear as data are of very low quality, Summary of findings for the main comparison.

#### Secondary outcomes

We formally systematically reviews secondary outcomes, in that we included all relevant trials that collected data on any of these outcomes. Summary of findings 2 displays GRADE assessments for the key outcomes not included in this review's primary outcomes.

#### **Cardiovascular mortality**

Increasing PUFA intake may have little or no effect on cardiovascular mortality (low-quality evidence).

Sixteen trials randomising 15,107 participants of whom 729 died of cardiovascular causes were included. Meta-analysis suggested little effect of PUFA intake on cardiovascular disease deaths (RR 1.02, 95% CI 0.82 to 1.26,  $I^2 = 31\%$ ; Analysis 2.1). Sensitivity analyses suggested small non-significant benefits (limiting to trials at low risk of bias for attention) or non-significant harms (limiting to trials at low risk of bias for allocation concealment, compliance, summary risk of bias, trials registry entry or pre-2010, no industry funding, and larger trials; Analysis 2.2), and fixed-effect analysis suggested no effect (RR 1.01, 95% CI 0.88 to 1.16; Analysis 2.3). The funnel plot suggested that one or two smaller trials with RRs greater than 1.00 might be missing - replacing these would tend to raise the RR, suggesting slight harm.

Subgrouping by PUFA dose suggested no statistically significant subgroup differences (Analysis 2.4). Meta-regression did not suggest any relationship with dose (P = 0.54). Subgrouping by duration showed no important differences between subgroups (P = 0.72; Analysis 2.5). Meta-regression on duration was not statistically significant (P = 0.11).

Subgrouping by primary or secondary prevention, replacement, sex, statin use, and intervention type did not explain any of the heterogeneity and subgroups did not differ significantly (Analysis 2.6; Analysis 2.8; Analysis 2.9; Analysis 2.11; Analysis 2.12). Subgrouping by baseline PUFA intake included six trials and suggested benefit of increasing PUFA intake in groups with baseline total PUFA intake less than 6% E (RR 0.71, 95% CI 0.52 to 0.97,  $I^2 =$ 

0%, 141 cardiovascular disease deaths), but harm in groups with higher baseline PUFA intake (RR 1.32, 95% CI 1.07 to 1.62,  $I^2$ = 0%, 326 cardiovascular disease deaths), removing heterogeneity and suggesting a statistically significant test for subgroup differences (P = 0.003; Analysis 2.7). Subgrouping by participant age also reduced heterogeneity and suggested significant subgroup differences (P = 0.02; Analysis 2.10), suggesting harm from additional PUFA in adults aged under 50 years, more modest harm in those aged 50 to 65 years, and benefit in those aged at least 65 years. These data could suggest greater utility of increasing total PUFA when baseline intake is low, and in older adults, but given the small number of trials caution is appropriate.

We downgraded the GRADE assessment twice for imprecision (as important benefits and harms were included in the 95% confidence intervals). Increasing PUFA intake may have little or no effect on cardiovascular mortality (low-quality evidence).

#### **Cardiovascular events**

Increasing PUFA intake probably reduces risk of cardiovascular events a little (NNT 59, moderate-quality evidence).

Twenty trials randomising 17,799 participants reported at least one cardiovascular event in 2442 participants. Meta-analysis suggested that increasing total PUFA intake reduced the risk of cardiovascular disease events by 11%, with little heterogeneity (RR 0.89, 95% CI 0.79 to 1.01,  $I^2 = 30\%$ ; Analysis 2.13), as did fixedeffect analysis (RR 0.92, 95% CI 0.86 to 0.98; Analysis 2.15). Sensitivity analyses limiting to trials with low risk of bias from attention bias, trials registry entry or pre-2010, trials with at least 100 or at least 250 participants all retained suggestion of benefit from increased PUFA, while sensitivity analyses for allocation concealment, compliance, and industry funding suggested no important effects, and limiting to studies with low summary risk of bias suggested increased risk (Analysis 2.14). The funnel plot did not suggest small study bias (not shown).

Subgrouping by PUFA dose and trial duration did not show statistically significant differences between subgroups (P = 0.17 and 0.18 respectively; Analysis 2.16; Analysis 2.17). Meta-regression did not suggest relationships between cardiovascular disease events and PUFA dose (P = 0.78) or trial duration (P = 0.70).

Subgrouping by primary or secondary prevention, baseline PUFA dose, replacement, sex, statin use, and intervention type did not reduce heterogeneity and did not suggest significant differences between subgroups (Analysis 2.18; Analysis 2.19; Analysis 2.20; Analysis 2.21; Analysis 2.23; Analysis 2.24). Subgrouping by participant age suggested harm in younger participants (RR 1.66, 95% CI 1.05 to 2.61,  $I^2 = 0\%$ ), but benefit in middle-aged and older participants (RR 0.86, 95% CI 0.78 to 0.96,  $I^2 = 0\%$ ), with statistically significant differences between subgroups (P = 0.03; Analysis 2.22).

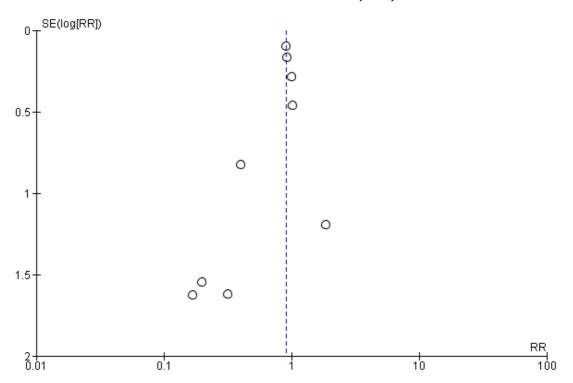
We downgraded the GRADE assessment for risk of bias (as sensitivity analyses suggested benefit, no effect and some harm from increased PUFA). Increasing PUFA intake probably reduces risk of cardiovascular events from 14.6% to 13.0% in study populations, NNT 63 (moderate-quality evidence).

#### Coronary heart disease mortality

Increasing PUFA intake may reduce risk of coronary heart disease death by a small amount (NNT 200, low-quality evidence).

Nine trials randomised 8810 participants of whom 556 died of coronary heart disease. Meta-analysis suggested that increasing PUFA intake reduced risk of coronary heart disease death, without heterogeneity (RR 0.91, 95% CI 0.78 to 1.06,  $I^2 = 0\%$ ; Analysis 2.25). Results from the fixed-effect analysis were very similar (RR 0.90, 95% CI 0.77 to 1.05,  $I^2 = 0\%$ ; Analysis 2.27). Although nine trials provided data, of the 556 deaths, 340 occurred in DART fat 1989, which carried 65% of the weight of the meta-analysis, and 138 occurred in AlphaOmega - ALA, which carried 23% of the weight. Results of all the sensitivity analyses were similar, all suggesting modest protection from increased PUFA (Analysis 2.26), although no subgroups were statistically significant. The funnel plot suggested that some small trials with RR over 1.0 may be missing, and if these trials were added back in they would tend to raise the RR towards 1.0 (Figure 4).

# Figure 4. Funnel plot of comparison 2. Higher PUFA vs lower PUFA - dichotomous secondary outcomes, outcome: 2.25 CORONARY HEART DISEASE (CHD) MORTALITY



Subgrouping by dose and duration did not suggest subgroup differences (P = 0.92 and 0.90 respectively), though there was a counter-intuitive suggestion that lower doses and shorter durations produced greater benefits (Analysis 2.28; Analysis 2.29). Meta-regression did not suggest strong relationships between PUFA dose (P = 0.62) or trial duration (P = 0.71) and risk of coronary heart disease death.

Subgrouping by primary or secondary cardiovascular disease prevention, baseline PUFA dose, replacement, sex, age, statin use, or intervention type did not suggest important differences between subgroups (Analysis 2.30; Analysis 2.31; Analysis 2.32; Analysis 2.33; Analysis 2.34; Analysis 2.35; Analysis 2.36).

We downgraded the GRADE assessment for imprecision and publication bias. Increasing PUFA intake may reduce risk of coronary heart disease death a little from 6.6% to 6.1% in the study populations, NNT 200 (low-quality evidence).

#### Myocardial infarction

Increasing PUFA may reduce risk of myocardial infarction. Fifteen trials randomising 15,609 participants recorded 880 myocardial infarctions. Meta-analysis suggested that increasing PUFA reduced the risk of myocardial infarction by 12% without heterogeneity (RR 0.88, 95% CI 0.78 to 0.99,  $I^2 = 0\%$ ; Analysis 2.37). We did not plan to carry out sensitivity analyses, subgroup analyses or meta-regression for this outcome.

#### Sudden cardiac death

The effect of increasing PUFA on sudden cardiac death is unclear. Five trials recruited 1731 participants of whom 69 experienced sudden cardiac death. Meta-analysis suggested some benefit from increasing PUFA (RR 0.80, 95% CI 0.50 to 1.29,  $I^2 = 0\%$ ; Analysis 2.38), but the effect was not statistically significant, and did not exclude important harms. There were insufficient trials to assess the funnel plot. We did not plan to carry out sensitivity analyses, subgroup analyses or meta-regression for this outcome.

#### Atrial fibrillation

The effect of increasing PUFA intake on atrial fibrillation is unclear as the evidence is of very low quality.

Eleven trials recruited 11,692 participants of whom 811 experienced new or recurrent atrial fibrillation. Meta-analysis suggested that increasing PUFA reduced the risk of atrial fibrillation by 13%

with substantial heterogeneity (RR 0.87, 95% CI 0.72 to 1.06, I <sup>2</sup> = 57%, Analysis 2.39). Fixed-effect analysis suggested marginal statistical significance (RR 0.87, 95% CI 0.72 to 1.06, I<sup>2</sup> = 57%; Analysis 2.39). Sensitivity analyses generally suggested a non-significant protective effect of the trials at lower risk of bias, but trials without industry funding and those at low risk from allocation concealment suggested a statistically significant reduction(Analysis 2.40). No trials were at low risk of bias from compliance problems. Subgrouping by new or recurrent atrial fibrillation suggested no important differences between subgroups (P = 0.31; Analysis 2.39). Subgrouping by PUFA dose did not suggest important differences between subgroups (Analysis 2.42), but subgrouping by duration suggested greater protection in shorter trials (P = 0.001; Analysis 2.43). Meta-regression suggested that there was no relationship between PUFA dose and atrial fibrillation (P = 0.91), but there was a marginally significant relationship between duration and risk of atrial fibrillation (with benefit in shorter trials and harm in longer trials, P = 0.056).

Subgrouping suggested no important effects by replacement, sex, age, intervention type or statin use (no subgroup differences; Analysis 2.46; Analysis 2.47; Analysis 2.48; Analysis 2.49; Analysis 2.50). Subgrouping suggested that PUFA was harmful in primary prevention (RR 1.33, 95% CI 0.99 to 1.79,  $I^2 = 0\%$ ) and beneficial in secondary prevention of cardiovascular disease (RR 0.80, 95% CI 0.67 to 0.96,  $I^2 = 58\%$ ), with significant subgroup differences (P = 0.004; Analysis 2.44). Only one trial had a known baseline PUFA intake so subgrouping was unhelpful (Analysis 2.45).

We downgraded the GRADE assessment for risk of bias, inconsistency and imprecision. The effect of increasing PUFA intake on atrial fibrillation is unclear as the evidence is of very low quality.

#### Angina

The effect of increasing PUFA intake on angina is unclear.

Seven trials including 2070 participants reported 100 participants experiencing new or worsening angina. Meta-analysis suggested that increasing PUFA reduced risk of angina (RR 0.64, 95% CI 0.35 to 1.16,  $I^2 = 46\%$ ; Analysis 2.51). There were insufficient trials to assess the funnel plot and we did not plan to carry out sensitivity analyses, subgroup analyses or meta-regression for this outcome. One included trial had adequate allocation concealment and none were at low summary risk of bias.

#### Heart failure

The effect of increasing PUFA intake on heart failure is unclear. Seven trials including 25,257 participants reported 137 participants experiencing new or worsening heart failure. Meta-analysis suggested that increasing PUFA reduced risk of heart failure but results were heterogeneous and important harms were not excluded (RR 0.74, 95% CI 0.40 to 1.36,  $I^2 = 54\%$ ; Analysis 2.52). There were insufficient trials to assess the funnel plot and we did not

plan to carry out sensitivity analyses, subgroup analyses or metaregression for this outcome. Two included trials had adequate allocation concealment and one was at low summary risk of bias.

#### Peripheral arterial disease

Increasing PUFA intake may increase the risk of peripheral arterial disease.

Four trials including 8937 participants reported 97 participants experiencing new or worsening peripheral arterial disease. Metaanalysis suggested that increasing PUFA increased risk of peripheral arterial disease but important benefits were not excluded (RR 1.20, 95% CI 0.81 to 1.77,  $I^2 = 0\%$ ; Analysis 2.53). There were insufficient trials to assess the funnel plot and we did not plan to carry out sensitivity analyses, subgroup analyses or meta-regression for this outcome. Two included trials had adequate allocation concealment and two were at low summary risk of bias.

#### Revascularisation

The effect of increasing PUFA intake on revascularisation is unclear.

Six trials including 1182 participants reported 46 participants undergoing revascularisation. Meta-analysis suggested that increasing PUFA reduced risk of revascularisation but important harms were not excluded (RR 0.70, 95% CI 0.40 to 1.24,  $I^2 = 0\%$ ; Analysis 2.54). There were insufficient trials to assess the funnel plot and we did not plan to carry out sensitivity analyses, subgroup analyses or meta-regression for this outcome. One included trial had adequate allocation concealment and one was at low summary risk of bias.

#### Adiposity - body weight

Higher PUFA intake probably results in greater weight gain (moderate-quality evidence).

Twelve trials presenting 15 comparisons, of which 13 could be included in meta-analyses, included 7100 participants with data on body weight. Meta-analyses suggested that weight increased with increased PUFA intake, although trials were heterogeneous (MD 0.76 kg, 95% CI 0.34 to 1.19,  $I^2 = 59\%$ ; Analysis 3.1). The funnel plot suggested that some trials with smaller weight increases or reductions in the increased PUFA group may be missing. If replaced, these trials would tend to reduce the weight increase in the higher PUFA participants. Two trials (both also suggesting increased weight in the higher PUFA arm) did not provide variance data so could not be included in the meta-analysis, though they are shown in the forest plot (Analysis 3.1). A further five trials collected data on weight but did not provide those data in a way that could be included in meta-analysis (MARINA - Sanders 2011; NDHS Faribault 1968; NDHS Open 1st 1968; Simon 1997; Vijayakumar 2014).

The effect was larger when we used fixed-effect analysis (MD 1.08 kg, 95% CI 0.96 to 1.21; Analysis 3.3). Sensitivity analyses all suggested increased body weight with increased PUFA intake (although not statistically significantly when we limited to trials at low risk of compliance bias, Analysis 3.2).

Subgrouping by PUFA dose, duration, primary or secondary prevention, replacement, sex, age and statin use did not differ significantly by subgroups (Analysis 3.4; Analysis 3.5; Analysis 3.6; Analysis 3.8; Analysis 3.9; Analysis 3.10; Analysis 3.11). There were important differences between subgroups when grouping by baseline PUFA dose, with greater weight increases for those with lower baseline PUFA intake (Analysis 3.7). Subgrouping by intervention type suggested differences between subgroups (P = 0.01; Analysis 3.12), suggesting greater weight increases with increased PUFA intake by dietary advice (MD 2.37 kg, 95% CI 1.19 to 3.55,  $I^2 = 0\%$ ) than in trials of supplemental foods or diet provided (MD 0.71 kg, 95% CI 0.18 to 1.25,  $I^2 = 73\%$ ), or in supplemental trials (MD 0.37 kg, 95% CI -0.18 to 0.91,  $I^2 = 0\%$ ). We downgraded the GRADE assessment of evidence for publication bias, leading to a moderate quality of evidence. Higher PUFA intake probably results in greater weight gain.

#### Adiposity - BMI

Higher PUFA intake may lead to higher BMI (low-quality evidence).

Eight trials reported 11 comparisons including 4798 participants with BMI reported. Meta-analysis suggested that increasing PUFA intake results in greater BMI, but effects were heterogeneous (MD 0.17 kg/m<sup>2</sup>, 95% CI -0.08 to 0.42, I<sup>2</sup> = 80%, Analysis 3.13). Fixed-effect analysis was statistically significant (MD 0.27 kg/m<sup>2</sup>, 95% CI 0.20 to 0.35, I<sup>2</sup> = 80%; Analysis 3.15). The funnel plot did not suggest any small study bias, and we are aware of two trials that assessed BMI but did not provide data that could be used in metaanalysis (Simon 1997; Vijayakumar 2014). Sensitivity analyses all confirmed slightly increased BMI with increased PUFA intake (Analysis 3.14).

Subgrouping by PUFA dose, duration, primary or secondary prevention, baseline PUFA intake, replacement, sex, age, statin use and intervention type did not suggest important differences between subgroups (Analysis 3.16; Analysis 3.17; Analysis 3.18; Analysis 3.19; Analysis 3.20; Analysis 3.21; Analysis 3.22; Analysis 3.23; Analysis 3.24), and did not reduce heterogeneity.

We downgraded the GRADE assessment for inconsistency and imprecision, leading to low-quality evidence. Higher PUFA intake may lead to higher BMI.

#### Adiposity - other measures

Several trials reported waist circumference (1298 participants in two trials; Analysis 3.25), percentage body fat (309 participants in two trials; Analysis 3.26) and body fat in kg (214 participants in a

single trial; Analysis 3.27). Meta-analyses on waist circumference and percentage body fat both suggested greater weight gain in those on higher PUFA intake, while the single trial with data on body fat in kg suggested no difference in body fat regardless of PUFA intake. We are aware of several trials that assessed adiposity but did not provide data in a format that could be included in meta-analysis. HERO-Tapsell 2009 and Simon 1997 assessed percentage of body fat, and WAHA - Ros 2016 assessed waist circumference (shown in the meta-analysis but without variance data).

#### Lipids - serum total cholesterol

Higher PUFA intake leads to lower total cholesterol (high-quality evidence).

Twenty six trials, incorporating data from 8072 participants (and 28 trial arms), provided data on serum total cholesterol. Meta-analysis suggested that increasing PUFA intake reduced total cholesterol, although data were heterogeneous (MD -0.12 mmol/L, 95% CI -0.23 to -0.02,  $I^2 = 79\%$ ; Analysis 3.28). The funnel plot was difficult to interpret, but we were aware of one trial (MRC 1968) that provided total cholesterol data without variance information, so could not be included in meta-analysis. This trial also suggested reduced total cholesterol in the higher PUFA arm (Analysis 3.28). Total cholesterol data from five trials (Dullaart 1992; EPOCH 2011; ORL 2013; Veterans Admin 1969; WINS 2006) could not be included in meta-analysis, so are missing.

Sensitivity analyses, including fixed-effect analysis, all suggested greater total cholesterol reduction with higher PUFA intake, although some were not statistically significant (Analysis 3.29; Analysis 3.30).

Subgrouping by PUFA dose and duration did not suggest important differences between subgroups (Analysis 3.31; Analysis 3.32). We did not plan to run meta-regressions for continuous outcomes. Subgrouping by primary or secondary prevention, baseline PUFA intake, replacement, age, sex, statin use and intervention type did not suggest important differences between subgroups (Analysis 3.33; Analysis 3.34; Analysis 3.35; Analysis 3.36; Analysis 3.37; Analysis 3.38; Analysis 3.39).

We did not downgrade the GRADE assessment of evidence. Higher PUFA intake leads to lower total cholesterol (high-quality evidence).

#### Lipids - serum fasting triglyceride

Higher PUFA intake probably leads to lower triglyceride levels (moderate-quality evidence).

Twenty trials incorporating data from 3905 participants (and 22 trial arms) provided data on serum triglycerides. Meta-analysis suggested that increasing PUFA intake reduced triglycerides, al-though data were heterogeneous (MD -0.12 mmol/L, 95% CI - 0.20 to -0.04,  $I^2 = 50\%$ ; Analysis 3.40). The funnel plot did not suggest small study bias, but we are aware of a further eight trials

that did not report triglycerides in a way that could be incorporated into meta-analysis (Ahn 2016; EPOCH 2011; NDHS Faribault 1968; NDHS Open 1st 1968; ORL 2013; Rossing 1996; WAHA - Ros 2016; WINS 2006).

Sensitivity analyses, including fixed-effect analysis, all suggested greater triglyceride reduction with higher PUFA intake, although some were not statistically significant (Analysis 3.41; Analysis 3.42).

Subgroup analyses did not suggest differential effects by dose, duration, baseline PUFA intake, replacement, statin use, intervention type, primary or secondary prevention, sex, or age (Analysis 3.43; Analysis 3.44; Analysis 3.45; Analysis 3.46; Analysis 3.47; Analysis 3.48; Analysis 3.49; Analysis 3.50).

We downgraded the GRADE evidence once for inconsistency. Higher PUFA intake probably leads to lower triglyceride levels (moderate-quality evidence).

#### Lipids - high density lipoprotein (HDL)

Higher PUFA intake probably has no important effects on HDL (moderate-quality evidence).

Eighteen trials incorporating data from 4674 participants (and 20 trial arms) provided data on HDL. Meta-analysis suggested that increasing PUFA intake had little or no effect on HDL, without heterogeneity (MD -0.01 mmol/L, 95% CI -0.02 to 0.01,  $I^2 = 0\%$ ; Analysis 3.52). The funnel plot suggested that some trials with lower HDL in the higher PUFA arms may be missing, and adding any such trials into the meta-analysis would tend to lead to lower HDL with higher PUFA. We are aware of five trials that measured HDL but did not report the data in a way that could be incorporated into meta-analysis (EPOCH 2011; ORL 2013; Rossing 1996; WAHA - Ros 2016; WINS 2006).

Sensitivity analyses, including fixed-effect analysis, all confirmed lack of an important effect (Analysis 3.53; Analysis 3.54).

Subgrouping did not suggest differential effects of PUFA dose, duration, primary or secondary prevention, baseline PUFA intake, replacement, sex, age, statin use or intervention type (Analysis 3.55; Analysis 3.56; Analysis 3.57; Analysis 3.58; Analysis 3.59; Analysis 3.60; Analysis 3.61; Analysis 3.62; Analysis 3.63).

We downgraded the GRADE assessment for publication bias. Higher PUFA intake probably has no important effects on HDL (moderate-quality evidence).

#### Lipids - low density lipoprotein (LDL)

Higher PUFA intake probably has no important effects on LDL (moderate-quality evidence).

Fifteen trials incorporating data from 3362 participants (and 17 trial arms) provided data on LDL. Meta-analysis suggested that increasing PUFA intake had little or no effect on LDL, without major heterogeneity (MD -0.01 mmol/L, 95% CI -0.09 to 0.06, I  $^2$  = 44%; Analysis 3.64). The funnel plot suggested that some trials

with lower LDL associated with higher PUFA may be missing, adding such trials in would tend to suggest that increasing PUFA reduces LDL. We are aware of three trials that measured LDL but did not report it in a way that could be included in meta-analysis (Dullaart 1992; EPOCH 2011; ORL 2013).

Sensitivity analyses, including fixed-effect analysis, all confirmed this lack of effect (Analysis 3.65; Analysis 3.66).

Subgrouping did not suggest differential effects of PUFA dose, duration, primary or secondary prevention, baseline PUFA intake, replacement, sex, age, statin use or intervention type (Analysis 3.68; Analysis 3.69; Analysis 3.70; Analysis 3.71; Analysis 3.72; Analysis 3.73; Analysis 3.74; Analysis 3.75).

We downgraded the GRADE assessment for publication bias. Higher PUFA intake probably has no important effects on LDL (moderate-quality evidence).

### **Tertiary outcomes**

We did not formally systematically review tertiary outcomes. Where the included trials reported these outcomes, we collated and analysed them.

#### Blood pressure, systolic and diastolic

Nine trials reported systolic blood pressure from 7356 participants, and eight trials reported diastolic blood pressure from 7327 participants. There was no suggestion of an effect of increased PUFA on systolic (MD -0.47 mmHg, 95% CI -2.20 to 1.26, I<sup>2</sup> = 47%; Analysis 4.1) or diastolic blood pressure (MD 0.24 mmHg, 95% CI -0.55 to 1.02,  $I^2 = 31\%$ ; Analysis 4.2). There were insufficient trials to assess the funnel plots, but we are aware of four trials that assessed blood pressure and did not report it fully (EPOCH 2011; MRC 1968; NDHS Open 1st 1968; Rossing 1996), though the data from MRC 1968 are displayed in the forest plot. We did not plan to carry out sensitivity analyses, subgroup analyses or metaregressions for these outcomes. Six of the trials in each analysis had low risk of bias from allocation concealment, and six were at low summary risk of bias. Lack of reporting of this commonly collected outcome may suggest publication bias, and the four trials with missing data would tend to confirm this.

## Quality of life

One trial (Dodin 2005) assessed the effect of their flaxseed intervention on quality of life, using the MENQOL scale. MEN-QOL assesses the impact of four domains (vasomotor, psychosocial, physical and sexual) of menopausal symptoms over the previous month with scores ranging from 0 (no impact, high quality of life) to 32 (very poor quality of life in all domains). They found that over 12 months the MENQOL score fell slightly in both groups (intervention group -0.23, SD 0.62, N = 85, control group -0.14, SD 0.58, N = 94). This suggested little effect of the intervention on quality of life related to menopausal symptoms.

We found no further data on quality of life in the included trials, though dropouts may provide some information on how willing to continue the interventions participants were.

## **Economic costs**

We did not find any data on economic costs in the included trials.

#### Serious adverse events

Adverse events reported in one or two trials each included the following, with no clear effects for any outcomes (Analysis 4.3).

1. Pulmonary embolism (RR 2.15, 95% CI 0.48 to 9.57,  $I^2 = 0\%$ , 2 trials, 2087 participants, 7 events)

2. Mutliple sclerosis worsened or acute attack (RR 1.11, 95%

CI 0.95 to 1.30, I<sup>2</sup> = 0%, 2 trials, 268 participants, 142 events) 3. Bleeding (RR 0.80, 95% CI 0.34 to 1.85, I<sup>2</sup> = 0%, 2 trials,

748 participants, 21 events)4. Gastrointestinal hospitalisation (RR 1.75, 95% CI 0.53 to

5.79, 1 trial, 200 participants, 11 events)

5. Retinopathy diagnosis (RR 1.02, 95% CI 0.56 to 1.86, 1 trial, 2424 participants, 42 events)

Effects of increased PUFA intake on dementia and neurocognitive outcomes (Jimoh 2017), type 2 diabetes and measures of glucose metabolism (Brown 2017), inflammatory bowel disease and inflammatory markers (Thorpe 2017), cancers (Hanson 2017b), depression and anxiety (Hanson 2017a) and functional outcomes (Abdelhamid 2017) are systematically reviewed elsewhere, so we have not reported results of effects seen in trials included in this review, as they are a potentially misleading subset. The systematic reviews on these health outcomes are not yet published, so we have provided references to their protocols so that the systematic reviews can be located.

Effects of increasing PUFA on pulmonary embolism and bleeding are unclear as the evidence is of very low quality.

#### Dropouts

Twenty-seven trials reported 1675 dropouts, suggesting that being in the higher or lower PUFA arm did not make much difference to the likelihood of dropping out (RR 0.99, 95% CI 0.87 to 1.13,  $I^2 = 41\%$ ; Analysis 4.4). This may suggest that increasing PUFA is an acceptable intervention.

# ADDITIONAL SUMMARY OF FINDINGS [Explanation]

# Higher PUFA compared to lower PUFA - dichotomous secondary outcomes for prevention of cardiovascular disease

Patient or population: people with or without existing cardiovascular disease, men and women

Setting: includes free-living participants and those living in institutions. Includes participants from all continents but most events and assessments occurred in trials carried out in Europe or North America.

Intervention: higher PUFA intake

Comparison: lower PUFA intake

Eligible trials compared higher with lower total PUFA intakes. The intervention had to be dietary supplementation, or a provided diet, or advice on diet. The advice, foodstuffs or supplements had to aim to increase or decrease total PUFA intake, or a dietary component high in total PUFA intake such as vegetable oil, or, if no clear aim was stated (but implied, such as aiming to provide a 'heart health', 'reduced fat' or 'Mediterranean' diet) then the intervention had to achieve an increase or decrease of at least 10% of the baseline total PUFA level

-	Outcomes .	Anticipated absolute effects* (95% CI)		Relative effect (95% Cl)	№ of participants (trials)	Certainty of the evi- dence (GRADE)	Comments
		Risk with lower PUFA	Risk with higher PUFA			(GRADE)	
of cardiovascular dise	ity Follow-up: range 12 months to 96 months	No CVD at baseline (primary prevention)		RR 1.02 (0.82 to 1.26)	15,107 (16 RCTs)	⊕⊕⊖⊖ Low <sup>a</sup>	Increasing PUFA intake may have little or no
		36 per 1000	31 per 1000 (19 to 50)				effect on cardiovascu- lar mortality (risk alters from 4.8% to 4.9% in the
ì		CVD at baseline (secondary prevention)					study population), low- quality evidence
,		57 per 1000	64 per 1000 (52 to 77)				
	<b>Cardiovascular events</b> Follow-up: range 12 months to 96 months	No CVD at baseline (primary prevention)		RR 0.89 (0.79 to 1.01)	17,799 (21 RCTs)	⊕⊕⊕⊖ Moderate <sup>b</sup>	Increasing PUFA intake probably reduces risk of CVD events (from 14. 6%to 13.0%in the study population, NNT = 63) , moderate-quality evi- dence

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		54 per 1000	46 per 1000 (39 to 54)				
		CVD at baseline (secondary prevention)					
		233 per 1000	208 per 1000 (175 to 245)				
	<b>Coronary heart disease mortality</b> Follow-up: range 12 months to 96 months	No CVD at baseline (primary prevention)		RR 0.91 (0.78 to 1.06)	8810 (9 RCTs)	⊕⊕⊖⊖ Low <sup>c</sup>	Increasing PUFA intake may reduce risk of CHD
		52 per 1000	44 per 1000 (16 to 122)				death (from 6.6% to 6. 1% in the study popula- tion, NNT = 200), low-
		CVD at baseline (secondary prevention)					quality evidence
		68 per 1000	61 per 1000 (53 to 72)				
	arrhythmias Follow-up: range 12 <sup>-</sup> months to 60 months	No CVD at baseline (primary prevention)		RR 0.87 (0.72 to 1.06)	11692 (11 RCTs)	$\oplus \bigcirc \bigcirc \bigcirc$ Very low <sup>d</sup>	The effect of increasing PUFA intake on atrial fibrillation is unclear as
		26 per 1000	34 per 1000 (25 to 46)				the evidence is of very low quality
		CVD at baseline (secondary prevention)					
		119 per 1000	95 per 1000 (80 to 114)				
	Adiposity - body weight, kg Follow-up: range 12 months to 60 months	Mean body weight was 81.0 kg	MD 0.76 higher (0.34 higher to 1.19 higher)	-	7100 (13 RCTs)	⊕⊕⊕⊖ Moderate <sup>e</sup>	Higher PUFA intake probably causes in- creased weight gain.

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Adiposity - BMI, kg/m <sup>2</sup> follow-up: range 12 months to 60 months	Mean BMI was 26.9 kg/ m <sup>2</sup>	MD 0.17 higher (0.08 lower to 0.4 higher)	2	4798 (8 RCTs)	$\oplus \oplus \bigcirc \bigcirc$ Low $^f$	Higher PUFA intake may increase BMI.
	Mean serum TC was 5. 46 mmol/L	MD 0.12 lower (0.23 lower to 0.0 lower)	2	8072 (27 RCTs)	⊕⊕⊕⊕ High <sup>g</sup>	Higher PUFA intake leads to lower TC.
	Mean serum TG was 1. 57 mmol/L	MD 0.12 lower (0.2 lower to 0.0 lower)	- 4	3905 (20 RCTs)	⊕⊕⊕⊖ Moderate <sup>h</sup>	Higher PUFA intake probably reduces TG levels.
Serumhigh-den-sitylipoprotein(HDL,mmol/L)Follow-up:range12monthsto 60 months	Mean serum HDL 1.31 mmol/L	MD 0.01 lower (0.02 lower to 0.0 higher)		4674 (18 RCTs)	⊕⊕⊕⊜ Moderate <sup>i</sup>	Higher PUFA intake probably has little or no effect on HDL.
Serum low-density lipoprotein (LDL, mmol/L) Follow-up: range 12 months to 60 months		MD 0.01 lower (0.09 lower to 0.0 higher)	- 6	3362 (15 RCTs)	⊕⊕⊕⊖ Moderate <sup>j</sup>	Higher PUFA intake probably has little or no effect on LDL.

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

BMI: Body Mass Index; CI: confidence interval; CVD: cardiovascular disease; MD: mean difference; OR: odds ratio; PUFA: polyunsaturated fatty acids; RR: risk ratio

# GRADE Working Group grades of evidence

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

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

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

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

# <sup>a</sup>Cardiovascular mortality

1. **Risk of bias**: limiting trials to those at low summary risk of bias, low risk from allocation concealment, from attention bias, from compliance, by trial funding and trial size suggests small benefits and harms from increasing PUFA intake. Tends to confirm lack of important effect. Not downgraded.

2. Inconsistency: I<sup>2</sup> statistic less than 50%, not downgraded.

3. Indirectness: most events occurred in men, and in trials carried out in high-income nations. Not downgraded.

4. Imprecision: 95% confidence intervals range from important benefit to important harm. Downgraded twice.

5. **Publication bias**: some suggestion that one or two small trials may be missing. If added in they would tend to increase the RR. Not a large effect, not downgraded.

## <sup>b</sup>Cardiovascular events

1. **Risk of bias**: sensitivity analyses suggested reduced risk of CVD events with more PUFA, lack of effect, and some harm. Downgraded once.

2. Inconsistency:  $I^2$  statistic less than 50%, not downgraded.

3. Indirectness: most events occurred in men, and in trials carried out in high-income nations. Not downgraded.

4. Imprecision: over 17,000 participants randomised, of whom more than 2400 experienced CVD events. 95% confidence intervals excluded important harms. Not downgraded.

5. Publication bias: no suggestion of missing trials in the funnel plot. Not downgraded.

# <sup>c</sup>Coronary heart disease mortality (CHD)

1. Risk of bias: all sensitivity analyses concurred that increased PUFA reduced risk of CHD deaths. Not downgraded.

2. Inconsistency:  $I^2$  statistic less than 50%, not downgraded.

3. Indirectness: most events occurred in men, and in trials carried out in high-income nations. Not downgraded.

4. Imprecision: over 8800 participants randomised and over 500 CHD deaths. However, the 95% confidence intervals didn't exclude important harm. Downgraded once.

5. **Publication bias**: some suggestion of publication bias. If present replacing missing trials would tend to raise the risk ratio towards 1.0 (no effect). Downgraded once.

# <sup>d</sup>Atrial fibrillation and arrhythmias

1. **Risk of bias**: no included trials were at low risk of compliance problems, all other sensitivity analyses suggested reduced risk of AF with increased PUFA. However there was no dose response, a suggestion of benefit in short trials, and harm in longer trials supported by meta-regression. Downgraded once.

2. Inconsistency: I<sup>2</sup> statistic greater than 50%. Downgraded once.

3. Indirectness: most events occurred in men, and in trials carried out in high-income nations. Not downgraded.

4. Imprecision: 95% confidence intervals exclude serious harm, but included the null. Downgraded once.

5. Publication bias: no suggestion of missing trials in the funnel plot. Not downgraded.

# <sup>e</sup>Adiposity - body weight

1. **Risk of bias**: sensitivity analyses assessing effects of different biases all suggested greater weight gain in those taking higher total PUFA. Not downgraded.

2. Inconsistency: I<sup>2</sup> statistic greater than 50% but partially explained by type of intervention and duration of intervention. Not downgraded.

3. Indirectness: weight was assessed in both men and women, but all trials were conducted in high-income countries. Not downgraded.

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4. Imprecision: 95% confidence intervals only included increased weight with increased PUFA intake. Not downgraded.
5. Publication bias: the funnel plot suggests that some trials with less weight gain in the higher PUFA arm may be missing. Two trials with weight data could not be included in meta-analysis, but they also suggested greater weight gain in the higher PUFA arm. Other missing trials, if due to publication bias, are likely to have not been published because they suggested increased weight in the higher PUFA arm. so are likely to support the main analysis. Downgraded once.

## <sup>f</sup>Adiposity - Body Mass Index (BMI)

1. **Risk of bias**: sensitivity analyses assessing effects of different biases all suggested greater weight gain in those taking higher total PUFA. Not downgraded.

2. Inconsistency: I<sup>2</sup> statistic greater than 50%, and not explained by subgrouping. Downgraded once.

3. Indirectness: weight was assessed in both men and women, but all trials were conducted in high-income countries. Not downgraded.

4. Imprecision: 95% confidence intervals did not include important benefits, but did include the null. Downgraded once.

5. Publication bias: no suggestion of missing data. Not downgraded.

# <sup>8</sup>Serum total cholesterol (TC)

1. Risk of bias: sensitivity analyses all suggested greater lipid reduction with higher PUFA intake. Not downgraded.

2. Inconsistency: I<sup>2</sup> statistic greater than 50%, and while no single factor explains this there were greater TC reductions

with low statin use, higher PUFA dose, lower baseline PUFA, and replacement of saturated fats and monounsaturated fats. Not downgraded.

3. **Indirectness**: data provided by men and women, and comes from high-income and low- to middle-income countries. Not downgraded.

4. **Imprecision**: data came from thousands of participants and 95% confidence intervals did not include harm. Not downgraded.

5. **Publication bias**: funnel plot not interpretable, known missing data are consistent with data used in meta-analysis. Not downgraded.

# <sup>h</sup>Serum triglycerides (TG)

1. Risk of bias: sensitivity analyses all suggested greater lipid reduction with higher PUFA intake. Not downgraded.

2. Inconsistency: I<sup>2</sup> statistic = 50%, without any clear explanation from subgrouping. Downgraded once.

3. Indirectness: data provided by men and women, and comes from high-income and industrialising countries. Not downgraded.

4. Imprecision: data came from thousands of participants and 95% confidence intervals did not include harm. Not downgraded.

5. **Publication bias**: no suggestion of missing data. Not downgraded.

<sup>i</sup>Serum HDL

1. Risk of bias: consistent lack of effect of PUFA in all sensitivity analyses. Not downgraded.

2. Inconsistency:  $\mathsf{I}^2$  statistic less than 50%. Not downgraded.

3. Indirectness: data provided by men and women, and comes from high-income and industrialising countries. Not downgraded.

4. Imprecision: data came from thousands of participants and confidence interval excludes important effects. Not downgraded.

5. Publication bias: some trials with lower HDL appear to be missing. Downgraded once.

# <sup>j</sup>Serum LDL

1. Risk of bias: consistent lack of effect of PUFA in all sensitivity analyses. Not downgraded.

2. Inconsistency: I<sup>2</sup> statistic less than 50%. Not downgraded.

3. Indirectness: data provided by men and women, and comes from high-income and industrialising countries. Not downgraded.

4. Imprecision: data came from thousands of participants and confidence interval excludes important effects. Not downgraded.

5. Publication bias: some trials with lower LDL appear to be missing. Downgraded once.

## DISCUSSION

## Summary of main results

This Cochrane Review included 49 RCTs randomising 24,272 participants, for one to eight years. We identified 22 potential ongoing trials. Total PUFA dose (the difference in total PUFA between intervention and control arms) was 0.6% E to less than 1% E for 13 trials, 1% E to less than 2% E in 17 trials, 2% E to less than 5% E in eight trials, and 5% E or more from total PUFA in 11 trials. We assessed 11 of the 49 included trials as being at low summary risk of bias.

Increasing PUFA intake probably has little or no effect on all-cause mortality (risk changes from 7.8% to 7.6%, RR 0.98, 95% CI 0.89 to 1.07,  $I^2 = 0\%$ , 1443 deaths, 24 trials, moderate-quality evidence, downgraded for imprecision). Increasing PUFA probably reduces the risk of coronary heart disease events (from 14.2% to 12.3%, RR 0.87, 95% CI 0.72 to 1.06, I<sup>2</sup> = 45%, 1351 people with coronary heart disease events, 15 trials, moderate quality evidence, downgraded for imprecision and risk of bias combined) and stroke (from 1.2% to 1.1%, RR 0.91, 95% CI 0.58 to 1.44, I  $^{2}$  = 24%, 166 strokes, 11 trials, however the confindence intervals included important harm, low-quality evidence downgraded once for imprecision and once for risk of bias and imprecision combined). Effects on MACCEs (RR 0.84, 95% CI 0.59 to 1.20, I  $^{2}$  = 79%, 817 events, 2 trials) are unclear as evidence is of very low quality (downgraded for risk of bias, imprecision and inconsistency).

For secondary outcomes we found that increasing PUFA intake probably reduces risk of cardiovascular disease events (from 14.6% to 13.0%, RR 0.89, 95% CI 0.79 to 1.01, I<sup>2</sup> = 30%, 2442 events, 21 trials, moderate-quality evidence). Increasing PUFA intake may slightly reduce risk of coronary heart disease death from 6.6% to 6.1% (RR 0.91, 95% CI 0.78 to 1.06,  $I^2 = 0\%$ , 556 coronary heart disease deaths, 9 trials) and myocardial infarction (RR 0.88, 95% CI 0.78 to 0.99, I<sup>2</sup> = 0%, 880 myocardial infarctions, 15 trials) but may increase the risk of peripheral arterial disease (RR 1.20, 95% CI 0.81 to 1.77, I<sup>2</sup> = 0%, 97 events, 4 trials) and have little or no effect on cardiovascular mortality (4.8% to 4.9%, RR 1.02, 95% CI 0.82 to 1.26,  $I^2 = 31\%$ , 729 cardiovascular disease deaths, 16 trials), all low-quality evidence. The effect of increasing PUFA on sudden cardiac death, angina, atrial fibrillation, heart failure and revascularisation is unclear as the evidence is of very low quality.

High-quality evidence suggests that increasing PUFA intake slightly reduces total serum cholesterol over at least one year (MD -0.12 mmol/L, 95% CI -0.23 to -0.02,  $I^2 = 79\%$ , 8072 participants, 26 trials). Increasing PUFA intake probably causes some weight gain (MD 0.76 kg, 95% CI 0.34 to 1.19,  $I^2 = 59\%$ , 7100 participants, 12 trials), decreases triglycerides (MD -0.12 mmol/L, 95% CI -0.20 to -0.04,  $I^2 = 50\%$ , 3905 participants, 20 trials) and has little effect on HDL (MD -0.01 mmol/L, 95% CI -0.02 to 0.01,  $I^2 = 0\%$ , 4674 participants, 18 trials) or LDL (MD -0.01

mmol/L, 95% CI -0.09 to 0.06,  $I^2 = 44\%$ , 3362 participants, 15 trials) (all moderate-quality evidence).

There was limited information on blood pressure, quality of life, economic outcomes or adverse health effects. Effects of increasing PUFA on pulmonary embolism and bleeding are unclear as the evidence is of very low quality. Effects of PUFA intake on other serious adverse health effects (cancers, inflammatory bowel disease, depression or anxiety, neurocognitive outcomes, functional outcomes and diabetes) are systematically reviewed and reported elsewhere.

We looked for dose and duration effects using subgrouping and meta-regression, finding none except a duration effect in atrial fibrillation, with protective effects in shorter trials (up to two years), little or no effect in trials of two to less than four years, and harm in longer trials (Analysis 2.43). We found no evidence of no linear dose effects, though assessment of PUFA doses actually delivered by trials were difficult to ascertain, often due to missing control information. Baseline PUFA intake (or PUFA intake in the control group as a proxy) were poorly reported, reducing our ability to see subgroup differences - there was a suggestion of greater benefit of PUFA with lower baseline PUFA intake for cardiovascular disease mortality, but not for other cardiovascular outcomes.

There were no clear patterns of differential effects across outcomes by primary or secondary prevention, replacement, sex, age, statin use or intervention type. Subgrouping did not suggest differences between effects in primary or secondary prevention, except for atrial fibrillation, where increasing PUFA in primary prevention was harmful and increasing PUFA in secondary prevention was beneficial (Analysis 2.44). There were no differential effects by replacement, sex or statin use. For cardiovascular disease mortality there was a suggestion of harm from increasing PUFA intake in younger adults, smaller levels of harm in middle-aged adults and benefit in those aged at least 65 years (Analysis 2.10). This pattern was repeated for cardiovascular disease events, except that some benefit was seen in the middle-aged group (Analysis 2.22), although this pattern was not seen for other outcomes. Dietary advice appeared to lead to greater increases in body weight and BMI (Analysis 3.12; Analysis 3.24), while dietary advice and supplements to increase PUFA appeared to reduce triglyceride to a greater extent than supplemental foods or diet provided (Analysis 3.51).

# Overall completeness and applicability of evidence

Included trials randomised 24,272 participants over periods of at least a year. Participants were men and women aged from their 20s into their 80s but most trials recruited participants with a mean age of 50 to 65 years. Most coronary heart disease events occurred in these 'middle-aged' trials, but most deaths occurred in trials of older adults. Twenty-two trials included 70% or more men, and many of these were exclusively in men, six included 70% or more

women, and sixteen included a balanced proportion of men and women. Despite this, most coronary heart disease events (1289 of 1351) and deaths (1134 of 1443) occurred in trials mainly of men, so while women are included it is not clear whether any effects are generalisable to them. Similarly, while younger adults are included, most events occurred in older adults, which partly explains the lack of appearance of some trials of younger adults in many of the analyses on health events. We included these trials as they reported data on lipids or adiposity, or both, and sometimes one or two health events.

Two included trials were from countries with developing economies (Mendis 2001 from Sri Lanka and Vijayakumar 2014 from India) but while both provided lipid data, the only events were two deaths in Vijayakumar 2014. This means that the bulk of the information in this review is from countries with developed economies. Some trials were from areas with non-western dietary practices, including South Korea (Ahn 2016), Japan (DIPP-Tokudome 2015; Doi 2014; Mita 2007; ORL 2013), Sri Lanka (Mendis 2001), and India (Vijayakumar 2014), however often the dietary intakes of these populations at baseline and during the trial were not well described.

Our data spring from trials conducted from the 1960s (MRC 1968; NDHS Faribault 1968; NDHS Open 1st 1968; Rose 1965; Veterans Admin 1969) to the present, and during this sixty year period cardiovascular disease incidence has altered. For example, in 2010 one in four deaths worldwide was from ischaemic heart disease or stroke, up from one in five in 1990 (Lozano 2012). But this worldwide increase hides more complex trends, with different rates and trends in different parts of the world. Death rates from CHD in men aged 35 to 74 were 839/100,000 in Ukraine in 2000, but ~200/100,000 in the USA and UK, and only 54/100,000 in Japan. Rates in women were lower but followed the same trends by country (WHO 2004). In the UK as in most high-income countries age-standardised death rates from coronary heart disease in adults of all ages fell by 72% between 1979 and 2013, and stroke mortality fell by 71% over the same period (Bhatnagar 2016). Globally age-adjusted annual incidence of stroke in men and women of all ages has increased slightly from 1990 to 2010, but this masks falls in high-income countries and rises in low and middle-income countries (Feigin 2014; Carandang 2006). While we assess effects using risk ratios in this review so that we can see relative effects regardless of baseline incidence, baseline incidence affects absolute effects including numbers needed to treat. Our results suggest that we need to increase total PUFA intake in ~53 people to prevent one person experiencing a CHD event, in ~63 people to prevent a CVD event, and even more for CHD death and stroke. But in populations at greater risk NNTs will be lower (fewer people needing to increase their PUFA to prevent one person experiencing an event), and in lower risk populations NNTs will be higher. The greatest import of dietary increases in total PUFA intake is likely to be in low- and middleincome countries where rates of CVD are higher (and rising).

Results relate to both primary and secondary prevention of cardiovascular disease. However, as would be expected, most events occurred in those with existing cardiovascular disease. For example, 1130 of 1443 deaths (78%) were in participants with cardiovascular disease at baseline (Analysis 1.6). Effects in the secondary prevention group (risk barely altering from 11.7% in the lower PUFA arm to 11.5% (95% CI 10.1 to 13.1%) in the higher PUFA arm) were similar to those without cardiovascular disease at baseline (primary prevention, risk barely altering from 3.4% in the lower PUFA arm to 3.3% (95% CI 2.7 to 4.1%) in the higher PUFA arm). For cardiovascular disease events 2013 of 2435 people (83%) experiencing cardiovascular disease events had existing cardiovascular disease at baseline (Analysis 2.18). Risk of a cardiovascular disease event fell by 2.5% from 23.3% to 20.8% (95% CI 17.5% to 24.5%) in secondary prevention, and fell by 0.9% from 5.8% to 4.9% (95% CI 4.2% to 5.9%) in primary prevention when increasing PUFA intake.

We are aware of missing trials. We were unable to access data for AFORRD; NCT00309439; NCT00410020; Chandrakala 2010 or ACTRN12610000594022, which all appeared likely to be eligible. They were all registered before the end of 2010 or had planned finish dates up to the end of 2015, hence appear to be completed but unpublished (see Characteristics of ongoing studies). We are also aware of some missing data within included trials for example there were deaths in Bates 1977 but they were reported combined with dropouts and the trial author no longer has the data, and two deaths in Simon 1997 not reported by intervention arm. Houtsmuller 1979 reported coronary heart disease events and mortality, but not all-cause deaths or cardiovascular disease events. Sixteen trials (Ahn 2016; Black 1994; Dullaart 1992; EPOCH 2011; HERO-Tapsell 2009; MARINA - Sanders 2011; MRC 1968; NDHS Faribault 1968; NDHS Open 1st 1968; ORL 2013; Rossing 1996; Simon 1997; Veterans Admin 1969; Vijayakumar 2014; WAHA - Ros 2016; WINS 2006) reported at least one continuous outcome without variance data or without change data and with baseline data too different to allow us to use end data (so we missed at least six sets of data on total cholesterol, eight on triglyceride, seven on body weight and four sets on blood pressure). On the other hand, we were provided the full dataset on events for DART fat 1989, so were able to include data for almost all of our outcomes, data for Sydney Diet-Heart 1978 were well reported in recent re-analyses and the trial authors kindly augmented these data, and outcome data in Veterans Admin 1969 were very well reported, so data are probably almost complete for these large trials. Authors of many other trials provided some additional data on outcomes and/or confirmed that no participants experienced specific outcomes.

We identified 22 potential ongoing trials (Characteristics of ongoing studies), but these trials are very difficult to assess for inclusion in terms of total PUFA dose, until further details are published. We will formally assess these trials for inclusion when we update this review. Two of these trials specifically include women,

who are underrepresented in trials already included in this review (NCT01784042; NCT02295059). Other ongoing trials appear generally to be in both men and women, which will increase the proportion of data provided by women. Two trials appear to be planned for developing economies (India Chandrakala 2010 and China n-3 on plasma lipid), but the majority appear to be carried out in Europe, North America and Australia. It is not possible to assess whether any of these trials will document trans fat intake or status, or indeed intake or status of other key fats and nutrients. There is no suggestion that any of these trials are targeting participants with low baseline total PUFA intakes. Overall, they may begin to address information about women more thoroughly, but not deficiencies in the database of information on participants from lower-income countries, and they are not clearly of higher quality when it comes to assessment of dietary intakes and nutritional status before and during the trials.

We all consume PUFA already (it is essential in our diets). It would be useful to understand whether increasing PUFA in people who eat very little has the same effect as increasing PUFA in people already consuming large amounts. Unfortunately few trials assessed overall dietary intake of participants at baseline or through the trial. Only 16 of the 49 included trials provide information on baseline or control-arm PUFA intake (we used control-arm PUFA intake in lieu of baseline PUFA intake where no baseline intake was given and the control arm were on 'usual intake'). Of these 16 trials, participants in seven consumed less than 6% E from PUFA and nine 6% E and above. Despite these limited data there is a pattern across the review that effects in participants with less than 6% E PUFA intake at baseline are positive, but effects in those with higher baseline PUFA intake are negative or neutral - though we do not see statistically significant differences between subgroups and data are very limited. The pattern is evident for coronary heart disease events (Analysis 1.19), stroke (Analysis 1.31), MACCEs (Analysis 1.45), cardiovascular disease mortality (Analysis 2.7), and cardiovascular disease events (Analysis 2.19), but not in all-cause mortality where no effects are seen in any group (Analysis 1.7) or coronary heart disease mortality (Analysis 2.31), and we lack data for atrial fibrillation. This relationship needs to be checked in future trials, but suggests that increasing total PUFA intake to at least 6% E may be appropriate.

Other subgrouping and meta-regression effects that would tend to support true effects of increasing total PUFA on some cardiovascular outcomes include seeing greater effects with higher PUFA doses or with longer duration (for dichotomous outcomes). We consistently do not see dose or duration effects within the review, and this weakens our findings of health effects arising from increasing PUFA.

Total PUFA is the sum of omega-3, omega-6 and some omega-9 fats, which may have their own specific effects on our outcomes. We have assessed specific effects of omega-3 (Abdelhamid 2018) and omega-6 (Hooper 2018) in separate reviews, but this review aims to assess whether there is a group effect of PUFAs. It would

be useful to assess effects of omega-3/omega-6 ratio in this review - but these data are not available. Similarly data on trans fats would be useful, as it is possible that some trials increased trans fats when providing PUFA (through use of partially hydrogenated fats). There is evidence that trans fats may be harmful (de Souza 2015), and so may confound our understanding of the PUFA trials. Unfortunately almost no information on trans fat intake was found, so we could not assess this issue.

Despite systematic review evidence that omega-3 fats do not influence cardiovascular disease risk (Abdelhamid 2018) there is a theory that the ratio of omega-3 to omega-6 fats is important for cardiovascular health and body weight (Simopoulos 2016). We planned to subgroup by change in the omega-3/omega-6 fat ratio, assessing whether the intervention primarily increased omega-3 fats (putting up the ratio) or omega-6 fats (lowering the ratio). However, only three trials (DIPP-Tokudome 2015; PREDIMED 2013; WAHA - Ros 2016) reported both omega-3 and omega-6 intakes (understanding supplemental intakes only would not be adequate). This means that we cannot use this review to assess health effects of altering the omega-3/omega-6 ratio.

There were no clear dose or duration effects in the review. While we would expect that replacing saturated fat, MUFA or carbohydrate with PUFA would give different health effects, we do see greatest reduction in total cholesterol with replacement of saturated fat (Analysis 3.35), and greatest reduction of triglyceride with replacement of MUFA (Analysis 3.47). However, there are no statistically significant differences between subgroups for these outcomes or any other health outcomes. There are no clear replacement effects. It is also surprising to see increased PUFA intake reducing total cholesterol and triglyceride (Analysis 3.28; Analysis 3.40), with no change in LDL (Analysis 3.64). The Friedewald equation (Friedewald 1972) states that 'total cholesterol = LDL + HDL + triglyceride/2.19' (all components in mmol/L), so for the changes of total cholesterol and triglyceride we see, we would expect similar falls in LDL, but this is not seen. Reasons for this are not clear, but it is possible that changes in very low density lipoprotein (VLDL) added to triglyceride reductions and very small changes in HDL and LDL could add up to the overall total cholesterol reduction. Overall, included data are applicable, but not entirely complete. While further trials of increasing PUFA intake in women and in developing economies are needed, they should include participants with low PUFA intakes at baseline, as well as those with higher intakes. Dietary advice needs to ensure that trans fat intake is kept low as PUFA increases, and intakes of all fat fractions, including trans fat intakes should be assessed and checked using reliable biomarkers.

## Quality of the evidence

GRADE assessment includes consideration of risk of bias, inconsistency, indirectness, publication bias and imprecision (Summary of findings for the main comparison and Summary of findings 2).

We assessed risk of bias by assessing whether effect sizes and directions altered when limited to trials at low risk of bias from allocation concealment, from attention bias, from compliance, trials at low summary risk of bias, with trials registry registration (or pre-2010), without industry funding, and that randomised at least 100 or 250 participants. Sensitivity analyses generally supported the primary analysis for all-cause mortality, coronary heart disease mortality, cardiovascular disease mortality, weight and lipid outcomes (Analysis 1.2; Analysis 2.2; Analysis 2.14; Analysis 2.26; Analysis 3.2; Analysis 3.14; Analysis 3.29; Analysis 3.41; Analysis 3.53; Analysis 3.65), so we did not downgrade these for risk of bias. Either sensitivity analyses contradicted the primary analyses (for coronary heart disease events and stroke; Analysis 1.14; Analysis 1.26) or there were no trials at low summary risk of bias, or low risk of compliance problems (MACCEs and atrial fibrillation; Analysis 1.40; Analysis 2.40), so we downgraded these outcomes for risk of bias.

We judged imprecision by whether the 95% CI included the null, and whether it included important benefits and harms. Where both important benefits and harms were included within the confidence interval we downgraded twice, where it only included the null we downgraded once unless there was a very small overlap. We downgraded the evidence on all primary and some secondary outcomes for imprecision, suggesting that included trials may still be underpowered to determine effectiveness on these outcomes. There was no evidence of under-powering for lipid outcomes.

We judged inconsistency using the  $I^2$  statistic for each primary and secondary outcome. We considered an  $I^2$  statistic greater than 50% to be a problem and led to us downgrading for inconsistency unless we found an element that explained that inconsistency (through subgrouping or meta-regression). We downgraded the primary outcome, MACCEs for inconsistency, and also secondary outcomes, atrial fibrillation, BMI and triglyceride.

We judged indirectness according to whether data on an outcome related to both women and men, those with and without cardiovascular disease at baseline, and whether low- and middle-income, and high-income countries were represented. While indirectness is important, we suspect that the mechanisms of action of PUFA are similar in all these populations so we did not downgrade for indirectness.

We judged publication bias according to whether there was any suggestion of publication or small study bias in the funnel plot, or where we knew that data were missing that differed from the summary assessment. We downgraded the secondary outcomes, coronary heart disease mortality, body weight, HDL and LDL for publication bias.

Trial funding can be an important indicator of study bias but is not included in 'Risk of bias' assessment. Sixteen trials reported funding sources, which appeared to be purely from national or charitable agencies, seven trials appeared to be directly funded by industrial sources, two funded by bodies set up to promote specific foods, 16 by some governmental or charity sources with additional funding or support from commercial sources, two trials included authors on industry honoraria, and five trials did not report funding.

Trial pre-registration or early publication of a trial protocol is helpful in understanding potential biases in data presentation (including outcome selection bias). We ran sensitivity analyses assessing whether trials that were pre-registered or had a published protocol suggested different effects than trials without such documentation. We found trials registry entries for most included trials published after 2010. Making datasets of all outcomes available via trials registers would also help systematic reviewers to gather all appropriate data, and minimise publication bias.

Applying the GRADE criteria suggests that we have high-quality evidence on effects of PUFA on serum total cholesterol (not downgraded), moderate-quality evidence on all-cause mortality, coronary heart disease events, cardiovascular disease events, body weight, triglyceride, HDL and LDL (each downgraded once), and low-quality evidence for stroke, cardiovascular disease mortality, coronary heart disease mortality and BMI (each downgraded twice). All other evidence was of very low quality. Reasons for grading, and statements of findings based on these levels of evidence are found in Summary of findings for the main comparison and Summary of findings 2.

## Potential biases in the review process

We conducted a large number of sensitivity analyses and subgroup analyses for each primary outcome, as well as some secondary outcomes (key outcomes). The danger in these is that subgroups may be spuriously statistically significant, but we used them to check the stability of our primary analyses, as well as to try to explain heterogeneity, assessing for dose effects, duration effects and differential effects by what PUFA replaces in the diet. We have tried not to over-interpret any of these analyses.

We only considered trials with interventions or follow-up periods of 12 months or more, making the review relevant for public health interventions. We considered including shorter trials, but were concerned that if we found no effect then this might be due to including trials too short to reflect health effects of increasing or decreasing PUFA intake. The decision on duration depended on assumed mechanism of action of PUFA. If we assumed a cholesterol-led atherosclerotic mechanism then we could justify deciding only to include trials of at least two years' duration. However another mechanism discussed for omega-3 and omega-6 fats includes inflammation - likely to work more quickly than atherosclerosis, so allowing six months for equilibration of body tissues with the new dietary intake, and a further six months to allow for reflection of this new status in health outcomes, appears most appropriate to us. We ran subgroup analyses to assess whether trial duration made an important difference to our primary outcomes. We did not find any suggestion of greater effects in longer trials (those of at least four years) compared to shorter trials (one to less than

two years, or two to less than four years) for all-cause mortality (Analysis 1.5), coronary heart disease events (Analysis 1.17), or stroke (Analysis 1.29). Only two trials provided data on MACCEs, but these two trials did suggest a protective effect in the longer trial (Analysis 1.43). Meta-regression did not suggest duration effects for any primary outcome. Similarly there were no duration effects in subgrouping or meta-regression for cardiovascular disease mortality (Analysis 2.5), cardiovascular disease events (Analysis 2.17), or coronary heart disease mortality (Analysis 2.29), though visual inspection tended to suggest greater protection in the shortest trials, despite them reporting few events. There was a suggestion of a duration effect for atrial fibrillation, but the suggestion was for greater effect in shorter trials, and no effect in longer trials (Analysis 2.43). Conversely participants taking more PUFA gained more weight and their BMI rose more in longer trials (Analysis 3.5; Analysis 3.17).

Our inclusion criteria could potentially cause some bias. Few trials directly aimed to assess effects of increasing PUFA with usual or lower PUFA intake, so included trials are a combination of trials that aimed to increase PUFA, trials that aimed to increase omega-3 or omega-6 fats and resulted in an increase of at least 10% of baseline PUFA intake, and trials that aimed to reduce total fat intake and resulted in a decrease of at least 10% of baseline PUFA intake (while not aiming to alter dietary components other than fat or replacements for the change in PUFA). This allowed assessment of effects of altering PUFA intake, but we had to exclude trials that may have been relevant but did not report aims for or effects on total PUFA, so we may be missing other trials that would be relevant to this review. It is also possible that we included trials that aimed to increase or decrease total PUFA but did not achieve the planned changes in PUFA intake. To help guard against this we also conducted sensitivity analyses around compliance, removing trials where we did not have biomarker confirmation of a difference in PUFA status between trial arms.

Even though we excluded clearly multifactorial trials, when we alter one dietary component, other components inevitably alter too. For example, when PUFA intake is increased we need to reduce energy intake elsewhere, so saturated fat or carbohydrate intake may fall to compensate. The danger is that we may see a health effect from increasing PUFA that is actually due to a reduction in saturated fat. However, in this review some trials that increased PUFA reduced saturated fat, and in other trials PUFA and saturated fat were both reduced in the intervention arm. Regardless of which arm the trial considered to be the intervention arm we compared the arm with higher PUFA against the arm with lower PUFA to look for consistent effects of higher PUFA intake. Because saturated fat (and other dietary components) sometimes moved with PUFA and sometimes moved in the opposite direction the only consistent difference between arms was in PUFA intake. This means that health effects noted are unlikely to be spurious effects of other dietary components. Combining higher versus lower PUFA intake across different types of trials may balance out effects of other dietary (fat and non-fat) components while providing power to assess health effects of changing PUFA.

# Agreements and disagreements with other studies or reviews

We recently published a Cochrane Review of long-term RCTs that assessed effects of reducing saturated fats, replacing them with a variety of other energy sources (Hooper 2015a). This review found no effect of reducing saturated fats on all-cause mortality or cardiovascular disease mortality, but the evidence suggested that reducing saturated fats reduced the risk of cardiovascular disease events (RR 0.83, 95% CI 0.72 to 0.96, I<sup>2</sup> = 65%, including 4377 events in over 53,000 randomised participants). Subgrouping, assessing whether the saturated fats were being replaced by PUFA, MUFA, carbohydrate and/or protein found that there were no statistically significant effects in these subgroups except where saturated fat was being replaced by PUFA (RR 0.73, 95% CI 0.58 to 0.92,  $I^2 =$ 69%, 884 events in over 3000 participants). Hooper 2015a confirmed results expected from the Friedewald equation (Friedewald 1972). The trials included in the saturated fat review and this one are distinct due to rather different inclusion criteria (for example, the saturated fat review only included trials of at least two years duration, and included trials with dietary interventions decreasing saturated fat plus altering other dietary variables). The implications of the reviews are similar - Hooper 2015a suggests that reducing saturated fat and replacement by polyunsaturated fats reduces the risk of cardiovascular disease events, while this review also suggests that increasing PUFA may reduce the risk of cardiovascular disease events, as well as coronary heart disease mortality (as well as reducing total cholesterol and triglyceride). However, this current review also suggests that increasing PUFA intake also leads to slight weight gain.

Two previous systematic reviews of RCTs assessed effects of PUFA replacing saturated fat: Ramsden 2010 and Mozaffarian 2010. Ramsden 2010 included seven trials that compared increasing mixed omega-3 and omega-6 PUFA or omega-6 alone and replacing dietary saturated fat with usual dietary intake. Their data suggested no effect on all-cause mortality (RR 0.99, 95% CI 0.89 to 1.11), but likely reductions in coronary heart disease mortality (RR 0.91, 95% CI 0.74 to 1.10), and myocardial infarction and cardiac death combined (RR 0.85, 95% CI 0.73 to 0.99). These are similar results to this review (no effect on all-cause mortality, reductions in coronary heart disease mortality and myocardial infarction). Ramsden 2010 included fewer trials than this review, four trials that we included (MRC 1968; Rose 1965; Sydney Diet-Heart 1978; Veterans Admin 1969), and three we excluded. We excluded two for being multifactorial (Oslo Diet-Heart 1966; STARS 1992) and one for having inconsistent enrolment so that many participants were included for less than 12 months continuously (Minnesota Coronary 1989). The other systematic review, Mozaffarian 2010, also included seven trials replacing sat-

urated fat with PUFA, three that we included (DART fat 1989; MRC 1968; Veterans Admin 1969), and four that we excluded. One we excluded due to lack of randomisation (Finnish Mental Hosp 1972), one for inconsistent enrolment (Minnesota Coronary 1989), and two because the intervention was multifactorial (Oslo Diet-Heart 1966; STARS 1992). Mozaffarian 2010 found that increasing PUFA by replacing saturated fat reduced coronary heart disease events by 19% (RR 0.81, 95% CI 0.70 to 0.95), unlike this review, where we found that the evidence was of very low quality, so could not assess effects on this outcome.

Recent observational data of more than 30,000 adults aged over 30 years from the National Health and Nutrition Examination Survey (NHANES) was not entirely consistent with our results. They suggested that the tertile of adults with highest PUFA intake were at lowest risk of all-cause mortality (HR 0.94, 95% CI 0.90 to 0.98 compared to the tertile with lowest intake) and cardiovascular disease mortality (HR 0.93, 95% CI 0.89 to 0.97), when adjusted for ethnicity, BMI, alcohol intake, smoking, education, physical activity, fibre intake and blood pressure (Ricci 2018).

The suggestion of weight gain with increased PUFA intake reflects data from other systematic reviews that reducing dietary fat (including PUFAs) appears to result in lower weight in adults. As weight gain may increase cardiovascular risk, this may work against more positive lowering of total cholesterol and triglycerides when assessing overall effects of increasing PUFA on cardiovascular disease (Hooper 2015b).

We interpreted the total cholesterol and weight results using QRisk 2-2017 (QRISK 2-2017). In a Pakistani non-smoking male aged 64 years without existing cardiovascular disease or diabetes, height 173 cm, weighing 81 kg with systolic blood pressure of 145 mmHg and total cholesterol 5.46 mmol/L, HDL 1.31 (total cholesterol/ HDL 4.17) at baseline (typical values for the trials in this review) their 10-year QRISK 2-2017 score would be 23.5%. A reduction of total cholesterol by 0.12 mmol/L, HDL by 0.01 mmol/L and weight rise of 0.76 kg reduces the QRISK 2-2017 score to 23.2%. QRISK 2-2017 suggests that in 1000 people with the same risk factors, 235 are likely to have a heart attack or stroke within the next 10 years at baseline, falling to 232 having a heart attack or stroke following increased PUFA intake. Three people of the 1000 would be prevented from experiencing a heart attack or stroke by the increased PUFA. This is a smaller effect than the estimated reduction from 58 per 1000 to 49 (95% CI 42 to 59) per 1000 predicted for primary prevention of cardiovascular disease events within this review (Summary of findings 2).

## AUTHORS' CONCLUSIONS

## Implications for practice

Increasing polyunsaturated fatty acid (PUFA) intake probably makes little or no difference (neither benefit nor harm) to allcause mortality and probably slightly reduces the risk of coronary heart disease events and cardiovascular disease events (all moderate-quality evidence). Increased PUFA intake may slightly reduce risk of coronary heart disease mortality and stroke (although for stroke the confidence intervals include important harm), but may have little or no effect on cardiovascular disease mortality (all lowquality evidence). Increasing PUFA does reduce total cholesterol, probably reduces triglyceride, probably has little or no effect on high-density lipoprotein (HDL) or low-density lipoprotein (LDL) and probably increases body weight.

This suggests that increasing PUFA intake may have beneficial effects on risk of cardiovascular disease events, coronary heart disease mortality, coronary heart disease events and stroke. The mechanism may be via reduction of total cholesterol and triglyceride. However increasing PUFA will probably lead to slight body weight increase.

## Implications for research

Further trials assessing cardiovascular effects of increasing PUFA intake in women and people living in developing economies are needed. Given the low power for assessing effects by baseline PUFA, more research in populations with a low baseline intake of less than 6% E is needed to understand whether there is greater benefit from increasing PUFA intake in these groups. Further trials should include participants with low PUFA intakes at baseline, as well as those with higher intakes. Dietary advice needs to ensure that trans fat intake is kept low as PUFA increases. Intake and status of all fat fractions, including trans fat, should be assessed and checked using reliable biomarkers.

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\* Indicates the major publication for the study

# CHARACTERISTICS OF STUDIES

# Characteristics of included studies [ordered by study ID]

### Ahn 2016

Methods	RCT, parallel, (n3 EPA + DHA versus nil, both with statins), 12 months Summary risk of bias: moderate or high
Participants	Statin-treated CAD patients undergoing PCI N: 38 intervention, 36 control Level of risk for CVD: high Male: 63.2% intervention, 72.2% control Mean age (SD): 59.6 (9.1) intervention, 60.7 (0.8) [sic] control Age range: unclear Smokers: 36.8% intervention, 58.3% control Hypertension: 50% in both groups Medications taken by $\geq$ 50% of those in the control group: aspirin, clopidogrel, ACEi/ ARB, beta blockers, atorvastatin Medications taken by 20%-49% of those in the control group: cilostazol Medications taken by some, but < 20% of the control group: rosuvastatin, nitrates, calcium antagonists Location: South Korea Ethinicity: not reported
Interventions	Type: supplement (capsule) Comparison: EPA + DHA vs unclear (nil) Intervention: 3 g of $\omega$ -3 PUFA containing 1395 mg of EPA and 1125 mg of DHA/d. No further details Control: unclear whether control group were given placebo or only statins <b>Dose aim</b> : increase 2.5 g/d EPA + DHA, <b>1% E n-3</b> Baseline PUFA unclear <b>Compliance by biomarkers</b> : no tissue fatty acids reported, but TC was reduced by 31. 5% in intervention and by 20.9% in the control group, supporting greater PUFA intake in the intervention arm <b>Compliance by dietary intake:</b> not reported • Energy intake: not reported • Energy intake: not reported • Total fat intake: not reported • SFA intake: not reported • PUFA n-3 intake: not reported • PUFA n-6 intake: not reported • Trans fat intake: not reported • MUFA intake: not reported • CHO intake: not reported • Alcohol intake: not reported • Alcohol intake: not reported • Alcohol intake: not reported Compliance, other methods: unclear how it was measured but reported good compliance with no numbers

# Ahn 2016 (Continued)

	<b>Inclusion basis:</b> planned dose suggested total PUFA intake 2.5 g/d higher in interven- tion, or 1.13% E PUFA dose. There were no biomarker or dietary intake data to confirm this, but greater reductions in TC in the intervention arm supports. > 10% increase from assumed baseline of 6% E PUFA <b>PUFA dose:</b> 1.13% E Length of intervention: 12 months
Outcomes	Main trial outcome: change in atherosclerotic burden Dropouts: none Available outcomes: lipids (TG reported as median , IQR so not used), atheroma volume, neointimal volume index Response to contact: contact attempted but no response to date
Notes	Trial funding: the trial was supported by clinical research grant from Pusan National University Hospital

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Simple randomisation was carried out us- ing random number tables to assign each participant to the intervention or control group
Allocation concealment (selection bias)	Low risk	Participants were assigned randomisation numbers sequentially on recruitment to the trial, and the randomisation codes were re- tained by the clinical research co-ordinator
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No details
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The personnel responsible for randomisa- tion as well as those performing labora- tory measurements were blinded to the ran- domisation assignments
Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropouts reported
Selective reporting (reporting bias)	Unclear risk	No protocol or trial register entry found
Attention bias	Unclear risk	No details
Compliance	Low risk	No fatty acid levels reported, but TC lower in higher PUFA arm

# Ahn 2016 (Continued)

Other bias	High risk	It's unclear whether the trial was placebo controlled or the control group had no in- tervention. Also, some of the SDs appear to be incorrectly reported	
AlphaOmega - ALA			
Methods	RCT, 2 x 2 (n3 ALA vs MUF. Summary risk of bias: low	RCT, 2 x 2 (n3 ALA vs MUFA), 40 months Summary risk of bias: low	
Participants	N: intervention 2409 (1197 MUFA, 1192 EPA + DHA). A Level of risk for CVD: high Male: 77.9% intervention, 78 Mean age (SD): 69.0 (5.6) into Age range: 60-80 years Smokers: 17.4% intervention, Hypertension: unclear Medications taken by $\geq$ 50% antihypertensives, antithromb Medications taken by 20%-49	Male: 77.9% intervention, 78.7% control         Mean age (SD): 69.0 (5.6) intervention, 68.9 (5.6) control         Age range: 60-80 years         Smokers: 17.4% intervention, 18% control         Hypertension: unclear         Medications taken by ≥ 50% of those in the control group: lipid-lowering medication, antihypertensives, antithrombotics         Medications taken by 20%-49% of those in the control group: not reported         Medications taken by some, but < 20% of the control group: antiarrythmic drugs, antidiabetic drugs	
Interventions	Comparsion: ALA vs MUFA Intervention: 20 g/d of enrich- tubs delivered every 12 weeks Control: 20 g/d of margarine. placebo <b>Dose aim</b> : increase 2 g/d, 1% Baseline PUFA unclear <b>Compliance by biomarkers</b> : two ALA arms, no data for to <b>Compliance by dietary intak</b> DPA and DHA total PUFA de E. As planned intake was 20 g PUFA. Total PUFA in ALA + 11.3% E, or 2.26 g/d total PU • Energy intake: not report • Total fat intake: not report • SFA intake: not report	Type: supplementary margarine Comparsion: ALA vs MUFA Intervention: 20 g/d of enriched margarine incorporating: 2 g ALA. 8 x 250 g margarine tubs delivered every 12 weeks Control: 20 g/d of margarine. No additional n-3 PUFAs. Identical margarine (oleic acid) placebo <b>Dose aim</b> : increase 2 g/d, 1% E n-3	

# AlphaOmega - ALA (Continued)

	<ul> <li>PUFA n-6 intake: not reported</li> <li>Trans fat intake: not reported</li> <li>MUFA intake: not reported</li> <li>CHO intake: not reported</li> <li>Sugars intake: not reported</li> <li>Protein intake: not reported</li> <li>Alcohol intake: not reported</li> <li>Alcohol intake: not reported</li> <li>Compliance, other methods: unused margarine tubs were returned- daily intakes of margarine and n-3 fatty acids were calculated on the basis of the amount unused. Adherence was measured by levels of fatty acids in plasma cholesteryl esters, margarine and questionnaires. 90.5% of participants adhered to the protocol and consumed 20.6 (2.8) g/d of margarine</li> <li>Inclusion basis: planned total PUFA intake 1.02 and 1.30% E higher in control than intervention, &gt; 10% higher than assumed 6% E from total PUFA at baseline</li> <li>PUFA dose: 1.02% E in ALA + EPA + DHA vs EPA + DHA, 1.3% E in ALA margarine vs placebo margarine</li> <li>Duration of intervention: 40 months</li> </ul>
Outcomes	Main trial outcome: CVD events Dropouts: 91 died, 98 discontinued intervention, 93 died, 93 discontinued control Available outcomes: deaths, MI, CVD events, VF/VT, incident CVD Response to contact: yes (data provided)
Notes	This is a 2 x 2 trial, using ALA margarine vs MUFA margarine (this part) and EPA/ DHA margarine vs MUFA margarine (the next trial). The 4 arms were ALA margarine, EPA/DHA margarine, mixture of the 2 interventions and MUFA margarine. This ta- ble represents the AL- only intervention. Where possible data represent the full trial population for each comparison (ALA margarine plus combined intervention vs MUFA margarine plus EPA/DHA margarine). As this review assesses effects of total PUFA, and doses of total PUFA were higher in the ALA arms we have omitted the EPA/DHA data when pooling would otherwise have meant that each participant was represented twice in meta-analysis Trial funding: Netherlands Heart Foundation, National Institutes of Health and Unilever R&D (latter provided unrestricted grant for distribution of trial margarines)

# Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	On the computer by a random-number generator before the start of the trial
Allocation concealment (selection bias)	Low risk	Trial author confirmed allocation was con- cealed from clinicians/ researchers
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The 4 types of margarine were "similar in taste, texture and colour". A trained test panel did not perceive a fishy taste or odour. Randomisation tables were stored safely

### AlphaOmega - ALA (Continued)

		under supervision
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Randomisation tables were stored safely under supervision. There was an indepen- dent statistician for data analysis Quote: "Events were coded by three mem- bers of the end-point adjudication commit- tee who were unaware of the identity of the patient, the identity of the treating physi- cian and the patients assigned study group"
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants were followed up for events. Computerised linkage with munic- ipal registries. 2531 participants were only followed up for baseline anthropometric and medical measurements
Selective reporting (reporting bias)	High risk	Sudden cardiac death endpoint omitted. Registered in August 2005, recruitment was from 2002-2006. Outcomes papers published in 2010
Attention bias	Low risk	All participants appear to have had simi- lar frequency and quantity of attention and follow-up
Compliance	Unclear risk	Only plasma cholesteryl esters of ALA were reported and were higher in intervention arms (unclear regarding total PUFA), no TC reported
Other bias	Low risk	None noted
Bassey 2000-Post		
Methods	RCT, (high PUFA GLA+DHA+EPA vs low PUFA, both with Ca), 12 months Summary risk of bias: moderate or high	
Participants	Healthy postmenopausal women	

N: 21 intervention, 24 control (total randomised 57)

Mean age (SD): 58 (4.6) intervention, 55 (4.6) control

Medications taken by  $\geq$  50% of those in the control group: not reported Medications taken by 20%-49% of those in the control group: not reported

Level of risk for CVD: low Male: 0% intervention, 0% control

Hypertension: not reported

Age range: 50-65 years (inclusion)

Smokers: 20.8% intervention, 19% control

# Bassey 2000-Post (Continued)

	Medications taken by some, but < 20% of the control group: not reported (Women on confounding drug therapy were excluded.) Location: UK Ethinicty: not reported	
Interventions	Type: capsules Comparsion: evening primrose oil + fish oil vs nil Intervention 10 large capsules/d of efacal (Ca 1.0 g, evening primrose oil 4.0 g (85% or 3.4 g/d PUFA) and marine fish oil 440 mg), divided in doses with meals Control: large capsules of 1 g Ca <b>Dose aim</b> : increase -3.5 g/d PUFA, <b>1.6% E PUFA</b> Baseline PUFA unclear <b>Compliance by biomarkers</b> : neither biomarkers nor TC data reported <b>Compliance by dietary intake</b> : not reported • Energy intake: not reported • Total fat intake: not reported • SFA intake: not reported • PUFA n-3 intake: not reported • PUFA n-6 intake: not reported • Trans fat intake: not reported • Trans fat intake: not reported • MUFA intake: not reported • Trans fat intake: not reported • CHO intake: not reported • Sugars intake: not reported • Sugars intake: not reported • Sugars intake: not reported • Alcohol intake: not rep	
Outcomes	Main trial outcome: BMD Dropouts: 23% (unclear by arm) Available outcomes: weight Response to contact: not attempted	
Notes	Trial funding: Scotia Pharmaceuticals Plc, Guildford, UK Mortality reported (1 death but unclear in which arm)	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "women were randomized by staff at Scotia Pharmaceuticals Plc"
Allocation concealment (selection bias)	Unclear risk	No details

# Bassey 2000-Post (Continued)

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Double-blind stated but no further details
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Assessors were blinded for the BMD mea- surements but unclear for other outcomes
Incomplete outcome data (attrition bias) All outcomes	High risk	23% were lost to follow-up, unclear by arm and not all were accounted for
Selective reporting (reporting bias)	Unclear risk	No protocol or trial registry record
Attention bias	Low risk	No difference was noted for intervention/ control groups
Compliance	Unclear risk	Neither biomarkers nor TC data reported
Other bias	Low risk	None noted

# Bassey 2000-Pre

Methods	RCT, (high PUFA GLA+DHA+EPA vs low PUFA, both with Ca), 12 months Summary risk of bias: moderate or high	
Participants	Healthy pre-menopausal women N: 19 intervention, 24 control (total randomised 64) Level of risk for CVD: low Male: 0% intervention, 0% control Mean age (SD): 34 (4.4) intervention, 35 (4.9) control Age range: 25-40 years (inclusion) Smokers: 0% intervention, 0% control Hypertension: not reported Medications taken by $\geq$ 50% of those in the control group: not reported Medications taken by 20%-49% of those in the control group: not reported Medications taken by some, but < 20% of the control group: not reported (Women on confounding drug therapy were excluded) Location: UK Ethinicty: not reported	
Interventions	Type: capsules Comparsion: evening primrose oil + fish oil vs nil Intervention 10 large capsules/d of efacal (Ca 1.0 g, evening primrose oil 4.0 g and marine fish oil 440 mg), divided in doses with meals Control: large capsules of 1 g Ca <b>Dose aim</b> : increase -3.5 g/d PUFA, 1.6% E PUFA Baseline PUFA unclear <b>Compliance by biomarkers</b> : neither biomarkers nor TC data reported	

# Bassey 2000-Pre (Continued)

	Compliance by dietary intake: not reported • Energy intake: not reported • Total fat intake: not reported • SFA intake: not reported • PUFA intake: not reported • PUFA n-3 intake: not reported • PUFA n-6 intake: not reported • Trans fat intake: not reported • MUFA intake: not reported • CHO intake: not reported • Sugars intake: not reported • Sugars intake: not reported • Alcohol intake: not reported • Alcohol intake: not reported • Compliance, other methods: assessed by counting returned capsules at each visit, re- ported compliance > 90% (median > 9 capsules/d in both treatment and control groups) Inclusion basis: no intention to increase total PUFA, planned dose ~3.5 g/d PUFA, 1. 6% E PUFA, > 10% higher than assumed 6% E from total PUFA at baseline PUFA dose: 1.6% E PUFA Length of intervention: 12 months
Outcomes	Main trial outcome: BMD Dropouts: 31% (unclear by arm) Available outcomes: weight Response to contact: not attempted
Notes	Trial funding: Scotia Pharmaceuticals Plc, Guildford, UK

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "women were randomized by staff at Scotia Pharmaceuticals Plc"
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Double-blind stated but no further details
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Assessors were blinded for the BMD mea- surements but unclear for other outcomes
Incomplete outcome data (attrition bias) All outcomes	High risk	31% were lost to follow-up, unclear by arm and not all were accounted for
Selective reporting (reporting bias)	Unclear risk	No protocol or trial registry record

# Bassey 2000-Pre (Continued)

Attention bias	Low risk	No difference was noted for intervention/ control groups	
Compliance	Unclear risk	Neither biomarkers nor TC data reported	
Other bias	Low risk	None noted	
Bates 1977			
Methods	-	RCT, parallel, 4 arms (n6 GLA+LA vs MUFA), 2 years Summary risk of bias: moderate to high	
Participants	CVD risk: low N; intervention A, C: 38 per a Mean years in trial: 2 % male: unclear (no statistical Age: unclear (no statistically s Age range: unclear Smokers: unclear Hypertension: unclear Medications taken by $\geq$ 50% Medications taken by 20%-49	N; intervention A, C: 38 per arm; control B, D: 38 per arm Mean years in trial: 2 % male: unclear (no statistically significant difference between groups) Age: unclear (no statistically significant difference between groups) Age range: unclear Smokers: unclear Hypertension: unclear Medications taken by $\geq$ 50% of those in the control group: not reported Medications taken by 20%-49% of those in the control group: not reported Medications taken by some, but < 20% of the control group: not reported Location: UK	
Interventions	Intervention aims A: increase capsules (360 mg/d GLA plus Control aims B: increase MUI (4.8 g oleic acid/d) <b>A vs B dose aim</b> : increase 0.3 Intervention aims C: increase Control aims D: increase oleic <b>C vs D dose aim</b> : increase 11 Baseline PUFA: unclear <b>Compliance by biomarkers:</b> ported <b>Compliance by dietary intal</b> • Energy intake: not report • Total fat intake: not report • SFA intake: not report • PUFA intake: not report	Type: supplement Comparison: GLA + linoleic (n6) vs oleic (MUFA) Intervention aims A: increase PUFAs with addition of 8 x 0.6 mL/d of Naudicelle oil in capsules (360 mg/d GLA plus 3.42 g/d linoleic acid plus < 1% ALA) Control aims B: increase MUFAs with addition of 8 x 0.6 mL/d of oleic acid in capsules (4.8 g oleic acid/d) <b>A vs B dose aim</b> : increase 0.34 g/d GLA, 3.78 g/d or 34 kcal or <b>1.7% E n-6</b> Intervention aims C: increase linoleic acid with addition of 11.5 g/d in a spread Control aims D: increase oleic acid with addition of 4 g/d in a spread Control aims D: increase oleic acid with addition of 4 g/d in a spread <b>C vs D dose aim</b> : increase 11.5 g/d or 104 kcal or <b>5% E n-6</b> Baseline PUFA: unclear <b>Compliance by biomarkers:</b> unclear, no serum TC reported, no tissue fatty acids re- ported <b>Compliance by dietary intake assessment:</b> unclear, not reported • Energy intake: not reported • SFA intake: not reported • PUFA intake: not reported • PUFA n-3 intake: not reported • PUFA n-6 intake: not reported	

# Bates 1977 (Continued)

	<ul> <li>MUFA intake: not reported</li> <li>CHO intake: not reported</li> <li>Sugars intake: not reported</li> <li>Protein intake: not reported</li> <li>Alcohol intake: not reported</li> <li>Compliance, other methods: not reported</li> <li>Inclusion basis: aimed to increase total PUFA intake</li> <li>PUFA dose: A vs B 1.7% E PUFA, C vs D 5% E PUFA</li> <li>Duration of intervention: 2 years</li> </ul>
Outcomes	Main trial outcome: progression or regression of multiple sclerosis Dropouts: unclear in all arms (deaths and dropouts reported together) Available outcomes: multiple sclerosis progression (deaths occurred but reported with dropouts, so numbers and arms unclear) Response to contact: yes, Professor Bates stated that data on mortality are no longer available
Notes	Trial funding: Multiple Sclerosis Society, Van den Berghs provided intervention and control spreads free

# Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomly allocated"
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Paper states "double blind", capsules of "identical appearance" and "similar spread"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Paper states "double blind" with no further details
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Deaths and dropouts combined, no reasons for dropping out provided
Selective reporting (reporting bias)	Unclear risk	No protocol or trials registry entry located
Attention bias	Low risk	Capsules and spreads provided to all par- ticipants, no suggestion of attention bias
Compliance	Unclear risk	Neither tissue PUFA biomarkers nor TC data reported

# Bates 1977 (Continued)

Other bias	Low risk	None found	
Bates 1978			
Methods	n6 LA vs MUFA using supple	RCT, parallel, 2 arms (n6 GLA+LA vs MUFA), using supplements (further 2 arms of n6 LA vs MUFA using supplementary foods not included as no outcome data), 2 years Summary risk of bias: moderate to high	
Participants	CVD risk: low N; intervention A, C: 29 per Mean years in trial: 2 % male: intervention A 34.48 37.93% Age (SD) years: intervention A D 33 (5) Age range: unclear Smokers: unclear Hypertension: unclear Medications taken by $\geq$ 50% Medications taken by 20%-49	People with acute remitting multiple sclerosis CVD risk: low N; intervention A, C: 29 per arm; control B, D: 29 per arm Mean years in trial: 2 % male: intervention A 34.48%; intervention C 17.24%; control B 34.48%; control D 37.93% Age (SD) years: intervention A 35 (9); intervention C 34 (8); control B 32 (7); control D 33 (5) Age range: unclear Smokers: unclear Hypertension: unclear Medications taken by $\geq$ 50% of those in the control group: not reported Medications taken by 20%-49% of those in the control group: not reported Medications taken by some, but < 20% of the control group: not reported Location: UK	
Interventions	Intervention aims A: 8 x Nau Control aims B: 8 x capsules/ A vs B dose aim: increase 0.3 Intervention aims C: linoleic Control aims D: oleic acid sp C vs D dose aim: increase 23 Baseline PUFA: unclear Compliance by biomarkers: "estimations of total fatty aci showed that the percentage of in those patients taking the lin Compliance by dietary intal • Energy intake: not report • Total fat intake: not report • SFA intake: not report • PUFA n-3 intake: not report • PUFA n-6 intake: not report • Trans fat intake: not report • MUFA intake: not report	Type: supplement Comparison: GLA and linoleic (n6) vs oleic (MUFA) Intervention aims A: 8 x Naudicelle capsules/d, 2.92 g/d LA plus 0.34 g/d GLA Control aims B: 8 x capsules/d (4 g/d oleic acid), 4 g/d MUFA <b>A vs B dose aim</b> : increase 0.34 g/d GLA, 3.26 g/d or 29 kcal or <b>1.5% E n-6</b> Intervention aims C: linoleic acid spread (23 g/d linoleic acid) Control aims D: oleic acid spread (16 g/d oleic acid) <b>C vs D dose aim</b> : increase 23 g/d LA or 207 kcal or <b>10.4% E n-6</b>	

# Bates 1978 (Continued)

	<ul> <li>Sugars intake: not reported</li> <li>Protein intake: not reported</li> <li>Alcohol intake: not reported</li> <li>Compliance, other methods: not reported</li> <li>Inclusion basis: aimed to increase PUFA intake, but C vs D had no outcome data so was excluded</li> <li>PUFA dose: A vs B 1.5% E PUFA, C vs D 10.4% E PUFA (assumed from omega-6 doses)</li> <li>Duration of intervention: 2 years</li> </ul>
Outcomes	Main trial outcome: progression or regression of multiple sclerosis Dropouts: A 0, B 1, C 3, D 6 Available outcomes: multiple sclerosis progression, deaths (nil in arms A, C and D) Response to contact: contact with Dr Bates
Notes	Trial funding: Multiple Sclerosis Society, Van den Berghs provided intervention and control spreads free

# Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomly allocated"
Allocation concealment (selection bias)	Unclear risk	Quote: "randomly allocated"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Paper states "double blind", capsules of "identical appearance" and "similar spread"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Paper states "double blind" with no further details
Incomplete outcome data (attrition bias) All outcomes	Low risk	Fairly well described, from 0-6 dropouts per arm over 2 years (each 29 randomised)
Selective reporting (reporting bias)	Unclear risk	No protocol or trials registry entry located
Attention bias	Low risk	Appears equivalent
Compliance	High risk	No serum TC reported. Paper reports Quote: "estimations of total fatty acids in patients before and after 12-24 months' treatment showed that the percentage of linoleic and arachidonic acids increased sig- nificantly only in those patients taking the linoleic acid spread (group C)"

# Bates 1978 (Continued)

		Only A vs B had outcomes for this review, data suggests poor compliance in this group	
Other bias	Low risk	None found	
Bates 1989			
Methods	RCT, parallel, (n3 EPA + D Summary risk of bias: mode	DHA vs MUFA), 24 months erate or high	
Participants	N: 155 intervention, 157 cc Level of risk for CVD: low Male: 34.2% intervention, Mean age (SD): 34.0 (6.6) Age range: not reported but Smokers: not reported Hypertension: not reported Medications taken by $\geq$ 50 Medications taken by 20%-	Male: 34.2% intervention, 30.6% control Mean age (SD): 34.0 (6.6) intervention, 33.7 (6.3) control Age range: not reported but 16-45 years inclusion criteria Smokers: not reported Hypertension: not reported Medications taken by $\geq$ 50% of those in the control group: not reported Medications taken by 20%-49%: not reported Medications taken by some, but < 20%: not reported Location: UK	
Interventions	Comparison: EPA + DHA Intervention: 20 x 0.5 g/d o 71 g/d EPA + 1.14 g/d DHJ and ensure plentiful omega- Control: 20 x 0.5 g/d capsul fat and ensure plentiful ome ppm dodecylgallate to mini <b>Dose aim</b> : intervention in- unclear. Control assumed to + DHA, dose 1.3% E PUFA Baseline PUFA not reported <b>Compliance by biomarker</b> 5% PUFA, control 47.6% I <b>Compliance using dietary</b> • Energy intake: not rep • Total fat intake: not rep • Total fat intake: not rep • PUFA intake: not report • PUFA n-3 intake: not • PUFA n-6 intake: not rep	Type: supplement (fish oil capsule) Comparison: EPA + DHA vs MUFA Intervention: 20 x 0.5 g/d capsules MaxEPA fish body oil (10 g/d fish oil providing 1. 71 g/d EPA + 1.14 g/d DHA + 10 IU/d vitamin E), plus all advised to reduce animal fat and ensure plentiful omega-6 fats. EPA + DHA 2.85 g/d Control: 20 x 0.5 g/d capsules olive oil (10 g/d olive oil), plus all advised to reduce animal fat and ensure plentiful omega-6 fats. All capsules contained 0.5 IU vitamin E and 100 ppm dodecylgallate to minimise peroxide formation <b>Dose aim</b> : intervention increase 2.85 g/d EPA + DHA, 1.3% E n-3, omega-6 dose unclear. Control assumed to have similar PUFA content to intervention, apart from EPA + DHA, dose 1.3% E PUFA Baseline PUFA not reported <b>Compliance by biomarkers</b> : adding serum EPA, DHA, LA and AA intervention 51. 5% PUFA, control 47.6% PUFA. TC not reported <b>Compliance using dietary assessment</b> : not reported <b>E</b> nergy intake: not reported <b>S</b> FA intake: not reported <b>9</b> PUFA intake: not reported <b>9</b> PUFA n-3 intake: not reported <b>9</b> PUFA n-6 intake: not reported <b>9</b> PUFA n-6 intake: not reported <b>9</b> Trans fat intake: not reported <b>9</b> MUFA intake: not reported	

# Bates 1989 (Continued)

	<ul> <li>Sugars intake: not reported</li> <li>Protein intake: intervention 1.07 g/kg/d (0.10), control 1.10 g/kg/d (0.07)</li> <li>Alcohol intake: not reported</li> <li>Compliance, other measures: not reported</li> <li>Inclusion basis: intended doses suggested total PUFA intake 1.3% E higher in intervention than control &gt; 10% more than assumed 6% E PUFA at baseline</li> <li>PUFA dose: 1.3% E</li> <li>Duration of intervention: 24 months (5 years mentioned but outcomes not reported)</li> </ul>
Outcomes	Main trial outcome: multiple sclerosis progress Dropouts: 10 intervention, 10 control Available outcomes: all-cause mortality, progress of multiple sclerosis, rate of multiple sclerosis relapse Response to contact: yes (no data provided)
Notes	Trial funding: Multiple Sclerosis Society of Great Britain and Northern Ireland but Marfleet Refining provided fish oil and placebo capsules

# Risk of bias

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

# Bates 1989 (Continued)

Compliance	Low risk	Adding serum EPA, DHA, LA and AA in- tervention 51.5% PUFA, control 47.6% PUFA. TC not reported	
Other bias	Low risk	Not noted	
Black 1994			
Methods	-	RCT, parallel, (low fat diet vs usual diet), 24 months Summary risk of bias: moderate or high	
Participants	N: 66 intervention, 67 contr Level of risk for CVD: low Male: 54% intervention, 679 Mean age (SD): 50.6 (9.7) in Age range: not reported Smokers: not reported Hypertension: not reported Medications taken by $\geq$ 50% Medications taken by 20%-4 Medications taken by some, b Location: USA	Male: 54% intervention, 67% control         Mean age (SD): 50.6 (9.7) intervention, 52.3 (13.2) control         Age range: not reported         Smokers: not reported         Hypertension: not reported         Medications taken by ≥ 50% of those in the control group: not reported         Medications taken by 20%-49% of those in the control group: not reported         Medications taken by some, but < 20% of the control group: not reported	
Interventions	Intervention: aims total fat 2 classes plus monthly follow-u lowing individual approach clinic examination by dermat Control: aims usual diet; met tion by dermatologist <b>Dose aim</b> : reduce total fat to 2 CHO (fat reduction included Baseline PUFA 8% E <b>Compliance by biomarkers:</b> <b>Compliance by dietary inta</b> food records verified by a die e Energy intake, kcal/d: co e Total fat intake, % E: co 17.10, 95% CI -18.88 to -15 e SFA intake, % E: con 95% CI -6.90 to -5.50) signi e PUFA intake, % E: con	Type: dietary advice Comparison: reduced fat (lower omega-6 and total PUFA) vs usual diet Intervention: aims total fat 20% E, protein 15% E, CHO 65% E; methods 8 x weekly classes plus monthly follow-up sessions, with behavioural techniques being taught fol- lowing individual approach (not clear if in a group or individual). 4-month intervals clinic examination by dermatologist. Intervention delivered face to face by a dietitian Control: aims usual diet; methods no dietary change, 4-month intervals clinic examina- tion by dermatologist <b>Dose aim</b> : reduce total fat to 20% E, 15% E protein, 65% E CHO, particularly complex CHO (fat reduction included reducing omega-6 and total PUFA, no aim provided)	

# Black 1994 (Continued)

	<ul> <li>PUFA n-6 intake: LA, Control 16.9 (SD 5.6) g, intervention 8.5 (SD 3.3) g</li> <li>Trans fat intake: not reported</li> <li>MUFA intake, % E: control 14.4 (SD 1.7), intervention 7.6 (SD 2.2), (MD -6.</li> <li>80, 95% CI -7.52 to -6.08) significant reduction</li> <li>CHO intake, % E: control 44.6 (SD 6.9), intervention 60.3 (SD 6.3), (MD 15.</li> <li>70, 95% CI 13.29 to 18.11) significant increase</li> <li>Sugars intake: not reported</li> <li>Protein intake, % E: control 15.7 (SD 2.4), intervention 17.7 (SD 2.2), (MD 2.</li> <li>00, 95% CI 1.16 to 2.84) significant increase</li> <li>Alcohol intake, % E: control 3.2 (SD 3.9), intervention 3.2 (SD 3.4)</li> <li>Inclusion basis: dietary intake data suggested total PUFA intake 3.3% E higher in control than intervention</li> <li>PUFA dose: -3.3% E</li> <li>Duration of intervention: 24 months (mean 1.9 years in trial)</li> </ul>
Outcomes	Main trial outcome: incidence of actinic keratosis and non-melanoma skin cancer Dropouts: unclear intervention, unclear control Available outcomes: deaths, CVD deaths, cancer deaths (none), (weight data provided but without variance) Response to contact: Prof Black provided data on mortality
Notes	Trial funding: National Cancer Institute <b>NOTE</b> : for this trial the higher PUFA arm is the control, and lower PUFA arm is the intervention

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"list of randomly generated numbers"
Allocation concealment (selection bias)	Unclear risk	Randomisation method not clearly de- scribed
Blinding of participants and personnel (performance bias) All outcomes	High risk	Dietary advice provided, so participants not blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"examined by dermatologists unaware of their treatment assignments". Deaths (all-cause and CVD) not considered rele- vant to the intervention
Incomplete outcome data (attrition bias) All outcomes	Low risk	For mortality. Unclear for other outcomes
Selective reporting (reporting bias)	Unclear risk	No protocol or trials registry entry found

# Black 1994 (Continued)

Attention bias	High risk	Weekly classes and monthly follow-up in intervention group, 4-monthly check-ups only in control	
Compliance	Unclear risk	Neither tissue PUFA biomarkers nor TC data reported	
Other bias	Low risk	None noted	
Brox 2001			
Methods	oil vs nil), 14 months	RCT, parallel, 3 arms (n3 EPA + DHA from cod liver oil vs n3 EPA + DHA from seal oil vs nil), 14 months Summary risk of bias: moderate or high	
Participants	N: 40 seal oil (SO), 40 cod live Level of risk for CVD: moderat Male: 53% seal oil, 50% cod liv Mean age, SD: 53.2 seal oil, 55 Age range: 43-66 Smokers: unclear Hypertension: unclear Medications taken by $\geq$ 50% o Medications taken by 20%-499	Smokers: unclear Hypertension: unclear Medications taken by $\geq$ 50% of those in the control group: none allowed Medications taken by 20%-49% of those in the control group: not reported Medications taken by some, but < 20% of the control group: not reported Location: Norway	
Interventions	Intervention: intervention: seal n-3 3.9 g/d, total PUFA 4.2 g/d Cod liver oil, 15 mL/d (3.3 g, PUFA 4.35 g/d): EPA + DHA Control: nil, no supplement <b>PUFA dose seal oil aim</b> : (inter <b>E PUFA</b> <b>PUFA dose cod liver oil aim</b> : <b>2.0% E PUFA</b> Baseline PUFA unclear <b>Compliance by biomarkers</b> : se 2.4 (seal oil), 2.1 (cod liver oil) was 10.3 mmol/L seal oil, 9.9 reported in intervention arms b	Type: supplement (oil) Comparison: EPA + DHA vs nil Intervention: intervention: seal oil, 15 mL/d (2.6 g, 1.1 g/d EPA + 1.5 g/d DHA) (total n-3 3.9 g/d, total PUFA 4.2 g/d): EPA + DHA 2.6 g/d Cod liver oil, 15 mL/d (3.3 g, 1.5 g/d EPA + 1.8 g/d DHA) (total n-3 4.1 g/d, total PUFA 4.35 g/d): EPA + DHA 3.3 g/d Control: nil, no supplement <b>PUFA dose seal oil aim</b> : (intended) increase 2.6 g/d EPA + DHA, <b>1.2% E n-3, 1.9%</b> <b>E PUFA</b> <b>PUFA dose cod liver oil aim</b> : (intended) increase 3.3 g/d EPA + DHA, <b>1.5% E n-3,</b> <b>2.0% E PUFA</b> Baseline PUFA unclear <b>Compliance by biomarkers</b> : serum omega-3 fatty acids, rose from around 1 mmol/L to 2.4 (seal oil), 2.1 (cod liver oil) and 1.2 mmol/L (control). Latest total PUFA in serum was 10.3 mmol/L seal oil, 9.9 mmol/L cod liver oil, 7.3 mmol/L control. Serum TC reported in intervention arms but not control, fell from 8.2 mmol/L at baseline to 7.8 mmol/L at 14 months in seal oil, 8.3 to 8.0 in cod liver oil (further data provided by trial authors)	

	<ul> <li>Energy intake: not reported</li> <li>Total fat intake: not reported</li> <li>SFA intake: not reported</li> <li>PUFA intake: not reported</li> <li>PUFA n-3 intake: not reported</li> <li>PUFA n-6 intake: not reported</li> <li>Trans fat intake: not reported</li> <li>MUFA intake: not reported</li> <li>CHO intake: not reported</li> <li>Sugars intake: not reported</li> <li>Protein intake: not reported</li> <li>Alcohol intake: not reported</li> <li>Compliance, other measures: no other data</li> <li>Inclusion basis: intended dose appeared to be 1.9% or 2.0% increase in intervention arms compared to control, &gt; 10% greater intake than the assumed 6% E from PUFA at baseline. Supported by serum fatty acid composition being higher in both intervention arms at 14 months than the control arm</li> </ul>
	Length of intervention: 14 months
Outcomes	Main trial outcome: serum lipids Dropouts: 8 seal oil, 2 cod liver oil, 1 control Available outcomes: total and CV deaths, MI, combined CV events, TC, TG and HDL, adverse events (no stroke or SCD occurred, weight reported but too different at baseline and only reported to 6 months, data also provided by trial authors on apolipoproteins A1 and B, and Lp(a), but not used) Response to contact: yes (trial author provided methodological details and outcome data)
Notes	Data of 2 intervention groups combined for dichotomous outcomes and cod liver oil vs control data used for continuous outcomes Trial funding: the trial was supported by the program Medical Research in Finnmark County, University of Tromsø

# Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	J Brox stated (personal communication, January 2017) Quote: "The randomisation of the 120 par- ticipants was done by first generating 3 groups (seal oil, cod liver oil, control), then giving each participant a number (1-120) , putting all the numbers into the same hat and blindly drawing one number at the time from the hat. The first 40 numbers (1- 40) were allocated to the seal oil group, the next 40 numbers (41-80) to the cod liver oil group and the rest (81-120) were allo-

# Brox 2001 (Continued)

		cated to the control group."
Allocation concealment (selection bias)	Low risk	J Brox stated (personal communication, January 2017) Quote: "The researcher/clinician who in- vited the participants had no knowledge of to which group the participants would be allocated"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "controls were aware - not given a supplement"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	J Brox stated (personal communication, 2003) Quote: "All the persons involved in the drawing & analysing of blood were unaware of treatment. The technicians analysing the blood did not have any per- sonal contact with the participants except K. Olaussen who did the FA analysis she only had access to the sample numbers not names and code. The participants did not know their number" [says elsewhere that K Olaussen did not know allocations]. "The only assessor was J Brox who did not have any personal contact with the participants, had nothing to do with the randomising or analysing process, or the collecting of re- sults."
Incomplete outcome data (attrition bias) All outcomes	High risk	Seal oil group 10 dropouts, cod liver oil 3 dropouts, control group 3 dropouts. So substantial differences in rates of dropouts between the groups
Selective reporting (reporting bias)	Unclear risk	No trial protocol or trials register entry was found.
Attention bias	Low risk	No suggestion of differential attention
Compliance	Low risk	Latest total PUFA in serum was 10.3 mmol/L seal oil, 9.9 mmol/L cod liver oil, 7.3 mmol/L control. Serum TC reported in intervention arms but not control
Other bias	Low risk	No further bias noted

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Methods	Diet And Reinfarction Trial (DART) RCT, 2 x 2 x 2 factorial (n6 LA vs mixed fats), also increased fish and increased fibre arms, 2 years Summary risk of bias: moderate to high
Participants	Men recovering from an MI CVD risk: high N: intervention: randomised 1018, analysed unclear; control: randomised 1015, analysed unclear Mean years in trial: control 1.9, randomised 1.9 % male: 100% Age: mean control 56.8, intervention 56.4 years Age range: all < 70 years Smokers: control 62.7%, intervention 61.2% Hypertension: intervention 24%, control 23.3% Medications taken by $\geq$ 50% of those in the control group: not reported Medications taken by 20%-49% of those in the control group: beta-blockers, other anti- hypertensives, anti-anginals Medications taken by some, but < 20% of the control group: anti-coagulant, aspirin, other anti-platelet, digoxin, other cardiac drugs Location: UK Ethenicty: not reported
Interventions	Type: dietary advice Comparison: polyunsaturated oil and margarines (n6) vs usual dietary fats (SFA) Intervention aims: reduce fat intake to 30% E, increase polyunsaturated to saturated ratio (P/S) to 1.0 (using polyunsaturated oils and margarines), weight-reducing advice if BMI > 30 (dietitians provided the participants and their wives with initial individual advice and a diet information sheet, participants were revisited for further advice, recipes, encouragement at 1, 3, 6, 9, 12, 15, 18 and 21 months) Control aims: no dietary advice on fat, weight-reducing advice if BMI > 30 (dietitians provided 'sensible eating' advice without specific information on fats) <b>Dose aim</b> : unclear Baseline n-6: unclear, but control PUFA intake 6.8% E <b>Compliance by biomarkers:</b> good, serum TC significantly reduced in intervention compared to control (-0.26 mmol/L, 95% CI -0.37 to -0.15) <b>Compliance by dietary intake:</b> assessed using a 7-day weighted food diary, of a 25% random subsample • Energy intake, MJ/d: intervention 7.3 (SD 1.8), control 7.7 (SD 1.9) • Total fat intake, % E: intervention 31 (SD 7), control 35 (SD 6) • SFA intake: intervention 11% E (SD 3), control 15% E (SD 3), dose -4% E • PUFA intake: intervention 9.4% E, control 6.6% E, dose +2.8% E (most of which omega-6) • PUFA n-3 intake: not reported • PUFA n-6 intake: not reported • PUFA n-6 intake: not reported • PUFA n-6 intake: not reported • Trans fat intake: not reported • MUFA intake: not reported

# **DART fat 1989** (Continued)

	<ul> <li>CHO intake: intervention 46% E (SD 7), control 44% E (SD 6)</li> <li>Sugars intake: not reported</li> <li>Protein intake: % E: intervention 18 (SD 4), control 17 (SD 4)</li> <li>Alcohol intake: intervention 5% E (SD 6), control 4% E (SD 6)</li> <li>Compliance, other measures: no other data</li> <li>Inclusion basis: intended to increase PUFA/SFA ratio, as well as reduce total fat. TC was lower in intervention than control, and intake data suggest PUFA intake higher by 2.8% E in intervention than control, &gt; 10% greater than baseline of 6.8% E</li> <li>PUFA dose: 2.8% E</li> <li>Duration of intervention: 2 years</li> </ul>
Outcomes	Main trial outcomes: mortality, reinfarction Dropouts: all followed for events regardless of compliance (ITT) Available outcomes: CV events (CV deaths plus non-fatal MI), cancer deaths, total MI, non-fatal MI, TC, HDL Response to contact: yes, Professor Burr provided additional data and information on methodology
Notes	Note: this was a 2 x 2 x 2 factorial trial, and so some in each group were randomised to increased fatty fish and/or increased cereal fibre Trial funding: Welsh Scheme for Development of Health and Social Research, Welsh Heart Research Foundation, Flora Project (commercial), Health Promotion Research Trust

# Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised using sealed envelopes
Allocation concealment (selection bias)	Unclear risk	Unclear if envelopes were opaque
Blinding of participants and personnel (performance bias) All outcomes	High risk	Very difficult to blind trials where par- ticipants need to make their own dietary changes
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "outcome assessors were not aware of study allocation" (Prof Burr, personal communication) Method of blinding not stated
Incomplete outcome data (attrition bias) All outcomes	Low risk	GPs contacted for information on mortal- ity and morbidity when participants did not attend, data collected from mortality register
Selective reporting (reporting bias)	Unclear risk	No protocol or trials registry entry located

# **DART fat 1989** (Continued)

Attention bias	High risk	Those given dietary advice almost certainly given more time and attention than those in the control group (with no dietary advice)	
Compliance	Low risk	TC significantly reduced in intervention compared to control (-0.26 mmol/L, 95% CI -0.37 to -0.15)	
Other bias	Low risk	None found	
DIPP-Tokudome 2015			
Methods	-	nts Polypectomized for tumours of the colorectum (DIPP) A + DHA + ALA vs nil), 24 months ate or high	
Participants	N: 104 intervention, 101 cont Level of risk for CVD: low Male: 73.1% intervention, 74 Mean age (SD): 58.3 (9.5) int Age range: 35-75 Smokers: 65.4% intervention, Hypertension: not reported Medications taken by $\geq$ 50% Medications taken by 20%-49	Male: 73.1% intervention, 74.3% control Mean age (SD): 58.3 (9.5) intervention, 59.7 (8.9) control Age range: 35-75 Smokers: 65.4% intervention, 61.4% control Hypertension: not reported Medications taken by $\geq$ 50% of those in the control group: supplements Medications taken by 20%-49% of those in the control group: none Medications taken by some, but < 20% of the control group: oral contraceptive pills Location: Japan	
Interventions	Comparison: n3 EPA + DHA Intervention: advice to reduct increase intake of n-3 PUFAs f perilla oil rich in ALA, and ta EPA and 360 mg/day of DHA Control: advice to decrease im <b>Dose aim</b> : increase 0.46 g/d I perilla, unclear <b>n3, unclear PU</b> Baseline PUFA: unclear but co <b>Compliance by biomarkers:</b> in the membranes of red blooc higher total PUFA intakes in i in intervention group, 4.59 mr (5.52 mmol/L, SD 0.9) than of <b>Compliance by dietary intak</b> tionnaire	Type: advice plus supplement (fish oil capsules) Comparison: n3 EPA + DHA + ALA vs nil Intervention: advice to reduce total fat intake, decrease consumption of n-6 PUFAs, increase intake of n-3 PUFAs from fish/marine foods, increase intake of n-3 PUFAs from perilla oil rich in ALA, and take 8 capsules of fish oil/day (equivalent to 96 mg/day of EPA and 360 mg/day of DHA) Control: advice to decrease intake of fats/oils as a whole <b>Dose aim</b> : increase 0.46 g/d EPA + DHA plus EPA + DHA from fish plus ALA from perilla, unclearn3, unclear PUFA Baseline PUFA: unclear but control 6.3% E PUFA <b>Compliance by biomarkers:</b> plasma fatty acid concentrations, fatty acid compositions in the membranes of red blood cells and the sigmoid colon. Plasma fatty acids suggested higher total PUFA intakes in intervention group (at 24 months 4.91 mmol/L, SD 1.23 in intervention group, 4.59 mmol/L, SD 0.76 in control). But TC higher in intervention (5.52 mmol/L, SD 0.9) than control (5.40 mmol/L, SD 0.79) at 24 months <b>Compliance by dietary intake:</b> assessed using semi-quantitative food frequency ques- tionnaire • Energy intake, kcal/d: intervention 2268 (SD 535), control 2131 (SD 563)	

# **DIPP-Tokudome 2015** (Continued)

	<ul> <li>Total fat intake, g/1000 kcal: intervention 28.4 (SD 5.1), control 28.07 (SD 6.27)</li> <li>SFA intake, g/1000 kcal: intervention 7.02 (SD 1.74), control 7.27 (SD 2.03)</li> <li>PUFA intake, % E: intervention 7.4, control 6.3</li> <li>PUFA n-3 intake, g/1000 kcal: intervention 3.24 (SD 1.15), control 1.49 (SD 0. 39)</li> <li>PUFA n-6 intake, g/1000 kcal: intervention 4.38 (SD 1.01), control 4.90 (SD 1. 46)</li> <li>Trans fat intake: not reported</li> <li>MUFA intake, g/1000 kcal: intervention 9.07 (SD 2.05), control 10.09 (SD 2.67)</li> <li>CHO intake, g/1000 kcal: intervention 129.5 (SD 15.8), control 133.96 (SD 17. 98)</li> <li>Sugars intake: not reported</li> <li>Protein intake, g/1000 kcal: intervention 39.0 (SD 5.6), control 36.6 (SD 5.72)</li> <li>Alcohol intake: not reported</li> <li><b>Compliance, other measures:</b> none</li> <li>Inclusion basis: no intention to increase total PUFA. Intention was to increase omega-3 but dose unclear. Total PUFA intakes were higher in intervention than control by 1.</li> </ul>
	1%E, > 10% more than control <b>PUFA dose:</b> 1.1% E Length of intervention: 24 months
Outcomes	Main trial outcome: number and size of colorectal tumours Dropouts: 3 intervention, 5 control Available outcomes: all-cause mortality, dietary intake, plasma fatty acids, lipids, side effects, glucose Response to contact: yes (methodological details provided)
Notes	Trial funding: all were either government or charity grants.

# Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomly allocated using random digit number for allocation of participants
Allocation concealment (selection bias)	Low risk	Trial author confirmed "Allocation infor- mation was blinded to clinicians and re- searchers" but no methodology provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	From the 2015 paper, "The attending physicians as well as the participants were blinded to the assignment information". However in the discussion section they say "complete participant blinding could not have been achieved because free-living par- ticipants might have exchanged informa- tion on their dietary intervention, say in the hospital waiting room"

# **DIPP-Tokudome 2015** (Continued)

		Trial author confirmed blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "physicians, including colono- scopists, a scientist who conducted blood and specimen analyses, and pathologists were blinded"
Incomplete outcome data (attrition bias) All outcomes	Low risk	All those randomised were accounted for.
Selective reporting (reporting bias)	High risk	The researchers chose not to report data on the number, size and pathological type of the colorectal tumours as they said they would in the trials register. They reported more outcomes in the paper than initially stated. UMIN000000461 Registered 03 August 2006, recruitment completed 01 March 2007
Attention bias	Low risk	Participants were given equal follow-up.
Compliance	Unclear risk	Plasma fatty acids suggested higher total PUFA intakes in intervention group (at 24 months 4.91 mmol/L, SD 1.23 in inter- vention group, 4.59 mmol/L, SD 0.76 in control). But TC higher in intervention (5. 52 mmol/L, SD 0.9) than control (5.40 mmol/L, SD 0.79) at 24 months
Other bias	Low risk	None noted
Dodin 2005		
Methods	RCT, parallel, (n3 ALA vs n6 LA), 12 m Summary risk of bias: moderate or high	onths
Participants	Healthy menopausal women N: 101 intervention, 98 control (analysed, intervention: 85 control: 94) Level of risk for CVD: low Male: 0% intervention, 0% control Mean age (SD): 54.0 (4.0) intervention, 55.4 (4.5) control Age range: 49-65 Smokers: 8% intervention, 6% control Hypertension: not reported Medications taken by $\geq$ 50% of those in the control group: not reported Medications taken by 20%-49% of those in the control group: not reported Medications taken by some, but < 20% of the control group: not reported Location: Canada Ethnicity: French Canadian	

Interventions	Type: food supplement (flaxsed) Comparison: more ALA vs less ALA Intervention: 40 g/d flaxseed incorporated into diets (providing 21,071 g total lignans, 180 calories, 16 g lipids (57% ALA), and 11 g total dietary fibre): 9.1 g/d ALA Control: 40 g/d wheat germ incorporated into diets (providing 196 g total lignans, 144 calories, 4 g lipids (6.9% ALA), and 6 g total dietary fibre: 0.26 g/d PUFA <b>Dose aim</b> : increase 8.8 g/d PUFA, <b>4.0% E PUFA</b> Baseline PUFA 5.4% E <b>Compliance by biomarkers</b> : plasma fatty acid total PUFA (summing LA, GLA, AA, EPA, DHA, DPA, ALA) increased 3.02% from baseline to 12 months in control, in- creased 1.99% in intervention <b>Compliance by dietary intake</b> : assessed by 3-day food diary at baseline and 12 months • Energy intake, kcal/d: intervention 1878, change -36 SD 413, control baseline 2021, change -138, SD 461 • Total fat intake, change % E: intervention +1.4 (SD 6.5), control -1.4 (SD 7.7) • SFA intake, change % E: intervention -0.3 (SD 3.5), control -0.5 (SD 3.9) • PUFA n-3 intake: not reported • PUFA n-6 intake: not reported • PUFA n-6 intake: not reported • MUFA intake, change % E: intervention -0.3 (SD 3.6), control -1.4 (SD 4.2) • CHO intake, change % E: intervention -0.3 (SD 3.6), control -1.4 (SD 4.2) • CHO intake, change % E: intervention -0.3 (SD 3.6), control -1.4 (SD 4.2) • CHO intake, change % E: intervention -0.3 (SD 3.6), control -1.4 (SD 4.2) • CHO intake, change % E: intervention -0.3 (SD 3.6), control -0.7 (SD 3.1) • Alcohol intake, change % E: intervention -0.3 (SD 3.6), control -0.7 (SD 4.1) <b>Compliance, other methods</b> : first morning urine collection was performed at randomi- sation and at month 12 to measure urinary lignin levels. In addition, trial participants recorded their daily intake of seeds on diary cards and were asked to return unused bread and packages of seeds at each visit. Good compliance reported <b>Inclusion basis:</b> no intention to increase total PUFA, planned dose -4.0% E PUFA, dietary intake dose of 1. 5% E PUFA higher in intervention, > 10% higher
Outcomes	Main trial outcome: BMD Dropouts: 26 intervention, 17 control (but 13/17 had an endpoint evaluation) Available outcomes: weight, BMI, QoL, BP, lipids, glucose, adverse events, dietary intake, plasma fatty acids Response to contact: yes, trial author confirmed that no CV events or deaths occurred during the trial
Notes	Trial authors replied to tell us that there were no deaths or CV events during the trial Trial funding: not reported
Risk of bias	

# **Dodin 2005** (Continued)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The randomisation schedule was prepared by the clinical unit of the research centre us- ing computer-generated randomisation in blocks of 4-8
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants, investigators, staff, and statis- ticians were blinded to dietary assignments for the duration of the trial Quote: "a local baker prepared loaves of bread. Each week, the loaves of bread were delivered in sealed, opaque unmarked wrappers to the Department of Food and Nutrition Sciences at Laval University. The seeds were ground up and vacuum-packed in the same laboratory. The Department of Food and Nutrition Sciences was responsi- ble for labelling the bags of bread and pack- ages of seeds with the subject's randomiza- tion number. Bread and packages of seeds were provided on a 3-month basis. The foods that both groups received was similar in appearance and packaging and was kept frozen until consumption to avoid essential fatty acid."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Participants, investigators, staff, and statis- ticians were blinded to dietary assignments for the duration of the trial
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT. Loss to follow-up 10%, reasons given.
Selective reporting (reporting bias)	Unclear risk	No protocol or clinical trials registry entry found
Attention bias	Low risk	All participants had same number of visits
Compliance	High risk	Plasma fatty acid total PUFA (summing LA, GLA, AA, EPA, DHA, DPA, ALA) increased 3.02% from baseline to 12 months in control, increased 1.99% in intervention
Other bias	Low risk	None noted

**Doi 2014** 

Methods	RCT, parallel, (n3 EPA vs nil, both with statins), 12 months Summary risk of bias: moderate or high	
Participants	Patients having PCI after acute MI N: 119 intervention, 119 control analysed Level of risk for CVD: high Male: 77% intervention, 76% control Mean age (SD): 70 (11) intervention, 71 (12) control Age range: unclear Smokers: 28% intervention, 32% control Hypertension: 71% intervention, 69% control Medications taken by $\geq$ 50% of those in the control group: aspirin, ticlopidine, ß- blockers, statins (as part of treatment) Medications taken by 20%-49% of those in the control group: ARB/ ACE inhibitors Medications taken by some, but < 20% of the control group: none Location: Japan Ethnicity: not reported	
Interventions	Type: supplement (EPA) Comparison: EPA vs nil Intervention: purified EPA ethyl esters (> 98%) 1.8 g/d EPA within 24 h after PCI plus statins Control: statins with no EPA Dose aim: increase 1.8 g/d EPA + DHA, <b>0.8% E n-3, 0.8 %E PUFA</b> Baseline PUFA: unclear <b>Compliance by biomarkers:</b> plasma EPA reported at 6-8 months, higher in intervention (162.8 mg/L) than control (65.5 mg/L). No further biomarker or TC data reported <b>Compliance by dietary intake:</b> not reported • Energy intake: not reported • Total fat intake: not reported • Total fat intake: not reported • SFA intake: not reported • PUFA n-3 intake: not reported • PUFA n-6 intake: not reported • PUFA n-6 intake: not reported • Trans fat intake: not reported • MUFA intake: not reported • CHO intake: not reported • Sugars intake: not reported • Sugars intake: not reported • Alcohol intake: not reported • Alcohol intake: not reported <b>Inclusion basis:</b> no intention to increase total PUFA. Intention was to increase omega- 3 by 0.8% E. Total PUFA appear to be 0.8% E higher in intervention, > 10% more than assumed 6% E baseline <b>PUFA dose:</b> 0.8% E Length of intervention: 12 months	
Outcomes	Main trial outcome: CV events Dropouts: 1 intervention, 2 control Available outcomes: mortality, stroke, MI, sudden death, CV death, revascularisation	

# **Doi 2014** (Continued)

	Response to contact: contact attempted but no response to date	
Notes	Trial funding: trial registry states "self-funded". The trial authors received honoraria from Mochida Pharmaceutical Co	

# Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A computer-generated randomisation plan, which included stratification by age and sex
Allocation concealment (selection bias)	Unclear risk	Carried out by research technician but un- clear
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label but blind endpoint
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Data on outcomes were collected from clin- ical charts. Unclear if blinded. Diagnoses were confirmed by investigator blind to treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	Only 3 dropouts, similar rates between the groups and reasons given
Selective reporting (reporting bias)	High risk	Data collection completed before trial reg- istry entry. Only 1% dropout
Attention bias	Low risk	Timing of follow-ups similar
Compliance	Unclear risk	Plasma EPA reported at 6-8 months, higher in intervention (162.8 mg/L) than control (65.5 mg/L). No further biomarker or TC data reported
Other bias	Low risk	None observed

### Dullaart 1992

Methods	RCT, parallel, 2 arms (n6 LA vs mixed fats), 2 years Summary risk of bias: moderate to high
Participants	People with type I diabetes with elevated urinary albumin CVD risk: moderate Intervention: randomised 18, analysed 16 Control: randomised 20, analysed 20

# **Dullaart 1992** (Continued)

	% male: 81% intervention, 75% control Age: mean (SD) intervention 44 (12), control 41 (14) Age range: unclear (21-65 inclusion) Smokers: intervention 50%, control 55% Hypertension: intervention 6%, control 10% Medications taken by $\geq$ 50% of those in the control group: insulin Medications taken by 20%-49% of those in the control group: not reported Medications taken by some, but < 20% of the control group: anti-hypertensives Location: Netherlands Ethnicty: not reported
Interventions	Type: dietary advice Comparison: LA (n6) vs usual diet Intervention: diet advice given at every visit throughout the 2-year period to increase linoleic acid achieving a polyunsaturated: saturated fatty acid ratio close to 1.0. Advice to replace butter or saturated margarines by polyunsaturated margarines and to restrict the intake of SFA from meat and milk products Control: to continue their usual diet. All participants were urged not to alter total fat and protein content <b>Dose:</b> aim unclear Baseline PUFA: 6.6% E PUFA <b>Compliance:</b> TC fell more in intervention (-0.45 mmol/L) than control (0.10 mmol/ L) from baseline to 2 years. Significant difference between plasma cholesteryl ester LA in intervention and control at 2 years <b>Plasma cholesteryl esters at 2 years</b> • LA mol%: intervention 62.2 (SD 4.2), control 57.4 (SD 4.9) • oleic acid mol%: intervention 7.42 (SD 2.02), control 5.5 (SD 1.4) <b>Dietary assessment using 1 week dietary recall, reported at 2 years.</b> • Energy intake, MJ/d: intervention 7.42 (SD 2.02), control 48.48 (SD 2.48) • Total fat intake, % E: intervention 37 (SD 4), control 40 (SD 7) • SFA intake, % E: intervention 13 (SD 2), control 16 (SD 3) • PUFA intake, % E: intervention 13 (SD 2), control 16 (SD 3) • PUFA intake, % E: intervention 13 (SD 2), control 10 (SD 7) • SFA intake, % E: intervention 0.96 (SD 0.16), control 0.56 (SD 0.25) • MUFA n-3 intake; M E: intervention 13 (SD 4), control 1.56 (SD 0.25) • MUFA intake, % E: intervention 13 (SD 4), control 1.56 (SD 0.25) • MUFA intake, % E: intervention 13 (SD 4), control 17 (SD 3) • Trans fat intake: not reported • CHO intake, % E: intervention 13 (SD 4), control 17 (SD 3) • Trans fat intake: not reported • Cholesterol intake, mg/d: intervention 174 (SD 49), control 245 (SD 120) <b>Compliance, other methods</b> : not reported <b>Inclusion basis:</b> aimed to increase LA rather than total PUFA intake. Intake data suggests 3.5% E PUFA dose, > 10% increase from control 9% E intake Supported by plasma cholesteryl ester LA and TC <b>PUFA dose:</b> 3.5% E PUFA

# **Dullaart 1992** (Continued)

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

# Risk of bias

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

EPIC-1 2008

Methods	EPANOVA in Crohn's disease, trial 1 (EPIC-1) RCT, parallel, 2 arms (n3 EPA + DHA vs mixed fats), 52 weeks Summary risk of bias: moderate or high
Participants	Adults with quiescent Crohn's Disease Activity Index score < 150 N: 188 intervention, 186 control Level of risk for CVD: low Male: 48.1% intervention, 41.1% control Mean age (SD): 40.5 (15.2) intervention, 38.2 (13.1) control Age range: 18-70 years Smokers: 30.6% intervention, 34.4% control Hypertension: unclear Medications taken by $\geq$ 50% of those in the control group: oral 5-ASA therapy, systemic corticosteroids - prednisolone, budesonide Medications taken by 20%-49% of those in the control group: not reported Medications taken by some, but < 20% of the control group: antibiotic therapy, topical rectal therapy, immune-modifying agents, immune modifiers/biologics Location: Canada, Europe, Israel, USA Ethnicity: not reported
Interventions	Type: supplement (capsule) Comparison: EPA + DHA vs MCT Intervention: 2 x 2 1 g gelatine capsules omega-3-free fatty acids (Epanova- 2.2 g EPA, 0.8 g DHA) Control: 4 x1 g capsules medium-chain triglycerides <b>Dose aim</b> : increase 3.0 g/d EPA + DHA, <b>1.4% E n-3, 1.4% E PUFA</b> Baseline PUFA: unclear <b>Compliance by biomarkers</b> : not reported, neither fatty acids nor TC <b>Compliance by dietary intake</b> : not reported • Energy intake, kcal/d: not reported • Total fat intake, % E: not reported • SFA intake, % E: not reported • PUFA intake, % E: not reported • PUFA n-3 intake: not reported • PUFA n-6 intake: not reported • Trans fat intake: not reported • MUFA intake, % E: not reported • MUFA intake, % E: not reported • Alcohol intake, %

# EPIC-1 2008 (Continued)

Outcomes	Main trial outcome: Crohns relapse-free time Dropouts: 80 intervention, 91 control
	Available outcomes: total deaths, non-fatal arrhythmias, cancer diagnoses, cancer deaths, adverse events
	Response to contact: yes (data provided)
Notes	Trial funding: Tillotts Pharma, trial authors had extensive financial disclosures

# Notes

Risk of bias

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

EPIC-2 2008

Methods	EPANOVA in Crohn's disease, trial 2 (EPIC-2) RCT, parallel, 2 arms (n3 EPA + DHA vs mixed fats), 58 weeks Summary risk of bias: moderate or high
Participants	Adults with a confirmed diagnosis of Crohn's disease and a Crohn's Disease Activity Index score < 150 who are responding to steroid induction therapy N: intervention, 189, control 190 (187 intervention, 188 control analysed) Level of risk for CVD: low (people with quiescent Crohn's disease) Male: 48.1% intervention, 41.1% control Mean age (SD): 38.5 (13.8) intervention, 40.0 (13.6) years control Age range: > 16 years Smokers: 25.1% intervention, 37.2% control Hypertension: unclear Medications taken by $\geq$ 50% of those in the control group: systemic corticosteroids - prednisolone, budesonide (but tapered and discontinued during the trial) Medications taken by 20%-49% of those in the control group: only reported for prior 12 months Medications taken by some, but < 20% of the control group: only reported for prior 12 months Location: Canada, Europe, Israel, USA Ethnicity: not reported
Interventions	Type: supplement (capsule) Comparison: EPA + DHA vs MCT Intervention: 2 x 2 1 g gelatine capsules omega-3-free fatty acids (Epanova) providing total dose ~2.2 g/d EPA, 0.8 g/d DHA: EPA + DHA ~3.0 g/d Control: 2 x 2 1 g capsules medium-chain triglyceride oil <b>Dose aim</b> : increase 3.0 g/d EPA + DHA, <b>1.4% E n-3</b> , <b>1.4% E PUFA</b> Baseline PUFA: unclear <b>Compliance by biomarkers:</b> not reported, neither fatty acids nor TC <b>Compliance by dietary intake</b> : not reported • Energy intake, kcal/d: not reported • Total fat intake, % E: not reported • Total fat intake, % E: not reported • PUFA intake, % E: not reported • PUFA n-3 intake: not reported • PUFA n-6 intake: not reported • Trans fat intake: not reported • MUFA intake, % E: not reported • Sugars intake: not reported • Alcohol intake, % E: not reported • PUFA. Intention was to increase 3.0 g/d EPA + DHA, <b>1.4% E n-3</b> , <b>1.4% E PUFA</b> , > 10% greater than assumed baseline of 6% E <b>PUFA dose:</b> 1.4% E

## EPIC-2 2008 (Continued)

	Length of intervention: mean 58 weeks
Outcomes	Main trial outcome: maintain Crohns symptomatic remission Dropouts: 114 intervention, 112 control Available outcomes: mortality, CV events (nil), cancer diagnoses, adverse events Response to contact: yes (data provided)
Notes	Trial funding: Tillotts Pharma, trial authors had extensive financial disclosures

# Risk of bias

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

### **EPOCH 2011**

Methods	Older People, Omega-3 and Cognitive Health (EPOCH) RCT, parallel (n3 EPA + DHA vs MUFA), 18 months Summary risk of bias: low
Participants	Healthy older adults with no cognitive impairment N: 195 intervention, 196 control (reported by trial author) Level of risk for CVD: low Male: not reported Mean age (SD): not reported Age range: not reported, but 65-90 recruited Smokers: not reported Hypertension: not reported Medications taken by $\geq$ 50% of those in the control group: not reported Medications taken by 20%-49% of those in the control group: not reported Medications taken by some, but < 20% of the control group: not reported Location: Australia Ethnicity: not reported
Interventions	Type: supplement (fish oil capsules) Comparison: high EPA + DHA vs MUFA and low EPA + DHA Intervention: 4 capsules/d (1.72 g/d DHA and 0.60 g/d EPA): EPA + DHA 2.32 g/d Control: 4 capsules/d (3.960 g/d olive oil and 40 mg/d fish oil), 0.8 g/d PUFA (assuming 20% of olive oil is PUFA) <b>Dose aim</b> : increase 2.28 g/d EPA + DHA, or 1.52 g/d PUFA (subtracting control data) , 0.68% E PUFA Baseline PUFA unclear <b>Compliance by biomarkers</b> : erythrocyte membrane n-3 LC PUFA status assessed but no useful data reported, no TC data <b>Compliance by dietary intake</b> : not reported • Energy intake: not reported • Total fat intake: not reported • SFA intake: not reported • SFA intake: not reported • PUFA n-3 intake: not reported • PUFA n-6 intake: not reported • PUFA n-6 intake: not reported • MUFA intake: not reported • MUFA intake: not reported • CHO intake: not reported • Alcohol intake: not reported • SP% (re calendars), they were contacted by a researcher who noted the reasons <b>Inclusion basis:</b> no intention to increase total PUFA, > 10% increase from assumed 6% E PUFA dose: 0.68% E Length of intervention: 18 months

Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease (Review) Copyright © 2018 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

# **EPOCH 2011** (Continued)

Outcomes	Main trial outcome: change in cognitive performance Dropouts: not reported Available outcomes: mortality (nil), MI, stroke, revascularisation, atrial fibrillation, CV events. Planned outcomes, not reported in publications, included: cognitive outcomes, functional outcomes, glucose, lipids, plasma fatty acids, BP, inflammation and oxidative stress Response to contact: yes (data provided)
Notes	Trial authors reported some events, but don't appear to be published Trial funding: EPAX donated the Omega-3 concentrate and Blackmores Pty Ltd donated the placebo and packaging of the Omega-3 concentrate. The trial was supported by the Brailsford Robertson Award 2007-2008 (University of Adelaide and CSIRO Food and Nutritional Sciences), and is funded by a National Health and Medical Research Project Grant (#578800)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Age-stratified, permuted-block randomisa- tion, with mixed block-sizes (2-8, size un- known to trial investigators), 1:1 alloca- tion. Computer-generated randomisation schedule
Allocation concealment (selection bias)	Low risk	An independent researcher prepared allo- cation to treatment.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The researchers, project staff, and partici- pants remained blinded to treatment allo- cation until the trial was completed and the database locked. No information provided on capsules' appearance, taste or smell, but fish oil added to control to make taste sim- ilar
Blinding of outcome assessment (detection bias) All outcomes	Low risk	As above
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No data for each group presented, and no attrition data presented
Selective reporting (reporting bias)	High risk	Registered at ACTRN12607000278437. Only cognitive functions reported for whole population (not by arm). No sec- ondary outcomes reported (Mini Mental State Examination; perceived health status, depressive symptoms, positive and negative

## **EPOCH 2011** (Continued)

		affect, life satisfaction, self-reported cogni- tive functioning, and functional capacity; BP; biomarkers of glucose, glycated haemo- globin, TGs, TC, HDL, LDL, homocys- teine, CRP, Malondialdehyde (MDA), and telomere length)
Attention bias	Low risk	All had the same contact and attention
Compliance	Unclear risk	Compliance assessed by erythrocyte mem- brane n-3 long-chain PUFA status but re- sults not reported, no TC or biomarker data on total PUFA
Other bias	Low risk	None noted

## FAAT - Leaf 2005

Methods	Fatty Acid Antiarrhythmia Trial - FAAT Randomisation: RCT, parallel, 2 arms, (n3 EPA + DHA vs MUFA), 12 months Summary risk of bias: moderate or high
Participants	People with implanted cardioverter defibrillators (ICDs) N: intervention 200, control 202 Level of risk for CVD: high (participants with ICDs). Male: intervention 84.5%, control 81.7% Mean age (SD): intervention 65.7 (11.6), control 65.3 (11.7) years Age range: unclear Smokers: intervention 15%, control 11.4% Hypertension: unclear Medications taken by $\geq$ 50% of those in the control group: ACEi, beta-blockers Medications taken by 20%-49%: diuretics Medications taken by some, but < 20%: Ca channel blockers, amiodarone, sotalol, type 1 antiarrhythmics Location: USA Ethnicity: intervention 95.5% white, control 96.5% white
Interventions	Type: supplement/capsule Comparison: EPA + DHA vs MUFA Intervention: 4 x 1 g/d fish oil gelatin capsules, 2.6 g EPA + DHA/d (Pronova Biocare, quantities of EPA + DHA unclear): EPA + DHA 2.6 g/d Control: 4 x 1 g/d olive oil capsules, 4 g/d (in identical gelatin capsules, < 0.06 g/d EPA + < 0.06 g/d DHA) All were advised to use olive oil rather than the common plant seed oils for cooking, dressings, and sauces <b>PUFA Dose</b> : (intended) <b>Dose aim</b> : intervention 2.6 g/d EPA + DHA, 1.2% E n3, 1.2% E PUFA, control 4 g olive oil, 20% LA, 0.8 g/d PUFA, 0.36% E PUFA. Difference 0.84% E PUFA Baseline PUFA: unclear

# FAAT - Leaf 2005 (Continued)

	<b>Compliance by biomarkers:</b> platelet phospholipid EPA + DHA higher in intervention
	group than control, no data on total PUFA or TC
	Compliance by dietary intake: not reported
	• Energy intake: not reported
	• Total fat intake: not reported
	• SFA intake: not reported
	• PUFA intake: not reported
	• PUFA n-3 intake: not reported
	• PUFA n-6 intake: not reported
	• Trans fat intake: not reported
	MUFA intake: not reported
	CHO intake: not reported
	Sugars intake: not reported
	Protein intake: not reported
	Alcohol intake: not reported
	Compliance, other measures: pill counts suggested greater omega-3 intake in interven-
	tion participants. 35% were non-compliers (36.5% intervention, 34.2% control)
	Inclusion basis: no intention to increase total PUFA. Intention was to increase omega-
	3, difference between arms was 0.84% E PUFA, > 10% more than control
	<b>PUFA dose:</b> 0.84% E
	Duration of intervention: 12 months
Outcomes	Main trial outcome: fatal VF/VT
	Dropouts: intervention 13 deaths, unclear number of dropouts; control 12 deaths, drop-
	outs unclear
	Available outcomes: deaths, CV deaths, deaths from heart failure, fatal arrhythmias, MI,
	angina
	Response to contact: yes (data provided)
Notes	Trial funding: the trial was supported in part by a grant from the NHLBI, NIH
	(HL62154)

#### Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation tables for each collaborating site, stratified by site
Allocation concealment (selection bias)	Low risk	Trial author confirmed allocation was con- cealed from investigators
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Trial referred to as "double blind" and gelatin capsules (verum and placebo) were stated as being of identical appearance but no discussion of taste or smell. Trial au- thor confirmed that investigators and par- ticipants were blinded

## FAAT - Leaf 2005 (Continued)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	VT and VF events were assessed blinded to allocation
Incomplete outcome data (attrition bias) All outcomes	High risk	Large numbers dropped out so some deaths etc. may have been missed, 35% discontin- ued early due to non-compliance but were assessed at trial end, data censored for some participants
Selective reporting (reporting bias)	High risk	Trials registry data received September 2005, paper published November 2005
Attention bias	Low risk	Time and attention appeared similar be- tween the 2 arms
Compliance	High risk	Platelet phospholipid EPA + DHA higher in intervention group than control, no data on total PUFA or TC
Other bias	Low risk	None noted
Methods	Gamma Linolenic Acid Multicentre Trial (GLAMT) RCT, 2-arm, parallel (n6 GLA vs non-fat), 1 year Summary risk of bias: moderate to high	
GLAMT 1993 Methods Participants	Summary risk of bias: moderate to high People with mild diabetic neuropathy CVD risk: moderate Control: randomised 57, analysed 48 (with ≥ 1 evaluation) Intervention: randomised 54, analysed 52 Mean years in trial: control 1.0, randomised 1.0 % male: intervention 67%, control 79%, Age, mean (SD) years: intervention 53.3 (11.1), control 52.9 (11.4) Age range: unclear	
	Smokers: unclear Hypertension: unclear Medications taken by ≥ 50% of those in the control group: insulin Medications taken by 20%-49% of those in the control group: not reported Medications taken by some, but < 20% of the control group: not reported Location: UK and Finland Ethenicty: not reported	
Interventions	Type: supplement Comparison: GLA (n-6) vs placebo (paraffin) Control aims: 12 capsules/d paraffin Intervention aims: 12 capsules/d evening primrose oil (EP4, equivalent to Epogam): 0.	

#### GLAMT 1993 (Continued)

(performance bias)

All outcomes

Blinding of outcome assessment (detection Unclear risk Unclear, though trial described as doublebias) blind no methods or statement of blinding of outcome assessors was mentioned

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Quote: "Active and placebo capsules were

indistinguishable in taste or appearance"

## GLAMT 1993 (Continued)

Incomplete outcome data (attrition bias) All outcomes	High risk	Reasons for withdrawal usually given, but high and dissimilar
Selective reporting (reporting bias)	Unclear risk	No clear protocol or trials registry entry found
Attention bias	Low risk	Appeared similar
Compliance	Unclear risk	Neither tissue PUFA biomarkers nor TC data reported
Other bias	Low risk	None identified

## HARP- Sacks 1995

Methods	Harvard Atherosclerosis Reversibility Project (HARP) RCT, (n3 EPA + DHA vs MUFA), 24 months Summary risk of bias: moderate or high
Participants	People with coronary heart disease N: 41 intervention, 39 control (99.9% follow-up at trial end) Level of risk for CVD: high Male: 93.5% intervention, 92.9 % control Mean age (SD): 62 (7) intervention, 62 (7) years control Age range: 30-75 Smokers: 0% (exclusion criteria) Hypertension: 48% intervention, 36% control Medications taken by $\geq$ 50% of those in the control group: beta blockers, antiplatelet agents Medications taken by 20%-49% of those in the control group: Ca channel blockers, nitrates Medications taken by some, but < 20% of the control group: ACE inhibitors, oral hypoglycaemic drugs Location: USA Ethenicity: not reported
Interventions	Type: supplement (capsule) Comparison: n3 vs MUFA Intervention: 12 fish oil capsules/d (Promega, Parke-Davis) in divided doses, preferably after meals. Each fish oil capsule contained 500 mg of n-3 PUFAs composed of EPA (240 mg), DHA (160 mg) and other (100 mg) (mainly DPA) providing total daily dose of 6 g/d of n-3 fatty acids. Control: olive oil capsules identical in appearance to the fish oil capsules, 6 g/d olive oil, 1.2 g/d LA <b>Dose aim</b> : increase 4.8 g/d PUFA, <b>2.2% E PUFA</b> Baseline PUFA: unclear <b>Compliance by biomarkers:</b> adipose fatty acids (sum of LCn3 fats, AA & LA) were 21. 2% in intervention group, 20.4% in control group. TC was slightly higher in intervention

# HARP- Sacks 1995 (Continued)

	<ul> <li>(5.02 mmol/L, SD 0.96) than control (4.99 mmol/L, SD 0.62) at 28 months</li> <li>Compliance by dietary intake: not reported</li> <li>Energy intake: not reported</li> <li>Total fat intake: not reported</li> <li>PUFA intake: not reported</li> <li>PUFA n-3 intake: not reported</li> <li>PUFA n-6 intake: not reported</li> <li>Trans fat intake: not reported</li> <li>MUFA intake: not reported</li> <li>CHO intake: not reported</li> <li>Sugars intake: not reported</li> <li>Protein intake: not reported</li> <li>Alcohol intake: not reported</li> <li>Alcohol intake: not reported</li> <li>Muses intake: not reported</li> <li>Sugars intake: not reported</li> <li>Nure reported</li> <li>Sugars intake: not reported</li> <li>Sugars intake: not reported</li> <li>Alcohol intake: not reported</li> <li>Alcohol intake: not reported</li> <li>Muses intake: not reported</li> <li>Alcohol intake: not reported</li> <li>Alcohol intake: not reported</li> <li>Muses intake: not reported</li> <li>Alcohol intake: not reported</li> <li>Alcohol intake: not reported</li> <li>Alcohol intake: not reported</li> <li>Muses intake: not reported</li> <li>Alcohol intake: not reported</li> <li>Muses intake: not reported</li> <li>Alcohol intake: not reported</li> <li>Muses intervention to increase total PUFA. Intention was to increase omega-3, difference between arms was 4.8 g/d PUFA, 2.2% E PUFA, &gt; 10% increase from assumed baseline of 6% E PUFA</li> <li>PUFA dose: 2.2% E PUFA</li> <li>Duration of intervention: average 28 months</li> </ul>
Outcomes	Main trial outcome: regression of coronary artery lesions Dropouts: 10 intervention, 11 control Available outcomes: total and CV deaths, fatal and non-fatal MI, stroke, angioplasty or coronary artery bypass graft, unstable angina, CHD, cancer diagnosis, combined CV events, side effects Response to contact: yes
Notes	Trial funding: National Heart, Lung, and Blood Institute (NHLBI), National Institutes of Health, Bethesda, Maryland, Warner Lambert-Parke Davis (pharmaceutical company) , East Hanover, New Jersey; and by an Established Investigator Award to Dr. Sacks from the American Heart Association, Dallas, Texas

# Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"randomization" stratified by clinical man- agement regime and TC/HDL ratio
Allocation concealment (selection bias)	Unclear risk	No further details
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "patients and personnel responsible for lab measurements, cardiac catheteriza- tion, and analysis of angiography films were blinded to the treatment assignment" Although capsules were identical in appear- ance, no information on their taste and

#### HARP- Sacks 1995 (Continued)

		smell
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "patients and personnel responsible for lab measurements, cardiac catheteriza- tion, and analysis of angiography films were blinded to the treatment assignment"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low attrition rate over 28 months and all reasons are well-documented
Selective reporting (reporting bias)	High risk	Trial registered retrospectively after publi- cation
Attention bias	Low risk	Nothing in description implies the arms were treated differently
Compliance	Unclear risk	Adipose fatty acids (sum of LCn3 fats, AA & LA) were 21.2% in intervention group, 20.4% in control group. TC was slightly higher in intervention (5.02 mmol/L, SD 0.96) than control (4.99 mmol/L, SD 0. 62) at 28 months
Other bias	Low risk	None noted

# HERO-Tapsell 2009

Methods	Healthy Eating to Reduce Overweight in people with type 2 diabetes (HERO) RCT, parallel, (n3 ALA vs low n3), 12 months Summary risk of bias: moderate or high
Participants	Overweight adults with non-insulin treated diabetes N: 26 intervention, 24 control (analysed, int: 18 cont: 17) Level of risk for CVD: moderate Male %: not reported Mean age (SD): 54 (8.7), not reported by arm Age range: 33-70 Smokers: not reported Hypertension: not reported Medications taken by $\geq$ 50% of those in the control group: lipid-lowering drugs, oral hypoglycemics Medications taken by 20%-49% of those in the control group: not reported Medications taken by some, but < 20% of the control group: not reported Location: Australia Ethnicity: not reported
Interventions	Type: food supplement (walnuts) Comparison: ALA vs nil Intervention: 30 g/d snack portions of walnuts, aim 30% E fat (10% SFA, 10% MUFA,

## HERO-Tapsell 2009 (Continued)

## HERO-Tapsell 2009 (Continued)

Random sequence generation (selection bias)	Low risk	Randomisation was conducted using a computerised random-number generator by a researcher independent of the subject interface
Allocation concealment (selection bias)	Unclear risk	No further details
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "Subjects, but not dietitians, were blinded to the type of overall diet (a prepackaged 30 g snack portion of walnuts was given to the walnut group unbeknown to the controls)" However, there was no placebo supplement so blinding not truly feasible
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Paper states "code was concealed from the researchers collecting data, as well as from subjects." However as participants could not be blinded outcome assessors may not have been (problem for measures of adiposity, not for biochemical measures)
Incomplete outcome data (attrition bias) All outcomes	High risk	High dropout rate, 35 of 50 analysed (30% attrition rate)
Selective reporting (reporting bias)	Unclear risk	Trial was registered but post-analysis
Attention bias	Low risk	Both groups appear to have had same level of attention
Compliance	High risk	Omega-3 fats measured by erythrocyte membrane fatty acid levels which were sim- ilar in both groups, no other PUFAs re- ported. TC fell by 0.3 mmol/L from base- line to 12 months in control, and fell by 0. 1 mmol/L in the intervention
Other bias	Low risk	None noted

## Houtsmuller 1979

Methods	RCT, parallel, (increase LA vs usual diet), 72 months maximum Summary risk of bias: moderate or high
Participants	Adults with newly diagnosed diabetes N: 51 intervention, 51 control (analysed unclear intervention, unclear control) Level of risk for CVD: moderate

## Houtsmuller 1979 (Continued)

	Male: 56% overall (not stated by intervention arm) Mean age (SD): not reported intervention, not reported control Age range: not reported Smokers: not reported Hypertension: not reported Medications taken by $\geq$ 50% of those in the control group: not reported Medications taken by 20%-49% of those in the control group: not reported Medications taken by some, but < 20% of the control group: statins (probably) Location: Netherlands
	Ethenicity: not reported
Interventions	Type: dietary advice Comparison: omega-6 vs SFA and CHO Intervention: aims total fat 40% E, 1/3 LA, CHO 45% E, protein 15% E; methods unclear, surveyed by dietitian. Intervention appears to have been delivered by dietitian but no details on format or frequency Control: aims SFA 35% E, CHO 50% E, protein 15% E; methods unclear, surveyed by dietitian <b>Dose aims:</b> increase -9% E LA (aims imply no LA in control, but paper states LA was 4 x higher in intervention than control, est 3% E control, 12% E int, so increase of -9% E) Baseline PUFA: unclear <b>Compliance by biomarkers:</b> good, serum TC significantly reduced in intervention compared to control (-0.47 mmol/L, 95% CI -0.76 to -0.18), no significant differences in men, but significant improvements in women from 3 years <b>Compliance by dietary intake: unclear</b> (not reported) • Energy intake: not reported • Total fat intake: not reported • SFA intake: not reported • PUFA n-3 intake: not reported • PUFA n-3 intake: not reported • PUFA n-6 intake: not reported • Trans fat intake: not reported • PUFA n-6 intake: not reported • MUFA intake: not reported • MUFA intake: not reported • Sugars intake: not reported • Sugars intake: not reported • Alcohol intake: not reported • Alcohol intake: not reported • Alcohol intake: not reported <b>Inclusion basis:</b> aimed to increase LA, not total PUFA. Appears to have increased LA by -9% E so assume increase in total PUFA also -9% E, > 10% increase from control group baseline of -3% E from PUFA <b>PUFA dose</b> : 9% E PUFA
Outcomes	Main trial outcome: progression of diabetic retinopathy Dropouts: unclear intervention, unclear control Available outcomes: CV events (total MI and angina), TC, TGs (data read off graph), CHD mortality (fatal MI), CHD events (MI, angina), progression of retinopathy

## Houtsmuller 1979 (Continued)

	Response to contact: contact attempted but no response to date
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nding: Dutch Heart Foundation

## Risk of bias

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

## Kumar 2012

Methods	RCT, parallel, (n3 EPA + DHA vs nil), 12 months Summary risk of bias: moderate or high
Participants	People with persistent AF on warfarin N: 92 intervention, 90 control (91 and 87 analysed ITT) Level of risk for CVD: high Male %: 82.4 intervention, 72.4 control

## Kumar 2012 (Continued)

	Mean age (SD): 63 (10) intervention, 61 (13) control Age range: 18-85 (inclusion criteria) Smokers: 22.2% intervention, 11.5% control Hypertension: 45.6% intervention, 58.6% control Medications taken by $\geq$ 50% of those in the control group: anti-arrhythmic drugs, renin- angiotensin system inhibitors Medications taken by 20%-49% of those in the control group: statins Medications taken by some, but < 20% of the control group: not reported Location: Australia Ethnicity: not reported
Interventions	Type: fish oil capsule Comparison: EPA + DHA vs nil Intervention: 6 capsules/d of a fish oil preparation containing a total dose of 1.02 g of EPA and 0.72 g DHA. Participants in the omega-3 group were asked to continue fish oils till a maximum of 1 year or till return of persistent AF Control: no supplements. Participants were advised not to take any fish oil supplements All participants underwent cardioversion following randomisation <b>Dose aim</b> : increase 1.74 g/d EPA + DHA, <b>0.8% E n-3, 0.8% E PUFA</b> Baseline PUFA: unclear <b>Compliance by biomarkers</b> : phospholipid fatty acid status measured at cardioversion, DHA and EPA higher in intervention (EPA 2.5% fat, DHA 6.3% fat) than control (EPA 1.2% fat, DHA 3.4% fat), both P < 0.001. No other PUFAs, or TC, reported <b>Compliance by dietary intake</b> : not reported • Energy intake, kcal/d: not reported • Energy intake, kcal/d: not reported • Total fat intake, % E: not reported • SFA intake, % E: not reported • PUFA n-3 intake: not reported • PUFA n-6 intake: not reported • MUFA intake, % E: not reported • Sugars intake: not reported • Sugars intake: not reported • Alcohol intake, % E: not reported • Compliance, other measures: monitored on a weekly basis via telephone and during follow-up by using a pill count, results not reported Inclusion basis: no intention to increase total PUFA. Intention was to increase 1.74 g/d EPA + DHA, 0.8% E PUFA > 10% greater than assumed baseline of 6% E. No biomarker, TC or intake data to confirm <b>PUFA dose</b> : 0.8% E Duration of intervention: 1 year (or AF recurrence)
Outcomes	Main trial outcome: AF recurrence Dropouts: 4 intervention, 0 control Available outcomes: all-cause mortality (nil death), AF recurrence, time to AF recurrence, adverse events Response to contact: written but no answer yet

#### Kumar 2012 (Continued)

NotesTrial funding: the trial was funded in part by the National Heart Foundation of Australiaand the Pfizer Cardiovascular Lipid Research Grant

## Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Participants were randomised to a control or an omega-3 group in a 1:1 fashion (no methodological details)
Allocation concealment (selection bias)	Unclear risk	No further details
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label with no placebo control
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT conducted
Selective reporting (reporting bias)	Unclear risk	Trial registered 2005 but data collection started 2003
Attention bias	Unclear risk	Intervention group had capsules, while control group did not. Potential for greater contact and checking with intervention group, otherwise groups seem to have had the same care
Compliance	Unclear risk	Phospholipid fatty acid status measured at cardioversion, DHA and EPA higher in intervention (EPA 2.5% fat, DHA 6.3% fat) than control (EPA 1.2% fat, DHA 3.4% fat), both P < 0.001. No other PUFAs, or TC, reported
Other bias	Low risk	None noted

Kumar 2013

Methods	RCT, parallel, (n3 EPA + DHA vs nil), 12 months Summary risk of bias: moderate or high
Participants	Adults > 60 years with sinoatrial node disease and dual chamber pacemakers N: 39 intervention, 39 control (only 18 vs 39 for 12-month analyses) Level of risk for CVD: moderate/high Male %: 46% intervention, 56% control Mean age (SD): 78 (7) intervention, 77 (8) control Age range: not reported Smokers: not reported Hypertension: 72% Medications taken by $\geq$ 50% of those in the control group: statins, renin-angiotensin system inhibitors Medications taken by 20%-49% of those in the control group: anti-arrhythmic drugs Medications taken by some, but < 20% of the control group: not reported Location: Australia Ethnicity: not reported
Interventions	Type: omega-3 capsule Comparison: EPA + DHA vs nil Intervention: a triglyceride preparation containing a total of 6 g/day of omega-3 PUFAs of which 1.8 g/day were n-3 (1.02 g EPA and 0.72 g DHA) Control: no supplements <b>Dose aim</b> : increase 1.74 g/d EPA + DHA, <b>0.8% E n-3, 0.8% E PUFA</b> Baseline PUFA: unclear <b>Compliance by biomarkers:</b> phospholipid fatty acid status measured at randomisation and at 1-3 months, DHA and EPA increased in intervention, not in control. No other PUFAs, or TC, reported <b>Compliance by dietary intake:</b> measured via weekly diet history, but no results reported • Energy intake, kcal/d: not reported • Total fat intake, % E: not reported • SFA intake, %E: not reported • PUFA n-3 intake: not reported • PUFA n-6 intake: not reported • PUFA n-6 intake: not reported • MUFA intake, % E: not reported • MUFA intake, % E: not reported • Alcohol intake, % E: not reported • Duration to increase total PUFA. Intention was to increase 1.74 g/d EPA + DHA, 0.8% E PUFA >10% greater than assumed baseline of 6% E. No biomarker, TC or intake data to confirm <b>PUFA dose:</b> 0.8% E Duration of intervention: median 378 days

# Kumar 2013 (Continued)

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

# Notes

Trial funding: unclear

## Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was performed using se- quentially numbered, opaque, sealed en- velopes
Allocation concealment (selection bias)	Low risk	As above
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label design
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "At each visit, stored AT/AF diag- nostic data were retrieved in an un-blinded fashion"
Incomplete outcome data (attrition bias) All outcomes	High risk	Only 1 lost, and reason explained. But group baseline size to cross-over is huge. Doesn't report just the 17 or 18 metrics at baseline, no idea why the 21 were the ones switched and mixed with the control
Selective reporting (reporting bias)	Low risk	Trial prospectively registered and outcomes stated were reported
Attention bias	Unclear risk	Only difference would be handing out the capsules, rest seems the same. However, one group is getting supplements and the other nil
Compliance	Unclear risk	Phospholipid fatty acid status measured at randomisation and at 1-3 months, DHA and EPA increased in intervention, not in control. No other PUFAs, or TC, reported
Other bias	High risk	21 of the 39 randomised to the intervention were crossed over to control at six months so 12-month outcomes are reported for 17/

18 intervention group while baseline characteristics are reported for all 39 participants Ley 2004 Methods RCT, parallel, (reduced total fat vs usual diet), 12 months Summary risk of bias: low (dietary advice trial) Participants Adults with impaired glucose intolerance or high normal blood glucose N: 85 intervention, 90 control (176 between both groups) (analysed 66 intervention: 70 control at 1 year, 112 between both groups at 5 years) Level of risk for CVD: moderate Male: 80% intervention, 68% control Mean age (SD): 52.5 (SE 0.8) intervention, 52.0 (SE 0.8) control Age range: not reported Smokers: 23% intervention, 9% control Hypertension: not reported Medications taken by  $\geq$  50% of those in the control group: not reported Medications taken by 20%-49% of those in the control group: not reported Medications taken by some, but < 20% of the control group: BP medication taken by 27% intervention, 18% control Location: New Zealand Ethnicity: European 67% intervention, 77% control, Maori 11% intervention, 7% control, Pacific islander 20% intervention, 13% control, other 3% intervention, 4% control (outcomes not provided by ethnicity) Interventions Type: diet advice Comparison: reduced fat vs usual diet Intervention: aim reduced fat diet (no specific goal stated); methods monthly small group meetings to follow a 1-year structured programme aimed at reducing dietary fat, includes education, personal goal setting, self-monitoring Control: aim usual diet; methods usual intake plus general advice on healthy eating consistent with the New Zealand guidelines and standard dietary information for people with nutrition-related problems upon entering the trial Dose aim: no goal stated Baseline PUFA: unclear but lower PUFA arm 4% E PUFA Compliance by biomarkers: erythrocyte ALA increased by 28% in control, reduced by 17% in intervention (in a subsample of participants, % of total fatty acids in red blood cells also increased in control group compared to intervention), no other erythrocyte fatty acids reported. TC fell by 0.15 mmol/L (SE 0.09) in control, and by 0.05 mmol/ L (SE 0.17) in intervention to 1 year Compliance by dietary intake: mean of five, 24-h diet recalls over 2 years of trial • Energy intake, kcal/d: intervention 1821 (SD not reported), control 1593 (SD not reported) • Total fat intake, % E: intervention 33.6 (SE 7.8), control 26.1 (SE 7.7) • SFA intake, %E: intervention 10.0 (SE 0.6), control 13.4 (SE 0.6) • PUFA intake, % E: intervention 4.0 (SE 0.2), control 4.8 (SE 0.2)

	<ul> <li>PUFA n-3 intake: not reported</li> <li>PUFA n-6 intake: not reported</li> <li>Trans fat intake: not reported</li> <li>MUFA intake, % E: intervention 8.9 (SE 0.4), control 11.8 (SE 0.4)</li> <li>CHO intake, % E: intervention 54.2 (SE 1.5), control 45.8 (SE 1.4)</li> <li>Sugars intake: not reported</li> <li>Protein intake, % E: intervention 18.4 (SE 0.5), control 16.6 (SE 0.5)</li> </ul>	
	<ul> <li>Protein intake, % E: intervention 18.4 (SE 0.5), control 16.6 (SE 0.5)</li> <li>Alcohol intake, % E: intervention 3.6 (SE 1.0), control 5.7 (SE 0.9)</li> </ul>	
	Compliance, other methods: not reported	
	Inclusion basis: aimed to reduce total fat, not to alter total PUFA. Resulted in fall of 0. 8% E total PUFA in intervention, > 10% increase from 5.3% E PUFA at baseline PUFA dose: 0.8% E PUFA (from dietary intake data) Duration of intervention: 12 months (later data reported, but intervention only lasted 1 year)	
Outcomes	Main trial outcome: lipids, glucose, BP Dropouts: unclear intervention, unclear control Available outcomes: mortality, CVD mortality, combined CV events (including MI, angina, stroke, heart failure), diabetes diagnosis, total MI, stroke, cancer diagnoses, cancer deaths, CHD events (MI or angina), weight, total, LDL and HDL, TGs, BP Author contact: Dr Metcalf provided additional methodology and outcome data	
Notes	Trial funding: National Heart Foundation of New Zealand, Aukland Medical Research Foundation, Lotteries Medical Board and the Health Research Council of New Zealand NOTE: total PUFA intake lower in intervention than control group	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Unmarked opaque envelopes were opened by the person recruiting, unable to alter al- location later (trial author stated in their reply to us that randomisation and prepa- ration of the envelopes was by people not involved in recruitment)
Allocation concealment (selection bias)	Low risk	Unmarked opaque envelopes were opened by the person recruiting, unable to alter al- location later
Blinding of participants and personnel (performance bias) All outcomes	High risk	Dietary advice, not blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Trial authors stated that those assessing lipids were blinded

# Ley 2004 (Continued)

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear, deaths, cancer and CV events are dropouts, trialists asked for data but they were unable to provide any - unclear if any data missing
Selective reporting (reporting bias)	Low risk	No protocol or trials registry entry found
Attention bias	High risk	Regular meetings in intervention group, not in control
Compliance	Low risk	Erythrocyte ALA increased by 28% in con- trol, reduced by 17% in intervention (in a subsample of participants, % of total fatty acids in red blood cells also increased in control group compared to intervention), no other erythrocyte fatty acids reported. TC fell by 0.15 mmol/L (SE 0.09) in con- trol (the arm higher in PUFA), and by 0.05 mmol/L (SE 0.17) in intervention to 1 year (control group should have been higher in total PUFA in this trial)
Other bias	Low risk	None noted

## MARINA - Sanders 2011

Methods	Modulation of Atherosclerosis Risk by Increasing dose of N-3 fatty Acids (MARINA) RCT, parallel, 4 arms (n3 EPA + DHA at 3 doses vs MUFA), G2 vs control included, 12 months Summary risk of bias: low
Participants	Non-smoking men and women aged 45-70 years N: intervention 279 in 3 groups (G1 0.45 g/d N = 94, G2 0.9 g/d N = 93, G3 1.8 g/d N = 92), control: 88 (analysed G1 0.45 g/d N = 81, G2 0.9 g/d N = 80, G3 1.8 g/d N = 80, control 71) Level of risk for CVD: low Male: 38.7% intervention, 38.6% control Mean age (CI): G1:55 (53, 56), G2:55 (54, 56), G3: 55 (54, 57) intervention 55 (54, 57) control Age range: 45-70 Smokers: 0% intervention, 0% control Hypertension: 5.4% intervention, 5% control Medications taken by $\geq$ 50% of those in the control group: none Medications taken by 20%-49% of those in the control group: none Medications taken by some, but < 20% of the control group: statins, antihypertensives, hormone replacement therapy, thyroxine Location: UK Ethnicity: G1: white 80.9%, black 4.3%, Asian 6.4%, Far Eastern 4.3%, other 4.3%

## MARINA - Sanders 2011 (Continued)

	G2: white 78.5%, black 6.5%, Asian 10.8%, Far Eastern 0%, other 4.3% G3: white 85.9%, black 1.1%, Asian 2.2%, Far Eastern 4.3%, other 6.5% Control: white 77.3%, black 10.2%, Asian 6.8%, Far Eastern 2.3%, other 3.4%
Interventions	<ul> <li>Type: supplement (fish oil capsules)</li> <li>Comparison 1: EPA + DHA vs MUFA</li> <li>Comparison 2: high EPA + DHA vs low EPA + DHA</li> <li>Intervention: 3 x 1 g oil gelatin capsule/day consisting of blend of EPA concentrate, DHA concentrate, refined olive oil and 0.1 wt% peppermint oil Providing a daily dose of 0.45 g, 0.9 g, or 1.8 g/d (all with EPA/DHA ratio of 1.51)</li> <li>Control: 3 gelatin capsules/d containing refined olive oil + 0.1% peppermint oil</li> <li>Dose aim: (intended) increase 0.45 g/d EPA + DHA, 0.2% E n-3 or increase 0.9 g/d EPA + DHA, 0.4% E n-3 or increase 1.8 g/d EPA + DHA, 0.8% E n-3</li> <li>Baseline PUFA 6.2% E</li> <li>Compliance by biomarkers: EPA and DHA in erythrocyte lipids increased in dose-dependent manner compared with placebo, indicating long-term compliance with intervention. TC rose by 0.1 mmol/L in both the control and intervention (G2, 0.9 g/d group) from baseline to end. No other biomarkers reported</li> <li>Compliance by dietary intake: all assessed after treatment (assumed at 12 months), using food frequency questionnaire (checked for completeness). Intervention group refers to G2 (0.9 g/d):</li> <li>Energy intake, MJ/d (95% CI): intervention 7.98 (7.28 to 8.68), control 7.79 (6. 92 to 8.67)</li> <li>Total fat intake, % E (95% CI): intervention 34.0 (32.4 to 35.5), control 30.8 (28.9 to 32.6)</li> <li>SFA intake, % E (95% CI): intervention 6.4 (6.0 to 6.8), control 5.7 (5.3 to 6.1)</li> <li>PUFA n-3 intake: not reported</li> <li>PUFA n-6 intake: not reported</li> <li>MUFA intake, % E (95% CI): intervention 16.3 (15.7 to 16.9), control 15.8 (15.1 to 16.6)</li> <li>Alcohol intake, % E: not reported</li> <li>POrtein intake, % E: not reported</li> <li>POrtein intake, % E: not reported</li> <li>POTein intake, % E: not reported</li> <li>MUFA intake, % E: not reported</li> <li>POTein intake, % E: not reported</li> <li>Ontoil intake, % E: not reported</li> <li>Alcohol intake, % E: not reported</li> <li>Nucreating and and asset assugested total PUFA intake 0.7% E hi</li></ul>
Outcomes	Main trial outcome: endothelial function, arterial stiffness Dropouts: 38 intervention (13,13,12), 17 control Available outcomes (for G2 vs control used): lipids, dietary intake, CRP, BP (supine and

## MARINA - Sanders 2011 (Continued)

	ambulatory - numeric data not provided, but trial states that there were no significant differences between arms). Weight data not used, as baseline is different between groups (FMD, arterials stiffness, carotid intima media thickness, heart rate variability, heart rate, endothelial progenitor cells reported but not used) Contact with authors: yes (many outcomes above provided in end of trial report from authors)
Notes	NOTE: outcome data used G2 (0.9 g/d EPA + DHA) vs placebo for continuous out- comes, as this was the comparison where dietary data suggested that total PUFA increased by > 10% compared with placebo Trial funding: Food Standards Agency

## Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "the random allocation sequence was generated with a computer program by using the process of minimisation to bal- ance age, sex and ethnicity between treat- ment groups."
Allocation concealment (selection bias)	Low risk	Quote: "We enrolled eligible participants and the trial database program allocated a series of capsules to the participant"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "blends of the test fat with 0.1wt% peppermint oil to disguise the fish taste of the EPA and DHA" Peppermint oil in both intervention and control capsules.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "The treatments associated with the capsule codes were concealed from all in- vestigators and associated clinical staff until the data analysis was complete. The code breaker was an employee of MedSciNet who constructed the trial database."
Incomplete outcome data (attrition bias) All outcomes	Low risk	15% withdrawal, reasons for attrition reported
Selective reporting (reporting bias)	Low risk	Outcomes published match trials register. Registered September 2008, trial started June 2008, ended December 2010, main publication 2011
Attention bias	Low risk	No difference between groups

## MARINA - Sanders 2011 (Continued)

Compliance	High risk	EPA and DHA in erythrocyte lipids in- creased in dose-dependent manner com- pared with placebo, indicating long-term compliance with intervention. TC rose by 0.1 mmol/L in both the control and inter- vention (G2, 0.9 g/d group) from baseline to end. No other biomarkers reported	
Other bias	Low risk	None noted	
McIllmurray 1987			
Methods		RCT, parallel, 2 arms (GLA vs "inert placebo"), 40 months Summary risk of bias: moderate to high	
Participants	N: intervention 25 (plus some intervention 25, control 24). 5 Level of risk for CVD: low Male: not reported Mean age (SD) years: intervent Age range: intervention 48-81, Smokers: not reported Hypertension: not reported Medications taken by $\geq$ 50% of Medications taken by 20%-499	Male: not reported Mean age (SD) years: intervention 62.1 (not reported), control 64.8 (not reported) Age range: intervention 48-81, control 45-77 Smokers: not reported Hypertension: not reported Medications taken by $\geq$ 50% of those in the control group: not reported Medications taken by 20%-49% of those in the control group: not reported Medications taken by some, but < 20% of the control group: not reported Location: UK	
Interventions	Intervention: 6 capsules/d cor (Efamol). GLA 0.5 g/d, 60 mg/d C, zinc sulphate and pyridoxind Control: 6 capsules/d containin what). Plus vitamin supplemen <b>Dose aim</b> : (assuming placeboo <b>2% E GLA</b> , assume 70% LA*, Baseline PUFA: unclear <b>Compliance by biomarkers:</b> u <b>Compliance by dietary intake</b> supplements at 12 months • Energy intake: not reported • Total fat intake: not reported • PUFA intake: not reported	Type: supplement (Efamol) Comparison: GLA vs "inert placebo" (unclear what) Intervention: 6 capsules/d containing 500 mg GLA plus 10 mg natural vitamin E (Efamol). GLA 0.5 g/d, 60 mg/d vitamin E. Plus vitamin supplements including vitamin C, zinc sulphate and pyridoxine Control: 6 capsules/d containing an inert placebo, identical in appearance (not specified what). Plus vitamin supplements including vitamin C, zinc sulphate and pyridoxine <b>Dose aim</b> : (assuming placebo contains no PUFA) increase <b>0.5 g/d GLA</b> , 5 kcal or <b>0.</b> <b>2% E GLA</b> , assume 70% LA*, 4.2 g/d or 37.8 kcal/d or <b>1.9% E LA</b> , <b>2.1% E n6</b> Baseline PUFA: unclear <b>Compliance by biomarkers:</b> unclear, no serum TC or tissue fatty acid levels reported. <b>Compliance by dietary intake:</b> unclear, states that one participant stopped taking the supplements at 12 months • Energy intake: not reported • Total fat intake: not reported	

## McIllmurray 1987 (Continued)

	<ul> <li>PUFA n-6 intake: not reported</li> <li>Trans fat intake: not reported</li> <li>MUFA intake: not reported</li> <li>CHO intake: not reported</li> <li>Sugars intake: not reported</li> <li>Protein intake: not reported</li> <li>Alcohol intake: not reported</li> <li>Compliance, other methods: not reported</li> <li>Inclusion basis: aimed to increase GLA rather than total PUFA. Aimed to increase omega-6 by 2.1% E, assume 2.2% E increase for PUFA, &gt; 10% of assumed 6% E PUFA baseline. No confirmatory biomarker, TC or intake data</li> <li>PUFA dose: 2.2% E PUFA</li> <li>Duration of intervention: 40 months</li> </ul>
Outcomes	Main trial outcome: unclear, "survival", probably mortality Dropouts: 5 (unclear from which groups) Available outcomes: mortality, cancer mortality (face flushing reported as a side effect, but no numbers provided and assumed due to concomitant pyridoxine) Response to contact: Professor McIllmurray replied, "I don't have the recordsso I have nothing more than what appears in the publication. I do not recall there being any cardiovascular events."
Notes	Trial funding: not stated, Efamol Ltd provided the Efamol capsules and inert capsules *EPO described as being ~70% LA in some publications, this and a 1 g capsule size have been assumed where no other details are provided

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "assigned at random"
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No details apart from the placebo was iden- tical in appearance to the Efamol capsules
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	5 dropouts, unclear from which arms
Selective reporting (reporting bias)	Unclear risk	No protocol or trials register entry found

## McIllmurray 1987 (Continued)

Attention bias	Low risk	Supplement provided, no suggestion of at- tention bias	
Compliance	Unclear risk	Neither tissue PUFA biomarkers nor TC data reported	
Other bias	Unclear risk	None noted, but contents of placebo cap- sules unclear	
Mendis 2001			
Methods	RCT, 2 arms, parallel (n6 LA v Summary risk of bias: moderate	rs non-fat) dietary advice, 1 year e to high	
Participants	CVD risk: low N: 30 intervention, 30 control % male: 78% (total) Mean age: not reported Age range: 20-65 years Smokers: not reported Hypertension: not reported Medications taken by $\geq$ 50% of Medications taken by 20%-49% Medications taken by some, but	N: 30 intervention, 30 control (analysed 26 intervention, 28 control) % male: 78% (total) Mean age: not reported Age range: 20-65 years Smokers: not reported Hypertension: not reported Medications taken by $\geq$ 50% of those in the control group: not reported Medications taken by 20%-49% of those in the control group: not reported Medications taken by some, but < 20% of the control group: not reported *lipid-lowering medications as well as many others were not allowed Location: Sri Lanka	
Interventions	Comparison: n-6 vs non-fat (uu Intervention: group B received a 5 g/d test fat containing soybea 2). Fat intake in group B was, th 5 g/d PUFA mainly LA) Control: Group A received a di <b>Dose aim</b> : increase 5 g/d PUFA Baseline PUFA: unclear <b>Compliance by biomarkers:</b> p vention compared to control (0 group were stated as having hig levels of fatty acids were reporte <b>Compliance by dietary intake</b> diaries • Energy intake, kJ/d: interv • Total fat intake, % E: inter reported)	Type: diet advice plus test fat supplement Comparison: n-6 vs non-fat (unclear if CHO, protein or both) Intervention: group B received a diet containing 20% E as fat (4.7% coconut fat) plus 7. 5 g/d test fat containing soybean fat-sesame fat (3:1, v/v containing PUFA:MUFA ratio 2). Fat intake in group B was, therefore, 24% energy intake. (test fat provided additional 5 g/d PUFA mainly LA) Control: Group A received a diet containing 20% E as fat (4.7% E coconut fat) <b>Dose aim</b> : increase 5 g/d PUFA, <b>2.2% E PUFA</b> Baseline PUFA: unclear <b>Compliance by biomarkers:</b> poor, serum TC was not significantly reduced in inter- vention compared to control (0.16 mmol/L, 95% CI -0.18 to 0.50). The intervention group were stated as having higher dietary PUFA:SFA ratio than controls, but no blood levels of fatty acids were reported <b>Compliance by dietary intake:</b> unclear, measured by field workers' visits and using food diaries • Energy intake, kJ/d: intervention 7962 (SD 1568), control 8030 (SD 1465) • Total fat intake, % E: intervention 24 (SD not reported), control 20 (SD not	

# Mendis 2001 (Continued)

	reported)
	• PUFA intake: not reported (unsaturated fat intake intervention 12.6% E, control
	8.2% E, test fat reported as mainly LA)
	• PUFA n-3 intake: not reported
	• PUFA n-6 intake: (unsaturated fat intake intervention 12.6% E, control 8.2% E,
	test fat reported as mainly LA)
	• Trans fat intake: not reported
	MUFA intake: not reported
	• CHO intake, % E: intervention 64 (SD not reported), control 67 (SD not
	reported)
	• Sugars intake: not reported
	• Protein intake, % E: intervention 12.2 (SD not reported), control 12.1 (SD not
	reported)
	Alcohol intake: not reported
	Compliance, other methods: not reported
	Inclusion basis: did not aim to increase PUFA (but replace SFA with unsaturated fats)
	. Did appear to increase unsaturated fat by 4.4% E, and test fat reported as mainly LA.
	Aim was to increase PUFA by 2.2% E, assume this achieved though no biomarker or
	dietary intake data and TC was not reduced in intervention
	PUFA dose: 2.2% E PUFA
	Duration of intervention: 1 year
Outcomes	Main trial outcome: serum lipids
	Dropouts: intervention 4, control 2
	Available outcomes: lipids
	Response to contact: contact attempted but no response to date
Notes	Trial funding: funded by the National Science Foundation of Sri Lanka

## Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Participants were randomised to 2 groups (groups A and B). This was done in such a way that the 38 hyperlipidaemic partici- pants were equally divided between the two groups.
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias) All outcomes	High risk	The groups had different diets with test fat added to intervention group
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details

# Mendis 2001 (Continued)

Incomplete outcome data (attrition bias) All outcomes	High risk	Six participants dropped out at 6 months but their data are not included in the anal- ysis at all
Selective reporting (reporting bias)	Unclear risk	No protocol or trial register entry found
Attention bias	Low risk	Appeared similar
Compliance	High risk	TC was higher in intervention than control (0.16 mmol/L, 95% CI -0.18 to 0.50). The intervention group were stated as having higher dietary PUFA:SFA ratio than con- trols, but no blood levels of FAs were re- ported
Other bias	Unclear risk	No details provided on the form or method of supply of diet or test fat
Mita 2007		
Methods	RCT, parallel, (n3 EPA vs nil), 2 years Summary risk of bias: moderate or high	
Participants	Japanese people with type 2 diabetes N: intervention 40, control 41 (analysed 30, 30) Level of risk for CVD: moderate Male: 53% intervention, 67% control Mean age (SD): 59 (11.2) intervention 61.2 (8.4) control Age range: not reported Smokers: 40% intervention, 43% control Hypertension: not reported Medications taken by $\geq$ 50% of those in the control group: oral hypoglycemics Medications taken by 20%-49% of those in the control group: insulin, lipid-lowering drugs, antihypertensives Medications taken by some, but < 20% of the control group: antithrombotics Location: Japan Ethnicity: 100% Japanese	
Interventions	Type: supplement (EPA oil capsules) Comparison: EPA vs nil Intervention: 1.8 g/d EPA as EPADEL capsules (Mochida Pharmaceutical Co Ltd Japan) 98% pure ethyl-ester EPA (unclear how many capsules) Control: no intervention <b>Dose aim</b> : increase 1.8 g/d EPA + DHA, 0.8% E n-3, assumed 0.8% E from total PUFA as no control Baseline PUFA not reported <b>Compliance by biomarkers</b> : no tissue fatty acids reported, but TC lower in intervention arm (5.37 mmol/L SD 0.74 at baseline, 5.15 mmol/L SD 0.83 at 2 years), than control	

	(5.37 mmol/L SD 1.03 at baseline, 5.27 mmol/L SD 0.99 at 2 years)
	Compliance by dietary intake: not reported
	• Energy intake, kcal/d: not reported
	• Total fat intake, % E: not reported
	• SFA intake, %E: not reported
	• PUFA intake, % E: not reported
	• PUFA n-3 intake: not reported
	• PUFA n-6 intake: not reported
	• Trans fat intake: not reported
	• MUFA intake, % E: not reported
	• CHO intake, % E: not reported
	• Sugars intake: not reported
	• Protein intake, % E: not reported
	• Alcohol intake, % E: not reported
	Compliance, other methods: checked during 3-month reviews throughout trial and 5
	participants were excluded for poor compliance but no details on method or results
	Inclusion basis: planned dose suggested in increase in total PUFA (by 0.8% E, > 10%
	increase from an assumed baseline of 6% E), and higher PUFA in the intervention is
	backed up by TC data
	PUFA dose: 0.8% E
	Length of intervention: mean 2.1 (0.2) years
Outcomes	Main trial outcome: progression of diabetic macroangiopathy measured by carotid in-
	tima-media thickness and brachial-ankle pulse wave velocity
	Dropouts: 10 intervention, 11 control
	Available outcomes: BMI, lipids, BP, HbA1c, cancer diagnosis (BP data not used as
	groups very different at baseline)
	Response to contact: not yet attempted
Notes	Trial funding: not stated

#### Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants randomly divided into 2 groups matched for age and gender
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Assessors of main trial outcomes were blinded to the treatment

# Mita 2007 (Continued)

Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropout rate (26%) over 2 years. All drop- outs explained, however, 5 were excluded for poor compliance but no clear prede- fined protocol for exclusion
Selective reporting (reporting bias)	Unclear risk	No protocol
Attention bias	Low risk	All participants had the same contact
Compliance	Low risk	No tissue fatty acids reported, but TC lower in intervention arm (5.37 mmol/L SD 0. 74 at baseline, 5.15 mmol/L SD 0.83 at 2 years), than control (5.37 mmol/L SD 1. 03 at baseline, 5.27 mmol/L SD 0.99 at 2 years)
Other bias	Low risk	None noted
MRC 1968		
Methods	Medical Research Council (MRC) RCT, 2 arm, parallel (n6 LA vs mixed fats) Summary risk of bias: moderate to high	, 4 years
Participants	Free-living men who have survived a first MI (UK) CVD risk: high Control: randomised 194, analysed 181 at 2 years Intervention: randomised 199, analysed 172 at 2 years Mean years in trial: control 3.7, intervention 3.8 % male: 100 Age: unclear Age range: all < 60 years Smokers: control 84%, intervention 81% Hypertension: control 12%, intervention 8% Medications taken by $\geq$ 50% of those in the control group: not reported Medications taken by 20%-49% of those in the control group: not reported Medications taken by some, but < 20% of the control group: not reported Location: UK Ethnicty: not reported	
Interventions	18.9% E LA, assume 58% PUFA so21.9% Baseline PUFA: unclear	g/d fat, add 84 g/d soya oil kcal or <b>37.8% E soya</b> (assume 50% LA, so

	lower in intervention than control consistently post-baseline. Report stated that, "tissue fat of the men on the soya-bean oil diet was less saturated than that of the controls" and that further information would be published elsewhere. No statistical significance or variance data mentioned <b>Compliance by dietary intake:</b> unclear • Energy intake, kcal/d: intervention 2380 (SD not reported), control 2274 (SD not reported) • Total fat intake: not reported • SFA intake: not reported • PUFA intake: not reported • PUFA n-3 intake: not reported • PUFA n-6 intake: not reported • Trans fat intake: not reported • MUFA intake: not reported • CHO intake; g/d: intervention 243 (SD not reported), control 228 (SD not reported) • Sugars intake, g/d: intervention 66 (SD not reported), control 60 (SD not reported) • Protein intake, g/d: intervention 80 (SD not reported), control 88 (SD not reported) • Alcohol intake: not reported <b>Compliance, other methods</b> : not reported <b>Inclusion basis:</b> aimed to replace SFA with PUFA. <b>PUFA dose:</b> 21.9% E PUFA (aim) Duration of intervention: 4 years
Outcomes	Main trial outcomes: MI or sudden death Dropouts: intervention 199 randomised, 181 at 2 years, 91 at 4 years. Control: 194 randomised, 172 at 2 years, 85 at 4 years Available outcomes: mortality, CV mortality (CV deaths plus non-fatal MI), total MI, non-fatal MI (data for weight, TC and BP, but no variance info) Response to contact: reply from trial statistician, JA Heady, in 1999
Notes	Some data not usable due to lack of variance. For all, data at 4 years, control N = 89, intervention N = 88 Weight change: intervention 0 kg, control -3 kg TC change: intervention -1.11 mmol/L, control -0.47 mmol/L Systolic BP change: intervention +2 mmHg, control 0 mmHg Diastolic BP change: intervention -1 mmHg, control +3 mmHg Trial funding: Medical Research Council

## Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "using random numbers, by blocks within hospitals"
Allocation concealment (selection bias)	Unclear risk	Not described

## MRC 1968 (Continued)

Blinding of participants and personnel (performance bias) All outcomes	High risk	Big changes to fat intake in intervention group while control group ate their usual diet
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Suspected relapses were assessed at regular intervals by a review committee un- aware of the patients diet group"
Incomplete outcome data (attrition bias) All outcomes	High risk	Data collection was thorough, but some participants dropped out and contact was lost
Selective reporting (reporting bias)	Unclear risk	No protocol or trials registry entry located
Attention bias	High risk	Dietary intervention, control ate usual diet, so likely that intervention group received more time and support, though this is not clear from paper
Compliance	Low risk	TC lower in intervention than control con- sistently post-baseline. Report stated that "tissue fat of the men on the soya-bean oil diet was less saturated than that of the con- trols" and that further information would be published elsewhere
Other bias	Low risk	None noted

#### NDHS Faribault 1968

Methods	National Diet-Heart Study (NDHS) - Faribault site RCT, several arms, parallel (n6 LA vs SFA), 1 year Summary risk of bias: low
Participants	Men living in a mental health institute CVD risk: low N: interventions B, C, E combined: randomised 167, analysed 143; control: randomised 57, analysed 52 Mean years in trial: interventions 0.9, control 1.0, % male: 100 Age: unclear Age range: all 45-54 years Smokers: 55%-59% current smokers in each arm Hypertension: unclear Medications taken by $\geq$ 50% of those in the control group: not reported Medications taken by 20%-49% of those in the control group: not reported Medications taken by some, but < 20% of the control group: not reported Location: USA

## NDHS Faribault 1968 (Continued)

	Ethnicty: not reported
Interventions	<ul> <li>Type: diet provided (residential institution)</li> <li>Comparison: PUFA (n-6) vs usual institutional diet (SFA and MUFA)</li> <li>Control aims: total fat 40% E, SFA 16%-18% E, dietary cholesterol 650-750 mg/d, P/</li> <li>S0.4 (so PUFA 6.8% E) (whole diet provided)</li> <li>Intervention aims: B (C, E) total fat 30% E (40% E, 40% E), SFA &lt; 9% E (&lt; 9% E, not stated), dietary cholesterol 350-450 mg/d (350-450 mg/d, not stated), PUFA 15%</li> <li>E (18-20% E, nor stated), P/S 1.5 (2.0, 4.4) (equivalent to Minnesota Coronary Trial diet) (whole diet provided)</li> <li>Dose aim: increase B 8.2% E, C 12.2% E, E unclear n-6</li> <li>Baseline n-6 (table IX2): 4.4% E LA, 4.8% E PUFA</li> <li>Compliance by biomarkers: serum TC significantly reduced in intervention compared to control (0.91 mmol/L, 95% CI-1.17 to -0.65). Fatty acid composition of red blood cells suggests that LA was higher in intervention arms (table X6: LA rose by 4 in control, by 5-7 in other arms, at the expense of MUFA, which rose by 1 in control, fell by 4 or 5 in other arms. Palmitic acid fell by 5 in control, and fell by 4 in intervention arms - no statistical significance or variance info provided, units unclear, probably % of LA+oleic+palmitic+stearic)</li> <li>Compliance by dietary intake: good. Assessed from 7-day food records after 28 and 44 weeks combined (tables IX8829)</li> <li>Energy intake, ka/ld: intervention B 2549, intervention C 2599, intervention E 37.1, control 39.5 (decrease B 10.5% E, C 1.0% E, E 2.4 total fat)</li> <li>SFA intake, % E: intervention B 12.0, intervention C 13.8, intervention E 24.3, control D 15.6 (decrease B 7.5% E, C 13.2% E, E 17.7% E PUFA)</li> <li>PUFA n-3 intake: not reported</li> <li>PUFA n-4 intake, % E: intervention B 11.6, intervention C 16.9, intervention E 21.9, ontrol D 14.3 (increase B 7.3% E, C 12.6% E, E 17.6% E LA)</li> <li>Trans fat intake, % E: intervention B 11.6, intervention C 16.9, intervention E 4.6, control D 15.3 (decrease B 8.5% E, C 5.6% E, E 13.5% E, C 16.7% E, E 17.6% E LA)</li></ul>
Outcomes	Main trial outcomes: lipid levels and dietary assessment Dropouts: B 7, C 10, E 7, D (control) 5

### NDHS Faribault 1968 (Continued)

	Available outcomes: mortality, TC (weight and TG data available but without SDs) Response to contact: not attempted as trial completed in 1967
Notes	Data entered as all interventions combined (B+C+E) vs control (D) Dose calculations Interventions: B PUFA 15% E, 8.2% E Control: 17% E SFA, P/S 0.4 so PUFA 6.8% E C PUFA 19% E, 12.2% E D unclear % E? Mean for all interventions 10.2% E Trial funding: National Heart Institute

# Risk of bias

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

# NDHS Open 1st 1968

Methods	National Diet-Heart Study (NDHS) - open first phase RCT, several arms, parallel (n6 LA vs SFA), 1 year Summary risk of bias: low	
Participants	Free-living men aged 45-54 years CVD risk: low Interventions B, C, X combined: randomised 829, analysed 726 Control: randomised 382, analysed 341 Mean years in trial: control 0.95, Interventions 0.93 % male: 100 Age: unclear Age range: all 45-54 years Smokers: 39%-40% current smokers in each arm Hypertension: unclear Medications taken by $\geq$ 50% of those in the control group: not reported Medications taken by 20%-49% of those in the control group: not reported Medications taken by some, but < 20% of the control group: not reported Location: USA Ethnicty: white 98.2%, non-white 1.8% (not reported by intervention arm)	
Interventions	Location: USA	

### NDHS Open 1st 1968 (Continued)

	<ul> <li>control D 4.9 (increase B 5.0% E, C 8.3% E, X 1.6 PUFA)</li> <li>PUFA n-3 intake: not reported</li> <li>PUFA n-6 intake: not reported, probably similar to PUFA</li> <li>Trans fat intake: not reported</li> <li>MUFA intake, % E (by subtraction of SFA and PUFA from total fat): intervention B 12.7, intervention C 13.8, intervention X 16.3, control D 18.4 (decrease B 5.7% E, C 4.6% E, X 2.1% E MUFA)</li> <li>CHO intake, % E: intervention B 48.7, intervention C 45.3, intervention X 49.</li> <li>5, control D 44.7 (increase B 4.0% E, C 0.6% E, X 4.8% E CHO)</li> <li>Sugars intake: not reported</li> <li>Protein intake, % E: intervention B 18.6, intervention C 17.6, intervention X 17.</li> <li>1, control D 17.4 (increase B 1.2% E, C 0.2% E, X -0.3% E protein, little change)</li> <li>Alcohol intake, % E: intervention B 2.1, intervention C 2.1, intervention X 1.7, control D 2.2 (minimal change)</li> <li>Compliance, other methods: also assessed adherence ratings by nutritionists, subjectively, by recall and by food records. Poor adherence by 17%-29%, others were fair, good or excellent</li> <li>Inclusion basis: aimed to increase PUFA intake as well as increase PUFA/SFA, reduce SFA slightly and reduce dietary cholesterol</li> <li>PUFA dose: achieved B 5.0% E, C 8.3% E, X 1.6 PUFA</li> <li>Duration of intervention: 1 year</li> </ul>
Outcomes	Main trial outcomes: lipid levels and dietary assessment Dropouts: intervention B 42, C 34, X 5, control D 36 Available outcomes: CV events (MI and PAD events), cancer diagnoses, TC (weight, diastolic BP and TG data available but without SDs) Response to contact: not attempted as trial completed in 1967
Notes	All intervention arms combined for data analysis Aim was to replace saturates with polyunsaturates, but oils used were omega-6 fats Dose calculations Control: assume from Faribault 17% E SFA, P/S 0.4 so PUFA 6.8% E Interventions: B PUFA 15% E, 8.2% E C PUFA 19% E, 12.2% E X PUFA 15% E, 8.2% E Mean for all interventions 10% E Trial funding: National Heart Institute

Risk of bias

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

### NDHS Open 1st 1968 (Continued)

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

#### Nodari 2011 AF

Methods	RCT, parallel, (n3 DHA + EPA vs MUFA), 12 months Summary risk of bias: moderate or high
Participants	Adults with persistent AF with $\geq 1$ relapse after cardioversion N: 102 intervention, 103 control (analysed, intervention: 94 control: 94) Level of risk for CVD: high Male: 70% intervention, 63% control Mean age (SD): 70 (6) intervention, 69 (9) control Age range: not reported (18-80 inclusion criteria) Smokers: 10% intervention, 9.1% control Hypertension: 47% intervention, 40% control Medications taken by $\geq 50\%$ of those in the control group: beta-blockers, ACE in- hibitors, anticoagulant therapy, amiodarone Medications taken by 20%-49% of those in the control group: diuretics, antiplatelet, statins Medications taken by some, but < 20% of the control group: Ca channel blockers

#### Nodari 2011 AF (Continued)

	Location: Italy Ethnicity: not reported
Interventions	Type: supplement (Omacor) Comparison: EPA and DH+A vs MUFA Intervention: 2 x1 g/d Omacor (total 1.7 g/d EPA + DHA at a ratio of 0.9-1.5) Control: 2 x1 g/d olive oil (gelatin capsules identical in appearance to Omacor) Dose aim: increase 1.7 g/d EPA + DHA, 0.8% E n-3, 0.8% E PUFA Baseline PUFA not reported Compliance by biomarkers: unclear, no biomarkers, no TC reported. Compliance by dietary intake: not reported • Energy intake, kcal/d: not reported • Total fat intake, % E: not reported • Total fat intake, % E: not reported • PUFA intake, % E: not reported • PUFA n-3 intake: not reported • PUFA n-6 intake: not reported • Trans fat intake; % E: not reported • MUFA intake, % E: not reported • MUFA intake, % E: not reported • Sugars intake: not reported • Sugars intake: not reported • Alcohol intake, % E: not reported • Alcohol intake, % E: not reported Inclusion basis: intended dose was an increase 1.7 g/d EPA + DHA without differences in other PUFAs, so assumed dose 0.8% E PUFA, > 10% increase in total PUFA from assumed baseline of 6% E. No biomarker, TC or dietary intake data to support this PUFA dose: 0.8% E Duration of intervention: 12 months
Outcomes	Main trial outcome: probability of maintenance of sinus rhythm Dropouts: 6 intervention, 5 control Available outcomes: adverse events, AF recurrence (nil death) Response to contact: no (contact established with trial author but no data received in this trial)
Notes	Trial funding: 'Centro per lo Studio ed il Trattamento dello Scompenso Cardiaco' of the University of Brescia, Brescia, Italy. The work of Dr Campia was supported by National Institutes of Health grant K12 HL083790-01a1
Risk of bias	Institutes of Health grant K12 HL085/90-01a1

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random assignment followed a computer- generated randomisation list obtained us- ing blocks of size 4

### Nodari 2011 AF (Continued)

Allocation concealment (selection bias)	Low risk	The randomisation schedule was kept in the research pharmacy area and was avail- able only to unblinded pharmacy person- nel until after the database was locked. At that time, the unblinded patient treatment information was made available to the in- vestigators
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Placebo gelatin capsules identical in ap- pearance to Omacor. However no informa- tion provided as to their smell and taste
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomised were accounted for. ITT for main outcomes
Selective reporting (reporting bias)	Unclear risk	NCT01198275. Registered retrospectively in September 2010, trial started January 2006, completed May 2008, main publi- cation 2011
Attention bias	Low risk	No difference between groups
Compliance	Unclear risk	No biomarkers, no TC reported
Other bias	Low risk	None noted
Nodari 2011 HF		
Methods	RCT, parallel, (n3 DHA + EPA vs MUFA), 12 months Summary risk of bias: moderate or high	
Participants	People with heart failure (non-ischaemic dilated cardiomyopathy) N: 67 intervention, 66 control (analysed, intervention: 67 control: 66) Level of risk for CVD: high Male: 95.5% intervention, 84.9% control Mean age (SD): 61 (11) intervention, 64 (9) control Age range: not reported (18-75 inclusion criteria) Smokers: not reported Hypertension: not reported Hypertension: not reported Medications taken by $\geq$ 50% of those in the control group: beta-blockers, ACEi, furosemide, amiodarone, aldosterone blockers Medications taken by 20%-49% of those in the control group: not reported Medications taken by 20%-49% of those in the control group: not reported Medications taken by 20%-49% of those in the control group: not reported	

Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease (Review)

Location: Italy

Medications taken by some, but < 20% of the control group: statins, ARB

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#### Nodari 2011 HF (Continued)

bias)

	Ethnicity: not reported		
Interventions	Type: supplement (Omacor) Comparison: EPA + DHA vs MUFA Intervention: 2 x1 g/d Omacor (1.7 g/d EPA + DHA at a ratio of 0.9:1.5) Control: 2 x1 g/d olive oil (gelatin capsules identical in appearance to Omacor) <b>Dose aim</b> : increase 1.7 g/d EPA + DHA, <b>0.8% E n-3, 0.8% E PUFA</b> Baseline PUFA not reported <b>Compliance by biomarkers</b> : circulating free fatty acid EPA + DHA 0.83% of circulating FFAs in intervention group, 0.41% in control group, but no omega-6 or total PUFA reported. TC equivalent at baseline (187 mg/dL) and similar at 1 year (4.8 mmol/L, SD 0.62 intervention, 4.9 mmol/L, SD 0.62 control) <b>Compliance by dietary intake</b> : not reported • Energy intake, kcal/d: not reported • Energy intake, kcal/d: not reported • Total fat intake, % E: not reported • Total fat intake, % E: not reported • PUFA n-3 intake: not reported • PUFA n-6 intake: not reported • PUFA n-6 intake: not reported • MUFA intake, % E: not reported • MUFA intake, % E: not reported • CHO intake, % E: not reported • Sugars intake: not reported • Alcohol intake, % E: not reported • Compliance, other measures: pill counts - participants were withdrawn if < 80% capsules taken (none were withdrawn) <b>Inclusion basis:</b> intended dose was an increase 1.7 g/d EPA + DHA without differences in other PUFAs, so assumed dose 0.8% E PUFA, > 10% increase in total PUFA from assumed baseline of 6% E. No biomarker or dietary intake data but supported by TC <b>PUFA dose:</b> 0.8% E		
Outcomes	Main trial outcome: left ventricular function and functional capacity Dropouts: 0 intervention, 0 control Available outcomes: mortality (nil death), combined CVD events, AF, BMI, hospitali- sation for CV reasons, hospitalisation for worsening heart failure, lipids, blood glucose (but too different at baseline to use), serum cytokine Response to contact: yes, additional data and methodological data provided		
Notes	Trial funding: Centro per lo Studio ed il Trattamento dello Scompenso Cardiaco, one author was a consultant for 8 pharmaceutical companies		
Risk of bias	Risk of bias		
Bias	Authors' judgement Support for judgement		
Random sequence generation (selection	Unclear risk	Quote: "randomised"	

### Nodari 2011 HF (Continued)

Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Paper states that placebo and verum were identical and that the trial was double- blind, but blinding of participants not checked. Trial author confirmed investiga- tors not blinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Trial author confirmed assessors not blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear whether all participants were as- sessed for all outcomes (e.g. hospitalisation) , but some outcomes report no attrition
Selective reporting (reporting bias)	Unclear risk	NCT01223703 - trial registration Octpber 2010, recruitment November 2007-June 2009. Retrospective
Attention bias	Low risk	No suggestion of this, and investigators ap- peared blinded (so could not differ in at- tention provided by allocation)
Compliance	High risk	Circulating free fatty acid EPA + DHA 0.83% of circulating FFAs in interven- tion group, 0.41% in control group, but no omega-6 or total PUFA reported. TC equivalent at baseline (187 mg/dL) and similar at 1 year (4.8 mmol/L, SD 0.62 in- tervention, 4.9 mmol/L, SD 0.62 control)
Other bias	Low risk	None noted

## Nye 1990

Methods	Randomisation: parallel, 3 groups (n3 EPA vs MUFA vs aspirin and dipyridamole), 1 year Risk of bias: moderate or high
Participants	People undergoing percutaneous transluminal coronary angioplasty N: 36 intervention, 37 control (also 35 allocated to arm 3, aspirin and dipyridamole) Level of risk for CVD: high (people undergoing angioplasty) Male: 78% intervention, 76% control Mean age (SD): 54 (8) intervention, 55 (8) control years Age range: unclear Smokers: unclear Hypertension: unclear

Risk of bias Bias	Authors' judgement Support for judgement	
Notes	Trial funding: Medical Rsearch Council of New Zealand and Scherer Ltd (who supplied MaxEPA and the olive oil capsules)	
Outcomes	Main trial outcome: angina, restenosis Dropouts: none Available outcomes: angina, interventions, lipids (nil death) Response to contact: not attempted	
Interventions	Ethnicity: unclear Type: supplement (capsules) Comparison: EPA vs MUFA Intervention: maxEPA capsules 12/d (2.2 g EPA) Control: olive oil capsules, 12/d, identical to MaxEPA. Both capsules had vit E <b>Dose aim</b> : increase 2.2 g/d EPA + DHA, <b>1.0% E n-3, 1.0% E PUFA</b> Baseline PUFA not reported <b>Compliance by biomarkers</b> : plasma EPA increased in the intervention group by 0.49 mmol/L (95% CI 0.34-0.64), while were "unchanged" in the control group, but no other PUFA data were presented. However, TC appeared higher in the intervention group (6. 55 mmol/L, SD 1.09 in intervention, 6.07 mmol/L, SD 1.33 in control, presumably at the end of the intervention) <b>Compliance by dietary intake</b> : not reported • Energy intake, kcal/d: not reported • Energy intake, kcal/d: not reported • SFA intake, % E: not reported • PUFA intake, % E: not reported • PUFA n-3 intake: not reported • PUFA n-6 intake: not reported • PUFA n-6 intake: not reported • MUFA intake, % E: not reported • MUFA intake, % E: not reported • MUFA intake, % E: not reported • Alcohol intake, % E: not reported • Sugars intake: not reported • Alcohol intake, % E: not reported • Alcohol intake, % E: not reported <b>Compliance, other measures:</b> none reported <b>Inclusion basis:</b> intended dose was an increase 2.2 g/d EPA + DHA. With no suggestion of differences in other PUFAs assumed dose was 1.0% E PUFA, > 10% increase in total PUFA from assumed baseline of 6%E. No biomarker or dietary intake data but challenged by TC	
	Medications taken by $\geq$ 50% of those in the Medications taken by 20%-49% of those in Medications taken by some, but < 20% of the Location: New Zealand Ethnicity: unclear	the control group: not reported

### Nye 1990 (Continued)

Random sequence generation (selection bias)	Unclear risk	Quote: "randomly divided without exclu- sions into 3 groups"
Allocation concealment (selection bias)	Unclear risk	Unclear, no further info
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	States that placebo capsules were identical to the MaxEPA, and Quote: "neither the patient nor the attend- ing cardiologist knew which capsules were being used" But no masking of taste was reported, and participant guesses as to allocation were not reported
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Neither the patient, nor the at- tending cardiologist knew which capsules were being used" "Angioplasty was re- peated electively at one year or before where symptoms recurred, and assessed without knowledge of the patient's treatment group. "
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Some participants were lost to follow-up and reasons for this were unclear
Selective reporting (reporting bias)	Unclear risk	No protocol or trials registration found
Attention bias	Low risk	No suggestion of attention bias, symp- tomatic participants were reviewed be- tween scheduled visits, otherwise all on the same schedule
Compliance	High risk	Plasma EPA increased in the intervention group by 0.49 mmol/L (95% CI 0.34-0. 64), while were "unchanged" in the control group, but no other PUFA data were pre- sented. However, TC appeared higher in the intervention group (6.07 mmol/L, SD 1.33 in control, 6.55 mmol/L, SD 1.09 in intervention, presumably at the end of the intervention)
Other bias	Low risk	No further bias noted

Methods	RCT- parallel, 3 arms (n3 EPA + DHA high dose vs n3 EPA + DHA low dose vs n3 EPA), 12 months Summary risk of bias: moderate or high
Participants	Population: Japanese adults with hypertriglyceridaemia N: 171 intervention (4 g TAK), 165 control (2 g TAK) Level of risk for CVD: moderate Male: 70.8% intervention, 71.5% control Mean age (SD): 55.9 (10.12) intervention, 56 (10.95) control Age range: 20-74 Smokers (current): 27.5% intervention, 31.5% control Hypertension: 66.7% intervention, 67.3% control Medications taken by $\geq$ 50% of those in the control group: not reported Medications taken by 20%-49%: statin Medications taken by some, but < 20%: not reported Location: Japan Ethnicity: unclear
Interventions	Type: supplement (TAK-085 capsules) Comparison: EPA + DHA higher vs lower dose Intervention: 1 x2 /d capsule each containing 2 g of TAK-085 (1 g of fatty acid in TAK- 085 capsules contains approximately 465 mg of EPA-E plus 375 mg of DHA-E). Total dose of 1.86 g/d EPA & 1.5 g/d DHA Control: 1 capsule/d containing 2 g of TAK-085 (1 g of fatty acid in TAK-085 capsules contains approximately 465 mg of EPA-E plus 375 mg of DHA-E) Total dose of 0.93 g/d EPA and 0.75 g/d DHA <b>Dose aim high TAK vs low TAK</b> : increase 1.68 g/d EPA + DHA, 0.8% E n3, <b>0.8% E</b> <b>PUFA assumed</b> (no details of other capsule components provided) Baseline PUFA not reported <b>Compliance by biomarkers</b> : plasma free fatty acids did not differ between high and low TAK for AA, while EPA and DHA were higher in high TAK by 52 weeks. There was a small difference in change in TC between high and low TAK, statistical significance unclear <b>Compliance by dietary intake:</b> not reported • Energy intake, kcal/d: not reported • SFA intake, % E: not reported • SFA intake, % E: not reported • PUFA n-3 intake: not reported • PUFA n-6 intake: not reported • PUFA intake, % E: not reported • MUFA intake, % E: not reported • CHO intake, % E: not reported • Sugars intake: not reported • Alcohol intake, % E: not reported

### **ORL 2013** (Continued)

	TAK, and no suggestion of different intakes of other PUFAs between arms <b>PUFA dose:</b> 0.8% E Duration of intervention: 12 months
Outcomes	Main trial outcome: safety outcomes and adverse events Dropouts: 8 G1, 14 G2, 21 G3 Available outcomes: adverse events (including CVD events, cancers), CRP, waist cir- cumference, weight, BP (nil death), lipids provided as % change from baseline, but no baseline data available, so not used in meta-analyses Response to contact: contact attempted but no response to date
Notes	A third arm of EPA-E 1.8 g supplementation is not used here. Outcome data used TAK- 4 vs TAK-2 Trial funding: funded by Takeda Pharmaceutical Company

### Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was stratified according to statin use and performed by an indepen- dent registration centre
Allocation concealment (selection bias)	Low risk	Randomisation was stratified according to statin use and performed by an indepen- dent registration centre
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open- label
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants were accounted for and analysed for main outcomes
Selective reporting (reporting bias)	Low risk	Trials registry entry May 2011, trial start date November 2009, completion Novem- ber 2011, so partially retrospective. How- ever, entry appears to reflect reported out- comes
Attention bias	Low risk	Capsules, appeared equivalent
Compliance	Unclear risk	Plasma free fatty acids did not differ be- tween high and low TAK for AA, while EPA and DHA were higher in high TAK

### **ORL 2013** (Continued)

		by 52 weeks. There was a 1% difference in change in TC between high and low TAK, statistical significance unclear	
Other bias	Low risk	None noted	
PREDIMED 2013			
Methods	RCT, parallel, 3 arms (high oil), also low-fat arm, 60 m	PREvención con Dieta MEDiterránea (PREDIMED) RCT, parallel, 3 arms (high PUFA vs low PUFA, Mediterranean diet with nuts or olive oil), also low-fat arm, 60 months Summary risk of bias: moderate to high	
Participants	$\geq$ 3 CVD risk factors N: intervention (Med with arm, not discussed here, 24 Level of risk for CVD: mod Male: intervention 46%, cc Mean age (SD): intervention Age range: 55-80 years Smokers: intervention 14.5 Hypertension: intervention Medications taken by $\geq$ 50 Medications taken by 20% antihypertensives, statins, c Medications taken by some lowering, hormone replaces Location: Spain	N: intervention (Med with nuts) 2454, control (Med with olive oil) 2543 - also low-fat arm, not discussed here, 2450 Level of risk for CVD: moderate Male: intervention 46%, control 41.3% Mean age (SD): intervention 67 (6), control 67 (6) years Age range: 55-80 years Smokers: intervention 14.5%, control 13.9% (current smokers) Hypertension: intervention 82.4%, control 82.1% Medications taken by $\geq$ 50% of those in the control group: nil Medications taken by $\geq$ 50% of those in the control group: ACEi, diuretics, other antihypertensives, statins, oral hypoglycaemics, antiplatelet therapy Medications taken by some, but < 20% of the control group: insulin, non-statin lipid- lowering, hormone replacement therapy Location: Spain Ethinicty: white from Europe 97%, Hispanic from Central or South America 1%-2%,	
Interventions	hazelnuts, 7.5 g almonds, µ diet with individual and up Control: Mediterranean die intensive education on diet <b>Dose aim</b> : unclear, food ra (MUFA) Baseline PUFA 6.4% E in i <b>Compliance by biomarke</b> <b>Compliance by dietary in</b> quency questionnaire • Energy intake, kcal/d: • Total fat intake, % E: (SD 5.4)		

### **PREDIMED 2013** (Continued)

	<ul> <li>PUFA intake, % E: intervention 7.7 (SD 1.8), (MD +1.6% E), control 6.1 (SD 1.4)</li> <li>PUFA n-3 intake (ALA plus marine omega-3), g/d: intervention 2.7 (SD not reported), (MD +0.5 g/d), control 2.2 (SD not reported)</li> <li>PUFA n-6 intake, g/d: LA, intervention 16.0 (SD 5.5), (MD +3.8 g/d), control 12.2 (SD 4.6) g</li> <li>Trans fat intake: not reported</li> <li>MUFA intake, % E: intervention 20.9 (SD 4.1), (MD -1.2% E), control 22.1 (SD 3.7)</li> <li>CHO intake, % E: intervention 39.7 (SD 6.3), (MD -0.7% E), control 40.4 (SD 5.9)</li> <li>Sugars intake: not reported</li> <li>Protein intake, % E: intervention 16.4 (SD 2.5), (MD 0.2% E), control 16.2 (SD 2.4)</li> <li>Alcohol intake, % E: not reported</li> <li>Compliance by other methods: scores on the 14-item Mediterranean-diet screener increased for the participants in both Mediterranean diet groups. Participants assigned to a Mediterranean diet with nuts significantly increased their consumption of extra virgin olive oil (to 50 g/d and 32 g/d, respectively) and nuts (to 0.9 and 6 servings/week, respectively)</li> <li>Inclusion basis: dietary intake data suggested total PUFA intake 1.6% E higher in intervention than control</li> </ul>
Outcomes	Main trial outcome: CVD events Dropouts: intervention 6.3% lost to follow-up for $\geq 2$ years, control 3.6% lost to follow- up for $\geq 2$ years Available outcomes: deaths, CV mortality, stroke, MI, CV events. Outcome data not altered in the republication of the main paper (Estruch 2018) Response to contact: contact established but no additional data provided
Notes	All data used were for the Mediterranean diet with nuts vs Mediterranean diet with olive oil, which is higher vs lower PUFA. As nuts were mixed it is not clear whether they were high in ALA or not (probably varied) Trial funding: mainly governmental funding, but olive oil and nuts were provided by companies

### Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Tables of random allocation were centrally elaborated. However the main paper (Es- truch 2013) was retracted and republished (as Estruch 2018) following a statistical analysis suggesting that baseline variables did not appear consistent with randomi- sation (Carlisle 2017). The republication

### **PREDIMED 2013** (Continued)

		states that partners were included in the trial without randomisation (in the same arms as family members) and that some clinics allocated by clinic rather than apply- ing the protocol specified individual ran- domisation. This puts allocation conceal- ment of some participants at high risk
Allocation concealment (selection bias)	High risk	Trial nurses in charge of the random alloca- tion were independent of the nursing staff, allocation was performed centrally. How- ever, see note on random sequence genera- tion
Blinding of participants and personnel (performance bias) All outcomes	High risk	Olive oil and nuts arms could not be blinded to participants
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "All medical records related to end points were examined by the end-point adjudication committee, whose members were unaware of the trial-group assign- ments."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "We used four sources of informa- tion to identify end points: repeated con- tacts with participants, contacts with fam- ily physicians, a yearly review of medical records, and consultation of the National Death Index." Attrition was < 10% per year, explained and balanced.
Selective reporting (reporting bias)	High risk	Many outcomes in the trials registry entry are not reported by allocated group for the full set of trial participants (for example, cognition)
Attention bias	Low risk	These appear very similar between the two Mediterranean diet groups
Compliance	Unclear risk	Neither tissue PUFA biomarkers nor TC data reported
Other bias	High risk	Retraction and republication in 2018 due to randomisation problems not reported in the initial publication. However, new out- come data not provided

Proudman 2015

Methods	RCT, parallel, (n3 EPA + DHA high dose vs n3 EPA + DHA low dose), 12 months Summary risk of bias: low
Participants	People with rheumatoid arthritis < 12 months' duration, disease-modifying anti- rheumatic drugs (DMARD)-naive N: 87 intervention, 53 control (analysed, intervention: 75 control: 47) Level of risk for CVD: low Male: 29% intervention, 25% control Mean age (SD): 56.1 (15.9) intervention, 55.5 (14.1) control Age range: unclear Smokers: 65.1% intervention, 54.7% control (includes current & previous smokers) Hypertension: not reported Medications taken by $\geq$ 50% of those in the control group: triple DMARD therapy (sulfasalazine 0.5 g/d, hydroxychloroquine 200 mg twice/day and methotrexate 10 mg once/week) Medications taken by 20%-49% of those in the control group: NSAIDS Medications taken by some, but < 20% of the control group: oral or parenteral steroids Location: Australia Ethnicity: not reported
Interventions	Type: supplement (fish oil) Comparison: high EPA + DHA vs low EPA + DHA + MUFA Intervention: 10 mL/d fish oil concentrate (BLT Incromega TG3525) providing 5.5 g/ d (3.2 EPA + 2.3 DHA) Control: 10 mL/d Sunola oil:capelin oil (2:1) providing 0-21 g EPA + 0-19 g/d DHA as TG (0.40 g/d EPA + DHA). Sunola oil was stated to be a monounsaturated oil <b>Dose aim</b> : increase 5.1 g/d EPA + DHA, <b>2.3% E n-3, 2.3% E PUFA</b> Baseline PUFA not reported <b>Compliance by biomarkers</b> : unclear, no serum TC reported, plasma phospholipid EPA and DHA reported, but not by intervention group, no other tissue fatty acids reported <b>Compliance by dietary intake</b> : not reported • Energy intake, kcal/d: not reported • Total fat intake, % E: not reported • SFA intake, % E: not reported • PUFA n-3 intake: not reported • PUFA n-6 intake: not reported • PUFA n-6 intake: not reported • MUFA intake, % E: not reported • MUFA intake, % E: not reported • MUFA intake, % E: not reported • Sugars intake: not reported • Sugars intake: not reported • Alcohol intake, % E: not reported • Alcohol intake of 2482

### Proudman 2015 (Continued)

	+ DHA, or 29.7 kcal/d, or 1.5% E. This is > 10% increase of assumed 6% E total PUFA intake at baseline, assuming no or minor PUFA in control (described as MUFA oil) <b>PUFA dose:</b> 1.5% E total PUFA Duration of intervention: 12 months
Outcomes	Main trial outcome: DMARD failure and remission Dropouts: 11 intervention, 6 control Available outcomes: mortality (nil death), adverse events including CVD, Disease Ac- tivity Score, diabetes, BMI change Response to contact: yes, trial authors supplied methodology data plus BMI change
Notes	DAS scores are reported as median and IQR in Proudman 2012 abstract (see Proudman 2015) Trial funding: the trial was supported by 'the National Health Medical Research Council of Australia and Royal Adelaide Hospital Research Committee. Melrose Health has provided support for ongoing studies.' The oil used in the trial was made by the Royal Adelaide Hospital Pharmacy

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The randomisation schedule was prepared using an online random num- ber generator and involved randomly per- muted blocks of size six."
Allocation concealment (selection bias)	Low risk	Quote: "Randomisation was performed by the RAH pharmacy, which also prepared and provided the study oils in 500 mL iden- tical dark brown bottles labelled with con- secutive study numbers"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Both participants and investiga- tors/assessors were blinded to the group al- location. Although the control oil was paler in colour than the fish oil, this was not evi- dent in the brown bottles. The 'fishy' odour of each oil was similar."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Both participants and investiga- tors/assessors were blinded to the group al- location" Quote: "Investigators and subjects re- mained blinded for all withdrawals."
Incomplete outcome data (attrition bias) All outcomes	Low risk	The flow of all trial participants shown in FIGURE 2

### Proudman 2015 (Continued)

Selective reporting (reporting bias)	Unclear risk	Outcomes reported in trial register matched with the outcomes reported in publications. However, the trial was retrospectively registered - registered in 2013, recruitment began in 2001
Attention bias	Low risk	No difference between groups
Compliance	Unclear risk	No TC reported, plasma phospholipid EPA and DHA reported, but not by interven- tion group, no other tissue fatty acids re- ported
Other bias	Low risk	None noted

### Puri 2005

Methods	RCT, parallel (n3 EPA vs non-fat), 2 arms, 12 months Summary risk of bias: low
Participants	People with Huntington's disease N: 67 intervention, 68 control (analysed, intervention: 39 control: 44) Level of risk for CVD: low Male: 57% intervention, 44% control Mean age (SD): 50 (9.3) intervention, 49 (9.0) control Age range: not reported Smokers: not reported Hypertension: not reported Medications taken by $\geq$ 50% of those in the control group: not reported Medications taken by 20%-49% of those in the control group: antidepressants Medications taken by some, but < 20%: neuroleptics Location: Australia, Canada, UK, USA Ethnicity: white (black, Asian) 94% (4%, 1%) intervention, 97% (3%, 0%) control
Interventions	Type: supplement (ethyl-EPA) Comparison: EPA vs paraffin (non-fat) Intervention: 2 x 2 x 500 mg capsules/d, total dose of 2 g/d ethyl-EPA (code name LAX- 101, purity 95%) Control: 2 x 2 x 500 mg capsules/d liquid paraffin <b>Dose aim</b> : increase 1.9 g/d EPA + DHA, <b>0.86% E n-3, 0.86% E PUFA</b> Baseline PUFA not reported <b>Compliance by biomarkers</b> : no serum TC reported, no tissue fatty acids reported <b>Compliance by dietary intake:</b> not reported • Energy intake, kcal/d: not reported • Total fat intake, % E: not reported • SFA intake, % E: not reported • PUFA intake, % E: not reported • PUFA n-3 intake: not reported

	<ul> <li>PUFA n-6 intake: not reported</li> <li>Trans fat intake: not reported</li> <li>MUFA intake, % E: not reported</li> <li>CHO intake, % E: not reported</li> <li>Sugars intake: not reported</li> <li>Protein intake, % E: not reported</li> <li>Alcohol intake, % E: not reported</li> <li>Compliance by other methods: 38 were excluded for protocol violations, 4 intervention and 16 control were non-compliant with capsules</li> <li>Inclusion basis: intended that omega-3 fats increased by 1.9 g/d EPA + DHA, or 0.86% E from omega-3 fats. This was compared to paraffin (no fat), so dose of total PUFA was 0.86% E. This is &gt; 10% increase of assumed 6% E total PUFA intake at baseline</li> <li>PUFA dose: 0.86% E total PUFA</li> <li>Duration of intervention: 12 months</li> </ul>
Outcomes	Main trial outcome: functional status in Huntington's disease Dropouts: 7 intervention, 7 control Available outcomes: measures of functional capacity, CV events, cancers (no deaths) Response to contact: yes (replied to say that no CV mortality or fatal MI occurred)
Notes	Trial funding: "Amarin Neuroscience Ltd. (formerly known as Laxdale Ltd.) was respon- sible for organizing and funding this clinical trial" as well as paying the salaries of several investigators

### Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "After screening and acceptance patients were assigned to treatment by re- ceiving a numbered pack supplied by a clinical trials packaging orga- nization independent of all other aspects of the trial. Randomization was stratified in a block size of four, with the appropriate number of blocks al- located to each centre. PCI Clinical Ser- vices held the randomization code until the database had been closed and all patients had been assigned"
Allocation concealment (selection bias)	Low risk	As above
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Placebo and ethyl-EPA capsules were of identical appearance" (though taste and smell not reported)

### Puri 2005 (Continued)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Randomisation described as "double- blind", "neither the participants nor the participating medical staff had access to this code during the course of the study"
Incomplete outcome data (attrition bias) All outcomes	High risk	Clearly reported and complete, however > 20% attrition
Selective reporting (reporting bias)	Unclear risk	No protocol or trials registry entry identi- fied
Attention bias	Low risk	Unlikely
Compliance	Unclear risk	No TC or tissue fatty acids reported
Other bias	Low risk	None noted

### Raitt 2005

Methods	RCT, parallel, (n3 EPA + DHA vs MUFA), 24 months Summary risk of bias: moderate or high
Participants	People with implantable cardioverter defibrillators and recent sustained VT/VF N: 100 intervention, 100 control Level of risk for CVD: high Male: 86% intervention, 86% control Mean age (SD): 63 (13) intervention, 62 (13) control Age range: not reported but 18-75 inclusion criteria Smokers: not reported Hypertension: 46% intervention, 55% control Medications taken by $\geq$ 50% of those in the control group: diuretic, beta blockers, ACEi Medications taken by 20%-49% of those in the control group: digoxin, statins Medications taken by some, but < 20% of the control group: Ca channel blocker Location: USA Ethnicity: white 94% intervention, 97% control
Interventions	Type: supplement (fish oil capsules vs olive oil capsules) Comparison: EPA + DHA vs MUFA Intervention: 1.8 g/d fish oil capsules (Hoffman LaRoche, including ethyl esters of EPA and DHA, 0.76 g/d EPA, 0.54 g/d DHA) Control: 1.8 g/d olive oil capsules (Hoffman LaRoche, 73% oleic acid) <b>Dose aim</b> : increase 1.3 g/d EPA + DHA, <b>0.6% E n-3, 0.6% E PUFA</b> Baseline PUFA not reported <b>Compliance by biomarkers</b> : while control group plasma and platelet DHA and EPA did not change, there were increases of 2%-8.3% in the intervention group. Plasma and red blood cell omega-3 fats were higher in intervention than control participants at all time points (P < 0.001). No data on total PUFA or LA plasma or red blood cell fats, and no TC reported

	Compliance by dietary intake: not reported
	• Energy intake, kcal/d: not reported
	• Total fat intake, % E: not reported
	• SFA intake, %E: not reported
	• PUFA intake, % E: not reported
	• PUFA n-3 intake: not reported
	• PUFA n-6 intake: not reported
	• Trans fat intake: not reported
	• MUFA intake, % E: not reported
	• CHO intake, % E: not reported
	Sugars intake: not reported
	• Protein intake, % E: not reported
	Alcohol intake, % E: not reported
	Compliance by other methods: no others reported
	Inclusion basis: aims suggested total PUFA intake 0.6% E higher in intervention than
	control, a 10% increase on assumed 6% E from PUFA at baseline
	PUFA dose: 0.6% E
	Duration of intervention: 24 months (median 718 days)
Outcomes	Main trial outcome: time to first episode of VT/VF
	Dropouts: 17 intervention, 26 control
	Available outcomes: deaths, CV death, MI, angina, revascularisation, atrial fibrillation,
	sudden cardiac death, cancer
	Response to contact: contact attempted but no response to date
Notes	Trial funding: NIH and Hoffman LaRoche

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "computer generated block ran- domisation scheme"
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Participant blinding unclear
Blinding of outcome assessment (detection bias) All outcomes	Low risk	ICD traces were viewed by researchers blinded to allocation, "double blind placebo-controlled"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Almost all participants were included in outcome assessment, well described

### Raitt 2005 (Continued)

Selective reporting (reporting bias)	High risk	NCT registered in February 2000, trial car- ried out from February 1999 to January 2004. Most outcomes stated in registry en- try reported, but quality of life missing
Attention bias	Low risk	Capsules were the only different interven- tions between arms, little opportunity for attention bias
Compliance	Unclear risk	No data on total PUFA or LA plasma or red blood cell fats, and no TC reported
Other bias	Low risk	None noted

### Rose 1965

Methods	RCT, 2 arms, parallel (n6 LA vs MUFA), 24 months Summary risk of bias: moderate to high
Participants	People with ischaemic heart disease CVD risk: high N: 28 intervention, 26 control (analysed 15 intervention, 12 control) % male: not reported Mean age: 52.6 intervention, 55 control (no SDs) Age range: not reported Smokers: not reported Hypertension: not reported Medications taken by $\geq$ 50% of those in the control group: not reported Medications taken by 20%-49% of those in the control group: not reported Medications taken by some, but < 20% of the control group: not reported Location: UK Ethnicty: not reported
Interventions	Type: test oil provided (equivalent advice to both arms) Comparison: n-6 vs MUFA Intervention: 80 g/day corn oil to be taken in 3 equal doses at meal-times plus participants were instructed to avoid fried foods. Fatty meat, sausages, pastry, ice-cream, cheese, cakes, milk, eggs, butter were restricted: assuming 80% LA in corn oil, 64 g/d LA or 576 kcal/ d or 28.8% E from LA Control: 80 g/day olive oil plus participants were instructed to avoid fried foods, fatty meat, sausages, pastry, ice-cream, cheese, cakes, milk, eggs, butter were restricted. as- suming 12% LA and 69% MUFA in olive oil, 9.6 g/d LA or 4.3% E LA and 55.2 g/d MUFA or 24.8% E <b>Dose aim: +24.5% E from LA, -24.8% E MUFA</b> Baseline PUFA: unclear <b>Compliance using biomarkers:</b> serum TC reduced, but not statistically significantly reduced in intervention compared to control (-0.49 mmol/L, 95% CI -1.34 to 0.36). No fatty acid biomarkers reported

	<ul> <li>Compliance using dietary assessment: poor. Measured using questionnaire. Mean intake of oil in intervention was 595 kcal/d or 476 kcal/d LA or 23.8% E, in control 540 kcal/d or 3.2% E LA and 18.6% E MUFA, achieved: +20.6% E from LA, -18.6% E MUFA within the oils, unclear how diet altered</li> <li>Energy intake: intervention 2070 kcal/d control 2045 kcal/d</li> <li>Total fat intake: intervention 50 g/d + 595 kcal from oil or 1045 kcal/d or 52% E, control 45 g/d + 540 kcal from oil or 945 kcal/d or 47.3% E</li> <li>SFA intake: not reported</li> <li>PUFA n-3 intake: not reported</li> <li>PUFA n-6 intake: +20.6% E (higher in intervention than control)</li> <li>Trans fat intake: not reported (oils provided so not likely to be a problem)</li> <li>MUFA intake: intervention 189 g/d or 756 kcal/d or 37.8% E, control 216 g/d or 864 kcal/d or 43.2% E</li> <li>Sugars intake: not reported</li> <li>Protein intake: intervention 57 g/d or 228 kcal/d or 11.4% E, control 49 g/d or 196 kcal/d or 9.8% E</li> <li>Alcohol intake: not reported</li> <li>Compliance by other methods: no others reported</li> <li>Inclusion basis: aim was to increase omega-6 fats, not total PUFA. Total PUFA not reported but LA dose so big that total PUFA must have been increased in intervention compared to control. Best estimate 20.6% E from LA, assume equivalent to 20.6% E from total PUFA</li> </ul>
Outcomes	Main trial outcome: occurrence of infraction Dropouts: 6 intervention, 11 control?, details provided in table but unclear how many dropped out. Available outcomes: major CVD events, MI (fatal and non-fatal), sudden death, serum cholesterol Response to contact: not attempted as published in the 1960s
Notes	Trial funding: no details The trial had a 3rd control arm (no intervention), which has not been used here

### Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	When a new participant was accepted for the trial a sealed envelope was opened con- taining the allocation instructions. In the case of participants allocated to an oil group the instructions referred only to a code number

### Rose 1965 (Continued)

Allocation concealment (selection bias)	Unclear risk	Unclear
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The physicians in charge knew which par- ticipants were receiving oil, but they did not know until the end of the trial the kind of oil that they were receiving
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The electrocardiograms were assessed with- out the knowledge of the participant's treat- ment group
Incomplete outcome data (attrition bias) All outcomes	Low risk	52% intervention, and 57% control re- mained in the trial after 24 months. How- ever, the list of reasons and complications is provided
Selective reporting (reporting bias)	Unclear risk	No trial registry record or protocol found
Attention bias	Low risk	Oil provided to both groups, appeared sim- ilar
Compliance	Low risk	TC somewhat reduced in intervention compared to control (-0.49 mmol/L, 95% CI -1.34 to 0.36). No fatty acid biomarkers reported
Other bias	Low risk	None noted

### Rossing 1996

Methods	RCT, parallel, (n3 EPA + DHA vs MUFA), 12 months Summary risk of bias: moderate or high
Participants	Adults with insulin-dependant diabetes mellitus, diabetic nephropathy and normal BP N: 18 intervention, 18 control (analysed, 17 intervention, 15 control) Level of risk for CVD: moderate Male: 64% intervention, 67% control Mean age (SD) years: 32 (7) intervention, 34 (10) control Age range: 18-55 years Smokers: 50% intervention, 47% control Hypertension: not reported Medications taken by $\geq$ 50% of those in the control group: insulin Medications taken by 20%-49% of those in the control group: not reported Iccation: Denmark Ethnicity: not reported

Interventions	Type: supplement Comparison: fish oil vs olive oil Intervention: cod-liver oil emulsion (Pharma-Vinci A/S Denmark). EPA 2 g/d, DHA 2. 6 g/d, plus 24.1% SFA, 45.6% MUFA, 23.6% EPA + DHA, 6.7% other fats. Assumed total PUFA 4.6 g/d Control: olive oil emulsion (Pharma-Vinci A/S Denmark). 15.1% SFA, 76.9% MUFA, 8.0% other fats. Assumed total PUFA 0 g/d <b>Dose aim</b> : increase 4.6 g/d EPA + DHA, <b>2.1% E n-3</b> , <b>2.1% E PUFA</b> Baseline PUFA: unclear <b>Compliance using biomarkers:</b> assessed through omega-3 incorporation in platelets, and the paper reports significantly higher omega-3 levels in platelets at 12 months. EPA % was 0.59 (SE 0.07) in control, 2.70 (SE 0.29) in intervention arm latest reading. DHA % was 1.99 (SE0.13) control, 3.57 (SE 0.18) intervention (P < 0.001 between intervention and control for both). Total PUFA not reported. HOWEVER serum TC rose more in the intervention arm (+ 0.46 mmol/L) than control (+ 0.13 mmol/L) during the trial <b>Compliance using dietary assessment:</b> poor. Unclear how measured, only protein re- ported • Energy intake: not reported • SFA intake: not reported • PUFA n-3 intake: not reported • PUFA intake: not reported • PUFA intake: not reported • PUFA intake: not reported • Trans fat intake: not reported • Trans fat intake: not reported • CHO intake: not reported • Sugars intake: not reported • Protein intake: not reported • Stass intake: not reported • Protein intake: not reported • Sugars intake: not reported • Protein intake: not reported • Protein intake: not reported • Protein intake: not reported • Protein intake: not reported • Sugars intake: not reported • Protein intake: not reported • Protein intake: not reported • PuFA. Total PUFA not reported but omega-3 dose rose by 2.1% E, so assume total PUFA. Total PUFA not reported but omega-3 dose rose by 2.1% E, so assume total PUFA did also as compared to MUFA. Best estimate 2.1% E total PUFA dose, more than 10% increase from assumed baseline of 6% E <b>PUFA dose:</b> interded dose only, 2.1% E
Outcomes	Main trial outcome: diabetic nephropathy Dropouts: 1 intervention, 3 control (though 3 further intervention participants are not included in all data) Available outcomes: mortality (nil), breast cancer, TC, LDL, systolic BP (TGs reported as medians so not used, albuminuria, fractional albumin clearance, transcapillary escape rate of albumin, prothrombin fragment reported as geometric means or medians, HbA1c, HDL and diastolic BP too different at baseline to include, glomerular filtration rate (GFR), plasminogen activator inhibitor-1 (PAI1), tissue plasminogen activator (TPA), fibrinogen etc. not relevant) Trial author reply: yes

### Rossing 1996 (Continued)

NotesTrial funding: supported by The Danish Heart Association. Eskisol Fish oil and placebo<br/>oil emulsions were provided by Pharma-Vinci A/S, Frederiksvaerk, Denmark

### Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomised using "con- cealed randomization to receive either fish oil or olive oil in blocks of 4 according to their glomerular filtration rate."
Allocation concealment (selection bias)	Unclear risk	No further details
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Active and placebo (olive oil) were given as emulsions with orange flavour. At the end patients were allowed to guess about treatment and ~50% were right" (from trial author response)
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropouts similar between groups although relatively high for small sample size. 3 drop- outs from fish oil and 1 from control due to side effects. ITT appears to have been given for albuminuria only
Selective reporting (reporting bias)	Unclear risk	No trials registry entry or protocol found
Attention bias	Low risk	Time and attention appear to be the same. All participants were given dietary advice
Compliance	High risk	Total PUFA in body fractions not reported. However, serum TC rose more in the inter- vention arm (+0.46 mmol/L) than control (+0.13 mmol/L) during the trial
Other bias	Low risk	None noted

Simon 1997

Methods	RCT, parallel, (low fat with low PUFA vs usual diet), 24 months Summary risk of bias: moderate or high
Participants	Women with a high risk of breast cancer N: 98 intervention, 96 control (analysed 72 intervention: 75 control) Level of risk for CVD: low Male: 0% intervention, 0% control Mean age (SD): 46 (not reported) intervention, 46 (not reported) control Age range: not reported Smokers: not reported Hypertension: not reported Medications taken by $\geq$ 50% of those in the control group: not reported Medications taken by 20%-49% of those in the control group: not reported Medications taken by some, but < 20% of the control group: not reported (those on statins excluded) Location: USA Ethenicity: white 89%, African American 9%, Hispanic 2%
Interventions	Type: dietary advice Comparison: reduced fat including PUFA (intervention) vs usual diet Intervention: aims total fat 15% E; methods biweekly individual dietetic appointments over 3 months followed by monthly individual or group appointments, including ed- ucation, goal setting, evaluation, feedback and self-monitoring. Intervention delivered face to face by a dietitian Control: aim usual diet, no stated intervention(s) <b>Dose aim</b> : unclear PUFA Baseline 7.7% E PUFA <b>Compliance by biomarkers</b> : no fatty acid biomarkers reported, TC reported in a sub- group and fell by 0.34 mmol/L in intervention and fell by 0.08 mmol/L in control over 1 year <b>Compliance by dietary intake:</b> assessed using 3-day 24-h recalls every 3 months, 1 year data reported • Energy intake, kcal/d: intervention 1570 (SE 47.0), control 1594 (SE 63.6) • Total fat intake, % E: intervention 1570 (SE 47.0), control 1594 (SE 63.6) • Total fat intake, % E: intervention 17.6 (SD 5.8), control 33.8 (SD 7.4) • SFA intake, % E: intervention 3.8 (SD 1.7), control 7.3 (SD 4.1) • PUFA n-3 intake: not reported • PUFA n-6 intake: not reported • PUFA n-6 intake: not reported • Trans fat intake: not reported • MUFA intake, % E: intervention 6.1 (SD 3.0), control 12.8 (SD 6.3) • CHO intake: not reported • Sugars intake: not reported • Protein intake, not reported • Alcohol intake: not reported • Alcohol intake: not reported <b>Compliance, other methods</b> : not reported <b>Inclusion basis:</b> no intention to increase total PUFA stated. Acheived total PUFA re- duction of 6.7% E in intervention compared to control at 1 year, > 10% higher than baseline 7.7% E from total PUFA

### Simon 1997 (Continued)

	<b>Compliance: dietary assessment</b> Duration of intervention: 24 months (mean years in trial: control 1.8, intervention 1.7)
Outcomes	Main trial outcome: intervention feasibility Dropouts: unclear intervention, unclear control Available outcomes: TC, TG, LDL and HDL (2 deaths, but unclear in which arms, 8 cancer diagnosis but not clear in which arms), (weight, BMI, % body fat and waist-hip ratio reported but all too unbalanced at baseline to use) Trial author contact: Dr Simon confirmed that some deaths occurred (but not in which arms) and sent a further reference
Notes	Trial funding: Marilyn J Smith Fund, Harper-Grace Hospitals, the Wesley Foundation, National Cancer Institute, Karmanos Cancer Institute Core Grant, the United Founda- tion of Detroit Trial <b>aim</b> was to reduce total fat to 15% E (SFA not mentioned), but PUFA fat intake in the intervention group was significantly lower than in the control group Note: PUFA lower in intervention arm, so higher PUFA arm is the control

### Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Stratified by age and randomised (block size 2)
Allocation concealment (selection bias)	Unclear risk	Allocation method not clearly enough de- scribed
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants not blinded (as given dietary advice or not), personnel unclear
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear, deaths, cancer and CV events are dropouts - unclear if any data missing
Selective reporting (reporting bias)	Unclear risk	No protocol or trials registry entry found
Attention bias	High risk	Time and attention in the intervention group not mirrored in control
Compliance	High risk	No fatty acid biomarkers reported, TC re- ported in a subgroup and fell by 0.34 mmol/L in intervention and fell by 0.08 mmol/L in control over 1 year (but control group should have been higher in PUFA in

#### Simon 1997 (Continued)

		this trial)	
Other bias	Low risk	None noted	
Sydney Diet-Heart 1978			
Methods	-	Sydney Diet-Heart Study RCT, 2 arm, parallel (n6 LA vs SFA), 4.3 years Summary risk of bias: low (as diet advice trial)	
Participants	Intervention: randomised 2 Mean years in trial: control % male: 100 Age: mean intervention 48 Age range: 30-59 years Smokers: intervention 71.5 Hypertension: unclear Medications taken by $\geq$ 50 Medications taken by 20%	CVD risk: high Control: randomised 237, analysed 221 at 2 years Intervention: randomised 221, analysed 205 at 2 years Mean years in trial: control 4.3, intervention 4.3 % male: 100 Age: mean intervention 48.7 (SD 6.8), control 49.1 (SD 6.5) Age range: 30-59 years Smokers: intervention 71.5%, control 68.8% Hypertension: unclear Medications taken by $\geq$ 50% of those in the control group: not reported Medications taken by 20%-49% of those in the control group: not reported Medications taken by some, but < 20% of the control group: not reported Location: Australia	
Interventions	Comparison: safflower oil a SFA and MUFA) Control aims: reduction in a to use PUFA margarine insta Intervention aims: SFA 109 cholesterol < 300 mg/day (advised and tutored indiv thereafter) <b>Dose aim</b> : increase <b>6.6% H</b> Baseline n-6: unclear, 6.1% <b>Compliance by biomarker</b> to control (-0.30 mmol/L, 9 <b>Compliance by dietary in</b> • Energy intake, kcal/d: • Total fat intake, % E: <b>fat</b> , not statistically significant • PUFA intake, % E: inte statistically significant)	<ul> <li>Type: diet advice and supplemental foods</li> <li>Comparison: safflower oil and safflower oil-based margarine (n-6) vs usual diet (reduced SFA and MUFA)</li> <li>Control aims: reduction in energy if overweight, no other specific dietary advice, allowed to use PUFA margarine instead of butter (no specific dietary instruction, except re weight)</li> <li>Intervention aims: SFA 10% E, PUFA 15% E, reduction in energy if overweight, dietary cholesterol &lt; 300 mg/day through provision of safflower oil and safflower margarine (advised and tutored individually, diet assessed 3 times in first year, twice annually thereafter)</li> <li>Dose aim: increase 6.6% E PUFA, most of which n6</li> <li>Baseline n-6: unclear, 6.1% E PUFA, mostly n6</li> <li>Compliance by biomarkers: serum TC significantly reduced in intervention compared to control (-0.30 mmol/L, 95% CI -0.51 to -0.09). No body fatty acid markers reported</li> <li>Compliance by dietary intake: good. From diet records, medians provided</li> <li>Energy intake, kcal/d: intervention -1.9, control -1.1 (reduction of 0.8% E total fat, not statistically significant)</li> <li>SFA intake, % E: intervention -6.9, control -2.1 (reduction of 4.8% E SFA, statistically significant)</li> <li>PUFA intake, % E: intervention +9.3, control +2.2 (increase of 7.1% E PUFA,</li> </ul>	

### Sydney Diet-Heart 1978 (Continued)

	<ul> <li>PUFA n-6 intake: not reported</li> <li>Trans fat intake: not reported</li> <li>MUFA intake, % E: intervention -3.4, control -0.7 (reduction of 2.7% E MUFA, statistically significant)</li> <li>CHO intake, % E: intervention +1.4, control +0.1 (increase of 1.3% E CHO, not statistically significant)</li> <li>Sugars intake: not reported</li> <li>Protein intake, % E: intervention +0.4, control +1.2 (decrease of 0.8% E protein, not statistically significant)</li> <li>Alcohol intake, % E: intervention +0.7, control +1.7 (decrease of 1.0% E alcohol, not statistically significant)</li> <li>Compliance, other methods: not reported</li> <li>Inclusion basis: aimed to increase total PUFA intake as well as reduce SFA PUFA dose: 7.1% E PUFA (from dietary intake data)</li> <li>Duration of intervention: 2-7 years</li> </ul>
Outcomes	Main trial outcomes: CV mortality and morbidity Dropouts: unclear, probably 16 dropouts in each arm, but participants were included from 2-7 years Available outcomes: mortality, TC, TG Response to contact: yes, further data provided
Notes	Trial funding: Life Insurance Medical Research Fund of Australia and New Zealand

### Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "table of random numbers gen- erated by a research assistant and was con- cealed until after medical evaluations and testing at baseline were completed"
Allocation concealment (selection bias)	Low risk	As above
Blinding of participants and personnel (performance bias) All outcomes	High risk	Very difficult to blind trials where par- ticipants need to make their own dietary changes
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Initially masked to group assignment (though success of blinding not checked)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Survival analysis used
Selective reporting (reporting bias)	Unclear risk	No protocol or trials registry entry located

### Sydney Diet-Heart 1978 (Continued)

Attention bias	High risk	Different levels of dietary support (non-di- etary aspects were equivalent)	
Compliance	Low risk	TC significantly reduced in intervention compared to control (-0.30 mmol/L, 95% CI -0.51 to -0.09). No body fatty acid markers reported	
Other bias	Low risk	None noted	
Veterans Admin 1969			
Methods	Veterans Administration Trial RCT, 2 arms, parallel (n6 LA Summary risk of bias: modera		
Participants	CVD risk: low Control: randomised 422, ana Intervention: randomised 424 Mean years in trial: control 3. % male: 100 Age: mean control 65.6, inter Age range: all 54-88 years Smokers: intervention 283, co Hypertension: unclear Medications taken by $\geq$ 50% Medications taken by 20%-49 Medications taken by some, b gens, corticoids, androgens, co Location: USA	<ul> <li>Control: randomised 422, analysed 422</li> <li>Intervention: randomised 424, analysed 424</li> <li>Mean years in trial: control 3.7, intervention 3.7</li> <li>% male: 100</li> <li>Age: mean control 65.6, intervention 65.4</li> <li>Age range: all 54-88 years</li> <li>Smokers: intervention 283, control 279 (unknown intervention 41, control 58)</li> <li>Hypertension: unclear</li> <li>Medications taken by ≥ 50% of those in the control group: not reported</li> <li>Medications taken by 20%-49% of those in the control group: not reported</li> <li>Medications taken by some, but &lt; 20% of the control group: digitalis, diuretics, oestrogens, corticoids, androgens, coumarins, nicotinic acid</li> </ul>	
Interventions	Comparison: corn, soybean, diet Control aims: provided, total Intervention aims: total fat 40 soybean, safflower and cottonse <b>Dose aim</b> : 2/3 of baseline SFA Baseline n-6: 4% E LA, contro <b>Compliance by biomarkers:</b> to 12.8% fat in control and 3 diet). Serum TC reduced, but control (-0.37 mmol/L, 95%) <b>Compliance by dietary intak</b> room attendance - described a	Type: diet provided (residential institution) Comparison: corn, soybean, safflower and cottonseed oils (n-6) vs usual institutional diet Control aims: provided, total fat 40% E (whole diet provided) Intervention aims: total fat 40% E, 2/3 of SFA replaced by unsaturated fats (from corn, soybean, safflower and cottonseed oils), dietary cholesterol reduced (whole diet provided) <b>Dose aim</b> : 2/3 of baseline SFA is increase of ~ <b>12%E PUFA</b> Baseline n-6: 4% E LA, control arm 4.8% E PUFA <b>Compliance by biomarkers:</b> subcutaneous 18:2 + 18:3 11.7% fat at baseline, rising to 12.8% fat in control and 34.8% fat in intervention (after "prolonged" adherence to diet). Serum TC reduced, but not statistically significantly in intervention compared to control (-0.37 mmol/L, 95% CI -0.77 to 0.03) <b>Compliance by dietary intake: unclear,</b> checked using coloured tickets to assess dining room attendance - described as 49% in intervention and 56% in controls. Laboratory analysis of the mean of over 400 weekly collections of diet provided:	

### Veterans Admin 1969 (Continued)

	<ul> <li>Energy intake, kcal/d: intervention 2496, control 2496</li> <li>Total fat intake, % E: intervention 38.9 (SD 1.9), control 40.1 (SD 2.2)</li> <li>SFA intake, % E: intervention 8.3, control 18.5 (decrease 10.2% E SFA)</li> <li>PUFA intake: not reported but shown in graph as 18:2 + 18:3 -12% of dietary fat (4.8% E) in control and 43% in intervention (17.2% E), increase 12.4% E</li> <li>PUFA n-3 intake, % E: not reported</li> <li>PUFA n-6 intake; w E: intervention 16.1, control 4.4 (increase 11.7% E LA)</li> <li>Trans fat intake: not reported</li> <li>MUFA intake; w E: intervention 14.6, control 17.1 (decrease 2.5% E MUFAs)</li> <li>CHO intake: not reported</li> <li>Sugars intake: not reported</li> <li>Protein intake, % E: intervention 15.6 (SD not reported), control 15.4 (SD not reported)</li> <li>Alcohol intake: not reported</li> <li>Inclusion basis: aim was to increase unsaturated fats, not total PUFA. Total PUFA not reported but LA dose 11.7% E (best estimate), &gt; 10% increase from baseline of -5% E PUFA dose: 11.7% E from total PUFA (best estimate from food composition data) Duration of intervention: up to 8-9 years</li> </ul>
Outcomes	Main trial outcomes: mortality, heart disease Dropouts: intervention 117, control 58 withdrawals over whole trial, a few participants were involved for up to 8-9 years Available outcomes: mortality, CV mortality (sudden death, definite MI, definite stroke, angina, PAD events), cancer deaths, cancer diagnoses, stroke, non-fatal MI, total MI, CHD deaths (fatal MI and sudden death due to CHD), CHD events (any MI or sudden death due to CHD), some data on TC, but no variance info Response to contact: attempted but no author contact established (trial published in 1969)
Notes	Trial dates: recruitment 1959-1967 Trial funding: mainly US Public Health Service, Los Angeles County Heart Assoc, Arthur Dodd Fuller Assoc, but Corn Products Co (provided Corn oil and margarine), National Soybean Processors Assoc (provided soybean oil), Pitman-Moore Co (provided mar- garine), Frozen Desserts Co (imitation ice cream). All trial authors worked for academic or health institutions

# Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "table of random numbers used"
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Institution provided diet in a masked fash- ion

### Veterans Admin 1969 (Continued)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Physician knowledge of allocation was as- sessed and found not much better than ran- dom
Incomplete outcome data (attrition bias) All outcomes	Low risk	All followed up via Veterans Admin system
Selective reporting (reporting bias)	Unclear risk	No protocol or trials registry entry located
Attention bias	Low risk	Appeared equivalent, diet provided to both arms
Compliance	Low risk	Subcutaneous 18:2 + 18:3 11.7% fat at baseline, rising to 12.8% fat in control and 34.8% fat in intervention (after "pro- longed" adherence to diet). TC reduced, but not statistically significantly in inter- vention compared to control (-0.37 mmol/ L, 95% CI -0.77 to 0.03)
Other bias	Low risk	None found
	Summary risk of bias: moderate to high	
Methods Participants	RCT, 2 arms, parallel (n6 LA vs SFA), 2 years Summary risk of bias: moderate to high People with stable coronary artery disease CVD risk: high N: intervention (sunflower oil): 100 randomised, analysed at 2 years 94; control (coconut oil): 100 randomised, analysed at 2 years 96 Mean years in trial: 2 % male: intervention 92.9%, control 93.9% Age, mean (SD) years: intervention 59.0 (8.9), control 59.0 (8.4) Age range: unclear Smokers, ex: intervention 57.1%, control 54.1% Hypertension: intervention 55.1%, control 58.2% Medications taken by $\geq$ 50% of those in the control group: statins Medications taken by 20%-49% of those in the control group: not reported Medications taken by some, but < 20% of the control group: fibrates, nicotinic acid	
	Location: India Ethnicity: not reported	
Interventions	Type: food (cooking oil) provided Comparison: sunflower oil (n6) vs coconut oil (SFA) Intervention aims: whole family to use branded sunflower oil for cooking (15% E pro- vided in form of sunflower oil, ~66% PUFA) Control aims: whole family to use branded coconut oil for cooking (15% E provided in	

### Vijayakumar 2014 (Continued)

	form of coconut oil, ~5% PUFA) Dose aim: increase 9.2% E PUFA Baseline PUFA: unclear Compliance by biomarkers: Serum TC reduced but not significantly reduced in inter- vention compared to control (-0.06 mmol/L, 95% CI -0.22 to 0.34) though rose slightly in control, fell slightly in intervention. No biomarker data reported Compliance by dietary intake: unclear. Reports that 7-day recall and diet diaries were used to monitor intake, but results not provided • Energy intake: not reported • Total fat intake: not reported • SFA intake: not reported • PUFA n-3 intake: not reported • PUFA n-6 intake: not reported • Trans fat intake: not reported • MUFA intake: not reported • CHO intake: not reported • Sugars intake: not reported • Alcohol intake: not reported • Alcohol intake: not reported Inclusion basis: did not aim to increase total PUFA intake. Quantity and standard compositions suggest dose -9.2% E total PUFA, > 10% more than assumed baseline of 6% E PUFA PUFA dose: 9.2% E PUFA Duration of intervention: 2 years
Outcomes	Main trial outcome: CV risk factors Dropouts: intervention 6 lost, control 4 lost Available outcomes: lipids, death, revascularisation, (glycaemic control, weight, BMI available but unbalanced at baseline) Response to contact: author replied and provided additional outcome data
Notes	Trial funding: coconut development board, Amrita Institute of Medical Science and Research. Sponsors had no role in trial design or analysis

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Block randomisation with 5 blocks of 40
Allocation concealment (selection bias)	Unclear risk	Unclear
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Unlikely as participants and their families used branded oils

### Vijayakumar 2014 (Continued)

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unclear
Incomplete outcome data (attrition bias) All outcomes	Low risk	5% withdrawals. Clear, with reasons
Selective reporting (reporting bias)	Unclear risk	Unclear, no protocol or trials register entry found
Attention bias	Low risk	Appeared equivalent
Compliance	Low risk	TC reduced in intervention compared to control (-0.06 mmol/L, 95% CI -0.22 to 0.34, rose slightly in control, fell slightly in intervention). No biomarker data reported
Other bias	Low risk	None noted
Methods	The Walnut and Healthy Aging Study (WAHA) 2 arms, parallel RCT (n3 ALA vs mixed fats, ALA provided as walnuts), 2 years Summary risk of bias: moderate to high	
Methods Participants	2 arms, parallel RCT (n3 ALA vs mixed fats, ALA provided as walnuts), 2 years	
	Medications taken by 20%-499	% of those in the control group: not reported t < 20% of the control group: not reported
Interventions	Type: supplement (food) Comparison: ALA vs nil Intervention: 15% of daily energy intake as walnuts. The estimated amount of walnuts ranged from 1-2 oz/d (~30-60 g/day). Sachets for daily consumption containing 30, 45, or 60 g of raw, pieced walnuts were provided as 8-week allotments to be eaten daily, preferably as the raw product, either as a snack or by incorporating them into shakes, yogurts, cereals, or salads. To improve participants' compliance, 1- kg extra walnut allowances were provided every 2 months to take into account family needs	

Control: usual diet without walnuts

Compliance: assessed by dietitians through Food Frequency Questionnaires, recount of empty packages, and changes in fatty acids concentrations. 95% consumed  $\geq 1$  oz./ d. The proportion of  $\alpha$ -linolenic acid in red blood cell counts increased in the walnut group by 0.162% (95% CI 0.143 to 0.181) and in the control group by 0.015% (95% CI -0.005 to 0.035) (P < 0.001)

**Dose aim**: increase (assuming 10% E in walnuts is ALA) 1.5% E n3 ALA. 45 g walnut gives ~65% or 29.3 g oil, of which ~68% PUFA, 19.9 g/d oil, 9% E PUFA Baseline PUFA: unclear, control 7.9% E PUFA

**Compliance by biomarkers:** erythrocyte ALA increased by 28% in intervention, reduced by 17% in control (in a subsample of participants, percentage of total fatty acids in red blood cells also increased in intervention group compared to control, no other erythrocyte fatty acids reported. TC fell by 0.19 mmol/L (SD 0.04) in intervention, and by 0.01 mmol/L (SD 0.04) in control to 1 year

**Compliance by dietary intake:** mean of five, 24-h diet recalls over 2 years of trial

• Energy intake, kcal: intervention 1821 (SD not reported), control 1593 (SD not reported)

• Total fat intake, % E: intervention 41.5 (SD not reported), control 35.6 (SD not reported) (increase of 5.9% E)

• SFA intake, % E: intervention 10.9 (SD not reported), control 11.9 (SD not reported) (reduction of 1.0%E SFA)

• PUFA intake, % E: intervention 15.3 (SD not reported), control 7.9 (SD not reported) (increase of 7.4% E PUFA)

• PUFA n-3 intake, % E: intervention 2.5 (SD not reported), control 0.9 (SD not reported) (increase of 1.6% E)

• PUFA n-6 intake, % E: intervention 12.9 (SD not reported), control 7.0 (SD not reported (increase of 5.9% E)

• Trans fat intake: not reported

• MUFA intake, % E: intervention 12.4 (SD not reported), control 12.4 (SD not reported (0% E)

• CHO intake, % E: intervention 44.8 (SD NRnot reported, control 48.2 (SD not reported) (reduction of 3.4% E)

• Sugars intake: not reported

• Protein intake, % E: intervention 15.4 (SD not reported), control 16.3 (SD not reported) (decrease of 0.9% E)

- Alcohol intake, not reported
- (Also slightly higher intakes of most micronutrients reported)

**Compliance, other methods**: assessed by dietitians through Food Frequency Questionnaires and recount of empty packages, 95% consumed  $\geq 28g/d$ 

**Inclusion basis:** aimed to increase walnuts, not total PUFA. Resulted in increase of 7. 4% E total PUFA

**PUFA dose:** 7.4% E PUFA (from dietary intake data)

Duration of intervention: 2 years

Outcomes

Main trial outcome: change in cognitive decline (results not yet published) Dropouts: 36 intervention, 21 control (after 1 year)

Available outcomes: CVD events, cancers, lipids (for TG and HDL only data states "no between diet differences were observed"), weight (waist circumference was provided but without variance, abstract stated that "there were no significant changes in body fat and

### WAHA - Ros 2016 (Continued)

	waist-to-hip ratio over time and between the two groups"). Cognitive, ophthalmological, inflammatory markers, glycaemic status and other outcomes are not yet available. Response to contact: author replied and provided additional outcome and methodolog- ical data
Notes	Trial funding: funding was provided by the Calfornia Walnut Commission The 2-year results as well the full 1-year results are yet to be published

## Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "randomized to either the control or walnut group using a computerized ran- dom number table with stratification by center, sex, and age range. Couples entering the trial were treated as one number and were randomized into the same group"
Allocation concealment (selection bias)	Low risk	Author reply stated "Baseline subject data was collected before randomization. Ran- domization was done by the clinician, pressing the key on the computer"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Single-blind. Quote: "An unavoidable limitation of the study is not being able to blind participants to the intervention since it consists of a whole food" Rajaram 2017
Blinding of outcome assessment (detection bias) All outcomes	High risk	Single-blind. Author reply stated "Study personnel not in contact with the sub- jects were blind to the treatment assign- ment. So (lab technicians, ophthalmology technician, neuro cognitive testers) were not aware of the treatment assignment. Of course clinicians who were visited by sub- jects every two months, knew the treatment assignment"
Incomplete outcome data (attrition bias) All outcomes	Low risk	38/362 dropouts in intervention group = 10.5%. 34/346 dropouts in control group = 9.8%. Similar dropout in groups over 2 years
Selective reporting (reporting bias)	Unclear risk	Although prospectively registered, no full results paper published - results from con- ference abstracts and papers only report some secondary outcomes and dietary data

## WAHA - Ros 2016 (Continued)

Attention bias	Unclear risk	Not enough detail to assess	
Compliance	Low risk	Erythrocyte ALA increased by 28% in in- tervention, reduced by 17% in control (in a subsample of participants), percentage of total fatty acids in red blood cells also in- creased in intervention group compared to control, no other erythrocyte fatty acids re- ported. TC fell by 0.19 mmol/L (SD 0.04) in intervention, and by 0.01 mmol/L (SD 0.04) in control to 1 year	
Other bias	Low risk	None noted	
WELCOME 2015			
Methods	RCT, parallel, (n3 EPA + D Summary risk of bias: low	RCT, parallel, (n3 EPA + DHA vs MUFA), 15-18 months Summary risk of bias: low	
Participants	Level of risk for CVD: mode Male: 49% intervention, 67 Mean age (SD): 48.6 (11.1) Age range: not reported (18- Smokers: 14.3% interventio Hypertension: not reported Medications taken by $\geq$ 50% Medications taken by 20% formin (data not provided b	N: 51 intervention, 52 control (analysed, 47 intervention, 48 control) Level of risk for CVD: moderate Male: 49% intervention, 67% control Mean age (SD): 48.6 (11.1) intervention, 54 (9.6) control Age range: not reported (18-75 inclusion criteria) Smokers: 14.3% intervention, 11.8% control Hypertension: not reported Medications taken by $\geq$ 50% of those in the control group: lipid-lowering drugs Medications taken by 20%-49% of those in the control group: antihypertensives, met- formin (data not provided by group) Medications taken by some, but < 20% of the control group: none reported Location: UK	
Interventions	Comparison: DHA + EPA v Intervention: 4 g Omacor/d g/d EPA + DHA Control: 4 g olive oil capsu 15%, stearic acid 2%, n-6 fa <b>Dose aim</b> : increase 2.72 g/d Baseline PUFA unclear <b>Compliance by biomarker</b> not in control (EPA% 1.0% latest point, DHA% 5.0 SD fatty acids reported. TC rem mmol/L in intervention at 1	Control: 4 g olive oil capsules/d (providing; ALA 1%, oleic acid 67%, palmitic acid 15%, stearic acid 2%, n-6 fat: 15%), 0.64 g/d PUFA <b>Dose aim</b> : increase 2.72 g/d PUFA, <b>1.22% E PUFA</b>	

## **WELCOME 2015** (Continued)

	<ul> <li>Energy intake: not reported</li> <li>Total fat intake: not reported</li> <li>SFA intake: not reported</li> <li>PUFA intake: not reported</li> <li>PUFA n-3 intake: not reported</li> <li>PUFA n-6 intake: not reported</li> <li>Trans fat intake: not reported</li> <li>MUFA intake: not reported</li> <li>CHO intake: not reported</li> <li>Sugars intake: not reported</li> <li>Protein intake: not reported</li> <li>Alcohol intake: not reported</li> <li>Compliance, other methods: assessed by recording the returned unused capsules, but results not reported</li> <li>Inclusion basis: no intention to increase total PUFA stated. Planned total PUFA increase</li> <li>2.72 g/d PUFA, 1.22% E PUFA, &gt; 10% higher than assumed 6% E from total PUFA at baseline. Confirmed by TC fall in intervention, no other biomarker or intake data</li> <li>PUFA dose: 1.22%E PUFA</li> <li>Duration of intervention: 15-18 months</li> </ul>
Outcomes	Main trial outcome: changes in mean liver fat %, changes in 2 liver fibrosis scores, change in serum biomarkers Dropouts: 4 intervention, 4 control Available outcomes: weight, BMI, lipids, BP, glucose, insulin sensitivity, body fat mea- sures, liver enzymes, HbA1c, serum n-3 fatty acids, trial authors provided details of di- abetes diagnoses, % body fat, BP and carotid intima media thickness Response to contact: yes
Notes	Trial funding: Omacor and placebo were provided by Pronova Biopharma through Ab- bott Laboratories, Southampton, UK. This work was supported by a National Institute for Health Research (NIHR) Southampton Biomedical Research Unit grant and by a Diabetes UK Allied Health Research training fellowship awarded to KGM (Diabetes UK. BDA 09/ 0003937). CDB, PCC and ES were supported in part by the NIHR Southampton Biomedical Research Centre (McCormick-2015, p9; see WELCOME 2015)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were block randomised by an independent clinical trials pharmacist randomised according to standardised pro- cedures (computerised block randomisa- tion) by a research pharmacist at University Hospital Southampton NHS Foundation Trust. Simple randomisation in blocks of 4

## **WELCOME 2015** (Continued)

Allocation concealment (selection bias)	Low risk	Only the clinical trials pharmacist was un- blinded, and randomisation group alloca- tion was concealed from all trial members throughout the trial. (McCormick-2015, p2)
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Paper states that only the clinical trials pharmacist was unblinded, and randomi- sation group allocation was concealed from all trial members throughout the trial. However, the trial register record states "single blind (investigator)". Although the capsules were identical, no information provided as to their smell and taste
Blinding of outcome assessment (detection bias) All outcomes	Low risk	As above
Incomplete outcome data (attrition bias) All outcomes	Low risk	The ITT included all participants ran- domised who had complete data (baseline and end-of-trial measurements), regardless of whether they were later found to be inel- igible, a protocol violator, given the wrong treatment allocation, or never treated). (Scorletti 2014, p4; see WELCOME 2015)
Selective reporting (reporting bias)	Unclear risk	Prospectively registered September 2008, trial start September 2009, end February 2017. Outcome data for cardiac function not yet published (may be ongoing as trial only recently completed), though other CV measures reported
Attention bias	Low risk	Both groups had the same attention
Compliance	Low risk	Erythrocyte EPA + DHA both increased in intervention, not in control (EPA% 1.0%, SD 0.2% in control vs 2.4% SD 1.8% in intervention at latest point, DHA% 5.0 SD 1.0 in control, 7.1% SD 1.3% in interven- tion), no other fatty acids reported. TC re- mained 4.8 mmol/L in control but fell by 0.2 mmol/L to 4.7 mmol/L in intervention at 15-18 months
Other bias	Low risk	None noted

WINS 2006

Methods	Women's Intervention Nutrition Study (WINS) RCT, parallel, (reduced fat with reduced PUFA vs usual diet), 60 months Summary risk of bias: low (as diet advice trial)
Participants	Women with localised resected breast cancer N: 975 intervention, 1462 control (analysed 975 int, 1462 cont) Level of risk for CVD: low Male: 0% intervention, 0% control Mean age (95% CI): 58.6 (44.4-72.8) intervention, 58.5 (43.6-73.4) control Age range: not reported, all postmenopausal Smokers: 49.9% intervention, 48.7% control never smokers Hypertension: not reported Medications taken by $\geq$ 50% of those in the control group: menopausal hormone therapy (65.3% intervention, 64.0% control), tamoxifen (47.7% tamoxifen alone, 38. 5% tamoxifen plus chemotherapy in intervention, 47.4% and 38.0% respectively in control), all were on chemotherapy, most on radiotherapy Medications taken by 20%-49% of those in the control group: not reported Medications taken by some, but < 20% of the control group: not reported Location: USA Ethnicity: 85% white, 5% black, 4% Hispanic, 5% Asian or Pacific Islander, < 1% American Indian or unknown (no outcome data based on ethnicity)
Interventions	<ul> <li>American Indian or unknown (no outcome data based on ethnicity)</li> <li>Type: dietary advice</li> <li>Comparison: reduced fat intake (with reduced PUFA) vs usual diet</li> <li>Intervention: aims total fat 15%-20% E; methods 8 biweekly individual dietetic sessions plus 3-monthly contact and optional monthly group sessions, incorporating individual fat gram goals, social cognitive theory, self-monitoring, goal setting, modelling, social support and relapse prevention and management. Intervention was delivered face to face individually by trained dietitian</li> <li>Control: aims minimal nutritional counselling focused on nutritional adequacy; methods one baseline dietetic session plus 3-monthly sessions</li> <li>Dose aim: unclear PUFA</li> <li>Baseline 5.4% E PUFA</li> <li>Compliance by biomarkers: no fatty acid biomarkers reported, TC reported but only in a subgroup (N = 18 at 2 years) and unbalanced at baseline so not used in analyses, little change but TC fell by 6 mg/dL in intervention and increased by 0.8 mg/dL in control over 2 years</li> <li>Compliance by dietary intake: assessed using unannounced phone calls over several days, 1-year data reported apart from protein and carbohydrate which were 6-month data</li> <li>Energy intake, MJ/d: intervention 7.3 (SD 1.8), control 7.7 (SD 1.9)</li> <li>Total fat intake, % E: intervention 20.3 (SD 8.1), control 29.2 (SD 7.4)</li> <li>SFA intake: intervention 6.4 (SD 0.14 (4.4)), control 9.8 (SD 0.15 (5.7))</li> <li>PUFA n-3 intake: not reported</li> <li>PUFA n-6 intake: not reported</li> <li>PUFA n-6 intake: not reported</li> <li>MUFA intake: intervention 7.6 (SD 0.14 (4.4)), control 11.5 (SD 0.16 (6.1))</li> <li>CHO intake: intervention 6.8 (SD 19.6), control 50.5 (SD 14.8)</li> </ul>

## WINS 2006 (Continued)

	<ul> <li>Sugars intake: not reported</li> <li>Protein intake, % E: intervention 19.1 (SD 5.2), control 17.6 (SD 4.1)</li> <li>Alcohol intake: intervention 5% E (SD 6), control 4% E (SD 6)</li> <li>Compliance, other methods: not reported</li> <li>Inclusion basis: no intention to increase total PUFA stated. Acheived total PUFA reduction of 1.9% E in intervention compared to control at 1 year, &gt; 10% higher than baseline 5.4% E from total PUFA</li> <li>PUFA dose: -1.9% E PUFA</li> </ul>
	Duration of intervention: 60 months
Outcomes	Main trial outcome: dietary fat intake, TC, weight and waist Dropouts: 45 lost to follow-up, 170 discontinued intervention, 66 lost and 106 discon- tinued control Available outcomes: all-cause mortality, cancer diagnoses (including recurrences), new breast cancer diagnoses, weight, BMI (TC, TG, HDL, insulin provided in tiny subgroup - 9 participants in each group at 2 years - and unbalanced at baseline, not useable) Author contact: limited information received
Notes	Trial funding: National Cancer Institute, Breast Cancer Research Foundation, American Institute for Cancer Research *SDs appear incorrect, probably SEs? NOTE: control arm is the arm higher in PUFA, intervention arm lower in PUFA

## Risk of bias

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Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random stratified permuted block design, carried out at the statistical co-ordinating centre of WINS
Allocation concealment (selection bias)	Low risk	Random stratified permuted block design, carried out at the statistical co-ordinating centre of WINS
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not for dietary advice and participants
Blinding of outcome assessment (detection bias) All outcomes	Low risk	All outcomes assessed by the blinded out- come committee
Incomplete outcome data (attrition bias) All outcomes	Low risk	All assessed
Selective reporting (reporting bias)	Low risk	Outcomes stated in protocol all appear to have been published

#### WINS 2006 (Continued)

Attention bias	High risk	Intervention group appear to have received more time and attention
Compliance	Unclear risk	No fatty acid biomarkers reported, TC reported but only in a subgroup ( $n = 18$ at 2 years) and unbalanced at baseline so not used in analyses, little change but TC fell by 6 mg/dL in intervention and increased by 0.8 mg/dL in control over 2 years (note, control group should be higher in PUFA in this trial). Overall changes not reported
Other bias	Low risk	None noted

AA: arachidonic acid; ACEi: angiotensin-converting-enzyme inhibitor; AF: atrial fibrillation; ALA: alpha-linolenic acid (a plant-based omega-3 fat); ARB: Angiotensin II receptor blockers; BMD: bone mineral density; BMI: body mass index (weight in kg divided by height in m squared); BP: blood pressure; Ca: calcium; CAD: coronary artery disease; CHO: carbohydrate; CLO: cod-liver oil; CRP: C-reactive protein; CV: cardiovascular; CVD: cardiovascular diseases; DHA: docosahexaenoic acid (a fish-based omega-3 polyunsaturated fatty acid); DPA: docosapentaenoic acid (a fish-based omega-3 polyunsaturated fatty acid); DPA: docosapentaenoic acid (a fish-based omega-3 polyunsaturated fatty acid); HDL: high density lipoprotein (a fraction of TC, measured in human blood); ICD: implanted cardioverter defibrillator; ITT: intention to treat analysis; IQR: interquartile range; kcal: calories; LDL: low density lipoprotein (a fraction of TC, measured in human blood); LA: linoleic acid (an omega-6 polyunsaturated fatty acid); MDF: mean difference; MI: myocardial infarction; MUFA: monounsaturated fatty acid or monounsaturated fat; IQR: interquartile range; N: number or participants; NAFLD: non-alcoholic fatty liver disease; NSAIDs: nonsteroidal antiflammatory drugs; P: P value; PCI: percutaneous coronary intervention; PUFA: polyunsaturated fatty acid; P/S: polyunsaturated to saturated fatty acid ratio; PAD: peripheral arterial disease; QoL: quality oflife; RCT: randomised controlled trial; SCD: sudden cardiac death; SD: standard deviation; SE: standard error; SFA: saturated fatty acid or saturated fat; SO: seal oil; TC: total cholesterol (measured in human blood); TG: triglycerides (measured in human blood); VF: ventricular fibrillation; VT: ventricular tachycardia

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

Study	Reason for exclusion
ADCS-Quinn 2010	Compared DHA vs omega-6, no intention to increase total PUFA. Intervention 1.02 g/d algal- derived DHA compared to 2 g of soy or corn oil. Biggest difference would be 1 g/d total PUFA, 0.45% E, < 10% change from assumed 6% E baseline PUFA
AFFORD 2014	Aim was to assess effects of high-dose fish oils, compared EPA + DHA (1.6 g/d EPA + 0.8 g/ d DHA) vs omega-6 safflower oil (4 g/d, ~80% LA). Assumed 2.4 g/d or 1.08% E omega-3 in intervention, 3.2 g/d or 1.44% E omega-6 fats in control, difference 0.8 g/d or 0.36% E total PUFA. This was < 10% increase from assumed baseline of 6% E total PUFA. No biomarker, lipid or dietary intake data to support

AlphaOmega - EPA+DHA	Aim was to increase omega-3 fats. Margarine composition data - summing LA, ALA, EPA, DPA and DHA total PUFA suggested dose in EPA + DHA margarine (compared to placebo) was 3.8% E. As planned intake was 20 g/d, intake was 0.76 g/d total PUFA, or 0.3% E from total PUFA. Total PUFA in ALA + EPA + DHA (compared to ALA margarine) was 0.7% E, or 0.14 g/d total PUFA, 0.06%E total PUFA. These were both < 10% higher than assumed 6% E from PUFA at baseline. TC levels did not alter by intervention
AREDS2 2014	Aimed to increase omega-3 fats, compared EPA + DHA (350 mg/d DHA plus 650 mg/d EPA) vs nil. Intended increase 1.0 g/d, 0.5% E n-3, assume 0.5% E PUFA (< 10% increase from assumed 6% E PUFA at baseline). No biomarker, lipid or dietary intake data to support or refute
ASCEND	Ongoing trial. Intervention omega-3 (1 g/d: 0.41 g EPA, 0.34 g DHA) vs olive oil placebo (plus or minus aspirin). Dose appears < 1.33 g/d total PUFA, < 0.6% E PUFA, so excluded
Azadbakht 2007	Weight reduction goals as well as fat modification, multifactorial
Baldassarre 2006	Aim to increase omega-3. Compared LCn3 (1.8 g/d EPA + DHA, 0.12 g LA, 1.92 g/d PUFA) vs MUFA (~20% LA or 1.2 g/d PUFA). Dose 0.72 g/d PUFA, 0.3% E total PUFA, < 10% of baseline assumed 6% E PUFA. No biomarker data except on EPA + DHA, no dietary intake data presented, no postbaseline TC data but LDL increased in intervention arm and remained static in control
Berson 2004	DHA vs omega-6, there appeared to be roughly the same amount of PUFA in both intervention and control supplements, but exact composition unclear (1.2g/d DHA plus 1.8 g vegetable oil vs 3 g/d mixed soy and corn oils (half each). Appeared to be < 10% difference in total PUFA between arms
Caldwell 2011	Compared EPA + DHA vs omega-6, did not report intention to increase total PUFA. Intervention 2.1 g/d n3 (1050 mg EPA, 750 mg DHA and 300 mg other n3), control 3 g/d soybean oil (approx 60% PUFA plus 8% fish oil, 2.04 g/d), PUFA Dose 0.06 g/d, 0.03% E PUFA, < 10% increase from assumed 6% E baseline. Only erythrocyte fatty acid ratio reported, no TC or dietary intake data reported
DART 2 - Burr 2003	Aimed to increase oily fish intake or update of fish oil capsules. No PUFA aim, no PUFA biomarkers (though plasma EPA rose 1.23 mg/dl in intervention, fell 0.16 mg/dL in control over 6 months) or intake data reported. Aim for those on capsules was increase 0.5 g/d EPA + DHA, 0.2% E n-3, 0.2% E PUFA. < 10% increase from assumed 6% E from PUFA baseline
DART fish Burr 1989	EPA + DHA vs nil, aimed to increase omega-3 intake by increasing fatty fish intake. No total PUFA goals or data on intake, serum fatty acids or serum cholesterol. Dose aim increase 0.5 g/d EPA + DHA, 0.2% E n-3, 0.2% E PUFA. < 10% increase over assumed 6% E PUFA at baseline
Derosa 2016	Compared EPA + DHA vs filler (non-fat), no intention to increase total PUFA. Omega-3 dose unclear, states intention in intervention of $3 \times 1$ g capsule/d n-3 PUFAs (ethylic esters, each 1-g capsule of n-3 PUFAs contains highly concentrated ethyl esters of omega-3 fatty acids, primarily EPA, and DHA in the proportion of 0.9-1.5), compared to placebo of "sucrose, mannitol and mineral salts magnesium stearate and silicon dioxide, used as anti-caking agents". Both groups were given diet and exercise advice. No biomarker or intake data provided on omega-3 or total PUFAs, TC not significantly different between arms. If omega-3 dose was 1 g/d, or 0.45% E this

	would be < 10% E increase from an assumed baseline of 6% E
Deslypere 1992	Compared LCN3 vs MUFA, no intention to increase total PUFA. Intended dose appeared relevant for 6 and 6 capsule arms (increase 1.12 g/d EPA + DHA, 0.5% E n-3, 0.5% E PUFA or 2.24g/d EPA + DHA, 1.0% E n-3, 1.0% E PUFA or 3.4 g/d EPA + DHA, 1.5% E n-3, 1.5% E PUFA) but total PUFA intake appeared equal in all arms (subtracting SFA and MUFA from total fat), and erythrocyte membrane fatty acids similar in all arms (summing EPA, DHA, DPA, LA and AA, 30.6% fatty acids for 9-capsule arm, 30.5% 6 capsules, 29.9% 3 capsules and 29.1% fatty acids in control arm. Did not appear to be > 10% increase in total PUFA between intervention and control arms
DISAF - Harrison 2005	Compared EPA + DHA vs nil, did not aim to increase total PUFA. Aimed to increase 1.4 g/d EPA + DHA, 0.6% E n-3, this equates to 0.6% E PUFA in intervention arm, no change in control. While red cell membrane EPA and DHA increased in the intervention group, not in control, AA was reported as falling in intervention. PUFA (summed EPA + DHA and AA was 17.8% in intervention, 17.6% in control. Other PUFAs and TC not reported. Difference in total PUFA between intervention and control < 10% control
DO Health	Ongoing trial. Intervention omega-3 (1 g/d, ratio EPA:DHA = 1:2) vs placebo capsules (plus or minus vitamin D3 and strength home exercise). Dose of total PUFA appears < $1.33$ g/d, < $0.6\%$ E PUFA, so excluded
DO IT - Einvik 2010	Compared EPA + DHA vs omega-6, no aim to increase total PUFA. Intervention aim 2.4 g/d of omega-3 PUFA (EPA + DHA 1.32 g/d, assume 1.08 g/d ALA or other omega-3) vs corn oil (2.24 g/d LA). 2.4 g/d omega-3, 1.1% E n3 vs 2.24 g/d LA or 1.0% E LA, PUFA dose 0.1% E. < 10% increase from assumed 6% E baseline. Serum fatty acids suggest < 10% more total PUFA in both intervention arms than controls, no difference in TC between arms
DO IT 2006	Dietary advice arm provided multifactorial dietary advice, while the supplementary arm was a specifically omega-3 intervention (so included in the omega-3 review)
EPE-A study 2014	Compared: high EPA vs low EPA vs placebo (contents not reported). PUFA content of placebo unknown. High EPA (increase 2.7 g/d EPA + DHA, 1.2% E omega-3, 1.2% E PUFA) vs low EPA (increase 1.8 g/d EPA + DHA, 0.8% E omega-3, 0.8% E PUFA), PUFA dose 0.4% E, < 10% increase from assumed 6% E at baseline. Serum EPA to AA (0.57 in high dose, 0.40 in low dose, 0.09 in control), TC rose by 8 mg/dL in control, by 4 mg/dL in high dose and by 3 mg/dL in moderate dose)
Erdogan 2007	Intervention and control group contents unclear, so unclear if more PUFA vs less
Finnish Mental Hosp 1972	Not randomised (cluster-randomised, but < 6 clusters)
FLAX-PAD 2013	Compared ALA (in milled flaxseed) vs mixed dietary oils (composition unclear). No intention to increase total PUFA. Quantity of ALA and other PUFA unclear in both arms. Plasma levels of enterolignans and ALA rose in ALA arm, no details for control. No suggestion that total PUFA intake was higher in either arm, exclude
FORWARD 2013	Compared EPA + DHA vs MUFA, no aim to increase total PUFA. Intervention provided 0.86 g/ d EPA + DHA, 0.4% E n-3, 0.4% E PUFA, control provided 1 g/d olive oil, or 0.2 g/d LA. Total

	PUFA dose 0.66 g/d PUFA, 0.3% E, < 10% higher than assumed 6% E PUFA baseline
FOSTAR 2016	Compared high EPA + DHA vs low EPA + DHA plus ALA. Intervention fruit juice mixed with fish oil supplement (18% EPA, 12% DHA, 4.5 g/day total omega-3), control 15 mL Sunola oil/d (fish oil 2 mL plus 13 mL canola oil, omega-3 $\leq$ 0.45 g EPA + DHA plus 3.9 g/d PUFA in canola, 4.4 g/d PUFA). ~0.1 g/d PUFA more in intervention, < 10% more than assumed 6% E PUFA at baseline
Franzen 1993	Compared EPA + DHA vs MUFA. No intention to increase total PUFA stated but increased omega-3 (20% EPA, 15% DHA, 3.15 g/day total omega-3) vs increased olive oil (6.3 g/day MUFA, 1.35 g/day SFA, 1.35 g/d total omega-6 fat). This suggests increase 1.8 g/d PUFA, 0.8% E PUFA, but serum fatty acids (summing EPA, DHA, ALA, LA, AA, DPA) suggested higher total PUFA in control (182 mg/dL PUFA in intervention, 195 mg/dL in control). However, TC rose more in control than intervention. Change in total PUFA unclear, exclude
Gill 2012	Compared omega-3 with placebo (unclear what), no aim to increase total PUFA. Control group contents unclear, so unclear if more PUFA vs less, no biomarker or intake data, TC reported only as "no significant change". Change in total PUFA unclear, exclude
GISSI-HF 2008	Compared EPA + DHA vs MUFA, no aim to increase total PUFA. Intervention increased 1 g/ d omega-3, 1 g/d olive oil, or 0.2 g/d LA in control, dose 0.8 g/d total PUFA, 0.36% E PUFA, < 10% increase from assumed 6% E PUFA. Fatty acid status did not provide total PUFA or any omega-6 PUFAs, TC data provided for intervention but not control
GISSI-P 1999	Compared EPA + DHA vs nil, no aim to increase total PUFA. Intervention dose 0.86 g/d EPA + DHA, 0.4% E n-3, 0.4% E PUFA, < 10% increase from assumed 6% E PUFA. No biomarker or intake data, TC appeared to rise slightly more in intervention than control arms to 6 months
JELIS 2007	Compared EPA fats with nil, no intention to increase total PUFA. Intended omega-3 dose was 1. 8 g/d EPA, compared to nil, and both groups received "appropriate" dietary advice (not described further). This suggests increases in total PUFA (0.8% E n-3, 0.8% E PUFA), but increase in plasma PUFAs (sum of omega-3 and omega-6 fats, including EPA, DHA, DPA, ALA, LA, GLA, AA), was higher in control (+26.2 mg/mL) than intervention (+ 20 mg/mL). TC not reported, LDL change was equivalent (but all on statins). Difference in total PUFA appears < 10% of baseline PUFA intake assumed to be 6% E
Lorenz-Meyer 1996	Compared EPA + DHA vs omega-6, no intention to increase total PUFA. Intervention increased EPA + DHA 5.1 g/d vs 6 g/d LA, 0.9 g/d or 0.45% E difference, < 10% increase over assumed 6% E PUFA. No biomarker or TC or intake data reported
Mansel 1990	Did not aim to alter total PUFA, aimed to increase 0.48 g/d GLA or 4 kcal or 0.2% EGLA, increase ~8.4 g/d LA or 76 kcal or 3.8% ELA, total 4% En6, estimated total PUFA dose 4% E. No serum TC or tissue fatty acid levels reported, no dietary intake data. No deaths or cardiovascular events occurred, only breast cancer diagnoses reported
MAPT 2017	Compared EPA + DHA vs paraffin oil (non fat). Intervention 1.025 g/d DHA + EPA compared to flavoured paraffin oil. (Also aims 3 and 4 as above plus multi-domain intervention (nutrition, physical exercise, cognitive stimulation, social activities). Intended increase 1.03 g/d EPA + DHA, 0.5% E n3, 0.5% E PUFA, < 10% more than assumed 6% E PUFA baseline

MARGARIN Bemelmans 2002	Omega-3 vs omega-6. Compared omega-3 (ALA-rich margarine, 80% fat of which 15% was ALA and 46% LA) with omega-6 (LA-rich margarine, 80% fat of which 0.3% was ALA and 58% LA) . Margarines eaten as desired, so doses unclear. Serum cholesterol ester fatty acid changes suggest rises in ALA in omega-3 arm and rises in LA in the LA arm, with rough equivalence in total PUFA between arms. TC fell slightly more in LA arms than ALA arms, but fell in all arms. Arms appear equivalent in total PUFA intake
MENU - Rock 2016	Compared walnut-rich moderate fat diet (ALA) vs moderate fat diet (MUFA), did not aim to increase total PUFA. Intervention was advice to follow walnut-rich higher fat diet (35% E fat with limited SFA, MUFA encouraged, including 42 g/d walnuts, 45% E CHO, 20% E protein) vs exactly as intervention goals without walnuts. Unclear how total PUFA altered in each arm, mean LDL at 1 year was 2.97 mmol/L in both arms, TC not reported. Red blood cell fatty acid ALA and LA reported at 1 year (summed 12.5% in intervention, 12.2% in control) but other fatty acids not reported. PUFA dose unclear, excluded
Michalsen 2006	Multifactorial - combination of diet (focusing on ALA and oily fish as well as Mediterranean diet more generally), exercise and stress-reduction programme and advice in intervention, general written dietary and stress advice in control
Middleton 2002	Intervention and control descriptions unclear. Compared EPA + DHA + GLA vs LA, but unclear which arm was higher in PUFA, or quantity of PUFA in either arm
Minnesota Coronary 1989	While participants were involved in this trial for over 1 year on average they could move in and out of the institution in which the trial took place, and therefore in and out of the trial over the duration of the trial. Most participants were not involved in the trial continuously for $\geq 1$ year
Moy 2001	Aim was to reduce dietary fat (total and saturated fat reductions appear to have been achieved) but effects on PUFAs unclear (total PUFA, omega-6 and omega-3 intakes not reported)
NAT2 2015	No aim to increase total PUFA, aimed to increase omega-3 fats. Intervention was 1110 mg/d n- 3 FAs (EPA: 270 mg/day DHA: 840 mg/day) vs olive oil capsules (containing 0.2 g total PUFA) . Total PUFA dose would be 0.91 g/d, or 0.4% E PUFA. Red blood cell lipid EPA and DHA presented, but not total PUFA. Dietary intake data suggest 0.5% E difference in total PUFA between arms (< 10% increase from assumed 6% E from PUFA at baseline)
Norouzi 2014	Compared LCn3 with placebo (no details). Intervention 1.056 g/d LCn3 plus 0.056 g/d omega-6, 1.112 g/d PUFA in intervention, control group contents unclear, so unclear whether more PUFA vs less. No biomarker, TC or dietary intake data to help. No intention to increase total PUFA and no information on whether PUFA was increased substantially in one arm compared to the other, exclude
Norwegian - Natvig 1968	Aim was to increase vegetable oil intake, comparing ALA (linseed oil) with omega-6 (sunflower oil) . Intervention was linseed oil, 10 mL/d (55% ALA), 5.5 g/d ALA, 1.5g/d LA (7.04 g total PUFA) , control was sunflower oil, 10 mL/d (1.4% ALA), 0.14 g/d ALA, 6.3 g/d LA or 6.42 g/d omega-6 (6.56 g/d total PUFA). Intended total PUFA dose was 0.48 g/d lower total PUFA or 0.22% E from PUFA lower in intervention (< 10% change from assumed 6% E baseline). No biomarker or dietary intake data, except slightly lower TC at 6 months in intervention arm

NutriStroke 2009	Compared LCn3 with unclear placebo. No intention to increase total PUFA. Intervention 0.5 g/d LCn3, assume 0.5 g/d PUFA. Control group contents unclear, but state no PUFA. PUFA dose 0.5 g/d or 0.23% E PUFA, < 10% increase from assumed 6% E PUFA baseline. No biomarker, TC or dietary intake data to confirm
OFAMI - Nilsen 2001	Omega-3 vs omega-6 comparison, aim to assess effects of omega-3 increase, total PUFA doses in each arm unclear, no dietary intake data provided
OMEGA 2014	Did not aim to alter total PUFA. Aimed to increase omega-3 fats, vs MUFA control, but only increased omega-3 fats by 0.4% E (< 10% of assumed baseline of 6% E from PUFA). No dietary intake data provided
OPAL - Dangour 2010	Aimed to increase omega-3 fats, not total PUFA, compared omega-3 supplement with olive oil, omega-3 dose 0.7 g/d or 0.3% E (< 10% of assumed baseline of 6% E from PUFA). No dietary intake data provided
ORIGIN 2012	Aimed to increase omega-3 fats, not total PUFA. Compared omega-3 supplement with olive oil placebo, EPA + DHA vs MUFA. Aimed to increase 0.84 g/d EPA + DHA, 0.4% E n-3, 0.4% E PUFA (< 10% of assumed baseline of 6% E from PUFA). No dietary intake data provided
Oslo Diet-Heart 1966	Multifactorial dietary intervention (cannot separate out the effects of PUFAs from other dietary interventions)
Oxford Retinopathy 1978	Multifactorial dietary intervention (cannot separate out the effects of PUFAs from other dietary interventions)
POUNDS Lost Sacks 2009	Manipulation of total fat intake, but no details of fat types aimed for or achieved in any arms
Ramirez-Ramirez 2013	Omega-3 vs omega-6 (DHA + EPA vs sunflower oil). Quantities of total PUFA in each arm unclear, but likely to have been similar (< 10% of assumed baseline of 6% E from PUFA). Aimed to assess omega-3 effects, no dietary intake data provided
Reed 2014	Omega-3 vs omega-6 (EPA + DHA vs GLA + sunflower oil). Doses of total PUFA in each arm unclear but likely to have been similar (< 10% of assumed baseline of 6% E from PUFA). Aimed to assess omega-3 effects and omega-6 effects, not total PUFA. Paper states that there were no differences between arms for TC or dietary intake
Risk and Prevention	Omega-3 vs MUFA, but small PUFA dose (intended to increase 0.86 g/d EPA + DHA, 0.4% E n3, 0.4% E PUFA). Aimed to assess effects of omega-3 fats, not total PUFA, intended dose too small (< 10% of assumed baseline of 6% E from PUFA). No difference between arms for change in TC from baseline to 5 years (P = 0.52)
Sandhu 2016	Aimed to increase omega-3 fats. Intended dose suggested higher omega-3 fats in Lovaza and Lovaza & Raloxifee compared to control and Raloxifene 30 mg (as no placebo was provided. However, plasma fatty acid concentration suggested that total PUFA was not higher in these arms. Mean summed plasma fatty acid omega-3 fats higher in Lovaza and Lovaza & Raloxifee arms compared to control and Raloxifene 30 mg at 2 years. However omega-6 fats were equivalently lower, mean total PUFA (summing omega-3 and omega-6) similar in both arms

Schirmer 2007	Compared n-6 (GLA) vs MUFA, did not aim to increase total PUFA. Intervention included 0.89 g/d GLA plus ~0.9 g/d LA or 0.8% E n6. control included 1 g/d LA, 0.45% E LA. Difference 0. 35% E omega-6, assume same for PUFA, < 10% more than assumed 6% E baseline total PUFA. No biomarker, TC or dietary intake data
SCIMO - von Schacky 1999	Aimed to increase omega-3 fats. Intended omega-3 dose was 1.03 g/d EPA + DHA, 0.5% E n-3. This would translate to 0.5% E PUFA, but the placebo was probably fairly rich in total PUFA. Excluded as probably < 10% increase in total PUFA in intervention compared to control. Erythrocyte phospholipid fatty acid composition confirmed rise in EPA and DHA but didn't report further PUFAs. Serum total cholesterol dropped very slightly more in intervention than control (TC -0.1mmol/L in int, -0.05mmol/L in cont from baseline to 24 months)
Shinto 2014	Compared EPA + DHA vs n-6, did not intend to increase total PUFA. Intervention 1.650 g/d LCn3, 1.65 g/d PUFA vs 3 g/d soybean oil (~60% PUFA), 1.8 g/d PUFA. Dose is 0.15 g/d PUFA, 0.07% E PUFA, < 10% change from assumed 6% E PUFA baseline. No biomarker (except red blood cell EPA + DHA), dietary intake or TC data
SHOT - Eritsland 1996	Aim was to increase omega-3 fats. Intervenion was omega-3 vs nil, and provided 3.3 g/d EPA + DHA, or 1.5% E from omega-3 fats. This suggests increase of 1.5% E from PUFA, but serum fatty acid PUFA assessments were 645 mg/L in the control (up 43 mg/L from 603 at baseline), and 621 mg/L (up 28 mg/L from 593) in the intervention group at 9 months, suggesting lower or equivalent total PUFA intake in the intervention compared with control. Serum TC remained constant over the trial in both arms
Sianni 2013	Control group contents unclear, so unclear if more PUFA vs less. Aimed to increase omega-3 fats, intervention group received 4 g/d omega-3 fats, placebo not described. As only an abstract could be found, and contact could not be established with the authors we excluded this trial
SMART Tapsell 2013	Compared fish + fish oil supplements vs fish + olive oil supplements vs olive oil supplements. Did not aim to increase total PUFA. Comparisons with olive oil supplement arm are multifactorial so excluded. Fish + fish oil supplements (capsules including 420 mg/d EPA + 210 mg/d DHA, 0.63 g/d EPA + DHA) vs fish plus olive oil supplements (1 g olive oil/d, assume 0.2 g/d PUFA) has equivalent diets with differing supplements between arms. Dose 0.43 g/d PUFA, 0.2% E from PUFA, < 10% increase from assumed 6% E PUFA at baseline
SOFA 2006	Aimed to increase omega-3 fats. Comparison was EPA + DHA (961 mg n-3 PUFAS) vs MUFA + omega-6 (2 g/d high-oleic acid sunflower oil). Omega-3 dose was only 0.96 g/d, or 0.4% E from omega-3. As there was some PUFA in the placebo it was unlikely that total PUFA was increased more than 10% of baseline. No biomarker data found to confirm or refute this
Sofi 2010	Aimed to increase omega-3 fats. Comparison was EPA + DHA (6.5 mL/d olive oil enriched with n-3 plus dietary recommendations, 0.83 g n-3/d of which 0.47 g/d EPA & 0.24 g/d DHA) vs MUFA (6.5 mL/d olive oil plus dietary recommendations). Omega-3 dose was 0.71 g/d EPA + DHA, 0.3% E n-3, equivalent to 0.3% E PUFA (< 10% increase from assumed 6% E PUFA baseline). No fatty acid biomarker data, TC fell more in control than intervention
STARS 1992	Intervention encouraged to increase plant-derived soluble fibre as well as alter dietary fats, multi- factorial

Stoll 2001	Ongoing trial. NCT00010868. The PI, Andrew Stoll, appears to have been struck off the medical register in Massachusetts in 2011 (Commonwealth of Massachusetts Board of Registration in Medicine, Adjudicatory Case number 2011-026) so it has not been possible to contact him and no publication of results has been found
STRENGTH	Ongoing trial. Intervention omega-3 carboxylic acid capsule (Epanova, not less than 800 mg/g) and statin vs corn oil placebo capsule and statin. Omega-3 vs omega-6, unlikely to reach PUFA dose of > 1.33 g/d or 0.6% E
SU.FOL.OM3 Galan 2010	Compared EPA + DHA vs non-fat placebo, no intention to increase total PUFA. Intervention 400 mg/d EPA and 200 mg/d DHA compared to liquid paraffin with fish flavour. Intended dose 0.6 g/ d EPA + DHA, 0.3% E PUFA, < 10% change from assumed 6% E PUFA baseline. No biomarker (aside from plasma EPA + DHA), TC (apart from baseline) or dietary intake data provided
Søndergaard 2003	Multifactorial dietary intervention (cannot separate out the effects of PUFAs from other dietary interventions)
Tande 2016	Compared EPA + DHA vs MUFA, did not intend to increase total PUFA. Intervention 2 g/d calanus oil (85% wax ester with a sum of neutral lipids > 90%, 11% oil is EPA + DHA, or 0.22 g/d EPA + DHA), control 2 g/d olive oil (analysis indicated this olive oil was primarily oleic acid (76.9%), palmitic acid (10.2%), and linoleic acid (7.7%), assumed 0.14 g/d LA), overall dose 0. 08 g/d PUFA, 0.04% PUFA. < 10% increase from assumed 6% E PUFA. TC increased by 0.02 mmoL/L in intervention to 1 year, fell 0.08 mmoL/L in control, no further biomarker or intake data
Tay 2015	Multifactorial dietary intervention (cannot separate out the effects of PUFAs from other dietary interventions)
THIS DIET - Tuttle 2008	Aim was to achieve a Mediterranean-style diet, and compare it to a low-fat diet. All intervention and control participants were advised to reduce SFA and dietary cholesterol, increase fruits and vegetables and whole grains. In addition intervention participants were encouraged to increase cold- water fish and oils from olives, canola and soybeans. Plasma fatty acid composition suggested that omega-3 increased in the intervention arm compared to control (rising 0.1% in control, rising 0. 6% in intervention) while omega-6 fats reduced in the intervention (rising 0.7% in control, falling 0.1% in intervention). This confirms dietary intake data suggesting that total PUFA increased by 0.9% E in control, and increased by only 0.1% E in intervention, to equivalence at 24 months (total PUFA intake at 24 months 5.7% E, SD 3.1 in control, 5.7% E, SD 2.4 in intervention). No total PUFA difference between arms during trial, so excluded
VITAL	Ongoing trial. Intervention omega-3 (Omacor fish oil, EPA + DHA 1 g/d: 465 mg EPA; 375 mg DHA) vs placebo (plus or minus vitamin D3). Placebo unclear but very unlikely to attain a dose of > 1.33 g/d PUFA or 0.6% E
Weinstock-Guttman 2005	Aim was to compare low fat diet (15% E from fat) plus EPA + DHA supplements (3.3 g/d EPA + DHA, 1.5% E n3) with low-fat diet (30% E from fat) plus olive oil capsules. Total PUFA in each arm (aimed or achieved) is not clear. Serum fatty acids were assessed, data reported on MUFA, EPA, DHA, DPA, combined omega-3 fats and SFA, but not total fat intake or total PUFAs. TC was not reported and LDL rose slightly in both groups, more in the control (30% E fat) than

	intervention (15% E fat). Dietary intake not reported
WHI 2006	Dietary intervention was of dietary fat and also fruit and vegetables, multifactorial
Zhang 2016	Compared DHA vs corn oil (n6). No aim to increase total PUFA, intervention 1.0 g/d DHA, 0.45% E n3, control 1.1 g/d PUFA, 0.5% E PUFA, dose 0.05% E PUFA, < 10% increase from assumed 6% E PUFA baseline. No fatty acid (except very small increase in serum DHA in intervention, unclear if statistically significant), TC or dietary intake data
Özaydin 2011	Compared omega-3 supplement with nil (no placebo). Intended omega-3 dose was increase 0.6 g/d EPA + DHA, 0.3% E n-3, 0.3% E PUFA. Baseline total PUFA not reported, nor intake or body marker data. Assume baseline 6% E PUFA, dose < 10% increase

AA: arachidonic acid; ALA: alpha-linolenic acid (a plant-based omega-3 fat); CHO: carbohydrate; DHA: docosahexaenoic acid (a fish-based omega-3 polyunsaturated fat); DPA: docosapentaenoic acid (a fish-based omega-3 polyunsaturated fat); EPA: eicosapentaenoic acid (a fish-based omega-3 polyunsaturated fat); LA: linoleic acid (an omega-6 polyunsaturated fat); LA: linoleic acid (an omega-6 polyunsaturated fat); LDL: low density lipoprotein (a fraction of TC, measured in human blood); MUFA: monounsaturated fat; acid or monounsaturated fat; PUFA: polyunsaturated faty acid or polyunsaturated fat; SFA: saturated faty acid or saturated fat; TC: total cholesterol (measured in human blood)

#### Characteristics of ongoing studies [ordered by study ID]

#### AC Omega3

Trial name or title	The Aboriginal cardiovascular omega-3 randomised controlled trial (AC Omega3)
Methods	RCT
Participants	Indigenous Australian adults with stable coronary artery disease
Interventions	Each for 12 months: Arm 1: omega-3 (1800 mg/d AlaskOmega: 3 capsules/d: 400 mg EPA and 200 mg DHA) Arm 2: placebo mixed oil capsules (1000 mg/d: 3 capsules/d containing palm oil, gelatin, glycerol, sunflower oil, rapeseed oil, mixed tocopherols, and a "small amount" of fish oil ((or taste) to aid blinding)
Outcomes	Primary: serum non-HDL cholesterol Secondary: triglycerides, total cholesterol, LDL, HDL, lipid functionality by cholesterol efflux and CETP, heart rate variability, platelet function and thrombosis markers, inflammation markers, cumulative combined rate of major adverse cardiac events (including death, non-fatal MI, unstable angina, non-fatal stroke, revas- cularisation and cardiac-related hospital admissions)
Starting date	Registered on Trials Registry: 10 July 2014 Trial start date: 1 October 2014 Trial completion date est: unclear

## AC Omega3 (Continued)

Contact information	Alex Brown (PI), Wardliparingga Aboriginal Unit, Adelaide, Australia, alex.brown@sahmri.com
Notes	ACTRN12614000732684 Alex Brown contacted in 2016: confirmed trial is actively recruiting

Trial name or title	Clinical efficacy of fish oil as adjunct therapy for patients with chronic periodontitis
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Methods	RCT
Participants	Adults (25-80 years, non-smokers) with newly diagnosed severe but non aggressive periodontitis
Interventions	Each for 13 months: Arm 1: fish oil rich in EPA (6 x 500 mg capsules/d: 277 mg EPA; 27 mg DHA) and standard periodontal treatment (scaling and debridement) Arm 2: fish oil rich in DHA (6 x 500 mg capsules/d: 66 mg EPA; 258 mg DHA) and standard periodontal treatment Arm 3: soya oil placebo (6 x 500 mg capsules/d) and standard periodontal treatment
Outcomes	Primary: probing pocket depth, clinical attachment level (CAL) Secondary: inflammatory biomarkers in gingival crevicular fluid, erythrocyte omega-3, C-reactive protein
Starting date	Registered on Trials Registry: 23 July 2010 Trial start date: July 2010 Trial completion date est: unclear
Contact information	Mark Bartold, University of Adelaide, mark.bartold@adelaide.edu.au
Notes	ACTRN12610000594022 PhD, Boram Park, available giving 4-month outcome data for pilot trial n = 33 participants Mark Bartold written to in 2016. Confirmed preparing full publications for submission

#### ACTRN12610000594022

## ACTRN12613000034730

Trial name or title	Intervention of testosterone & fish oil for the prevention of Alzheimer's disease: InTrePad
Methods	RCT
Participants	PiB-PET (Pittsburgh compound B)-positive men aged $\geq 60$ years with subjective memory complaints
Interventions	Each for 56 weeks: Arm 1: DHA capsules (1720 mg/d) and testosterone undecanoate (intramuscular injection 1000 mg/4 mL every 8 weeks) Arm 2: placebo DHA and testosterone undecanoate (intramuscular injection 1000 mg/4 mL every 8 weeks) Arm 3: placebo DHA and placebo testosterone

### ACTRN12613000034730 (Continued)

Outcomes	Primary: PiB score Secondary: neuropsychological, mood and daily functioning questionnaires, beta amyloid levels, fluo- rodeoxyglucose to assess brain glucose metabolism, inflammatory and oxidative biomarkers, hippocampal volume, quality of life, safety and tolerability of treatment
Starting date	Registered on Trials Registry: 14 January 2013 Trial start date: 28 February 2013 Trial completion date est:
Contact information	Ralph Martins (PI), Sir James McCusker Alzheimer's Disease Research Unit, Hollywood Medical Centre, Nedlands, Australia, r.martins@ecu.edu.au
Notes	ACTRN12613000034730 Ralph Martins written to in 2016- no response

## AFORRD

Trial name or title	Atorvastatin in factorial with omega-3 fatty acid risk reduction in diabetes (AFORRD)
Methods	RCT
Participants	People with type 2 diabetes with no known CVD and not taking lipid-lowering therapy, adults (> 18 years) N: intervention 397, control 403 (analysed intervention 371, control 361)
Interventions	Each for 12 months: Arm 1: atorvastatin (Lipitor 20 mg/d) and olive oil placebo (2 g/d) Arm 2: omega-3 (Omacor 2 g/d: 46% EPA, 38% DHA) and placebo tablets for atorvastatin Arm 3: atorvastatin (Lipitor 20 mg/d) and Omega-3 (Omacor 2 g/d: 46% EPA, 38% DHA) Arm 4: placebo tablets for atorvastatin and olive oil placebo (2 g/d)
Outcomes	Primary: lipid profiles Secondary: phytosterol changes, HbA <sub>1c</sub> ,estimated CVD risk using the UK Prospective Diabetes Study risk engine
Starting date	Registered on Trials Registry: 4 April 2004 Trial start date: 1 November 2004 Trial completion date est: 31 July 2006
Contact information	Rury Holman, Oxford Centre for Diabetes
Notes	ISRCTN76737502 Rury Holman contacted in 2016: confirmed results are not yet published, but planned

Trial name or title	The Beyond Ageing Project phase 2: a selective prevention trial using novel pharmacotherapies in an older age cohort at risk for depression
Methods	RCT
Participants	Older adults ( $\geq$ 60 years) at risk of depression (K-10 score ranging from 16-29) who initially participated in the first Beyond Ageing Project
Interventions	Each for 12 months: Arm 1: omega-3 (4 capsules, total 2 g/d: 1200 mg EPA and 800 mg DHA) and placebo microcrystalline cellulose (1 capsule) Arm 2: paraffin oil placebo (4 capsules) and sertraline hydrochloride (1 capsule, 50 mg) Arm 3: paraffin oil placebo (4 capsules) and placebo microcrystalline cellulose (1 capsule)
Outcomes	Primary: depressive symptoms (PHQ-9) Secondary: cognitive decline, Mini Mental State Exam, brain metabolism, hippocampal volume, anxiety (Generalized Anxiety Disorder-7 (GAD-7)), disability (World Health Organziation Disability Assessment Schedule-II (WHODAS-II)), sleeping problems (Pittsburgh Sleep Quality Index (PSQI)), exercise (Active Australian Survey)
Starting date	Registered on Trials Registry: 12 January 2010 Trial start date: June 2011 Trial completion date est: Main results expected in 2017
Contact information	Ian Hickie (PI), Brain and Mind Centre, University of Sydney, ian.hickie@sydney.adu.au
Notes	ACTRN12610000032055

# **Beyond Aging Project**

## Chandrakala 2010

Trial name or title	Long-term effects of a reduced fat diet intervention in pre-diabetes
Methods	RCT
Participants	Participants with pre-diabetes (IFG/IGT), 201 participants discussed in 1 abstract, 134 in a later abstract
Interventions	Each for 3 years: Arm 1: reduced-fat diet (fat content ≤ 20% total energy, ratio of PUFA/SFA 0.8 to 1.0) Arm 2: normal/control diet
Outcomes	Incidence of diabetes, BMI, lipids, insulin, plasma glucose, HbA1c, BP, nutritional intake
Starting date	Registered on Trials Registry: no registration found Trial start date: not stated Trial completion date est: not stated
Contact information	Chandrakala Galla, chandrakala.galla@gmail.com; Arpana Gaddam, dr.arpanag@gmail.com

## Chandrakala 2010 (Continued)

Notes	We wrote to trial authors in 2016: Dr Gaddam confirmed work submitted as a PhD but not published in
	full. Requested copy of PhD thesis, but no reply to date
	Funding: DiabetOmics India

## n-3 for Vascular Cognitive Aging

Trial name or title	n-3 PUFA for vascular cognitive aging
Methods	RCT
Participants	Older adults ( $\geq$ 80 years) at high risk for cognitive decline and dementia of Alzheimer's type
Interventions	Each for 3 years: Arm 1: omega-3 fish oil (1.65 g/d EPA + DHA) Arm 2: soybean oil placebo (1.65 g/d)
Outcomes	Primary: total cerebral white matter volume Secondary: biomarkers of endothelial health, total brain atrophy, medial temporal lobe atrophy, ventricular expansion, Trail Making Test part B, digit symbol Wechsler Adult Intelligence Scale-Revised (WAIS-R), cerebral blood flow, fractional anisotropy within frontal gyri
Starting date	Registered on Trials Registry: 24 September 2013 Trial start date: May 2014 Trial completion date est: March 2019
Contact information	Alena Borgatti, borgatti@ohsu.edu; James Dursch, dursch@ohsu.edu; Gene Bowman and Lynne Shinto (PIs) , Oregon Health and Science University
Notes	NCT01953705

## n-3 on plasma lipid

Trial name or title	Influence of different sources of n-3 fatty acid on plasma lipid in moderately hypercholesterolaemic subjects
Methods	RCT
Participants	Adults (40-65 years) with mild to moderate hypercholesterolaemia
Interventions	Arm 1: EPA/DHA 1.8 g/d Arm 2: EPA/DHA 3.6 g/d Arm 3: ALA 4 g/d Arm 4: placebo
Outcomes	Fatty acids, lipids, cytokines (IL-6, IL-1a)

## n-3 on plasma lipid (Continued)

Starting date	Registered on Trials Registry: 13 March 2012 Trial start date: unclear Trial completion date est: unclear
Contact information	Su Yixiang, Sun-Yat Sen University, China, suyx@mail.sysu.edu.cn; Zhou Quan, Guangzhou Medical Uni- versity, joan_zq@126.com
Notes	ChiCTR-TRC-12002014 Su Yixiang and Zhou Quan contacted in 2016: no response

#### NCT00309439

Trial name or title	Studies of serum PSA to help resolve the current implication of alpha-linolenic acid and prostate cancer
Methods	RCT
Participants	Adults 18-77 years
Interventions	Arm 1: ALA-rich diet Arm 2: control (not detailed)
Outcomes	PSA, atrial fibrillation
Starting date	Registered on Trials Registry: 29 March 2006 Trial start date: unclear Trial completion date est: unclear
Contact information	David Jenkins, University of Toronto, nutritionproject@smh.toronto.on.ca
Notes	NCT00309439 David Jenkins written to in 2016: confirmed not published in full and data incomplete

## NCT00410020

Trial name or title	Arrhythmia prevention with an alpha-linolenic enriched diet
Methods	RCT, parallel, 2 arms, 12 months
Participants	98 people with successful atrial fibrillation electrical cardioversion
Interventions	Canola margarine and oil, rich in ALA, versus a conventional diet (control), for 1 year
Outcomes	Length of time to first recurrence of atrial fibrillation
Starting date	June 1999, expected finish date June 2003, registered December 2006 so appears to have been carried out

## NCT00410020 (Continued)

Contact information	Principal Investigator: Jean-Paul Broustet, MD, PhD, Universitary Hospital Haut-Lévêque Bordeaux France
Notes	NCT00410020, registered Dec 2006, no publication found

## NCT01047449

Trial name or title	Improving the results of heart bypass surgery using new approaches to surgery and medication (SUPERI-ORSVG)
Methods	RCT
Participants	Adults having coronary artery bypass graft (CABG) using saphenous vein graft (SVG)
Interventions	Each for 12 months: Arm 1: fish oil supplements (2 x 1 g/d Ocean Nutrition capsules: 55% fish oils EPA:DHA 33%:22%) and SVG conventionally harvested Arm 2: placebo and SVG conventionally harvested Arm 3: fish oil supplements (2 x 1 g/d Ocean Nutrition capsules: 55% fish oils EPA:DHA 33%:22%) and SVG no-touch harvest Arm 4: placebo and SVG no-touch harvest
Outcomes	Primary: proportion of grafts occluded Secondary: significant stenosis, adverse SVG harvesting events, composite outcome of all-cause mortality, non-fatal MI and repeat revascularisation
Starting date	Registered on Trials Registry: 12 Jan 2010 Trial start date: July 2011 Trial completion date est: Dec 2016
Contact information	Stephen Fremes, Sunnybrook Health Sciences Centre (PI)
Notes	NCT01047449

## NCT01513252

Trial name or title	Long-term effects of interventional strategies to prevent cognitive decline in elderly (MAPT PLUS)
Methods	RCT - extension of MAPT trial
Participants	Participants of MAPT trial
Interventions	Follow-up, 2-year extension of participants in MAPT, after completion of MAPT interventions
Outcomes	Primary: cognitive and functional status (Grober and Buschke test) Secondary: markers of cerebral atrophy, cost effectiveness

### NCT01513252 (Continued)

Starting date	Registered on Trials Registry: 30 December 2011 Trial start date: December 2011 Trial completion date est: November 2016
Contact information	Bruno Vellas (PI), University Hospital, Toulouse, vellas.b@chu-toulouse.fr
Notes	NCT01513252 Bruno Vellas written to in 2016- no response

## NCT01784042

Trial name or title	Dietary energy restriction and omega-3 fatty acids on mammary tissue
Methods	RCT
Participants	Overweight women (30-55 years) with increased breast cancer risk
Interventions	For 1 year: Arm 1: Lovaza (omega-3-acid ethyl esters) Arm 2: Lovaza and dietary energy restriction Arm 3: placebo Arm 4: placebo and dietary energy restriction
Outcomes	Ki67 expression at 1 year
Starting date	Registered on Trials Registry: 31 January 2013 Trial start date: March 2013 Trial completion date est: March 2018
Contact information	Andrea Manni, Hershey Medical Centre, amanni@hmc.psu.edu (PI) or Cynthia DuBrock, cdubrock@hmc. psu.edu
Notes	NCT01784042

## NCT02128763

Trial name or title	Dry eye assessment and management trial (DREAM)
Methods	RCT
Participants	Adults with dry eye
Interventions	Each for 2 years Arm 1: omega-3 supplements (2000 mg EPA + 1000 mg DHA/d as 5 gelcaps) Arm 2: olive oil supplements (5 gelcaps)

## NCT02128763 (Continued)

Outcomes	Primary: Ocular Surface Disease Index (OSDI) score Secondary: other eye health measures, SF-36, healthcare utilisation costs, cost effectiveness
Starting date	Registered on Trials Registry 28 April 2014 Trial start date: November 2014 Trial completion date est: July 2017
Contact information	Penny Asbell, Mount Sinai Icahn School of Medicine (Trial Chair), Maureen Maguire, University of Penn- sylvania (PI)
Notes	NCT02128763

# NCT02211560

Trial name or title	Investigating a phosphatidylserine based dietary approach for the management of mild cognitive impairment
Methods	RCT
Participants	People with mild cognitive impairment (MCI) aged 65-85 years
Interventions	Each for 24 months: Arm 1: phosphatidylserine omega-3 (DHA enriched) Arm 2: placebo cellulose capsules
Outcomes	Primary: selective reminding test (SRT) Secondary: MMSE, neurological battery test (NBT), dementia (DSM-4 criteria), mini sleep questionnaire (MSQ), Hamilton Anxiety rating scale (HAM-A), safety and adverse events
Starting date	Registered on Trials Registry: 6 August 2014 Trial start date: September 2014 Trial completion date est: September 2019
Contact information	Nadia Niemerzyanski, nadiaN@enzymotec.com; Yael Richter, yaelr@enzymotec.com
Notes	NCT02211560

#### NCT02295059

Trial name or title	Omega-3 fatty acids and ERPR(-)HER2(+/-) breast cancer prevention
Methods	RCT
Participants	Women at risk for recurrent breast cancer- with prior diagnosis of stage 0-III breast cancer and completion of surgery, chemotherapy or trastuzumab or radiation therapy

## NCT02295059 (Continued)

Interventions	Each for 12 months: Arm 1: omega-3 high-dose capsules (5 g/d EPA + DHA) Arm 2: omega-3 low-dose capsules (0.9 g/d EPA + DHA)
Outcomes	Primary: breast adipose tissue metabolites Secondary: cytomorphology or cell proliferation of mammary epithelial cells, DNA promoter methylation and pro-inflammatory gene expression in mammary epithelial and adipose tissue
Starting date	Registered on Trials Registry: 14 October 2014 Trial start date: August 2014 Trial completion date est: January 2019
Contact information	Anitra Sumbry, anitra.sumbry@osumc.edu; Lisa Yee (PI), Ohio State University
Notes	NCT02295059

## NCT02676466

Trial name or title	Enabling reduction of low-grade inflammation in seniors (ENRGISE)
Methods	RCT
Participants	People aged 70+ years with self-reported walking or stair-climbing difficulty
Interventions	Each for 1 year Arm 1: omega-3 fish oil (1.4 g/d for 6 months, possibly increasing to 2.8 g/d) Arm 2: losartan 25 mg/d Arm 3: placebo corn oil (for omega-3) plus placebo cellulose (for losartan) Arm 4: omega-3 plus losartan Arm 5: placebo corn oil (for omega-3) Arm 6: placebo cellulose (for losartan)
Outcomes	Primary: IL6, 400-meter walk test Secondary: short physical performance battery, frailty, hand grip strength, knee dynamometry, Short Form (SF)-36
Starting date	Registered on Trials Registry 3 February 2016 Trial start date: February 2016 Trial completion date est: March 2018
Contact information	Jane Lu janelu@ufl.edu Michael Stancil mstancil@ufl.edu
Notes	NCT02676466

#### NCT02719327

Trial name or title	Impact of icosapent ethyl on Alzheimer's disease (AD) biomarkers in preclinical adults
Methods	RCT
Participants	Cognitively healthy adults aged 50-70 years whose parents had AD
Interventions	Each for 18 months: Arm 1: icosapent ethyl EPA (Vascepa) 4 g/d gel cap Arm 2: matching gel cap placebo
Outcomes	Primary: cerebral blood flow by magnetic resonance imaging Secondary: cerebrospinal fluid biomarkers of Alzheimer's disease, cognitive performance (preclinical Alzheimer's cognitive composite, PACC)
Starting date	Registered on Trials Registry: 21 March 2016 Trial start date: December 2016 Trial completion date est: November 2021
Contact information	Cynthia Carlsson, cynthia.carlsson@va.gov; Elena Beckman, elena.beckman@va.gov
Notes	NCT02719327

#### OMEMI

Trial name or title	Omega-3 fatty acids in elderly patients with myocardial infarction trial (OMEMI)
Methods	RCT
Participants	Elderly patients (70-82 years) with acute MI
Interventions	Each for 24 months: Arm 1: omega-3 capsules, 3/d (Pikasol, total of 1.8 g/d EPA + DHA) and standard therapy Arm 2: corn oil placebo, 3/d and standard therapy
Outcomes	Primary: composite of total mortality, first non-fatal recurring acute MI, stroke and revascularisation Secondary: new onset atrial fibrillation, adipose tissue, serum fatty acids, makers of endothelial function, inflammation, coagulation and fibrinolytic activity, genes associated with atherothrombosis
Starting date	Registered on Trials Registry: 16 April 2013 Trial start date: November 2012 Trial completion date est: November 2019
Contact information	Svein Solheim, Center for Clinical Heart Research, Oslo University Hospital, arnljot.tveit@vestreviken.no
Notes	NCT01841944

# **REDUCE-IT**

Trial name or title	Reduction of cardiovascular events with EPA-intervention trial (REDUCE-IT)
Methods	RCT
Participants	Patients (45 years or over) with hypertriglyceridaemia, with cardiovascular disease or at high risk for cardio- vascular disease, and on statin
Interventions	Each for 4-6 years: Arm 1: EPA ethyl ester (AMR101 4 g/d) Arm 2: placebo
Outcomes	Primary: composite of CV death, MI, stroke, coronary revascularisation and hospitalisation for unstable angina Secondary: incidence of additional cardiovascular events, lipid and lipoprotein levels
Starting date	Registered on Trials Registry: 13 December 2011 Trial start date: November 2011 Trial completion date est: December 2017
Contact information	Deepak Bhatt (PI), Brigham and Women's Hospital
Notes	NCT01492361

#### seAFOOD

Trial name or title	The seafood (systematic evaluation of aspirin and fish oil) polyp prevention trial
Methods	RCT
Participants	NHS Bowel Cancer Screening Programme patients (55-73 years) identified as "high risk" ( $\geq$ 5 small adenomas; or $\geq$ 3 adenomas with at least one being $\geq$ 10 mm in diameter) after their 1st screening colonoscopy
Interventions	Each for 12 months: Arm 1: EPA (ALFA capsules: 2 x 500 mg/d = 2 g/d) and aspirin placebo (1/d) Arm 2: EPA placebo (capric and caprylic acid triglycerides: 2/d) and aspirin EC (1/d = 300 mg/d) Arm 3: EPA (ALFA capsules: 2 x 500 mg/d = 2 g/d) and aspirin EC (1/d = 300 mg/d) Arm 4: EPA placebo (capric and caprylic acid triglycerides: 2/d) and aspirin placebo (1/d)
Outcomes	Primary: number of participants with $\geq 1$ adenomas at 12 months Secondary: adverse events, number of "advanced" adenomas per participant, number of "high risk" participants re-classified as "intermediate risk", number participants with $\geq 1$ advanced adenomas, adenoma region in the colorectum, total number of adenomas per participant, number of participants with colorectal cancer, levels of bioactive lipid mediators e.g. omega-3
Starting date	Trial Registration entry: 6 May 2011 Trial start date: 30 May 2011 Estimated trial completion: 31 July 2017

#### seAFOOD (Continued)

Contact information	Mark Hull, Leeds Institute of Molecular Medicine, m.a.hull@leeds.ac.uk
Notes	ISRCTN05926847 EudraCT 2010-020943-10 www.seafood-trial.co.uk

#### UMIN000012825

Trial name or title	Effect of PUFA on vascular healing process in hypercholesterolemic patients with ACS
Methods	RCT
Participants	Hypercholesterolemic patients (20-80 years) with acute coronary syndrome who have received successful optical coherence tomography (OCT)-guided percutaneous coronary intervention (PCI)
Interventions	Each for 12 months: Arm 1: intensive lipid-lowering therapy with both statin and EPA + DHA Arm 2: intensive lipid-lowering therapy with both statin and EPA Arm 3: standard lipid-lowering therapy with statins
Outcomes	Primary: changes in OCT parameter Secondary: lipids, serum plasma profile, inflammatory parameters, adverse cardiovascular events
Starting date	Registered on Trials Registry: 1 February 2014 Trial start date: 1 February 2014 Trial completion date est: 30 June 2019
Contact information	Shiro Uemura (PI), Nara Medical University, Japan, suemura@naramed-u.ac.jp
Notes	UMIN000012825

**BMI**: Body Mass Index; **CETP**: cholesteryl ester transfer protein; **CVD**: cardiovascular disease; **DHA**: docosahexaenoic acid;**EPA**: eicosapentaenoic acid;**HDL**: high density lipoprotein: **LDL**: low density lipoprotein:**MI**: myocardial infarction; **MMSE**: Mini Mental State Examination; **PSA**: prostate-specific antigen; **RCT**: randomised controlled trial;

## DATA AND ANALYSES

## Comparison 1. Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 ALL-CAUSE MORTALITY	24	19290	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.89, 1.07]
2 All-cause mortality - SA	24		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Low risk of bias for allocation concealment	11	9639	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.87, 1.22]
2.2 Low risk of bias for attention	17	13622	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.87, 1.07]
2.3 Low risk of bias for compliance	10	4776	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.89, 1.14]
2.4 Low summary risk of bias	5	8092	Risk Ratio (M-H, Random, 95% CI)	1.04 [0.87, 1.26]
2.5 Trials registry or pre-2010	22	18852	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.90, 1.08]
2.6 No industry funding	9	4508	Risk Ratio (M-H, Random, 95% CI)	1.09 [0.84, 1.42]
2.7 Randomised 100+ participants	20	19029	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.89, 1.08]
2.8 Randomised 250+ participants	11	17457	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.91, 1.10]
3 All-cause mortality - SA fixed-effect	24	19290	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.89, 1.07]
4 All-cause mortality - subgroup by PUFA dose	24	19290	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.89, 1.07]
4.1 total PUFA < 1.0% E	5	1054	Risk Ratio (M-H, Random, 95% CI)	0.66 [0.33, 1.34]
4.2 total PUFA 1.0 to < 2.0% E	9	13766	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.84, 1.13]
4.3 total PUFA 2.0 to < 5.0% E	4	2295	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.76, 1.20]
4.4 total PUFA $\geq$ 5.0% E	6	2175	Risk Ratio (M-H, Random, 95% CI)	1.04 [0.86, 1.26]
5 All-cause mortality - subgroup by duration	24	19290	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.89, 1.07]
5.1 Medium duration 1 to < 2 years	8	1940	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.48, 1.55]
5.2 Medium-long duration 2 to < 4 years	11	8219	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.82, 1.10]
5.3 Long duration 4+ years	5	9131	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.89, 1.14]
6 All-cause mortality - subgroup by primary or secondary prevention	24	19290	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.89, 1.07]
6.1 Primary prevention of CVD	13	9549	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.78, 1.20]
6.2 Secondary prevention of CVD	11	9741	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.86, 1.12]
7 All-cause mortality - subgroup by baseline PUFA dose	24	19290	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.89, 1.07]

7.1 Baseline total PUFA < 6% E	4	3643	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.84, 1.14]
7.2 Baseline total PUFA 6 to < 11% E	5	7826	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.89, 1.24]
7.3 Baseline total PUFA 11+% E	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
7.4 Baseline total PUFA unclear	15	7821	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.78, 1.08]
8 All-cause mortality - subgroup	24		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
by replacement 8.1 PUFA replaced SFA	6	4154	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.88, 1.15]
8.2 PUFA replaced	11	12526	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.90, 1.12]
monounsaturated fats	11	12)20	Nisk Ratio (WEI), Randolli, 7970 Cly	1.00 [0.90, 1.12]
8.3 PUFA replaced	5	2965	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.58, 1.70]
carbohydrate	)	2)0)		0.99 [0.90, 1.70]
8.4 PUFA replaced protein	2	529	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.57, 1.44]
8.5 PUFA replaced unclear	6	1227	Risk Ratio (M-H, Random, 95% CI)	0.66 [0.39, 1.14]
9 All-cause mortality - subgroup	24	19290	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.89, 1.07]
by sex				
9.1 > 70% men	13	10252	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.88, 1.10]
9.2 > 70% women	1	2437	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.43, 1.65]
9.3 men & women	8	6498	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.79, 1.29]
9.4 sex not reported	2	103	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.51, 1.59]
10 All-cause mortality - subgroup	24	19290	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.89, 1.07]
by age				
10.1 Mean age < 50 years	6	1852	Risk Ratio (M-H, Random, 95% CI)	1.47 [0.95, 2.27]
10.2 Mean age 50 to < 65	12	6040	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.75, 1.10]
years				
10.3 Mean age 65+ years	6	11398	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.88, 1.09]
11 All-cause mortality - subgroup by statin use	24	19290	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.89, 1.07]
11.1 < 50% on statins	18	13399	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.89, 1.10]
11.2 50+% on statins	4	5353	Risk Ratio (M-H, Random, 95% CI)	0.62 [0.26, 1.51]
11.3 Percentage on statins unclear	2	538	Risk Ratio (M-H, Random, 95% CI)	1.15 [0.56, 2.37]
12 All-cause mortality - subgroup by intervention type	24	19290	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.89, 1.07]
12.1 Dietary advice	4	4739	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.77, 1.23]
12.2 Supplemental foods &	5	11104	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.88, 1.10]
diet provided				
12.3 Supplements (capsules & unusual foods)	12	2391	Risk Ratio (M-H, Random, 95% CI)	0.76 [0.52, 1.11]
12.4 Any combination	3	1056	Risk Ratio (M-H, Random, 95% CI)	1.12 [0.72, 1.74]
13 CORONARY HEART	15	10076	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.72, 1.06]
DISEASE (CHD) EVENTS: myocardial infarction (fatal or				
non-fatal) or angina 14 CHD events - SA	15		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
14.1 Low risk of bias for	5	5946	Risk Ratio (M-H, Random, 95% CI)	1.14 [0.73, 1.78]
allocation concealment	)	<i>JJ</i> <b>H</b> 0	Nos Natio (191-11, Raildolli, 77/0 CI)	1.17 [0./ J, 1./0]
anotation concenticit				

14.2 Low risk of bias for attention	11	7090	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.72, 1.02]
14.3 Low risk of bias for	7	4006	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.65, 1.17]
compliance	/	4000	Risk Ratio (Mi-ri, Randolli, 99% CI)	0.87 [0.03, 1.17]
14.4 Low summary risk of	4	5826	Risk Ratio (M-H, Random, 95% CI)	1.18 [0.76, 1.81]
bias	4	J820	Nisk Ratio (im-11, Randonii, 9970 Ci)	1.10 [0.70, 1.01]
14.5 Trials registry or pre-	15	10076	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.72, 1.06]
2010	1)	100/0	Kisk Ratio (191-11, Randolli, 7970 CI)	0.07 [0.72, 1.00]
14.6 No industry funding	4	1073	Risk Ratio (M-H, Random, 95% CI)	0.72 [0.31, 1.63]
14.7 Randomised 100+	12	9869	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.70, 1.08]
participants		,,		
14.8 Randomised 250+	6	8958	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.82, 1.09]
participants		-,,,-	(	
15 CHD events - SA fixed-effect	15	10076	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.82, 0.99]
16 CHD events - subgroup by	15	10076	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.72, 1.06]
PUFA dose				
16.1 total PUFA < 1.0% E	3	829	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.20, 4.89]
16.2 total PUFA 1.0 to < 2.	4	5170	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.66, 1.13]
0% E				
16.3 total PUFA 2.0 to < 5.	3	2224	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.82, 1.04]
0% E				
16.4 total PUFA > 5.0% E	5	1853	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.54, 1.36]
17 CHD events - subgroup by	15	10076	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.72, 1.06]
duration				
17.1 Medium duration 1 to $<$	6	1073	Risk Ratio (M-H, Random, 95% CI)	0.59 [0.27, 1.30]
2 years				
17.2 Medium-long duration 2	5	7204	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.84, 1.03]
to < 4 years				
17.3 Long duration 4+ years	4	1799	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.46, 1.35]
18 CHD events - subgroup	15	10076	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.72, 1.06]
by primary or secondary				
prevention				
18.1 Primary prevention of	6	1710	Risk Ratio (M-H, Random, 95% CI)	0.53 [0.25, 1.11]
CVD	0	02((		
18.2 Secondary prevention of	9	8366	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.85, 1.09]
CVD	15	10076		0.07 [0.72, 1.0/]
19 CHD events - subgroup by	15	10076	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.72, 1.06]
baseline PUFA dose	1	040	Did Datis (M II Dandams 050/ CI)	0.77 [0.5(.1.0)]
19.1 Baseline total PUFA < 6% E	1	846	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.56, 1.04]
19.2 Baseline total PUFA 6 to	2	2491	Diale Datia (M. H. Dandam, 0504 CI)	1 17 [0 69 2 01]
< 11% E	L	2491	Risk Ratio (M-H, Random, 95% CI)	1.17 [0.68, 2.01]
19.3 Baseline total PUFA	0	0	Risk Ratio (M-H, Random, 95% CI)	$0.0 \ [0.0, \ 0.0]$
11+% E	0	0	Nisk Natio (ivi-11, Nationit, 7570 Ci)	0.0 [0.0, 0.0]
19.4 Baseline total PUFA	12	6739	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.55, 1.06]
unclear	12	0/3)	Kisk Ratio (191-11, Randolli, 7970 CI)	0.77 [0.99, 1.00]
20 CHD events - subgroup by	15		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
replacement	1)			Subtotals only
20.1 PUFA replaced saturated	4	3730	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.78, 1.19]
fats	-	5,50		, [0., 0, 1.1)]

20.2 PUFA replaced	9	7079	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.75, 1.20]
monounsaturated fats				
20.3 PUFA replaced	2	156	Risk Ratio (M-H, Random, 95% CI)	0.57 [0.12, 2.65]
carbohydrate	1	202		0.07 [0.(0, 1.27]
20.4 PUFA replaced protein	1 3	393 469	Risk Ratio (M-H, Random, 95% CI) Risk Ratio (M-H, Random, 95% CI)	0.97 [0.69, 1.37]
20.5 PUFA replaced unclear 21 CHD events - subgroup by sex	15	10076	Risk Ratio (M-H, Random, 95% CI)	0.56 [0.09, 3.52] 0.87 [0.72, 1.06]
21.1 > 70% men	10	9269	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.82, 1.05]
21.1 > 70% men 21.2 > 70% women	10	140	Risk Ratio (M-H, Random, 95% CI)	1.84 [0.08, 44.38]
21.2 × 7070 women 21.3 men & women	2	222	Risk Ratio (M-H, Random, 95% CI)	0.26 [0.13, 0.51]
21.4 sex not reported	2	445	Risk Ratio (M-H, Random, 95% CI)	1.29 [0.66, 2.50]
22 CHD events - subgroup by age	15	10076	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.72, 1.06]
22.1 Mean age < 50 years	1	458	Risk Ratio (M-H, Random, 95% CI)	1.63 [1.00, 2.67]
22.2 Mean age 50 to < 65	9	3204	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.83, 1.03]
years		0-0-		
22.3 Mean age 65+ years	3	5921	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.71, 1.04]
22.4 Mean age unclear	2	493	Risk Ratio (M-H, Random, 95% CI)	0.53 [0.06, 4.64]
23 CHD events - subgroup by	15	10076	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.72, 1.06]
statin use				
23.1 < 50% on statins	13	5001	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.66, 1.09]
23.2 50+% on statins	2	5075	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.73, 1.17]
24 CHD events - subgroup by	15	10076	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.72, 1.06]
intervention type				
24.1 Dietary advice	2	2135	Risk Ratio (M-H, Random, 95% CI)	0.52 [0.15, 1.77]
24.2 Supplemental foods &	2	5683	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.71, 1.04]
diet provided				
24.3 Supplements (capsules &	9	1407	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.56, 1.37]
unusual foods)				
24.4 Any combination	2	851	Risk Ratio (M-H, Random, 95% CI)	1.22 [0.74, 2.02]
25 STROKE - fatal & non fatal	11	14742	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.58, 1.44]
26 Stroke - SA	11		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
26.1 Low risk of bias for	4	6022	Risk Ratio (M-H, Random, 95% CI)	1.14 [0.55, 2.38]
allocation concealment				
26.2 Low risk of bias for	8	11858	Risk Ratio (M-H, Random, 95% CI)	0.71 [0.51, 0.98]
attention	,			
26.3 Low risk of bias for	4	3730	Risk Ratio (M-H, Random, 95% CI)	1.36 [0.45, 4.11]
compliance		- (0)		
26.4 Low summary risk of	3	5686	Risk Ratio (M-H, Random, 95% CI)	1.04 [0.49, 2.23]
bias		1/7/2		
26.5 Trials registry or pre-	11	14742	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.58, 1.44]
2010 26.6 No industry funding	2	851	Risk Ratio (M-H, Random, 95% CI)	1 67 [0 22 8 62]
26.6 No industry funding 26.7 Randomised 100+	2 10	14662	Risk Ratio (M-H, Random, 95% CI)	1.67 [0.32, 8.62] 0.90 [0.56, 1.45]
participants	10	14002	Risk Ratio (M-FI, Random, 93% CI)	0.90 [0.96, 1.49]
26.8 Randomised 250+	8	14291	Disk Datis (M H Dandom 950/ CI)	0.98 [0.60, 1.60]
participants	0	14291	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.00, 1.00]
27 Stroke - SA fixed-effect	11	14742	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.61, 1.11]
28 Stroke - subgroup by PUFA	11	14742	Risk Ratio (M-H, Random, 95% CI)	$0.82 \ [0.01, 1.11]$ $0.91 \ [0.58, 1.44]$
dose	11	17/74	Nos Natio (191-11, Rainolii, 7770 CI)	0.71 [0.70, 1.14]
28.1 total PUFA < 1.0% E	4	1098	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.14, 6.55]
			······································	

28.2 total PUFA 1.0 to < 2. 0% E	2	9834	Risk Ratio (M-H, Random, 95% CI)	0.72 [0.49, 1.07]
28.3 total PUFA 2.0 to < 5.	2	2113	Risk Ratio (M-H, Random, 95% CI)	3.25 [0.99, 10.72]
0% E				
28.4 total PUFA > 5.0% E	3	1697	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.36, 1.33]
29 Stroke - subgroup by duration	11	14742	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.58, 1.44]
29.1 Medium duration 1 to <	4	1098	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.14, 6.55]
2 years				
29.2 Medium-long duration 2	3	6950	Risk Ratio (M-H, Random, 95% CI)	1.60 [0.61, 4.16]
to < 4 years				
29.3 Long duration 4+ years	4	6694	Risk Ratio (M-H, Random, 95% CI)	0.68 [0.47, 0.97]
30 Stroke - subgroup by primary	11	14742	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.58, 1.44]
or secondary prevention				
30.1 Primary prevention of	4	6570	Risk Ratio (M-H, Random, 95% CI)	0.70 [0.45, 1.11]
cardiovascular disease (CVD)	-	0,7,0		01, 0 [0119, 1111]
30.2 Secondary prevention of	7	8172	Risk Ratio (M-H, Random, 95% CI)	1.24 [0.59, 2.62]
CVD	/	01/2		1.21 [0.99, 2.02]
31 Stroke - subgroup by baseline	11	14742	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.58, 1.44]
PUFA dose	11	14/42	Risk Ratio (191-11, Randonii, 7570 Ci)	0.71 [0.76, 1.44]
31.1 Baseline total PUFA <	1	846	Risk Ratio (M-H, Random, 95% CI)	0.59 [0.30, 1.15]
6% E	1	040	Risk Ratio (191-11, Randolli, 9970 CI)	0.99[0.90, 1.19]
31.2 Baseline total PUFA 6 to	2	7/00	Did Datis (M II Dandam 050/ CI)	1 21 [0 /1 2 50]
	3	7488	Risk Ratio (M-H, Random, 95% CI)	1.21 [0.41, 3.59]
< 11% E	0	0		
31.3 Baseline total PUFA	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
11+% E	_	<i>( ( a a</i>		
31.4 Baseline total PUFA	7	6408	Risk Ratio (M-H, Random, 95% CI)	1.10 [0.51, 2.41]
unclear				
32 Stroke - subgroup by	11		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
replacement				
32.1 PUFA replaced saturated	4	3730	Risk Ratio (M-H, Random, 95% CI)	1.36 [0.45, 4.11]
fats				
32.2 PUFA replaced	7	11742	Risk Ratio (M-H, Random, 95% CI)	0.72 [0.52, 0.99]
monounsaturated fats				
32.3 PUFA replaced	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
carbohydrates				
32.4 PUFA replaced protein	1	393	Risk Ratio (M-H, Random, 95% CI)	4.88 [0.24, 100.89]
32.5 PUFA replaced unclear	2	574	Risk Ratio (M-H, Random, 95% CI)	0.71 [0.02, 29.08]
33 Stroke - subgroup by sex	11	14742	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.58, 1.44]
33.1 > 70% men	9	9354	Risk Ratio (M-H, Random, 95% CI)	1.04 [0.56, 1.93]
33.2 > 70% women	0	0	Risk Ratio (M-H, Random, 95% CI)	$0.0 \ [0.0, \ 0.0]$
33.3 men & women	1	4997	Risk Ratio (M-H, Random, 95% CI)	0.68 [0.43, 1.05]
33.4 sex not reported	1	391	Risk Ratio (M-H, Random, 95% CI)	5.03 [0.24, 104.01]
34 Stroke - subgroup by age	11	14742	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.58, 1.44]
34.1 Mean age < 50 years	1	458	Risk Ratio (M-H, Random, 95% CI)	1.07 [0.15, 7.55]
34.2 Mean age 50 to < 65	5	2975	Risk Ratio (M-H, Random, 95% CI)	2.84 [1.05, 7.64]
years				
34.3 Mean age 65+ years	4	10918	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.48, 0.94]
34.4 Mean age unclear	1	391	Risk Ratio (M-H, Random, 95% CI)	5.03 [0.24, 104.01]
35 Stroke - subgroup by statin use	11	14742	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.58, 1.44]
35.1 < 50% on statins	9	9667	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.59, 1.78]
35.2 50+% on statins	2	5075	Risk Ratio (M-H, Random, 95% CI)	0.50 [0.07, 3.40]

36 Stroke - subgroup by intervention type	11	14742	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.58, 1.44]
36.1 Dietary advice	1	2033	Risk Ratio (M-H, Random, 95% CI)	3.32 [0.92, 12.04]
36.2 Supplemental foods &	3	10680	Risk Ratio (M-H, Random, 95% CI)	0.68 [0.49, 0.96]
diet provided	5	10000		0.00 [0.1), 0.90]
36.3 Supplements (capsules & unusual foods)	5	1178	Risk Ratio (M-H, Random, 95% CI)	1.18 [0.25, 5.62]
36.4 Any combination	2	851	Risk Ratio (M-H, Random, 95% CI)	1.67 [0.32, 8.62]
37 Stroke - subgroup by fatal & non fatal	11		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
37.1 Fatal stroke	4	6534	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.38, 1.60]
37.2 Non-fatal stroke	2	1084	Risk Ratio (M-H, Random, 95% CI)	0.48 [0.09, 2.51]
37.3 Only combined fatal &	6	7970	Risk Ratio (M-H, Random, 95% CI)	1.51 [0.56, 4.07]
non fatal data provided				
38 Stroke - subgroup by ischaemic	11		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
& haemorrhagic 38.1 Ischaemic stroke	3	2762	Risk Ratio (M-H, Random, 95% CI)	4.66 [1.00, 21.63]
38.2 Haemorrhagic stroke	3	2762	Risk Ratio (M-H, Random, 95% CI)	1.93 [0.48, 7.85]
38.3 Only combined	8	11980	Risk Ratio (M-H, Random, 95% CI)	0.70 [0.50, 0.97]
ischaemic and haemorrhagic data provided	0	11/00		0.70 [0.90, 0.97]
39 MAJOR ADVERSE CARDIAC & CEREBROVASCULAR	2	2879	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.59, 1.20]
EVENTS (MACCEs)	2			
40 MACCEs - SA	2	0	Risk Ratio (M-H, Random, 95% CI)	Subtotals only
40.1 Low risk of bias for allocation concealment	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
40.2 Low risk of bias for attention	1	846	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.51, 0.93]
40.3 Low risk of bias for compliance	2	2879	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.59, 1.20]
40.4 Low summary risk of bias	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
40.5 Trials registry or pre-	2	2879	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.59, 1.20]
2010 40.6 No industry funding	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
40.7 Randomised 100+ participants	2	2879	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.59, 1.20]
40.8 Randomised 250+	2	2879	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.50, 1.20]
participants	Z	20/9	Risk Ratio (M-FI, Randoni, 99% CI)	0.84 [0.59, 1.20]
41 MACCEs - SA fixed-effect	2	2879	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.82, 1.04]
42 MACCEs - subgroup by PUFA	2	2879	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.59, 1.20]
dose	2	2079		0.04 [0.99, 1.20]
42.1 total PUFA < 1.0% E	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
42.2 total PUFA 1.0 to < 2.	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
0% E	-	÷	(	[, 0.0]
42.3 total PUFA 2.0 to < 5.	1	2033	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.87, 1.12]
0% E				
42.4 total PUFA > 5.0% E	1	846	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.51, 0.93]

43 MACCEs - subgroup by duration	2	2879	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.59, 1.20]
43.1 Medium duration 1 to <	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2 years	÷		(	
43.2 Medium-long duration 2 to < 4 years	1	2033	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.87, 1.12]
43.3 Long duration 4+ years	1	846	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.51, 0.93]
44 MACCEs - subgroup	2	2879	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.59, 1.20]
by primary or secondary		>		
prevention				
44.1 Primary prevention of CVD	1	846	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.51, 0.93]
44.2 Secondary prevention of CVD	1	2033	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.87, 1.12]
45 MACCEs - subgroup by	2	2879	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.59, 1.20]
baseline PUFA dose				
45.1 Baseline total PUFA <	1	846	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.51, 0.93]
6% E	1	2022		0.00 [0.07, 1.12]
45.2 Baseline total PUFA 6 to < 11% E	1	2033	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.87, 1.12]
45.3 Baseline total PUFA	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
11+% E				[,]
45.4 Baseline total PUFA	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
unclear				
46 MACCEs - subgroup by	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
replacement	2	2070		0.04 [0.50, 1.20]
46.1 PUFA replaced saturated fats	2	2879	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.59, 1.20]
46.2 PUFA replaced	1	846	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.51, 0.93]
monounsaturated fats				
46.3 PUFA replaced	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
carbohydrates				
46.4 PUFA replaced protein	0	0	Risk Ratio (M-H, Random, 95% CI)	$0.0 \ [0.0, \ 0.0]$
46.5 PUFA replaced unclear	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
47 MACCEs - subgroup by sex	2	2879	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.59, 1.20]
47.1 > 70% men	2	2879	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.59, 1.20]
47.2 > 70% women	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
47.3 men & women	0	0	Risk Ratio (M-H, Random, 95% CI)	$0.0 \ [0.0, \ 0.0]$
47.4 sex not reported	0	0	Risk Ratio (M-H, Random, 95% CI)	$0.0 \ [0.0, \ 0.0]$
48 MACCEs - subgroup by age	2	2879	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.59, 1.20]
48.1 Mean age < 50 years	0	0	Risk Ratio (M-H, Random, 95% CI)	$0.0 \ [0.0, \ 0.0]$
48.2 Mean age 50 to < 65	1	2033	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.87, 1.12]
years				
48.3 Mean age 65+ years	1	846	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.51, 0.93]
49 MACCEs - subgroup by statin	2	2879	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.59, 1.20]
use	2	2070		
49.1 < 50% on statins	2	2879	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.59, 1.20]
49.2 50+% on statins	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
50 MACCEs - subgroup by intervention type	2	2879	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.59, 1.20]
50.1 Dietary advice	1	2033	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.87, 1.12]
Jo.1 Dietary advice	1	2033	Kisk Kalio (M-FI, Kalidolli, 95% CI)	0.99 [0.87, 1.12]

50.2 Supplemental foods & diet provided	1	846	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.51, 0.93]
50.3 Supplements (capsules & unusual foods)	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
50.4 Any combination	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

## Comparison 2. Higher PUFA vs lower PUFA - dichotomous secondary outcomes

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 CARDIOVASCULAR MORTALITY	16	15107	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.82, 1.26]
2 Cardiovascular mortality - SA	16		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Low risk of bias for allocation concealment	6	6031	Risk Ratio (M-H, Random, 95% CI)	1.08 [0.85, 1.38]
2.2 Low risk of bias for attention	9	11774	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.69, 1.07]
2.3 Low risk of bias for compliance	8	4142	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.75, 1.49]
2.4 Low summary risk of bias	3	5431	Risk Ratio (M-H, Random, 95% CI)	1.18 [0.77, 1.83]
2.5 Trials registry or pre-2010	16	15107	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.82, 1.26]
2.6 No industry funding	7	1744	Risk Ratio (M-H, Random, 95% CI)	1.19 [0.79, 1.79]
2.7 Randomised 100+ participants	13	14895	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.80, 1.28]
2.8 Randomised 250+ participants	7	13966	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.85, 1.32]
3 Cardiovascular mortality - SA fixed-effect	16	15107	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.88, 1.16]
4 Cardiovascular mortality - subgroup by PUFA dose	16	15107	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.82, 1.26]
4.1 total PUFA < 1.0% E	5	1054	Risk Ratio (M-H, Random, 95% CI)	0.76 [0.38, 1.51]
4.2 total PUFA 1.0 to < 2.0% E	3	9954	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.76, 1.30]
4.3 total PUFA 2.0 to < 5.0% E	3	2246	Risk Ratio (M-H, Random, 95% CI)	1.25 [0.96, 1.62]
4.4 total PUFA > 5.0% E	5	1853	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.62, 1.63]
5 Cardiovascular mortality - subgroup by duration	16	15107	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.82, 1.26]
5.1 Medium duration 1 to <2 years	5	974	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.39, 1.67]
5.2 Medium-long duration 2 to < 4 years	6	7337	Risk Ratio (M-H, Random, 95% CI)	1.09 [0.88, 1.36]
5.3 Long duration 4+ years	5	6796	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.67, 1.55]
6 Cardiovascular mortality - subgroup by primary or secondary prevention	16	15107	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.82, 1.26]
6.1 Primary prevention of cardiovascular disease (CVD)	7	6412	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.54, 1.41]

6.2 Secondary prevention of CVD	9	8695	Risk Ratio (M-H, Random, 95% CI)	1.12 [0.92, 1.36]
7 Cardiovascular mortality - subgroup by baseline PUFA dose	16	15107	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.82, 1.26]
7.1 Baseline total PUFA < 6% E	2	982	Risk Ratio (M-H, Random, 95% CI)	0.71 [0.52, 0.97]
7.2 Baseline total PUFA 6 to < 11% E	4	7621	Risk Ratio (M-H, Random, 95% CI)	1.32 [1.07, 1.62]
7.3 Baseline total PUFA 11+% E	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
7.4 Baseline total PUFA unclear	10	6504	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.72, 1.16]
8 Cardiovascular mortality - subgroup by replacement	16		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
8.1 PUFA replaced saturated fats	4	3730	Risk Ratio (M-H, Random, 95% CI)	1.08 [0.76, 1.54]
8.2 PUFA replaced monounsaturated fats	8	11874	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.76, 1.30]
8.3 PUFA replaced carbohydrates	4	425	Risk Ratio (M-H, Random, 95% CI)	1.19 [0.30, 4.71]
8.4 PUFA replaced protein	2	529	Risk Ratio (M-H, Random, 95% CI)	1.08 [0.66, 1.77]
8.5 PUFA replaced unclear	3	436	Risk Ratio (M-H, Random, 95% CI)	0.31 [0.07, 1.37]
9 Cardiovascular mortality -	16	15107	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.82, 1.26]
subgroup by sex				
9.1 > 70% men	10	9623	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.78, 1.27]
9.2 > 70% women	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
9.3 men & women	5	5430	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.30, 2.47]
9.4 sex not reported	1	54	Risk Ratio (M-H, Random, 95% CI)	1.55 [0.41, 5.84]
10 Cardiovascular mortality -	16	15107	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.82, 1.26]
subgroup by age				
10.1 Mean age < 50 years	1	458	Risk Ratio (M-H, Random, 95% CI)	1.59 [0.99, 2.55]
10.2 Mean age 50 to < 65	8	3149	Risk Ratio (M-H, Random, 95% CI)	1.18 [0.95, 1.48]
years				
10.3 Mean age 65+ years	6	11398	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.69, 1.09]
10.4 Mean age unclear	1	102	Risk Ratio (M-H, Random, 95% CI)	0.09 [0.01, 1.60]
11 Cardiovascular mortality - subgroup by statin use	16	15107	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.82, 1.26]
11.1 < 50% on statins	11	9416	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.78, 1.40]
11.2 50+% on statins	3	5153	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.67, 1.22]
11.3 Percentage on statins unclear	2	538	Risk Ratio (M-H, Random, 95% CI)	1.09 [0.47, 2.54]
12 Cardiovascular mortality -	16	15107	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.82, 1.26]
subgroup by intervention type				
12.1 Dietary advice	4	2404	Risk Ratio (M-H, Random, 95% CI)	1.15 [0.42, 3.12]
12.2 Supplemental foods & diet provided	3	10680	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.66, 1.19]
12.3 Supplements (capsules & unusual foods)	7	1172	Risk Ratio (M-H, Random, 95% CI)	0.76 [0.42, 1.40]
12.4 Any combination	2	851	Risk Ratio (M-H, Random, 95% CI)	1.31 [0.87, 1.95]

13 CARDIOVASCULAR Events	21	17799	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.79, 1.01]
14 CVD events - SA	21		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
14.1 Low risk of bias for	11	8714	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.84, 1.08]
allocation concealment				
14.2 Low risk of bias for attention	16	14111	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.72, 0.97]
14.3 Low risk of bias for compliance	8	5697	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.81, 1.14]
14.4 Low summary risk of bias	6	7014	Risk Ratio (M-H, Random, 95% CI)	1.18 [0.83, 1.67]
14.5 Trials registry or pre- 2010	21	17799	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.79, 1.01]
14.6 No industry funding	5	2440	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.67, 1.44]
14.7 Randomised 100+ participants	18	17587	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.77, 1.00]
14.8 Randomised 250+ participants	11	16524	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.85, 1.02]
15 CVD events - SA fixed-effect	21	17799	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.86, 0.98]
16 CVD events - subgroup by PUFA dose	21	17799	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.79, 1.01]
16.1 total PUFA < 1.0% E	7	1563	Risk Ratio (M-H, Random, 95% CI)	0.63 [0.42, 0.96]
16.2 total PUFA 1.0 to < 2. 0% E	5	10468	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.80, 1.03]
16.3 total PUFA 2.0 to < 5. 0% E	3	2224	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.90, 1.09]
16.4 total PUFA > 5.0% E	6	3544	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.76, 1.29]
17 CVD events - subgroup by duration	21	17799	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.79, 1.01]
17.1 Medium duration 1 to < 2 years	11	3175	Risk Ratio (M-H, Random, 95% CI)	0.68 [0.47, 0.99]
17.2 Medium-long duration 2 to < 4 years	6	7930	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.90, 1.05]
17.3 Long duration 4+ years	4	6694	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.73, 1.16]
18 CVD events - subgroup by primary or secondary prevention	21	17799	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.79, 1.01]
18.1 Primary prevention of CVD	10	8893	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.72, 1.01]
18.2 Secondary prevention of CVD	11	8906	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.75, 1.05]
19 CVD events - subgroup by baseline PUFA dose	21	17799	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.79, 1.01]
19.1 Baseline total PUFA < 6% E	2	1913	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.64, 1.01]
19.2 Baseline total PUFA 6 to < 11% E	4	8214	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.85, 1.22]
19.3 Baseline total PUFA 11+% E	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
19.4 Baseline total PUFA unclear	15	7672	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.69, 0.98]

20 CVD events - subgroup by replacement	21		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
20.1 PUFA replaced saturated fats	6	5523	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.79, 1.14]
20.2 PUFA replaced monounsaturated fats	12	13605	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.76, 1.08]
20.3 PUFA replaced carbohydrates	2	780	Risk Ratio (M-H, Random, 95% CI)	1.19 [0.70, 2.01]
20.4 PUFA replaced protein	2	1119	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.62, 1.07]
20.5 PUFA replaced unclear	6	1042	Risk Ratio (M-H, Random, 95% CI)	0.52 [0.29, 0.95]
21 CVD events - subgroup by sex	21	17799	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.79, 1.01]
21.1 > 70% men	12	10798	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.74, 1.00]
21.2 > 70% women	1	140	Risk Ratio (M-H, Random, 95% CI)	1.84 [0.08, 44.38]
21.3 men & women	6	6416	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.68, 1.18]
21.4 sex not reported	2	445	Risk Ratio (M-H, Random, 95% CI)	1.33 [0.80, 2.20]
22 CVD events - subgroup by age	21	17799	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.79, 1.01]
22.1 Mean age < 50 years	4	2020	Risk Ratio (M-H, Random, 95% CI)	1.66 [1.05, 2.61]
22.2 Mean age 50 to < 65 years	9	3264	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.66, 1.08]
22.3 Mean age 65+ years	7	12124	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.78, 0.96]
22.4 Mean age unclear	1	391	Risk Ratio (M-H, Random, 95% CI)	1.61 [0.54, 4.83]
23 CVD events - subgroup by statin use	21	17799	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.79, 1.01]
23.1 < 50% on statins	16	11518	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.78, 1.08]
23.2 50+% on statins	3	5153	Risk Ratio (M-H, Random, 95% CI)	0.73 [0.43, 1.25]
23.3 Percentage on statins	2	1128	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.53, 1.21]
unclear	2	1120		0.00 [0.95, 1.21]
24 CVD events - subgroup by	21	17799	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.79, 1.01]
intervention type	21	1/////		0.09 [0.79, 1.01]
24.1 Dietary advice	1	2033	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.91, 1.09]
24.2 Supplemental foods & diet provided	5	12473	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.79, 0.99]
24.3 Supplements (capsules & unusual foods)	13	2442	Risk Ratio (M-H, Random, 95% CI)	0.75 [0.54, 1.04]
24.4 Any combination	2	851	Risk Ratio (M-H, Random, 95% CI)	1.11 [0.57, 2.13]
25 CORONARY HEART	9	8810	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.78, 1.06]
DISEASE (CHD) MORTALITY	2	0010		0,01 [0,0,0,000]
26 CHD mortality - SA	9		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
26.1 Low risk of bias for	3	5359	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.68, 1.25]
allocation concealment	5	))))		0.92 [0.00, 1.29]
26.2 Low risk of bias for attention	8	6777	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.70, 1.18]
26.3 Low risk of bias for	4	3053	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.76, 1.10]
compliance	_	1		0.00 10 11 1 10
26.4 Low summary risk of bias	1	4837	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.66, 1.28]
26.5 Trials registry or pre- 2010	9	8810	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.78, 1.06]
26.6 No industry funding	2	522	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.25, 2.58]

26.7 Randomised 100+	7	8676	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.77, 1.06]
participants 26.8 Randomised 250+	4	8118	Did Decis (M II Decidence 050/ CI)	0.02 [0.70, 1.09]
participants	4	8118	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.79, 1.08]
27 CHD mortality - SA	9	8810	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.77, 1.05]
fixed-effect				
28 CHD mortality - subgroup by	9	8810	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.78, 1.06]
PUFA dose		- 1-		
28.1 total PUFA < 1.0% E	3	840	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.35, 1.59]
28.2 total PUFA 1.0 to < 2.	2	4957	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.41, 1.76]
0% E 28.3 total PUFA 2.0 to < 5.	2	2113	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.74, 1.10]
28.5 total 1 01A 2.0 to < 5. 0% E	2	2115	Risk Ratio (W-11, Randolli, 9970 CI)	0.90 [0./4, 1.10]
28.4 total PUFA > 5.0% E	2	900	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.60, 1.78]
29 CHD mortality - subgroup by	9	8810	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.78, 1.06]
duration				
29.1 Medium duration 1 to <	3	760	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.34, 1.83]
2 years				
29.2 Medium-long duration 2	5	7204	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.77, 1.07]
to < 4 years				
29.3 Long duration 4+ years	1	846	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.57, 1.75]
30 CHD mortality - subgroup	9	8810	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.78, 1.06]
by primary or secondary prevention				
30.1 Primary prevention of	2	966	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.30, 2.34]
CVD	2	700		0.01 [0.90, 2.91]
30.2 Secondary prevention of	7	7844	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.77, 1.06]
CVD				
31 CHD mortality - subgroup by	9	8810	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.78, 1.06]
baseline PUFA dose				
31.1 Baseline total PUFA <	1	846	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.57, 1.75]
6% E		2022		
31.2 Baseline total PUFA 6 to	1	2033	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.75, 1.10]
< 11% E	0	0	Dick Paris (M H Dandom 05% CI)	
31.3 Baseline total PUFA 11+% E	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
31.4 Baseline total PUFA	7	5931	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.66, 1.19]
unclear	,	<i>,,,</i> ,,		0.00 [0.00, 1.17]
32 CHD mortality - subgroup by	9		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
replacement				,
32.1 PUFA replaced saturated	2	2879	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.76, 1.10]
fats				
32.2 PUFA replaced	6	6419	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.71, 1.21]
monounsaturated fats				
32.3 PUFA replaced	1	54	Risk Ratio (M-H, Random, 95% CI)	1.86 [0.18, 19.29]
carbohydrates	0	0	Disk Datio (M H Dandom 050/ CI)	
32.4 PUFA replaced protein 32.5 PUFA replaced unclear	0 2	0 358	Risk Ratio (M-H, Random, 95% CI) Risk Ratio (M-H, Random, 95% CI)	$0.0 \ [0.0, \ 0.0] \\ 0.18 \ [0.02, \ 1.65]$
33 CHD mortality - subgroup by	2	8810	Risk Ratio (M-H, Random, 95% CI)	0.18[0.02, 1.05] 0.91[0.78, 1.06]
sex	/	0010		0.71 [0.70, 1.00]
33.1 > 70% men	7	8636	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.78, 1.06]
		-		

33.2 > 70% women	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
33.3 men & women	1	120	Risk Ratio (M-H, Random, 95% CI)	0.17 [0.01, 4.05]
33.4 sex not reported	1	54	Risk Ratio (M-H, Random, 95% CI)	1.86 [0.18, 19.29]
34 CHD mortality - subgroup by	9	8810	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.78, 1.06]
age	0	0		
34.1 Mean age < 50 years	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
34.2 Mean age 50 to < 65	5	2487	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.74, 1.08]
years	1	(222		0.0/[0.71.1.22]
34.3 Mean age 65+ years	4	6323	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.71, 1.23]
35 CHD mortality - subgroup by	9	8810	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.78, 1.06]
statin use 35.1 < 50% on statins	(	2222	Did Derie (M II Der dere 050/ CI)	0.00 [0.75, 1.09]
35.2 50+% on statins	6 2	3333 5075	Risk Ratio (M-H, Random, 95% CI) Risk Ratio (M-H, Random, 95% CI)	0.90 [0.75, 1.08] 0.91 [0.65, 1.26]
35.3 Percentage on statins	1	402	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.41, 2.49]
unclear	1	402	Risk Ratio (IVI-11, Randoni, 95% CI)	1.01 [0.41, 2.49]
36 CHD mortality - subgroup by	9	8810	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.78, 1.06]
intervention type				
36.1 Dietary advice	1	2033	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.75, 1.10]
36.2 Supplemental foods &	2	5683	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.71, 1.25]
diet provided				
36.3 Supplements (capsules &	6	1094	Risk Ratio (M-H, Random, 95% CI)	0.72 [0.36, 1.43]
unusual foods)				
36.4 Any combination	0	0	Risk Ratio (M-H, Random, 95% CI)	$0.0 \ [0.0, \ 0.0]$
37 MYOCARDIAL	15	15609	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.78, 0.99]
INFARCTION (MI) - fatal				
and non fatal				
38 SUDDEN CARDIAC	5	1731	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.50, 1.29]
DEATH (SCD)				
<b>39 ATRIAL FIBRILLATION</b>	11	11692	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.72, 1.06]
(AF) & ARRHYTHMIAS				
(including AF, ventricular				
tachycardia (VT), ventricular fibrillation(VF)				
39.1 Recurrent arrhythmia	4	979	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.65, 1.01]
39.2 New arrhythmia	7	10713	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.70, 1.46]
40 AF - SA	11	10/15	Risk Ratio (M-H, Random, 95% CI)	Subtotals only
40.1 Low risk of bias for	7	6679	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.63, 0.88]
allocation concealment	,	0079		0.7 1 [0.05, 0.00]
40.2 Low risk of bias for	10	11514	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.72, 1.13]
attention	10	,		01/0 [01/2, 1110]
40.3 Low risk of bias for	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
compliance	-	÷		
40.4 Low summary risk of	3	5368	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.59, 1.12]
bias				[]
40.5 Trials registry or pre-	11	11692	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.72, 1.06]
2010				
40.6 No industry funding	2	601	Risk Ratio (M-H, Random, 95% CI)	0.72 [0.58, 0.88]
40.7 Randomised 100+	11	11692	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.72, 1.06]
participants				-
40.8 Randomised 250+	6	10842	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.69, 1.28]
participants				
an an				

41 AF - SA fixed-effect	11	11692	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.80, 1.00]
41.1 Recurrent arrhythmia	4	979	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.72, 0.91]
41.2 New arrhythmia	7	10713	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.83, 1.28]
42 AF - subgroup by PUFA dose	11	11692	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.72, 1.06]
42.1 total PUFA < 1.0% E	7	1839	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.65, 0.99]
42.2 total PUFA 1.0 to < 2.	4	9853	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.70, 1.60]
0% E				
42.3 total PUFA 2.0 to < 5.	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
0% E				
42.4 total PUFA 5.0+% E	0	0	Risk Ratio (M-H, Random, 95% CI)	$0.0 \ [0.0, 0.0]$
43 AF - subgroup by duration	11	11692	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.72, 1.06]
43.1 Medium duration 1 to <	8	2153	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.65, 0.83]
2 years	2	5027		0.05 [0.(( 1.2()
43.2 Medium-long duration 2	2	5037	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.66, 1.36]
to < 4 years 43.3 Long duration 4+ years	1	4502	Risk Ratio (M-H, Random, 95% CI)	1.33 [0.98, 1.79]
44 AF - subgroup by primary or	11	4 <i>)</i> 02 11692	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.72, 1.06]
secondary prevention	11	11092	Kisk Kalio (M-FI, Kalidolli, 99% CI)	0.87 [0.72, 1.00]
44.1 Primary prevention of	5	5743	Risk Ratio (M-H, Random, 95% CI)	1.33 [0.99, 1.79]
CVD	J	)/4)	Kisk Ratio (M-11, Random, 99% CI)	1.33 [0.99, 1./9]
44.2 Secondary prevention of	6	5949	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.67, 0.96]
CVD	0	JJ49	Kisk Ratio (M-11, Random, 99% CI)	0.80 [0.07, 0.90]
45 Atrial fibrillation - subgroup by	11	11692	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.72, 1.06]
baseline PUFA dose	11	110)2	Nisk Katlo (W-11, Kaldolii, 7)/6 Cl/	0.07 [0.72, 1.00]
45.1 Baseline total PUFA <	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
6% E	0	Ū		0.0 [0.0, 0.0]
45.2 Baseline total PUFA 6 to	1	4502	Risk Ratio (M-H, Random, 95% CI)	1.33 [0.98, 1.79]
< 11% E	-	1902		100 [0000, 1079]
45.3 Baseline total PUFA	0	0	Risk Ratio (M-H, Random, 95% CI)	$0.0 \ [0.0, \ 0.0]$
11+% E				
45.4 Baseline total PUFA	10	7190	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.69, 0.95]
unclear				
46 AF - subgroup by replacement	11		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
46.1 PUFA replaced saturated	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
fats				
46.2 PUFA replaced	8	10804	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.71, 1.14]
monounsaturated fats				
46.3 PUFA replaced	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
carbohydrates				
46.4 PUFA replaced protein	0	0	Risk Ratio (M-H, Random, 95% CI)	$0.0 \ [0.0, \ 0.0]$
46.5 PUFA replaced unclear	3	888	Risk Ratio (M-H, Random, 95% CI)	0.75 [0.64, 0.88]
47 Atrial fibrillation - subgroup by	11	11692	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.72, 1.06]
sex				
47.1 > 70% men	6	6086	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.69, 1.01]
47.2 > 70% women	1	140	Risk Ratio (M-H, Random, 95% CI)	1.84 [0.08, 44.38]
47.3 men & women	3	5075	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.50, 1.93]
47.4 sex not reported	1	391	Risk Ratio (M-H, Random, 95% CI)	2.01 [0.18, 21.99]
48 AF - subgroup by age	11	11692	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.72, 1.06]
48.1 Mean age < 50 years	1	374	Risk Ratio (M-H, Random, 95% CI)	2.97 [0.12, 72.40]
48.2 Mean age 50 to < 65	5	987	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.62, 1.23]
years				

48.4 Mean age unclear       1       391       Risk Ratio (M-H, Random, 95% CI)       2.01 [0.18, 21.9]         49 AF - subgroup by statin use       11       11692       Risk Ratio (M-H, Random, 95% CI)       0.87 [0.72, 1.06]         49 AF - subgroup by statin use       11       11692       Risk Ratio (M-H, Random, 95% CI)       0.87 [0.72, 1.06]         49.1 < 50% on statins       9       6453       Risk Ratio (M-H, Random, 95% CI)       0.91 [0.68, 1.21]         49.2 50+% on statins       1       4837       Risk Ratio (M-H, Random, 95% CI)       0.79 [0.57, 1.10]         49.3 Percentage on statins       1       402       Risk Ratio (M-H, Random, 95% CI)       0.77 [0.58, 1.01]         unclear       50 AF - subgroup by intervention       11       11692       Risk Ratio (M-H, Random, 95% CI)       0.87 [0.72, 1.06]         type       50.1 Dietary advice       0       0       Risk Ratio (M-H, Random, 95% CI)       0.00 [0.0, 0.0]         50.2 Supplemental foods &       2       9339       Risk Ratio (M-H, Random, 95% CI)       1.03 [0.62, 1.70]         diet provided       10       9339       Risk Ratio (M-H, Random, 95% CI)       1.03 [0.62, 1.70]	48.4 Mean age unclear 49 AF - subgroup by statin use 49.1 < 50% on statins 49.2 50+% on statins	1 11	391 11692	Risk Ratio (M-H, Random, 95% CI) Risk Ratio (M-H, Random, 95% CI)	0.85 [0.63, 1.15] 2.01 [0.18, 21.99] 0.87 [0.72, 1.06]
49 AF - subgroup by statin use       11       11692       Risk Ratio (M-H, Random, 95% CI)       0.87 [0.72, 1.06]         49.1 < 50% on statins	49 AF - subgroup by statin use 49.1 < 50% on statins 49.2 50+% on statins		11692	Risk Ratio (M-H, Random, 95% CI)	
49.1 < 50% on statins	49.1 < 50% on statins 49.2 50+% on statins				0.87 [0.72, 1.06]
49.2 50+% on statins       1       4837       Risk Ratio (M-H, Random, 95% CI)       0.79 [0.57, 1.10]         49.3 Percentage on statins       1       402       Risk Ratio (M-H, Random, 95% CI)       0.77 [0.58, 1.01]         unclear       0       AF - subgroup by intervention       11       11692       Risk Ratio (M-H, Random, 95% CI)       0.87 [0.72, 1.06]         type       50.1 Dietary advice       0       0       Risk Ratio (M-H, Random, 95% CI)       0.00 [0.0, 0.0]         50.2 Supplemental foods &       2       9339       Risk Ratio (M-H, Random, 95% CI)       1.03 [0.62, 1.70]         diet provided       50.3 Supplements (capsules & 9       2353       Risk Ratio (M-H, Random, 95% CI)       0.81 [0.67, 0.98]         unusual foods)       1       1001       1001       1001       1001       1001	49.2 50+% on statins	9	6/153		
49.3 Percentage on statins       1       402       Risk Ratio (M-H, Random, 95% CI)       0.77 [0.58, 1.01]         unclear       50 AF - subgroup by intervention       11       11692       Risk Ratio (M-H, Random, 95% CI)       0.87 [0.72, 1.06]         type       50.1 Dietary advice       0       0       Risk Ratio (M-H, Random, 95% CI)       0.00 [0.0, 0.0]         50.2 Supplemental foods &       2       9339       Risk Ratio (M-H, Random, 95% CI)       1.03 [0.62, 1.70]         diet provided       50.3 Supplements (capsules & 9       2353       Risk Ratio (M-H, Random, 95% CI)       0.81 [0.67, 0.98]         unusual foods)       1       1       1       1       1       1       1			04))	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.68, 1.21]
unclear       50 AF - subgroup by intervention       11       11692       Risk Ratio (M-H, Random, 95% CI)       0.87 [0.72, 1.06]         type       50.1 Dietary advice       0       0       Risk Ratio (M-H, Random, 95% CI)       0.0 [0.0, 0.0]         50.2 Supplemental foods &       2       9339       Risk Ratio (M-H, Random, 95% CI)       1.03 [0.62, 1.70]         diet provided       50.3 Supplements (capsules &       9       2353       Risk Ratio (M-H, Random, 95% CI)       0.81 [0.67, 0.98]         unusual foods)       0       0       1.03       0.67, 0.98]       0.81	49.3 Percentage on statins	1	4837	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.57, 1.10]
50 AF - subgroup by intervention       11       11692       Risk Ratio (M-H, Random, 95% CI)       0.87 [0.72, 1.06]         type       50.1 Dietary advice       0       0       Risk Ratio (M-H, Random, 95% CI)       0.0 [0.0, 0.0]         50.2 Supplemental foods &       2       9339       Risk Ratio (M-H, Random, 95% CI)       1.03 [0.62, 1.70]         diet provided       50.3 Supplements (capsules &       9       2353       Risk Ratio (M-H, Random, 95% CI)       0.81 [0.67, 0.98]         unusual foods)       1003       1.05       1.05       1.05       1.05	-,age on otacino	1	402	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.58, 1.01]
type       50.1 Dietary advice       0       0       Risk Ratio (M-H, Random, 95% CI)       0.0 [0.0, 0.0]         50.2 Supplemental foods & 2       9339       Risk Ratio (M-H, Random, 95% CI)       1.03 [0.62, 1.70]         diet provided       50.3 Supplements (capsules & 9       2353       Risk Ratio (M-H, Random, 95% CI)       0.81 [0.67, 0.98]         unusual foods)       0       0       0       0       0.0 [0.0, 0.0]       0.0 [0.0, 0.0]	unclear				
50.1 Dietary advice       0       0       Risk Ratio (M-H, Random, 95% CI)       0.0 [0.0, 0.0]         50.2 Supplemental foods &       2       9339       Risk Ratio (M-H, Random, 95% CI)       1.03 [0.62, 1.70]         diet provided       50.3 Supplements (capsules &       9       2353       Risk Ratio (M-H, Random, 95% CI)       0.81 [0.67, 0.98]         unusual foods)       0 </td <td>50 AF - subgroup by intervention</td> <td>11</td> <td>11692</td> <td>Risk Ratio (M-H, Random, 95% CI)</td> <td>0.87 [0.72, 1.06]</td>	50 AF - subgroup by intervention	11	11692	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.72, 1.06]
50.2 Supplemental foods &       2       9339       Risk Ratio (M-H, Random, 95% CI)       1.03 [0.62, 1.70]         diet provided       50.3 Supplements (capsules &       9       2353       Risk Ratio (M-H, Random, 95% CI)       0.81 [0.67, 0.98]         unusual foods)       0.81       0.81       0.81       0.81       0.81	type				
diet provided 50.3 Supplements (capsules & 9 2353 Risk Ratio (M-H, Random, 95% CI) 0.81 [0.67, 0.98] unusual foods)	50.1 Dietary advice	0	0	Risk Ratio (M-H, Random, 95% CI)	$0.0 \ [0.0, \ 0.0]$
50.3 Supplements (capsules & 9 2353 Risk Ratio (M-H, Random, 95% CI) 0.81 [0.67, 0.98] unusual foods)	50.2 Supplemental foods &	2	9339	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.62, 1.70]
unusual foods)	diet provided				
	50.3 Supplements (capsules &	9	2353	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.67, 0.98]
50.4 Any combination 0 0 Risk Ratio (M-H, Random, 95% CI) 0.0 [0.0, 0.0]	unusual foods)				
	50.4 Any combination	0	0	Risk Ratio (M-H, Random, 95% CI)	$0.0 \ [0.0, \ 0.0]$
51 ANGINA         7         2070         Risk Ratio (M-H, Random, 95% CI)         0.64 [0.35, 1.16]	51 ANGINA	7	2070	Risk Ratio (M-H, Random, 95% CI)	0.64 [0.35, 1.16]
52 HEART FAILURE         7         25257         Risk Ratio (M-H, Random, 95% CI)         0.74 [0.40, 1.36]	52 HEART FAILURE	7	25257	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.40, 1.36]
53 PERIPHERAL ARTERIAL 4 8937 Risk Ratio (M-H, Random, 95% CI) 1.20 [0.81, 1.77]	53 PERIPHERAL ARTERIAL	4	8937	Risk Ratio (M-H, Random, 95% CI)	1.20 [0.81, 1.77]
DISEASE (PAD)	DISEASE (PAD)				
54 REVASCULARISATION - 6 1182 Risk Ratio (M-H, Random, 95% CI) 0.70 [0.40, 1.24]	54 REVASCULARISATION -	6	1182	Risk Ratio (M-H, Random, 95% CI)	0.70 [0.40, 1.24]
angioplasty and/or coronary	angioplasty and/or coronary				
artery bypass grafting					

#### Comparison 3. Higher PUFA vs lower PUFA - continuous secondary outcomes

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 ADIPOSITY - BODY WEIGHT, kg	13	7100	Mean Difference (IV, Random, 95% CI)	0.76 [0.34, 1.19]
2 Body weight, kg - SA	13		Mean Difference (IV, Random, 95% CI)	Subtotals only
2.1 Low risk of bias for allocation concealment	5	2586	Mean Difference (IV, Random, 95% CI)	1.72 [0.29, 3.15]
2.2 Low risk of bias for attention	7	4156	Mean Difference (IV, Random, 95% CI)	0.57 [0.08, 1.06]
2.3 Low risk of bias for compliance	5	756	Mean Difference (IV, Random, 95% CI)	1.59 [-0.11, 3.28]
2.4 Low summary risk of bias	4	2550	Mean Difference (IV, Random, 95% CI)	1.81 [0.23, 3.38]
2.5 Trials registry or pre-2010	13	7100	Mean Difference (IV, Random, 95% CI)	0.76 [0.34, 1.19]
2.6 No industry funding	6	2783	Mean Difference (IV, Random, 95% CI)	1.62 [0.11, 3.14]
2.7 Randomised 100+ participants	8	6885	Mean Difference (IV, Random, 95% CI)	0.89 [0.41, 1.36]
2.8 Randomised 250+ participants	5	6539	Mean Difference (IV, Random, 95% CI)	0.81 [0.34, 1.28]
3 Body weight, kg - SA fixed-effect	13	7100	Mean Difference (IV, Fixed, 95% CI)	1.08 [0.96, 1.21]
4 Body weight, kg - subgroup by PUFA dose	13	7100	Mean Difference (IV, Random, 95% CI)	0.76 [0.34, 1.19]
4.1 total PUFA < 1.0% E	2	287	Mean Difference (IV, Random, 95% CI)	1.78 [-1.46, 5.01]

4.2 total PUFA 1.0 to < 2.0% E	5	6079	Mean Difference (IV, Random, 95% CI)	0.74 [0.18, 1.30]
4.3 total PUFA 2.0 to < 5.0% E	3	210	Mean Difference (IV, Random, 95% CI)	1.47 [-3.60, 6.53]
4.4 total PUFA 5.0+% E	3	524	Mean Difference (IV, Random, 95% CI)	0.75 [-0.10, 1.60]
5 Body weight, kg - subgroup by	13	7100	Mean Difference (IV, Random, 95% CI)	0.76 [0.34, 1.19]
duration				
5.1 Medium duration 1 to < 2 years	6	502	Mean Difference (IV, Random, 95% CI)	0.47 [-0.20, 1.14]
5.2 Medium-long duration 2 to < 4 years	4	522	Mean Difference (IV, Random, 95% CI)	0.78 [-0.06, 1.62]
5.3 Long duration 4+ years	3	6076	Mean Difference (IV, Random, 95% CI)	0.90 [0.27, 1.54]
6 Body weight, kg - subgroup	13	7100	Mean Difference (IV, Random, 95% CI)	0.76 [0.34, 1.19]
by primary or secondary prevention				
6.1 Primary prevention of CVD	11	6864	Mean Difference (IV, Random, 95% CI)	0.76 [0.33, 1.19]
6.2 Secondary prevention of CVD	2	236	Mean Difference (IV, Random, 95% CI)	2.0 [-5.43, 9.43]
7 Body weight, kg - subgroup by baseline PUFA dose	13	7100	Mean Difference (IV, Random, 95% CI)	0.76 [0.34, 1.19]
7.1 Baseline total PUFA < 6% E	3	2339	Mean Difference (IV, Random, 95% CI)	2.37 [1.18, 3.56]
7.2 Baseline total PUFA 6 to < 11% E	5	4345	Mean Difference (IV, Random, 95% CI)	0.68 [0.21, 1.15]
7.3 Baseline total PUFA 11+% E	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
7.4 Baseline total PUFA unclear	5	416	Mean Difference (IV, Random, 95% CI)	0.18 [-0.68, 1.03]
8 Body weight, kg - subgroup by replacement	13		Mean Difference (IV, Random, 95% CI)	Subtotals only
8.1 PUFA replaced saturated fats	3	248	Mean Difference (IV, Random, 95% CI)	0.59 [-5.15, 6.34]
8.2 PUFA replaced monounsaturated fats	4	4036	Mean Difference (IV, Random, 95% CI)	0.69 [0.15, 1.23]
8.3 PUFA replaced	5	2882	Mean Difference (IV, Random, 95% CI)	1.23 [0.27, 2.20]
carbohydrates				
8.4 PUFA replaced protein	4	660	Mean Difference (IV, Random, 95% CI)	1.56 [-0.64, 3.75]
8.5 unclear	2	85	Mean Difference (IV, Random, 95% CI)	0.08 [-0.80, 0.95]
9 Body weight, kg - subgroup by sex	13	7100	Mean Difference (IV, Random, 95% CI)	0.76 [0.34, 1.19]
9.1 > 70% men	4	408	Mean Difference (IV, Random, 95% CI)	3.14 [0.31, 5.98]
9.2 > 70% women	3	2253	Mean Difference (IV, Random, 95% CI)	0.78 [-0.60, 2.17]
9.3 men & women	5	4404	Mean Difference (IV, Random, 95% CI)	0.70 [0.22, 1.18]
9.4 sex not reported	1	35	Mean Difference (IV, Random, 95% CI)	-0.30 [-10.57, 9.97]
10 Body weight, kg - subgroup by	13	7100	Mean Difference (IV, Random, 95% CI)	0.76 [0.34, 1.19]
age 10.1 Mean age < 50 years	2	79	Mean Difference (IV, Random, 95% CI)	0.21 [-1.12, 1.54]
10.1 Mean age $< 50$ years 10.2 Mean age 50 to $< 65$	2 9	2978	Mean Difference (IV, Random, 95% CI)	1.15 [0.12, 2.18]
years	)	2)/0		1.17 [0.12, 2.10]
10.3 Mean age 65+ years	2	4043	Mean Difference (IV, Random, 95% CI)	0.71 [0.16, 1.26]

11 Body weight, kg - subgroup by statin use	13	7100	Mean Difference (IV, Random, 95% CI)	0.76 [0.34, 1.19]
11.1 < 50% on statins	9	6522	Mean Difference (IV, Random, 95% CI)	0.69 [0.21, 1.17]
11.2 50+% on statins	2	130	Mean Difference (IV, Random, 95% CI)	2.70 [-2.43, 7.83]
11.3 Percentage on statins unclear	2	448	Mean Difference (IV, Random, 95% CI)	1.88 [-1.08, 4.84]
12 Body weight, kg - subgroup by intervention type	13	7100	Mean Difference (IV, Random, 95% CI)	0.76 [0.34, 1.19]
12.1 Dietary advice	4	2455	Mean Difference (IV, Random, 95% CI)	2.37 [1.19, 3.55]
12.2 Supplemental foods &	3	4078	Mean Difference (IV, Random, 95% CI)	0.71 [0.18, 1.25]
diet provided	U	, -		•••, - [•••••, -•->]
12.3 Supplements (capsules & unusual foods)	5	390	Mean Difference (IV, Random, 95% CI)	0.37 [-0.18, 0.91]
12.4 Any combination	1	177	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
13 ADIPOSITY - Body Mass	8	4798	Mean Difference (IV, Random, 95% CI)	0.17 [-0.08, 0.42]
Index (BMI), kg/m2				
14 BMI, kg/m2 - SA	8		Mean Difference (IV, Random, 95% CI)	Subtotals only
14.1 Low risk of bias for allocation concealment	4	3894	Mean Difference (IV, Random, 95% CI)	0.37 [-0.15, 0.88]
14.2 Low risk of bias for attention	6	2259	Mean Difference (IV, Random, 95% CI)	0.15 [-0.12, 0.42]
14.3 Low risk of bias for compliance	3	526	Mean Difference (IV, Random, 95% CI)	0.96 [-0.86, 2.78]
14.4 Low summary risk of bias	4	3894	Mean Difference (IV, Random, 95% CI)	0.37 [-0.15, 0.88]
14.5 Trials registry or pre- 2010	8	4798	Mean Difference (IV, Random, 95% CI)	0.17 [-0.08, 0.42]
14.6 No industry funding	2	2539	Mean Difference (IV, Random, 95% CI)	0.28 [-0.70, 1.26]
14.7 Randomised 100+	7	4738	Mean Difference (IV, Random, 95% CI)	0.16 [-0.09, 0.41]
participants				
14.8 Randomised 250+ participants	4	4331	Mean Difference (IV, Random, 95% CI)	0.21 [-0.04, 0.46]
15 BMI, kg/m2 - SA fixed-effect	8	4798	Mean Difference (IV, Fixed, 95% CI)	0.27 [0.20, 0.35]
16 BMI, kg/m2 - subgroup by PUFA dose	8	4798	Mean Difference (IV, Random, 95% CI)	0.17 [-0.08, 0.42]
16.1 total PUFA < 1.0% E	2	193	Mean Difference (IV, Random, 95% CI)	0.01 [-0.17, 0.18]
16.2 total PUFA 1.0 to < 2.	5	4234	Mean Difference (IV, Random, 95% CI)	0.26 [-0.03, 0.55]
0% E				
16.3 total PUFA 2.0 to < 5. 0% E	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
16.4 total PUFA 5.0+% E	1	371	Mean Difference (IV, Random, 95% CI)	-0.20 [-0.56, 0.16]
17 BMI, kg/m2 - subgroup by duration	8	4798	Mean Difference (IV, Random, 95% CI)	0.17 [-0.08, 0.42]
17.1 Medium duration 1 to < 2 years	3	407	Mean Difference (IV, Random, 95% CI)	0.21 [-1.40, 1.81]
17.2 Medium-long duration 2 to < 4 years	2	1320	Mean Difference (IV, Random, 95% CI)	0.16 [-0.03, 0.34]
17.3 Long duration 4+ years	3	3071	Mean Difference (IV, Random, 95% CI)	0.22 [-0.12, 0.55]
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18.1 Primary prevention of CVD	5	3034	Mean Difference (IV, Random, 95% CI)	0.30 [-0.09, 0.69]
18.2 Secondary prevention of CVD	3	1764	Mean Difference (IV, Random, 95% CI)	0.03 [-0.13, 0.19]
19 BMI, kg/m2 - subgroup by baseline PUFA dose	8	4798	Mean Difference (IV, Random, 95% CI)	0.17 [-0.08, 0.42]
19.1 Baseline total PUFA < 6% E	2	2347	Mean Difference (IV, Random, 95% CI)	-0.26 [-2.51, 1.99]
19.2 Baseline total PUFA 6 to < 11% E	2	903	Mean Difference (IV, Random, 95% CI)	0.10 [-0.27, 0.47]
< 11% E 19.3 Baseline total PUFA 11+% E	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
19.4 Baseline total PUFA	4	1548	Mean Difference (IV, Random, 95% CI)	0.16 [-0.16, 0.48]
unclear 20 BMI, kg/m2 - subgroup by	8		Mean Difference (IV, Random, 95% CI)	Subtotals only
replacement 20.1 PUFA replaced saturated	1	371	Mean Difference (IV, Random, 95% CI)	-0.20 [-0.56, 0.16]
fats 20.2 PUFA replaced	5	2391	Mean Difference (IV, Random, 95% CI)	0.14 [-0.11, 0.39]
monounsaturated fats 20.3 PUFA replaced	2	2347	Mean Difference (IV, Random, 95% CI)	-0.26 [-2.51, 1.99]
carbohydrates				
20.4 PUFA replaced protein	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
20.5 PUFA replaced unclear	1	60	Mean Difference (IV, Random, 95% CI)	1.0 [-1.18, 3.18]
21 BMI, kg/m2 - subgroup by sex	8	4798	Mean Difference (IV, Random, 95% CI)	0.17 [-0.08, 0.42]
21.1 > 70% men	3	1764	Mean Difference (IV, Random, 95% CI)	0.03 [-0.13, 0.19]
21.2 > 70% women 21.3 men & women	2	2347 687	Mean Difference (IV, Random, 95% CI)	-0.26 [-2.51, 1.99]
	3 8	687 4798	Mean Difference (IV, Random, 95% CI) Mean Difference (IV, Random, 95% CI)	0.31 [-0.08, 0.71] 0.17 [-0.08, 0.42]
22 BMI, kg/m2 - subgroup by age 22.1 Mean age < 50 years	8 1	4/98 371	Mean Difference (IV, Random, 95% CI)	-0.20 [-0.56, 0.16]
<b>e</b> .		2635	Mean Difference (IV, Random, 95% CI)	
22.2 Mean age 50 to < 65 years	5	2035	Mean Difference (IV, Kandolii, 93% CI)	0.38 [-0.42, 1.18]
22.3 Mean age 65+ years	2	1792	Mean Difference (IV, Random, 95% CI)	0.21 [-0.04, 0.47]
23 BMI, kg/m2 - subgroup by	8	4798	Mean Difference (IV, Random, 95% CI)	0.17 [-0.08, 0.42]
statin use				
23.1 < 50% on statins	6	3443	Mean Difference (IV, Random, 95% CI)	0.12 [-0.17, 0.42]
23.2 50+% on statins	2	1355	Mean Difference (IV, Random, 95% CI)	1.19 [-1.19, 3.56]
23.3 Percentage on statins unclear	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
24 BMI, kg/m2 - subgroup by intervention type	8	4798	Mean Difference (IV, Random, 95% CI)	0.17 [-0.08, 0.42]
24.1 Dietary advice	1	2168	Mean Difference (IV, Random, 95% CI)	0.80 [0.30, 1.30]
24.2 Supplemental foods & diet provided	2	1792	Mean Difference (IV, Random, 95% CI)	0.21 [-0.04, 0.47]
24.3 Supplements (capsules & unusual foods)	4	467	Mean Difference (IV, Random, 95% CI)	0.33 [-0.99, 1.64]
24.4 Any combination	1	371	Mean Difference (IV, Random, 95% CI)	-0.20 [-0.56, 0.16]
25 Adiposity - waist circumference, cm	3	1298	Mean Difference (IV, Random, 95% CI)	0.25 [-0.32, 0.83]
26 Adiposity - % body fat	2	309	Mean Difference (IV, Random, 95% CI)	1.90 [-1.41, 5.21]
27 Adiposity - body fat, kg	1	214	Mean Difference (IV, Random, 95% CI)	0.0 [-1.12, 1.12]
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28 Serum TOTAL	27	8072	Mean Difference (IV, Random, 95% CI)	-0.12 [-0.23, -0.02]
CHOLESTEROL (TC, mmoL/L)				
29 TC, mmoL/L - SA	27		Mean Difference (IV, Random, 95% CI)	Subtotals only
29.1 Low risk of bias for	10	3548	Mean Difference (IV, Random, 95% CI)	-0.16 [-0.36, 0.03]
allocation concealment				[
29.2 Low risk of bias for	19	4830	Mean Difference (IV, Random, 95% CI)	-0.10 [-0.23, 0.04]
attention				
29.3 Low risk of bias for	15	5642	Mean Difference (IV, Random, 95% CI)	-0.27 [-0.39, -0.14]
compliance				
29.4 Low summary risk of	7	3204	Mean Difference (IV, Random, 95% CI)	-0.23 [-0.46, 0.01]
bias				
29.5 Trials registry or pre-	25	7808	Mean Difference (IV, Random, 95% CI)	-0.13 [-0.24, -0.03]
2010 29.6 No industry funding	11	2570	Mean Difference (IV, Random, 95% CI)	-0.19 [-0.39, 0.01]
29.7 Randomised 100+	19	7711	Mean Difference (IV, Random, 95% CI)	-0.16 [-0.27, -0.05]
participants	1)	//11	Weat Difference (17, Randolli, 9970 Cl)	0.10[0.2/, 0.09]
29.8 Randomised 250+	9	6348	Mean Difference (IV, Random, 95% CI)	-0.17 [-0.30, -0.05]
participants				
30 TC, mmoL/L - SA fixed-effect	27	8072	Mean Difference (IV, Fixed, 95% CI)	-0.22 [-0.26, -0.18]
31 TC, mmoL/L - subgroup by	27	8072	Mean Difference (IV, Random, 95% CI)	-0.12 [-0.23, -0.02]
PUFA dose				
31.1 total PUFA < 1.0% E	4	480	Mean Difference (IV, Random, 95% CI)	-0.01 [-0.15, 0.13]
31.2 total PUFA 1.0 to < 2. 0% E	8	2170	Mean Difference (IV, Random, 95% CI)	-0.06 [-0.16, 0.04]
31.3 total PUFA 2.0 to < 5.	4	1857	Mean Difference (IV, Random, 95% CI)	-0.03 [-0.31, 0.25]
0% E	ч	10)/	Wear Difference (1V, Randolli, 7770 Cl)	-0.05 [-0.51, 0.25]
31.4 total PUFA 5.0+% E	11	3565	Mean Difference (IV, Random, 95% CI)	-0.28 [-0.45, -0.10]
32 TC, mmoL/L - subgroup by	27	8072	Mean Difference (IV, Random, 95% CI)	-0.12 [-0.23, -0.02]
duration				
32.1 Medium duration 1 to <	13	2168	Mean Difference (IV, Random, 95% CI)	-0.11 [-0.30, 0.08]
2 years				
32.2 Medium-long duration 2	9	4012	Mean Difference (IV, Random, 95% CI)	-0.07 [-0.19, 0.05]
to < 4 years	E	1902	Mean Difference (IV, Random, 95% CI)	0.22 [ 0.40 0.00]
32.3 Long duration 4+ years 33 TC, mmoL/L - subgroup	5 27	1892 8072	Mean Difference (IV, Random, 95% CI) Mean Difference (IV, Random, 95% CI)	-0.23 [-0.40, -0.06] -0.12 [-0.23, -0.02]
by primary or secondary	27	8072	Weat Difference (1V, Kandolii, 99% CI)	-0.12 [-0.23, -0.02]
prevention				
33.1 Primary prevention of	17	4006	Mean Difference (IV, Random, 95% CI)	-0.12 [-0.26, 0.02]
CVD				
33.2 Secondary prevention of	10	4066	Mean Difference (IV, Random, 95% CI)	-0.12 [-0.24, -0.00]
CVD				
34 TC, mmoL/L - subgroup by	27	8072	Mean Difference (IV, Random, 95% CI)	-0.12 [-0.23, -0.02]
baseline PUFA dose				
34.1 Baseline total PUFA <	6	2347	Mean Difference (IV, Random, 95% CI)	-0.33 [-0.56, -0.09]
6% E	7	2204	Marr Difference (IV D 1 050/ CD)	0.00[0.21_0.0/]
34.2 Baseline total PUFA 6 to < 11% E	7	3394	Mean Difference (IV, Random, 95% CI)	-0.09 [-0.21, 0.04]
34.3 Baseline total PUFA	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
11+% E	v	0		5.5 [0.0, 0.0]

34.4 Baseline total PUFA unclear	14	2331	Mean Difference (IV, Random, 95% CI)	-0.06 [-0.16, 0.04]
35 TC, mmoL/L - subgroup by	27		Mean Difference (IV, Random, 95% CI)	Subtotals only
replacement	27		Wear Difference (17, Nandolli, 9976 Cl)	Subtotals only
35.1 PUFA replaced saturated	8	4572	Mean Difference (IV, Random, 95% CI)	-0.32 [-0.50, -0.14]
fats	0	4)/2	Mean Difference (IV, Kandolii, 99% CI)	-0.32 [-0.30, -0.14]
	10	(500		0.17[0.22_0.00]
35.2 PUFA replaced	13	4500	Mean Difference (IV, Random, 95% CI)	-0.17 [-0.33, -0.00]
monounsaturated fats	0	122 (		
35.3 PUFA replaced	9	1394	Mean Difference (IV, Random, 95% CI)	-0.06 [-0.23, 0.10]
carbohydrates	,			
35.4 PUFA replaced protein	4	862	Mean Difference (IV, Random, 95% CI)	-0.03 [-0.30, 0.24]
35.5 PUFA replaced unclear	3	238	Mean Difference (IV, Random, 95% CI)	-0.09 [-0.29, 0.12]
36 TC, mmoL/L - subgroup by sex	27	8072	Mean Difference (IV, Random, 95% CI)	-0.12 [-0.23, -0.02]
36.1 > 70% men	15	6393	Mean Difference (IV, Random, 95% CI)	-0.15 [-0.30, -0.01]
36.2 > 70% women	2	251	Mean Difference (IV, Random, 95% CI)	-0.01 [-0.64, 0.61]
36.3 men & women	8	1367	Mean Difference (IV, Random, 95% CI)	-0.11 [-0.22, 0.01]
36.4 sex not reported	2	61	Mean Difference (IV, Random, 95% CI)	-0.04 [-0.80, 0.73]
37 TC, mmoL/L - subgroup by	27	8072	Mean Difference (IV, Random, 95% CI)	-0.12 [-0.23, -0.02]
age				
37.1 Mean age < 50 years	5	1713	Mean Difference (IV, Random, 95% CI)	-0.30 [-0.59, -0.02]
37.2 Mean age 50 to < 65	15	3250	Mean Difference (IV, Random, 95% CI)	-0.05 [-0.17, 0.06]
years	-			
37.3 Mean age 65+ years	4	2885	Mean Difference (IV, Random, 95% CI)	-0.10 [-0.21, 0.00]
37.4 Mean age unclear	3	224	Mean Difference (IV, Random, 95% CI)	-0.16 [-0.52, 0.20]
38 TC, mmoL/L - subgroup by	27	8072	Mean Difference (IV, Random, 95% CI)	-0.12 [-0.23, -0.02]
statin use	21	0072	Wear Difference (iv, Kandolii, 9970 Ci)	-0.12 [-0.23, -0.02]
38.1 < 50% on statins	20	5818	Mean Difference (IV, Random, 95% CI)	0 15 [ 0 28 0 03]
		1604		-0.15 [-0.28, -0.03]
38.2 50+% on statins	5		Mean Difference (IV, Random, 95% CI)	-0.02 [-0.11, 0.08]
38.3 Percentage on statins	2	650	Mean Difference (IV, Random, 95% CI)	-0.10 [-0.35, 0.15]
unclear				
39 TC, mmoL/L - subgroup by	27	8072	Mean Difference (IV, Random, 95% CI)	-0.12 [-0.23, -0.02]
intervention type				
39.1 Dietary advice	4	2019	Mean Difference (IV, Random, 95% CI)	-0.13 [-0.41, 0.15]
39.2 Supplemental foods &	8	4264	Mean Difference (IV, Random, 95% CI)	-0.19 [-0.37, -0.01]
diet provided				
39.3 Supplements (capsules &	11	934	Mean Difference (IV, Random, 95% CI)	-0.09 [-0.19, 0.02]
unusual foods)				
39.4 Any combination	4	855	Mean Difference (IV, Random, 95% CI)	-0.02 [-0.34, 0.29]
40 Serum fasting	20	3905	Mean Difference (IV, Random, 95% CI)	-0.12 [-0.20, -0.04]
TRIGLYCERIDE (TG,			( ), , , , , , , , , , , , , , , , , , ,	[,]
mmoL/L)				
41 TG, mmoL/L - SA	20		Mean Difference (IV, Random, 95% CI)	Subtotals only
41.1 Low risk of bias for	9	2686	Mean Difference (IV, Random, 95% CI)	-0.17 [-0.28, -0.06]
allocation concealment	2	2080	Mean Difference (1V, Kandolii, 99% CI)	-0.1/ [-0.28, -0.00]
	15	2100		0.11[0.20_0.01]
41.2 Low risk of bias for	15	3108	Mean Difference (IV, Random, 95% CI)	-0.11 [-0.20, -0.01]
attention				
41.3 Low risk of bias for	8	1175	Mean Difference (IV, Random, 95% CI)	-0.08 [-0.19, 0.03]
compliance				
41.4 Low summary risk of	5	2050	Mean Difference (IV, Random, 95% CI)	-0.14 [-0.26, -0.03]
bias				

41.5 Trials registry or pre- 2010	19	3715	Mean Difference (IV, Random, 95% CI)	-0.13 [-0.21, -0.05]
41.6 No industry funding	8	1196	Mean Difference (IV, Random, 95% CI)	-0.08 [-0.25, 0.09]
41.7 Randomised 100+ participants	14	3637	Mean Difference (IV, Random, 95% CI)	-0.12 [-0.19, -0.06]
41.8 Randomised 250+ participants	5	2472	Mean Difference (IV, Random, 95% CI)	-0.17 [-0.27, -0.07]
42 TG, mmoL/L - SA fixed-effect	20	3905	Mean Difference (IV, Fixed, 95% CI)	-0.11 [-0.16, -0.06]
43 TG, mmoL/L - subgroup by PUFA dose	20	3905	Mean Difference (IV, Random, 95% CI)	-0.12 [-0.20, -0.04]
43.1 total PUFA < 1.0% E	5	815	Mean Difference (IV, Random, 95% CI)	-0.20 [-0.37, -0.02]
43.2 total PUFA 1.0 to < 2. 0% E	7	2091	Mean Difference (IV, Random, 95% CI)	-0.08 [-0.15, -0.01]
43.3 total PUFA 2.0 to < 5. 0% E	3	149	Mean Difference (IV, Random, 95% CI)	-0.08 [-0.91, 0.75]
43.4 total PUFA 5.0+% E	5	850	Mean Difference (IV, Random, 95% CI)	-0.07 [-0.20, 0.06]
44 TG, mmoL/L - subgroup by duration	20	3905	Mean Difference (IV, Random, 95% CI)	-0.12 [-0.20, -0.04]
44.1 Medium duration 1 to < 2 years	10	1246	Mean Difference (IV, Random, 95% CI)	-0.12 [-0.28, 0.04]
44.2 Medium-long duration 2 to < 4 years	7	1787	Mean Difference (IV, Random, 95% CI)	-0.06 [-0.18, 0.07]
44.3 Long duration 4+ years	3	872	Mean Difference (IV, Random, 95% CI)	-0.13 [-0.23, -0.03]
45 TG, mmoL/L - subgroup by primary or secondary	20	3905	Mean Difference (IV, Random, 95% CI)	-0.12 [-0.20, -0.04]
prevention 45.1 Primary prevention of CVD	14	1831	Mean Difference (IV, Random, 95% CI)	-0.10 [-0.21, 0.01]
45.2 Secondary prevention of CVD	6	2074	Mean Difference (IV, Random, 95% CI)	-0.11 [-0.22, 0.00]
46 TG, mmoL/L - subgroup by baseline PUFA dose	20	3905	Mean Difference (IV, Random, 95% CI)	-0.12 [-0.20, -0.04]
46.1 Baseline total PUFA < 6% E	3	350	Mean Difference (IV, Random, 95% CI)	0.01 [-0.16, 0.17]
46.2 Baseline total PUFA 6 to < 11% E	6	1195	Mean Difference (IV, Random, 95% CI)	-0.14 [-0.23, -0.06]
46.3 Baseline total PUFA 11+% E	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
46.4 Baseline total PUFA unclear	11	2360	Mean Difference (IV, Random, 95% CI)	-0.13 [-0.27, 0.01]
47 TG, mmoL/L - subgroup by replacement	20		Mean Difference (IV, Random, 95% CI)	Subtotals only
47.1 PUFA replaced saturated fats	4	719	Mean Difference (IV, Random, 95% CI)	-0.02 [-0.13, 0.09]
47.2 PUFA replaced monounsaturated fats	8	2448	Mean Difference (IV, Random, 95% CI)	-0.16 [-0.24, -0.08]
47.3 PUFA replaced carbohydrates	7	848	Mean Difference (IV, Random, 95% CI)	-0.05 [-0.23, 0.14]
47.4 PUFA replaced protein	2	171	Mean Difference (IV, Random, 95% CI)	0.12 [-0.26, 0.51]
47.5 PUFA replaced unclear	3	499	Mean Difference (IV, Random, 95% CI)	-0.14 [-0.50, 0.21]

48 TG, mmoL/L - subgroup by	20	3905	Mean Difference (IV, Random, 95% CI)	-0.12 [-0.20, -0.04]
sex 48.1 > 70% men	11	2796	Mean Difference (IV, Random, 95% CI)	-0.10 [-0.23, 0.03]
48.2 > 70% women	2	2790	Mean Difference (IV, Random, 95% CI)	-0.03 [-0.20, 0.13]
48.3 men & women	6	824	Mean Difference (IV, Random, 95% CI)	-0.19 [-0.28, -0.09]
48.4 sex not reported	1	35	Mean Difference (IV, Random, 95% CI)	0.30 [-0.39, 0.99]
49 TG, mmoL/L - subgroup by	20	3905	Mean Difference (IV, Random, 95% CI)	-0.12 [-0.20, -0.04]
age	20	5705	Wear Difference (17, Nandolli, 7576 Cl)	0.12 [ 0.20, 0.01]
49.1 Mean age < 50 years	3	565	Mean Difference (IV, Random, 95% CI)	-0.11 [-0.26, 0.04]
49.2 Mean age 50 to < 65	13	1662	Mean Difference (IV, Random, 95% CI)	-0.15 [-0.26, -0.03]
years				
49.3 Mean age 65+ years	2	1528	Mean Difference (IV, Random, 95% CI)	-0.08 [-0.17, 0.01]
49.4 Mean age unclear	2	150	Mean Difference (IV, Random, 95% CI)	0.14 [-0.68, 0.96]
50 TG, mmoL/L - subgroup by	20	3905	Mean Difference (IV, Random, 95% CI)	-0.12 [-0.20, -0.04]
statin use				
50.1 < 50% on statins	15	2239	Mean Difference (IV, Random, 95% CI)	-0.14 [-0.24, -0.04]
50.2 50+% on statins	4	1530	Mean Difference (IV, Random, 95% CI)	-0.03 [-0.15, 0.08]
50.3 Percentage on statins	1	136	Mean Difference (IV, Random, 95% CI)	0.04 [-0.42, 0.50]
unclear				
51 TG, mmoL/L - subgroup by	20	3905	Mean Difference (IV, Random, 95% CI)	-0.12 [-0.20, -0.04]
intervention type				
51.1 Dietary advice	4	339	Mean Difference (IV, Random, 95% CI)	-0.18 [-0.37, 0.00]
51.2 Supplemental foods &	4	1753	Mean Difference (IV, Random, 95% CI)	-0.04 [-0.12, 0.03]
diet provided				
51.3 Supplements (capsules &	9	1140	Mean Difference (IV, Random, 95% CI)	-0.22 [-0.35, -0.10]
unusual foods)				
51.4 Any combination	3	673	Mean Difference (IV, Random, 95% CI)	0.12 [-0.22, 0.46]
52 Serum HIGH DENSITY	18	4674	Mean Difference (IV, Random, 95% CI)	-0.01 [-0.02, 0.01]
LIPOPROTEIN (HDL,				
mmoL/L)	10			
53 HDL, mmoL/L - SA	18		Mean Difference (IV, Random, 95% CI)	Subtotals only
53.1 Low risk of bias for	8	1968	Mean Difference (IV, Random, 95% CI)	-0.01 [-0.04, 0.01]
allocation concealment	10	26/1		
53.2 Low risk of bias for	13	2641	Mean Difference (IV, Random, 95% CI)	-0.01 [-0.03, 0.01]
attention	0	2/10		0.00[0.02.0.02]
53.3 Low risk of bias for	8	2410	Mean Difference (IV, Random, 95% CI)	-0.00 [-0.02, 0.02]
compliance	6	1502	Mean Difference (IV, Random, 95% CI)	0.01 [ 0.04 0.01]
53.4 Low summary risk of bias	4	1592	Mean Difference (1V, Random, 95% CI)	-0.01 [-0.04, 0.01]
53.5 Trials registry or pre-	16	4410	Mean Difference (IV, Random, 95% CI)	-0.01 [-0.02, 0.01]
2010	10	4410	Mean Difference (17, Random, 95% CI)	-0.01 [-0.02, 0.01]
53.6 No industry funding	7	717	Mean Difference (IV, Random, 95% CI)	0.01 [-0.04, 0.05]
53.7 Randomised 100+	11	4332	Mean Difference (IV, Random, 95% CI)	-0.01 [-0.02, 0.01]
participants	11	4332	Wear Difference (17, Kandolii, 7770 Ci)	-0.01 [-0.02, 0.01]
53.8 Randomised 250+	4	3394	Mean Difference (IV, Random, 95% CI)	-0.01 [-0.03, 0.01]
participants	1	5574	Wear Difference (17, Nandolli, 9976 Ci)	-0.01 [-0.03, 0.01]
54 HDL, mmoL/L - SA	18	4674	Mean Difference (IV, Fixed, 95% CI)	-0.01 [-0.02, 0.01]
fixed-effect	10	107 1	Weat Difference (19, 1 med, 7976 Ci)	0.01 [ 0.02, 0.01]
55 HDL, mmoL/L - subgroup by	18	4674	Mean Difference (IV, Random, 95% CI)	-0.01 [-0.02, 0.01]
PUFA dose	10	10/ 1		0.01 [ 0.02, 0.01]
55.1 total PUFA < 1.0% E	3	347	Mean Difference (IV, Random, 95% CI)	0.02 [-0.05, 0.09]

55.2 total PUFA 1.0 to < 2. 0% E	8	2166	Mean Difference (IV, Random, 95% CI)	-0.01 [-0.03, 0.01]
55.3 total PUFA 2.0 to < 5. 0% E	4	1864	Mean Difference (IV, Random, 95% CI)	-0.01 [-0.04, 0.02]
55.4 total PUFA 5.0+% E	3	297	Mean Difference (IV, Random, 95% CI)	0.05 [-0.04, 0.14]
56 HDL, mmoL/L - subgroup by	18	4674	Mean Difference (IV, Random, 95% CI)	-0.01 [-0.02, 0.01]
duration	10	107 1		0.01 [ 0.02, 0.01]
56.1 Medium duration 1 to <	9	852	Mean Difference (IV, Random, 95% CI)	-0.00 [-0.04, 0.04]
2 years	0	2504		0.01 [ 0.02 .0.01]
56.2 Medium-long duration 2 to < 4 years	8	3504	Mean Difference (IV, Random, 95% CI)	-0.01 [-0.03, 0.01]
56.3 Long duration 4+ years	1	318	Mean Difference (IV, Random, 95% CI)	0.03 [-0.02, 0.09]
57 HDL, mmoL/L - subgroup	18	4674	Mean Difference (IV, Random, 95% CI)	-0.01 [-0.02, 0.09]
by primary or secondary prevention	10	40/4	Mean Difference (IV, Kandolii, 95% CI)	-0.01 [-0.02, 0.01]
57.1 Primary prevention of CVD	12	1402	Mean Difference (IV, Random, 95% CI)	0.01 [-0.02, 0.04]
57.2 Secondary prevention of CVD	6	3272	Mean Difference (IV, Random, 95% CI)	-0.01 [-0.03, 0.01]
58 HDL, mmoL/L - subgroup by baseline PUFA dose	18	4674	Mean Difference (IV, Random, 95% CI)	-0.01 [-0.02, 0.01]
58.1 Baseline total PUFA < 6% E	3	350	Mean Difference (IV, Random, 95% CI)	-0.01 [-0.11, 0.09]
58.2 Baseline total PUFA 6 to < 11% E	6	2454	Mean Difference (IV, Random, 95% CI)	-0.00 [-0.03, 0.02]
58.3 Baseline total PUFA 11+% E	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
58.4 Baseline total PUFA unclear	9	1870	Mean Difference (IV, Random, 95% CI)	-0.01 [-0.03, 0.01]
59 HDL, mmoL/L - subgroup by replacement	18		Mean Difference (IV, Random, 95% CI)	Subtotals only
59.1 PUFA replaced saturated fats	4	1976	Mean Difference (IV, Random, 95% CI)	-0.01 [-0.03, 0.02]
59.2 PUFA replaced	6	1857	Mean Difference (IV, Random, 95% CI)	-0.01 [-0.03, 0.02]
monounsaturated fats	0	10)/	Wear Difference (17, Nandolli, 7770 Cl)	-0.01 [-0.05, 0.02]
59.3 PUFA replaced	6	754	Mean Difference (IV, Random, 95% CI)	-0.02 [-0.06, 0.03]
carbohydrates	Ū	/ ) 1		0.02 [ 0.00, 0.05]
59.4 PUFA replaced protein	2	171	Mean Difference (IV, Random, 95% CI)	0.04 [-0.06, 0.14]
59.5 PUFA replaced unclear	3	238	Mean Difference (IV, Random, 95% CI)	0.05 [-0.04, 0.14]
60 HDL, mmoL/L - subgroup by	18	4674	Mean Difference (IV, Random, 95% CI)	-0.01 [-0.02, 0.01]
sex				
60.1 > 70% men	10	3660	Mean Difference (IV, Random, 95% CI)	-0.01 [-0.03, 0.01]
60.2 > 70% women	2	251	Mean Difference (IV, Random, 95% CI)	-0.02 [-0.21, 0.17]
60.3 men & women	5	728	Mean Difference (IV, Random, 95% CI)	0.03 [-0.02, 0.07]
60.4 sex not reported	1	35	Mean Difference (IV, Random, 95% CI)	0.10 [-0.17, 0.37]
61 HDL, mmoL/L - subgroup by	18	4674	Mean Difference (IV, Random, 95% CI)	-0.01 [-0.02, 0.01]
age				
61.1 Mean age < 50 years	2	108	Mean Difference (IV, Random, 95% CI)	0.05 [-0.13, 0.23]
61.2 Mean age 50 to < 65	12	2910	Mean Difference (IV, Random, 95% CI)	-0.01 [-0.03, 0.02]

61.4 Mean age unclear	2	128	Mean Difference (IV, Random, 95% CI)	0.01 [-0.08, 0.10]
62 HDL, mmoL/L - subgroup by	18	4674	Mean Difference (IV, Random, 95% CI)	-0.01 [-0.02, 0.01]
statin use				
62.1 < 50% on statins	12	2934	Mean Difference (IV, Random, 95% CI)	-0.00 [-0.03, 0.02]
62.2 50+% on statins	5	1604	Mean Difference (IV, Random, 95% CI)	-0.01 [-0.04, 0.01]
62.3 Percentage on statins unclear	1	136	Mean Difference (IV, Random, 95% CI)	0.03 [-0.08, 0.14]
63 HDL, mmoL/L - subgroup by intervention type	18	4674	Mean Difference (IV, Random, 95% CI)	-0.01 [-0.02, 0.01]
63.1 Dietary advice	4	1959	Mean Difference (IV, Random, 95% CI)	-0.01 [-0.03, 0.02]
63.2 Supplemental foods &	4	1753	Mean Difference (IV, Random, 95% CI)	-0.01 [-0.03, 0.02]
diet provided				
63.3 Supplements (capsules & unusual foods)	8	746	Mean Difference (IV, Random, 95% CI)	-0.01 [-0.05, 0.04]
63.4 Any combination	2	216	Mean Difference (IV, Random, 95% CI)	-0.02 [-0.10, 0.06]
64 Serum LOW DENSITY	15	3362	Mean Difference (IV, Random, 95% CI)	-0.01 [-0.09, 0.06]
LIPOPROTEIN (LDL, mmoL/L)				
65 LDL, mmoL/L - SA	15		Mean Difference (IV, Random, 95% CI)	Subtotals only
65.1 Low risk of bias for	6	1915	Mean Difference (IV, Random, 95% CI)	0.04 [-0.03, 0.10]
allocation concealment				
65.2 Low risk of bias for attention	11	2566	Mean Difference (IV, Random, 95% CI)	-0.01 [-0.09, 0.07]
65.3 Low risk of bias for	5	1009	Mean Difference (IV, Random, 95% CI)	-0.05 [-0.17, 0.06]
compliance				
65.4 Low summary risk of bias	4	1506	Mean Difference (IV, Random, 95% CI)	0.02 [-0.06, 0.09]
65.5 Trials registry or pre- 2010	13	3098	Mean Difference (IV, Random, 95% CI)	-0.02 [-0.10, 0.07]
65.6 No industry funding	4	415	Mean Difference (IV, Random, 95% CI)	0.05 [-0.11, 0.21]
65.7 Randomised 100+ participants	10	3114	Mean Difference (IV, Random, 95% CI)	-0.03 [-0.11, 0.06]
65.8 Randomised 250+ participants	5	2442	Mean Difference (IV, Random, 95% CI)	-0.04 [-0.15, 0.08]
66 LDL, mmoL/L - SA fixed-effect	15	3362	Mean Difference (IV, Fixed, 95% CI)	-0.03 [-0.07, 0.02]
67 LDL, mmoL/L - subgroup by PUFA dose	15	3362	Mean Difference (IV, Random, 95% CI)	-0.01 [-0.09, 0.06]
67.1 total PUFA < 1.0% E	3	622	Mean Difference (IV, Random, 95% CI)	0.08 [-0.03, 0.19]
67.2 total PUFA 1.0 to < 2.	5	1790	Mean Difference (IV, Random, 95% CI)	-0.05 [-0.19, 0.09]
0% E	)	1/ )0		0.09 [ 0.19, 0.09]
67.3 total PUFA 2.0 to < 5.	3	142	Mean Difference (IV, Random, 95% CI)	0.12 [-0.13, 0.38]
0% E	-			
67.4 total PUFA 5.0+% E	4	808	Mean Difference (IV, Random, 95% CI)	-0.06 [-0.21, 0.09]
68 LDL, mmoL/L - subgroup by	15	3362	Mean Difference (IV, Random, 95% CI)	-0.01 [-0.09, 0.06]
duration				
68.1 Medium duration 1 to <	9	1085	Mean Difference (IV, Random, 95% CI)	0.01 [-0.07, 0.10]
2 years				
68.2 Medium-long duration 2	5	1959	Mean Difference (IV, Random, 95% CI)	-0.00 [-0.13, 0.12]
to < 4 years				_
68.3 Long duration 4+ years	1	318	Mean Difference (IV, Random, 95% CI)	-0.11 [-0.49, 0.28]

69 LDL, mmoL/L - subgroup by primary or secondary	15	3362	Mean Difference (IV, Random, 95% CI)	-0.01 [-0.09, 0.06]
prevention 69.1 Primary prevention of CVD	11	1915	Mean Difference (IV, Random, 95% CI)	-0.03 [-0.14, 0.07]
69.2 Secondary prevention of CVD	4	1447	Mean Difference (IV, Random, 95% CI)	0.02 [-0.05, 0.09]
70 LDL, mmoL/L - subgroup by baseline PUFA dose	15	3362	Mean Difference (IV, Random, 95% CI)	-0.01 [-0.09, 0.06]
70.1 Baseline total PUFA < 6% E	3	347	Mean Difference (IV, Random, 95% CI)	-0.07 [-0.30, 0.15]
70.2 Baseline total PUFA 6 to < 11%E	4	1055	Mean Difference (IV, Random, 95% CI)	-0.05 [-0.22, 0.12]
70.3 Baseline total PUFA 11+% E	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
70.4 Baseline total PUFA unclear	8	1960	Mean Difference (IV, Random, 95% CI)	0.03 [-0.03, 0.10]
71 LDL, mmoL/L - subgroup by replacement	15		Mean Difference (IV, Random, 95% CI)	Subtotals only
71.1 PUFA replaced saturated fats	2	222	Mean Difference (IV, Random, 95% CI)	-0.04 [-0.21, 0.14]
71.2 PUFA replaced monounsaturated fats	6	1776	Mean Difference (IV, Random, 95% CI)	-0.00 [-0.12, 0.12]
71.3 PUFA replaced carbohydrates	6	1106	Mean Difference (IV, Random, 95% CI)	-0.06 [-0.18, 0.06]
71.4 PUFA replaced protein	3	682	Mean Difference (IV, Random, 95% CI)	-0.08 [-0.26, 0.10]
71.5 PUFA replaced unclear	2	409	Mean Difference (IV, Random, 95% CI)	0.10 [-0.03, 0.23]
72 LDL, mmoL/L - subgroup by sex	15	3362	Mean Difference (IV, Random, 95% CI)	-0.01 [-0.09, 0.06]
72.1 > 70% men	7	1972	Mean Difference (IV, Random, 95% CI)	0.04 [-0.03, 0.10]
72.2 > 70% women	2	251	Mean Difference (IV, Random, 95% CI)	0.02 [-0.46, 0.49]
72.3 men & women	5	1107	Mean Difference (IV, Random, 95% CI)	-0.07 [-0.21, 0.06]
72.4 sex not reported	1	32	Mean Difference (IV, Random, 95% CI)	-0.10 [-0.59, 0.39]
73 LDL, mmoL/L - subgroup by age	15	3362	Mean Difference (IV, Random, 95% CI)	-0.01 [-0.09, 0.06]
73.1 Mean age < 50 years	2	101	Mean Difference (IV, Random, 95% CI)	0.25 [-0.11, 0.61]
73.2 Mean age 50 to < 65 years	8	1177	Mean Difference (IV, Random, 95% CI)	0.01 [-0.08, 0.10]
73.3 Mean age 65+ years	3	1956	Mean Difference (IV, Random, 95% CI)	-0.08 [-0.23, 0.07]
73.4 Mean age unclear	2	128	Mean Difference (IV, Random, 95% CI)	0.05 [-0.26, 0.36]
74 LDL, mmoL/L - subgroup by statin use	15	3362	Mean Difference (IV, Random, 95% CI)	-0.01 [-0.09, 0.06]
74.1 < 50% on statins	8	1197	Mean Difference (IV, Random, 95% CI)	0.00 [-0.13, 0.13]
74.2 50+% on statins	5	1515	Mean Difference (IV, Random, 95% CI)	0.01 [-0.07, 0.08]
74.3 Percentage on statins unclear	2	650	Mean Difference (IV, Random, 95% CI)	-0.04 [-0.33, 0.25]
75 LDL, mmoL/L - subgroup by intervention type	15	3362	Mean Difference (IV, Random, 95% CI)	-0.01 [-0.09, 0.06]
75.1 Dietary advice	2	208	Mean Difference (IV, Random, 95% CI)	0.22 [-0.05, 0.48]
75.2 Supplemental foods & diet provided	5	2178	Mean Difference (IV, Random, 95% CI)	-0.07 [-0.18, 0.05]

75.3 Supplements (capsules &	7	922	Mean Difference (IV, Random, 95% CI)	0.02 [-0.09, 0.13]
unusual foods)				
75.4 Any combination	1	54	Mean Difference (IV, Random, 95% CI)	-0.07 [-0.51, 0.37]

#### Comparison 4. Higher PUFA vs lower PUFA intake - tertiary outcomes

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 SYSTOLIC BLOOD PRESSURE (sBP, mmHg)	10	7356	Mean Difference (IV, Random, 95% CI)	-0.47 [-2.20, 1.26]
2 DIASTOLIC BLOOD PRESSURE (dBP, mmHg)	9	7327	Mean Difference (IV, Random, 95% CI)	0.24 [-0.55, 1.02]
3 SERIOUS ADVERSE EVENTS (SAEs)	8		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 Pulmonary embolism	2	2087	Risk Ratio (M-H, Random, 95% CI)	2.15 [0.48, 9.57]
3.2 Multiple Sclerosis worsened or had acute attack - GLA supplement	2	268	Risk Ratio (M-H, Random, 95% CI)	1.11 [0.95, 1.30]
3.3 Bleeding	2	748	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.34, 1.85]
3.4 GI hospitalisation	1	200	Risk Ratio (M-H, Random, 95% CI)	1.75 [0.53, 5.79]
3.5 Retinopathy	1	2424	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.56, 1.86]
4 DROPOUTS	27	8574	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.87, 1.13]

## Analysis I.I. Comparison I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes, Outcome I ALL-CAUSE MORTALITY.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

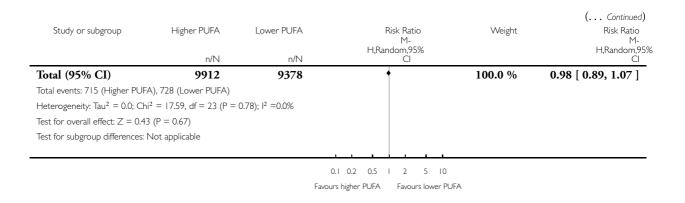
Comparison: I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes

#### Outcome: I ALL-CAUSE MORTALITY

Study or subgroup	Higher PUFA	Lower PUFA	Risk Ratio M-	Weight	Risk Ratio M-
	n/N	n/N	H,Random,95% Cl		H,Random,955 Cl
AlphaOmega - ALA	182/2409	188/2428	-	22.3 %	0.98 [ 0.80, 1.19 ]
Bates 1978	0/58	2/58	← ·	0.1 %	0.20 [ 0.01, 4.08 ]
Bates 1989	1/155	0/157		0.1 %	3.04 [ 0.12, 74.02 ]
Black 1994	2/67	1/66		0.2 %	1.97 [ 0.18, 21.21 ]
Brox 200 l	0/80	1/40	<b>← ·</b>	0.1 %	0.17 [ 0.01, 4.05 ]
DART fat 1989	111/1018	113/1015	-	14.0 %	0.98 [ 0.76, 1.25 ]
DIPP-Tokudome 2015	2/104	3/101		0.3 %	0.65 [ 0.11, 3.79 ]
Doi 2014	2/119	9/119	•	0.4 %	0.22 [ 0.05, 1.01 ]
EPIC-1 2008	1/183	0/180		0.1 %	2.95 [ 0.12, 71.97 ]
EPIC-2 2008	0/189	1/190	• • • • • • • • • • • • • • • • • • •	0.1 %	0.34 [ 0.01, 8.17 ]
AAT - Leaf 2005	13/200	12/202		1.5 %	1.09 [ 0.51, 2.34 ]
HARP- Sacks 1995	0/41	1/39	•	0.1 %	0.32 [ 0.01, 7.57 ]
Kumar 2013	1/39	1/39	•	0.1 %	1.00 [ 0.06, 15.43 ]
ley 2004	2/70	1/66		0.2 %	1.89 [ 0.18, 20.31 ]
McIIImurray 1987	10/25	12/24		2.2 %	0.80 [ 0.43, 1.49 ]
MRC 1968	28/199	31/194		3.9 %	0.88 [ 0.55, 1.41 ]
NDHS Faribault 1968	4/167	0/57		0.1 %	3.11 [ 0.17, 56.84 ]
PREDIMED 2013	116/2454	8/2543	+	13.7 %	1.02 [ 0.79, 1.31 ]
Raitt 2005	4/100	10/100		0.7 %	0.40 [ 0.13, 1.23 ]
Rose 1965	5/28	3/26		0.5 %	1.55 [ 0.41, 5.84 ]
Sydney Diet-Heart 1978	38/221	27/237		4.1 %	1.51 [ 0.95, 2.39 ]
/eterans Admin 1969	174/424	177/422	+	33.5 %	0.98 [ 0.83, 1.15 ]
/ijayakumar 2014	0/100	2/100	<b>←</b> · · · · · · · · · · · · · · · · · · ·	0.1 %	0.20 [ 0.01, 4.11 ]
WINS 2006	19/1462	15/975		1.9 %	0.84 [ 0.43, 1.65 ]

0.1 0.2 0.5 1 2 5 10 Favours higher PUFA Favours lower PUFA

(Continued ...)



#### Analysis I.2. Comparison I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes, Outcome 2 All-cause mortality - SA.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes

Outcome: 2 All-cause mortality - SA

Study or subgroup	Higher PUFA	Lower PUFA	Risk Ratio M-	Weight	Risk Ratio M-
	n/N	n/N	H,Random,95% Cl		H,Random,95%
I Low risk of bias for allocation	concealment				
AlphaOmega - ALA	182/2409	188/2428	=	72.8 %	0.98 [ 0.80, 1.19 ]
Brox 200 I	0/80	1/40	· · · · · · · · · · · · · · · · · · ·	0.3 %	0.17 [ 0.01, 4.05 ]
DIPP-Tokudome 2015	2/104	3/101		0.9 %	0.65 [ 0.11, 3.79 ]
EPIC-1 2008	1/183	0/180		0.3 %	2.95 [ 0.12, 71.97 ]
EPIC-2 2008	0/189	1/190	·	0.3 %	0.34 [ 0.01, 8.17 ]
FAAT - Leaf 2005	13/200	12/202		4.8 %	1.09 [ 0.51, 2.34 ]
Kumar 2013	1/39	1/39		0.4 %	1.00 [ 0.06, 15.43 ]
Ley 2004	2/70	1/66		0.5 %	1.89 [ 0.18, 20.31 ]
NDHS Faribault 1968	4/167	0/57		0.3 %	3.11 [ 0.17, 56.84 ]
Sydney Diet-Heart 1978	38/221	27/237	-	13.3 %	1.51 [ 0.95, 2.39 ]
		Fave	0.05 0.2 I 5 20 ours higher PUFA Favours lower PUI	Ā	

(Continued ...)

Study or subgroup	Higher PUFA	Lower PUFA	Risk Ratio M-	Weight	( Continued) Risk Ratio M-
	n/N	n/N	H,Random,95% Cl		H,Random,95 Cl
WINS 2006	19/1462	15/975		6.2 %	0.84 [ 0.43, 1.65 ]
Subtotal (95% CI)	5124	4515	+	100.0 %	1.03 [ 0.87, 1.22 ]
Total events: 262 (Higher PUFA Heterogeneity: Tau <sup>2</sup> = 0.0; Chi <sup>2</sup> Test for overall effect: $Z = 0.34$ 2 Low risk of bias for attention	= 6.53, df = 10 (P = 0	0.77); I <sup>2</sup> =0.0%			
AlphaOmega - ALA	182/2409	188/2428	+	29.5 %	0.98 [ 0.80, 1.19 ]
Bates 1978	0/58	2/58	•	0.1 %	0.20 [ 0.01, 4.08 ]
Bates 1989	1/155	0/157		0.1 %	3.04 [ 0.12, 74.02 ]
Brox 2001	0/80	1/40	•	0.1 %	0.17[0.01,4.05]
DIPP-Tokudome 2015	2/104	3/101		0.4 %	0.65 [ 0.11, 3.79 ]
Doi 2014	2/119	9/119		0.5 %	0.22 [ 0.05, 1.01 ]
EPIC-1 2008	1/183	0/180		0.1 %	2.95 [ 0.12, 71.97 ]
EPIC-2 2008	0/189	1/190	· · · · · · · · · · · · · · · · · · ·	0.1 %	0.34 [ 0.01, 8.17 ]
FAAT - Leaf 2005	13/200	12/202	<u> </u>	2.0 %	1.09 [ 0.51, 2.34 ]
HARP- Sacks 1995	0/41	1/39	•	0.1 %	0.32 [ 0.01, 7.57 ]
McIIImurray 1987	10/25	12/24		2.9 %	0.80 [ 0.43, 1.49 ]
NDHS Faribault 1968	4/167	0/57		0.1 %	3.11 [ 0.17, 56.84 ]
PREDIMED 2013	116/2454	118/2543	+	18.1 %	1.02 [ 0.79, 1.31 ]
Raitt 2005	4/100	10/100		0.9 %	0.40 [ 0.13, 1.23 ]
Rose 1965	5/28	3/26		0.6 %	1.55 [ 0.41, 5.84 ]
Veterans Admin 1969	174/424	177/422	•	44.2 %	0.98 [ 0.83, 1.15 ]
Vijayakumar 2014	0/100	2/100	•	0.1 %	0.20 [ 0.01, 4.11 ]
Subtotal (95% CI) Total events: 514 (Higher PUFA Heterogeneity: Tau <sup>2</sup> = 0.0; Chi <sup>2</sup> Test for overall effect: Z = 0.69 3 Low risk of bias for complianc	= 13.08, df = 16 (P = (P = 0.49))	<b>6786</b> 0.67); l <sup>2</sup> =0.0%	•	100.0 %	0.96 [ 0.87, 1.07 ]
Bates 1989	e 1/155	0/157		0.1 %	3.04 [ 0.12, 74.02 ]
Brox 2001	0/80	1/40	• • • · · · · · · · · · · · · · · · · ·	0.2 %	0.17 [ 0.01, 4.05 ]
DART fat 1989	111/1018	113/1015	+	24.9 %	0.98 [ 0.76, 1.25 ]
Ley 2004	2/70	1/66		0.3 %	1.89 [ 0.18, 20.31 ]
Ley 2004		21/12/	<b>_</b>	6.8 %	0.88 [ 0.55, 1.41 ]
MRC 1968	28/199	31/194			

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Study or subgroup	Higher PUFA	Lower PUFA	Risk Ratio M-	Weight	Risk Ratio M-
	n/N	n/N	H,Random,95% Cl		H,Random,9 Cl
Rose 1965	5/28	3/26		0.9 %	1.55 [ 0.41, 5.84 ]
Sydney Diet-Heart 1978	38/221	27/237		7.2 %	1.51 [ 0.95, 2.39 ]
Veterans Admin 1969	174/424	177/422	-	59.3 %	0.98 [ 0.83, 1.15 ]
Vijayakumar 2014	0/100	2/100	· · · · · · · · · · · · · · · · · · ·	0.2 %	0.20 [ 0.01, 4.11 ]
Subtotal (95% CI)	2462	2314	•	100.0 %	1.01 [ 0.89, 1.14 ]
otal events: 363 (Higher PUFA) leterogeneity: Tau <sup>2</sup> = 0.0; Chi <sup>2</sup> est for overall effect: Z = 0.11 Low summary risk of bias	= 7.5 I, df = 9 (P = 0.5	58); I <sup>2</sup> =0.0%			
AlphaOmega - ALA	182/2409	188/2428	-	75.3 %	0.98 [ 0.80, 1.19 ]
Ley 2004	2/70	1/66		0.6 %	1.89 [ 0.18, 20.31 ]
NDHS Faribault 1968	4/167	0/57		0.4 %	3.11 [ 0.17, 56.84 ]
Sydney Diet-Heart 1978	38/221	27/237		16.1 %	1.51 [ 0.95, 2.39 ]
				7.6 %	0.84 [ 0.43, 1.65 ]
WINS 2006	19/1462	15/975		7.0 %	
<b>Subtotal (95% CI)</b> otal events: 245 (Higher PUFA) leterogeneity: Tau <sup>2</sup> = 0.00; Chi	<b>4329</b> ), 231 (Lower PUFA) <sup>2</sup> = 4.10, df = 4 (P = 0	3763	•	100.0 %	
<b>Subtotal (95% CI)</b> otal events: 245 (Higher PUFA) Heterogeneity: Tau <sup>2</sup> = 0.00; Chi est for overall effect: $Z = 0.45$	<b>4329</b> ), 231 (Lower PUFA) <sup>2</sup> = 4.10, df = 4 (P = 0	3763	+		1.04 [ 0.87, 1.26 ]
<b>Subtotal (95% CI)</b> total events: 245 (Higher PUFA) deterogeneity: Tau <sup>2</sup> = 0.00; Chi est for overall effect: Z = 0.45	<b>4329</b> ), 231 (Lower PUFA) <sup>2</sup> = 4.10, df = 4 (P = 0	3763	+		
<b>ubtotal (95% CI)</b> otal events: 245 (Higher PUFA) leterogeneity: Tau <sup>2</sup> = 0.00; Chi est for overall effect: Z = 0.45 Trials registry or pre-2010	<b>4329</b> ), 231 (Lower PUFA) <sup>2</sup> = 4.10, df = 4 (P = 0 (P = 0.65)	<b>3763</b> 0.39); I <sup>2</sup> =2%	•	100.0 %	1.04 [ 0.87, 1.26 ]
<b>Subtotal (95% CI)</b> otal events: 245 (Higher PUFA) leterogeneity: Tau <sup>2</sup> = 0.00; Chi ast for overall effect: Z = 0.45 Trials registry or pre-2010 AlphaOmega - ALA	<b>4329</b> ), 231 (Lower PUFA) <sup>2</sup> = 4.10, df = 4 (P = 0 (P = 0.65) 182/2409	<b>3763</b> 0.39); I <sup>2</sup> =2% 188/2428	•	<b>100.0 %</b> 22.4 %	<b>1.04 [ 0.87, 1.26 ]</b> 0.98 [ 0.80, 1.19 ]
ubtotal (95% CI) otal events: 245 (Higher PUFA) leterogeneity: Tau <sup>2</sup> = 0.00; Chi ast for overall effect: Z = 0.45 Trials registry or pre-2010 AlphaOmega - ALA Bates 1978	<b>4329</b> ), 231 (Lower PUFA) <sup>2</sup> = 4.10, df = 4 (P = 0 (P = 0.65) 182/2409 0/58	<b>3763</b> 0.39); I <sup>2</sup> =2% I 88/2428 2/58		<b>100.0 %</b> 22.4 % 0.1 %	0.98 [ 0.80, 1.19 ] 0.20 [ 0.01, 4.08 ]
ubtotal (95% CI) otal events: 245 (Higher PUFA) eterogeneity: Tau <sup>2</sup> = 0.00; Chi est for overall effect: Z = 0.45 Trials registry or pre-2010 AlphaOmega - ALA Bates 1978 Bates 1989	<b>4329</b> ), 231 (Lower PUFA) <sup>2</sup> = 4.10, df = 4 (P = 0 (P = 0.65) 182/2409 0/58 1/155	<b>3763</b> 0.39); I <sup>2</sup> =2% 188/2428 2/58 0/157		<b>100.0 %</b> 22.4 % 0.1 % 0.1 %	1.04 [ 0.87, 1.26 ] 0.98 [ 0.80, 1.19 ] 0.20 [ 0.01, 4.08 ] 3.04 [ 0.12, 74.02 ] 1.97 [ 0.18, 21.21 ]
ubtotal (95% CI) otal events: 245 (Higher PUFA) eterogeneity: Tau <sup>2</sup> = 0.00; Chi est for overall effect: Z = 0.45 Trials registry or pre-2010 AlphaOmega - ALA Bates 1978 Bates 1989 Black 1994	<b>4329</b> ), 231 (Lower PUFA) <sup>2</sup> = 4.10, df = 4 (P = 0 (P = 0.65) 182/2409 0/58 1/155 2/67	<b>3763</b> 0.39); I <sup>2</sup> =2% 188/2428 2/58 0/157 1/66		100.0 % 22.4 % 0.1 % 0.1 % 0.2 %	<b>1.04 [ 0.87, 1.26 ]</b> 0.98 [ 0.80, 1.19 ] 0.20 [ 0.01, 4.08 ] 3.04 [ 0.12, 74.02 ] 1.97 [ 0.18, 21.21 ] 0.17 [ 0.01, 4.05 ]
ubtotal (95% CI) tal events: 245 (Higher PUFA) leterogeneity: Tau <sup>2</sup> = 0.00; Chi est for overall effect: Z = 0.45 Trials registry or pre-2010 AlphaOmega - ALA Bates 1978 Bates 1989 Black 1994 Brox 2001	<b>4329</b> ), 231 (Lower PUFA) <sup>2</sup> = 4.10, df = 4 (P = 0 (P = 0.65) 182/2409 0/58 1/155 2/67 0/80	<b>3763</b> 0.39); I <sup>2</sup> =2% 188/2428 2/58 0/157 1/66 1/40		100.0 % 22.4 % 0.1 % 0.1 % 0.2 % 0.1 %	1.04 [ 0.87, 1.26 ] 0.98 [ 0.80, 1.19 ] 0.20 [ 0.01, 4.08 ] 3.04 [ 0.12, 74.02 ] 1.97 [ 0.18, 21.21 ] 0.17 [ 0.01, 4.05 ] 0.98 [ 0.76, 1.25 ]
ubtotal (95% CI) tal events: 245 (Higher PUFA) eterogeneity: Tau <sup>2</sup> = 0.00; Chi est for overall effect: Z = 0.45 Trials registry or pre-2010 AlphaOmega - ALA Bates 1978 Bates 1989 Black 1994 Brox 2001 DART fat 1989	<b>4329</b> ), 231 (Lower PUFA) <sup>2</sup> = 4.10, df = 4 (P = 0 (P = 0.65) 182/2409 0/58 1/155 2/67 0/80 111/1018	<b>3763</b> 0.39); I <sup>2</sup> =2% 188/2428 2/58 0/157 1/66 1/40 113/1015		100.0 % 22.4 % 0.1 % 0.2 % 0.1 % 14.1 %	1.04 [ 0.87, 1.26 ] 0.98 [ 0.80, 1.19 ] 0.20 [ 0.01, 4.08 ] 3.04 [ 0.12, 74.02 ] 1.97 [ 0.18, 21.21 ] 0.17 [ 0.01, 4.05 ] 0.98 [ 0.76, 1.25 ] 0.65 [ 0.11, 3.79 ]
ubtotal (95% CI) btal events: 245 (Higher PUFA) leterogeneity: Tau <sup>2</sup> = 0.00; Chi est for overall effect: Z = 0.45 Trials registry or pre-2010 AlphaOmega - ALA Bates 1978 Bates 1989 Black 1994 Brox 2001 DART fat 1989 DIPP-Tokudome 2015	<b>4329</b> ), 231 (Lower PUFA) <sup>2</sup> = 4.10, df = 4 (P = 0 (P = 0.65) 182/2409 0/58 1/155 2/67 0/80 1111/1018 2/104	<b>3763</b> 0.39); l <sup>2</sup> =2% 188/2428 2/58 0/157 1/66 1/40 113/1015 3/101		100.0 % 22.4 % 0.1 % 0.1 % 0.2 % 0.1 % 14.1 % 0.3 %	1.04 [ 0.87, 1.26 ] 0.98 [ 0.80, 1.19 ] 0.20 [ 0.01, 4.08 ] 3.04 [ 0.12, 74.02 ] 1.97 [ 0.18, 21.21 ] 0.17 [ 0.01, 4.05 ] 0.98 [ 0.76, 1.25 ] 0.65 [ 0.11, 3.79 ] 2.95 [ 0.12, 71.97 ]
ubtotal (95% CI) tal events: 245 (Higher PUFA) teterogeneity: Tau <sup>2</sup> = 0.00; Chi est for overall effect: Z = 0.45 Trials registry or pre-2010 AlphaOmega - ALA Bates 1978 Bates 1978 Black 1994 Brox 2001 DART fat 1989 DIPP-Tokudome 2015 EPIC-1 2008	<b>4329</b> ), 231 (Lower PUFA) <sup>2</sup> = 4.10, df = 4 (P = 0 (P = 0.65) 182/2409 0/58 1/155 2/67 0/80 1111/1018 2/104 1/183	<b>3763</b> 0.39); l <sup>2</sup> =2% 188/2428 2/58 0/157 1/66 1/40 113/1015 3/101 0/180		100.0 % 22.4 % 0.1 % 0.1 % 0.2 % 0.1 % 14.1 % 0.3 % 0.1 %	1.04 [ 0.87, 1.26 ] 0.98 [ 0.80, 1.19 ] 0.20 [ 0.01, 4.08 ] 3.04 [ 0.12, 74.02 ] 1.97 [ 0.18, 21.21 ] 0.17 [ 0.01, 4.05 ] 0.98 [ 0.76, 1.25 ] 0.65 [ 0.11, 3.79 ] 2.95 [ 0.12, 71.97 ] 0.34 [ 0.01, 8.17 ]
ubtotal (95% CI) tal events: 245 (Higher PUFA) eterogeneity: Tau <sup>2</sup> = 0.00; Chi est for overall effect: Z = 0.45 Trials registry or pre-2010 AlphaOmega - ALA Bates 1978 Bates 1989 Black 1994 Brox 2001 DART fat 1989 DIPP-Tokudome 2015 EPIC-1 2008 EPIC-2 2008	<b>4329</b> ), 231 (Lower PUFA) <sup>2</sup> = 4.10, df = 4 (P = 0 (P = 0.65) 182/2409 0/58 1/155 2/67 0/80 111/1018 2/104 1/183 0/189	<b>3763</b> 0.39); l <sup>2</sup> =2% 188/2428 2/58 0/157 1/66 1/40 113/1015 3/101 0/180 1/190		100.0 % 22.4 % 0.1 % 0.1 % 0.1 % 14.1 % 0.3 % 0.1 %	1.04 [ 0.87, 1.26 ] 0.98 [ 0.80, 1.19 ] 0.20 [ 0.01, 4.08 ] 3.04 [ 0.12, 74.02 ] 1.97 [ 0.18, 21.21 ] 0.17 [ 0.01, 4.05 ] 0.98 [ 0.76, 1.25 ] 0.65 [ 0.11, 3.79 ] 2.95 [ 0.12, 71.97 ] 0.34 [ 0.01, 8.17 ] 1.09 [ 0.51, 2.34 ]
ubtotal (95% CI) btal events: 245 (Higher PUFA) leterogeneity: Tau <sup>2</sup> = 0.00; Chi est for overall effect: Z = 0.45 Trials registry or pre-2010 AlphaOmega - ALA Bates 1978 Bates 1989 Black 1994 Brox 2001 DART fat 1989 DIPP-Tokudome 2015 EPIC-1 2008 EPIC-2 2008 FAAT - Leaf 2005	<b>4329</b> ), 231 (Lower PUFA) <sup>2</sup> = 4.10, df = 4 (P = 0 (P = 0.65) 182/2409 0/58 1/155 2/67 0/80 111/1018 2/104 1/183 0/189 13/200	<b>3763</b> 0.39); l <sup>2</sup> =2% 188/2428 2/58 0/157 1/66 1/40 113/1015 3/101 0/180 1/190 12/202		100.0 % 22.4 % 0.1 % 0.1 % 0.2 % 0.1 % 14.1 % 0.3 % 0.1 % 0.1 % 1.5 %	0.98 [ 0.80, 1.19 ] 0.20 [ 0.01, 4.08 ] 3.04 [ 0.12, 74.02 ]
ubtotal (95% CI) bala events: 245 (Higher PUFA) leterogeneity: Tau <sup>2</sup> = 0.00; Chi est for overall effect: Z = 0.45 Trials registry or pre-2010 AlphaOmega - ALA Bates 1978 Bates 1978 Bates 1989 Black 1994 Brox 2001 DART fat 1989 DIPP-Tokudome 2015 EPIC-1 2008 EPIC-2 2008 FAAT - Leaf 2005 HARP- Sacks 1995	<b>4329</b> ), 231 (Lower PUFA) <sup>2</sup> = 4.10, df = 4 (P = 0 (P = 0.65) 182/2409 0/58 1/155 2/67 0/80 111/1018 2/104 1/183 0/189 13/200 0/41	<b>3763</b> 0.39); l <sup>2</sup> =2% 188/2428 2/58 0/157 1/66 1/40 113/1015 3/101 0/180 1/190 12/202 1/39		100.0 % 22.4 % 0.1 % 0.2 % 0.1 % 14.1 % 0.3 % 0.1 % 1.5 % 0.1 %	1.04 [ 0.87, 1.26 ] 0.98 [ 0.80, 1.19 ] 0.20 [ 0.01, 4.08 ] 3.04 [ 0.12, 74.02 ] 1.97 [ 0.18, 21.21 ] 0.17 [ 0.01, 4.05 ] 0.98 [ 0.76, 1.25 ] 0.65 [ 0.11, 3.79 ] 2.95 [ 0.12, 71.97 ] 0.34 [ 0.01, 8.17 ] 1.09 [ 0.51, 2.34 ] 0.32 [ 0.01, 7.57 ]
Aubtotal (95% CI) botal events: 245 (Higher PUFA) leterogeneity: Tau <sup>2</sup> = 0.00; Chi est for overall effect: Z = 0.45 Trials registry or pre-2010 AlphaOmega - ALA Bates 1978 Bates 1978 Bates 1989 Black 1994 Brox 2001 DART fat 1989 DIPP-Tokudome 2015 EPIC-1 2008 EPIC-2 2008 FAAT - Leaf 2005 HARP- Sacks 1995 Kumar 2013	<b>4329</b> ), 231 (Lower PUFA) <sup>2</sup> = 4.10, df = 4 (P = 0 (P = 0.65) 182/2409 0/58 1/155 2/67 0/80 1111/1018 2/104 1/183 0/189 13/200 0/41 1/39	<b>3763</b> 0.39); l <sup>2</sup> =2% 188/2428 2/58 0/157 1/66 1/40 113/1015 3/101 0/180 1/190 12/202 1/39		100.0 % 22.4 % 0.1 % 0.2 % 0.1 % 14.1 % 0.3 % 0.1 % 1.5 % 0.1 %	1.04 [ 0.87, 1.26 ] 0.98 [ 0.80, 1.19 ] 0.20 [ 0.01, 4.08 ] 3.04 [ 0.12, 74.02 ] 1.97 [ 0.18, 21.21 ] 0.17 [ 0.01, 4.05 ] 0.98 [ 0.76, 1.25 ] 0.65 [ 0.11, 3.79 ] 2.95 [ 0.12, 71.97 ] 0.34 [ 0.01, 8.17 ] 1.09 [ 0.51, 2.34 ] 0.32 [ 0.01, 7.57 ] 1.00 [ 0.06, 15.43 ]

(Continued  $\dots$ )

(... Continued)

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	Higher PUFA	Lower PUFA	Risk Ratio M-	Weight	( Continued Risk Ratio M-
	n/N	n/N	H,Random,95% Cl		H,Random,9 Cl
NDHS Faribault 1968	4/167	0/57		0.1 %	3.11 [ 0.17, 56.84 ]
PREDIMED 2013	116/2454	8/2543	+	13.8 %	1.02 [ 0.79, 1.31 ]
Raitt 2005	4/100	10/100		0.7 %	0.40 [ 0.13, 1.23 ]
Rose 1965	5/28	3/26		0.5 %	1.55 [ 0.41, 5.84 ]
Sydney Diet-Heart 1978	38/221	27/237		4.1 %	1.51 [ 0.95, 2.39 ]
Veterans Admin 1969	174/424	177/422	+	33.6 %	0.98 [ 0.83, 1.15 ]
WINS 2006	19/1462	15/975		1.9 %	0.84 [ 0.43, 1.65 ]
ubtotal (95% CI)	9693	9159	•	100.0 %	0.99 [ 0.90, 1.08 ]
est for overall effect: Z = 0.28 (P = No industry funding Black 1994	= 0.78) 2/67	1/66		1.3 %	1.97 [ 0.18, 21.21 ]
Brox 2001	0/80	1/40	4	0.7 %	0.17 [ 0.01, 4.05 ]
DIPP-Tokudome 2015	2/104	3/101		2.3 %	0.65 [ 0.11, 3.79 ]
FAAT - Leaf 2005	13/200	12/202	_	12.3 %	1.09 [ 0.51, 2.34 ]
Ley 2004	2/70	1/66		1.3 %	1.89 [ 0.18, 20.31 ]
MRC 1968	28/199	31/194		31.9 %	0.88 [ 0.55, 1.41 ]
		0/57			
NDHS Faribault 1968	4/167			0.8 %	3.11 [ 0.17, 56.84 ]
Sydney Diet-Heart 1978	38/221	27/237		33.8 %	1.51 [ 0.95, 2.39 ]
WINS 2006	19/1462	15/975		15.7 %	0.84 [ 0.43, 1.65 ]
ubtotal (95% CI) otal events: 108 (Higher PUFA), 91 eterogeneity: Tau <sup>2</sup> = 0.0; Chi <sup>2</sup> = 5 est for overall effect: Z = 0.64 (P = Randomised 100+ participants AlphaOmega - ALA	5.88, df = 8 (P = 0.6	<b>1938</b> 66); I <sup>2</sup> =0.0% I 88/2428		<b>100.0 %</b> 23.0 %	<b>1.09 [ 0.84, 1.42 ]</b> 0.98 [ 0.80, 1.19 ]
Bates 1978	0/58	2/58	· · · · · · · · · · · · · · · · · · ·	0.1 %	0.20 [ 0.01, 4.08 ]
Bates 1989	1/155	0/157		0.1 %	3.04 [ 0.12, 74.02 ]
Black 1994	2/67	1/66		0.2 %	1.97 [ 0.18, 21.21 ]
Brox 2001	0/80	1/40	<u>د ، ا</u>	0.1 %	0.17 [ 0.01, 4.05 ]
	111/1018	113/1015	+	14.5 %	0.98 [ 0.76, 1.25 ]
DART fat 1989					
DART fat 1989 DIPP-Tokudome 2015	2/104	3/101		0.3 %	0.65 [ 0.11, 3.79 ]

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	Higher PUFA	Lower PUFA	Risk Ratio M-	Weight	Risk Ratio M
	n/N	n/N	H,Random,95% Cl		H,Random, C
EPIC-1 2008	1/183	0/180		0.1 %	2.95 [ 0.12, 71.97
EPIC-2 2008	0/189	1/190	•	0.1 %	0.34 [ 0.01, 8.17
FAAT - Leaf 2005	13/200	12/202		1.5 %	1.09 [ 0.51, 2.34
Ley 2004	2/70	1/66		0.2 %	1.89 [ 0.18, 20.31
MRC 1968	28/199	31/194		4.0 %	0.88 [ 0.55, 1.41
NDHS Faribault 1968	4/167	0/57		0.1 %	3.11 [ 0.17, 56.84
PREDIMED 2013	116/2454	118/2543	+	14.1 %	1.02 [ 0.79, 1.31
Raitt 2005	4/100	10/100		0.7 %	0.40 [ 0.13, 1.23
Sydney Diet-Heart 1978	38/221	27/237		4.2 %	1.51 [ 0.95, 2.39
Veterans Admin 1969	174/424	177/422	-	34.5 %	0.98 [ 0.83, 1.15
Vijayakumar 2014	0/100	2/100	·····	0.1 %	0.20 [ 0.01, 4.11
WINS 2006	19/1462	15/975		2.0 %	0.84 [ 0.43, 1.65
111113 2000					
<b>ubtotal (95% CI)</b> otal events: 699 (Higher PUFA)	,	9250	ł	100.0 %	0.98   0.89, 1.08
<b>ubtotal (95% CI)</b> otal events: 699 (Higher PUFA) leterogeneity: Tau <sup>2</sup> = 0.0; Chi <sup>2</sup> est for overall effect: Z = 0.36 ( Randomised 250+ participant:	), 711 (Lower PUFA) = 16.24, df = 19 (P = (P = 0.72)		•	100.0 %	0.98 [ 0.89, 1.08
<b>ubtotal (95% CI)</b> otal events: 699 (Higher PUFA) eterogeneity: Tau <sup>2</sup> = 0.0; Chi <sup>2</sup> est for overall effect: Z = 0.36	), 711 (Lower PUFA) = 16.24, df = 19 (P = (P = 0.72)		•	<b>100.0 %</b> 23.5 %	0.98 [ 0.89, 1.08 0.98 [ 0.80, 1.19
<b>ubtotal (95% CI)</b> tal events: 699 (Higher PUFA) eterogeneity: Tau <sup>2</sup> = 0.0; Chi <sup>2</sup> est for overall effect: $Z = 0.36$ ( Randomised 250+ participant)	), 711 (Lower PUFA) = 16.24, df = 19 (P = (P = 0.72) s	0.64); l <sup>2</sup> =0.0%	• 		0.98 [ 0.80, 1.19
ubtotal (95% CI) tal events: 699 (Higher PUFA) eterogeneity: Tau <sup>2</sup> = 0.0; Chi <sup>2</sup> est for overall effect: Z = 0.36 o Randomised 250+ participant: AlphaOmega - ALA	), 711 (Lower PUFA) = 16.24, df = 19 (P = (P = 0.72) s 182/2409	0.64); l <sup>2</sup> =0.0% I 88/2428	•	23.5 %	0.98 [ 0.80, 1.19 3.04 [ 0.12, 74.02
ubtotal (95% CI) otal events: 699 (Higher PUFA) eterogeneity: Tau <sup>2</sup> = 0.0; Chi <sup>2</sup> est for overall effect: Z = 0.36 ( Randomised 250+ participant: AlphaOmega - ALA Bates 1989	), 711 (Lower PUFA) = 16.24, df = 19 (P = (P = 0.72) s 182/2409 1/155	0.64); I <sup>2</sup> =0.0% 188/2428 0/157	• • •	23.5 % 0.1 %	0.98 [ 0.80, 1.19 3.04 [ 0.12, 74.02 0.98 [ 0.76, 1.25
ubtotal (95% CI) tal events: 699 (Higher PUFA) eterogeneity: Tau <sup>2</sup> = 0.0; Chi <sup>2</sup> est for overall effect: Z = 0.36 i Randomised 250+ participant: AlphaOmega - ALA Bates 1989 DART fat 1989	), 711 (Lower PUFA) = 16.24, df = 19 (P = (P = 0.72) s 182/2409 1/155 111/1018	0.64); I <sup>2</sup> =0.0% 188/2428 0/157 113/1015	•	23.5 % 0.1 % 14.8 %	0.98 [ 0.80, 1.19 3.04 [ 0.12, 74.02 0.98 [ 0.76, 1.25 2.95 [ 0.12, 71.97
ubtotal (95% CI) otal events: 699 (Higher PUFA) eterogeneity: Tau <sup>2</sup> = 0.0; Chi <sup>2</sup> est for overall effect: Z = 0.36 i Randomised 250+ participant: AlphaOmega - ALA Bates 1989 DART fat 1989 EPIC-1 2008	), 711 (Lower PUFA) = 16.24, df = 19 (P = (P = 0.72) s 182/2409 1/155 111/1018 1/183	0.64); I <sup>2</sup> =0.0% 188/2428 0/157 113/1015 0/180		23.5 % 0.1 % 14.8 % 0.1 %	
ubtotal (95% CI) tal events: 699 (Higher PUFA) eterogeneity: Tau <sup>2</sup> = 0.0; Chi <sup>2</sup> est for overall effect: Z = 0.36 ( Randomised 250+ participant: AlphaOmega - ALA Bates 1989 DART fat 1989 EPIC-1 2008 EPIC-2 2008	), 711 (Lower PUFA) = 16.24, df = 19 (P = (P = 0.72) s 182/2409 1/155 111/1018 1/183 0/189	0.64); I <sup>2</sup> =0.0% 188/2428 0/157 113/1015 0/180 1/190		23.5 % 0.1 % 14.8 % 0.1 % 0.1 %	0.98 [ 0.80, 1.19 3.04 [ 0.12, 74.02 0.98 [ 0.76, 1.25 2.95 [ 0.12, 71.97 0.34 [ 0.01, 8.17 1.09 [ 0.51, 2.34
ubtotal (95% CI) tal events: 699 (Higher PUFA) eterogeneity: Tau <sup>2</sup> = 0.0; Chi <sup>2</sup> est for overall effect: Z = 0.36 o Randomised 250+ participant: AlphaOmega - ALA Bates 1989 DART fat 1989 EPIC-1 2008 EPIC-2 2008 FAAT - Leaf 2005	), 711 (Lower PUFA) = 16.24, df = 19 (P = (P = 0.72) s 182/2409 1/155 111/1018 1/183 0/189 13/200	0.64);   <sup>2</sup> =0.0%  88/2428 0/157  13/1015 0/180  /190  2/202		23.5 % 0.1 % 14.8 % 0.1 % 0.1 % 1.6 %	0.98 [ 0.80, 1.19 3.04 [ 0.12, 74.02 0.98 [ 0.76, 1.25 2.95 [ 0.12, 71.97 0.34 [ 0.01, 8.17 1.09 [ 0.51, 2.34 0.88 [ 0.55, 1.41
ubtotal (95% CI) tal events: 699 (Higher PUFA) eterogeneity: Tau <sup>2</sup> = 0.0; Chi <sup>2</sup> est for overall effect: Z = 0.36 H Randomised 250+ participant: AlphaOmega - ALA Bates 1989 DART fat 1989 EPIC-1 2008 EPIC-2 2008 FAAT - Leaf 2005 MRC 1968	), 711 (Lower PUFA) = 16.24, df = 19 (P = (P = 0.72) s 182/2409 1/155 111/1018 1/183 0/189 13/200 28/199	0.64); I <sup>2</sup> =0.0% 188/2428 0/157 113/1015 0/180 1/190 12/202 31/194		23.5 % 0.1 % 14.8 % 0.1 % 0.1 % 1.6 % 4.1 %	0.98 [ 0.80, 1.19 3.04 [ 0.12, 74.02 0.98 [ 0.76, 1.25 2.95 [ 0.12, 71.97 0.34 [ 0.01, 8.17
ubtotal (95% CI) tal events: 699 (Higher PUFA) eterogeneity: Tau <sup>2</sup> = 0.0; Chi <sup>2</sup> est for overall effect: Z = 0.36 o Randomised 250+ participant: AlphaOmega - ALA Bates 1989 DART fat 1989 EPIC-1 2008 EPIC-2 2008 FAAT - Leaf 2005 MRC 1968 PREDIMED 2013	), 711 (Lower PUFA) = 16.24, df = 19 (P = (P = 0.72) s 182/2409 1/155 111/1018 1/183 0/189 13/200 28/199 116/2454	0.64); I <sup>2</sup> =0.0% 188/2428 0/157 113/1015 0/180 1/190 12/202 31/194 118/2543		23.5 % 0.1 % 14.8 % 0.1 % 1.6 % 4.1 % 14.4 %	0.98 [ 0.80, 1.19 3.04 [ 0.12, 74.02 0.98 [ 0.76, 1.25 2.95 [ 0.12, 71.97 0.34 [ 0.01, 8.17 1.09 [ 0.51, 2.34 0.88 [ 0.55, 1.41 1.02 [ 0.79, 1.31
ubtotal (95% CI) tal events: 699 (Higher PUFA) eterogeneity: Tau <sup>2</sup> = 0.0; Chi <sup>2</sup> st for overall effect: Z = 0.36 i Randomised 250+ participant: AlphaOmega - ALA Bates 1989 DART fat 1989 EPIC-1 2008 EPIC-2 2008 FAAT - Leaf 2005 MRC 1968 PREDIMED 2013 Sydney Diet-Heart 1978	), 711 (Lower PUFA) = 16.24, df = 19 (P = (P = 0.72) s 182/2409 1/155 111/1018 1/183 0/189 13/200 28/199 116/2454 38/221	0.64); I <sup>2</sup> =0.0% 188/2428 0/157 113/1015 0/180 1/190 12/202 31/194 118/2543 27/237		23.5 % 0.1 % 14.8 % 0.1 % 0.1 % 1.6 % 4.1 % 14.4 % 4.3 %	0.98 [ 0.80, 1.19 3.04 [ 0.12, 74.02 0.98 [ 0.76, 1.25 2.95 [ 0.12, 71.97 0.34 [ 0.01, 8.17 1.09 [ 0.51, 2.34 0.88 [ 0.55, 1.41 1.02 [ 0.79, 1.31 1.51 [ 0.95, 2.39

## Analysis I.3. Comparison I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes, Outcome 3 All-cause mortality - SA fixed-effect.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes

Outcome: 3 All-cause mortality - SA fixed-effect

Study or subgroup	Higher PUFA n/N	Lower PUFA n/N	Risk Ratio M-H,Fixed,95% Cl	Weight	Risk Ratio M-H,Fixed,95% Cl
AlphaOmega - ALA	182/2409	188/2428	-	25.5 %	0.98 [ 0.80, 1.19 ]
Bates 1978	0/58	2/58	<b>←</b> +	0.3 %	0.20 [ 0.01, 4.08 ]
Bates 1989	1/155	0/157	<b>-</b>	0.1 %	3.04 [ 0.12, 74.02 ]
Black 1994	2/67	1/66	·	0.1 %	1.97 [ 0.18, 21.21 ]
Brox 2001	0/80	1/40	• · · · · · · · · · · · · · · · · · · ·	0.3 %	0.17 [ 0.01, 4.05 ]
DART fat 1989	111/1018	113/1015	-	15.4 %	0.98 [ 0.76, 1.25 ]
DIPP-Tokudome 2015	2/104	3/101		0.4 %	0.65 [ 0.11, 3.79 ]
Doi 2014	2/119	9/119	<del> </del>	1.2 %	0.22 [ 0.05, 1.01 ]
EPIC-1 2008	1/183	0/180	<b>-</b>	0.1 %	2.95 [ 0.12, 71.97 ]
EPIC-2 2008	0/189	1/190	· · · · · · · · · · · · · · · · · · ·	0.2 %	0.34 [ 0.01, 8.17 ]
FAAT - Leaf 2005	13/200	12/202		1.6 %	1.09 [ 0.51, 2.34 ]
HARP- Sacks 1995	0/41	1/39	• • • · · · · · · · · · · · · · · · · ·	0.2 %	0.32 [ 0.01, 7.57 ]
Kumar 2013	1/39	1/39	•	0.1 %	1.00 [ 0.06, 15.43 ]
Ley 2004	2/70	1/66		0.1 %	1.89 [ 0.18, 20.31 ]
McIIImurray 1987	10/25	12/24		1.7 %	0.80 [ 0.43, 1.49 ]
MRC 1968	28/199	31/194		4.3 %	0.88 [ 0.55, 1.41 ]
NDHS Faribault 1968	4/167	0/57		0.1 %	3.11 [ 0.17, 56.84 ]
PREDIMED 2013	116/2454	118/2543	-	15.8 %	1.02 [ 0.79, 1.31 ]
Raitt 2005	4/100	10/100		1.4 %	0.40 [ 0.13, 1.23 ]
Rose 1965	5/28	3/26		0.4 %	1.55 [ 0.41, 5.84 ]
Sydney Diet-Heart 1978	38/221	27/237		3.6 %	1.51 [ 0.95, 2.39 ]
Veterans Admin 1969	174/424	177/422	+	24.2 %	0.98 [ 0.83, 1.15 ]
Vijayakumar 2014	0/100	2/100	<b>←</b> + − − − −	0.3 %	0.20 [ 0.01, 4.11 ]

0.1 0.2 0.5 1 2 5 10

Favours higher PUFA Favours lower PUFA

(Continued ...)

Study or subgroup	Higher PUFA n/N	Lower PUFA n/N	Risk Ratio M-H,Fixed,95% Cl	Weight	( Continued) Risk Ratio M-H,Fixed,95% Cl
WINS 2006	19/1462	15/975		2.5 %	0.84 [ 0.43, 1.65 ]
Total (95% CI)	9912	9378	•	100.0 %	0.98 [ 0.89, 1.07 ]
Total events: 715 (Higher PUF	A), 728 (Lower PUFA)				
Heterogeneity: Chi <sup>2</sup> = 17.59,	df = 23 (P = 0.78); $I^2 = 0$	.0%			
Test for overall effect: $Z = 0.5$	(P = 0.61)				
Test for subgroup differences:	Not applicable				
			0.1 0.2 0.5 1 2 5 10		

Favours higher PUFA Favours lower PUFA

## Analysis I.4. Comparison I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes, Outcome 4 All-cause mortality - subgroup by PUFA dose.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

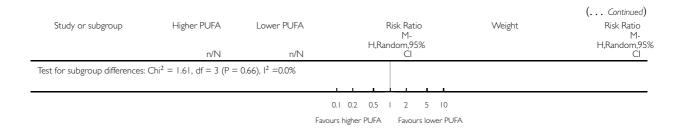
Comparison: I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes

Outcome: 4 All-cause mortality - subgroup by PUFA dose

Study or subgroup	Higher PUFA	Lower PUFA	Risk Ratio M-	Weight	Risk Ratio M-
	n/N	n/N	H,Random,95% Cl		H,Random,95% Cl
total PUFA < 1.0% E					
Doi 2014	2/119	9/119	<u>← + </u>	0.4 %	0.22 [ 0.05, 1.01 ]
FAAT - Leaf 2005	3/200	12/202		1.5 %	1.09 [ 0.51, 2.34 ]
Kumar 2013	1/39	1/39	· · · · · · · · · · · · · · · · · · ·	0.1 %	1.00 [ 0.06, 15.43 ]
Ley 2004	2/70	1/66	+	0.2 %	1.89 [ 0.18, 20.31 ]
Raitt 2005	4/100	10/100		0.7 %	0.40 [ 0.13, 1.23 ]
Subtotal (95% CI)	528	526		2.8 %	0.66 [ 0.33, 1.34 ]
Total events: 22 (Higher PUFA	A), 33 (Lower PUFA)				
Heterogeneity: $Tau^2 = 0.16$ ; C	$Chi^2 = 5.27$ , df = 4 (P = 0.1)	.26); l <sup>2</sup> =24%			
Test for overall effect: $Z = 1.1$	5 (P = 0.25)				
2 total PUFA 1.0 to < 2.0% E					
AlphaOmega - ALA	182/2409	188/2428	+	22.3 %	0.98 [ 0.80, 1.19 ]
			0.1 0.2 0.5 1 2 5 10		
			Favours higher PUFA Favours lower PUFA		

(Continued ...)

Study or subgroup	Higher PUFA	Lower PUFA	Risk Ratio M- H,Random,95%	Weight	( Continued Risk Ratio M- H,Random,?
	n/N	n/N	Cl		CI
Bates 1978	0/58	2/58	<b>←</b> • • • • • • • • • • • • • • • • • • •	0.1 %	0.20 [ 0.01, 4.08 ]
Bates 1989	1/155	0/157		0.1 %	3.04 [ 0.12, 74.02 ]
Brox 2001	0/80	1/40	<b>← ↓</b>	0.1 %	0.17 [ 0.01, 4.05 ]
DIPP-Tokudome 2015	2/104	3/101		0.3 %	0.65 [ 0.11, 3.79 ]
EPIC-1 2008	1/183	0/180		0.1 %	2.95 [ 0.12, 71.97 ]
EPIC-2 2008	0/189	1/190	· · · ·	0.1 %	0.34 [ 0.01, 8.17 ]
PREDIMED 2013	116/2454	118/2543	-	13.7 %	1.02 [ 0.79, 1.31 ]
WINS 2006	19/1462	15/975	<b>.</b>	1.9 %	0.84 [ 0.43, 1.65 ]
Subtotal (95% CI)	7094	6672	•	38.6 %	0.98 [ 0.84, 1.13 ]
Heterogeneity: Tau <sup>2</sup> = 0.0; Chi <sup>2</sup> est for overall effect: Z = 0.32 total PUFA 2.0 to < 5.0% E		35); I <sup>2</sup> =0.0%			
Black 1994	2/67	1/66		0.2 %	1.97 [ 0.18, 21.21 ]
DART fat 1989	111/1018	113/1015	+	14.0 %	0.98 [ 0.76, 1.25
HARP- Sacks 1995	0/41	1/39	<b>←</b>	0.1 %	0.32 [ 0.01, 7.57
McIIImurray 1987	10/25	12/24	<u> </u>	2.2 %	0.80 [ 0.43, 1.49
<b>Subtotal (95% CI)</b> Total events: 123 (Higher PUFA Heterogeneity: Tau <sup>2</sup> = 0.0; Chi <sup>2</sup> Test for overall effect: $Z = 0.41$ total PUFA $\geq$ 5.0% E MRC 1968	= 1.17, df = 3 (P = 0.7	<b>1144</b> 76); I <sup>2</sup> =0.0% 31/194		<b>16.5 %</b>	0.95 [ 0.76, 1.20
					2
NDHS Faribault 1968	4/167	0/57		0.1 %	3.11 [ 0.17, 56.84 ]
Rose 1965	5/28	3/26		0.5 %	1.55 [ 0.41, 5.84
Sydney Diet-Heart 1978	38/221	27/237		4.1 %	1.51 [ 0.95, 2.39
Veterans Admin 1969	174/424	177/422	+	33.5 %	0.98 [ 0.83, 1.15
Vijayakumar 2014	0/100	2/100	<b>←</b> i	0.1 %	0.20 [ 0.01, 4.11
Subtotal (95% CI)	1139	1036	+	42.1 %	1.04 [ 0.86, 1.26 ]
otal events: 249 (Higher PUFA leterogeneity: Tau <sup>2</sup> = 0.01; Ch est for overall effect: Z = 0.39	$i^2 = 5.53$ , df = 5 (P = C	0.35); I <sup>2</sup> = I 0%			
otal (95% CI) tal events: 715 (Higher PUFA eterogeneity: Tau <sup>2</sup> = 0.0; Chi <sup>2</sup> est for overall effect: $Z = 0.43$	<b>9912</b> ), 728 (Lower PUFA) = 17.59, df = 23 (P =	<b>9378</b> 0.78); I <sup>2</sup> =0.0%	•	100.0 %	0.98 [ 0.89, 1.07
		F	0.1 0.2 0.5 1 2 5 10 avours higher PUFA Favours lower PU	JFA	(Continued



#### Analysis 1.5. Comparison I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes, Outcome 5 All-cause mortality - subgroup by duration.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes

Outcome: 5 All-cause mortality - subgroup by duration

Study or subgroup	Higher PUFA	Lower PUFA	Risk Ratio M-	Weight	Risk Ratio M-
	n/N	n/N	H,Random,95% Cl		H,Random,95% Cl
Medium duration   to < 2 $_{ m N}$	years				
Brox 2001	0/80	1/40	<b>←                                    </b>	0.1 %	0.17 [ 0.01, 4.05 ]
Doi 2014	2/119	9/119	<b>←</b> ,	0.4 %	0.22 [ 0.05, 1.01 ]
EPIC-1 2008	1/183	0/180		0.1 %	2.95 [ 0.12, 71.97 ]
EPIC-2 2008	0/189	1/190	•	0.1 %	0.34 [ 0.01, 8.17 ]
FAAT - Leaf 2005	3/200	12/202		1.5 %	1.09 [ 0.51, 2.34 ]
Kumar 2013	1/39	1/39	·	0.1 %	1.00 [ 0.06, 15.43 ]
Ley 2004	2/70	1/66		0.2 %	1.89 [ 0.18, 20.31 ]
NDHS Faribault 1968	4/167	0/57		0.1 %	3.11 [ 0.17, 56.84 ]
Subtotal (95% CI)	1047	893	-	2.5 %	0.86 [ 0.48, 1.55 ]
Total events: 23 (Higher PUFA Heterogeneity: Tau <sup>2</sup> = 0.0; Ch Test for overall effect: $Z = 0.5$	$m^2 = 6.59$ , df = 7 (P = 0.5)	47); I <sup>2</sup> =0.0%			
2 Medium-long duration 2 to	, ,				
AlphaOmega - ALA	182/2409	188/2428	• • • • • • • •	22.3 %	0.98 [ 0.80, 1.19 ]
			0.1 0.2 0.5 1 2 5 10		
			Favours higher PUFA Favours lower PUF	FA	

(Continued ...)

Higher PUFA n/N	Lower PUFA	Risk Ratio M- H,Random,95% Cl	Weight	( Continued) Risk Ratio H,Random,959 Cl
0/58	2/58	<b></b>	0.1 %	0.20 [ 0.01, 4.08 ]
1/155	0/157		0.1 %	3.04 [ 0.12, 74.02 ]
2/67	1/66		0.2 %	1.97 [ 0.18, 21.21 ]
111/1018	113/1015	+	14.0 %	0.98 [ 0.76, 1.25 ]
2/104	3/101		0.3 %	0.65 [ 0.11, 3.79 ]
0/41	1/39	•	0.1 %	0.32 [ 0.01, 7.57 ]
10/25	12/24	<u> </u>	2.2 %	0.80 [ 0.43, 1.49 ]
4/100	10/100		0.7 %	0.40 [ 0.13, 1.23 ]
5/28	3/26		0.5 %	1.55 [ 0.41, 5.84 ]
0/100	2/100	•	0.1 %	0.20 [ 0.01, 4.11 ]
<b>4105</b> ), 335 (Lower PUFA) = 6.77, df = 10 (P = 0 (P = 0.49)	<b>4114</b> 0.75); I <sup>2</sup> =0.0%	•	40.5 %	0.95 [ 0.82, 1.10 ]
28/199	31/194		3.9 %	0.88 [ 0.55, 1.41 ]
6/2454	118/2543	+	13.7 %	1.02 [ 0.79, 1.31 ]
38/221	27/237		4.1 %	1.51 [ 0.95, 2.39 ]
174/424	177/422	+	33.5 %	0.98 [ 0.83, 1.15 ]
19/1462	15/975		1.9 %	0.84 [ 0.43, 1.65 ]
<b>4760</b> ), 368 (Lower PUFA) = 3.72, df = 4 (P = 0:	<b>4371</b> 45);   <sup>2</sup> =0.0%	•	<b>57.0</b> %	1.01 [ 0.89, 1.14 ]
(P = 0.91) <b>9912</b> ), 728 (Lower PUFA)	9378	•	100.0 %	0.98 [ 0.89, 1.07 ]
	n/N 0/58 1/155 2/67 111/1018 2/104 0/41 10/25 4/100 5/28 0/100 <b>4105</b> ), 335 (Lower PUFA) = 6.77, df = 10 (P = 0 (P = 0.49) 28/199 116/2454 38/221 174/424 19/1462 <b>4760</b> ), 368 (Lower PUFA) = 3.72, df = 4 (P = 0. (P = 0.91) <b>9912</b>	n/N       n/N         0/58       2/58         1/155       0/157         2/67       1/66         111/1018       113/1015         2/104       3/101         0/41       1/39         10/25       12/24         4/100       10/100         5/28       3/26         0/100       2/100         4105       4114         ), 335 (Lower PUFA)       = 0.77, df = 10 (P = 0.75); l <sup>2</sup> = 0.0%         (P = 0.49)       28/199       31/194         116/2454       118/2543       38/221         38/221       27/237       174/424         19/1462       15/975         4760       4371         ), 368 (Lower PUFA)       = 3.72, df = 4 (P = 0.45); l <sup>2</sup> = 0.0%         (P = 0.91)       9912       9378	$\begin{array}{c c c c c c c c c c c c c c c c c c c $	$\begin{array}{c c c c c c c c c c c c c c c c c c c $

0.1 0.2 0.5 1 2 5 10

Favours higher PUFA Favours lower PUFA

## Analysis 1.6. Comparison I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes, Outcome 6 All-cause mortality - subgroup by primary or secondary prevention.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes

Outcome: 6 All-cause mortality - subgroup by primary or secondary prevention

Study or subgroup	Higher PUFA	Lower PUFA	Risk Ratio M-	Weight	Risk Ratio M- H,Random,959
	n/N	n/N	H,Random,95% Cl		H,Kandom,955 Cl
Primary prevention of CVD					
Bates 1978	0/58	2/58	<b>←</b> +	0.1 %	0.20 [ 0.01, 4.08 ]
Bates 1989	1/155	0/157		0.1 %	3.04 [ 0.12, 74.02 ]
Black 1994	2/67	1/66		0.2 %	1.97 [ 0.18, 21.21 ]
Brox 2001	0/80	1/40	• • • • • • • • • • • • • • • • • • •	0.1 %	0.17 [ 0.01, 4.05 ]
DIPP-Tokudome 2015	2/104	3/101		0.3 %	0.65 [ 0.11, 3.79 ]
EPIC-1 2008	1/183	0/180		0.1 %	2.95 [ 0.12, 71.97 ]
EPIC-2 2008	0/189	1/190	•	0.1 %	0.34 [ 0.01, 8.17 ]
Kumar 2013	1/39	1/39	·	0.1 %	1.00 [ 0.06, 15.43 ]
Ley 2004	2/70	1/66		0.2 %	1.89 [ 0.18, 20.31 ]
McIIImurray 1987	10/25	12/24		2.2 %	0.80 [ 0.43, 1.49 ]
NDHS Faribault 1968	4/167	0/57		0.1 %	3.11 [ 0.17, 56.84 ]
PREDIMED 2013	116/2454	8/2543	+	13.7 %	1.02 [ 0.79, 1.31 ]
WINS 2006	19/1462	15/975		1.9 %	0.84 [ 0.43, 1.65 ]
Subtotal (95% CI)	5053	4496	+	19.0 %	0.97 [ 0.78, 1.20 ]
otal events: 158 (Higher PUF	A), 155 (Lower PUFA)				
Heterogeneity: $Tau^2 = 0.0$ ; Ch	,	0.93); l <sup>2</sup> =0.0%			
est for overall effect: Z = 0.28 Secondary prevention of CV	· /				
AlphaOmega - ALA	182/2409	188/2428	-	22.3 %	0.98 [ 0.80, 1.19 ]
DART fat 1989	111/1018	113/1015	+	14.0 %	0.98 [ 0.76, 1.25 ]
Doi 2014	2/119	9/119	•	0.4 %	0.22 [ 0.05, 1.01 ]
FAAT - Leaf 2005	13/200	12/202	<u> </u>	1.5 %	1.09 [ 0.51, 2.34 ]
	0/41	1/39	· · · · · · · · · · · · · · · · · · ·	0.1 %	0.32 [ 0.01, 7.57 ]
HARP- Sacks 1995	0/41				
HARP- Sacks 1995 MRC 1968	28/199	31/194		3.9 %	0.88 [ 0.55, 1.41 ]

Favours higher PUFA Favours lower PUFA

(Continued ...)

Study or subgroup	Higher PUFA	Lower PUFA	Risk Ratio M- H,Random,95%	Weight	( Continued) Risk Ratio M- H,Random,95%
	n/N	n/N	Cl		Cl
Rose 1965	5/28	3/26		0.5 %	1.55 [ 0.41, 5.84 ]
Sydney Diet-Heart 1978	38/221	27/237		4.1 %	1.51 [ 0.95, 2.39 ]
Veterans Admin 1969	174/424	177/422	+	33.5 %	0.98 [ 0.83, 1.15 ]
Vijayakumar 2014	0/100	2/100	<b>← ;</b>	0.1 %	0.20 [ 0.01, 4.11 ]
Subtotal (95% CI)	4859	4882	•	81.0 %	0.98 [ 0.86, 1.12 ]
Total events: 557 (Higher PUFA	A), 573 (Lower PUFA)				
Heterogeneity: $Tau^2 = 0.01$ ; Ch	ni <sup>2</sup> = 11.85, df = 10 (P =	= 0.29);   <sup>2</sup> =   6%			
Test for overall effect: Z = 0.27	(P = 0.79)				
Total (95% CI)	9912	9378	+	100.0 %	0.98 [ 0.89, 1.07 ]
Total events: 715 (Higher PUFA	A), 728 (Lower PUFA)				
Heterogeneity: $Tau^2 = 0.0$ ; Chi	<sup>2</sup> = 17.59, df = 23 (P =	0.78); l <sup>2</sup> =0.0%			
Test for overall effect: Z = 0.43	(P = 0.67)				
Test for subgroup differences: (	$Chi^2 = 0.01, df = 1 (P = 1)$	0.93), I <sup>2</sup> =0.0%			
			0.1 0.2 0.5 1 2 5 10		

0.1 0.2 0.5 1 2 5 10

Favours higher PUFA Favours lower PUFA

## Analysis 1.7. Comparison I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes, Outcome 7 All-cause mortality - subgroup by baseline PUFA dose.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes

Outcome: 7 All-cause mortality - subgroup by baseline PUFA dose

n/N 2/70 4/167 174/424	n/N 1/66 0/57	M- H,Random,95% Cl	0.2 %	M- H,Random,95 Cl 1.89 [ 0.18, 20.31 ]
4/167			0.2 %	1.89 [ 0.18, 20 31 ]
4/167			0.2 %	1.89 [ 0.18, 2031 ]
	0/57			
174/424			0.1 %	3.11 [ 0.17, 56.84 ]
	177/422	+	33.5 %	0.98 [ 0.83, 1.15 ]
19/1462	15/975		1.9 %	0.84 [ 0.43, 1.65 ]
2123	1520	+	35.6 %	0.98 [ 0.84, 1.14 ]
3 (Lower PUFA) .08, df = 3 (P = 0.7 : 0.77)	78); I <sup>2</sup> =0.0%			
2/67	1/66		0.2 %	1.97 [ 0.18, 21.21 ]
111/1018	113/1015	-	14.0 %	0.98 [ 0.76, 1.25 ]
2/104	3/101		0.3 %	0.65 [ 0.11, 3.79 ]
116/2454	118/2543		13.7 %	1.02 [ 0.79, 1.31 ]
38/221	27/237		4.1 %	1.51 [ 0.95, 2.39 ]
3864	3962	•	32.2 %	1.05 [ 0.89, 1.24 ]
2 (Lower PUFA) .33, df = 4 (P = 0.5 : 0.54)	50); I <sup>2</sup> =0.0%			
0	0			Not estimable
ower PUFA)				
182/2409	188/2428	+	22.3 %	0.98 [ 0.80, 1.19 ]
0/58	2/58	• • • • • • • • • • • • • • • • • • • •	0.1 %	0.20 [ 0.01, 4.08 ]
1/155	0/157		0.1 %	3.04 [ 0.12, 74.02 ]
0/80	1/40	• • • • • • • • • • • • • • • • • • •	0.1 %	0.17 [ 0.01, 4.05 ]
	3 (Lower PUFA) 08, df = 3 (P = 0.7 0.77) 2/67 111/1018 2/104 116/2454 38/221 <b>3864</b> 2 (Lower PUFA) 33, df = 4 (P = 0.5 0.54) 0 wer PUFA) 182/2409 0/58 1/155	3 (Lower PUFA) 08, df = 3 (P = 0.78); $ ^2 = 0.0\%$ 0.77) 2/67 1/66 111/1018 113/1015 2/104 3/101 116/2454 118/2543 38/221 27/237 <b>3864 3962</b> 2 (Lower PUFA) 33, df = 4 (P = 0.50); $ ^2 = 0.0\%$ 0.54) <b>0 0</b> wer PUFA) 182/2409 188/2428 0/58 2/58 1/155 0/157	3 (Lower PUFA) 08, df = 3 (P = 0.78); $ ^{2} = 0.0\%$ 0.77) 2/67 1/66 111/1018 113/1015 2/104 3/101 116/2454 118/2543 38/221 27/237 <b>3864 3962</b> 2 (Lower PUFA) 33, df = 4 (P = 0.50); $ ^{2} = 0.0\%$ 0.54) <b>0 0</b> wer PUFA) 182/2409 188/2428 0/58 2/58 1/155 0/157	3 (Lower PUFA) 08, df = 3 (P = 0.78); l <sup>2</sup> = 0.0% 0.77) 2/67 1/66 0.2% 111/1018 113/1015 14.0% 2/104 3/101 0.3% 116/2454 118/2543 13.7% 38/221 27/237 4.1% <b>3864 3962 32.2%</b> 2 (Lower PUFA) 33, df = 4 (P = 0.50); l <sup>2</sup> = 0.0% 0.54) <b>0 0</b> wer PUFA) 182/2409 188/2428 2.3% 0/58 2/58 0.1% 1/155 0/157 0.1%

(Continued . . . )

Study or subgroup	Higher PUFA	Lower PUFA	Risk Ratio M- H,Random,95%	Weight	( <i>Continued</i> ) Risk Ratio H- H,Random,95%
	n/N	n/N	Cl		Cl
Doi 2014	2/119	9/119	+ · · · · · · · · · · · · · · · · · · ·	0.4 %	0.22 [ 0.05, 1.01 ]
EPIC-1 2008	1/183	0/180		0.1 %	2.95 [ 0.12, 71.97 ]
EPIC-2 2008	0/189	1/190	· · · · · · · · · · · · · · · · · · ·	0.1 %	0.34 [ 0.01, 8.17 ]
FAAT - Leaf 2005	13/200	12/202		1.5 %	1.09 [ 0.51, 2.34 ]
HARP- Sacks 1995	0/41	1/39		0.1 %	0.32 [ 0.01, 7.57 ]
Kumar 2013	1/39	1/39	·	0.1 %	1.00 [ 0.06, 15.43 ]
McIIImurray 1987	10/25	12/24		2.2 %	0.80 [ 0.43, 1.49 ]
MRC 1968	28/199	31/194		3.9 %	0.88 [ 0.55,  .4  ]
Raitt 2005	4/100	10/100		0.7 %	0.40 [ 0.13, 1.23 ]
Rose 1965	5/28	3/26		0.5 %	1.55 [ 0.41, 5.84 ]
Vijayakumar 2014	0/100	2/100	•	0.1 %	0.20 [ 0.01, 4.11 ]
Subtotal (95% CI)	3925	3896	•	32.1 %	0.92 [ 0.78, 1.08 ]
Total events: 247 (Higher PUF/	A), 273 (Lower PUFA)				
Heterogeneity: $Tau^2 = 0.0$ ; Chi	<sup>2</sup> =   .8 , df =  4 (P =	0.62); l <sup>2</sup> =0.0%			
Test for overall effect: $Z = 1.06$	6 (P = 0.29)				
Total (95% CI)	9912	9378	•	100.0 %	0.98 [ 0.89, 1.07 ]
Total events: 715 (Higher PUF)	A), 728 (Lower PUFA)				
Heterogeneity: $Tau^2 = 0.0$ ; Chi	<sup>2</sup> = 17.59, df = 23 (P =	0.78); l <sup>2</sup> =0.0%			
Test for overall effect: $Z = 0.43$	8 (P = 0.67)				
Test for subgroup differences: (	$Chi^2 = 1.38, df = 2 (P =$	0.50), l <sup>2</sup> =0.0%			

0.1 0.2 0.5 1 2 5 10

Favours higher PUFA Favours lower PUFA

# Analysis I.8. Comparison I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes, Outcome 8 All-cause mortality - subgroup by replacement.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes

Outcome: 8 All-cause mortality - subgroup by replacement

Study or subgroup	Higher PUFA	Lower PUFA	Risk Ratio M-	Weight	Risk Ratic M-
	n/N	n/N	H,Random,95% Cl		H,Random, C
PUFA replaced SFA					
DART fat 1989	/ 0 8	113/1015	+	26.4 %	0.98 [ 0.76, 1.25
MRC 1968	28/199	31/194		7.6 %	0.88 [ 0.55, 1.41
NDHS Faribault 1968	4/167	0/57		0.2 %	3.11 [ 0.17, 56.84
Sydney Diet-Heart 1978	38/221	27/237		8.1 %	1.51 [ 0.95, 2.39
Veterans Admin 1969	174/424	177/422	-	57.5 %	0.98 [ 0.83, 1.15
Vijayakumar 2014	0/100	2/100	• · · · · · · · · · · · · · · · · · · ·	0.2 %	0.20 [ 0.01, 4.11
Subtotal (95% CI)	2129	2025	+	100.0 %	1.00 [ 0.88, 1.15
Heterogeneity: Tau <sup>2</sup> = 0.00; Ch est for overall effect: Z = 0.07 PUFA replaced monounsatura	(P = 0.94)				
AlphaOmega - ALA	182/2409	188/2428	<b>—</b>	29.2 %	0.98 [ 0.80, 1.19
Bates 1978	0/58	2/58		0.1 %	0.20 [ 0.01, 4.08
Bates 1989	1/155	0/157		0.1 %	3.04 [ 0.12, 74.02
FAAT - Leaf 2005	13/200	12/202		1.9 %	1.09 [ 0.51, 2.34
HARP- Sacks 1995	0/41	1/39	· · · ·	0.1 %	0.32 [ 0.01, 7.57
NDHS Faribault 1968	4/167	0/57		0.1 %	3.11 [ 0.17, 56.84
PREDIMED 2013	116/2454	118/2543	+	17.9 %	1.02 [ 0.79, 1.31
Raitt 2005	4/100	10/100		0.9 %	0.40 [ 0.13, 1.23
Rose 1965	5/28	3/26		0.6 %	1.55 [ 0.41, 5.84
Sydney Diet-Heart 1978	38/221	27/237		5.3 %	1.51 [ 0.95, 2.39
Veterans Admin 1969	174/424	177/422	-	43.7 %	0.98 [ 0.83, 1.15
ubtotal (95% CI)	6257	6269	•	100.0 %	1.00 [ 0.90, 1.12
otal events: 537 (Higher PUFA leterogeneity: Tau <sup>2</sup> = 0.0; Chi <sup>2</sup>	= 8.91, df = 10 (P = 0	0.54); I <sup>2</sup> =0.0%			
est for overall effect: $Z = 0.08$	(P = 0.93)				
			0.1 0.2 0.5 1 2 5 10		

<sup>(</sup>Continued . . . )

Study or subgroup	Higher PUFA n/N	Lower PUFA n/N	Risk Ratio M- H,Random,95% Cl	Weight	( Continued) Risk Ratio H,Random,95 Cl
3 PUFA replaced carbohydrate		1013	G		G
Black 1994	2/67	1/66		5.1 %	1.97 [ 0.18, 21.21 ]
DIPP-Tokudome 2015	2/104	3/101		9.3 %	0.65 [ 0.11, 3.79 ]
Ley 2004	2/70	1/66		5.1 %	1.89 [ 0.18, 20.31 ]
Rose 1965	5/28	3/26		16.4 %	1.55 [ 0.41, 5.84 ]
WINS 2006	19/1462	15/975	— <b>—</b> —	64.1 %	0.84 [ 0.43, 1.65 ]
Subtotal (95% CI)	1731	1234	-	100.0 %	0.99 [ 0.58, 1.70 ]
Test for overall effect: Z = 0.02 4 PUFA replaced protein Ley 2004	3 (P = 0.97) 2/70	1/66		3.8 %	1.89 [ 0.18, 20.31 ]
MRC 1968	28/199	31/194		96.2 %	0.88 [ 0.55, 1.41 ]
Subtotal (95% CI)	269	260		100.0 %	0.91 [ 0.57, 1.44 ]
Heterogeneity: Tau <sup>2</sup> = 0.0; Ch Test for overall effect: Z = 0.42 5 PUFA replaced unclear Brox 2001		54); I <sup>2</sup> =0.0%	· · · · · · · · · · · · · · · · · · ·	2.9 %	0.17 [ 0.01, 4.05 ]
Doi 2014	2/119	9/119	<b>←</b>	12.8 %	0.22 [ 0.05, 1.01 ]
EPIC-1 2008	1/183	0/180		2.9 %	2.95 [ 0.12, 71.97 ]
EPIC-2 2008	0/189	1/190	• • • · · · · · · · · · · · · · · · · ·	2.9 %	0.34 [ 0.01, 8.17 ]
Kumar 2013	1/39	1/39		3.9 %	1.00 [ 0.06, 15.43 ]
McIIImurray 1987	10/25	12/24		74.7 %	0.80 [ 0.43, 1.49 ]
Subtotal (95% CI)	635	592	-	100.0 %	0.66 [ 0.39, 1.14 ]
Total events: 14 (Higher PUFA Heterogeneity: Tau <sup>2</sup> = 0.0; Ch Test for overall effect: Z = 1.49 Test for subgroup differences: (	$f^2 = 4.43$ , df = 5 (P = 0. P (P = 0.14)	,			

Favours higher PUFA Favours lower PUFA

# Analysis I.9. Comparison I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes, Outcome 9 All-cause mortality - subgroup by sex.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes

Outcome: 9 All-cause mortality - subgroup by sex

Study or subgroup	Higher PUFA	Lower PUFA	Risk Ratio M-	Weight	Risk Ratio M-
	n/N	n/N	H,Random,95% Cl		H,Random,9: Cl
l > 70% men					
AlphaOmega - ALA	182/2409	188/2428	+	22.3 %	0.98 [ 0.80, 1.19 ]
DART fat 1989	/ 0 8	113/1015	+	14.0 %	0.98 [ 0.76, 1.25 ]
DIPP-Tokudome 2015	2/104	3/101		0.3 %	0.65 [ 0.11, 3.79 ]
Doi 2014	2/119	9/119	<b></b>	0.4 %	0.22 [ 0.05, 1.01 ]
FAAT - Leaf 2005	3/200	12/202		1.5 %	1.09 [ 0.51, 2.34 ]
HARP- Sacks 1995	0/41	1/39	• • • • • • • • • • • • • • • • • • •	0.1 %	0.32 [ 0.01, 7.57 ]
Ley 2004	2/70	1/66		0.2 %	1.89 [ 0.18, 20.31 ]
MRC 1968	28/199	31/194		3.9 %	0.88 [ 0.55, 1.41 ]
NDHS Faribault 1968	4/167	0/57		0.1 %	3.11 [ 0.17, 56.84 ]
Raitt 2005	4/100	10/100		0.7 %	0.40 [ 0.13, 1.23 ]
Sydney Diet-Heart 1978	38/221	27/237		4.1 %	1.51 [ 0.95, 2.39 ]
Veterans Admin 1969	174/424	177/422	+	33.5 %	0.98 [ 0.83, 1.15 ]
Vijayakumar 2014	0/100	2/100	·	0.1 %	0.20 [ 0.01, 4.11 ]
Subtotal (95% CI)	5172	5080	+	81.0 %	0.98 [ 0.88, 1.10 ]
Total events: 560 (Higher PUFA Heterogeneity: Tau <sup>2</sup> = 0.00; Ch Test for overall effect: Z = 0.34 2 > 70% women WINS 2006	i <sup>2</sup> = 12.50, df = 12 (P	= 0.41); I <sup>2</sup> =4% 15/975		1.9 %	0.84 [ 0.43, 1.65 ]
Subtotal (95% CI)	1462	975	-	1.9 %	0.84 [ 0.43, 1.65 ]
Total events: 19 (Higher PUFA), Heterogeneity: not applicable Test for overall effect: Z = 0.49	, 15 (Lower PUFA)				
3 men % women Bates 1978	0/58	2/58	<u>د ، </u>	0.1 %	0.20 [ 0.01, 4.08 ]
Bates 1989	1/155	0/157		0.1 %	3.04 [ 0.12, 74.02 ]
			0.1 0.2 0.5 1 2 5 10 Favours higher PUFA Favours lower PU	FA	(Continued

(Continued . . . )

( Continued Risk Ratio M-	Weight	Risk Ratio M-	Lower PUFA	Higher PUFA	Study or subgroup
H,Random,95 Cl		H,Random,95% Cl	n/N	n/N	
1.97 [ 0.18, 21.21 ]	0.2 %		1/66	2/67	Black 1994
0.17 [ 0.01, 4.05 ]	0.1 %	• • • • • • • • • • • • • • • • • • • •	1/40	0/80	Brox 2001
2.95 [ 0.12, 71.97 ]	0.1 %		0/180	1/183	EPIC-1 2008
0.34 [ 0.01, 8.17 ]	0.1 %	• • •	1/190	0/189	EPIC-2 2008
1.00 [ 0.06, 15.43 ]	0.1 %	·	1/39	1/39	Kumar 2013
1.02 [ 0.79, 1.31 ]	13.7 %	+	118/2543	116/2454	PREDIMED 2013
1.01 [ 0.79, 1.29 ]	14.4 %	+	3273	3225	Subtotal (95% CI)
				A), 124 (Lower PUFA)	Total events: 121 (Higher PUF)
			78); I <sup>2</sup> =0.0%	<sup>2</sup> = 3.98, df = 7 (P = 0.7	Heterogeneity: $Tau^2 = 0.0$ ; Chi
				8 (P = 0.93)	Test for overall effect: $Z = 0.08$
					4 sex not reported
0.80 [ 0.43, 1.49 ]	2.2 %		12/24	10/25	McIIImurray 1987
1.55 [ 0.41, 5.84 ]	0.5 %		3/26	5/28	Rose 1965
0.90 [ 0.51, 1.59 ]	2.7 %	-	50	53	Subtotal (95% CI)
				), 15 (Lower PUFA)	Total events: 15 (Higher PUFA
			37); I <sup>2</sup> =0.0%	$^{2} = 0.8$  , df =   (P = 0.3)	Heterogeneity: $Tau^2 = 0.0$ ; Chi
				6 (P = 0.72)	Test for overall effect: $Z = 0.36$
0.98 [ 0.89, 1.07 ]	100.0 %	•	9378	9912	Total (95% CI)
				A), 728 (Lower PUFA)	Total events: 715 (Higher PUF)
			0.78); l <sup>2</sup> =0.0%	<sup>2</sup> = 17.59, df = 23 (P =	Heterogeneity: $Tau^2 = 0.0$ ; Chi
				8 (P = 0.67)	Test for overall effect: $Z = 0.43$
			0.95), l <sup>2</sup> =0.0%	Chi <sup>2</sup> = 0.33, df = 3 (P =	Test for subgroup differences: (

0.1 0.2 0.5 1 2 5 10

Favours higher PUFA Favours lower PUFA

# Analysis 1.10. Comparison I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes, Outcome 10 All-cause mortality - subgroup by age.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes

Outcome: 10 All-cause mortality - subgroup by age

Study or subgroup	Higher PUFA	Lower PUFA	Risk Ratio M-	Weight	Risk Ratio M-
	n/N n/N	n/N	H,Random,95% Cl		H,Random,955 Cl
I Mean age < 50 years					
Bates 1978	0/58	2/58	• · · · · · · · · · · · · · · · · · · ·	0.1 %	0.20 [ 0.01, 4.08 ]
Bates 1989	1/155	0/157		0.1 %	3.04 [ 0.12, 74.02 ]
EPIC-1 2008	1/183	0/180		0.1 %	2.95 [ 0.12, 71.97 ]
EPIC-2 2008	0/189	1/190	• • •	0.1 %	0.34 [ 0.01, 8.17 ]
NDHS Faribault 1968	4/167	0/57		0.1 %	3.11 [ 0.17, 56.84 ]
Sydney Diet-Heart 1978	38/221	27/237	<b></b>	4.1 %	1.51 [ 0.95, 2.39 ]
Subtotal (95% CI)	973	879	•	4.5 %	1.47 [ 0.95, 2.27 ]
2 Mean age 50 to < 65 years					
Test for overall effect: $Z = 1.73$ (I	P = 0.084)				
Black 1994	2/67	1/66		0.2 %	1.97 [ 0.18, 21.21 ]
Brox 2001	0/80	1/40	<b>← .</b>	0.1 %	0.17 [ 0.01, 4.05 ]
DART fat 1989	111/1018	113/1015		14.0 %	0.98 [ 0.76, 1.25 ]
DIPP-Tokudome 2015	2/104	3/101		0.3 %	0.65 [ 0.11, 3.79 ]
HARP- Sacks 1995	0/41	1/39	· · · ·	0.1 %	0.32 [ 0.01, 7.57 ]
Ley 2004	2/70	1/66		0.2 %	1.89 [ 0.18, 20.31 ]
McIIImurray 1987	10/25	12/24	<u> </u>	2.2 %	0.80 [ 0.43, 1.49 ]
MRC 1968	28/199	31/194	<b>.</b>	3.9 %	0.88 [ 0.55, 1.41 ]
	4/100	10/100		0.7 %	0.40 [ 0.13, 1.23 ]
Raitt 2005	1/100				
Raitt 2005 Rose 1965	5/28	3/26		0.5 %	1.55 [ 0.41, 5.84 ]
		3/26 2/100	· · · · · · · · · · · · · · · · · · ·	0.5 %	I.55 [ 0.41, 5.84 ] 0.20 [ 0.01, 4.11 ]
Rose 1965	5/28				

0.1 0.2 0.5 1 2 5 10 Favours higher PUFA Favours lower PUFA

(Continued ...)

Risk Ratio M- H,Random,95%	Lower PUFA	Higher PUFA	Study or subgroup
Ci	10/1 N		Test for overall effect: $Z = 1.00$
		× /	3 Mean age 65+ years
+	188/2428	182/2409	AlphaOmega - ALA
<b>←</b> i	9/119	2/119	Doi 2014
	12/202	13/200	FAAT - Leaf 2005
•	1/39	1/39	Kumar 2013
+	118/2543	116/2454	PREDIMED 2013
+	177/422	174/424	Veterans Admin 1969
•	5753	5645	Subtotal (95% CI)
	57); I <sup>2</sup> =0.0%	$hi^2 = 3.89, df = 5 (P = 0.5)$	Total events: 488 (Higher PUFA Heterogeneity: Tau <sup>2</sup> = 0.0; Chi <sup>2</sup> Test for overall effect: Z = 0.36
•	9378	9912	Total (95% CI)
		A), 728 (Lower PUFA)	Total events: 715 (Higher PUFA
	0.78); l <sup>2</sup> =0.0%	ni² = 17.59, df = 23 (P =	Heterogeneity: Tau <sup>2</sup> = 0.0; Chi <sup>2</sup>
		3 (P = 0.67)	Test for overall effect: $Z = 0.43$
	0.14), 12 =49%	$Chi^2 = 3.94, df = 2 (P =$	Test for subgroup differences: C
M-	/N 228 19 02 339 43 222 <b>53</b> <b>78</b>	n 188/24 9/1 12/2 1/ 118/25 177/4 <b>575</b> 57); I <sup>2</sup> =0.0% <b>937</b> 0.78); I <sup>2</sup> =0.0%	n/N         n.           (P = 0.32)         182/2409         188/24           2/119         9/1           13/200         12/22           1/39         1/           116/2454         118/25           174/424         177/4           5645         575           x), 505 (Lower PUFA)         2           2         9912         937           x), 728 (Lower PUFA)         2         17.59, df = 23 (P = 0.78); l <sup>2</sup> = 0.0%

0.1 0.2 0.5 1 2 5 10

Favours higher PUFA Favours lower PUFA

# Analysis I.II. Comparison I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes, Outcome II All-cause mortality - subgroup by statin use.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes

Outcome: II All-cause mortality - subgroup by statin use

n/N 0/58 1/155 2/67 0/80 2/104 1/183 0/189 0/41 10/25 8/199	n/N 2/58 0/157 1/66 1/40 113/1015 3/101 0/180 1/190 1/39 12/24 31/194	M- H,Random,95% Cl	0.1 % 0.1 % 0.2 % 0.1 % 14.0 % 0.3 % 0.1 % 0.1 % 0.1 % 0.1 %	M- H,Random,92 0.20 [ 0.01, 4.08 ] 3.04 [ 0.12, 74.02 ] 1.97 [ 0.18, 21.21 ] 0.17 [ 0.01, 4.05 ] 0.98 [ 0.76, 1.25 ] 0.65 [ 0.11, 3.79 ] 2.95 [ 0.12, 71.97 ] 0.34 [ 0.01, 8.17 ] 0.32 [ 0.01, 7.57 ] 0.80 [ 0.43, 1.49 ]
1/155 2/67 0/80 1/1018 2/104 1/183 0/189 0/41 10/25 8/199	0/157 1/66 1/40 113/1015 3/101 0/180 1/190 1/39 12/24		0.1 % 0.2 % 0.1 % 14.0 % 0.3 % 0.1 % 0.1 %	3.04 [ 0.12, 74.02 ] 1.97 [ 0.18, 21.21 ] 0.17 [ 0.01, 4.05 ] 0.98 [ 0.76, 1.25 ] 0.65 [ 0.11, 3.79 ] 2.95 [ 0.12, 71.97 ] 0.34 [ 0.01, 8.17 ] 0.32 [ 0.01, 7.57 ]
1/155 2/67 0/80 1/1018 2/104 1/183 0/189 0/41 10/25 8/199	0/157 1/66 1/40 113/1015 3/101 0/180 1/190 1/39 12/24		0.1 % 0.2 % 0.1 % 14.0 % 0.3 % 0.1 % 0.1 %	3.04 [ 0.12, 74.02 ] 1.97 [ 0.18, 21.21 ] 0.17 [ 0.01, 4.05 ] 0.98 [ 0.76, 1.25 ] 0.65 [ 0.11, 3.79 ] 2.95 [ 0.12, 71.97 ] 0.34 [ 0.01, 8.17 ] 0.32 [ 0.01, 7.57 ]
2/67 0/80 11018 2/104 1/183 0/189 0/41 10/25 8/199	1/66 1/40 113/1015 3/101 0/180 1/190 1/39 12/24		0.2 % 0.1 % 14.0 % 0.3 % 0.1 % 0.1 %	1.97 [ 0.18, 21.21 ] 0.17 [ 0.01, 4.05 ] 0.98 [ 0.76, 1.25 ] 0.65 [ 0.11, 3.79 ] 2.95 [ 0.12, 71.97 ] 0.34 [ 0.01, 8.17 ] 0.32 [ 0.01, 7.57 ]
0/80 2/1018 2/104 1/183 0/189 0/41 10/25 8/199	1/40 113/1015 3/101 0/180 1/190 1/39 12/24		0.1 % 14.0 % 0.3 % 0.1 % 0.1 %	0.17 [ 0.01, 4.05 ] 0.98 [ 0.76, 1.25 ] 0.65 [ 0.11, 3.79 ] 2.95 [ 0.12, 71.97 ] 0.34 [ 0.01, 8.17 ] 0.32 [ 0.01, 7.57 ]
2/1018 2/104 1/183 0/189 0/41 10/25 8/199	113/1015 3/101 0/180 1/190 1/39 12/24		14.0 % 0.3 % 0.1 % 0.1 %	0.98 [ 0.76, 1.25 ] 0.65 [ 0.11, 3.79 ] 2.95 [ 0.12, 71.97 ] 0.34 [ 0.01, 8.17 ] 0.32 [ 0.01, 7.57 ]
2/104 1/183 0/189 0/41 10/25 8/199	3/101 0/180 1/190 1/39 12/24		0.3 % 0.1 % 0.1 %	0.65 [ 0.11, 3.79 ] 2.95 [ 0.12, 71.97 ] 0.34 [ 0.01, 8.17 ] 0.32 [ 0.01, 7.57 ]
1/183 0/189 0/41 10/25 8/199	0/180 1/190 1/39 12/24		0.1 % 0.1 % 0.1 %	2.95 [ 0.12, 71.97 ] 0.34 [ 0.01, 8.17 ] 0.32 [ 0.01, 7.57 ]
0/189 0/41 10/25 8/199	1/190 1/39 12/24	· · · · · · · · · · · · · · · · · · ·	0.1 % 0.1 %	0.34 [ 0.01, 8.17 ]
0/41 10/25 3/199	1/39	• ••	0.1 %	0.32 [ 0.01, 7.57 ]
10/25 3/199	12/24	·		
3/199			2.2 %	0.80 [ 0.43, 1.49 ]
	31/194			
			3.9 %	0.88 [ 0.55,  .4  ]
4/167	0/57		0.1 %	3.11 [ 0.17, 56.84 ]
2454	118/2543	+	3.7 %	1.02 [ 0.79, 1.31 ]
4/100	10/100		0.7 %	0.40 [ 0.13, 1.23 ]
5/28	3/26		0.5 %	1.55 [ 0.41, 5.84 ]
3/221	27/237		4.1 %	1.51 [ 0.95, 2.39 ]
1/424	177/422	+	33.5 %	0.98 [ 0.83, 1.15 ]
1462	15/975	<u> </u>	1.9 %	0.84 [ 0.43, 1.65 ]
975	6424	•	75.4 %	0.99 [ 0.89, 1.10 ]
r PUFA) = 17 (P = 0	0.77); l <sup>2</sup> =0.0%			
2409	188/2428	+	22.3 %	0.98 [ 0.80, 1.19 ]
2/119	9/119		0.4 %	0.22 [ 0.05, 1.01 ]
	5/28 3/221 4/424 1462 <b>975</b> - PUFA) = 17 (P = 0 2409	$5/28$ $3/26$ $3/221$ $27/237$ $4/424$ $177/422$ $1/462$ $15/975$ <b>975 6424</b> r PUFA)       =         = $17 (P = 0.77); I^2 = 0.0\%$ 2409 $188/2428$ $2/119$ $9/119$	5/28 3/26 3/22   27/237 4/424   177/422 1462   5/975 <b>975 6424</b> r PUFA) = 17 (P = 0.77); $ ^2 = 0.0\%$ 2409   188/2428 2/1   9 9/1   9 0.1 0.2 0.5   2 5 10	5/28   3/26   0.5%   3/22   0.7/237   4.1%

(Continued . . . )

( Continued) Risk Ratio M- H,Random,95 Cl	Weight	Risk Ratio M- H,Random,95% Cl	Lower PUFA n/N	Higher PUFA n/N	Study or subgroup
1.00 [ 0.06, 15.43 ]	0.1 %	• • • •	1/39	1/39	Kumar 2013
0.20 [ 0.01, 4.11 ]	0.1 %	<b></b>	2/100	0/100	Vijayakumar 2014
0.62 [ 0.26, 1.51 ]	22.9 %		2686	2667	Subtotal (95% CI)
				), 200 (Lower PUFA)	Total events: 185 (Higher PUFA
			$20) \cdot  ^2 = 36\%$	, , ,	Heterogeneity: Tau <sup>2</sup> = 0.32; Cł
			20),1 30/0		Test for overall effect: $Z = 1.04$
				. ,	3 Percentage on statins unclear
1.09 [ 0.51, 2.34 ]	1.5 %	<del></del>	12/202	13/200	FAAT - Leaf 2005
1.89 [ 0.18, 20.31 ]	0.2 %		1/66	2/70	Ley 2004
1.15 [ 0.56, 2.37 ]	1.6 %	-	268	270	Subtotal (95% CI)
				, 13 (Lower PUFA)	Total events: 15 (Higher PUFA)
			7); I <sup>2</sup> =0.0%	<sup>2</sup> = 0.18, df = 1 (P = 0.6	Heterogeneity: $Tau^2 = 0.0$ ; Chi
				(P = 0.70)	Test for overall effect: Z = 0.38
0.98 [ 0.89, 1.07 ]	100.0 %	•	9378	9912	Total (95% CI)
				), 728 (Lower PUFA)	Total events: 715 (Higher PUFA
			0.78); I <sup>2</sup> =0.0%	<sup>2</sup> = 17.59, df = 23 (P = 0	Heterogeneity: Tau <sup>2</sup> = 0.0; Chi <sup>:</sup>
				(P = 0.67)	Test for overall effect: Z = 0.43
			0.55), l <sup>2</sup> =0.0%	Chi <sup>2</sup> = 1.20, df = 2 (P =	Test for subgroup differences: (

0.1 0.2 0.5 1 2 5 10 Favours higher PUFA Favours lower PUFA

# Analysis 1.12. Comparison I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes, Outcome 12 All-cause mortality - subgroup by intervention type.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes

Outcome: 12 All-cause mortality - subgroup by intervention type

Study or subgroup	Higher PUFA	Lower PUFA	Risk Ratio M-	Weight	Risk Ratio M-
	n/N	n/N	H,Random,95% Cl		H,Random,S Cl
Dietary advice					
Black 1994	2/67	1/66		0.2 %	1.97 [ 0.18, 21.21 ]
DART fat 1989	/ 0 8	113/1015	+	14.0 %	0.98 [ 0.76, 1.25 ]
Ley 2004	2/70	1/66		0.2 %	1.89 [ 0.18, 20.31 ]
WINS 2006	19/1462	15/975	<b>-</b> _	1.9 %	0.84 [ 0.43, 1.65 ]
Subtotal (95% CI)	2617	2122	+	16.2 %	0.97 [ 0.77, 1.23 ]
Fotal events: 134 (Higher PUFA Heterogeneity: Tau <sup>2</sup> = 0.0; Chi <sup>2</sup> Fest for overall effect: $Z = 0.22$ 2 Supplemental foods % diet pr	= 0.81, df = 3 (P = 0.6) (P = 0.83) ovided	<i>y</i>		22.2 %	
AlphaOmega - ALA	182/2409	188/2428	Ī	22.3 %	0.98 [ 0.80, 1.19 ]
NDHS Faribault 1968	4/167	0/57		0.1 %	3.11 [ 0.17, 56.84 ]
PREDIMED 2013	116/2454	118/2543	+	13.7 %	1.02 [ 0.79, 1.31 ]
Veterans Admin 1969	174/424	177/422	+	33.5 %	0.98 [ 0.83, 1.15
Vijayakumar 2014	0/100	2/100	<u>←</u>	0.1 %	0.20 [ 0.01, 4.11
Subtotal (95% CI)	5554	5550	•	<b>69.</b> 7 %	0.98 [ 0.88, 1.10 ]
Fotal events: 476 (Higher PUFA Heterogeneity: Tau <sup>2</sup> = 0.0; Chi <sup>2</sup> Fest for overall effect: Z = 0.27 8 Supplements (capsules % unu:	P = 1.75, df = 4 (P = 0.79) (P = 0.79)	78); l <sup>2</sup> =0.0%			
Bates 1978	0/58	2/58	• • • • • • • • • • • • • • • • • • •	0.1 %	0.20 [ 0.01, 4.08 ]
Bates 1989	1/155	0/157		0.1 %	3.04 [ 0.12, 74.02 ]
Brox 200 I	0/80	1/40	· · · · · · · · · · · · · · · · · · ·	0.1 %	0.17 [ 0.01, 4.05
Doi 2014	2/119	9/119	<b>←</b> · · · · · · · · · · · · · · · · · · ·	0.4 %	0.22 [ 0.05, 1.01
EPIC-1 2008	1/183	0/180		0.1 %	2.95 [ 0.12, 71.97 ]
EPIC-2 2008	0/189	1/190	•	0.1 %	0.34 [ 0.01, 8.17 ]
	13/200	12/202		1.5 %	1.09 [ 0.51, 2.34

(Continued . . . )

( Continuec Risk Ratio M-	Weight	Risk Ratio M-	Lower PUFA	Higher PUFA	Study or subgroup	
H,Random,9 Cl		H,Random,95% Cl	n/N	n/N		
0.32 [ 0.01, 7.57 ]	0.1 %	• • • • • • • • • • • • • • • • • • •	1/39	0/41	HARP- Sacks 1995	
1.00 [ 0.06, 15.43 ]	0.1 %	•	1/39	1/39	Kumar 2013	
0.80 [ 0.43, 1.49 ]	2.2 %		12/24	10/25	McIIImurray 1987	
0.40 [ 0.13, 1.23 ]	0.7 %		10/100	4/100	Raitt 2005	
1.55 [ 0.41, 5.84 ]	0.5 %		3/26	5/28	Rose 1965	
0.76 [ 0.52, 1.11 ]	5.8 %	•	1174	1217	Subtotal (95% CI)	
				52 (Lower PUFA)	Total events: 37 (Higher PUFA),	
			7); I <sup>2</sup> =0.0%	= 9.53, df = 11 (P = 0.	Heterogeneity: $Tau^2 = 0.0$ ; Chi <sup>2</sup>	
			,	P = 0.15)	Test for overall effect: Z = 1.43 (	
				,	4 Any combination	
0.65 [ 0.11, 3.79 ]	0.3 %		3/101	2/104	DIPP-Tokudome 2015	
0.88 [ 0.55, 1.41 ]	3.9 %		31/194	28/199	MRC 1968	
1.51 [ 0.95, 2.39 ]	4.1 %	<u> </u>	27/237	38/221	Sydney Diet-Heart 1978	
1.12 [ 0.72, 1.74 ]	8.2 %	*	532	524	Subtotal (95% CI)	
				61 (Lower PUFA)	Total events: 68 (Higher PUFA),	
			2); I <sup>2</sup> =33%	= 2.99, df = 2 (P = 0.	Heterogeneity: Tau <sup>2</sup> = 0.05; Chi <sup>2</sup>	
				P = 0.62)	Test for overall effect: Z = 0.50 (	
0.98 [ 0.89, 1.07 ]	100.0 %	•	9378	9912	Total (95% CI)	
				728 (Lower PUFA)	Total events: 715 (Higher PUFA)	
			78); l <sup>2</sup> =0.0%	= 17.59, df = 23 (P = 0	Heterogeneity: Tau <sup>2</sup> = 0.0; Chi <sup>2</sup>	
				P = 0.67)	Test for overall effect: $Z = 0.43$ (	
			.55), l <sup>2</sup> =0.0%	$i^2 = 2.11$ , df = 3 (P =	Test for subgroup differences: Ch	

0.1 0.2 0.5 1 2 5 10 Favours higher PUFA Favours lower PUFA

#### Analysis 1.13. Comparison I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes, Outcome 13 CORONARY HEART DISEASE (CHD) EVENTS: myocardial infarction (fatal or nonfatal) or angina.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes

Outcome: 13 CORONARY HEART DISEASE (CHD) EVENTS: myocardial infarction (fatal or non-fatal) or angina

Study or subgroup	Higher PUFA	Lower PUFA	Risk Ratio M- H,Random,95%	Weight	Risk Ratio M- H,Random,955
	n/N	n/N	Cl		Cl
AlphaOmega - ALA	121/2409	133/2428	1	17.5 %	0.92 [ 0.72, 1.17 ]
Brox 2001	0/80	1/40		0.4 %	0.17 [ 0.01, 4.05 ]
DART fat 1989	339/1018	364/1015	-	21.8 %	0.93 [ 0.82, 1.05 ]
Doi 2014 (1)	1/119	0/119		0.4 %	3.00 [ 0.12, 72.91 ]
EPOCH 2011 (2)	1/195	0/196		0.4 %	3.02 [ 0.12, 73.57 ]
GLAMT 1993	0/54	1/57		0.4 %	0.35 [ 0.01, 8.45 ]
HARP- Sacks 1995	7/41	7/39		3.6 %	0.95 [ 0.37, 2.46 ]
Houtsmuller 1979	8/5	30/51	-	6.2 %	0.27 [ 0.14, 0.52 ]
MRC 1968	50/199	50/194	+	13.9 %	0.97 [ 0.69, 1.37 ]
Nye 1990 (3)	5/36	11/37	<b>-</b> _	3.6 %	0.47 [ 0.18, 1.21 ]
Proudman 2015 (4)	1/87	0/53		0.4 %	1.84 [ 0.08, 44.38 ]
Raitt 2005 (5)	1/100	3/100		0.7 %	0.33 [ 0.04, 3.15 ]
Rose 1965	12/28	9/26	-	6.2 %	1.24 [ 0.63, 2.44 ]
Sydney Diet-Heart 1978	35/221	23/237	-	9.5 %	1.63 [ 1.00, 2.67 ]
Veterans Admin 1969	60/424	78/422	-	15.0 %	0.77 [ 0.56, 1.04 ]
otal (95% CI)	5062	5014	•	100.0 %	0.87 [ 0.72, 1.06 ]
otal events: 641 (Higher PUFA	), 710 (Lower PUFA)				
leterogeneity: Tau <sup>2</sup> = 0.04; Chi		= 0.03); l <sup>2</sup> =45%			
est for overall effect: $Z = 1.35$	· /				
est for subgroup differences: N	ot applicable				

Favours higher PUFA Favours lower PUFA

(I) Total MI

(2) Total MI

(3) Angina

(4) Total MI

(5) Total MI

#### Analysis 1.14. Comparison I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes, Outcome 14 CHD events - SA.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes

#### Outcome: 14 CHD events - SA

Study or subgroup	Higher PUFA	Lower PUFA	Risk Ratio M-	Weight	Risk Ratic M-
	n/N	n/N	H,Random,95% Cl		H,Random,95 Cl
Low risk of bias for allocation of	concealment				
AlphaOmega - ALA	121/2409	133/2428	•	57.2 %	0.92 [ 0.72, 1.17 ]
Brox 2001 (1)	0/80	1/40		1.9 %	0.17 [ 0.01, 4.05 ]
EPOCH 2011 (2)	1/195	0/196		1.9 %	3.02 [ 0.12, 73.57 ]
Proudman 2015 (3)	1/87	0/53		1.9 %	1.84 [ 0.08, 44.38 ]
Sydney Diet-Heart 1978	35/221	23/237	•	37.2 %	1.63 [ 1.00, 2.67 ]
Subtotal (95% CI)	2992	2954	+	100.0 %	1.14 [ 0.73, 1.78 ]
Total events: 158 (Higher PUFA) Heterogeneity: Tau <sup>2</sup> = 0.07; Chi <sup>2</sup> Test for overall effect: Z = 0.58 ( 2 Low risk of bias for attention	P = 6.05, df = 4 (P = 0	0.20); I <sup>2</sup> =34%			
AlphaOmega - ALA	121/2409	133/2428	-	52.8 %	0.92 [ 0.72, 1.17
Brox 2001 (4)	0/80	1/40		0.3 %	0.17 [ 0.01, 4.05
Doi 2014 (5)	1/119	0/119		0.3 %	3.00 [ 0.12, 72.91
EPOCH 2011 (6)	1/195	0/196		0.3 %	3.02 [ 0.12, 73.57
GLAMT 1993	0/54	1/57		0.3 %	0.35 [ 0.01, 8.45
HARP- Sacks 1995	7/41	7/39		3.3 %	0.95 [ 0.37, 2.46
Nye 1990 (7)	5/36	11/37		3.3 %	0.47 [ 0.18, 1.21
Proudman 2015 (8)	1/87	0/53		0.3 %	1.84 [ 0.08, 44.38
Raitt 2005 (9)	1/100	3/100		0.6 %	0.33 [ 0.04, 3.15
Rose 1965	12/28	9/26	-	6.6 %	1.24 [ 0.63, 2.44
Veterans Admin 1969	60/424	78/422	-	31.9 %	0.77 [ 0.56, 1.04
Subtotal (95% CI)	3573	3517	•	100.0 %	0.86 [ 0.72, 1.02
Total events: 209 (Higher PUFA) Heterogeneity: Tau <sup>2</sup> = 0.0; Chi <sup>2</sup>	= 6.95, df = 10 (P = 0	0.73); I <sup>2</sup> =0.0%			
Test for overall effect: Z = 1.70 ( 3 Low risk of bias for compliance					

(Continued  $\dots$ )

Study or subgroup	Higher PUFA	Lower PUFA	Risk Ratio M-	Weight	( Continued Risk Ratio M-
	n/N	n/N	H,Random,95% Cl		H,Random,9 Cl
DART fat 1989	339/1018	364/1015	•	24.3 %	0.93 [ 0.82, 1.05 ]
Houtsmuller 1979	8/5	30/51	-	10.8 %	0.27 [ 0.14, 0.52 ]
MRC 1968	50/199	50/194	+	18.9 %	0.97 [ 0.69, 1.37 ]
Rose 1965	12/28	9/26		10.7 %	1.24 [ 0.63, 2.44 ]
Sydney Diet-Heart 1978	35/221	23/237	-	14.7 %	1.63 [ 1.00, 2.67 ]
Veterans Admin 1969	60/424	78/422	-	19.8 %	0.77 [ 0.56, 1.04 ]
Subtotal (95% CI)	2021	1985	•	100.0 %	0.87 [ 0.65, 1.17 ]
Heterogeneity: Tau <sup>2</sup> = 0.09; Chi Test for overall effect: Z = 0.92 ( 4 Low summary risk of bias AlphaOmega - ALA		33/2428	_	59.1 %	0.92 [ 0.72, 1.17 ]
EPOCH 2011 (11)	1/195	0/196		1.8 %	3.02 [ 0.12, 73.57 ]
				1.0.0/	1.84 [ 0.08, 44.38 ]
Proudman 2015 (12)	1/87	0/53		1.8 %	
Proudman 2015 (12) Sydney Diet-Heart 1978	1/87 35/221	0/53 23/237		37.3 %	.63 [  .00, 2.67 ]
Sydney Diet-Heart 1978 Subtotal (95% CI) Total events: 158 (Higher PUFA) Heterogeneity: Tau <sup>2</sup> = 0.07; Chi	35/22   <b>2912</b> ), 156 (Lower PUFA) <sup>2</sup> = 4.81, df = 3 (P = 0	23/237 <b>2914</b>	*		
	35/22   <b>2912</b> ), 156 (Lower PUFA) <sup>2</sup> = 4.81, df = 3 (P = 0	23/237 <b>2914</b>	•	37.3 %	1.63 [ 1.00, 2.67 ] 1.18 [ 0.76, 1.81 ]
Sydney Diet-Heart 1978 <b>Subtotal (95% CI)</b> Total events: 158 (Higher PUFA) Heterogeneity: Tau <sup>2</sup> = 0.07; Chi Test for overall effect: Z = 0.73 (	35/221 <b>2912</b> ), 156 (Lower PUFA) <sup>2</sup> = 4.81, df = 3 (P = 0 (P = 0.46) 121/2409	23/237 <b>2914</b> .19); I <sup>2</sup> =38% 133/2428	•	37.3 % <b>100.0 %</b> 17.5 %	<b>1.18 [ 0.76, 1.81 ]</b> 0.92 [ 0.72, 1.17 ]
Sydney Diet-Heart 1978 <b>Subtotal (95% CI)</b> Fotal events: 158 (Higher PUFA) Heterogeneity: Tau <sup>2</sup> = 0.07; Chi Fest for overall effect: Z = 0.73 Finals registry or pre-2010	35/221 <b>2912</b> ), 156 (Lower PUFA) <sup>2</sup> = 4.81, df = 3 (P = 0 (P = 0.46)	23/237 <b>2914</b> .19); I <sup>2</sup> =38%	•	37.3 % <b>100.0 %</b>	<b>1.18 [ 0.76, 1.81 ]</b> 0.92 [ 0.72, 1.17 ] 0.17 [ 0.01, 4.05 ]
Sydney Diet-Heart 1978 <b>Subtotal (95% CI)</b> Total events: 158 (Higher PUFA) Heterogeneity: Tau <sup>2</sup> = 0.07; Chi Fest for overall effect: Z = 0.73 Trials registry or pre-2010 AlphaOmega - ALA	35/221 <b>2912</b> ), 156 (Lower PUFA) <sup>2</sup> = 4.81, df = 3 (P = 0 (P = 0.46) 121/2409	23/237 <b>2914</b> .19); I <sup>2</sup> =38% 133/2428	•	37.3 % <b>100.0 %</b> 17.5 %	
Sydney Diet-Heart 1978 <b>Subtotal (95% CI)</b> Total events: 158 (Higher PUFA) Heterogeneity: Tau <sup>2</sup> = 0.07; Chi Test for overall effect: Z = 0.73 f 5 Trials registry or pre-2010 AlphaOmega - ALA Brox 2001 (13)	35/221 <b>2912</b> ), 156 (Lower PUFA) <sup>2</sup> = 4.81, df = 3 (P = 0 (P = 0.46) 121/2409 0/80	23/237 <b>2914</b> .19); I <sup>2</sup> =38% I 33/2428 I/40		37.3 % <b>100.0 %</b> 17.5 % 0.4 %	<b>1.18 [ 0.76, 1.81 ]</b> 0.92 [ 0.72, 1.17 ] 0.17 [ 0.01, 4.05 ] 0.93 [ 0.82, 1.05 ]
Sydney Diet-Heart 1978 <b>Subtotal (95% CI)</b> Total events: 158 (Higher PUFA) Heterogeneity: Tau <sup>2</sup> = 0.07; Chi Test for overall effect: Z = 0.73 f Trials registry or pre-2010 AlphaOmega - ALA Brox 2001 (13) DART fat 1989	35/221 <b>2912</b> ), 156 (Lower PUFA) <sup>2</sup> = 4.81, df = 3 (P = 0 (P = 0.46) 121/2409 0/80 339/1018	23/237 <b>2914</b> .(19); I <sup>2</sup> =38% I 33/2428 I/40 364/1015		37.3 % <b>100.0 %</b> 17.5 % 0.4 % 21.8 %	<b>1.18 [ 0.76, 1.81 ]</b> 0.92 [ 0.72, 1.17 ] 0.17 [ 0.01, 4.05 ]
Sydney Diet-Heart 1978 <b>Subtotal (95% CI)</b> Total events: 158 (Higher PUFA) Heterogeneity: Tau <sup>2</sup> = 0.07; Chi Test for overall effect: Z = 0.73 of 5 Trials registry or pre-2010 AlphaOmega - ALA Brox 2001 (13) DART fat 1989 Doi 2014 (14)	35/221 <b>2912</b> ), 156 (Lower PUFA) <sup>2</sup> = 4.81, df = 3 (P = 0 (P = 0.46) 121/2409 0/80 339/1018 1/119	23/237 <b>2914</b> .19); I <sup>2</sup> =38% I33/2428 I/40 364/1015 0/119		37.3 % <b>100.0 %</b> 17.5 % 0.4 % 0.4 %	<b>1.18 [ 0.76, 1.81 ]</b> 0.92 [ 0.72, 1.17 ] 0.17 [ 0.01, 4.05 ] 0.93 [ 0.82, 1.05 ] 3.00 [ 0.12, 72.91 ]
Sydney Diet-Heart 1978 <b>Subtotal (95% CI)</b> Fotal events: 158 (Higher PUFA) Heterogeneity: Tau <sup>2</sup> = 0.07; Chi Test for overall effect: Z = 0.73 f 5 Trials registry or pre-2010 AlphaOmega - ALA Brox 2001 (13) DART fat 1989 Doi 2014 (14) EPOCH 2011 (15)	35/221 <b>2912</b> ), 156 (Lower PUFA) <sup>2</sup> = 4.81, df = 3 (P = 0 (P = 0.46) 121/2409 0/80 339/1018 1/119 1/195	23/237 <b>2914</b> .19); I <sup>2</sup> =38% 133/2428 1/40 364/1015 0/119 0/196		37.3 % <b>100.0 %</b> 17.5 % 0.4 % 0.4 % 0.4 %	1.18 [ 0.76, 1.81 ] 0.92 [ 0.72, 1.17 ] 0.17 [ 0.01, 4.05 ] 0.93 [ 0.82, 1.05 ] 3.00 [ 0.12, 72.91 ] 3.02 [ 0.12, 73.57 ] 0.35 [ 0.01, 8.45 ]
Sydney Diet-Heart 1978 <b>Subtotal (95% CI)</b> Fotal events: 158 (Higher PUFA) Heterogeneity: Tau <sup>2</sup> = 0.07; Chi Test for overall effect: Z = 0.73 of Trials registry or pre-2010 AlphaOmega - ALA Brox 2001 (13) DART fat 1989 Doi 2014 (14) EPOCH 2011 (15) GLAMT 1993	35/221 <b>2912</b> ), 156 (Lower PUFA) <sup>2</sup> = 4.81, df = 3 (P = 0 (P = 0.46) 121/2409 0/80 339/1018 1/119 1/195 0/54	23/237 <b>2914</b> .19); I <sup>2</sup> =38% 133/2428 1/40 364/1015 0/119 0/196 1/57		37.3 % <b>100.0 %</b> 17.5 % 0.4 % 0.4 % 0.4 % 0.4 %	1.18 [ 0.76, 1.81 ] 0.92 [ 0.72, 1.17 ] 0.17 [ 0.01, 4.05 ] 0.93 [ 0.82, 1.05 ] 3.00 [ 0.12, 72.91 ] 3.02 [ 0.12, 73.57 ]
Sydney Diet-Heart 1978 <b>Subtotal (95% CI)</b> Fotal events: 158 (Higher PUFA) Heterogeneity: Tau <sup>2</sup> = 0.07; Chi Test for overall effect: Z = 0.73 f 5 Trials registry or pre-2010 AlphaOmega - ALA Brox 2001 (13) DART fat 1989 Doi 2014 (14) EPOCH 2011 (15) GLAMT 1993 HARP- Sacks 1995	35/221 <b>2912</b> ), 156 (Lower PUFA) <sup>2</sup> = 4.81, df = 3 (P = 0 (P = 0.46) 121/2409 0/80 339/1018 1/119 1/195 0/54 7/41	23/237 <b>2914</b> .19); I <sup>2</sup> =38% 133/2428 1/40 364/1015 0/119 0/196 1/57 7/39		37.3 % 100.0 % 17.5 % 0.4 % 21.8 % 0.4 % 0.4 % 0.4 % 3.6 %	1.18 [ 0.76, 1.81 ] 0.92 [ 0.72, 1.17 ] 0.17 [ 0.01, 4.05 ] 0.93 [ 0.82, 1.05 ] 3.00 [ 0.12, 72.91 ] 3.02 [ 0.12, 73.57 ] 0.35 [ 0.01, 8.45 ] 0.95 [ 0.37, 2.46 ]
Sydney Diet-Heart 1978 <b>Subtotal (95% CI)</b> Fotal events: 158 (Higher PUFA) Heterogeneity: Tau <sup>2</sup> = 0.07; Chi Test for overall effect: Z = 0.73 f 5 Trials registry or pre-2010 AlphaOmega - ALA Brox 2001 (13) DART fat 1989 Doi 2014 (14) EPOCH 2011 (15) GLAMT 1993 HARP- Sacks 1995 Houtsmuller 1979	35/221 <b>2912</b> ), 156 (Lower PUFA) <sup>2</sup> = 4.81, df = 3 (P = 0 (P = 0.46) 121/2409 0/80 339/1018 1/119 1/195 0/54 7/41 8/51	23/237 <b>2914</b> (19); 1 <sup>2</sup> =38% 133/2428 1/40 364/1015 0/119 0/196 1/57 7/39 30/51		37.3 % <b>100.0 %</b> 17.5 % 0.4 % 0.4 % 0.4 % 0.4 % 3.6 % 6.2 %	1.18 [ 0.76, 1.81 ] 0.92 [ 0.72, 1.17 ] 0.17 [ 0.01, 4.05 ] 0.93 [ 0.82, 1.05 ] 3.00 [ 0.12, 72.91 ] 3.02 [ 0.12, 73.57 ] 0.35 [ 0.01, 8.45 ] 0.95 [ 0.37, 2.46 ] 0.27 [ 0.14, 0.52 ] 0.97 [ 0.69, 1.37 ]
Sydney Diet-Heart 1978 <b>Subtotal (95% CI)</b> Fotal events: 158 (Higher PUFA) Heterogeneity: Tau <sup>2</sup> = 0.07; Chi Fest for overall effect: Z = 0.73 G Trials registry or pre-2010 AlphaOmega - ALA Brox 2001 (13) DART fat 1989 Doi 2014 (14) EPOCH 2011 (15) GLAMT 1993 HARP- Sacks 1995 Houtsmuller 1979 MRC 1968	35/221 <b>2912</b> ), 156 (Lower PUFA) <sup>2</sup> = 4.81, df = 3 (P = 0 (P = 0.46) 121/2409 0/80 339/1018 1/119 1/195 0/54 7/41 8/51 50/199	23/237 <b>2914</b> .19); I <sup>2</sup> =38% 133/2428 1/40 364/1015 0/119 0/196 1/57 7/39 30/51 50/194		37.3 % 100.0 % 17.5 % 0.4 % 0.4 % 0.4 % 0.4 % 3.6 % 6.2 % 13.9 %	1.18 [ 0.76, 1.81 ] 0.92 [ 0.72, 1.17 ] 0.17 [ 0.01, 4.05 ] 0.93 [ 0.82, 1.05 ] 3.00 [ 0.12, 72.91 ] 3.02 [ 0.12, 73.57 ] 0.35 [ 0.01, 8.45 ] 0.95 [ 0.37, 2.46 ] 0.27 [ 0.14, 0.52 ]
Sydney Diet-Heart 1978 <b>Subtotal (95% CI)</b> Total events: 158 (Higher PUFA) Heterogeneity: Tau <sup>2</sup> = 0.07; Chi Test for overall effect: Z = 0.73 f 5 Trials registry or pre-2010 AlphaOmega - ALA Brox 2001 (13) DART fat 1989 Doi 2014 (14) EPOCH 2011 (15) GLAMT 1993 HARP- Sacks 1995 Houtsmuller 1979 MRC 1968 Nye 1990 (16)	35/221 <b>2912</b> ), 156 (Lower PUFA) <sup>2</sup> = 4.81, df = 3 (P = 0 (P = 0.46) 121/2409 0/80 339/1018 1/119 1/195 0/54 7/41 8/51 50/199 5/36	23/237 <b>2914</b> (19); 1 <sup>2</sup> =38% 133/2428 1/40 364/1015 0/119 0/196 1/57 7/39 30/51 50/194 11/37		37.3 % 100.0 % 17.5 % 0.4 % 0.4 % 0.4 % 0.4 % 0.4 % 3.6 % 13.9 % 3.6 %	1.18 [ 0.76, 1.81 ] 0.92 [ 0.72, 1.17 ] 0.17 [ 0.01, 4.05 ] 0.93 [ 0.82, 1.05 ] 3.00 [ 0.12, 72.91 ] 3.02 [ 0.12, 73.57 ] 0.35 [ 0.01, 8.45 ] 0.95 [ 0.37, 2.46 ] 0.27 [ 0.14, 0.52 ] 0.97 [ 0.69, 1.37 ] 0.47 [ 0.18, 1.21 ]
Sydney Diet-Heart 1978 <b>Subtotal (95% CI)</b> Total events: 158 (Higher PUFA) Heterogeneity: Tau <sup>2</sup> = 0.07; Chi Test for overall effect: Z = 0.73 f 5 Trials registry or pre-2010 AlphaOmega - ALA Brox 2001 (13) DART fat 1989 Doi 2014 (14) EPOCH 2011 (15) GLAMT 1993 HARP- Sacks 1995 Houtsmuller 1979 MRC 1968 Nye 1990 (16) Proudman 2015 (17)	35/221 <b>2912</b> ), 156 (Lower PUFA) <sup>2</sup> = 4.81, df = 3 (P = 0 (P = 0.46) 121/2409 0/80 339/1018 1/119 1/195 0/54 7/41 8/51 50/199 5/36 1/87	23/237 <b>2914</b> (19);   <sup>2</sup> =38% 133/2428 1/40 364/1015 0/119 0/196 1/57 7/39 30/51 50/194 11/37 0/53		37.3 % 100.0 % 17.5 % 0.4 % 0.4 % 0.4 % 0.4 % 3.6 % 13.9 % 3.6 % 0.4 %	1.18 [ 0.76, 1.81 ] 0.92 [ 0.72, 1.17 ] 0.17 [ 0.01, 4.05 ] 0.93 [ 0.82, 1.05 ] 3.00 [ 0.12, 72.91 ] 3.02 [ 0.12, 73.57 ] 0.35 [ 0.01, 8.45 ] 0.95 [ 0.37, 2.46 ] 0.27 [ 0.14, 0.52 ] 0.97 [ 0.69, 1.37 ] 0.47 [ 0.18, 1.21 ] 1.84 [ 0.08, 44.38 ]

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Study or subgroup	Higher PUFA	Lower PUFA	Risk Ratio M- H,Random,95%	Weight	( Continued Risk Ratio M- H,Random,9
Veterans Admin 1969	n/N 60/424	n/N 78/422	Cl	15.0 %	CI 0.77 [ 0.56, 1.04 ]
Subtotal (95% CI)				100.0 %	L . ]
Total events: 641 (Higher PUFA Heterogeneity: Tau <sup>2</sup> = 0.04; Ch	i <sup>2</sup> = 25.69, df = 14 (P =	<b>5014</b> = 0.03); I <sup>2</sup> =45%		100.0 %	0.87 [ 0.72, 1.06 ]
Test for overall effect: Z = 1.35 6 No industry funding	(P = 0.18)				
Brox 2001 (19)	0/80	1/40		5.6 %	0.17 [ 0.01, 4.05 ]
Houtsmuller 1979	8/5 I	30/5 I	-	28.8 %	0.27 [ 0.14, 0.52 ]
MRC 1968	50/199	50/194	+	33.8 %	0.97 [ 0.69, 1.37 ]
Sydney Diet-Heart 1978	35/221	23/237	-	31.7 %	1.63 [ 1.00, 2.67 ]
Subtotal (95% CI) Total events: 93 (Higher PUFA)	<b>551</b> , 104 (Lower PUFA)	522	•	100.0 %	0.72 [ 0.31, 1.63 ]
Heterogeneity: Tau <sup>2</sup> = 0.49; Ch Test for overall effect: Z = 0.80 7 Randomised 100+ participant	(P = 0.42)	0.00024); l <sup>2</sup> =84%			
AlphaOmega - ALA	121/2409	133/2428	•	20.0 %	0.92 [ 0.72, 1.17 ]
Brox 2001 (20)	0/80	1/40		0.5 %	0.17 [ 0.01, 4.05 ]
DART fat 1989	339/1018	364/1015	•	24.4 %	0.93 [ 0.82, 1.05 ]
Doi 2014 (21)	1/119	0/119		0.5 %	3.00 [ 0.12, 72.91 ]
EPOCH 2011 (22)	1/195	0/196		0.5 %	3.02 [ 0.12, 73.57 ]
GLAMT 1993	0/54	1/57		0.5 %	0.35 [ 0.01, 8.45 ]
Houtsmuller 1979	8/51	30/5 I		7.5 %	0.27 [ 0.14, 0.52 ]
MRC 1968	50/199	50/194	-	16.2 %	0.97 [ 0.69, 1.37 ]
Proudman 2015 (23)	1/87	0/53		0.5 %	1.84 [ 0.08, 44.38 ]
Raitt 2005 (24)	1/100	3/100		0.9 %	0.33 [ 0.04, 3.15 ]
Sydney Diet-Heart 1978	35/221	23/237		11.3 %	1.63 [ 1.00, 2.67 ]
Veterans Admin 1969	60/424	78/422	-	17.3 %	0.77 [ 0.56, 1.04 ]
Subtotal (95% CI) Total events: 617 (Higher PUFA	, , ,	<b>4912</b>	•	100.0 %	0.87 [ 0.70, 1.08 ]
Heterogeneity: Tau <sup>2</sup> = 0.05; Ch Test for overall effect: $Z = 1.25$ 8 Randomised 250+ participant	(P = 0.21)	- v.vz); i*  —>2%			
AlphaOmega - ALA	121/2409	133/2428	+	22.0 %	0.92 [ 0.72, 1.17 ]
DART fat 1989	339/1018	364/1015	•	41.5 %	0.93 [ 0.82, 1.05 ]
	1/195	0/196		0.2 %	3.02 [ 0.12, 73.57 ]

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(... Continued)

Study or subgroup	Higher PUFA	Lower PUFA	Risk Ratio M-	Weight	Risk Ratio M-
	n/N	n/N	H,Random,95% Cl		H,Random,95% Cl
MRC 1968	50/199	50/194	-	13.5 %	0.97 [ 0.69, 1.37 ]
Sydney Diet-Heart 1978	35/221	23/237		7.3 %	1.63 [ 1.00, 2.67 ]
Veterans Admin 1969	60/424	78/422	-	15.6 %	0.77 [ 0.56, 1.04 ]
Subtotal (95% CI)	4466	4492	•	100.0 %	0.94 [ 0.82, 1.09 ]
Total events: 606 (Higher PUFA Heterogeneity: Tau <sup>2</sup> = 0.01; Ch	, , , ,	.21); I <sup>2</sup> =30%			
Test for overall effect: $Z = 0.79$	(P = 0.43)	,			
				J	
			0.01 0.1 1 10	100	
		Fa	wours higher PUFA Favours lo	ower PUFA	

- (I) Total MI
- (2) Total MI
- (3) Total MI
- (4) Total MI
- (5) Total MI
- (6) Total MI
- (7) Angina
- (8) Total MI
- (9) Total MI
- (10) Total MI
- (11) Total MI
- (12) Total MI
- (13) Total MI
- (14) Total MI
- (15) Total MI
- (16) Angina
- (17) Total MI
- (18) Total MI
- (19) Total MI
- (20) Total MI
- (21) Total MI
- (22) Total MI
- (23) Total MI
- (24) Total MI
- (25) Total MI

#### Analysis 1.15. Comparison I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes, Outcome 15 CHD events - SA fixed-effect.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes

Outcome: 15 CHD events - SA fixed-effect

Study or subgroup	Higher PUFA	Lower PUFA	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H,Fixed,95% Cl		M-H,Fixed,95% CI
AlphaOmega - ALA	121/2409	133/2428	-	18.6 %	0.92 [ 0.72, 1.17 ]
Brox 2001 (1)	0/80	1/40		0.3 %	0.17 [ 0.01, 4.05 ]
DART fat 1989	339/1018	364/1015	•	51.1 %	0.93 [ 0.82, 1.05 ]
Doi 2014 (2)	1/119	0/119		0.1 %	3.00 [ 0.12, 72.91 ]
EPOCH 2011 (3)	1/195	0/196		0.1 %	3.02 [ 0.12, 73.57 ]
GLAMT 1993	0/54	1/57		0.2 %	0.35 [ 0.01, 8.45 ]
HARP- Sacks 1995	7/41	7/39		1.0 %	0.95 [ 0.37, 2.46 ]
Houtsmuller 1979	8/51	30/5 I		4.2 %	0.27 [ 0.14, 0.52 ]
MRC 1968	50/199	50/194	+	7.1 %	0.97 [ 0.69, 1.37 ]
Nye 1990 (4)	5/36	11/37		1.5 %	0.47 [ 0.18, 1.21 ]
Proudman 2015 (5)	1/87	0/53		0.1 %	1.84 [ 0.08, 44.38 ]
Raitt 2005 (6)	1/100	3/100		0.4 %	0.33 [ 0.04, 3.15 ]
Rose 1965	12/28	9/26	_ <b></b>	1.3 %	1.24 [ 0.63, 2.44 ]
Sydney Diet-Heart 1978	35/221	23/237		3.1 %	1.63 [ 1.00, 2.67 ]
Veterans Admin 1969	60/424	78/422	-	11.0 %	0.77 [ 0.56, 1.04 ]
Total (95% CI)	5062	5014	•	100.0 %	0.90 [ 0.82, 0.99 ]
Total events: 641 (Higher PUFA	), 710 (Lower PUFA)				
Heterogeneity: $Chi^2 = 25.69$ , d	$f = 14 (P = 0.03); I^2 = 4$	-5%			
Test for overall effect: $Z = 2.21$	(P = 0.027)				
Test for subgroup differences: N	lot applicable				
			0.01 0.1 1 10 100		

Favours higher PUFA

Favours lower PUFA

(I) Total MI

(2) Total MI

(3) Total MI

(4) Angina

(5) Total MI

(6) Total MI

# Analysis 1.16. Comparison I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes, Outcome 16 CHD events - subgroup by PUFA dose.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes

Outcome: 16 CHD events - subgroup by PUFA dose

Study or subgroup	Higher PUFA	Lower PUFA	Risk Ratio M-	Weight	Risk Ratio M-
	n/N	n/N	H,Random,95% Cl		H,Random,S Cl
I total PUFA < 1.0% E					
Doi 2014 (1)	1/119	0/119		0.4 %	3.00 [ 0.12, 72.91 ]
EPOCH 2011 (2)	1/195	0/196		0.4 %	3.02 [ 0.12, 73.57 ]
Raitt 2005 (3)	1/100	3/100		0.7 %	0.33 [ 0.04, 3.15 ]
Subtotal (95% CI)	414	415		1.5 %	1.00 [ 0.20, 4.89 ]
Total events: 3 (Higher PUFA), 3 Heterogeneity: Tau <sup>2</sup> = 0.0; Chi <sup>2</sup> Test for overall effect: Z = 0.01 2 total PUFA 1.0 to < 2.0% E	= 1.83, df = 2 (P = 0.4) (P = 1.0)				
AlphaOmega - ALA	121/2409	133/2428	•	17.5 %	0.92 [ 0.72, 1.17 ]
Brox 2001 (4)	0/80	1/40		0.4 %	0.17 [ 0.01, 4.05 ]
Nye 1990 (5)	5/36	/37	<b>_</b> _	3.6 %	0.47 [ 0.18, 1.21 ]
Tye 1990 (3)					
Proudman 2015 (6)	1/87	0/53		0.4 %	1.84 [ 0.08, 44.38 ]
, , , ,	2612	0/53 <b>2558</b>	•	0.4 % <b>21.9 %</b>	1.84 [ 0.08, 44.38 ] <b>0.86 [ 0.66, 1.13 ]</b>
Proudman 2015 (6) <b>Subtotal (95% CI)</b> Total events: 127 (Higher PUFA) Heterogeneity: Tau <sup>2</sup> = 0.01; Chi Test for overall effect: Z = 1.07	<b>2612</b> ), 145 (Lower PUFA) i <sup>2</sup> = 3.05, df = 3 (P = 0	2558	•		0.86 [ 0.66, 1.13 ]
Proudman 2015 (6) <b>Subtotal (95% CI)</b> Total events: 127 (Higher PUFA) Heterogeneity: Tau <sup>2</sup> = 0.01; Chi Test for overall effect: $Z = 1.07$ 3 total PUFA 2.0 to $< 5.0\%$ E	<b>2612</b> ), 145 (Lower PUFA) i <sup>2</sup> = 3.05, df = 3 (P = 0 (P = 0.29)	<b>2558</b> 0.38); I <sup>2</sup> =2%	•	21.9 %	0.86 [ 0.66, 1.13 ]
Proudman 2015 (6) <b>Subtotal (95% CI)</b> Total events: 127 (Higher PUFA) Heterogeneity: Tau <sup>2</sup> = 0.01; Chi Test for overall effect: Z = 1.07 3 total PUFA 2.0 to < 5.0% E DART fat 1989	<b>2612</b> ), 145 (Lower PUFA) <sup>12</sup> = 3.05, df = 3 (P = 0 (P = 0.29) 339/1018	<b>2558</b> 0.38); I <sup>2</sup> =2% 364/1015	•	<b>21.9 %</b> 21.8 %	0.86 [ 0.66, 1.13 ] 0.93 [ 0.82, 1.05 0.35 [ 0.01, 8.45
Proudman 2015 (6) <b>Subtotal (95% CI)</b> Total events: 127 (Higher PUFA) Heterogeneity: Tau <sup>2</sup> = 0.01; Chi Test for overall effect: Z = 1.07 f 3 total PUFA 2.0 to < 5.0% E DART fat 1989 GLAMT 1993	<b>2612</b> ), 145 (Lower PUFA) <sup>12</sup> = 3.05, df = 3 (P = 0 (P = 0.29) 339/1018 0/54	<b>2558</b> 0.38); I <sup>2</sup> =2% 364/1015 1/57		21.9 % 21.8 % 0.4 %	
Proudman 2015 (6) <b>Subtotal (95% CI)</b> Total events: 127 (Higher PUFA) Heterogeneity: Tau <sup>2</sup> = 0.01; Chi Test for overall effect: Z = 1.07 f 3 total PUFA 2.0 to < 5.0% E DART fat 1989 GLAMT 1993 HARP- Sacks 1995	2612 ), 145 (Lower PUFA) 1 <sup>2</sup> = 3.05, df = 3 (P = 0 (P = 0.29) 339/1018 0/54 7/41 1113 ), 372 (Lower PUFA) = 0.36, df = 2 (P = 0.2)	<b>2558</b> 0.38); I <sup>2</sup> =2% 364/1015 1/57 7/39 <b>1111</b>		21.9 % 21.8 % 0.4 % 3.6 %	0.86 [ 0.66, 1.13 ] 0.93 [ 0.82, 1.05 ] 0.35 [ 0.01, 8.45 ] 0.95 [ 0.37, 2.46 ]
Proudman 2015 (6) <b>Subtotal (95% CI)</b> Total events: 127 (Higher PUFA) Heterogeneity: Tau <sup>2</sup> = 0.01; Chi Test for overall effect: Z = 1.07 of 3 total PUFA 2.0 to < 5.0% E DART fat 1989 GLAMT 1993 HARP- Sacks 1995 <b>Subtotal (95% CI)</b> Total events: 346 (Higher PUFA) Heterogeneity: Tau <sup>2</sup> = 0.0; Chi <sup>2</sup> Test for overall effect: Z = 1.24 of	2612 ), 145 (Lower PUFA) 1 <sup>2</sup> = 3.05, df = 3 (P = 0 (P = 0.29) 339/1018 0/54 7/41 1113 ), 372 (Lower PUFA) = 0.36, df = 2 (P = 0.2)	<b>2558</b> 0.38); I <sup>2</sup> =2% 364/1015 1/57 7/39 <b>1111</b>		21.9 % 21.8 % 0.4 % 3.6 %	0.86 [ 0.66, 1.13 ] 0.93 [ 0.82, 1.05 ] 0.35 [ 0.01, 8.45 ] 0.95 [ 0.37, 2.46 ]
Proudman 2015 (6) <b>Subtotal (95% CI)</b> Total events: 127 (Higher PUFA); Heterogeneity: Tau <sup>2</sup> = 0.01; Chi Test for overall effect: Z = 1.07 f 3 total PUFA 2.0 to < 5.0% E DART fat 1989 GLAMT 1993 HARP- Sacks 1995 <b>Subtotal (95% CI)</b> Total events: 346 (Higher PUFA); Heterogeneity: Tau <sup>2</sup> = 0.0; Chi <sup>2</sup> Test for overall effect: Z = 1.24 f 4 total PUFA > 5.0% E	2612 ), 145 (Lower PUFA) 1 <sup>2</sup> = 3.05, df = 3 (P = 0 (P = 0.29) 339/1018 0/54 7/41 1113 ), 372 (Lower PUFA) = 0.36, df = 2 (P = 0.4 (P = 0.21)	<b>2558</b> 0.38); I <sup>2</sup> =2% 364/1015 1/57 7/39 <b>1111</b> 833); I <sup>2</sup> =0.0%		21.9 % 21.8 % 0.4 % 3.6 % 25.8 %	0.86 [ 0.66, 1.13 0.93 [ 0.82, 1.05 0.35 [ 0.01, 8.45 0.95 [ 0.37, 2.46 0.93 [ 0.82, 1.04 ]

(Continued . . . )

Study or subgroup	Higher PUFA	Lower PUFA	Risk Ratio M-	Weight	( Continued) Risk Ratio M-
	n/N	n/N	H,Random,95% Cl		H,Random,95% Cl
Sydney Diet-Heart 1978	35/221	23/237	-	9.5 %	1.63 [ 1.00, 2.67 ]
Veterans Admin 1969	60/424	78/422	-	15.0 %	0.77 [ 0.56, 1.04 ]
Subtotal (95% CI)	923	930	•	50.8 %	0.86 [ 0.54, 1.36 ]
Total events: 165 (Higher PUFA	), 190 (Lower PUFA)				
Heterogeneity: Tau <sup>2</sup> = 0.21; Ch	ni <sup>2</sup> = 20.13, df = 4 (P =	0.00047); l <sup>2</sup> =80%			
Test for overall effect: Z = 0.66	(P = 0.51)				
Total (95% CI)	5062	5014	•	100.0 %	0.87 [ 0.72, 1.06 ]
Total events: 641 (Higher PUFA	), 710 (Lower PUFA)				
Heterogeneity: $Tau^2 = 0.04$ ; Ch	ni <sup>2</sup> = 25.69, df = 14 (P =	= 0.03); I <sup>2</sup> =45%			
Test for overall effect: $Z = 1.35$	(P = 0.18)				
Test for subgroup differences: C	Chi <sup>2</sup> = 0.32, df = 3 (P =	0.96), I <sup>2</sup> =0.0%			
			0.01 0.1 1 10 100		

Favours higher PUFA

Favours lower PUFA

(I) Total MI

(2) Total MI

(3) Total MI

(4) Total MI

(5) Angina

(6) Total MI

# Analysis 1.17. Comparison I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes, Outcome 17 CHD events - subgroup by duration.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes

Outcome: 17 CHD events - subgroup by duration

Study or subgroup	Higher PUFA	Lower PUFA	Risk Ratio M-	Weight	Risk Rati M
	n/N	n/N	H,Random,95% Cl		H,Random C
Medium duration 1 to < 2 ye	ears				
Brox 2001 (1)	0/80	1/40		0.4 %	0.17 [ 0.01, 4.05
Doi 2014 (2)	1/119	0/119		0.4 %	3.00 [ 0.12, 72.91
EPOCH 2011 (3)	1/195	0/196		0.4 %	3.02 [ 0.12, 73.57
GLAMT 1993	0/54	1/57		0.4 %	0.35 [ 0.01, 8.45
Nye 1990 (4)	5/36	11/37		3.6 %	0.47 [ 0.18, 1.21
Proudman 2015 (5)	1/87	0/53		0.4 %	1.84 [ 0.08, 44.38
Subtotal (95% CI)	571	502	-	5.5 %	0.59 [ 0.27, 1.30
Medium-long duration 2 to < AlphaOmega - ALA	· /	133/2428	-	17.5 %	0.92 [ 0.72, 1.17
Test for overall effect: $Z = 1.31$	· /				
1 0			•		2
DART fat 1989	339/1018	364/1015	•	21.8 %	0.93 [ 0.82, 1.05
HARP- Sacks 1995	7/41	7/39		3.6 %	0.95 [ 0.37, 2.46
Raitt 2005 (6)	1/100	3/100		0.7 %	0.33 [ 0.04, 3.15
Rose 1965	12/28	9/26		6.2 %	1.24 [ 0.63, 2.44
Subtotal (95% CI)	3596	3608	•	<b>49.9</b> %	0.93 [ 0.84, 1.03
otal events: 480 (Higher PUFA leterogeneity: Tau <sup>2</sup> = 0.0; Chi est for overall effect: Z = 1.34	$r^2 = 1.50$ , df = 4 (P = 0.	83); I <sup>2</sup> =0.0%			
Long duration 4+ years	(1 = 0.10)				
Houtsmuller 1979	8/5	30/51		6.2 %	0.27 [ 0.14, 0.52
MRC 1968	50/199	50/194	+	13.9 %	0.97 [ 0.69, 1.37
Sydney Diet-Heart 1978	35/221	23/237		9.5 %	1.63 [ 1.00, 2.67
Veterans Admin 1969	60/424	78/422	-	15.0 %	0.77 [ 0.56, 1.04
Subtotal (95% CI)	895	904	•	44.6 %	0.79 [ 0.46, 1.35
otal events: 153 (Higher PUFA	A), 181 (Lower PUFA)				
( 0					

(Continued . . . )

Study or subgroup	Higher PUFA	Lower PUFA	Risk F N H,Random	1-	Weight	( Continued) Risk Ratio M- H.Random,95%
	n/N	n/N	(	CI		CI
Heterogeneity: $Tau^2 = 0.24$ ; C	Chi <sup>2</sup> = 19.08, df = 3 (P =	0.00026); I <sup>2</sup> =84%				
Test for overall effect: $Z = 0.8$	36 (P = 0.39)					
Total (95% CI)	5062	5014	•		100.0 %	0.87 [ 0.72, 1.06 ]
Total events: 641 (Higher PUF	FA), 710 (Lower PUFA)					
Heterogeneity: $Tau^2 = 0.04$ ; C	Chi <sup>2</sup> = 25.69, df = 14 (P =	= 0.03); I <sup>2</sup> =45%				
Test for overall effect: $Z = 1.3$	35 (P = 0.18)					
Test for subgroup differences:	Chi <sup>2</sup> = 1.56, df = 2 (P =	0.46), I <sup>2</sup> =0.0%				
			0.01 0.1 1	10 100		

Favours higher PUFA Favours lower PUFA

(I) Total MI

(2) Total MI

(3) Total MI

(4) Angina

(5) Total MI

(6) Total MI

#### Analysis 1.18. Comparison I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes, Outcome 18 CHD events - subgroup by primary or secondary prevention.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes

Outcome: 18 CHD events - subgroup by primary or secondary prevention

Study or subgroup	Higher PUFA	Lower PUFA	Risk Ratio M-	Weight	Risk Ratio M
	n/N	n/N	H,Random,95% Cl		H,Random, C
Primary prevention of CVD					
Brox 2001 (1)	0/80	1/40		0.4 %	0.17 [ 0.01, 4.05
EPOCH 2011 (2)	1/195	0/196		0.4 %	3.02 [ 0.12, 73.57
GLAMT 1993	0/54	1/57		0.4 %	0.35 [ 0.01, 8.45
Houtsmuller 1979	8/51	30/51		6.2 %	0.27 [ 0.14, 0.52
Proudman 2015 (3)	1/87	0/53		0.4 %	1.84 [ 0.08, 44.38
Veterans Admin 1969	60/424	78/422	-	15.0 %	0.77 [ 0.56, 1.04
ubtotal (95% CI)	891	819	•	22.7 %	0.53 [ 0.25, 1.11
leterogeneity: Tau <sup>2</sup> = 0.30; Chi <sup>2</sup> est for overall effect: $Z = 1.68$ ( Secondary prevention of CVD	P = 0.094)	,			
AlphaOmega - ALA	121/2409	133/2428	1	17.5 %	0.92 [ 0.72, 1.17
DART fat 1989	339/1018	364/1015	•	21.8 %	0.93 [ 0.82, 1.05
Doi 2014 (4)	1/119	0/119		0.4 %	3.00 [ 0.12, 72.91
HARP- Sacks 1995	7/41	7/39		3.6 %	0.95 [ 0.37, 2.46
MRC 1968	50/199	50/194	+	13.9 %	0.97 [ 0.69, 1.37
Nye 1990 (5)	5/36	/37		3.6 %	0.47 [ 0.18, 1.21
Raitt 2005 (6)	1/100	3/100		0.7 %	0.33 [ 0.04, 3.15
Rose 1965	12/28	9/26		6.2 %	1.24 [ 0.63, 2.44
Sydney Diet-Heart 1978	35/221	23/237		9.5 %	1.63 [ 1.00, 2.67
<b>ubtotal (95% CI)</b> btal events: 571 (Higher PUFA) leterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup>	, , ,	<b>4195</b> 0.35); I <sup>2</sup> =10%	•	77.3 %	0.96 [ 0.85, 1.09
est for overall effect: $Z = 0.60$ (	· · · ·				
otal (95% CI)	5062	5014	•	100.0 %	0.87 [ 0.72, 1.06
otal events: 641 (Higher PUFA) leterogeneity: Tau <sup>2</sup> = 0.04; Chi <sup>2</sup>	, , ,	- 0.02), 12 - 45%			
est for overall effect: $Z = 1.35$ (	,	- 0.03); 143%			
	$h^2 = 2.41, df = 1 (P = 1)$	$(12)$ $l^2 - 58\%$			

(I) Total MI

(2) Total MI

(3) Total MI

(4) Total MI

(5) Angina

(6) Total MI

#### Analysis 1.19. Comparison I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes, Outcome 19 CHD events - subgroup by baseline PUFA dose.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes

Outcome: 19 CHD events - subgroup by baseline PUFA dose

Study or subgroup	Higher PUFA	Lower PUFA	Risk Ratio M-	Weight	Risk Ratio M-
	n/N	n/N	H,Random,95% Cl		H,Random,95% Cl
I Baseline total PUFA < 6% E					
Veterans Admin 1969	60/424	78/422	-	15.0 %	0.77 [ 0.56, 1.04 ]
Subtotal (95% CI)	424	422	•	15.0 %	0.77 [ 0.56, 1.04 ]
Total events: 60 (Higher PUFA),	78 (Lower PUFA)				
Heterogeneity: not applicable					
Test for overall effect: $Z = 1.70$ (	(P = 0.090)				
2 Baseline total PUFA 6 to < 11	% E				
DART fat 1989	339/1018	364/1015	-	21.8 %	0.93 [ 0.82, 1.05 ]
Sydney Diet-Heart 1978	35/221	23/237	-	9.5 %	1.63 [ 1.00, 2.67 ]
Subtotal (95% CI)	1239	1252	*	31.3 %	1.17 [ 0.68, 2.01 ]
Total events: 374 (Higher PUFA)	), 387 (Lower PUFA)				
Heterogeneity: $Tau^2 = 0.13$ ; Chi	$^{2} = 4.78, df = 1 (P = 0)$	0.03); I <sup>2</sup> =79%			
Test for overall effect: $Z = 0.56$ (	(P = 0.58)				
3 Baseline total PUFA 11+% E					
Subtotal (95% CI)	0	0			Not estimable
Total events: 0 (Higher PUFA), 0	(Lower PUFA)				
Heterogeneity: not applicable					
Test for overall effect: not applica	able				
			0.01 0.1 1 10	100	
		Fa	vours higher PUFA Favours lov	ver PUFA	
					(Cartinual)

(Continued . . . )

Study or subgroup	Higher PUFA	Lower PUFA	Risk Ratio M- H,Random,95%	Weight	( Continued) Risk Ratio H- H.Random,95%
	n/N	n/N	Cl		Cl
4 Baseline total PUFA unclear					
AlphaOmega - ALA	121/2409	133/2428	-	17.5 %	0.92 [ 0.72, 1.17 ]
Brox 2001 (1)	0/80	1/40		0.4 %	0.17 [ 0.01, 4.05 ]
Doi 2014 (2)	1/119	0/119		0.4 %	3.00 [ 0.12, 72.91 ]
EPOCH 2011 (3)	1/195	0/196		0.4 %	3.02 [ 0.12, 73.57 ]
GLAMT 1993	0/54	1/57		0.4 %	0.35 [ 0.01, 8.45 ]
HARP- Sacks 1995	7/41	7/39		3.6 %	0.95 [ 0.37, 2.46 ]
Houtsmuller 1979	8/5	30/5 I		6.2 %	0.27 [ 0.14, 0.52 ]
MRC 1968	50/199	50/194		13.9 %	0.97 [ 0.69, 1.37 ]
Nye 1990 (4)	5/36	/37		3.6 %	0.47 [ 0.18, 1.21 ]
Proudman 2015 (5)	1/87	0/53		0.4 %	1.84 [ 0.08, 44.38 ]
Raitt 2005 (6)	1/100	3/100		0.7 %	0.33 [ 0.04, 3.15 ]
Rose 1965	12/28	9/26		6.2 %	1.24 [ 0.63, 2.44 ]
Subtotal (95% CI)	3399	3340	•	53.7 %	0.77 [ 0.55, 1.06 ]
Total events: 207 (Higher PUFA	A), 245 (Lower PUFA)				
Heterogeneity: $Tau^2 = 0.09$ ; Ch		= 0.07); l <sup>2</sup> =40%			
Test for overall effect: $Z = 1.60$	( )				
Total (95% CI)	5062	5014	•	100.0 %	0.87 [ 0.72, 1.06 ]
Total events: 641 (Higher PUFA	, , ,				
Heterogeneity: $Tau^2 = 0.04$ ; Cł		= 0.03); l <sup>2</sup> =45%			
Test for overall effect: $Z = 1.35$	( )				
Test for subgroup differences: (	Chi <sup>2</sup> = 1.97, df = 2 (P =	0.37), l <sup>2</sup> =0.0%			
			0.01 0.1 1 10 100		
		Fa	vours higher PUFA Favours lower	PUFA	
			-		
(I) Total MI					

(2) Total MI

(3) Total MI

(4) Angina

(5) Total MI

(6) Total MI

# Analysis 1.20. Comparison I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes, Outcome 20 CHD events - subgroup by replacement.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes

Outcome: 20 CHD events - subgroup by replacement

Study or subgroup	Higher PUFA	Lower PUFA	Risk Ratio M-	Weight	Risk Ratio M-
	n/N	n/N	H,Random,95% Cl		H,Random,9 Cl
PUFA replaced saturated fats					
DART fat 1989	339/1018	364/1015	•	41.6 %	0.93 [ 0.82, 1.05 ]
MRC 1968	50/199	50/194	+	21.5 %	0.97 [ 0.69, 1.37 ]
Sydney Diet-Heart 1978	35/221	23/237	-	13.3 %	1.63 [ 1.00, 2.67 ]
Veterans Admin 1969	60/424	78/422	-	23.7 %	0.77 [ 0.56, 1.04 ]
Subtotal (95% CI)	1862	1868	•	100.0 %	0.97 [ 0.78, 1.19 ]
Total events: 484 (Higher PUFA) Heterogeneity: Tau <sup>2</sup> = 0.02; Chi <sup>2</sup> Test for overall effect: $Z = 0.32$ ( PUFA replaced monounsatura	$P^{2} = 6.59, df = 3 (P = 0.75)$ ted fats	,			
AlphaOmega - ALA	121/2409	133/2428	<b>-</b>	33.6 %	0.92 [ 0.72, 1.17 ]
EPOCH 2011 (1)	1/195	0/196		0.5 %	3.02 [ 0.12, 73.57 ]
HARP- Sacks 1995	7/41	7/39		5.5 %	0.95 [ 0.37, 2.46 ]
Nye 1990 (2)	5/36	11/37		5.5 %	0.47 [ 0.18, 1.21 ]
Proudman 2015 (3)	1/87	0/53		0.5 %	1.84 [ 0.08, 44.38 ]
Raitt 2005 (4)	1/100	3/100		1.1 %	0.33 [ 0.04, 3.15 ]
Rose 1965	12/28	9/26	-	9.8 %	1.24 [ 0.63, 2.44 ]
Sydney Diet-Heart 1978	35/221	23/237	-	15.9 %	1.63 [ 1.00, 2.67 ]
Veterans Admin 1969	60/424	78/422	-	27.4 %	0.77 [ 0.56, 1.04 ]
<b>Subtotal (95% CI)</b> Total events: 243 (Higher PUFA) Heterogeneity: Tau <sup>2</sup> = 0.03; Chi <sup>2</sup> Test for overall effect: $Z = 0.42$ (	<sup>2</sup> = 10.73, df = 8 (P =	<b>3538</b> 0.22); I <sup>2</sup> =25%	•	100.0 %	0.95 [ 0.75, 1.20 ]
3 PUFA replaced carbohydrate Houtsmuller 1979	8/51	30/51	-	50.0 %	0.27 [ 0.14, 0.52 ]
Rose 1965	12/28	9/26	-	50.0 %	1.24 [ 0.63, 2.44 ]
<b>Subtotal (95% CI)</b> otal events: 20 (Higher PUFA),	<b>79</b> 39 (Lower PUFA)	77	-	100.0 %	0.57 [ 0.12, 2.65 ]
			).01 0.1 1 10 100 s higher PUFA Favours lower		

Study or subgroup	Higher PUFA	Lower PUFA	Risk Ratio M- H,Random,95%	Weight	( Continued) Risk Ratio M- H,Random,95%
	n/N	n/N	Cl		CI
Heterogeneity: $Tau^2 = 1.10$ ; C	$Chi^2 = 10.18, df = 1 (P =$	0.001); I <sup>2</sup> =90%			
Test for overall effect: $Z = 0.7$	I (P = 0.48)				
4 PUFA replaced protein					
MRC 1968	50/199	50/194	<mark></mark>	100.0 %	0.97 [ 0.69, 1.37 ]
Subtotal (95% CI)	199	194	+	100.0 %	0.97 [ 0.69, 1.37 ]
Total events: 50 (Higher PUFA	N), 50 (Lower PUFA)				
Heterogeneity: not applicable					
Test for overall effect: $Z = 0.1$	5 (P = 0.88)				
5 PUFA replaced unclear					
Brox 2001 (5)	0/80	1/40		33.4 %	0.17 [ 0.01, 4.05 ]
Doi 2014 (6)	1/119	0/119		33.2 %	3.00 [ 0.12, 72.91 ]
GLAMT 1993	0/54	1/57		33.4 %	0.35 [ 0.01, 8.45 ]
Subtotal (95% CI)	253	216		100.0 %	0.56 [ 0.09, 3.52 ]
Total events: I (Higher PUFA)	, 2 (Lower PUFA)				
Heterogeneity: $Tau^2 = 0.0$ ; Ch	$i^2 = 1.70$ , $df = 2$ (P = 0.	43); l <sup>2</sup> =0.0%			
Test for overall effect: $Z = 0.6$	2 (P = 0.54)				
Test for subgroup differences:	Chi <sup>2</sup> = 0.78, df = 4 (P =	0.94), l <sup>2</sup> =0.0%			

0.01 0.1 1 10 100

Favours higher PUFA Favours lower PUFA

(I) Total MI

(2) Angina

(3) Total MI

(4) Total MI

(5) Total MI

(6) Total MI

# Analysis 1.21. Comparison I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes, Outcome 21 CHD events - subgroup by sex.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes

Outcome: 21 CHD events - subgroup by sex

	Higher PUFA	Lower PUFA	Risk Ratio M-	Weight	Risk Ratio M-
	n/N	n/N	H,Random,95% Cl		H,Random,9 Cl
> 70% men					
AlphaOmega - ALA	121/2409	133/2428		17.5 %	0.92 [ 0.72, 1.17 ]
DART fat 1989	339/1018	364/1015	+	21.8 %	0.93 [ 0.82, 1.05 ]
Doi 2014 (1)	1/119	0/119		0.4 %	3.00 [ 0.12, 72.91 ]
GLAMT 1993	0/54	1/57		0.4 %	0.35 [ 0.01, 8.45 ]
HARP- Sacks 1995	7/41	7/39		3.6 %	0.95 [ 0.37, 2.46 ]
MRC 1968	50/199	50/194	+	13.9 %	0.97 [ 0.69, 1.37 ]
Nye 1990 (2)	5/36	11/37		3.6 %	0.47 [ 0.18, 1.21 ]
Raitt 2005 (3)	1/100	3/100		0.7 %	0.33 [ 0.04, 3.15 ]
Sydney Diet-Heart 1978	35/221	23/237	-	9.5 %	1.63 [ 1.00, 2.67 ]
			_	15.0.0/	0.77 [ 0.56, 1.04 ]
Veterans Admin 1969	60/424	78/422	-	15.0 %	0.77 [ 0.50, 1.04 ]
Subtotal (95% CI) Total events: 619 (Higher PUFA Heterogeneity: Tau <sup>2</sup> = 0.01; Ch	<b>4621</b> ), 670 (Lower PUFA) <sup>j2</sup> = 10.29, df = 9 (P =	4648		15.0 % 86.5 %	
Subtotal (95% CI) Total events: 619 (Higher PUFA	<b>4621</b> ), 670 (Lower PUFA) <sup>j2</sup> = 10.29, df = 9 (P =	4648			0.93 [ 0.82, 1.05 ]
Subtotal (95% CI) Total events: 619 (Higher PUFA Heterogeneity: Tau <sup>2</sup> = 0.01; Ch Test for overall effect: Z = 1.23	<b>4621</b> ), 670 (Lower PUFA) <sup>j2</sup> = 10.29, df = 9 (P =	4648			
Subtotal (95% CI) Total events: 619 (Higher PUFA Heterogeneity: Tau <sup>2</sup> = 0.01; Ch Test for overall effect: Z = 1.23 2 > 70% women	<b>4621</b> ), 670 (Lower PUFA) $a^2 = 10.29$ , df = 9 (P = (P = 0.22)	<b>4648</b> = 0.33); I <sup>2</sup> = I 3%		86.5 %	0.93 [ 0.82, 1.05 ] I.84 [ 0.08, 44.38 ]
Subtotal (95% CI) Total events: 619 (Higher PUFA Heterogeneity: Tau <sup>2</sup> = 0.01; Ch Test for overall effect: Z = 1.23 2 > 70% women Proudman 2015 (4) Subtotal (95% CI) Total events: 1 (Higher PUFA), G	<b>4621</b> ), 670 (Lower PUFA) $a^2 = 10.29$ , df = 9 (P = (P = 0.22) 1/87 <b>87</b>	<b>4648</b> = 0.33); I <sup>2</sup> = I 3% 0/53		<b>86.5 %</b> 0.4 %	0.93 [ 0.82, 1.05 ] 1.84 [ 0.08, 44.38 ]
Subtotal (95% CI) Total events: 619 (Higher PUFA Heterogeneity: Tau <sup>2</sup> = 0.01; Ch Test for overall effect: Z = 1.23 2 > 70% women Proudman 2015 (4) Subtotal (95% CI)	<b>4621</b> ), 670 (Lower PUFA) i <sup>2</sup> = 10.29, df = 9 (P = (P = 0.22) 1/87 <b>87</b> 0 (Lower PUFA)	<b>4648</b> = 0.33); I <sup>2</sup> = I 3% 0/53		<b>86.5 %</b> 0.4 %	0.93 [ 0.82, 1.05 ] I.84 [ 0.08, 44.38 ]
Subtotal (95% CI) Total events: 619 (Higher PUFA Heterogeneity: Tau <sup>2</sup> = 0.01; Ch Test for overall effect: Z = 1.23 2 > 70% women Proudman 2015 (4) Subtotal (95% CI) Total events: 1 (Higher PUFA), C Heterogeneity: not applicable	<b>4621</b> ), 670 (Lower PUFA) i <sup>2</sup> = 10.29, df = 9 (P = (P = 0.22) 1/87 <b>87</b> 0 (Lower PUFA)	<b>4648</b> = 0.33); I <sup>2</sup> = I 3% 0/53		<b>86.5 %</b> 0.4 %	0.93 [ 0.82, 1.05 ]
Subtotal (95% CI) Total events: 619 (Higher PUFA Heterogeneity: Tau <sup>2</sup> = 0.01; Ch Test for overall effect: Z = 1.23 2 > 70% women Proudman 2015 (4) Subtotal (95% CI) Total events: 1 (Higher PUFA), C Heterogeneity: not applicable Test for overall effect: Z = 0.38	<b>4621</b> ), 670 (Lower PUFA) i <sup>2</sup> = 10.29, df = 9 (P = (P = 0.22) 1/87 <b>87</b> 0 (Lower PUFA)	<b>4648</b> = 0.33); I <sup>2</sup> = I 3% 0/53		<b>86.5 %</b> 0.4 %	0.93 [ 0.82, 1.05 ] I.84 [ 0.08, 44.38 ]
Subtotal (95% CI) Total events: 619 (Higher PUFA Heterogeneity: Tau <sup>2</sup> = 0.01; Ch Test for overall effect: Z = 1.23 2 > 70% women Proudman 2015 (4) Subtotal (95% CI) Total events: 1 (Higher PUFA), C Heterogeneity: not applicable Test for overall effect: Z = 0.38 3 men % women	<b>4621</b> ), 670 (Lower PUFA) $i^{2} = 10.29, df = 9 (P = 0.22)$ 1/87 <b>87</b> 0 (Lower PUFA) (P = 0.71)	<b>4648</b> = 0.33); I <sup>2</sup> = I 3% 0/53 <b>53</b>		86.5 % 0.4 % 0.4 %	0.93 [ 0.82, 1.05 ] 1.84 [ 0.08, 44.38 ] 1.84 [ 0.08, 44.38 ] 0.17 [ 0.01, 4.05 ]
Subtotal (95% CI) Total events: 619 (Higher PUFA Heterogeneity: Tau <sup>2</sup> = 0.01; Ch Test for overall effect: Z = 1.23 2 > 70% women Proudman 2015 (4) Subtotal (95% CI) Total events: 1 (Higher PUFA), C Heterogeneity: not applicable Test for overall effect: Z = 0.38 3 men % women Brox 2001 (5)	<b>4621</b> ), 670 (Lower PUFA) $i^2 = 10.29, df = 9 (P = (P = 0.22))$ 1/87 <b>87</b> 0 (Lower PUFA) (P = 0.71) 0/80	<b>4648</b> = 0.33); I <sup>2</sup> = I 3% 0/53 <b>53</b>		<b>86.5 %</b> 0.4 % <b>0.4 %</b>	0.93 [ 0.82, 1.05 ] 1.84 [ 0.08, 44.38 ] 1.84 [ 0.08, 44.38 ] 0.17 [ 0.01, 4.05 ] 0.27 [ 0.14, 0.52 ]
Subtotal (95% CI) Total events: 619 (Higher PUFA Heterogeneity: Tau <sup>2</sup> = 0.01; Ch Test for overall effect: Z = 1.23 2 > 70% women Proudman 2015 (4) Subtotal (95% CI) Total events: 1 (Higher PUFA), C Heterogeneity: not applicable Test for overall effect: Z = 0.38 3 men % women Brox 2001 (5) Houtsmuller 1979	<b>4621</b> ), 670 (Lower PUFA) $i^2 = 10.29, df = 9 (P = 10, 20, 20, 20, 20, 20, 20, 20, 20, 20, 2$	<b>4648</b> : 0.33); l <sup>2</sup> = 13% 0/53 <b>53</b> 1/40 30/51		<b>86.5 %</b> 0.4 % <b>0.4 %</b> 0.4 % 6.2 %	0.93 [ 0.82, 1.05 ] 1.84 [ 0.08, 44.38 ] 1.84 [ 0.08, 44.38 ]
Subtotal (95% CI) Total events: 619 (Higher PUFA Heterogeneity: Tau <sup>2</sup> = 0.01; Ch Test for overall effect: Z = 1.23 2 > 70% women Proudman 2015 (4) Subtotal (95% CI) Total events: 1 (Higher PUFA), 0 Heterogeneity: not applicable Test for overall effect: Z = 0.38 3 men % women Brox 2001 (5) Houtsmuller 1979 Subtotal (95% CI) Total events: 8 (Higher PUFA), 3 Heterogeneity: Tau <sup>2</sup> = 0.0; Chi <sup>2</sup>	<b>4621</b> ), 670 (Lower PUFA) $i^2 = 10.29, df = 9 (P = 10, 20, 20, 20, 20, 20, 20, 20, 20, 20, 2$	4648 : 0.33);   <sup>2</sup> = 13% 0/53 53 1/40 30/51 91		<b>86.5 %</b> 0.4 % <b>0.4 %</b> 0.4 % 6.2 %	0.93 [ 0.82, 1.05 ] 1.84 [ 0.08, 44.38 ] 1.84 [ 0.08, 44.38 ] 0.17 [ 0.01, 4.05 ] 0.27 [ 0.14, 0.52 ]
Subtotal (95% CI) Total events: 619 (Higher PUFA Heterogeneity: Tau <sup>2</sup> = 0.01; Ch Test for overall effect: Z = 1.23 2 > 70% women Proudman 2015 (4) Subtotal (95% CI) Total events: 1 (Higher PUFA), C Heterogeneity: not applicable Test for overall effect: Z = 0.38 3 men % women Brox 2001 (5) Houtsmuller 1979 Subtotal (95% CI) Total events: 8 (Higher PUFA), T	<b>4621</b> ), 670 (Lower PUFA) $i^2 = 10.29, df = 9 (P = 10, 20, 20, 20, 20, 20, 20, 20, 20, 20, 2$	4648 : 0.33);   <sup>2</sup> = 13% 0/53 53 1/40 30/51 91		<b>86.5 %</b> 0.4 % <b>0.4 %</b> 0.4 % 6.2 %	0.93 [ 0.82, 1.05 ] 1.84 [ 0.08, 44.38 ] 1.84 [ 0.08, 44.38 ] 0.17 [ 0.01, 4.05 ] 0.27 [ 0.14, 0.52 ]

(Continued . . . )

Study or subgroup	Higher PUFA	Lower PUFA	Risk Ratio M-	Weight	( Continued) Risk Ratio M-
	n/N	n/N	H,Random,95% Cl		H,Random,95% Cl
EPOCH 2011 (6)	1/195	0/196		0.4 %	3.02 [ 0.12, 73.57 ]
Rose 1965	12/28	9/26		6.2 %	1.24 [ 0.63, 2.44 ]
Subtotal (95% CI)	223	222	•	6.5 %	1.29 [ 0.66, 2.50 ]
Total events: 13 (Higher PUFA	A), 9 (Lower PUFA)				
Heterogeneity: $Tau^2 = 0.0$ ; Cł	$hi^2 = 0.29, df = 1 (P = 0)$	.59); l <sup>2</sup> =0.0%			
Test for overall effect: $Z = 0.7$	74 (P = 0.46)				
Total (95% CI)	5062	5014	•	100.0 %	0.87 [ 0.72, 1.06 ]
Total events: 641 (Higher PUF	FA), 710 (Lower PUFA)				
Heterogeneity: Tau <sup>2</sup> = 0.04; C	Chi <sup>2</sup> = 25.69, df = 14 (P	= 0.03); I <sup>2</sup> =45%			
Test for overall effect: $Z = 1.3$	85 (P = 0.18)				
Test for subgroup differences:	Chi <sup>2</sup> = 14.91, df = 3 (P	= 0.00), I <sup>2</sup> =80%			
			0.01 0.1 1 10 100	)	

Favours higher PUFA

Favours lower PUFA

(I) Total MI

(2) Angina

(3) Total MI

(4) Total MI

(5) Total MI

(6) Total MI

# Analysis 1.22. Comparison I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes, Outcome 22 CHD events - subgroup by age.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes

Outcome: 22 CHD events - subgroup by age

Study or subgroup	Higher PUFA	Lower PUFA	Risk Ratio M-	Weight	Risk Ratio M
	n/N	n/N	H,Random,95% Cl		H,Random, C
Mean age < 50 years					
Sydney Diet-Heart 1978	35/221	23/237	-	9.5 %	1.63 [ 1.00, 2.67
Subtotal (95% CI)	221	237	•	9.5 %	1.63 [ 1.00, 2.67
Fotal events: 35 (Higher PUFA), 2	23 (Lower PUFA)				
Heterogeneity: not applicable Test for overall effect: Z = 1.95 (	P = 0.052)				
2 Mean age 50 to < 65 years	1 – 0.052)				
Brox 2001 (1)	0/80	1/40		0.4 %	0.17 [ 0.01, 4.05
DART fat 1989	339/1018	364/1015	-	21.8 %	0.93 [ 0.82, 1.05
GLAMT 1993	0/54	1/57		0.4 %	0.35 [ 0.01, 8.45
HARP- Sacks 1995	7/41	7/39		3.6 %	0.95 [ 0.37, 2.46
MRC 1968	50/199	50/194	+	13.9 %	0.97 [ 0.69, 1.37
Nye 1990 (2)	5/36	11/37		3.6 %	0.47 [ 0.18, 1.21
Proudman 2015 (3)	1/87	0/53		0.4 %	1.84 [ 0.08, 44.38
Raitt 2005 (4)	1/100	3/100		0.7 %	0.33 [ 0.04, 3.15
Rose 1965	12/28	9/26		6.2 %	1.24 [ 0.63, 2.44
Subtotal (95% CI)	1643	1561	•	51.0 %	0.93 [ 0.83, 1.03
Fotal events: 415 (Higher PUFA), Heterogeneity: Tau <sup>2</sup> = 0.0; Chi <sup>2</sup> Fest for overall effect: Z = 1.34 ( 8 Mean age 65+ years AlphaOmega - ALA	= 5.22, df = 8 (P = 0.	73); I <sup>2</sup> =0.0% I 33/2428	_	17.5 %	0.92 [ 0.72, 1.17
Doi 2014 (5)	1/119	0/119		0.4 %	3.00 [ 0.12, 72.91
Veterans Admin 1969	60/424	78/422	-	15.0 %	0.77 [ 0.56, 1.04
Subtotal (95% CI) Fotal events: 182 (Higher PUFA),	<b>2952</b> , 211 (Lower PUFA)	2969	•	32.9 %	0.86 [ 0.71, 1.04
Heterogeneity: $Tau^2 = 0.0$ ; $Chi^2$ fest for overall effect: $Z = 1.56$ ( 4 Mean age unclear	= 1.41, df = 2 (P = 0.	49); I <sup>2</sup> =0.0%			

(Continued . . . )

Study or subgroup	Higher PUFA	Lower PUFA			Risk R M	-		Weight	( Continued) Risk Ratio M-
	n/N	n/N		Н,	Random, C				H,Random,95% Cl
EPOCH 2011 (6)	1/195	0/196		_				0.4 %	3.02 [ 0.12, 73.57 ]
Houtsmuller 1979	8/5	30/51			-			6.2 %	0.27 [ 0.14, 0.52 ]
Subtotal (95% CI)	246	247			-			6.6 %	0.53 [ 0.06, 4.64 ]
Total events: 9 (Higher PUFA)	, 30 (Lower PUFA)								
Heterogeneity: Tau <sup>2</sup> = 1.59; C	$Chi^2 = 2.14, df = 1 (P = 0)$	). I 4); I <sup>2</sup> =53%							
Test for overall effect: Z = 0.5	7 (P = 0.57)								
Total (95% CI)	5062	5014			•			100.0 %	0.87 [ 0.72, 1.06 ]
Total events: 641 (Higher PUF	A), 710 (Lower PUFA)								
Heterogeneity: Tau <sup>2</sup> = 0.04; C	Chi <sup>2</sup> = 25.69, df = 14 (P =	= 0.03); I <sup>2</sup> =45%							
Test for overall effect: $Z = 1.3$	5 (P = 0.18)								
Test for subgroup differences:	$Chi^2 = 5.90, df = 3 (P =$	0.12), 12 =49%							
				I.					
			0.01	0.1	Ι	10	00		

Favours higher PUFA Favours lower PUFA

(I) Total MI

(2) Angina

(3) Total MI

(4) Total MI

(5) Total MI

(6) Total MI

# Analysis 1.23. Comparison I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes, Outcome 23 CHD events - subgroup by statin use.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes

Outcome: 23 CHD events - subgroup by statin use

Study or subgroup	Higher PUFA Lower PUFA	Risk Ratio M-	Weight	Risk Ratio M-	
		n/N	H,Random,95% Cl		H,Random,959 Cl
< 50% on statins					
Brox 2001 (1)	0/80	1/40		0.4 %	0.17 [ 0.01, 4.05 ]
DART fat 1989	339/1018	364/1015	•	21.8 %	0.93 [ 0.82, 1.05 ]
EPOCH 2011 (2)	1/195	0/196		0.4 %	3.02 [ 0.12, 73.57 ]
GLAMT 1993	0/54	1/57		0.4 %	0.35 [ 0.01, 8.45 ]
HARP- Sacks 1995	7/41	7/39		3.6 %	0.95 [ 0.37, 2.46 ]
Houtsmuller 1979	8/51	30/51		6.2 %	0.27 [ 0.14, 0.52 ]
MRC 1968	50/199	50/194	+	13.9 %	0.97 [ 0.69, 1.37 ]
Nye 1990 (3)	5/36	11/37		3.6 %	0.47 [ 0.18, 1.21 ]
Proudman 2015 (4)	1/87	0/53		0.4 %	1.84 [ 0.08, 44.38 ]
Raitt 2005 (5)	1/100	3/100		0.7 %	0.33 [ 0.04, 3.15 ]
Rose 1965	12/28	9/26	-	6.2 %	1.24 [ 0.63, 2.44 ]
Sydney Diet-Heart 1978	35/221	23/237	-	9.5 %	1.63 [ 1.00, 2.67 ]
Veterans Admin 1969	60/424	78/422	-	15.0 %	0.77 [ 0.56, 1.04 ]
ubtotal (95% CI)	2534	2467	•	82.1 %	0.85 [ 0.66, 1.09 ]
btal events: 519 (Higher PUFA), leterogeneity: Tau <sup>2</sup> = 0.07; Chi <sup>2</sup> est for overall effect: Z = 1.30 ( 50+% on statins AlphaOmega - ALA	= 25.16, df = 12 (P =	= 0.01); I <sup>2</sup> =52% I 33/2428		17.5 %	0.92 [ 0.72, 1.17 ]
Doi 2014 (6)	1/119	0/119		0.4 %	3.00 [ 0.12, 72.91 -
<b>ubtotal (95% CI)</b> otal events: 122 (Higher PUFA), leterogeneity: Tau <sup>2</sup> = 0.0; Chi <sup>2</sup>	= 0.53, df = 1 (P = 0.	<b>2547</b> 47); I <sup>2</sup> =0.0%	•	17.9 %	0.92 [ 0.73, 1.17 ]
est for overall effect: Z = 0.66 ( Cotal (95% CI)	P = 0.51) <b>5062</b>	5014		100.0 %	0.87 [ 0.72, 1.06 ]
otal (99% CI) otal events: 641 (Higher PUFA),		5014	·	100.0 %	0.8/[0./2, 1.00]
leterogeneity: Tau <sup>2</sup> = 0.04; Chi <sup>2</sup>	· · · · · ·	= 0.03); I <sup>2</sup> =45%			
est for overall effect: $Z = 1.35$ (	P = 0.18)				
est for subgroup differences: Ch	$i^2 = 0.24$ , df = 1 (P =	0.63), l <sup>2</sup> =0.0%			

(I) Total MI

(2) Total MI

(3) Angina

(4) Total MI

(5) Total MI

(6) Total MI

#### Analysis 1.24. Comparison I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes, Outcome 24 CHD events - subgroup by intervention type.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes

Outcome: 24 CHD events - subgroup by intervention type

Study or subgroup	Higher PUFA	Lower PUFA	Risk Ratio M-	Weight	Risk Ratio M-
			H,Random,95%		H,Random,95
	n/N	n/N	CI		Cl
I Dietary advice					
DART fat 1989	339/1018	364/1015	•	21.8 %	0.93 [ 0.82, 1.05 ]
Houtsmuller 1979	8/5 I	30/51		6.2 %	0.27 [ 0.14, 0.52 ]
Subtotal (95% CI)	1069	1066	-	28.0 %	0.52 [ 0.15, 1.77 ]
Total events: 347 (Higher PUF	A), 394 (Lower PUFA)				
Heterogeneity: $Tau^2 = 0.72$ ; C	$Chi^2 = 12.76, df = 1 (P = 1)$	0.00035); l <sup>2</sup> =92%			
Test for overall effect: $Z = 1.0$	4 (P = 0.30)				
2 Supplemental foods % diet p	provided				
AlphaOmega - ALA	121/2409	133/2428	•	17.5 %	0.92 [ 0.72, 1.17 ]
Veterans Admin 1969	60/424	78/422	-	15.0 %	0.77 [ 0.56, 1.04 ]
Subtotal (95% CI)	2833	2850	•	32.5 %	0.86 [ 0.71, 1.04 ]
Total events: 181 (Higher PUF	A), 211 (Lower PUFA)				
Heterogeneity: $Tau^2 = 0.0$ ; Ch	$i^2 = 0.82$ , $df = 1$ (P = 0.	36); I <sup>2</sup> =0.0%			
Test for overall effect: $Z = 1.60$	0 (P = 0.11)				
3 Supplements (capsules % un	iusual foods)				
Brox 2001 (1)	0/80	1/40		0.4 %	0.17 [ 0.01, 4.05 ]
Doi 2014 (2)	1/119	0/119		0.4 %	3.00 [ 0.12, 72.91 ]
			0.01 0.1 1 10 100		
		Far	vours higher PUFA Favours lower F	PUFA	

(Continued . . . )

Study or subgroup	Higher PUFA	Lower PUFA	Risk Ratio M- H.Random,95%	Weight	( Continued) Risk Ratio H- H,Random,95%
	n/N	n/N	Cl		Cl
EPOCH 2011 (3)	1/195	0/196		0.4 %	3.02 [ 0.12, 73.57 ]
GLAMT 1993	0/54	1/57		0.4 %	0.35 [ 0.01, 8.45 ]
HARP- Sacks 1995	7/41	7/39		3.6 %	0.95 [ 0.37, 2.46 ]
Nye 1990 (4)	5/36	1/37		3.6 %	0.47 [ 0.18, 1.21 ]
Proudman 2015 (5)	1/87	0/53		0.4 %	1.84 [ 0.08, 44.38 ]
Raitt 2005 (6)	1/100	3/100		0.7 %	0.33 [ 0.04, 3.15 ]
Rose 1965	12/28	9/26		6.2 %	1.24 [ 0.63, 2.44 ]
Subtotal (95% CI)	740	667	•	16.0 %	0.88 [ 0.56, 1.37 ]
Heterogeneity: Tau <sup>2</sup> = 0.0; Chi Test for overall effect: Z = 0.57 4 Any combination MRC 1968		50/194	+	3.9 %	0.97 [ 0.69, 1.37 ]
Sydney Diet-Heart 1978	35/221	23/237	-	9.5 %	1.63 [ 1.00, 2.67 ]
Subtotal (95% CI)	420	431	+	23.4 %	1.22 [ 0.74, 2.02 ]
Total events: 85 (Higher PUFA) Heterogeneity: Tau <sup>2</sup> = 0.09; CH Test for overall effect: $Z = 0.78$	$m^2 = 2.87$ , df = 1 (P = 0)	0.09); I <sup>2</sup> =65%			
Total (95% CI)	5062	5014	•	100.0 %	0.87 [ 0.72, 1.06 ]
Total events: 641 (Higher PUFA	, , , ,				
Heterogeneity: $Tau^2 = 0.04$ ; Ch		= 0.03); l <sup>2</sup> =45%			
Test for overall effect: $Z = 1.35$	· /				
Test for subgroup differences: (	Chi <sup>2</sup> = 2.41, df = 3 (P =	: 0.49), I <sup>2</sup> =0.0%			

0.0 I 0.1 I 10 100 Favours higher PUFA Favours lower PUFA

Favours nigner

(I) Total MI

(2) Total MI

(3) Total MI

(4) Angina

(5) Total MI

(6) Total MI

# Analysis 1.25. Comparison I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes, Outcome 25 STROKE - fatal & non fatal.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes

#### Outcome: 25 STROKE - fatal % non fatal

Study or subgroup	Higher PUFA	Lower PUFA	Risk Ratio M- H,Random,95%	Weight	Risk Ratio M- H,Random,95%
	n/N	n/N	Cl		Cl
AlphaOmega - ALA	10/2409	11/2428		17.5 %	0.92 [ 0.39, 2.15 ]
DART fat 1989	10/1018	3/1015		9.8 %	3.32 [ 0.92, 12.04 ]
Doi 2014	0/119	4/119		2.3 %	0.11[0.01, 2.04]
EPOCH 2011	2/195	0/196		2.1 %	5.03 [ 0.24, 104.01 ]
HARP- Sacks 1995	1/41	0/39		2.0 %	2.86 [ 0.12, 68.10 ]
MRC 1968	2/199	0/194		2.1 %	4.88 [ 0.24, 100.89 ]
Nodari 2011 HF	0/67	1/66		2.0 %	0.33 [ 0.01, 7.92 ]
ORL 2013	2/171	0/165		2.1 %	4.83 [ 0.23, 99.76 ]
PREDIMED 2013	32/2454	49/2543	-	32.2 %	0.68 [ 0.43, 1.05 ]
Sydney Diet-Heart 1978	2/221	2/237	<u> </u>	4.9 %	1.07 [ 0.15, 7.55 ]
Veterans Admin 1969	13/424	22/422		23.0 %	0.59 [ 0.30, 1.15 ]
Fotal (95% CI)	7318	7424	•	100.0 %	0.91 [ 0.58, 1.44 ]
otal events: 74 (Higher PUFA), 9	2 (Lower PUFA)				
Heterogeneity: $Tau^2 = 0.12$ ; Chi <sup>2</sup>	= 13.10, df = 10 (P =	= 0.22); I <sup>2</sup> =24%			
Test for overall effect: $Z = 0.39$ (P	9 = 0.69)				
est for subgroup differences: Not	t applicable				

Favours higher PUFA Favours lower PUFA

# Analysis 1.26. Comparison I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes, Outcome 26 Stroke - SA.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes

#### Outcome: 26 Stroke - SA

Study or subgroup	Higher PUFA	Lower PUFA	Risk Ratio M-	Weight	Risk Ratio M-
	n/N n/N	n/N	H,Random,95% Cl		H,Random,95% Cl
Low risk of bias for allocation	concealment				
AlphaOmega - ALA	10/2409	11/2428		74.0 %	0.92 [ 0.39, 2.15 ]
EPOCH 2011	2/195	0/196		5.9 %	5.03 [ 0.24, 104.01 ]
ORL 2013	2/171	0/165		5.9 %	4.83 [ 0.23, 99.76 ]
Sydney Diet-Heart 1978	2/221	2/237	<b>_</b>	14.2 %	1.07 [ 0.15, 7.55 ]
Subtotal (95% CI)	2996	3026	+	100.0 %	1.14 [ 0.55, 2.38 ]
Fotal events: 16 (Higher PUFA), Heterogeneity: Tau <sup>2</sup> = 0.0; Chi <sup>2</sup> Fest for overall effect: Z = 0.35 2 Low risk of bias for attention	= 2.09, df = 3 (P = 0.	55); I <sup>2</sup> =0.0%			
AlphaOmega - ALA	10/2409	11/2428	-	14.8 %	0.92 [ 0.39, 2.15 ]
Doi 2014	0/119	4/119		1.3 %	0.11 [ 0.01, 2.04 ]
EPOCH 2011	2/195	0/196		1.2 %	5.03 [ 0.24,  04.0  ]
HARP- Sacks 1995	1/41	0/39		1.1 %	2.86 [ 0.12, 68.10 ]
Nodari 2011 HF	0/67	1/66		1.1 %	0.33 [ 0.01, 7.92 ]
ORL 2013	2/171	0/165		1.2 %	4.83 [ 0.23, 99.76 ]
PREDIMED 2013	32/2454	49/2543	=	55.4 %	0.68 [ 0.43, 1.05 ]
Veterans Admin 1969	13/424	22/422		24.0 %	0.59 [ 0.30, 1.15 ]
Subtotal (95% CI) Total events: 60 (Higher PUFA), Heterogeneity: Tau <sup>2</sup> = 0.0; Chi <sup>2</sup> Test for overall effect: Z = 2.07 3 Low risk of bias for complianc	= 6.36, df $= 7$ (P $= 0.000$ ) (P $= 0.000$ )	<b>5978</b> 50); I <sup>2</sup> =0.0%	•	100.0 %	0.71 [ 0.51, 0.98 ]
DART fat 1989	10/1018	3/1015		29.2 %	3.32 [ 0.92, 12.04 ]
MRC 1968	2/199	0/194	•	10.4 %	4.88 [ 0.24, 100.89 ]
Sydney Diet-Heart 1978	2/221	2/237		19.3 %	1.07 [ 0.15, 7.55 ]
Veterans Admin 1969	13/424	22/422		41.1 %	0.59 [ 0.30, 1.15 ]
Veteraris Admin 1707					

(Continued  $\dots$ )

Study or subgroup	Higher PUFA	Lower PUFA	Risk Ratio M-	Weight	( Continued Risk Ratio M-
	n/N	n/N	H,Random,95% Cl		H,Random,959 Cl
tal events: 27 (Higher PUFA), 27 (	Lower PUFA)				
eterogeneity: $Tau^2 = 0.65$ ; $Chi^2 = 0.65$ ;		.08); I <sup>2</sup> =56%			
st for overall effect: Z = 0.55 (P = .ow summary risk of bias	0.58)				
AlphaOmega - ALA	10/2409	/2428		78.7 %	0.92 [ 0.39, 2.15 ]
EPOCH 2011	2/195	0/196		6.3 %	5.03 [ 0.24, 104.01 ]
Sydney Diet-Heart 1978	2/221	2/237		15.1 %	1.07 [ 0.15, 7.55 ]
ıbtotal (95% CI)	2825	2861	•	100.0 %	1.04 [ 0.49, 2.23 ]
tal events: 14 (Higher PUFA), 13 (	-				[, ,0 ]
eterogeneity: $Tau^2 = 0.0$ ; $Chi^2 = 1$ .	14, df = 2 (P = 0.5	57); I <sup>2</sup> =0.0%			
st for overall effect: $Z = 0.11$ (P =	0.91)				
Frials registry or pre-2010 AlphaOmega - ALA	10/2409	/2428	_	17.5 %	0.92 [ 0.39, 2.15 ]
DART fat 1989	10/1018	3/1015		9.8 %	3.32 [ 0.92, 12.04 ]
Doi 2014	0/119	4/119		2.3 %	0.11 [ 0.01, 2.04 ]
EPOCH 2011	2/195	0/196		2.1 %	5.03 [ 0.24, 104.01
HARP- Sacks 1995	/4	0/39		2.0 %	2.86 [ 0.12, 68.10
MRC 1968	2/199	0/194		2.1 %	4.88 [ 0.24, 100.89
Nodari 2011 HF	0/67	1/66		2.0 %	0.33 [ 0.01, 7.92
ORL 2013	2/171	0/165		2.1 %	4.83 [ 0.23, 99.76 ]
PREDIMED 2013	32/2454	49/2543	-	32.2 %	0.68 [ 0.43, 1.05 ]
Sydney Diet-Heart 1978	2/221	2/237		4.9 %	1.07 [ 0.15, 7.55]
Veterans Admin 1969	13/424	22/422		23.0 %	0.59 [ 0.30, 1.15 ]
ıbtotal (95% CI)	7318	7424	•	100.0 %	0.91 [ 0.58, 1.44 ]
tal events: 74 (Higher PUFA), 92 (	Lower PUFA)				
eterogeneity: $Tau^2 = 0.12$ ; $Chi^2 =$		= 0.22); I <sup>2</sup> =24%			
st for overall effect: $Z = 0.39$ (P = No industry funding	0.69)				
MRC 1968	2/199	0/194	<b>_</b>	29.3 %	4.88 [ 0.24, 100.89 ]
Sydney Diet-Heart 1978	2/221	2/237	<b>_</b>	70.7 %	1.07 [ 0.15, 7.55 ]
ıbtotal (95% CI)	420	431		100.0 %	1.67 [ 0.32, 8.62 ]
tal events: 4 (Higher PUFA), 2 (Lo eterogeneity: Tau <sup>2</sup> = 0.0; Chi <sup>2</sup> = 0. st for overall effect: $Z = 0.61$ (P =	69, df = 1 (P = 0.4	40); I <sup>2</sup> =0.0%			
Randomised 100+ participants AlphaOmega - ALA	10/2409	11/2428	_	18.0 %	0.92 [ 0.39, 2.15 ]
DART fat 1989	10/1018	3/1015		10.3 %	3.32 [ 0.92, 12.04 ]

(Continued  $\dots$ )

Risk Ratio M-	Weight	Risk Ratio M-	Lower PUFA	Higher PUFA	Study or subgroup
H,Random,955 Cl		H,Random,95% Cl	n/N	n/N	
0.11 [ 0.01, 2.04 ]	2.5 %		4/119	0/119	Doi 2014
5.03 [ 0.24, 104.01 ]	2.3 %		0/196	2/195	EPOCH 2011
4.88 [ 0.24, 100.89 ]	2.3 %		0/194	2/199	MRC 1968
0.33 [ 0.01, 7.92 ]	2.1 %		1/66	0/67	Nodari 2011 HF
4.83 [ 0.23, 99.76 ]	2.3 %		0/165	2/171	ORL 2013
0.68 [ 0.43, 1.05 ]	31.7 %	-	49/2543	32/2454	PREDIMED 2013
1.07 [ 0.15, 7.55 ]	5.2 %		2/237	2/221	Sydney Diet-Heart 1978
0.59 [ 0.30, 1.15 ]	23.2 %		22/422	13/424	Veterans Admin 1969
0.90 [ 0.56, 1.45 ]	100.0 %	•	<b>7385</b> 0.19); l <sup>2</sup> =28%	= 12.47, df = 9 (P =	Subtotal (95% CI) Total events: 73 (Higher PUFA), 9 Heterogeneity: Tau <sup>2</sup> = 0.13; Chi <sup>2</sup> Test for overall effect: Z = 0.43 (1
			/2428	10/2400	8 Randomised 250+ participants
				10/2409	AlphaOmega - ALA
0.92 [ 0.39, 2.15	19.0 %				
-	19.0 %		3/1015	10/1018	DART fat 1989
0.92 [ 0.39, 2.15 3.32 [ 0.92, 12.04 5.03 [ 0.24, 104.01				10/1018 2/195	DART fat 1989 EPOCH 2011
3.32 [ 0.92, 12.04 5.03 [ 0.24, 104.01	10.9 %		3/1015		
3.32 [ 0.92, 12.04	10.9 %		3/1015 0/196	2/195	EPOCH 2011
3.32 [ 0.92, 12.04 5.03 [ 0.24, 104.01 4.88 [ 0.24, 100.89	10.9 % 2.5 % 2.5 %		3/1015 0/196 0/194	2/195 2/199	EPOCH 2011 MRC 1968
3.32 [ 0.92, 12.04 5.03 [ 0.24, 104.01 4.88 [ 0.24, 100.89 4.83 [ 0.23, 99.76	10.9 % 2.5 % 2.5 % 2.5 %		3/1015 0/196 0/194 0/165	2/195 2/199 2/171	EPOCH 2011 MRC 1968 ORL 2013
3.32 [ 0.92, 12.04 5.03 [ 0.24, 104.01 4.88 [ 0.24, 100.89 4.83 [ 0.23, 99.76 0.68 [ 0.43, 1.05	10.9 % 2.5 % 2.5 % 2.5 % 32.9 %		3/1015 0/196 0/194 0/165 49/2543	2/195 2/199 2/171 32/2454	EPOCH 2011 MRC 1968 ORL 2013 PREDIMED 2013
3.32 [ 0.92, 12.04 5.03 [ 0.24, 104.01 4.88 [ 0.24, 100.89 4.83 [ 0.23, 99.76 0.68 [ 0.43, 1.05 1.07 [ 0.15, 7.55	10.9 % 2.5 % 2.5 % 32.9 % 5.5 %		3/1015 0/196 0/194 0/165 49/2543 2/237	2/195 2/199 2/171 32/2454 2/221	EPOCH 2011 MRC 1968 ORL 2013 PREDIMED 2013 Sydney Diet-Heart 1978

# Analysis 1.27. Comparison I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes, Outcome 27 Stroke - SA fixed-effect.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes

#### Outcome: 27 Stroke - SA fixed-effect

Study or subgroup	Higher PUFA	Lower PUFA	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H,Fixed,95% Cl		M-H,Fixed,95% Cl
AlphaOmega - ALA	10/2409	11/2428	_	11.6 %	0.92 [ 0.39, 2.15 ]
DART fat 1989	10/1018	3/1015		3.2 %	3.32 [ 0.92, 12.04 ]
Doi 2014	0/119	4/119		4.8 %	0.11 [ 0.01, 2.04 ]
EPOCH 2011	2/195	0/196		0.5 %	5.03 [ 0.24,  04.0  ]
HARP- Sacks 1995	1/41	0/39		0.5 %	2.86 [ 0.12, 68.10 ]
MRC 1968	2/199	0/194		0.5 %	4.88 [ 0.24, 100.89 ]
Nodari 2011 HF	0/67	1/66		1.6 %	0.33 [ 0.01, 7.92 ]
ORL 2013	2/171	0/165		0.5 %	4.83 [ 0.23, 99.76 ]
PREDIMED 2013	32/2454	49/2543	-	51.1 %	0.68 [ 0.43, 1.05 ]
Sydney Diet-Heart 1978	2/221	2/237		2.1 %	1.07 [ 0.15, 7.55 ]
Veterans Admin 1969	13/424	22/422		23.4 %	0.59 [ 0.30, 1.15 ]
<b>Total (95% CI)</b> Total events: 74 (Higher PUFA), Heterogeneity: Chi <sup>2</sup> = 13.10, df Test for overall effect: Z = 1.27 Test for subgroup differences: N	$f = 10 (P = 0.22); I^2 = 2$ (P = 0.20)	<b>7424</b>	• 	100.0 %	0.82 [ 0.61, 1.11 ]

Favours higher PUFA Favour

Favours lower PUFA

# Analysis 1.28. Comparison I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes, Outcome 28 Stroke - subgroup by PUFA dose.

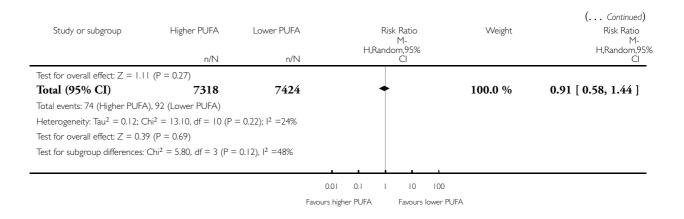
Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes

#### Outcome: 28 Stroke - subgroup by PUFA dose

Study or subgroup	Higher PUFA	Lower PUFA	Risk Ratio M-	Weight	Risk Ratio M-
	n/N	n/N	H,Random,95% Cl		H,Random, Cl
I total PUFA < 1.0% E					
Doi 2014	0/119	4/119		2.3 %	0.11 [ 0.01, 2.04 ]
EPOCH 2011	2/195	0/196		2.1 %	5.03 [ 0.24, 104.01 ]
Nodari 2011 HF	0/67	1/66		2.0 %	0.33 [ 0.01, 7.92 ]
ORL 2013	2/171	0/165		2.1 %	4.83 [ 0.23, 99.76 ]
Subtotal (95% CI)	552	546		8.6 %	0.96 [ 0.14, 6.55 ]
Heterogeneity: Tau <sup>2</sup> = 1.44; Chi <sup>2</sup> Test for overall effect: Z = 0.04 ( 2 total PUFA 1.0 to < 2.0% E		0.19); 1² =38%			
AlphaOmega - ALA	10/2409	11/2428	-	17.5 %	0.92 [ 0.39, 2.15 ]
PREDIMED 2013	32/2454	49/2543	-	32.2 %	0.68 [ 0.43, 1.05
Subtotal (95% CI)	4863	4971	•	<b>49.</b> 7 %	0.72 [ 0.49, 1.07 ]
<b>Subtotal (95% CI)</b> Total events: 42 (Higher PUFA), 4 Heterogeneity: Tau <sup>2</sup> = 0.0; Chi <sup>2</sup> Test for overall effect: Z = 1.63 (	60 (Lower PUFA) = 0.38, df = 1 (P = 0.		•	<b>49.7 %</b> 9.8 %	
<b>Subtotal (95% CI)</b> Total events: 42 (Higher PUFA), Heterogeneity: Tau <sup>2</sup> = 0.0; Chi <sup>2</sup> Test for overall effect: Z = 1.63 ( 3 total PUFA 2.0 to < 5.0% E	60 (Lower PUFA) = 0.38, df = 1 (P = 0. P = 0.10)	.54); l <sup>2</sup> =0.0%	• 		3.32 [ 0.92, 12.04 ]
Subtotal (95% CI) Total events: 42 (Higher PUFA), 4 Heterogeneity: Tau <sup>2</sup> = 0.0; Chi <sup>2</sup> Test for overall effect: $Z = 1.63$ ( 3 total PUFA 2.0 to < 5.0% E DART fat 1989 HARP- Sacks 1995 Subtotal (95% CI) Total events: 11 (Higher PUFA), 7 Heterogeneity: Tau <sup>2</sup> = 0.0; Chi <sup>2</sup> Test for overall effect: $Z = 1.94$ ( 4 total PUFA > 5.0% E	60 (Lower PUFA) = 0.38, df = 1 (P = 0. P = 0.10) 10/1018 1/41 <b>1059</b> 3 (Lower PUFA) = 0.01, df = 1 (P = 0. P = 0.053)	3/1015 0/39 <b>1054</b> 93); 1 <sup>2</sup> =0.0%		9.8 % 2.0 % <b>11.8 %</b>	3.32 [ 0.92, 12.04 2.86 [ 0.12, 68.10 <b>3.25 [ 0.99, 10.72</b> ]
Subtotal (95% CI) Total events: 42 (Higher PUFA), 6 Heterogeneity: Tau <sup>2</sup> = 0.0; Chi <sup>2</sup> Test for overall effect: Z = 1.63 ( 3 total PUFA 2.0 to < 5.0% E DART fat 1989 HARP- Sacks 1995 Subtotal (95% CI) Total events: 11 (Higher PUFA), 7 Heterogeneity: Tau <sup>2</sup> = 0.0; Chi <sup>2</sup> Test for overall effect: Z = 1.94 (	60 (Lower PUFA) = 0.38, df = 1 (P = 0. P = 0.10) 10/1018 1/41 <b>1059</b> 3 (Lower PUFA) = 0.01, df = 1 (P = 0.	.54); I <sup>2</sup> =0.0% 3/1015 0/39 <b>1054</b>		9.8 % 2.0 %	0.72 [ 0.49, 1.07 ] 3.32 [ 0.92, 12.04 ] 2.86 [ 0.12, 68.10 ] 3.25 [ 0.99, 10.72 ] 4.88 [ 0.24, 100.89 ]
Subtotal (95% CI) Total events: 42 (Higher PUFA), 4 Heterogeneity: Tau <sup>2</sup> = 0.0; Chi <sup>2</sup> Test for overall effect: $Z = 1.63$ ( 3 total PUFA 2.0 to < 5.0% E DART fat 1989 HARP- Sacks 1995 Subtotal (95% CI) Total events: 11 (Higher PUFA), 7 Heterogeneity: Tau <sup>2</sup> = 0.0; Chi <sup>2</sup> Test for overall effect: $Z = 1.94$ ( 4 total PUFA > 5.0% E	60 (Lower PUFA) = 0.38, df = 1 (P = 0. P = 0.10) 10/1018 1/41 <b>1059</b> 3 (Lower PUFA) = 0.01, df = 1 (P = 0. P = 0.053)	3/1015 0/39 <b>1054</b> 93); 1 <sup>2</sup> =0.0%		9.8 % 2.0 % <b>11.8 %</b>	3.32 [ 0.92, 12.04 2.86 [ 0.12, 68.10 <b>3.25 [ 0.99, 10.72</b> ]
<b>Subtotal (95% CI)</b> Fotal events: 42 (Higher PUFA), e Heterogeneity: Tau <sup>2</sup> = 0.0; Chi <sup>2</sup> Test for overall effect: Z = 1.63 ( B total PUFA 2.0 to < 5.0% E DART fat 1989 HARP- Sacks 1995 <b>Subtotal (95% CI)</b> Fotal events: 11 (Higher PUFA), T Heterogeneity: Tau <sup>2</sup> = 0.0; Chi <sup>2</sup> Test for overall effect: Z = 1.94 ( Hotal PUFA > 5.0% E MRC 1968	60 (Lower PUFA) = 0.38, df = 1 (P = 0. P = 0.10) 10/1018 1/41 <b>1059</b> 3 (Lower PUFA) = 0.01, df = 1 (P = 0. P = 0.053) 2/199	.54); 1 <sup>2</sup> =0.0% 3/1015 0/39 <b>1054</b> .93); 1 <sup>2</sup> =0.0% 0/194		9.8 % 2.0 % <b>11.8 %</b> 2.1 %	3.32 [ 0.92, 12.04 2.86 [ 0.12, 68.10 <b>3.25 [ 0.99, 10.72</b> ] 4.88 [ 0.24, 100.89 ]

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#### Analysis 1.29. Comparison I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes, Outcome 29 Stroke - subgroup by duration.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes

Outcome: 29 Stroke - subgroup by duration

Study or subgroup	Higher PUFA	Lower PUFA	Risk Ratio M-	Weight	Risk Ratio M-
	n/N	n/N	H,Random,95% Cl		H,Random,95% Cl
Medium duration   to < 2	years				
Doi 2014	0/119	4/119		2.3 %	0.11 [ 0.01, 2.04 ]
EPOCH 2011	2/195	0/196		2.1 %	5.03 [ 0.24, 104.01 ]
Nodari 2011 HF	0/67	1/66		2.0 %	0.33 [ 0.01, 7.92 ]
ORL 2013	2/171	0/165		2.1 %	4.83 [ 0.23, 99.76 ]
Subtotal (95% CI)	552	546	-	8.6 %	0.96 [ 0.14, 6.55 ]
Total events: 4 (Higher PUFA)	), 5 (Lower PUFA)				
Heterogeneity: $Tau^2 = 1.44$ ; C	$Chi^2 = 4.80, df = 3 (P = 0)$	.19); I <sup>2</sup> =38%			
Test for overall effect: $Z = 0.0$	)4 (P = 0.97)				
2 Medium-long duration 2 to	< 4 years				
AlphaOmega - ALA	10/2409	11/2428		17.5 %	0.92 [ 0.39, 2.15 ]
DART fat 1989	10/1018	3/1015		9.8 %	3.32 [ 0.92,   2.04 ]
			0.01 0.1 1 10 100		
		Favo	ours higher PUFA Favours lower PU	IFA	(Continued )

(Continued ...)

( Continued Risk Ratio M- H,Random,9: Cl	Weight	Risk Ratio M- H,Random,95% Cl	Lower PUFA n/N	Higher PUFA n/N	Study or subgroup
2.86 [ 0.12, 68.10 ]	2.0 %		0/39	1/41	HARP- Sacks 1995
1.60 [ 0.61, 4.16 ]	29.3 %	-	3482	3468	Subtotal (95% CI)
				14 (Lower PUFA)	Total events: 21 (Higher PUFA),
			24); I <sup>2</sup> =31%	= 2.89, df = 2 (P = 0.	Heterogeneity: Tau <sup>2</sup> = 0.24; Chi <sup>2</sup>
				P = 0.34)	Test for overall effect: $Z = 0.96$ (I
					3 Long duration 4+ years
4.88 [ 0.24, 100.89 ]	2.1 %		0/194	2/199	MRC 1968
0.68 [ 0.43, 1.05 ]	32.2 %	-	49/2543	32/2454	PREDIMED 2013
1.07 [ 0.15, 7.55 ]	4.9 %		2/237	2/221	Sydney Diet-Heart 1978
0.59 [ 0.30, 1.15 ]	23.0 %		22/422	13/424	Veterans Admin 1969
0.68 [ 0.47, 0.97 ]	62.1 %	•	3396	3298	Subtotal (95% CI)
				73 (Lower PUFA)	Total events: 49 (Higher PUFA), 7
			7); l <sup>2</sup> =0.0%	= 2.02, df = 3 (P = 0.5	Heterogeneity: $Tau^2 = 0.0$ ; Chi <sup>2</sup>
				P = 0.035)	Test for overall effect: $Z = 2.11$ (I
0.91 [ 0.58, 1.44 ]	100.0 %	•	7424	7318	Total (95% CI)
				92 (Lower PUFA)	Total events: 74 (Higher PUFA), 9
			0.22); I <sup>2</sup> =24%	= 13.10, df = 10 (P =	Heterogeneity: Tau <sup>2</sup> = 0.12; Chi <sup>2</sup>
				P = 0.69)	Test for overall effect: $Z = 0.39$ (I
			0.25), I <sup>2</sup> =27%	i <sup>2</sup> = 2.74, df = 2 (P =	Test for subgroup differences: Ch

0.01 0.1 1 10 100

Favours higher PUFA Favours lower PUFA

## Analysis 1.30. Comparison I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes, Outcome 30 Stroke - subgroup by primary or secondary prevention.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes

Outcome: 30 Stroke - subgroup by primary or secondary prevention

Study or subgroup	Higher PUFA	Lower PUFA	Risk Ratio M- H,Random,95%	Weight	Risk Ratio M- H,Random,9
	n/N	n/N	Cl		Cl
I Primary prevention of cardic	wascular disease (CVD)				
EPOCH 2011	2/195	0/196		2.1 %	5.03 [ 0.24, 104.01 ]
ORL 2013	2/171	0/165		2.1 %	4.83 [ 0.23, 99.76 ]
PREDIMED 2013	32/2454	49/2543	-	32.2 %	0.68 [ 0.43, 1.05 ]
Veterans Admin 1969	13/424	22/422		23.0 %	0.59 [ 0.30, 1.15 ]
Subtotal (95% CI)	3244	3326	•	<b>59.4</b> %	0.70 [ 0.45, 1.11 ]
Total events: 49 (Higher PUFA	), 71 (Lower PUFA)				
Heterogeneity: Tau <sup>2</sup> = 0.04; C	$hi^2 = 3.49, df = 3 (P = 0)$	0.32); I <sup>2</sup> = I 4%			
Test for overall effect: $Z = 1.52$	P = (P = 0.13)				
2 Secondary prevention of CV	D				
AlphaOmega - ALA	10/2409	11/2428		17.5 %	0.92 [ 0.39, 2.15 ]
DART fat 1989	10/1018	3/1015		9.8 %	3.32 [ 0.92,   2.04 ]
Doi 2014	0/119	4/119		2.3 %	0.11 [ 0.01, 2.04 ]
HARP- Sacks 1995	/4	0/39		2.0 %	2.86 [ 0.12, 68.10 ]
MRC 1968	2/199	0/194		2.1 %	4.88 [ 0.24, 100.89 ]
Nodari 2011 HF	0/67	1/66		2.0 %	0.33 [ 0.01, 7.92 ]
Sydney Diet-Heart 1978	2/221	2/237		4.9 %	1.07 [ 0.15, 7.55 ]
Subtotal (95% CI)	4074	4098	+	40.6 %	1.24 [ 0.59, 2.62 ]
Total events: 25 (Higher PUFA	), 21 (Lower PUFA)				
Heterogeneity: $Tau^2 = 0.16$ ; C	$hi^2 = 7.12, df = 6 (P = 0)$	0.31); I <sup>2</sup> =16%			
Test for overall effect: $Z = 0.57$	7 (P = 0.57)				
Total (95% CI)	7318	7424	+	100.0 %	0.91 [ 0.58, 1.44 ]
Total events: 74 (Higher PUFA	), 92 (Lower PUFA)				
Heterogeneity: $Tau^2 = 0.12$ ; C	$hi^2 = 13.10, df = 10 (P = 10)$	= 0.22); l <sup>2</sup> =24%			
Test for overall effect: $Z = 0.39$	9 (P = 0.69)				
Test for subgroup differences: (	$Chi^2 = 1.63, df = 1 (P =$	0.20), I <sup>2</sup> =39%			

Favours higher PUFA Favours lower PUFA

## Analysis 1.31. Comparison I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes, Outcome 31 Stroke - subgroup by baseline PUFA dose.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

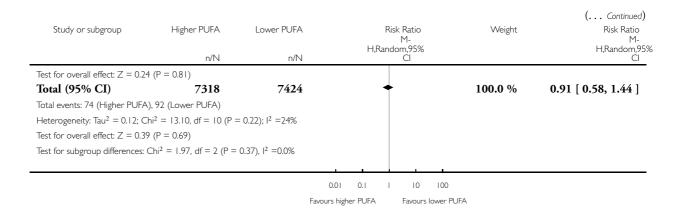
Comparison: I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes

Outcome: 31 Stroke - subgroup by baseline PUFA dose

Study or subgroup	Higher PUFA	Lower PUFA	Risk Ratio M-	Weight	Risk Ratio M-
	n/N	n/N	H,Random,95% Cl		H,Random,S Cl
Baseline total PUFA < 6% E					
Veterans Admin 1969	13/424	22/422		23.0 %	0.59 [ 0.30, 1.15 ]
Subtotal (95% CI)	424	422	•	23.0 %	0.59 [ 0.30, 1.15 ]
Total events: 13 (Higher PUFA)	, 22 (Lower PUFA)				
Heterogeneity: not applicable					
Test for overall effect: $Z = 1.55$	( )				
2 Baseline total PUFA 6 to < 11 DART fat 1989	1% E 10/1018	3/1015		9.8 %	3.32 [ 0.92, 12.04 ]
PREDIMED 2013	32/2454	49/2543	-	32.2 %	
	32/2454				0.68 [ 0.43, 1.05 ]
Sydney Diet-Heart 1978	2/221	2/237		4.9 %	1.07 [ 0.15, 7.55 ]
Subtotal (95% CI)	3693	3795	-	46.8 %	1.21 [ 0.41, 3.59 ]
Total events: 44 (Higher PUFA)					
Heterogeneity: Tau <sup>2</sup> = 0.57; Ch	,	0.07); I <sup>2</sup> =63%			
	(D - 0.72)				
	(P = 0.73)				
3 Baseline total PUFA   +% E		•			
Test for overall effect: Z = 0.34 3 Baseline total PUFA 11+% E Subtotal (95% CI)	0	0			Not estimable
3 Baseline total PUFA 11+% E <b>Subtotal (95% CI)</b> Total events: 0 (Higher PUFA), (	0	0			Not estimable
3 Baseline total PUFA 11+% E <b>Subtotal (95% CI)</b> Total events: 0 (Higher PUFA), ( Heterogeneity: not applicable	<b>0</b> 0 (Lower PUFA)	0			Not estimable
3 Baseline total PUFA 11+% E <b>Subtotal (95% CI)</b> Total events: 0 (Higher PUFA), 6 Heterogeneity: not applicable Test for overall effect: not applic	<b>0</b> 0 (Lower PUFA)	0			Not estimable
3 Baseline total PUFA 11+% E Subtotal (95% CI) Total events: 0 (Higher PUFA), 6 Heterogeneity: not applicable Test for overall effect: not applic	<b>0</b> 0 (Lower PUFA)	0		17.5 %	<b>Not estimable</b> 0.92 [ 0.39, 2.15 ]
3 Baseline total PUFA 11+% E Subtotal (95% CI) Total events: 0 (Higher PUFA), 6 Heterogeneity: not applicable Test for overall effect: not applic 4 Baseline total PUFA unclear	0 0 (Lower PUFA) cable			17.5 % 2.3 %	0.92 [ 0.39, 2.15 ]
3 Baseline total PUFA 11+% E <b>Subtotal (95% CI)</b> Total events: 0 (Higher PUFA), ( Heterogeneity: not applicable Test for overall effect: not applic 4 Baseline total PUFA unclear AlphaOmega - ALA	0 0 (Lower PUFA) cable 10/2409	11/2428			0.92 [ 0.39, 2.15 ] 0.11 [ 0.01, 2.04 ]
3 Baseline total PUFA 11+% E <b>Subtotal (95% CI)</b> Total events: 0 (Higher PUFA), ( Heterogeneity: not applicable Test for overall effect: not applica 4 Baseline total PUFA unclear AlphaOmega - ALA Doi 2014	0 0 (Lower PUFA) cable 10/2409 0/119	11/2428 4/119		2.3 %	0.92 [ 0.39, 2.15 ] 0.11 [ 0.01, 2.04 ] 5.03 [ 0.24, 104.01 ]
3 Baseline total PUFA 11+% E <b>Subtotal (95% CI)</b> Total events: 0 (Higher PUFA), 6 Heterogeneity: not applicable Test for overall effect: not applica 4 Baseline total PUFA unclear AlphaOmega - ALA Doi 2014 EPOCH 2011	0 0 (Lower PUFA) cable 10/2409 0/119 2/195	11/2428 4/119 0/196		2.3 % 2.1 %	0.92 [ 0.39, 2.15 ] 0.11 [ 0.01, 2.04 ] 5.03 [ 0.24, 104.01 ] 2.86 [ 0.12, 68.10 ]
3 Baseline total PUFA 11+% E <b>Subtotal (95% CI)</b> Total events: 0 (Higher PUFA), ( Heterogeneity: not applicable Test for overall effect: not applica 4 Baseline total PUFA unclear AlphaOmega - ALA Doi 2014 EPOCH 2011 HARP- Sacks 1995	0 0 (Lower PUFA) cable 10/2409 0/119 2/195 1/41	11/2428 4/119 0/196 0/39		2.3 % 2.1 % 2.0 %	0.92 [ 0.39, 2.15 ] 0.11 [ 0.01, 2.04 ] 5.03 [ 0.24, 104.01 ] 2.86 [ 0.12, 68.10 ] 4.88 [ 0.24, 100.89 ]
3 Baseline total PUFA 11+% E <b>Subtotal (95% CI)</b> Total events: 0 (Higher PUFA), 4 Heterogeneity: not applicable Test for overall effect: not applica 4 Baseline total PUFA unclear AlphaOmega - ALA Doi 2014 EPOCH 2011 HARP- Sacks 1995 MRC 1968	0 0 (Lower PUFA) cable 10/2409 0/119 2/195 1/41 2/199	11/2428 4/119 0/196 0/39 0/194		2.3 % 2.1 % 2.0 % 2.1 %	0.92 [ 0.39, 2.15 ] 0.11 [ 0.01, 2.04 ] 5.03 [ 0.24, 104.01 ] 2.86 [ 0.12, 68.10 ] 4.88 [ 0.24, 100.89 ] 0.33 [ 0.01, 7.92 ]
3 Baseline total PUFA 11+% E <b>Subtotal (95% CI)</b> Total events: 0 (Higher PUFA), 4 Heterogeneity: not applicable Test for overall effect: not applicable 4 Baseline total PUFA unclear AlphaOmega - ALA Doi 2014 EPOCH 2011 HARP- Sacks 1995 MRC 1968 Nodari 2011 HF ORL 2013	0 0 (Lower PUFA) cable 10/2409 0/119 2/195 1/41 2/199 0/67	11/2428 4/119 0/196 0/39 0/194 1/66		2.3 % 2.1 % 2.0 % 2.1 % 2.0 %	0.92 [ 0.39, 2.15 0.11 [ 0.01, 2.04 5.03 [ 0.24, 104.01 2.86 [ 0.12, 68.10 4.88 [ 0.24, 100.89 0.33 [ 0.01, 7.92 4.83 [ 0.23, 99.76
3 Baseline total PUFA 11+% E <b>Subtotal (95% CI)</b> Total events: 0 (Higher PUFA), 4 Heterogeneity: not applicable Test for overall effect: not applid 4 Baseline total PUFA unclear AlphaOmega - ALA Doi 2014 EPOCH 2011 HARP- Sacks 1995 MRC 1968 Nodari 2011 HF	0 0 (Lower PUFA) cable 10/2409 0/119 2/195 1/41 2/199 0/67 2/171 <b>3201</b>	11/2428 4/119 0/196 0/39 0/194 1/66 0/165		2.3 % 2.1 % 2.0 % 2.1 % 2.0 % 2.1 %	

Favours higher PUFA Favours lower PUFA

(Continued . . . )



#### Analysis 1.32. Comparison I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes, Outcome 32 Stroke - subgroup by replacement.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes

Outcome: 32 Stroke - subgroup by replacement

Study or subgroup	Higher PUFA	Lower PUFA	Risk Ratio M-	Weight	Risk Ratio M-
	n/N	n/N	H,Random,95% Cl		H,Random,95% Cl
I PUFA replaced saturated fats	5				
DART fat 1989	10/1018	3/1015		29.2 %	3.32 [ 0.92, 12.04 ]
MRC 1968	2/199	0/194		10.4 %	4.88 [ 0.24, 100.89 ]
Sydney Diet-Heart 1978	2/221	2/237	<b>+</b>	19.3 %	1.07 [ 0.15, 7.55 ]
Veterans Admin 1969	13/424	22/422		41.1 %	0.59 [ 0.30, 1.15 ]
Subtotal (95% CI)	1862	1868	-	100.0 %	1.36 [ 0.45, 4.11 ]
Total events: 27 (Higher PUFA)	), 27 (Lower PUFA)				
Heterogeneity: Tau <sup>2</sup> = 0.65; Cł	$hi^2 = 6.79, df = 3 (P =$	0.08); I <sup>2</sup> =56%			
Test for overall effect: Z = 0.55	6 (P = 0.58)				
2 PUFA replaced monounsatur	rated fats				
AlphaOmega - ALA	10/2409	11/2428		14.8 %	0.92 [ 0.39, 2.15 ]
EPOCH 2011	2/195	0/196		1.2 %	5.03 [ 0.24, 104.01 ]
		Fave	0.01 0.1 1 10 100 Durs higher PUFA Favours lower PU	JFA	(Continued )

(Continued . . . )

Study or subgroup	Higher PUFA	Lower PUFA	Risk Ratio	Weight	( Continued) Risk Ratio
	n/N	n/N	M- H,Random,95% Cl		M- H,Random,959 Cl
HARP- Sacks 1995	/4	0/39		1.1 %	2.86 [ 0.12, 68.10 ]
Nodari 2011 HF	0/67	1/66		1.1 %	0.33 [ 0.01, 7.92 ]
PREDIMED 2013	32/2454	49/2543	-	55.2 %	0.68 [ 0.43, 1.05 ]
Sydney Diet-Heart 1978	2/221	2/237		2.8 %	1.07 [ 0.15, 7.55 ]
Veterans Admin 1969	3/424	22/422		23.9 %	0.59 [ 0.30, 1.15 ]
Subtotal (95% CI)	5811	5931	•	100.0 %	0.72 [ 0.52, 0.99 ]
Total events: 60 (Higher PUFA)	), 85 (Lower PUFA)				
Heterogeneity: Tau <sup>2</sup> = 0.0; Chi	<sup>2</sup> = 3.43, df = 6 (P = 0	0.75); l <sup>2</sup> =0.0%			
Test for overall effect: Z = 2.00	(P = 0.046)				
3 PUFA replaced carbohydrate	s				
Subtotal (95% CI)	0	0			Not estimable
Total events: 0 (Higher PUFA),	0 (Lower PUFA)				
Heterogeneity: not applicable	× ,				
Test for overall effect: not appli	cable				
4 PUFA replaced protein					
MRC 1968	2/199	0/194		100.0 %	4.88 [ 0.24, 100.89 ]
Subtotal (95% CI)	199	194		100.0 %	4.88 [ 0.24, 100.89 ]
Total events: 2 (Higher PUFA),	0 (Lower PUFA)				
Heterogeneity: not applicable					
Test for overall effect: $Z = 1.02$	(P = 0.31)				
5 PUFA replaced unclear					
Doi 2014	0/119	4/119		50.6 %	0.11 [ 0.01, 2.04 ]
ORL 2013	2/171	0/165		49.4 %	4.83 [ 0.23, 99.76 ]
Subtotal (95% CI)	290	284		100.0 %	0.71 [ 0.02, 29.08 ]
Total events: 2 (Higher PUFA),	4 (Lower PUFA)				
Heterogeneity: Tau <sup>2</sup> = 4.85; Cł	$hi^2 = 3.11, df = 1 (P =$	0.08); l <sup>2</sup> =68%			
Test for overall effect: Z = 0.18	(P = 0.86)				
Test for subgroup differences: (	Chi <sup>2</sup> = 2.65. df = 3 (P =	= 0.45), l <sup>2</sup> =0.0%			

0.01 0.1 1 10 100

Favours higher PUFA Favours lower PUFA

## Analysis 1.33. Comparison I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes, Outcome 33 Stroke - subgroup by sex.

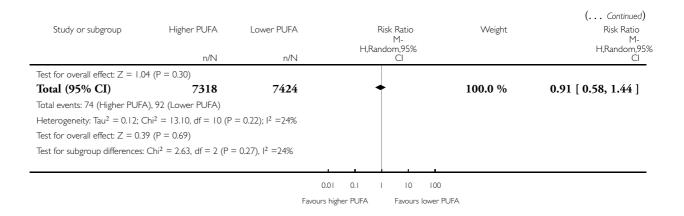
Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes

#### Outcome: 33 Stroke - subgroup by sex

Study or subgroup	Higher PUFA	Lower PUFA	Risk Ratio M-	Weight	Risk Ratic M-
	n/N	n/N	H,Random,95% Cl		H,Random, C
l > 70% men					
AlphaOmega - ALA	10/2409	11/2428		17.5 %	0.92 [ 0.39, 2.15 ]
DART fat 1989	10/1018	3/1015		9.8 %	3.32 [ 0.92, 12.04 ]
Doi 2014	0/119	4/119		2.3 %	0.11 [ 0.01, 2.04 ]
HARP- Sacks 1995	1/41	0/39		2.0 %	2.86 [ 0.12, 68.10 ]
MRC 1968	2/199	0/194		2.1 %	4.88 [ 0.24, 100.89 ]
Nodari 2011 HF	0/67	1/66		2.0 %	0.33 [ 0.01, 7.92 ]
ORL 2013	2/171	0/165		2.1 %	4.83 [ 0.23, 99.76 ]
Sydney Diet-Heart 1978	2/221	2/237		4.9 %	1.07 [ 0.15, 7.55 ]
Veterans Admin 1969	13/424	22/422		23.0 %	0.59 [ 0.30, 1.15 ]
Subtotal (95% CI)	4669	4685	+	<b>65.</b> 7 %	1.04 [ 0.56, 1.93 ]
Total events: 40 (Higher PUFA) Heterogeneity: Tau <sup>2</sup> = 0.21; Ch Test for overall effect: Z = 0.12	ni² = 10.79, df = 8 (P =	= 0.21); I <sup>2</sup> =26%			
Heterogeneity: Tau <sup>2</sup> = 0.21; Cr Test for overall effect: $Z = 0.12$ 2 > 70% women	h <sup>2</sup> = 10.79, df = 8 (P = (P = 0.91)	,			Not estimable
Heterogeneity: Tau <sup>2</sup> = 0.21; Cr Test for overall effect: Z = 0.12 2 > 70% women <b>Subtotal (95% CI)</b> Total events: 0 (Higher PUFA), Heterogeneity: not applicable	i <sup>2</sup> = 10.79, df = 8 (P = (P = 0.91) <b>0</b> 0 (Lower PUFA)	e 0.21); I <sup>2</sup> =26%			Not estimable
Heterogeneity: Tau <sup>2</sup> = 0.21; Cr Test for overall effect: Z = 0.12 2 > 70% women <b>Subtotal (95% CI)</b> Total events: 0 (Higher PUFA), Heterogeneity: not applicable Test for overall effect: not appli	i <sup>2</sup> = 10.79, df = 8 (P = (P = 0.91) <b>0</b> 0 (Lower PUFA)	,			Not estimable
Heterogeneity: Tau <sup>2</sup> = 0.21; Cr Test for overall effect: Z = 0.12 2 > 70% women <b>Subtotal (95% CI)</b> Total events: 0 (Higher PUFA), Heterogeneity: not applicable Test for overall effect: not appli	i <sup>2</sup> = 10.79, df = 8 (P = (P = 0.91) <b>0</b> 0 (Lower PUFA)	,	-	32.2 %	
Heterogeneity: Tau <sup>2</sup> = 0.21; Cr Test for overall effect: Z = 0.12 2 > 70% women <b>Subtotal (95% CI)</b> Total events: 0 (Higher PUFA), Heterogeneity: not applicable Test for overall effect: not applic 3 men % women PREDIMED 2013	i <sup>2</sup> = 10.79, df = 8 (P = (P = 0.91) 0 0 (Lower PUFA) cable	0	•	32.2 % <b>32.2 %</b>	0.68 [ 0.43, 1.05
Heterogeneity: Tau <sup>2</sup> = 0.21; Cr Test for overall effect: Z = 0.12 2 > 70% women <b>Subtotal (95% CI)</b> Total events: 0 (Higher PUFA), Heterogeneity: not applicable Test for overall effect: not applic 3 men % women PREDIMED 2013 <b>Subtotal (95% CI)</b> Total events: 32 (Higher PUFA) Heterogeneity: not applicable Test for overall effect: Z = 1.73	a <sup>2</sup> = 10.79, df = 8 (P = (P = 0.91) 0 (Lower PUFA) cable 32/2454 <b>2454</b> , 49 (Lower PUFA)	<b>0</b> 49/2543	•		Not estimable 0.68 [ 0.43, 1.05 0.68 [ 0.43, 1.05 ]
Heterogeneity: Tau <sup>2</sup> = 0.21; CH Test for overall effect: Z = 0.12 2 > 70% women <b>Subtotal (95% CI)</b> Total events: 0 (Higher PUFA), Heterogeneity: not applicable Test for overall effect: not applic 3 men % women PREDIMED 2013 <b>Subtotal (95% CI)</b> Total events: 32 (Higher PUFA) Heterogeneity: not applicable	a <sup>2</sup> = 10.79, df = 8 (P = (P = 0.91) 0 (Lower PUFA) cable 32/2454 <b>2454</b> , 49 (Lower PUFA)	<b>0</b> 49/2543	•		0.68 [ 0.43, 1.05

(Continued . . . )



#### Analysis 1.34. Comparison I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes, Outcome 34 Stroke - subgroup by age.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes

Outcome: 34 Stroke - subgroup by age

Study or subgroup	Higher PUFA	Lower PUFA	Risk Ratio M-	Weight	Risk Ratio M-
	n/N	n/N	H,Random,95% Cl		H,Random,95% Cl
Mean age < 50 years					
Sydney Diet-Heart 1978	2/221	2/237		4.9 %	1.07 [ 0.15, 7.55 ]
Subtotal (95% CI)	221	237	-	<b>4.9</b> %	1.07 [ 0.15, 7.55 ]
Total events: 2 (Higher PUFA),	2 (Lower PUFA)				
Heterogeneity: not applicable					
Test for overall effect: $Z = 0.07$	7 (P = 0.94)				
2 Mean age 50 to < 65 years					
DART fat 1989	10/1018	3/1015		9.8 %	3.32 [ 0.92, 12.04 ]
HARP- Sacks 1995	/4	0/39		2.0 %	2.86 [ 0.12, 68.10 ]
MRC 1968	2/199	0/194		2.1 %	4.88 [ 0.24, 100.89 ]
Nodari 2011 HF	0/67	1/66		2.0 %	0.33 [ 0.01, 7.92 ]
ORL 2013	2/171	0/165		2.1 %	4.83 [ 0.23, 99.76 ]
- -			0.01 0.1 1 10 100 urs higher PUFA Favours lower PU		

(Continued ...)

Study or subgroup	Higher PUFA	Lower PUFA	Risk Ratio M-	Weight	( Continued) Risk Ratio M-
	n/N	n/N	H,Random,95% Cl		H,Random,95% Cl
Subtotal (95% CI)	1496	1479	*	18.0 %	2.84 [ 1.05, 7.64 ]
Total events: 15 (Higher PUFA)	), 4 (Lower PUFA)				
Heterogeneity: Tau <sup>2</sup> = 0.0; Chi	$P^2 = 2.06$ , df = 4 (P = 0	0.72); I <sup>2</sup> =0.0%			
Test for overall effect: Z = 2.06	5 (P = 0.039)				
3 Mean age 65+ years					
AlphaOmega - ALA	10/2409	11/2428		17.5 %	0.92 [ 0.39, 2.15 ]
Doi 2014	0/119	4/119		2.3 %	0.11 [ 0.01, 2.04 ]
PREDIMED 2013	32/2454	49/2543	-	32.2 %	0.68 [ 0.43, 1.05 ]
Veterans Admin 1969	13/424	22/422		23.0 %	0.59 [ 0.30, 1.15 ]
Subtotal (95% CI)	5406	5512	•	75.0 %	0.67 [ 0.48, 0.94 ]
Total events: 55 (Higher PUFA)	), 86 (Lower PUFA)				
Heterogeneity: $Tau^2 = 0.0$ ; Chi	$P^2 = 2.14$ , df = 3 (P = 0	0.54); I <sup>2</sup> =0.0%			
Test for overall effect: $Z = 2.34$	+ (P = 0.019)				
4 Mean age unclear					
EPOCH 2011	2/195	0/196		2.1 %	5.03 [ 0.24, 104.01 ]
Subtotal (95% CI)	195	196		2.1 %	5.03 [ 0.24, 104.01 ]
Total events: 2 (Higher PUFA),	0 (Lower PUFA)				
Heterogeneity: not applicable					
Test for overall effect: $Z = 1.04$	+ (P = 0.30)				
Total (95% CI)	7318	7424	+	100.0 %	0.91 [ 0.58, 1.44 ]
Total events: 74 (Higher PUFA)	), 92 (Lower PUFA)				
Heterogeneity: Tau <sup>2</sup> = 0.12; Cł	hi <sup>2</sup> = 13.10, df = 10 (P	= 0.22); l <sup>2</sup> =24%			
Test for overall effect: $Z = 0.39$	· /				
Test for subgroup differences: (	$Chi^2 = 8.87, df = 3 (P + 1)$	= 0.03), I <sup>2</sup> =66%			

0.01 0.1 I 10 100 Favours higher PUFA Favours lower PUFA

# Analysis 1.35. Comparison I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes, Outcome 35 Stroke - subgroup by statin use.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes

Outcome: 35 Stroke - subgroup by statin use

Study or subgroup	Higher PUFA	Lower PUFA	Risk Ratio M-	Weight	Risk Ratio M-
	n/N	n/N	H,Random,95% Cl		H,Random,9 Cl
I < 50% on statins					
DART fat 1989	10/1018	3/1015		9.8 %	3.32 [ 0.92, 12.04 ]
EPOCH 2011	2/195	0/196		2.1 %	5.03 [ 0.24, 104.01 ]
HARP- Sacks 1995	1/41	0/39		2.0 %	2.86 [ 0.12, 68.10 ]
MRC 1968	2/199	0/194		2.1 %	4.88 [ 0.24, 100.89 ]
Nodari 2011 HF	0/67	1/66		2.0 %	0.33 [ 0.01, 7.92 ]
ORL 2013	2/171	0/165		2.1 %	4.83 [ 0.23, 99.76 ]
PREDIMED 2013	32/2454	49/2543	-	32.2 %	0.68 [ 0.43, 1.05 ]
Sydney Diet-Heart 1978	2/221	2/237		4.9 %	1.07 [ 0.15, 7.55 ]
Veterans Admin 1969	13/424	22/422		23.0 %	0.59 [ 0.30, 1.15 ]
Subtotal (95% CI)	4790	4877	+	80.1 %	1.02 [ 0.59, 1.78 ]
Total events: 64 (Higher PUFA), Heterogeneity: Tau <sup>2</sup> = 0.17; Ch Test for overall effect: Z = 0.08	i <sup>2</sup> = 11.31, df = 8 (P =	0.18); l <sup>2</sup> =29%			
2 50+% on stating	(1 – 0.24)				
AlphaOmega - ALA	10/2409	/2428		17.5 %	0.92 [ 0.39, 2.15 ]
Doi 2014	0/119	4/119		2.3 %	0.11 [ 0.01, 2.04 ]
Subtotal (95% CI)	2528	2547		19.9 %	0.50 [ 0.07, 3.40 ]
Total events: 10 (Higher PUFA), Heterogeneity: Tau <sup>2</sup> = 1.14; Ch Test for overall effect: Z = 0.70	$i^2 = 1.95$ , df = 1 (P = 0	0.16); I <sup>2</sup> =49%			
Total (95% CI)	(F = 0.46) <b>7318</b>	7424	•	100.0 %	0.91 [ 0.58, 1.44 ]
For the result of the result	92 (Lower PUFA) $h^2 = 13.10$ , df = 10 (P				
Test for subgroup differences: C	( )	0.40) 12 -0.000			

0.01 0.1 1 10 100

Favours higher PUFA Favours lower PUFA

## Analysis 1.36. Comparison I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes, Outcome 36 Stroke - subgroup by intervention type.

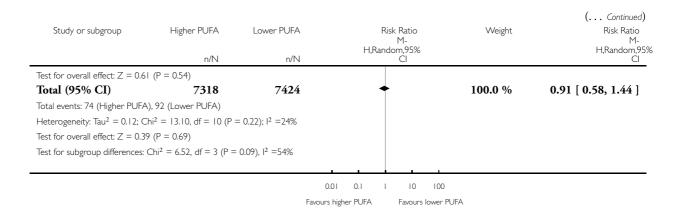
Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes

Outcome: 36 Stroke - subgroup by intervention type

Study or subgroup	Higher PUFA	Lower PUFA	Risk Ratio M-	Weight	Risk Ratio M-
	n/N	n/N	H,Random,95% Cl		H,Random,9 Cl
I Dietary advice					
DART fat 1989	10/1018	3/1015		9.8 %	3.32 [ 0.92, 12.04 ]
Subtotal (95% CI)	1018	1015	-	9.8 %	3.32 [ 0.92, 12.04 ]
Total events: 10 (Higher PUFA	A), 3 (Lower PUFA)				
Heterogeneity: not applicable					
Test for overall effect: $Z = 1.8$	· · · ·				
2 Supplemental foods % diet p AlphaOmega - ALA	10/2409	/2428		17.5 %	0.92 [ 0.39, 2.15
PREDIMED 2013	32/2454	49/2543	-	32.2 %	0.68 [ 0.43, 1.05
			_		-
Veterans Admin 1969	13/424	22/422		23.0 %	0.59 [ 0.30, 1.15 ]
Subtotal (95% CI)	5287	5393	•	72.7 %	0.68 [ 0.49, 0.96 ]
3 Supplements (capsules % un	· /				
Heterogeneity: Tau <sup>2</sup> = 0.0; Ch Test for overall effect: Z = 2.1'		.72); 1² =0.0%			
Doi 2014	0/119	4/119		2.3 %	0.11 [ 0.01, 2.04
EPOCH 2011	2/195	0/196		2.1 %	5.03 [ 0.24, 104.01
					L
HARP- Sacks 1995	/4	0/39		2.0 %	2.86 [ 0.12, 68.10
Nodari 2011 HF	0/67	1/66		2.0 %	0.33 [ 0.01, 7.92
ORL 2013	2/171	0/165		2.1 %	4.83 [ 0.23, 99.76 ]
Subtotal (95% CI)	593	585	-	10.5 %	1.18 [ 0.25, 5.62 ]
Total events: 5 (Higher PUFA)	, ,				
Heterogeneity: $Tau^2 = 0.74$ ; C		0.27); l <sup>2</sup> =23%			
Test for overall effect: Z = 0.2 4 Any combination	0 (P = 0.84)				
MRC 1968	2/199	0/194		2.1 %	4.88 [ 0.24, 100.89
Sydney Diet-Heart 1978	2/221	2/237		4.9 %	1.07 [ 0.15, 7.55
Subtotal (95% CI)	420	431		7 <b>.0</b> %	1.67 [ 0.32, 8.62 ]
Total events: 4 (Higher PUFA)		101		/.0 /0	107 [ 0152, 0102 ]
Heterogeneity: $Tau^2 = 0.0$ ; Ch	· · · · ·	.40); l <sup>2</sup> =0.0%			
			0.01 0.1 1 10 100 rs higher PUFA Favours lower F		

(Continued . . . )



#### Analysis 1.37. Comparison I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes, Outcome 37 Stroke - subgroup by fatal & non fatal.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes

Outcome: 37 Stroke - subgroup by fatal % non fatal

Study or subgroup	Higher PUFA	Lower PUFA	Risk Ratio M-	Weight	Risk Ratio M-
	n/N	n/N	H,Random,95% Cl		H,Random,95% Cl
I Fatal stroke					
AlphaOmega - ALA	10/2409	11/2428		54.4 %	0.92 [ 0.39, 2.15 ]
MRC 1968	2/199	0/194		5.5 %	4.88 [ 0.24, 100.89 ]
Sydney Diet-Heart 1978	2/221	2/237	<b>_</b>	12.9 %	1.07 [ 0.15, 7.55 ]
Veterans Admin 1969	3/424	9/422		27.2 %	0.33 [ 0.09, 1.22 ]
Subtotal (95% CI)	3253	3281	•	100.0 %	0.78 [ 0.38, 1.60 ]
Total events: 17 (Higher PUFA)	, 22 (Lower PUFA)				
Heterogeneity: $Tau^2 = 0.06$ ; Ch	$m^2 = 3.31$ , df = 3 (P = 0	0.35); I <sup>2</sup> =9%			
Test for overall effect: Z = 0.68	(P = 0.50)				
2 Non-fatal stroke					
Doi 2014	0/119	4/119		23.9 %	0.11 [ 0.01, 2.04 ]
Veterans Admin 1969	10/424	13/422	-	76.1 %	0.77 [ 0.34, 1.73 ]
			0.01 0.1 1 10 100		
		Fa	avours higher PUFA Favours lower F	PUFA	
					(Continued )

Study or subgroup	Higher PUFA n/N	Lower PUFA	Risk Ratio M- H,Random,95% Cl	Weight	( Continued) Risk Ratio H,Random,95% C
Subtotal (95% CI)	543	541		100.0 %	0.48 [ 0.09, 2.51 ]
otal events: 10 (Higher PUFA),	17 (Lower PUFA)	-			
leterogeneity: Tau <sup>2</sup> = 0.76; Chi	$^{2} = 1.64, df = 1 (P = 0)$	0.20); I <sup>2</sup> =39%			
Test for overall effect: $Z = 0.87$ (	(P = 0.39)				
Only combined fatal % non fat	al data provided				
DART fat 1989	10/1018	3/1015		25.5 %	3.32 [ 0.92, 12.04 ]
EPOCH 2011	2/195	0/196		8.6 %	5.03 [ 0.24, 104.01 ]
HARP- Sacks 1995	1/41	0/39		8.0 %	2.86 [ 0.12, 68.10 ]
Nodari 2011 HF	0/67	1/66		7.9 %	0.33 [ 0.01, 7.92 ]
ORL 2013	2/171	0/165		8.6 %	4.83 [ 0.23, 99.76 ]
PREDIMED 2013	32/2454	49/2543	-	41.3 %	0.68 [ 0.43, 1.05 ]
Subtotal (95% CI)	3946	4024	-	100.0 %	1.51 [ 0.56, 4.07 ]
otal events: 47 (Higher PUFA),	````				
Heterogeneity: Tau <sup>2</sup> = 0.56; Chi		).     );   <sup>2</sup> =44%			
Test for overall effect: $Z = 0.82$ (	,				
est for subgroup differences: Ch	$hi^2 = 1.77, df = 2 (P =$	0.41), 12 =0.0%			
			<u></u>		

Favours higher PUFA Favours lower PUFA

#### Analysis 1.38. Comparison I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes, Outcome 38 Stroke - subgroup by ischaemic & haemorrhagic.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes

Outcome: 38 Stroke - subgroup by ischaemic % haemorrhagic

Study or subgroup	Higher PUFA Lower PUFA	Risk Ratio M-	Weight	Risk Ratio M-	
	n/N	n/N	H,Random,95% Cl		H,Random, C
lschaemic stroke					
DART fat 1989	7/1018	1/1015		53.8 %	6.98 [ 0.86, 56.62
MRC 1968	1/199	0/194		23.1 %	2.93 [ 0.12, 71.37
ORL 2013	/ 7	0/165		23.1 %	2.90 [ 0.12, 70.57
Subtotal (95% CI)	1388	1374	-	100.0 %	4.66 [ 1.00, 21.63
otal events: 9 (Higher PUFA),   Heterogeneity: Tau <sup>2</sup> = 0.0; Chi <sup>2</sup> est for overall effect: Z = 1.96 : Haemorrhagic stroke	= 0.32, df = 2 (P = 0	.85); I <sup>2</sup> =0.0%			
DART fat 1989	3/1018	2/1015	<b>_</b>	61.5 %	1.50 [ 0.25, 8.93
MRC 1968	1/199	0/194		19.2 %	2.93 [ 0.12, 71.37
ORL 2013	1/171	0/165		19.3 %	2.90 [ 0.12, 70.57
Subtotal (95% CI)	1388	1374	-	100.0 %	1.93 [ 0.48, 7.85
Only combined ischaemic and AlphaOmega - ALA	10/2409	11/2428	-	14.6 %	0.92 [ 0.39, 2.15
Heterogeneity: Tau <sup>2</sup> = 0.0; Chi <sup>2</sup> Test for overall effect: Z = 0.92					
			]		-
Doi 2014	0/119	4/119		1.3 %	0.11 [ 0.01, 2.04
EPOCH 2011	2/195	0/196		1.2 %	5.03 [ 0.24, 104.01
HARP- Sacks 1995	1/41	0/39		1.1 %	2.86 [ 0.12, 68.10
Nodari 2011 HF	0/67	1/66		1.1 %	0.33 [ 0.01, 7.92
PREDIMED 2013	32/2454	49/2543	-	54.5 %	0.68 [ 0.43, 1.05
Sydney Diet-Heart 1978	2/221	2/237		2.8 %	1.07 [ 0.15, 7.55
Veterans Admin 1969	13/424	22/422		23.6 %	0.59 [ 0.30, 1.15
Subtotal (95% CI)	5930	6050	•	100.0 %	0.70 [ 0.50, 0.97
otal events: 60 (Higher PUFA),	89 (Lower PUFA)				
leterogeneity: Tau <sup>2</sup> = 0.0; Chi <sup>2</sup>		.66); I <sup>2</sup> =0.0%			
est for overall effect: $Z = 2.15$	· /				
est for subgroup differences: C					

#### Analysis 1.39. Comparison I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes, Outcome 39 MAJOR ADVERSE CARDIAC & CEREBROVASCULAR EVENTS (MACCEs).

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes

Outcome: 39 MAJOR ADVERSE CARDIAC % CEREBROVASCULAR EVENTS (MACCEs)

Study or subgroup	Higher PUFA	Lower PUFA		Risk Ratio M-	Weight	Risk Ratio M-
	n/N	n/N	H,Rar	ndom,95% Cl		H,Random,95% Cl_
DART fat 1989	333/1018	337/1015		•	57.4 %	0.99 [ 0.87, 1.12 ]
Veterans Admin 1969	60/424	87/422	-		42.6 %	0.69 [ 0.51, 0.93 ]
Total (95% CI)	1442	1437	•		100.0 %	0.84 [ 0.59, 1.20 ]
Total events: 393 (Higher PU	IFA), 424 (Lower PUFA)					
Heterogeneity: $Tau^2 = 0.05$ ;	$Chi^2 = 4.80, df = 1 (P =$	= 0.03); l <sup>2</sup> =79%				
Test for overall effect: $Z = 0.1$	94 (P = 0.35)					
Test for subgroup differences	:: Not applicable					
			0.01 0.1	1 10 100		
			Favours higher PUFA	Favours lower P	UFA	

## Analysis 1.40. Comparison I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes, Outcome 40 MACCEs - SA.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes

Outcome: 40 MACCEs - SA

Study or subgroup	Higher PUFA	Lower PUFA	Risk Ratio M-	Weight	Risk Ratio M-
	n/N	n/N	H,Random,95% Cl		H,Random,9 Cl
I Low risk of bias for allocation	n concealment				
Subtotal (95% CI)	0	0			Not estimable
Total events: 0 (Higher PUFA),	0 (Lower PUFA)				
Heterogeneity: not applicable					
Test for overall effect: not appli	icable				
2 Low risk of bias for attention	I.				
Veterans Admin 1969	60/424	87/422	<u>+</u>	100.0 %	0.69 [ 0.51, 0.93 ]
Subtotal (95% CI)	424	422	•	100.0 %	0.69 [ 0.51, 0.93 ]
Total events: 60 (Higher PUFA)	), 87 (Lower PUFA)				
Heterogeneity: not applicable					
Test for overall effect: $Z = 2.46$	P = 0.014				
3 Low risk of bias for complian	ce				
DART fat 1989	333/1018	337/1015	<mark>+</mark>	57.4 %	0.99 [ 0.87, 1.12 ]
Veterans Admin 1969	60/424	87/422	-	42.6 %	0.69 [ 0.51, 0.93 ]
	60/424 <b>1442</b>	87/422 <b>1437</b>	•	42.6 % <b>100.0 %</b>	0.69 [ 0.51, 0.93 ] <b>0.84 [ 0.59, 1.20 ]</b>
Veterans Admin 1969 Subtotal (95% CI)	1442	1437	•		
Veterans Admin 1969 Subtotal (95% CI) Total events: 393 (Higher PUFA	<b>1442</b> A), 424 (Lower PUFA)	1437	•		
Veterans Admin 1969 <b>Subtotal (95% CI)</b> Total events: 393 (Higher PUF/ Heterogeneity: Tau <sup>2</sup> = 0.05; Cf	<b>1442</b> A), 424 (Lower PUFA) hi <sup>2</sup> = 4.80, df = 1 (P =	1437	•		
Veterans Admin 1969 <b>Subtotal (95% CI)</b> Total events: 393 (Higher PUFA Heterogeneity: Tau <sup>2</sup> = 0.05; CP Test for overall effect: Z = 0.94	<b>1442</b> A), 424 (Lower PUFA) hi <sup>2</sup> = 4.80, df = 1 (P =	1437	•		
Veterans Admin 1969 <b>Subtotal (95% CI)</b> Total events: 393 (Higher PUFA Heterogeneity: Tau <sup>2</sup> = 0.05; CF Test for overall effect: Z = 0.94 4 Low summary risk of bias	<b>1442</b> A), 424 (Lower PUFA) hi <sup>2</sup> = 4.80, df = 1 (P =	1437	•		0.84 [ 0.59, 1.20 ]
Veterans Admin 1969 <b>Subtotal (95% CI)</b> Total events: 393 (Higher PUFA Heterogeneity: Tau <sup>2</sup> = 0.05; CH Test for overall effect: Z = 0.94 4 Low summary risk of bias <b>Subtotal (95% CI)</b>	<b>1442</b> A), 424 (Lower PUFA) $hi^2 = 4.80, df = 1 (P = 4, (P = 0.35))$ <b>0</b>	<b>1437</b> = 0.03);   <sup>2</sup> =79%			0.84 [ 0.59, 1.20 ]
Veterans Admin 1969 <b>Subtotal (95% CI)</b> Total events: 393 (Higher PUFA Heterogeneity: Tau <sup>2</sup> = 0.05; CH Test for overall effect: Z = 0.94 4 Low summary risk of bias <b>Subtotal (95% CI)</b> Total events: 0 (Higher PUFA),	<b>1442</b> A), 424 (Lower PUFA) $hi^2 = 4.80, df = 1 (P = 4, (P = 0.35))$ <b>0</b>	<b>1437</b> = 0.03);   <sup>2</sup> =79%			0.84 [ 0.59, 1.20 ]
Veterans Admin 1969 <b>Subtotal (95% CI)</b> Total events: 393 (Higher PUFA Heterogeneity: Tau <sup>2</sup> = 0.05; CP Test for overall effect: Z = 0.94 4 Low summary risk of bias <b>Subtotal (95% CI)</b> Total events: 0 (Higher PUFA), Heterogeneity: not applicable	<b>1442</b> A), 424 (Lower PUFA) hi <sup>2</sup> = 4.80, df = 1 (P = 4 (P = 0.35) <b>0</b> 0 (Lower PUFA)	<b>1437</b> = 0.03);   <sup>2</sup> =79%	•		0.84 [ 0.59, 1.20 ]
Veterans Admin 1969 <b>Subtotal (95% CI)</b> Total events: 393 (Higher PUFA Heterogeneity: Tau <sup>2</sup> = 0.05; CF Test for overall effect: Z = 0.94 4 Low summary risk of bias <b>Subtotal (95% CI)</b> Total events: 0 (Higher PUFA), Heterogeneity: not applicable Test for overall effect: not appli 5 Trials registry or pre-2010	<b>1442</b> A), 424 (Lower PUFA) hi <sup>2</sup> = 4.80, df = 1 (P = 4 (P = 0.35) <b>0</b> 0 (Lower PUFA) icable	1437 : 0.03); I <sup>2</sup> =79% 0	•	100.0 %	0.84 [ 0.59, 1.20 ] Not estimable
Veterans Admin 1969 <b>Subtotal (95% CI)</b> Total events: 393 (Higher PUFA Heterogeneity: Tau <sup>2</sup> = 0.05; CF Test for overall effect: Z = 0.94 4 Low summary risk of bias <b>Subtotal (95% CI)</b> Total events: 0 (Higher PUFA), Heterogeneity: not applicable Test for overall effect: not appli	<b>1442</b> A), 424 (Lower PUFA) hi <sup>2</sup> = 4.80, df = 1 (P = 4 (P = 0.35) <b>0</b> 0 (Lower PUFA)	<b>1437</b> = 0.03);   <sup>2</sup> =79%			0.84 [ 0.59, 1.20 ] Not estimable
Veterans Admin 1969 <b>Subtotal (95% CI)</b> Total events: 393 (Higher PUFA Heterogeneity: Tau <sup>2</sup> = 0.05; CH Test for overall effect: Z = 0.94 4 Low summary risk of bias <b>Subtotal (95% CI)</b> Total events: 0 (Higher PUFA), Heterogeneity: not applicable Test for overall effect: not appli 5 Trials registry or pre-2010	<b>1442</b> A), 424 (Lower PUFA) hi <sup>2</sup> = 4.80, df = 1 (P = 4 (P = 0.35) <b>0</b> 0 (Lower PUFA) icable	1437 : 0.03); I <sup>2</sup> =79% 0		100.0 %	0.84 [ 0.59, 1.20 ] Not estimable
Veterans Admin 1969 <b>Subtotal (95% CI)</b> Total events: 393 (Higher PUFA Heterogeneity: Tau <sup>2</sup> = 0.05; CH Test for overall effect: Z = 0.94 4 Low summary risk of bias <b>Subtotal (95% CI)</b> Total events: 0 (Higher PUFA), Heterogeneity: not applicable Test for overall effect: not appli 5 Trials registry or pre-2010 DART fat 1989 Veterans Admin 1969	1442 A), 424 (Lower PUFA) hi <sup>2</sup> = 4.80, df = 1 (P = 4 (P = 0.35) 0 0 (Lower PUFA) icable 333/1018	<b>1437</b> : 0.03); I <sup>2</sup> =79% <b>0</b> 337/1015		<b>100.0 %</b> 57.4 %	
Veterans Admin 1969 <b>Subtotal (95% CI)</b> Total events: 393 (Higher PUFA Heterogeneity: Tau <sup>2</sup> = 0.05; CF Test for overall effect: Z = 0.94 4 Low summary risk of bias <b>Subtotal (95% CI)</b> Total events: 0 (Higher PUFA), Heterogeneity: not applicable Test for overall effect: not appli 5 Trials registry or pre-2010 DART fat 1989 Veterans Admin 1969 <b>Subtotal (95% CI)</b>	1442 A), 424 (Lower PUFA) hi <sup>2</sup> = 4.80, df = 1 (P = 4 (P = 0.35) 0 0 (Lower PUFA) icable 333/1018 60/424 1442	1437 5 (0.03); 1 <sup>2</sup> =79% 0 337/1015 87/422 1437		<b>100.0 %</b> 57.4 % 42.6 %	0.84 [ 0.59, 1.20 ] Not estimable
Veterans Admin 1969 <b>Subtotal (95% CI)</b> Total events: 393 (Higher PUFA Heterogeneity: Tau <sup>2</sup> = 0.05; CF Test for overall effect: Z = 0.94 4 Low summary risk of bias <b>Subtotal (95% CI)</b> Total events: 0 (Higher PUFA), Heterogeneity: not applicable Test for overall effect: not appli 5 Trials registry or pre-2010 DART fat 1989 Veterans Admin 1969 <b>Subtotal (95% CI)</b> Total events: 393 (Higher PUFA	1442 A), 424 (Lower PUFA) hi <sup>2</sup> = 4.80, df = 1 (P = 4 (P = 0.35) 0 0 (Lower PUFA) icable 333/1018 60/424 1442 A), 424 (Lower PUFA)	1437 5 (0.03); 1 <sup>2</sup> =79% 0 337/1015 87/422 1437		<b>100.0 %</b> 57.4 % 42.6 %	0.84 [ 0.59, 1.20 ] Not estimable
Veterans Admin 1969 <b>Subtotal (95% CI)</b> Total events: 393 (Higher PUFA Heterogeneity: Tau <sup>2</sup> = 0.05; CP Test for overall effect: Z = 0.94 4 Low summary risk of bias <b>Subtotal (95% CI)</b> Total events: 0 (Higher PUFA), Heterogeneity: not applicable Test for overall effect: not appli 5 Trials registry or pre-2010 DART fat 1989	1442 A), 424 (Lower PUFA) hi <sup>2</sup> = 4.80, df = 1 (P = 4 (P = 0.35) 0 0 (Lower PUFA) icable 333/1018 60/424 1442 A), 424 (Lower PUFA) hi <sup>2</sup> = 4.80, df = 1 (P =	1437 5 (0.03); 1 <sup>2</sup> =79% 0 337/1015 87/422 1437		<b>100.0 %</b> 57.4 % 42.6 %	0.84 [ 0.59, 1.20 ] Not estimable
Veterans Admin 1969 <b>Subtotal (95% CI)</b> Total events: 393 (Higher PUFA Heterogeneity: Tau <sup>2</sup> = 0.05; Cf Test for overall effect: Z = 0.94 4 Low summary risk of bias <b>Subtotal (95% CI)</b> Total events: 0 (Higher PUFA), Heterogeneity: not applicable Test for overall effect: not appli 5 Trials registry or pre-2010 DART fat 1989 Veterans Admin 1969 <b>Subtotal (95% CI)</b> Total events: 393 (Higher PUFA Heterogeneity: Tau <sup>2</sup> = 0.05; Cf	1442 A), 424 (Lower PUFA) hi <sup>2</sup> = 4.80, df = 1 (P = 4 (P = 0.35) 0 0 (Lower PUFA) icable 333/1018 60/424 1442 A), 424 (Lower PUFA) hi <sup>2</sup> = 4.80, df = 1 (P =	1437 5 (0.03); 1 <sup>2</sup> =79% 0 337/1015 87/422 1437		<b>100.0 %</b> 57.4 % 42.6 %	0.84 [ 0.59, 1.20 ] Not estimable

(Continued ...)

Study or subgroup	Higher PUFA	Lower PUFA	Risk Ratio M- H,Random,95% Cl	Weight	( Continued) Risk Ratio H,Random,95%
Total events: 0 (Higher PUFA)		11/1N	CI CI		<u> </u>
Heterogeneity: not applicable					
Test for overall effect: not app					
7 Randomised 100+ participa					
DART fat 1989	333/1018	337/1015	=	57.4 %	0.99 [ 0.87, 1.12 ]
Veterans Admin 1969	60/424	87/422	-	42.6 %	0.69 [ 0.51, 0.93 ]
Subtotal (95% CI)	1442	1437	•	100.0 %	0.84 [ 0.59, 1.20 ]
Total events: 393 (Higher PUF	A), 424 (Lower PUFA)	l .			
Heterogeneity: Tau <sup>2</sup> = 0.05; C	Chi <sup>2</sup> = 4.80, df = 1 (P =	= 0.03); I <sup>2</sup> =79%			
Test for overall effect: $Z = 0.9$	4 (P = 0.35)				
8 Randomised 250+ participa	ints				
DART fat 1989	333/1018	337/1015	•	57.4 %	0.99 [ 0.87, 1.12 ]
Veterans Admin 1969	60/424	87/422	-	42.6 %	0.69 [ 0.51, 0.93 ]
Subtotal (95% CI)	1442	1437	•	100.0 %	0.84 [ 0.59, 1.20 ]
Total events: 393 (Higher PUF	A), 424 (Lower PUFA)	l .			
Heterogeneity: Tau <sup>2</sup> = 0.05; C	Chi <sup>2</sup> = 4.80, df = 1 (P =	= 0.03); I <sup>2</sup> =79%			
Test for overall effect: $Z = 0.9$	4 (P = 0.35)				

Favours higher PUFA Favours lower PUFA

### Analysis 1.41. Comparison I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes, Outcome 41 MACCEs - SA fixed-effect.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes

Outcome: 41 MACCEs - SA fixed-effect

Study or subgroup	Higher PUFA n/N	Lower PUFA n/N	Risk Ratio M-H,Fixed,95% Cl	Weight	Risk Ratio M-H,Fixed,95% Cl
			11-1 I, I Xeu, 73% CI		
DART fat 1989	333/1018	337/1015		79.5 %	0.99 [ 0.87, 1.12 ]
Veterans Admin 1969	60/424	87/422	-	20.5 %	0.69 [ 0.51, 0.93 ]
Total (95% CI)	1442	1437	•	100.0 %	0.92 [ 0.82, 1.04 ]
Total events: 393 (Higher PUFA	A), 424 (Lower PUFA)				
Heterogeneity: Chi <sup>2</sup> = 4.80, df	= I (P = 0.03); I <sup>2</sup> =79	9%			
Test for overall effect: Z = 1.35	(P = 0.18)				
Test for subgroup differences: N	Vot applicable				

Favours higher PUFA Favours lower PUFA

# Analysis 1.42. Comparison I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes, Outcome 42 MACCEs - subgroup by PUFA dose.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes

Outcome: 42 MACCEs - subgroup by PUFA dose

Study or subgroup	Higher PUFA	Lower PUFA	Risk Ratio M-	Weight	Risk Ratio M-
	n/N	n/N	H,Random,95% Cl		H,Random,9 Cl
total PUFA < 1.0% E					
Subtotal (95% CI)	0	0			Not estimable
Total events: 0 (Higher PUFA	A), 0 (Lower PUFA)				
Heterogeneity: not applicabl	e				
Test for overall effect: not ap	plicable				
2 total PUFA 1.0 to $< 2.0\%$	E				
Subtotal (95% CI)	0	0			Not estimable
Total events: 0 (Higher PUFA	A), 0 (Lower PUFA)				
Heterogeneity: not applicabl	e				
Test for overall effect: not ap	plicable				
3 total PUFA 2.0 to $< 5.0\%$	E				
DART fat 1989	333/1018	337/1015		57.4 %	0.99 [ 0.87, 1.12 ]
Subtotal (95% CI)	1018	1015	•	57.4 %	0.99 [ 0.87, 1.12 ]
Total events: 333 (Higher PU	JFA), 337 (Lower PUFA)				
Heterogeneity: not applicabl	e				
Test for overall effect: $Z = 0$	.24 (P = 0.81)				
4 total PUFA > 5.0% E					
Veterans Admin 1969	60/424	87/422	-	42.6 %	0.69 [ 0.51, 0.93 ]
Subtotal (95% CI)	424	422	•	42.6 %	0.69 [ 0.51, 0.93 ]
Subiolar (J) /0 CI					
, ,	-A), 87 (LOWER PUFA)				
Total events: 60 (Higher PUI	, , ,				
Total events: 60 (Higher PUF Heterogeneity: not applicabl Test for overall effect: Z = 2	e				
Total events: 60 (Higher PUI Heterogeneity: not applicabl	e	1437	•	100.0 %	0.84 [ 0.59, 1.20 ]
Total events: 60 (Higher PUI Heterogeneity: not applicabl Test for overall effect: $Z = 2$	e .46 (P = 0.014) <b>1442</b>		•	100.0 %	0.84 [ 0.59, 1.20 ]
Total events: 60 (Higher PUI Heterogeneity: not applicabl Test for overall effect: Z = 2 <b>Total (95% CI)</b> Total events: 393 (Higher PU	e .46 (P = 0.014) <b>1442</b> JFA), 424 (Lower PUFA)		•	100.0 %	0.84 [ 0.59, 1.20 ]
Total events: 60 (Higher PUI Heterogeneity: not applicabl Test for overall effect: Z = 2 <b>Total (95% CI)</b>	e .46 (P = 0.014) <b>1442</b> JFA), 424 (Lower PUFA) Chi <sup>2</sup> = 4.80, df = 1 (P =		•	100.0 %	0.84 [ 0.59, 1.20 ]

0.01 0.1 I 10 100 Favours higher PUFA Favours lower PUFA

# Analysis 1.43. Comparison I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes, Outcome 43 MACCEs - subgroup by duration.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes

Outcome: 43 MACCEs - subgroup by duration

Study or subgroup	Higher PUFA	Lower PUFA	Risk Ratio M-	Weight	Risk Ratio M-
	n/N	n/N	H,Random,95% Cl		H,Random,95 Cl
Medium duration   to < 2 )	years				
Subtotal (95% CI)	0	0			Not estimable
Total events: 0 (Higher PUFA)	), 0 (Lower PUFA)				
Heterogeneity: not applicable					
Test for overall effect: not app	licable				
2 Medium-long duration 2 to	< 4 years				
DART fat 1989	333/1018	337/1015	-	57.4 %	0.99 [ 0.87, 1.12 ]
Subtotal (95% CI)	1018	1015	•	57.4 %	0.99 [ 0.87, 1.12 ]
Total events: 333 (Higher PUF	A), 337 (Lower PUFA)				
Heterogeneity: not applicable	, , ,				
Test for overall effect: $Z = 0.2$	24 (P = 0.81)				
3 Long duration 4+ years					
Veterans Admin 1969	60/424	87/422	-	42.6 %	0.69 [ 0.51, 0.93 ]
Subtotal (95% CI)	424	422	•	42.6 %	0.69 [ 0.51, 0.93 ]
Total events: 60 (Higher PUFA	A), 87 (Lower PUFA)				
Heterogeneity: not applicable					
Test for overall effect: $Z = 2.4$	6 (P = 0.014)				
Total (95% CI)	1442	1437	•	100.0 %	0.84 [ 0.59, 1.20 ]
Total events: 393 (Higher PUF	FA), 424 (Lower PUFA)				
Heterogeneity: $Tau^2 = 0.05$ ; C	$Chi^2 = 4.80, df = 1 (P =$	0.03); l <sup>2</sup> =79%			
Test for overall effect: $Z = 0.9$	94 (P = 0.35)				
Test for subgroup differences:	$\rm Chi^2$ = 4.76, df = 1 (P	= 0.03), l <sup>2</sup> =79%			
			0.01 0.1 1 10 100		
			Favours higher PUFA Favours lower P	UFA	

# Analysis 1.44. Comparison I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes, Outcome 44 MACCEs - subgroup by primary or secondary prevention.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes

Outcome: 44 MACCEs - subgroup by primary or secondary prevention

Study or subgroup	Higher PUFA	Lower PUFA	Risk Ratio M-	Weight	Risk Ratio M-
	n/N	n/N n/N	H,Random,95% Cl		H,Random,95% Cl
I Primary prevention of CVD	)				
Veterans Admin 1969	60/424	87/422		42.6 %	0.69 [ 0.51, 0.93 ]
Subtotal (95% CI)	424	422	•	42.6 %	0.69 [ 0.51, 0.93 ]
Total events: 60 (Higher PUFA	A), 87 (Lower PUFA)				
Heterogeneity: not applicable					
Test for overall effect: $Z = 2.4$	6 (P = 0.014)				
2 Secondary prevention of C	VD				
DART fat 1989	333/1018	337/1015	•	57.4 %	0.99 [ 0.87, 1.12 ]
Subtotal (95% CI)	1018	1015	•	57.4 %	0.99 [ 0.87, 1.12 ]
Total events: 333 (Higher PUF	FA), 337 (Lower PUFA)				
Heterogeneity: not applicable					
Test for overall effect: $Z = 0.2$	24 (P = 0.81)				
Total (95% CI)	1442	1437	•	100.0 %	0.84 [ 0.59, 1.20 ]
Total events: 393 (Higher PUF	FA), 424 (Lower PUFA)				
Heterogeneity: $Tau^2 = 0.05$ ; C	$Chi^2 = 4.80, df = 1 (P =$	: 0.03); I <sup>2</sup> =79%			
Test for overall effect: $Z = 0.9$	94 (P = 0.35)				
Test for subgroup differences:	$Chi^2 = 4.76$ , $df = 1$ (P	= 0.03), I <sup>2</sup> =79%			

0.01 0.1 1 10 100

Favours higher PUFA Favours lower PUFA

# Analysis 1.45. Comparison I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes, Outcome 45 MACCEs - subgroup by baseline PUFA dose.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes

Outcome: 45 MACCEs - subgroup by baseline PUFA dose

Study or subgroup	Higher PUFA	Lower PUFA	Risk Ratio M-	Weight	Risk Ratio M-
	n/N	n/N	H,Random,95% Cl		H,Random,9 Cl
Baseline total PUFA < 6% E					
Veterans Admin 1969	60/424	87/422	-	42.6 %	0.69 [ 0.51, 0.93 ]
Subtotal (95% CI)	424	422	•	42.6 %	0.69 [ 0.51, 0.93 ]
Total events: 60 (Higher PUFA	A), 87 (Lower PUFA)				
Heterogeneity: not applicable					
Test for overall effect: $Z = 2.4$	6 (P = 0.014)				
2 Baseline total PUFA 6 to <	11% E				
DART fat 1989	333/1018	337/1015	•	57.4 %	0.99 [ 0.87, 1.12 ]
Subtotal (95% CI)	1018	1015	•	57.4 %	0.99 [ 0.87, 1.12 ]
Total events: 333 (Higher PUF	A), 337 (Lower PUFA)				
Heterogeneity: not applicable	, , ,				
Test for overall effect: $Z = 0.2$	4 (P = 0.81)				
3 Baseline total PUFA 11+% E					
Subtotal (95% CI)	0	0			Not estimable
Total events: 0 (Higher PUFA)	, 0 (Lower PUFA)				
Heterogeneity: not applicable					
Test for overall effect: not app	licable				
4 Baseline total PUFA unclear					
Subtotal (95% CI)	0	0			Not estimable
Total events: 0 (Higher PUFA)	, 0 (Lower PUFA)				
Heterogeneity: not applicable					
Test for overall effect: not app	licable				
Total (95% CI)	1442	1437	+	100.0 %	0.84 [ 0.59, 1.20 ]
Total events: 393 (Higher PUF	A), 424 (Lower PUFA)				
Heterogeneity: $Tau^2 = 0.05$ ; C	$Chi^2 = 4.80, df = 1 (P =$	= 0.03); I <sup>2</sup> =79%			
Test for overall effect: $Z = 0.9$	4 (P = 0.35)				
Test for subgroup differences:	$Chi^2 = 4.76, df = 1 (P$	= 0.03), I <sup>2</sup> =79%			

0.01 0.1 1 10 100 Favours higher PUFA Favours lower PUFA

# Analysis 1.46. Comparison I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes, Outcome 46 MACCEs - subgroup by replacement.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes

Outcome: 46 MACCEs - subgroup by replacement

Study or subgroup	Higher PUFA	Lower PUFA	Risk Ratio M-	Weight	Risk Ratio M-
	n/N	n/N	H,Random,95% Cl		H,Random,95% Cl
PUFA replaced saturated fa	ats				
DART fat 1989	333/1018	337/1015	=	57.4 %	0.99 [ 0.87, 1.12 ]
Veterans Admin 1969	60/424	87/422	-	42.6 %	0.69 [ 0.51, 0.93 ]
Subtotal (95% CI)	1442	1437	•	100.0 %	0.84 [ 0.59, 1.20 ]
Total events: 393 (Higher PU	IFA), 424 (Lower PUFA)	1			
Heterogeneity: $Tau^2 = 0.05;$	$Chi^2 = 4.80, df = 1 (P =$	= 0.03); I <sup>2</sup> =79%			
Test for overall effect: $Z = 0.1$	94 (P = 0.35)	,			
2 PUFA replaced monounsat	turated fats				
Veterans Admin 1969	60/424	87/422		100.0 %	0.69 [ 0.51, 0.93 ]
Subtotal (95% CI)	424	422	•	100.0 %	0.69 [ 0.51, 0.93 ]
Total events: 60 (Higher PUF	A), 87 (Lower PUFA)				
Heterogeneity: not applicable	2				
Test for overall effect: $Z = 2$ .	46 (P = 0.014)				
3 PUFA replaced carbohydra	ites				
Subtotal (95% CI)	0	0			Not estimable
Total events: 0 (Higher PUFA	N), 0 (Lower PUFA)				
Heterogeneity: not applicable	e				
Test for overall effect: not ap	plicable				
4 PUFA replaced protein					
Subtotal (95% CI)	0	0			Not estimable
Total events: 0 (Higher PUFA	A), 0 (Lower PUFA)				
Heterogeneity: not applicable	e				
Test for overall effect: not ap	plicable				
5 PUFA replaced unclear					
Subtotal (95% CI)	0	0			Not estimable
Total events: 0 (Higher PUFA	N), 0 (Lower PUFA)				
Heterogeneity: not applicable	2				
Test for overall effect: not ap	plicable				
	: Chi <sup>2</sup> = 0.77, df = 1 (P	-0.38) 1 <sup>2</sup> $-0.0%$			

Favours higher PUFA Favours lower PUFA

## Analysis 1.47. Comparison I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes, Outcome 47 MACCEs - subgroup by sex.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes

Outcome: 47 MACCEs - subgroup by sex

Study or subgroup	Higher PUFA	Lower PUFA	Risk Ratio M-	Weight	Risk Ratio M-
	n/N	n/N	H,Random,95% Cl		H,Random,S Cl
> 70% men					
DART fat 1989	333/1018	337/1015	=	57.4 %	0.99 [ 0.87, 1.12 ]
Veterans Admin 1969	60/424	87/422	-	42.6 %	0.69 [ 0.51, 0.93 ]
Subtotal (95% CI)	1442	1437	•	100.0 %	0.84 [ 0.59, 1.20 ]
Total events: 393 (Higher PU Heterogeneity: Tau <sup>2</sup> = 0.05; ( Test for overall effect: Z = 0.9	$Chi^2 = 4.80, df = 1 (P = 1)$				
2 > 70% women					
Subtotal (95% CI)	0	0			Not estimable
Total events: 0 (Higher PUFA	, , ,				
Heterogeneity: not applicable					
Test for overall effect: not app	olicable				
3 men % women					
Subtotal (95% CI)	0	0			Not estimable
Total events: 0 (Higher PUFA					
Heterogeneity: not applicable					
Test for overall effect: not app	olicable				
4 sex not reported		<u> </u>			
Subtotal (95% CI)	0	0			Not estimable
Total events: 0 (Higher PUFA					
Heterogeneity: not applicable					
Test for overall effect: not app					
Total (95% CI)	1442	1437	•	100.0 %	0.84 [ 0.59, 1.20 ]
Total events: 393 (Higher PU	, , ,				
Heterogeneity: Tau <sup>2</sup> = 0.05; (		= 0.03); 12 =79%			
Test for overall effect: $Z = 0.9$	( )				
Test for subgroup differences:	Not applicable				

0.01 0.1 I 10 100 Favours higher PUFA Favours lower PUFA

## Analysis 1.48. Comparison I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes, Outcome 48 MACCEs - subgroup by age.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes

Outcome: 48 MACCEs - subgroup by age

Study or subgroup	Higher PUFA	Lower PUFA	Risk Ratio M-	Weight	Risk Ratio M-
	n/N	n/N	H,Random,95% Cl		H,Random,95 Cl
Mean age < 50 years					
Subtotal (95% CI)	0	0			Not estimable
Total events: 0 (Higher PUFA)	), 0 (Lower PUFA)				
Heterogeneity: not applicable					
Test for overall effect: not app	licable				
2 Mean age 50 to < 65 years					
DART fat 1989	333/1018	337/1015	•	57.4 %	0.99 [ 0.87, 1.12 ]
Subtotal (95% CI)	1018	1015	•	57.4 %	0.99 [ 0.87, 1.12 ]
Total events: 333 (Higher PUF	A), 337 (Lower PUFA)				
Heterogeneity: not applicable					
Test for overall effect: Z = 0.2	4 (P = 0.81)				
3 Mean age 65+ years					
Veterans Admin 1969	60/424	87/422	-	42.6 %	0.69 [ 0.51, 0.93 ]
Subtotal (95% CI)	424	422	•	42.6 %	0.69 [ 0.51, 0.93 ]
Total events: 60 (Higher PUFA	A), 87 (Lower PUFA)				
Heterogeneity: not applicable					
Test for overall effect: $Z = 2.4$	6 (P = 0.014)				
Total (95% CI)	1442	1437	•	100.0 %	0.84 [ 0.59, 1.20 ]
Total events: 393 (Higher PUF	A), 424 (Lower PUFA)				
Heterogeneity: $Tau^2 = 0.05$ ; C	$Chi^2 = 4.80, df = 1 (P =$	0.03); l <sup>2</sup> =79%			
Test for overall effect: $Z = 0.9$	4 (P = 0.35)				
Test for subgroup differences:	$Chi^2 = 4.76, df = 1 (P = 1)$	= 0.03), I <sup>2</sup> =79%			
			0.01 0.1 1 10 100		
			Favours higher PUFA Favours lower P	UFA	

# Analysis 1.49. Comparison I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes, Outcome 49 MACCEs - subgroup by statin use.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes

Outcome: 49 MACCEs - subgroup by statin use

Study or subgroup	Higher PUFA	Lower PUFA	Risk Ratio M-	Weight	Risk Ratio M-
	n/N	n/N	H,Random,95% Cl		H,Random,95% Cl
< 50% on statins					
DART fat 1989	333/1018	337/1015	•	57.4 %	0.99 [ 0.87, 1.12 ]
Veterans Admin 1969	60/424	87/422	-	42.6 %	0.69 [ 0.51, 0.93 ]
Subtotal (95% CI)	1442	1437	•	100.0 %	0.84 [ 0.59, 1.20 ]
Total events: 393 (Higher PL	IFA), 424 (Lower PUFA)	)			
Heterogeneity: $Tau^2 = 0.05$ ;	$Chi^2 = 4.80, df = 1 (P =$	= 0.03); I <sup>2</sup> =79%			
Test for overall effect: $Z = 0$ .	94 (P = 0.35)				
2 50+% on statins					
Subtotal (95% CI)	0	0			Not estimable
Total events: 0 (Higher PUFA	A), 0 (Lower PUFA)				
Heterogeneity: not applicable	2				
Test for overall effect: not ap	plicable				
Total (95% CI)	1442	1437	•	100.0 %	0.84 [ 0.59, 1.20 ]
Total events: 393 (Higher PL	IFA), 424 (Lower PUFA)	)			
Heterogeneity: Tau <sup>2</sup> = 0.05;	$Chi^2 = 4.80, df = 1 (P =$	= 0.03); I <sup>2</sup> =79%			
Test for overall effect: $Z = 0$ .	94 (P = 0.35)				
	: Not applicable				

0.01 0.1 I 10 100 Favours higher PUFA Favours lower PUFA

## Analysis 1.50. Comparison I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes, Outcome 50 MACCEs - subgroup by intervention type.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: I Higher polyunsaturated fatty acids (PUFA) vs lower PUFA intake - primary outcomes

Outcome: 50 MACCEs - subgroup by intervention type

Study or subgroup	Higher PUFA	Lower PUFA	Risk Ratio M-	Weight	Risk Ratio M-
	n/N	n/N	H,Random,95% Cl		H,Random,9: Cl
I Dietary advice					
DART fat 1989	333/1018	337/1015	•	57.4 %	0.99 [ 0.87, 1.12 ]
Subtotal (95% CI)	1018	1015	+	57.4 %	0.99 [ 0.87, 1.12 ]
Total events: 333 (Higher PUF)	4), 337 (Lower PUFA)				
Heterogeneity: not applicable					
Test for overall effect: Z = 0.24	+ (P = 0.81)				
2 Supplemental foods % diet p	rovided				
Veterans Admin 1969	60/424	87/422	-	42.6 %	0.69 [ 0.51, 0.93 ]
Subtotal (95% CI)	424	422	•	42.6 %	0.69 [ 0.51, 0.93 ]
Total events: 60 (Higher PUFA	), 87 (Lower PUFA)				
Heterogeneity: not applicable					
Test for overall effect: $Z = 2.46$	5 (P = 0.014)				
3 Supplements (capsules % un	usual foods)				
Subtotal (95% CI)	0	0			Not estimable
Total events: 0 (Higher PUFA),	0 (Lower PUFA)				
Heterogeneity: not applicable					
Test for overall effect: not appl	icable				
4 Any combination					
Subtotal (95% CI)	0	0			Not estimable
Total events: 0 (Higher PUFA),	0 (Lower PUFA)				
Heterogeneity: not applicable					
Test for overall effect: not appl	icable				
Total (95% CI)	1442	1437	•	100.0 %	0.84 [ 0.59, 1.20 ]
Total events: 393 (Higher PUF)	A), 424 (Lower PUFA)				
Heterogeneity: $Tau^2 = 0.05$ ; C	$hi^2 = 4.80, df = 1 (P =$	= 0.03); I <sup>2</sup> =79%			
Test for overall effect: $Z = 0.9^{2}$	,				
Test for subgroup differences: (	$Chi^2 = 4.76, df = 1 (P$	= 0.03), l <sup>2</sup> =79%			

0.01 0.1 1 10 100 Favours higher PUFA Favours lower PUFA

# Analysis 2.1. Comparison 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes, Outcome I CARDIOVASCULAR MORTALITY.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes

#### Outcome: I CARDIOVASCULAR MORTALITY

Study or subgroup	Higher PUFA	Lower PUFA	Risk Ratio M- H,Random,95%	Weight	Risk Ratio M- H,Random,9!
	n/N	n/N	Cl		Cl
AlphaOmega - ALA	78/2409	84/2428	+	17.6 %	0.94 [ 0.69, 1.27 ]
Black 1994	2/67	0/66		0.5 %	4.93 [ 0.24, 100.70 ]
Brox 2001	0/80	1/40	•	0.4 %	0.17[0.01,4.05]
DART fat 1989	114/1018	91/1015	-	19.4 %	1.25 [ 0.96, 1.62 ]
Doi 2014	1/119	5/119	4	1.0 %	0.20 [ 0.02, 1.69 ]
FAAT - Leaf 2005	9/200	9/202		4.6 %	1.01 [ 0.41, 2.49 ]
HARP- Sacks 1995	0/41	1/39	• · · ·	0.4 %	0.32 [ 0.01, 7.57 ]
Houtsmuller 1979	0/51	5/51	<b>←</b> +	0.5 %	0.09 [ 0.01, 1.60 ]
Kumar 2013	1/39	1/39		0.6 %	1.00 [ 0.06, 15.43 ]
Ley 2004	2/70	1/66		0.8 %	1.89 [ 0.18, 20.31 ]
MRC 1968	27/199	25/194	-	10.7 %	1.05 [ 0.63, 1.75 ]
PREDIMED 2013	31/2454	26/2543		10.4 %	1.24 [ 0.74, 2.07 ]
Raitt 2005	2/100	5/100		1.6 %	0.40 [ 0.08, 2.01 ]
Rose 1965	5/28	3/26		2.3 %	1.55 [ 0.41, 5.84 ]
Sydney Diet-Heart 1978	37/221	25/237		11.6 %	1.59 [ 0.99, 2.55 ]
Veterans Admin 1969	57/424	81/422	-	17.3 %	0.70 [ 0.51, 0.96 ]
Total (95% CI)	7520	7587	+	100.0 %	1.02 [ 0.82, 1.26 ]
otal events: 366 (Higher PUFA	), 363 (Lower PUFA)				
leterogeneity: Tau <sup>2</sup> = 0.04; Chi	$i^2 = 21.84$ , df = 15 (P =	= 0.11); I <sup>2</sup> =31%			
est for overall effect: $Z = 0.17$	(P = 0.87)				
est for subgroup differences: N	lot applicable				

Favours higher PUFA

JFA Favours lower PUFA

#### Analysis 2.2. Comparison 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes, Outcome 2 Cardiovascular mortality - SA.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes

Outcome: 2 Cardiovascular mortality - SA

Study or subgroup	Higher PUFA	Lower PUFA	Risk Ratio M-	Weight	Risk Ratio M-
	n/N	n/N	H,Random,95% Cl		H,Random,9 Cl
I Low risk of bias for allocation c	oncealment				
AlphaOmega - ALA	78/2409	84/2428	-	64.1 %	0.94 [ 0.69, 1.27 ]
Brox 2001	0/80	1/40	•	0.6 %	0.17 [ 0.01, 4.05 ]
FAAT - Leaf 2005	9/200	9/202	<b>_</b>	7.2 %	1.01 [ 0.41, 2.49 ]
Kumar 2013	1/39	1/39		0.8 %	1.00 [ 0.06, 15.43 ]
Ley 2004	2/70	1/66		1.0 %	1.89 [ 0.18, 20.31 ]
Sydney Diet-Heart 1978	37/221	25/237		26.3 %	1.59 [ 0.99, 2.55 ]
Subtotal (95% CI)	3019	3012	•	100.0 %	1.08 [ 0.85, 1.38 ]
Heterogeneity: Tau <sup>2</sup> = 0.0; Chi <sup>2</sup> : Test for overall effect: Z = 0.61 (I 2 Low risk of bias for attention		42); I <sup>2</sup> =0.0%			
2 Low risk of bias for attention					
AlphaOmega - ALA	78/2409	84/2428	-	36.7 %	0.94 [ 0.69, 1.27 ]
Brox 2001	0/80	1/40	<b>←</b> · · · · · · · · · · · · · · · · · · ·	0.5 %	0.17 [ 0.01, 4.05 ]
Doi 2014	/  9	5/119	•	1.1 %	0.20 [ 0.02, 1.69 ]
FAAT - Leaf 2005	9/200	9/202		5.7 %	1.01 [ 0.41, 2.49 ]
HARP- Sacks 1995	0/41	1/39	<b>←</b>	0.5 %	0.32 [ 0.01, 7.57 ]
PREDIMED 2013	31/2454	26/2543		15.7 %	1.24 [ 0.74, 2.07 ]
Raitt 2005	2/100	5/100		1.8 %	0.40 [ 0.08, 2.01 ]
Rose 1965	5/28	3/26		2.7 %	1.55 [ 0.41, 5.84 ]
Veterans Admin 1969	57/424	81/422	-	35.4 %	0.70 [ 0.51, 0.96 ]
Subtotal (95% CI)	5855	5919	•	100.0 %	0.86 [ 0.69, 1.07 ]
Total events: 183 (Higher PUFA), Heterogeneity: Tau <sup>2</sup> = 0.01; Chi <sup>2</sup> Test for overall effect: Z = 1.36 (I	= 8.77, df = 8 (P = 0 P = 0.18)	0.36); I <sup>2</sup> =9%			
3 Low risk of bias for compliance					

(Continued . . . )

( Continue Risk Ratic M. H,Random,	Weight	Risk Ratio M- H,Random,95%	Lower PUFA	Higher PUFA	Study or subgroup
C		Cl	n/N	n/N	
1.25 [ 0.96, 1.62 ]	26.7 %	-	91/1015	114/1018	DART fat 1989
0.09 [ 0.01, 1.60 ]	1.4 %	• • • • • • • • • • • • • • • • • • • •	5/51	0/51	Houtsmuller 1979
1.89 [ 0.18, 20.31 ]	1.9 %		1/66	2/70	Ley 2004
1.05 [ 0.63, 1.75 ]	18.6 %	-+-	25/194	27/199	MRC 1968
1.55 [ 0.41, 5.84 ]	5.5 %		3/26	5/28	Rose 1965
1.59 [ 0.99, 2.55 ]	19.7 %	-	25/237	37/221	Sydney Diet-Heart 1978
0.70 [ 0.51, 0.96]	25.1 %	-	81/422	57/424	Veterans Admin 1969
1.06 [ 0.75, 1.49 ]	100.0 %	+	2051	2091	ubtotal (95% CI)
0.94 [ 0.69, 1.27 ]	56.4 %	-	84/2428	78/2409	est for overall effect: Z = 0.31 ( Low summary risk of bias AlphaOmega - ALA
1.89 [ 0.18, 20.31 ]	3.2 %		1/66	2/70	Ley 2004
1.59 [ 0.99, 2.55 ]	40.4 %		25/237	37/221	Sydney Diet-Heart 1978
1.18 [ 0.77, 1.83 ]	100.0 %	+	2731	2700	Subtotal (95% CI)
			17); l <sup>2</sup> =44%		Heterogeneity: $Tau^2 = 0.06$ ; Chinese for overall effect: $Z = 0.77$ (
0045070 107	17/0/			$^{2} = 3.60, df = 2 (P = 0.44)$	est for overall effect: Z = 0.77 ( Trials registry or pre-2010
0.94 [ 0.69, 1.27 ]	17.6 %		84/2428	<sup>2</sup> = 3.60, df = 2 (P = 0. (P = 0.44) 78/2409	est for overall effect: Z = 0.77 ( Trials registry or pre-2010 AlphaOmega - ALA
4.93 [ 0.24, 100.70 ]	0.5 %		84/2428 0/66	<sup>2</sup> = 3.60, df = 2 (P = 0. (P = 0.44) 78/2409 2/67	est for overall effect: Z = 0.77 ( Trials registry or pre-2010 AlphaOmega - ALA Black 1994
4.93 [ 0.24, 100.70 ] 0.17 [ 0.01, 4.05 ]	0.5 % 0.4 %		84/2428 0/66 1/40	<sup>2</sup> = 3.60, df = 2 (P = 0. (P = 0.44) 78/2409 2/67 0/80	est for overall effect: Z = 0.77 ( Trials registry or pre-2010 AlphaOmega - ALA Black 1994 Brox 2001
4.93 [ 0.24, 100.70 ] 0.17 [ 0.01, 4.05 ] 1.25 [ 0.96, 1.62 ]	0.5 % 0.4 % 19.4 %	•	84/2428 0/66 1/40 91/1015	<sup>2</sup> = 3.60, df = 2 (P = 0. (P = 0.44) 78/2409 2/67 0/80 114/1018	est for overall effect: Z = 0.77 ( Trials registry or pre-2010 AlphaOmega - ALA Black 1994 Brox 2001 DART fat 1989
4.93 [ 0.24, 100.70 ] 0.17 [ 0.01, 4.05 ] 1.25 [ 0.96, 1.62 ] 0.20 [ 0.02, 1.69 ]	0.5 % 0.4 % 19.4 % 1.0 %	• • • • •	84/2428 0/66 1/40 91/1015 5/119	<sup>2</sup> = 3.60, df = 2 (P = 0. (P = 0.44) 78/2409 2/67 0/80 114/1018 1/119	est for overall effect: Z = 0.77 ( Trials registry or pre-2010 AlphaOmega - ALA Black 1994 Brox 2001 DART fat 1989 Doi 2014
4.93 [ 0.24, 100.70 ] 0.17 [ 0.01, 4.05 ] 1.25 [ 0.96, 1.62 ] 0.20 [ 0.02, 1.69 ] 1.01 [ 0.41, 2.49 ]	0.5 % 0.4 % 19.4 % 1.0 % 4.6 %		84/2428 0/66 1/40 91/1015 5/119 9/202	2 = 3.60, df = 2 (P = 0. (P = 0.44) 78/2409 2/67 0/80 114/1018 1/119 9/200	est for overall effect: Z = 0.77 ( Trials registry or pre-2010 AlphaOmega - ALA Black 1994 Brox 2001 DART fat 1989 Doi 2014 FAAT - Leaf 2005
4.93 [ 0.24, 100.70 ] 0.17 [ 0.01, 4.05 ] 1.25 [ 0.96, 1.62 ] 0.20 [ 0.02, 1.69 ] 1.01 [ 0.41, 2.49 ] 0.32 [ 0.01, 7.57 ]	0.5 % 0.4 % 19.4 % 1.0 % 4.6 % 0.4 %		84/2428 0/66 1/40 91/1015 5/119 9/202 1/39	<sup>2</sup> = 3.60, df = 2 (P = 0. (P = 0.44) 78/2409 2/67 0/80 114/1018 1/119 9/200 0/41	est for overall effect: Z = 0.77 ( Trials registry or pre-2010 AlphaOmega - ALA Black 1994 Brox 2001 DART fat 1989 Doi 2014 FAAT - Leaf 2005 HARP- Sacks 1995
4.93 [ 0.24, 100.70 ] 0.17 [ 0.01, 4.05 ] 1.25 [ 0.96, 1.62 ] 0.20 [ 0.02, 1.69 ] 1.01 [ 0.41, 2.49 ] 0.32 [ 0.01, 7.57 ] 0.09 [ 0.01, 1.60 ]	0.5 % 0.4 % 19.4 % 1.0 % 4.6 % 0.4 % 0.5 %		84/2428 0/66 1/40 91/1015 5/119 9/202	2 = 3.60, df = 2 (P = 0. (P = 0.44) 78/2409 2/67 0/80 114/1018 1/119 9/200	est for overall effect: Z = 0.77 ( Trials registry or pre-2010 AlphaOmega - ALA Black 1994 Brox 2001 DART fat 1989 Doi 2014 FAAT - Leaf 2005 HARP- Sacks 1995 Houtsmuller 1979
4.93 [ 0.24, 100.70 ] 0.17 [ 0.01, 4.05 ] 1.25 [ 0.96, 1.62 ] 0.20 [ 0.02, 1.69 ] 1.01 [ 0.41, 2.49 ] 0.32 [ 0.01, 7.57 ]	0.5 % 0.4 % 19.4 % 1.0 % 4.6 % 0.4 %		84/2428 0/66 1/40 91/1015 5/119 9/202 1/39	<sup>2</sup> = 3.60, df = 2 (P = 0. (P = 0.44) 78/2409 2/67 0/80 114/1018 1/119 9/200 0/41	est for overall effect: Z = 0.77 ( Trials registry or pre-2010 AlphaOmega - ALA Black 1994 Brox 2001 DART fat 1989 Doi 2014 FAAT - Leaf 2005 HARP- Sacks 1995
4.93 [ 0.24, 100.70 ] 0.17 [ 0.01, 4.05 ] 1.25 [ 0.96, 1.62 ] 0.20 [ 0.02, 1.69 ] 1.01 [ 0.41, 2.49 ] 0.32 [ 0.01, 7.57 ] 0.09 [ 0.01, 1.60 ]	0.5 % 0.4 % 19.4 % 1.0 % 4.6 % 0.4 % 0.5 %		84/2428 0/66 1/40 91/1015 5/119 9/202 1/39 5/51	<sup>2</sup> = 3.60, df = 2 (P = 0. (P = 0.44) 78/2409 2/67 0/80 114/1018 1/119 9/200 0/41 0/51	est for overall effect: Z = 0.77 ( Trials registry or pre-2010 AlphaOmega - ALA Black 1994 Brox 2001 DART fat 1989 Doi 2014 FAAT - Leaf 2005 HARP- Sacks 1995 Houtsmuller 1979
4.93 [ 0.24, 100.70 ] 0.17 [ 0.01, 4.05 ] 1.25 [ 0.96, 1.62 ] 0.20 [ 0.02, 1.69 ] 1.01 [ 0.41, 2.49 ] 0.32 [ 0.01, 7.57 ] 0.09 [ 0.01, 1.60 ] 1.00 [ 0.06, 15.43 ]	0.5 % 0.4 % 19.4 % 1.0 % 4.6 % 0.4 % 0.5 % 0.6 %		84/2428 0/66 1/40 91/1015 5/119 9/202 1/39 5/51 1/39	<sup>2</sup> = 3.60, df = 2 (P = 0. (P = 0.44) 78/2409 2/67 0/80 114/1018 1/119 9/200 0/41 0/51 1/39	est for overall effect: Z = 0.77 ( Trials registry or pre-2010 AlphaOmega - ALA Black 1994 Brox 2001 DART fat 1989 Doi 2014 FAAT - Leaf 2005 HARP- Sacks 1995 Houtsmuller 1979 Kumar 2013
4.93 [ 0.24, 100.70 ] 0.17 [ 0.01, 4.05 ] 1.25 [ 0.96, 1.62 ] 0.20 [ 0.02, 1.69 ] 1.01 [ 0.41, 2.49 ] 0.32 [ 0.01, 7.57 ] 0.09 [ 0.01, 1.60 ] 1.00 [ 0.06, 15.43 ] 1.89 [ 0.18, 20.31 ]	0.5 % 0.4 % 19.4 % 1.0 % 4.6 % 0.4 % 0.5 % 0.6 % 0.8 %		84/2428 0/66 1/40 91/1015 5/119 9/202 1/39 5/51 1/39 1/66	<sup>2</sup> = 3.60, df = 2 (P = 0. (P = 0.44) 78/2409 2/67 0/80 114/1018 1/119 9/200 0/41 0/51 1/39 2/70	est for overall effect: Z = 0.77 ( Trials registry or pre-2010 AlphaOmega - ALA Black 1994 Brox 2001 DART fat 1989 Doi 2014 FAAT - Leaf 2005 HARP- Sacks 1995 Houtsmuller 1979 Kumar 2013 Ley 2004
4.93 [ 0.24, 100.70 ] 0.17 [ 0.01, 4.05 ] 1.25 [ 0.96, 1.62 ] 0.20 [ 0.02, 1.69 ] 1.01 [ 0.41, 2.49 ] 0.32 [ 0.01, 7.57 ] 0.09 [ 0.01, 1.60 ] 1.00 [ 0.06, 15.43 ] 1.89 [ 0.18, 20.31 ] 1.05 [ 0.63, 1.75 ]	0.5 % 0.4 % 19.4 % 1.0 % 4.6 % 0.4 % 0.5 % 0.6 % 0.8 % 10.7 %		84/2428 0/66 1/40 91/1015 5/119 9/202 1/39 5/51 1/39 1/66 25/194	<sup>2</sup> = 3.60, df = 2 (P = 0. (P = 0.44) 78/2409 2/67 0/80 114/1018 1/119 9/200 0/41 0/51 1/39 2/70 27/199	est for overall effect: Z = 0.77 ( Trials registry or pre-2010 AlphaOmega - ALA Black 1994 Brox 2001 DART fat 1989 Doi 2014 FAAT - Leaf 2005 HARP- Sacks 1995 Houtsmuller 1979 Kumar 2013 Ley 2004 MRC 1968

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Study or subgroup	Higher PUFA	Lower PUFA	Risk Ratio M- H.Random.95%	Weight	( Continue Risk Ratic M. H,Random,
	n/N	n/N	Cl		C
Sydney Diet-Heart 1978	37/221	25/237		11.6 %	1.59 [ 0.99, 2.55 ]
Veterans Admin 1969	57/424	81/422	-	17.3 %	0.70 [ 0.51, 0.96 ]
Subtotal (95% CI) Fotal events: 366 (Higher PUFA)	<b>7520</b>	7587	•	100.0 %	1.02 [ 0.82, 1.26 ]
Heterogeneity: Tau <sup>2</sup> = 0.04; Chi Fest for overall effect: Z = 0.17 5 No industry funding	<sup>2</sup> = 21.84, df = 15 (P =	= 0.  );   <sup>2</sup> =3 %			
Black 1994	2/67	0/66		1.8 %	4.93 [ 0.24, 100.70 ]
Brox 2001	0/80	1/40	·	1.6 %	0.17 [ 0.01, 4.05 ]
FAAT - Leaf 2005	9/200	9/202		16.5 %	1.01 [ 0.41, 2.49 ]
Houtsmuller 1979	0/51	5/51	•••	2.0 %	0.09 [ 0.01, 1.60
Ley 2004	2/70	1/66		2.9 %	1.89 [ 0.18, 20.31
MRC 1968	27/199	25/194	-	36.2 %	1.05 [ 0.63, 1.75
	1	25/237	-	39.0 %	1.59 [ 0.99, 2.55
Sydney Diet-Heart 1978	37/221				
<b>Subtotal (95% CI)</b> Total events: 77 (Higher PUFA), Heterogeneity: Tau <sup>2</sup> = 0.05; Chi Test for overall effect: Z = 0.81	<b>888</b> 66 (Lower PUFA) <sup>2</sup> = 7.34, df = 6 (P = 0 (P = 0.42)	<b>856</b> .29);   <sup>2</sup> = 18%	•	100.0 %	1.19 [ 0.79, 1.79
<b>Subtotal (95% CI)</b> Total events: 77 (Higher PUFA), Heterogeneity: Tau <sup>2</sup> = 0.05; Chi Test for overall effect: $Z = 0.81$ Randomised 100+ participant	<b>888</b> 66 (Lower PUFA) <sup>2</sup> = 7.34, df = 6 (P = 0 (P = 0.42)	1.29); I <sup>2</sup> = I 8%	•		
<b>Subtotal (95% CI)</b> otal events: 77 (Higher PUFA), leterogeneity: Tau <sup>2</sup> = 0.05; Chi est for overall effect: Z = 0.81 Randomised 100+ participant: AlphaOmega - ALA	<b>888</b> 66 (Lower PUFA) <sup>2</sup> = 7.34, df = 6 (P = 0 (P = 0.42) 5 78/2409	84/2428	•	17.6 %	0.94 [ 0.69, 1.27
<b>Subtotal (95% CI)</b> otal events: 77 (Higher PUFA), deterogeneity: Tau <sup>2</sup> = 0.05; Chi est for overall effect: Z = 0.81 f Randomised 100+ participant: AlphaOmega - ALA Black 1994	<b>888</b> 66 (Lower PUFA) <sup>2</sup> = 7.34, df = 6 (P = 0 (P = 0.42) 5 78/2409 2/67	84/2428 0/66	•	17.6 % 0.6 %	0.94 [ 0.69, 1.27 4.93 [ 0.24, 100.70
<b>Subtotal (95% CI)</b> total events: 77 (Higher PUFA), deterogeneity: Tau <sup>2</sup> = 0.05; Chi est for overall effect: Z = 0.81 Randomised 100+ participant: AlphaOmega - ALA Black 1994 Brox 2001	<b>888</b> 66 (Lower PUFA) <sup>2</sup> = 7.34, df = 6 (P = 0 (P = 0.42) 5 78/2409 2/67 0/80	84/2428 0/66	•	17.6 % 0.6 % 0.5 %	0.94 [ 0.69, 1.27 4.93 [ 0.24, 100.70 0.17 [ 0.01, 4.05
Subtotal (95% CI) total events: 77 (Higher PUFA), Heterogeneity: Tau <sup>2</sup> = 0.05; Chi test for overall effect: Z = 0.81 ( Randomised 100+ participant: AlphaOmega - ALA Black 1994 Brox 2001 DART fat 1989	<b>888</b> 66 (Lower PUFA) <sup>2</sup> = 7.34, df = 6 (P = 0 (P = 0.42) 5 78/2409 2/67 0/80 114/1018	84/2428 0/66 1/40 91/1015	•	17.6 % 0.6 % 0.5 % 19.0 %	0.94 [ 0.69, 1.27 4.93 [ 0.24, 100.70 0.17 [ 0.01, 4.05 1.25 [ 0.96, 1.62
<b>Subtotal (95% CI)</b> total events: 77 (Higher PUFA), deterogeneity: Tau <sup>2</sup> = 0.05; Chi est for overall effect: Z = 0.81 f Randomised 100+ participant: AlphaOmega - ALA Black 1994 Brox 2001 DART fat 1989 Doi 2014	<b>888</b> 66 (Lower PUFA) <sup>2</sup> = 7.34, df = 6 (P = 0 (P = 0.42) 5 78/2409 2/67 0/80 114/1018 1/119	29); I <sup>2</sup> =18% 84/2428 0/66 1/40 91/1015 5/119		17.6 % 0.6 % 0.5 % 19.0 % 1.2 %	0.94 [ 0.69, 1.27 4.93 [ 0.24, 100.70 0.17 [ 0.01, 4.05 1.25 [ 0.96, 1.62 0.20 [ 0.02, 1.69
Subtotal (95% CI) total events: 77 (Higher PUFA), leterogeneity: Tau <sup>2</sup> = 0.05; Chi est for overall effect: Z = 0.81 of Randomised 100+ participant: AlphaOmega - ALA Black 1994 Brox 2001 DART fat 1989 Doi 2014 FAAT - Leaf 2005	<b>888</b> 66 (Lower PUFA) <sup>2</sup> = 7.34, df = 6 (P = 0 (P = 0.42) 5 78/2409 2/67 0/80 114/1018 1/119 9/200	1.29); 1 <sup>2</sup> =18% 84/2428 0/66 1/40 91/1015 5/119 9/202		17.6 % 0.6 % 0.5 % 19.0 % 1.2 % 5.3 %	0.94 [ 0.69, 1.27 4.93 [ 0.24, 100.70 0.17 [ 0.01, 4.05 1.25 [ 0.96, 1.62 0.20 [ 0.02, 1.69 1.01 [ 0.41, 2.49
Subtotal (95% CI) total events: 77 (Higher PUFA), deterogeneity: Tau <sup>2</sup> = 0.05; Chi est for overall effect: Z = 0.81 of Randomised 100+ participant: AlphaOmega - ALA Black 1994 Brox 2001 DART fat 1989 Doi 2014 FAAT - Leaf 2005 Houtsmuller 1979	888 66 (Lower PUFA) 2 = 7.34, df = 6 (P = 0 (P = 0.42) 5 78/2409 2/67 0/80 114/1018 1/119 9/200 0/51	29); I <sup>2</sup> =18% 84/2428 0/66 1/40 91/1015 5/119 9/202 5/51		17.6 % 0.6 % 0.5 % 19.0 % 1.2 % 5.3 % 0.6 %	0.94 [ 0.69, 1.27 4.93 [ 0.24, 100.70 0.17 [ 0.01, 4.05 1.25 [ 0.96, 1.62 0.20 [ 0.02, 1.69 1.01 [ 0.41, 2.49 0.09 [ 0.01, 1.60
Subtotal (95% CI) Total events: 77 (Higher PUFA), Heterogeneity: Tau <sup>2</sup> = 0.05; Chi Test for overall effect: Z = 0.81 f Randomised 100+ participant: AlphaOmega - ALA Black 1994 Brox 2001 DART fat 1989 Doi 2014 FAAT - Leaf 2005 Houtsmuller 1979 Ley 2004	888 66 (Lower PUFA) 2 = 7.34, df = 6 (P = 0 (P = 0.42) 5 78/2409 2/67 0/80 114/1018 1/119 9/200 0/51 2/70	229); 1 <sup>2</sup> =18% 84/2428 0/66 1/40 91/1015 5/119 9/202 5/51 1/66		17.6 % 0.6 % 19.0 % 1.2 % 5.3 % 0.6 % 0.9 %	0.94 [ 0.69, 1.27 4.93 [ 0.24, 100.70 0.17 [ 0.01, 4.05 1.25 [ 0.96, 1.62 0.20 [ 0.02, 1.69 1.01 [ 0.41, 2.49 0.09 [ 0.01, 1.60 1.89 [ 0.18, 20.31
Subtotal (95% CI) Total events: 77 (Higher PUFA), Heterogeneity: Tau <sup>2</sup> = 0.05; Chi Test for overall effect: Z = 0.81 of Randomised 100+ participant: AlphaOmega - ALA Black 1994 Brox 2001 DART fat 1989 Doi 2014 FAAT - Leaf 2005 Houtsmuller 1979 Ley 2004 MRC 1968	888 66 (Lower PUFA) 2 = 7.34, df = 6 (P = 0 (P = 0.42) 5 78/2409 2/67 0/80 114/1018 1/119 9/200 0/51 2/70 27/199	29); 1 <sup>2</sup> = 18% 84/2428 0/66 1/40 91/1015 5/119 9/202 5/51 1/66 25/194		17.6 % 0.6 % 19.0 % 1.2 % 5.3 % 0.6 % 0.9 % 11.5 %	0.94 [ 0.69, 1.27 4.93 [ 0.24, 100.70 0.17 [ 0.01, 4.05 1.25 [ 0.96, 1.62 0.20 [ 0.02, 1.69 1.01 [ 0.41, 2.49 0.09 [ 0.01, 1.60 1.89 [ 0.18, 20.31 1.05 [ 0.63, 1.75
Subtotal (95% CI) Total events: 77 (Higher PUFA), Heterogeneity: Tau <sup>2</sup> = 0.05; Chi Test for overall effect: Z = 0.81 f Randomised 100+ participant: AlphaOmega - ALA Black 1994 Brox 2001 DART fat 1989 Doi 2014 FAAT - Leaf 2005 Houtsmuller 1979 Ley 2004 MRC 1968 PREDIMED 2013	888 66 (Lower PUFA) 2 = 7.34, df = 6 (P = 0 (P = 0.42) 5 78/2409 2/67 0/80 114/1018 1/119 9/200 0/51 2/70 27/199 31/2454	229); 1 <sup>2</sup> =18% 84/2428 0/66 1/40 91/1015 5/119 9/202 5/51 1/66 25/194 26/2543		17.6 % 0.6 % 19.0 % 1.2 % 5.3 % 0.6 % 0.9 % 11.5 % 11.2 %	<b>1.19 [ 0.79, 1.79 ]</b> 0.94 <b>[</b> 0.69, 1.27 4.93 <b>[</b> 0.24, 100.70 0.17 <b>[</b> 0.01, 4.05 1.25 <b>[</b> 0.96, 1.62 0.20 <b>[</b> 0.02, 1.69 1.01 <b>[</b> 0.41, 2.49 0.09 <b>[</b> 0.01, 1.60 <b>I</b> .89 <b>[</b> 0.18, 20.31 1.05 <b>[</b> 0.63, 1.75 1.24 <b>[</b> 0.74, 2.07
Subtotal (95% CI) Total events: 77 (Higher PUFA), Heterogeneity: Tau <sup>2</sup> = 0.05; Chi Test for overall effect: Z = 0.81 of Randomised 100+ participant: AlphaOmega - ALA Black 1994 Brox 2001 DART fat 1989 Doi 2014 FAAT - Leaf 2005 Houtsmuller 1979 Ley 2004 MRC 1968 PREDIMED 2013 Raitt 2005	888 66 (Lower PUFA) 2 = 7.34, df = 6 (P = 0 (P = 0.42) 5 78/2409 2/67 0/80 114/1018 1/119 9/200 0/51 2/70 27/199 31/2454 2/100	84/2428 84/2428 0/66 1/40 91/1015 5/119 9/202 5/51 1/66 25/194 26/2543 5/100		17.6 % 0.6 % 19.0 % 1.2 % 5.3 % 0.6 % 0.9 % 11.5 % 11.2 % 11.2 %	0.94 [ 0.69, 1.27 4.93 [ 0.24, 100.70 0.17 [ 0.01, 4.05 1.25 [ 0.96, 1.62 0.20 [ 0.02, 1.69 1.01 [ 0.41, 2.49 0.09 [ 0.01, 1.60 1.89 [ 0.18, 20.31 1.05 [ 0.63, 1.75 1.24 [ 0.74, 2.07 0.40 [ 0.08, 2.01
Subtotal (95% CI) Total events: 77 (Higher PUFA), Heterogeneity: Tau <sup>2</sup> = 0.05; Chi Test for overall effect: Z = 0.81 of Randomised 100+ participant: AlphaOmega - ALA Black 1994 Brox 2001 DART fat 1989 Doi 2014 FAAT - Leaf 2005 Houtsmuller 1979 Ley 2004 MRC 1968 PREDIMED 2013 Raitt 2005 Sydney Diet-Heart 1978	888 66 (Lower PUFA) <sup>2</sup> = 7.34, df = 6 (P = 0 (P = 0.42) 78/2409 2/67 0/80 114/1018 1/119 9/200 0/51 2/70 27/199 31/2454 2/100 37/221	229); 1 <sup>2</sup> =18% 84/2428 0/66 1/40 91/1015 5/119 9/202 5/51 1/66 25/194 26/2543 5/100 25/237		17.6 % 0.6 % 0.5 % 19.0 % 1.2 % 5.3 % 0.6 % 0.9 % 11.5 % 11.2 % 1.9 % 12.3 %	0,94 [ 0.69, 1.27 4.93 [ 0.24, 100.70 0.17 [ 0.01, 4.05 1.25 [ 0.96, 1.62 0.20 [ 0.02, 1.69 1.01 [ 0.41, 2.49 0.09 [ 0.01, 1.60 1.89 [ 0.18, 20.31 1.05 [ 0.63, 1.75 1.24 [ 0.74, 2.07 0.40 [ 0.08, 2.01 1.59 [ 0.99, 2.55
Subtotal (95% CI) total events: 77 (Higher PUFA), leterogeneity: Tau <sup>2</sup> = 0.05; Chi est for overall effect: Z = 0.81 of Randomised 100+ participant: AlphaOmega - ALA Black 1994 Brox 2001 DART fat 1989 Doi 2014 FAAT - Leaf 2005 Houtsmuller 1979 Ley 2004 MRC 1968 PREDIMED 2013 Raitt 2005	888 66 (Lower PUFA) 2 = 7.34, df = 6 (P = 0 (P = 0.42) 5 78/2409 2/67 0/80 114/1018 1/119 9/200 0/51 2/70 27/199 31/2454 2/100	84/2428 84/2428 0/66 1/40 91/1015 5/119 9/202 5/51 1/66 25/194 26/2543 5/100		17.6 % 0.6 % 19.0 % 1.2 % 5.3 % 0.6 % 0.9 % 11.5 % 11.2 % 11.2 %	0.94 [ 0.69, 1.27 4.93 [ 0.24, 100.70 0.17 [ 0.01, 4.05 1.25 [ 0.96, 1.62 0.20 [ 0.02, 1.69 1.01 [ 0.41, 2.49 0.09 [ 0.01, 1.60 1.89 [ 0.18, 20.31 1.05 [ 0.63, 1.75 1.24 [ 0.74, 2.07

0.05 0.2 I 5 20

Favours higher PUFA Favours lower PUFA

(Continued . . . )

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Study or subgroup	Higher PUFA	Lower PUFA	Risk Ratio M- H,Random,95%	Weight	( Continued) Risk Ratio M- H,Random,95%
	n/N	n/N	Cl		Cl
Test for overall effect: $Z = 0.09$	. ,				
8 Randomised 250+ participan	ts				
AlphaOmega - ALA	78/2409	84/2428	-	19.3 %	0.94 [ 0.69, 1.27 ]
DART fat 1989	4/ 0 8	91/1015	-	21.4 %	1.25 [ 0.96, 1.62 ]
FAAT - Leaf 2005	9/200	9/202		4.9 %	1.01 [ 0.41, 2.49 ]
MRC 1968	27/199	25/194	-	11.6 %	1.05 [ 0.63, 1.75 ]
PREDIMED 2013	31/2454	26/2543		11.3 %	1.24 [ 0.74, 2.07 ]
Sydney Diet-Heart 1978	37/221	25/237	-	12.6 %	1.59 [ 0.99, 2.55 ]
Veterans Admin 1969	57/424	81/422	-	19.0 %	0.70 [ 0.51, 0.96 ]
Subtotal (95% CI)	6925	7041	•	100.0 %	1.06 [ 0.85, 1.32 ]
Total events: 353 (Higher PUFA	A), 341 (Lower PUFA)				
Heterogeneity: Tau <sup>2</sup> = 0.04; Cł	ni <sup>2</sup> = 12.06, df = 6 (P =	0.06); l <sup>2</sup> =50%			
Test for overall effect: $Z = 0.50$	(P = 0.62)				
		(	D.05 0.2 I 5 20		
		Favour	s higher PUFA Favours lower	PUFA	

#### Analysis 2.3. Comparison 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes, Outcome 3 Cardiovascular mortality - SA fixed-effect.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes

Outcome: 3 Cardiovascular mortality - SA fixed-effect

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Study or subgroup	Higher PUFA n/N	Lower PUFA n/N	Risk Ratio M-H,Fixed,95% Cl	Weight	Risk Ratio M-H,Fixed,95% Cl
AlphaOmega - ALA	78/2409	84/2428	-	22.9 %	0.94 [ 0.69, 1.27 ]
Black 1994	2/67	0/66		0.1 %	4.93 [ 0.24,  00.70 ]
Brox 2001	0/80	1/40	•	0.5 %	0.17 [ 0.01, 4.05 ]
DART fat 1989	114/1018	91/1015	-	25.0 %	1.25 [ 0.96, 1.62 ]
Doi 2014	/  9	5/119	•	1.4 %	0.20 [ 0.02, 1.69 ]
FAAT - Leaf 2005	9/200	9/202		2.5 %	1.01 [ 0.41, 2.49 ]
HARP- Sacks 1995	0/41	1/39	· · · · · · · · · · · · · · · · · · ·	0.4 %	0.32 [ 0.01, 7.57 ]
Houtsmuller 1979	0/51	5/5	• · · · · · · · · · · · · · · · · · · ·	1.5 %	0.09 [ 0.01, 1.60 ]
Kumar 2013	1/39	1/39		0.3 %	1.00 [ 0.06, 15.43 ]
Ley 2004	2/70	1/66	·	0.3 %	1.89 [ 0.18, 20.31 ]
MRC 1968	27/199	25/194	+	6.9 %	1.05 [ 0.63, 1.75 ]
PREDIMED 2013	31/2454	26/2543		7.0 %	1.24 [ 0.74, 2.07 ]
Raitt 2005	2/100	5/100		1.4 %	0.40 [ 0.08, 2.01 ]
Rose 1965	5/28	3/26		0.9 %	1.55 [ 0.41, 5.84 ]
Sydney Diet-Heart 1978	37/221	25/237		6.6 %	1.59 [ 0.99, 2.55 ]
Veterans Admin 1969	57/424	81/422	-	22.3 %	0.70 [ 0.51, 0.96 ]
Total (95% CI)	7520	7587	•	100.0 %	1.01 [ 0.88, 1.16 ]
Total events: 366 (Higher PUFA) Heterogeneity: Chi <sup>2</sup> = 21.84, df Test for overall effect: $Z = 0.17$ Test for subgroup differences: N	$F = 15 (P = 0.11); 1^2 = 3$ (P = 0.86)	1%			
			0.05 0.2 1 5 20		

Favours higher PUFA Favours lower PUFA

#### Analysis 2.4. Comparison 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes, Outcome 4 Cardiovascular mortality - subgroup by PUFA dose.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes

Outcome: 4 Cardiovascular mortality - subgroup by PUFA dose

Study or subgroup	Higher PUFA	Lower PUFA	Risk Ratio M-	Weight	Risk Ratio M-
	n/N	n/N	H,Random,95% Cl		H,Random,S Cl
l total PUFA < 1.0% E					
Doi 2014	1/119	5/119	<b>←</b> →→	1.0 %	0.20 [ 0.02, 1.69 ]
FAAT - Leaf 2005	9/200	9/202		4.6 %	1.01 [ 0.41, 2.49 ]
Kumar 2013	1/39	1/39		0.6 %	1.00 [ 0.06, 15.43 ]
Ley 2004	2/70	1/66		0.8 %	1.89 [ 0.18, 20.31 ]
Raitt 2005	2/100	5/100		1.6 %	0.40 [ 0.08, 2.01 ]
Subtotal (95% CI)	528	526	-	8.6 %	0.76 [ 0.38, 1.51 ]
Total events: 15 (Higher PUFA	, , , ,				
Heterogeneity: $Tau^2 = 0.0$ ; Ch		54); l <sup>2</sup> =0.0%			
Test for overall effect: $Z = 0.73$	8 (P = 0.44)				
2 total PUFA 1.0 to < 2.0% E AlphaOmega - ALA	78/2409	84/2428	+	17.6 %	0.94 [ 0.69, 1.27 -
Brox 2001	0/80	1/40	• • • • • • • • • • • • • • • • • • •	0.4 %	0.17 [ 0.01, 4.05
PREDIMED 2013	31/2454	26/2543		10.4 %	1.24 [ 0.74, 2.07
	4943	5011		28.5 %	0.99 [ 0.76, 1.30 ]
<b>Subtotal (95% CI)</b> Fotal events: 109 (Higher PUF		5011	Ť	20.5 %	0.99 [ 0./0, 1.90 ]
Heterogeneity: Tau <sup>2</sup> = 0.00; C	, , ,	$(36) \cdot  ^2 = 1\%$			
Test for overall effect: $Z = 0.0$					
3 total PUFA 2.0 to < 5.0% E	· · ·				
Black 1994	2/67	0/66		0.5 %	4.93 [ 0.24, 100.70 ]
DART fat 1989	114/1018	91/1015	-	19.4 %	1.25 [ 0.96, 1.62 ]
HARP- Sacks 1995	0/41	1/39	· · · ·	0.4 %	0.32 [ 0.01, 7.57 ]
Subtotal (95% CI)	1126	1120	•	20.3 %	1.25 [ 0.96, 1.62 ]
Total events: 116 (Higher PUF	A), 92 (Lower PUFA)				
Heterogeneity: Tau <sup>2</sup> = 0.0; Ch	$mi^2 = 1.51$ , $df = 2$ (P = 0.	47); l <sup>2</sup> =0.0%			
Test for overall effect: $Z = 1.69$	9 (P = 0.092)				
ł total PUFA > 5.0% E					
Houtsmuller 1979	0/51	5/5 I	<b>←</b> →	0.5 %	0.09 [ 0.01, 1.60 ]
MRC 1968	27/199	25/194	+	10.7 %	1.05 [ 0.63, 1.75
			0.05 0.2 I 5 20		
		Fav	vours higher PUFA Favours lower F	PUFA	(Continued
					(continued

Study or subgroup	Higher PUFA	Lower PUFA	Risk Ratio M- H,Random,95%	Weight	( Continued) Risk Ratio M- H,Random,95%
	n/N	n/N	Cl		CI
Rose 1965	5/28	3/26		2.3 %	1.55 [ 0.41, 5.84 ]
Sydney Diet-Heart 1978	37/221	25/237		11.6 %	1.59 [ 0.99, 2.55 ]
Veterans Admin 1969	57/424	81/422	-	17.3 %	0.70 [ 0.51, 0.96 ]
Subtotal (95% CI)	923	930	•	42.6 %	1.01 [ 0.62, 1.63 ]
Total events: 126 (Higher PUFA	), 139 (Lower PUFA)				
Heterogeneity: Tau <sup>2</sup> = 0.16; Ch	i <sup>2</sup> = 11.43, df = 4 (P =	0.02); l <sup>2</sup> =65%			
Test for overall effect: $Z = 0.02$	(P = 0.98)				
Total (95% CI)	7520	7587	•	100.0 %	1.02 [ 0.82, 1.26 ]
Total events: 366 (Higher PUFA	), 363 (Lower PUFA)				
Heterogeneity: Tau <sup>2</sup> = 0.04; Ch	i <sup>2</sup> = 21.84, df = 15 (P	= 0.11); I <sup>2</sup> =31%			
Test for overall effect: $Z = 0.17$	(P = 0.87)				
Test for subgroup differences: C	Chi <sup>2</sup> = 2.68, df = 3 (P =	0.44), I <sup>2</sup> =0.0%			
			0.05 0.2 1 5 20		

Favours higher PUFA Favours lower PUFA

#### Analysis 2.5. Comparison 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes, Outcome 5 Cardiovascular mortality - subgroup by duration.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes

Outcome: 5 Cardiovascular mortality - subgroup by duration

Risk Rati M	nt	Weight	Risk Ratio M-		Lower PUFA	Higher PUFA	Study or subgroup
H,Random			H,Random,95% Cl		n/N	n/N	
							Medium duration I to <2 years
0.17 [ 0.01, 4.05	%	0.4 %		+	1/40	0/80	Brox 2001
0.20 [ 0.02, 1.69	%	1.0 %	•		5/119	1/119	Doi 2014
1.01 [ 0.41, 2.49	%	4.6 %			9/202	9/200	FAAT - Leaf 2005
1.00 [ 0.06, 15.43	%	0.6 %			1/39	1/39	Kumar 2013
1.89 [ 0.18, 20.31	%	0.8 %			1/66	2/70	Ley 2004
0 [ 0.39, 1.67	6 <b>0.</b>	7.4 %	-		466	508	ubtotal (95% CI)
0.94 [ 0.69. ].27	%	17.6 %	-		84/2428	,	est for overall effect: Z = 0.58 (P = Medium-long duration 2 to < 4 ye AlphaOmega - ALA
0.94 [ 0.69, 1.27	%	17.6 %	-		84/2428	78/2409	AlphaOmega - ALA
4.93 [ 0.24,  00.70	%	0.5 %			0/66	2/67	Black 1994
1.25 [ 0.96, 1.62	%	19.4 %	-		91/1015	4/ 0 8	DART fat 1989
0.32 [ 0.01, 7.57	%	0.4 %		+	1/39	0/41	HARP- Sacks 1995
0.40 [ 0.08, 2.01	%	1.6 %		_	5/100	2/100	Raitt 2005
1.55 [ 0.41, 5.84	%	2.3 %			3/26	5/28	Rose 1965
9 [ 0.88, 1.36	6 1.	41.9 %	•		<b>3674</b> .38); I <sup>2</sup> =6%	5.30, df = 5 (P = 0	abtotal (95% CI) tal events: 201 (Higher PUFA), 18 eterogeneity: Tau <sup>2</sup> = 0.01; Chi <sup>2</sup> = st for overall effect: Z = 0.79 (P =
0.09 [ 0.01, 1.60	%	0.5 %		<b>•</b>	5/51	0/51	Long duration 4+ years Houtsmuller 1979
1.05 [ 0.63, 1.75	%	10.7 %	- <b>-</b> -		25/194	27/199	MRC 1968
1.24 [ 0.74, 2.07	%	10.4 %			26/2543	31/2454	PREDIMED 2013
1.59 [ 0.99, 2.55	%	11.6 %			25/237	37/221	Sydney Diet-Heart 1978
0.70 [ 0.51, 0.96	%	17.3 %			81/422	57/424	Veterans Admin 1969
(	%		.2 I 5 20 PUFA Favours lower f	0.05 avours highe	81/422	57/424	Veterans Admin 1969

Study or subgroup	Higher PUFA	Lower PUFA	Risk Ratio	Weight	( Continued) Risk Ratio M-
	n/N	n/N	H,Random,95% Cl		H,Random,95% Cl
Subtotal (95% CI)	3349	3447	+	<b>50.</b> 7 %	1.02 [ 0.67, 1.55 ]
Total events: 152 (Higher PUF	A), 162 (Lower PUFA)				
Heterogeneity: $Tau^2 = 0.13$ ; C	chi <sup>2</sup> = 11.92, df = 4 (P =	0.02); l <sup>2</sup> =66%			
Test for overall effect: $Z = 0.0$	9 (P = 0.93)				
Total (95% CI)	7520	7587	+	100.0 %	1.02 [ 0.82, 1.26 ]
Total events: 366 (Higher PUF	A), 363 (Lower PUFA)				
Heterogeneity: $Tau^2 = 0.04$ ; C	chi <sup>2</sup> = 21.84, df = 15 (P =	= 0.  );   <sup>2</sup> =3 %			
Test for overall effect: $Z = 0.1$	7 (P = 0.87)				
Test for subgroup differences:	Chi <sup>2</sup> = 0.65, df = 2 (P =	0.72), I <sup>2</sup> =0.0%			
			0.05 0.2 1 5 20	1	
		Favou	rs higher PUFA Favours lower	PUFA	

#### Analysis 2.6. Comparison 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes, Outcome 6 Cardiovascular mortality - subgroup by primary or secondary prevention.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes

Outcome: 6 Cardiovascular mortality - subgroup by primary or secondary prevention

Study or subgroup	Higher PUFA	Lower PUFA	Risk Ratio M-	Weight	Risk Ratio M-
	n/N	n/N	H,Random,95% Cl		H,Random,95% Cl
I Primary prevention of cardio	vascular disease (CVD)				
Black 1994	2/67	0/66		0.5 %	4.93 [ 0.24, 100.70 ]
Brox 2001	0/80	1/40	·	0.4 %	0.17 [ 0.01, 4.05 ]
Houtsmuller 1979	0/5	5/51	<del>• • • • • • • • • • • • • • • • • • • </del>	0.5 %	0.09 [ 0.01, 1.60 ]
Kumar 2013	1/39	1/39		0.6 %	1.00 [ 0.06, 15.43 ]
Ley 2004	2/70	1/66		0.8 %	1.89 [ 0.18, 20.31 ]
PREDIMED 2013	31/2454	26/2543		10.4 %	1.24 [ 0.74, 2.07 ]
Veterans Admin 1969	57/424	81/422	+	17.3 %	0.70 [ 0.51, 0.96 ]
			0.05 0.2   5 20		<u> </u>
Favours higher PUFA Favours lower PUFA					

(Continued . . . )

Higher PUFA	Lower PUFA	Risk Ratio M-	Weight	( Continued) Risk Ratio M-
n/N	n/N	H,Random,95% Cl		H,Random,95% Cl
3185	3227	•	30.6 %	0.87 [ 0.54, 1.41 ]
115 (Lower PUFA)				
	0.2 l ); l <sup>2</sup> =29%			
( )				
)			17 / 0/	
78/2409	84/2428		17.6 %	0.94 [ 0.69, 1.27 ]
4/ 0 8	91/1015	-	19.4 %	1.25 [ 0.96, 1.62 ]
1/119	5/119	•	1.0 %	0.20 [ 0.02, 1.69 ]
9/200	9/202		4.6 %	1.01 [ 0.41, 2.49 ]
0/41	1/39	<u>د ا</u>	0.4 %	0.32 [ 0.01, 7.57 ]
27/199	25/194	+	10.7 %	1.05 [ 0.63, 1.75 ]
2/100	5/100		1.6 %	0.40 [ 0.08, 2.01 ]
5/28	3/26		2.3 %	1.55 [ 0.41, 5.84 ]
37/221	25/237		11.6 %	1.59 [ 0.99, 2.55 ]
4335	4360	•	<b>69.4</b> %	1.12 [ 0.92, 1.36 ]
), 248 (Lower PUFA)				
,	$(.33);  ^2 =  2\%$			
```				
	7587	•	100.0 %	1.02 [ 0.82, 1.26 ]
,				
	= 0.11); 1 <sup>2</sup> =31%			
( /				
$hi^2 = 0.88, df = 1 (P =$	0.35), l <sup>2</sup> =0.0%			
		0.05 0.2 I 5 20		
	$\frac{n/N}{3185}$ 115 (Lower PUFA) $^{2} = 8.44, df = 6 (P = 0)$ $P = 0.57)$ 78/2409 114/1018 1/119 9/200 0/41 27/199 2/100 5/28 37/221 4335 0, 248 (Lower PUFA) $^{2} = 9.14, df = 8 (P = 0)$ $P = 0.27)$ 7520 0, 363 (Lower PUFA) $^{2} = 21.84, df = 15 (P = 0)$ $P = 0.87)$	n/N = n/N 3185 3227 115 (Lower PUFA) 2 = 8.44, df = 6 (P = 0.21); l <sup>2</sup> =29% (P = 0.57) 78/2409 84/2428 114/1018 91/1015 1/119 5/119 9/200 9/202 0/41 1/39 27/199 25/194 2/100 5/100 5/28 3/26 37/221 25/237 4335 4360 0, 248 (Lower PUFA) 2 = 9.14, df = 8 (P = 0.33); l <sup>2</sup> = 12% (P = 0.27) 7520 7587 0, 363 (Lower PUFA) 2 = 21.84, df = 15 (P = 0.11); l <sup>2</sup> = 31% (P = 0.88, df = 1 (P = 0.35), l <sup>2</sup> =0.0%	$\begin{array}{c c c c c c c c c c c c c c c c c c c $	$\begin{array}{c c c c c c c c c c c c c c c c c c c $

Favours higher PUFA Favours lower PUFA

#### Analysis 2.7. Comparison 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes, Outcome 7 Cardiovascular mortality - subgroup by baseline PUFA dose.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes

Outcome: 7 Cardiovascular mortality - subgroup by baseline PUFA dose

					M-
	n/N	n/N	H,Random,95% Cl		H,Random,S Cl
Baseline total PUFA < 6% E					
Ley 2004	2/70	1/66		0.8 %	1.89 [ 0.18, 20.31 ]
Veterans Admin 1969	57/424	81/422	-	17.3 %	0.70 [ 0.51, 0.96 ]
Subtotal (95% CI)	494	488	•	18.1 %	0.71 [ 0.52, 0.97 ]
ōtal events: 59 (Higher PUFA),	82 (Lower PUFA)				
Heterogeneity: $Tau^2 = 0.0$ ; Chi <sup>2</sup>		42); I <sup>2</sup> =0.0%			
Test for overall effect: $Z = 2.16$	. ,				
Baseline total PUFA 6 to < 11 Black 1994	% E 2/67	0/66		0.5 %	4.93 [ 0.24, 100.70 -
DART fat 1989	4/ 0 8	91/1015	-	19.4 %	1.25 [ 0.96, 1.62 ]
PREDIMED 2013	31/2454	26/2543		10.4 %	1.24 [ 0.74, 2.07 ]
Sydney Diet-Heart 1978	37/221	25/237		11.6 %	1.59 [ 0.99, 2.55
ubtotal (95% CI)	3760	3861	•	42.0 %	1.32 [ 1.07, 1.62
Test for overall effect: $Z = 2.57$ Baseline total PUFA   +% E Subtotal (95% CI)		0			Not estimable
Subtotal (95% CI)	0	0			Not estimable
otal events: 0 (Higher PUFA), 0	) (Lower PUFA)				
Heterogeneity: not applicable					
est for overall effect: not applic	able				
Baseline total PUFA unclear AlphaOmega - ALA	78/2409	84/2428	-	17.6 %	0.94 [ 0.69, 1.27
Brox 2001	0/80	1/40	<b>4</b>	0.4 %	0.17 [ 0.01, 4.05
Doi 2014	1/119	5/119	<del> </del>	1.0 %	0.20 [ 0.02, 1.69
FAAT - Leaf 2005	9/200	9/202		4.6 %	-
					1.01 [ 0.41, 2.49
HARP- Sacks 1995	0/41	1/39		0.4 %	0.32 [ 0.01, 7.57
Houtsmuller 1979	0/51	5/5 I	<b>• • • • • • • •</b>	0.5 %	0.09 [ 0.01, 1.60
Kumar 2013	1/39	1/39		0.6 %	1.00 [ 0.06, 15.43
			0.05 0.2   5 20		
		Fave	ours higher PUFA Favours lower	PUFA	
			5		(Continued

Study or subgroup	Higher PUFA	Lower PUFA	Risk Ratio M- H,Random,95%	Weight	( Continued) Risk Ratio M- H,Random,95%
	n/N	n/N	CI		CI
MRC 1968	27/199	25/194	-	10.7 %	1.05 [ 0.63, 1.75 ]
Raitt 2005	2/100	5/100		1.6 %	0.40 [ 0.08, 2.01 ]
Rose 1965	5/28	3/26	<u> </u>	2.3 %	1.55 [ 0.41, 5.84 ]
Subtotal (95% CI)	3266	3238	•	<b>39.9</b> %	0.92 [ 0.72, 1.16 ]
Total events: 123 (Higher PUF	A), 139 (Lower PUFA)				
Heterogeneity: $Tau^2 = 0.0$ ; Ch	$m^2 = 8.04$ , df = 9 (P = 0.	53); l <sup>2</sup> =0.0%			
Test for overall effect: $Z = 0.7$	2 (P = 0.47)				
Total (95% CI)	7520	7587	•	100.0 %	1.02 [ 0.82, 1.26 ]
Total events: 366 (Higher PUF	A), 363 (Lower PUFA)				
Heterogeneity: $Tau^2 = 0.04$ ; C	Chi <sup>2</sup> = 21.84, df = 15 (P	= 0.11); I <sup>2</sup> =31%			
Test for overall effect: $Z = 0.1$	7 (P = 0.87)				
Test for subgroup differences:	$Chi^2 = 11.68, df = 2 (P$	= 0.00), l <sup>2</sup> =83%			
			0.05 0.2 I 5 20	)	

Favours higher PUFA Favours lower PUFA

#### Analysis 2.8. Comparison 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes, Outcome 8 Cardiovascular mortality - subgroup by replacement.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes

Outcome: 8 Cardiovascular mortality - subgroup by replacement

Study or subgroup	Higher PUFA	Lower PUFA	Risk Ratio M-	Weight	Risk Ratio M-
	n/N	n/N	H,Random,95% Cl		H,Random,9 Cl
I PUFA replaced saturated fats					
DART fat 1989	4/ 0 8	91/1015	-	29.7 %	1.25 [ 0.96, 1.62 ]
MRC 1968	27/199	25/194	-	20.6 %	1.05 [ 0.63, 1.75 ]
Sydney Diet-Heart 1978	37/221	25/237		21.8 %	1.59 [ 0.99, 2.55 ]
Veterans Admin 1969	57/424	81/422	-	27.9 %	0.70 [ 0.51, 0.96 ]
Subtotal (95% CI)	1862	1868	+	100.0 %	1.08 [ 0.76, 1.54 ]
Total events: 235 (Higher PUFA), Heterogeneity: Tau <sup>2</sup> = 0.09; Chi <sup>2</sup> Test for overall effect: Z = 0.43 ( 2 PUFA replaced monounsaturat	P = 11.14, df = 3 (P = 0.67)	0.01); l <sup>2</sup> =73% 84/2428		26.2 %	00410701071
AlphaOmega - ALA			I		0.94 [ 0.69, 1.27 ]
FAAT - Leaf 2005	9/200	9/202		7.2 %	1.01 [ 0.41, 2.49 ]
HARP- Sacks 1995	0/41	1/39	<b>←</b> +	0.7 %	0.32 [ 0.01, 7.57 ]
PREDIMED 2013	31/2454	26/2543		16.0 %	1.24 [ 0.74, 2.07 ]
Raitt 2005	2/100	5/100		2.6 %	0.40 [ 0.08, 2.01 ]
Rose 1965	5/28	3/26		3.7 %	1.55 [ 0.41, 5.84 ]
Sydney Diet-Heart 1978	37/221	25/237		17.7 %	1.59 [ 0.99, 2.55 ]
Veterans Admin 1969	57/424	81/422	-	25.8 %	0.70 [ 0.51, 0.96 ]
Subtotal (95% CI) Total events: 219 (Higher PUFA), Heterogeneity: Tau <sup>2</sup> = 0.05; Chi <sup>2</sup> Test for overall effect: Z = 0.06 ( 3 PUFA replaced carbohydrates	<sup>2</sup> = 11.30, df = 7 (P =	<b>5997</b> 0.13); I <sup>2</sup> =38%	+	100.0 %	0.99 [ 0.76, 1.30 ]
Black 1994	2/67	0/66		16.2 %	4.93 [ 0.24, 100.70 ]
Houtsmuller 1979	0/51	5/5 I	· •	17.5 %	0.09 [ 0.01, 1.60 ]
	2/70	1/66		23.0 %	1.89 [ 0.18, 20.31 ]
Ley 2004					

(Continued . . . )

Study or subgroup	Higher PUFA	Lower PUFA	Risk Ratio M- H.Random,95%	Weight	( Continued) Risk Ratio M- H.Random,95%
	n/N	n/N	Cl		ĊI
Subtotal (95% CI)	216	209		100.0 %	1.19 [ 0.30, 4.71 ]
Total events: 9 (Higher PUFA)	, 9 (Lower PUFA)				
Heterogeneity: $Tau^2 = 0.68$ ; C	$Chi^2 = 4.53, df = 3 (P = 0)$	0.21); I <sup>2</sup> =34%			
Test for overall effect: $Z = 0.2$	5 (P = 0.80)				
4 PUFA replaced protein					
Ley 2004	2/70	1/66		4.3 %	1.89 [ 0.18, 20.31 ]
MRC 1968	27/199	25/194		95.7 %	1.05 [ 0.63, 1.75 ]
Subtotal (95% CI)	269	260	+	100.0 %	1.08 [ 0.66, 1.77 ]
Total events: 29 (Higher PUFA Heterogeneity: Tau <sup>2</sup> = 0.0; Ch Test for overall effect: $Z = 0.3$	$m^2 = 0.22$ , df = 1 (P = 0.	64); I <sup>2</sup> =0.0%			
5 PUFA replaced unclear			_		
Brox 2001	0/80	1/40	• <b>•</b>	21.9 %	0.17 [ 0.01, 4.05 ]
Doi 2014	1/119	5/119	• <b>•</b>	48.6 %	0.20 [ 0.02, 1.69 ]
Kumar 2013	1/39	1/39	<b>+</b>	29.5 %	1.00 [ 0.06, 15.43 ]
Subtotal (95% CI)	238	198		100.0 %	0.31 [ 0.07, 1.37 ]
Total events: 2 (Higher PUFA) Heterogeneity: Tau <sup>2</sup> = 0.0; Ch Test for overall effect: $Z = 1.5$ Test for subgroup differences:	$hi^2 = 1.01, df = 2 (P = 0.4)$ 4 (P = 0.12)	<i>y.</i>			
		Fa	0.05 0.2 I 5 20 avours higher PUFA Favours lower	PUFA	

#### Analysis 2.9. Comparison 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes, Outcome 9 Cardiovascular mortality - subgroup by sex.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes

Outcome: 9 Cardiovascular mortality - subgroup by sex

	Higher PUFA	Lower PUFA	Risk Ratio M-	Weight	Risk Ratio M-
	n/N	n/N	H,Random,95% Cl		H,Random,9 Cl
> 70% men					
AlphaOmega - ALA	78/2409	84/2428	-	17.6 %	0.94 [ 0.69, 1.27 ]
DART fat 1989	4/ 0 8	91/1015	-	19.4 %	1.25 [ 0.96, 1.62 ]
Doi 2014	1/119	5/119	• · · · · · · · · · · · · · · · · · · ·	1.0 %	0.20 [ 0.02, 1.69 ]
FAAT - Leaf 2005	9/200	9/202		4.6 %	1.01 [ 0.41, 2.49 ]
HARP- Sacks 1995	0/41	1/39	•	0.4 %	0.32 [ 0.01, 7.57 ]
Ley 2004	2/70	1/66		0.8 %	1.89 [ 0.18, 20.31 ]
MRC 1968	27/199	25/194	-	10.7 %	1.05 [ 0.63, 1.75 ]
Raitt 2005	2/100	5/100		1.6 %	0.40 [ 0.08, 2.01 ]
Sydney Diet-Heart 1978	37/221	25/237		11.6 %	1.59 [ 0.99, 2.55 ]
Veterans Admin 1969	57/424	81/422	-	17.3 %	0.70 [ 0.51, 0.96 ]
				0.5.0.0/	
Total events: 327 (Higher PUF) Heterogeneity: Tau <sup>2</sup> = 0.05; Cl	ni <sup>2</sup> = 15.89, df = 9 (P =	<b>4822</b> 0.07); I <sup>2</sup> =43%		85.2 %	1.00 [ 0./8, 1.2/ ]
Total events: 327 (Higher PUF/ Heterogeneity: Tau <sup>2</sup> = 0.05; CI Test for overall effect: Z = 0.02 2 > 70% women	A), 327 (Lower PUFA) ni <sup>2</sup> = 15.89, df = 9 (P = . (P = 0.98)	0.07); l <sup>2</sup> =43%		85.2 %	
Total events: 327 (Higher PUF) Heterogeneity: Tau <sup>2</sup> = 0.05; Cl Test for overall effect: Z = 0.02 2 > 70% women Subtotal (95% CI)	A), 327 (Lower PUFA) $ni^2 = 15.89$ , df = 9 (P = (P = 0.98) 0			85.2 %	
Total events: 327 (Higher PUF/ Heterogeneity: Tau <sup>2</sup> = 0.05; CI Test for overall effect: Z = 0.02 2 > 70% women <b>Subtotal (95% CI)</b> Total events: 0 (Higher PUFA), Heterogeneity: not applicable Test for overall effect: not appli	A), 327 (Lower PUFA) ni <sup>2</sup> = 15.89, df = 9 (P = . (P = 0.98) <b>0</b> 0 (Lower PUFA)	0.07); l <sup>2</sup> =43%		85.2 %	
Total events: 327 (Higher PUF/ Heterogeneity: Tau <sup>2</sup> = 0.05; Cl Test for overall effect: Z = 0.02 2 > 70% women Subtotal (95% CI) Total events: 0 (Higher PUFA), Heterogeneity: not applicable Test for overall effect: not appli	A), 327 (Lower PUFA) ni <sup>2</sup> = 15.89, df = 9 (P = . (P = 0.98) <b>0</b> 0 (Lower PUFA)	0.07); l <sup>2</sup> =43%		<b>85.2 %</b> 0.5 %	Not estimable
Total events: 327 (Higher PUF/ Heterogeneity: Tau <sup>2</sup> = 0.05; CI Test for overall effect: Z = 0.02 2 > 70% women <b>Subtotal (95% CI)</b> Total events: 0 (Higher PUFA), Heterogeneity: not applicable Test for overall effect: not appli 8 men % women	A), 327 (Lower PUFA) ni <sup>2</sup> = 15.89, df = 9 (P = (P = 0.98) 0 0 (Lower PUFA) cable	0.07); l <sup>2</sup> =43%		-	<b>Not estimable</b> 4.93 [ 0.24, 100.70 ]
Total events: 327 (Higher PUF/ Heterogeneity: Tau <sup>2</sup> = 0.05; Cl Fest for overall effect: Z = 0.02 2 > 70% women Subtotal (95% CI) Total events: 0 (Higher PUFA), Heterogeneity: not applicable Fest for overall effect: not appli 8 men % women Black 1994	A), 327 (Lower PUFA) ni <sup>2</sup> = 15.89, df = 9 (P = (P = 0.98) 0 0 (Lower PUFA) cable 2/67	0.07); l <sup>2</sup> =43% <b>0</b> 0/66		0.5 %	<b>Not estimable</b> 4.93 [ 0.24, 100.70 ] 0.17 [ 0.01, 4.05 ]
Total events: 327 (Higher PUF/ Heterogeneity: Tau <sup>2</sup> = 0.05; Cl Test for overall effect: Z = 0.02 2 > 70% women Subtotal (95% CI) Total events: 0 (Higher PUFA), Heterogeneity: not applicable Test for overall effect: not appli 8 men % women Black 1994 Brox 2001	A), 327 (Lower PUFA) ni <sup>2</sup> = 15.89, df = 9 (P = (P = 0.98) 0 (Lower PUFA) cable 2/67 0/80	0.07); l <sup>2</sup> =43% <b>0</b> 0/66 1/40	· · · · · · · · · · · · · · · · · · ·	0.5 % 0.4 %	Not estimable 4.93 [ 0.24, 100.70 ] 0.17 [ 0.01, 4.05 ] 0.09 [ 0.01, 1.60 ]
Total events: 327 (Higher PUF/ Heterogeneity: Tau <sup>2</sup> = 0.05; Cl Fest for overall effect: Z = 0.02 2 > 70% women Subtotal (95% CI) Total events: 0 (Higher PUFA), Heterogeneity: not applicable Fest for overall effect: not appli 8 men % women Black 1994 Brox 2001 Houtsmuller 1979	A), 327 (Lower PUFA) ni <sup>2</sup> = 15.89, df = 9 (P = (P = 0.98) 0 0 (Lower PUFA) cable 2/67 0/80 0/5 1	0.07); l <sup>2</sup> =43% <b>0</b> 0/66 1/40 5/51		0.5 % 0.4 % 0.5 %	Not estimable 4.93 [ 0.24, 100.70 ] 0.17 [ 0.01, 4.05 ] 0.09 [ 0.01, 1.60 ] 1.00 [ 0.06, 15.43 ]
Total events: 327 (Higher PUF/ Heterogeneity: Tau <sup>2</sup> = 0.05; CI Test for overall effect: Z = 0.02 2 > 70% women Subtotal (95% CI) Total events: 0 (Higher PUFA), Heterogeneity: not applicable Test for overall effect: not appli 3 men % women Black 1994 Brox 2001 Houtsmuller 1979 Kumar 2013 PREDIMED 2013	A), 327 (Lower PUFA) hi <sup>2</sup> = 15.89, df = 9 (P = (P = 0.98) 0 0 (Lower PUFA) cable 2/67 0/80 0/5 I 1/39	0.07); l <sup>2</sup> =43% <b>0</b> 0/66 1/40 5/51 1/39		0.5 % 0.4 % 0.5 % 0.6 %	Not estimable 4.93 [ 0.24, 100.70 ] 0.17 [ 0.01, 4.05 ] 0.09 [ 0.01, 1.60 ] 1.00 [ 0.06, 15.43 ] 1.24 [ 0.74, 2.07 ]
Brox 2001 Houtsmuller 1979 Kumar 2013	A), 327 (Lower PUFA) ni <sup>2</sup> = 15.89, df = 9 (P = (P = 0.98) 0 0 (Lower PUFA) cable 2/67 0/80 0/51 1/39 31/2454 <b>2691</b>	0.07); l <sup>2</sup> =43% <b>0</b> 0/66 1/40 5/51 1/39 26/2543		0.5 % 0.4 % 0.5 % 0.6 % 10.4 %	1.00 [ 0.78, 1.27 ] Not estimable 4.93 [ 0.24, 100.70 ] 0.17 [ 0.01, 4.05 ] 0.09 [ 0.01, 1.60 ] 1.00 [ 0.06, 15.43 ] 1.24 [ 0.74, 2.07 ] 0.86 [ 0.30, 2.47 ]

(Continued  $\dots$ )

Study or subgroup	Higher PUFA	Lower PUFA	Risk Ratio M-	Weight	( Continued) Risk Ratio M-
	n/N	n/N	H,Random,95% Cl		H,Random,95% Cl
Heterogeneity: $Tau^2 = 0.45$ ; C	$chi^2 = 5.48, df = 4 (P = 0)$	0.24); I <sup>2</sup> =27%			
Test for overall effect: $Z = 0.2$	9 (P = 0.78)				
4 sex not reported					
Rose 1965	5/28	3/26		2.3 %	1.55 [ 0.41, 5.84 ]
Subtotal (95% CI)	28	26		2.3 %	1.55 [ 0.41, 5.84 ]
Total events: 5 (Higher PUFA)	, 3 (Lower PUFA)				
Heterogeneity: not applicable					
Test for overall effect: $Z = 0.6$	4 (P = 0.52)				
Total (95% CI)	7520	7587	+	100.0 %	1.02 [ 0.82, 1.26 ]
Total events: 366 (Higher PUF	A), 363 (Lower PUFA)				
Heterogeneity: $Tau^2 = 0.04$ ; C	chi <sup>2</sup> = 21.84, df = 15 (P	= 0.11); I <sup>2</sup> =31%			
Test for overall effect: $Z = 0.1$	7 (P = 0.87)				
Test for subgroup differences:	Chi <sup>2</sup> = 0.50, df = 2 (P =	0.78), l <sup>2</sup> =0.0%			
lest for subgroup differences:	Cni" – 0.50, dt = 2 (P =	0.78), 1~ -0.0%			

0.05 0.2 I 5 20

Favours higher PUFA Favours lower PUFA

## Analysis 2.10. Comparison 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes, Outcome 10 Cardiovascular mortality - subgroup by age.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes

Outcome: 10 Cardiovascular mortality - subgroup by age

Study or subgroup	Higher PUFA	Lower PUFA	Risk Ratio M-	Weight	Risk Ratic M-
	n/N	n/N	H,Random,95% Cl		H,Random, C
I Mean age < 50 years					
Sydney Diet-Heart 1978	37/221	25/237		11.6 %	1.59 [ 0.99, 2.55 ]
Subtotal (95% CI)	221	237	*	11.6 %	1.59 [ 0.99, 2.55 ]
Total events: 37 (Higher PUFA),	25 (Lower PUFA)				
Heterogeneity: not applicable Test for overall effect: Z = 1.91	(P = 0.056)				
2 Mean age 50 to < 65 years	(1 0.050)				
Black 1994	2/67	0/66		0.5 %	4.93 [ 0.24, 100.70
Brox 200 l	0/80	1/40	• · · · · · · · · · · · · · · · · · · ·	0.4 %	0.17 [ 0.01, 4.05
DART fat 1989	114/1018	91/1015	+	19.4 %	1.25 [ 0.96, 1.62
HARP- Sacks 1995	0/41	1/39	· · · · · · · · · · · · · · · · · · ·	0.4 %	0.32 [ 0.01, 7.57
Ley 2004	2/70	1/66		0.8 %	1.89 [ 0.18, 20.31
MRC 1968	27/199	25/194	+	10.7 %	1.05 [ 0.63, 1.75
Raitt 2005	2/100	5/100	<b>.</b>	1.6 %	0.40 [ 0.08, 2.01
Rose 1965	5/28	3/26		2.3 %	1.55 [ 0.41, 5.84
Subtotal (95% CI)	1603	1546	•	36.3 %	1.18 [ 0.95, 1.48
Total events: 152 (Higher PUFA	), 127 (Lower PUFA)				
Heterogeneity: $Tau^2 = 0.0$ ; Chi <sup>2</sup>		62); l <sup>2</sup> =0.0%			
Test for overall effect: $Z = 1.47$ 3 Mean age 65+ years	(P = 0.14)				
AlphaOmega - ALA	78/2409	84/2428	-	17.6 %	0.94 [ 0.69, 1.27
Doi 2014	1/119	5/119	<u>← → → → → → → → → → → → → → → → → → → →</u>	1.0 %	0.20 [ 0.02, 1.69
FAAT - Leaf 2005	9/200	9/202		4.6 %	1.01 [ 0.41, 2.49
Kumar 2013	1/39	1/39		0.6 %	1.00 [ 0.06, 15.43
PREDIMED 2013	31/2454	26/2543		10.4 %	1.24 [ 0.74, 2.07
11681168 2010	57/424	81/422	-8-	17.3 %	0.70 [ 0.51, 0.96
Veterans Admin 1969					
	5645	5753	•	51.6 %	0.87 [ 0.69, 1.09

(Continued . . . )

Study or subgroup	Higher PUFA	Lower PUFA	Risk Ratio	Weight	( Continued) Risk Ratio M-
	n/N	n/N	H,Random,95% Cl		H,Random,95% Cl
Heterogeneity: $Tau^2 = 0.01$ ; C	$hi^2 = 5.79, df = 5 (P = 0)$	$(0.33);  ^2 =  4\%$			
Test for overall effect: $Z = 1.19$	9 (P = 0.23)				
4 Mean age unclear					
Houtsmuller 1979	0/51	5/51	• · · · · · · · · · · · · · · · · · · ·	0.5 %	0.09 [ 0.01, 1.60 ]
Subtotal (95% CI)	51	51		0.5 %	0.09 [ 0.01, 1.60 ]
Total events: 0 (Higher PUFA),	5 (Lower PUFA)				
Heterogeneity: not applicable					
Test for overall effect: $Z = 1.64$	4 (P = 0.10)				
Total (95% CI)	7520	7587	+	100.0 %	1.02 [ 0.82, 1.26 ]
Total events: 366 (Higher PUF	A), 363 (Lower PUFA)				
Heterogeneity: $Tau^2 = 0.04$ ; C	hi <sup>2</sup> = 21.84, df = 15 (P	= 0.11); I <sup>2</sup> =31%			
Test for overall effect: $Z = 0.17$	7 (P = 0.87)				
Test for subgroup differences:	Chi <sup>2</sup> = 9.40, df = 3 (P =	0.02), l <sup>2</sup> =68%			

0.05 0.2 I 5 20

Favours higher PUFA Favours lower PUFA

#### Analysis 2.11. Comparison 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes, Outcome 11 Cardiovascular mortality - subgroup by statin use.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes

Outcome: II Cardiovascular mortality - subgroup by statin use

	Higher PUFA	Lower PUFA	Risk Ratio M-	Weight	Risk Ratic M-
	n/N	n/N	H,Random,95% Cl		H,Random, C
< 50% on statins					
Black 1994	2/67	0/66		0.5 %	4.93 [ 0.24, 100.70 ]
Brox 2001	0/80	1/40	• • • • • • • • • • • • • • • • • • • •	0.4 %	0.17 [ 0.01, 4.05 ]
DART fat 1989	4/ 0 8	91/1015	-	19.4 %	1.25 [ 0.96, 1.62 ]
HARP- Sacks 1995	0/41	1/39	• · · · ·	0.4 %	0.32 [ 0.01, 7.57
Houtsmuller 1979	0/51	5/51	<b>←</b> +	0.5 %	0.09 [ 0.01, 1.60
MRC 1968	27/199	25/194	-	10.7 %	1.05 [ 0.63, 1.75
PREDIMED 2013	31/2454	26/2543		10.4 %	1.24 [ 0.74, 2.07
Raitt 2005	2/100	5/100		1.6 %	0.40 [ 0.08, 2.01
Rose 1965	5/28	3/26		2.3 %	1.55 [ 0.41, 5.84
Sydney Diet-Heart 1978	37/221	25/237		11.6 %	1.59 [ 0.99, 2.55
Veterans Admin 1969	57/424	81/422	-	17.3 %	0.70 [ 0.51, 0.96
	4683	4733		75.4 %	1.05 [ 0.78, 1.40
Subtotal (95% CI)	4005	4/33	Ť	/ 5.4 %	1.05 [ 0./0, 1.40
Fotal events: 275 (Higher PUFA), Heterogeneity: Tau <sup>2</sup> = 0.08; Chi <sup>2</sup> Fest for overall effect: $Z = 0.31$ (	, 263 (Lower PUFA) <sup>2</sup> = 18.84, df = 10 (P =			/ J.4 %	1.09 [ 0.76, 1.40
Total events: 275 (Higher PUFA), Heterogeneity: Tau <sup>2</sup> = 0.08; Chi <sup>2</sup> Test for overall effect: $Z = 0.31$ (	, 263 (Lower PUFA) <sup>2</sup> = 18.84, df = 10 (P =		,	/ <b>3.4</b> %	
Fotal events: 275 (Higher PUFA), Heterogeneity: Tau <sup>2</sup> = 0.08; Chi <sup>2</sup> Fest for overall effect: Z = 0.31 ( 2 50+% on statins	, 263 (Lower PUFA) <sup>2</sup> = 18.84, df = 10 (P = P = 0.76)	= 0.04); l <sup>2</sup> =47%			0.94 [ 0.69, 1.27
Total events: 275 (Higher PUFA), Heterogeneity: Tau <sup>2</sup> = 0.08; Chi <sup>2</sup> Test for overall effect: Z = 0.31 ( 2 50+% on statins AlphaOmega - ALA	, 263 (Lower PUFA) 2 = 18.84, df = 10 (P = P = 0.76) 78/2409	= 0.04); I <sup>2</sup> =47% 84/2428	• • • •	17.6 %	0.94 [ 0.69, 1.27
Fotal events: 275 (Higher PUFA), Heterogeneity: Tau <sup>2</sup> = 0.08; Chi <sup>2</sup> Fest for overall effect: Z = 0.31 ( 2.50+% on statins AlphaOmega - ALA Doi 2014 Kumar 2013	, 263 (Lower PUFA) 2 = 18.84, df = 10 (P = P = 0.76) 78/2409 1/119	= 0.04); I <sup>2</sup> =47% 84/2428 5/119		17.6 %	0.94 [ 0.69, 1.27 0.20 [ 0.02, 1.69 1.00 [ 0.06, 15.43
Total events: 275 (Higher PUFA), Heterogeneity: Tau <sup>2</sup> = 0.08; Chi <sup>2</sup> Fest for overall effect: Z = 0.31 ( 2 50+% on statins AlphaOmega - ALA Doi 2014 Kumar 2013 Foubtotal (95% CI) Fotal events: 80 (Higher PUFA), Heterogeneity: Tau <sup>2</sup> = 0.0; Chi <sup>2</sup>	, 263 (Lower PUFA) <sup>2</sup> = 18.84, df = 10 (P = P = 0.76) 78/2409 1/119 1/39 <b>2567</b> 90 (Lower PUFA) = 1.99, df = 2 (P = 0.2)	= 0.04); 1 <sup>2</sup> =47% 84/2428 5/119 1/39 <b>2586</b>	• •	17.6 % 1.0 % 0.6 %	0.94 [ 0.69, 1.27 0.20 [ 0.02, 1.69 1.00 [ 0.06, 15.43
Doi 2014 Kumar 2013 <b>Subtotal (95% CI)</b> Total events: 80 (Higher PUFA), 4 Heterogeneity: Tau <sup>2</sup> = 0.0; Chi <sup>2</sup> Test for overall effect: $Z = 0.63$ ( B Percentage on statins unclear	, 263 (Lower PUFA) <sup>2</sup> = 18.84, df = 10 (P = P = 0.76) 78/2409 1/119 1/39 <b>2567</b> 90 (Lower PUFA) = 1.99, df = 2 (P = 0.27) P = 0.53)	= 0.04); l <sup>2</sup> =47% 84/2428 5/119 1/39 <b>2586</b> 377); l <sup>2</sup> =0.0%	•	17.6 % 1.0 % 0.6 % <b>19.2 %</b>	0.94 [ 0.69, 1.27 0.20 [ 0.02, 1.69 1.00 [ 0.06, 15.43 <b>0.91 [ 0.67, 1.22</b>
Total events: 275 (Higher PUFA), Heterogeneity: Tau <sup>2</sup> = 0.08; Chi <sup>2</sup> Fest for overall effect: Z = 0.31 ( 2 50+% on statins AlphaOmega - ALA Doi 2014 Kumar 2013 <b>Subtotal (95% CI)</b> Fotal events: 80 (Higher PUFA), Heterogeneity: Tau <sup>2</sup> = 0.0; Chi <sup>2</sup> Fest for overall effect: Z = 0.63 (	, 263 (Lower PUFA) <sup>2</sup> = 18.84, df = 10 (P = P = 0.76) 78/2409 1/119 1/39 <b>2567</b> 90 (Lower PUFA) = 1.99, df = 2 (P = 0.2)	= 0.04); 1 <sup>2</sup> =47% 84/2428 5/119 1/39 <b>2586</b>	•	17.6 % 1.0 % 0.6 %	0.94 [ 0.69, 1.27 0.20 [ 0.02, 1.69 1.00 [ 0.06, 15.43

(Continued . . . )

Study or subgroup	Higher PUFA	Lower PUFA		Ratio M-	Weight	( Continued) Risk Ratio M-
	n/N	n/N	H,Rando	om,95% Cl		H,Random,95% Cl
Subtotal (95% CI)	270	268	-	-	5.4 %	1.09 [ 0.47, 2.54 ]
Total events: 11 (Higher PUFA	A), 10 (Lower PUFA)					
Heterogeneity: $Tau^2 = 0.0$ ; Ch	$hi^2 = 0.23, df = 1 (P = 0.6)$	53); I <sup>2</sup> =0.0%				
Test for overall effect: $Z = 0.2$	21 (P = 0.84)					
Total (95% CI)	7520	7587	+		100.0 %	1.02 [ 0.82, 1.26 ]
Total events: 366 (Higher PUF	FA), 363 (Lower PUFA)					
Heterogeneity: $Tau^2 = 0.04$ ; C	Chi <sup>2</sup> = 21.84, df = 15 (P =	= 0.11); I <sup>2</sup> =31%				
Test for overall effect: $Z = 0.1$	7 (P = 0.87)					
Test for subgroup differences:	Chi <sup>2</sup> = 0.5 I, df = 2 (P =	0.78), I <sup>2</sup> =0.0%				
			0.05 0.2 I	5 20		
		Favou	ırs higher PUFA	Favours lower PU	JFA	

#### Analysis 2.12. Comparison 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes, Outcome 12 Cardiovascular mortality - subgroup by intervention type.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes

Outcome: 12 Cardiovascular mortality - subgroup by intervention type

Study or subgroup	Higher PUFA	Lower PUFA	Risk Ratio M-	Weight	Risk Ratio M-
	n/N	n/N	H,Random,95% Cl		H,Random,95% Cl
Dietary advice					
Black 1994	2/67	0/66		0.5 %	4.93 [ 0.24, 100.70 ]
DART fat 1989	4/ 0 8	91/1015	-	19.4 %	1.25 [ 0.96, 1.62 ]
Houtsmuller 1979	0/51	5/5 I	<b>←</b> +	0.5 %	0.09 [ 0.01, 1.60 ]
Ley 2004	2/70	1/66		0.8 %	1.89 [ 0.18, 20.31 ]
Subtotal (95% CI)	1206	1198		21.2 %	1.15 [ 0.42, 3.12 ]
Total events: 118 (Higher PUF Heterogeneity: Tau <sup>2</sup> = 0.37; C	, , , ,	0.25); I <sup>2</sup> =28%			
Test for overall effect: $Z = 0.26$	8 (P = 0.78)				
2 Supplemental foods % diet p	provided				
		E.	0.05 0.2 I 5 20	15.4	
		Fav	ours higher PUFA Favours lower PL	IFA.	(Continued)

Study or subgroup	Higher PUFA	Lower PUFA	Risk Ratio M-	Weight	( Continued) Risk Ratio M-
	n/N	n/N	H,Random,95% Cl		H,Random,95 Cl
AlphaOmega - ALA	78/2409	84/2428	-	17.6 %	0.94 [ 0.69, 1.27 ]
PREDIMED 2013	31/2454	26/2543		10.4 %	1.24 [ 0.74, 2.07 ]
Veterans Admin 1969	57/424	81/422		17.3 %	0.70 [ 0.51, 0.96 ]
Subtotal (95% CI)	5287	5393	•	45.4 %	0.89 [ 0.66, 1.19 ]
Total events: 166 (Higher PUFA	A), 191 (Lower PUFA)				
Heterogeneity: Tau <sup>2</sup> = 0.03; Ch	$m^2 = 3.86$ , df = 2 (P = 0)	).   4);   <sup>2</sup> =48%			
Test for overall effect: $Z = 0.80$	(P = 0.42)				
3 Supplements (capsules % unu	isual foods)				
Brox 2001	0/80	1/40	<b>← · · · · · · · · · · · · · · · · · · ·</b>	0.4 %	0.17 [ 0.01, 4.05 ]
Doi 2014	1/119	5/119	<del>، ، ،</del>	1.0 %	0.20 [ 0.02, 1.69 ]
FAAT - Leaf 2005	9/200	9/202		4.6 %	1.01 [ 0.41, 2.49 ]
HARP- Sacks 1995	0/41	1/39	·	0.4 %	0.32 [ 0.01, 7.57 ]
Kumar 2013	1/39	1/39		0.6 %	1.00 [ 0.06, 15.43 ]
Raitt 2005	2/100	5/100		1.6 %	0.40 [ 0.08, 2.01 ]
Rose 1965	5/28	3/26		2.3 %	1.55 [ 0.41, 5.84 ]
Subtotal (95% CI)	607	565	•	11.0 %	0.76 [ 0.42, 1.40 ]
Total events: 18 (Higher PUFA)	. 25 (Lower PUFA)				
Heterogeneity: Tau <sup>2</sup> = 0.0; Chi <sup>2</sup>	, ,	56); l <sup>2</sup> =0.0%			
Test for overall effect: Z = 0.87		<i>.</i>			
4 Any combination					
, MRC 1968	27/199	25/194	-	10.7 %	1.05 [ 0.63, 1.75 ]
Sydney Diet-Heart 1978	37/221	25/237		11.6 %	1.59 [ 0.99, 2.55 ]
Subtotal (95% CI)	420	431	•	22.4 %	1.31 [ 0.87, 1.95 ]
Total events: 64 (Higher PUFA)	, 50 (Lower PUFA)				
Heterogeneity: $Tau^2 = 0.02$ ; Ch	$hi^2 = 1.35, df = 1$ (P = 0	).25); I <sup>2</sup> =26%			
Test for overall effect: Z = 1.30		,- ,-			
Total (95% CI)	7520	7587	•	100.0 %	1.02 [ 0.82, 1.26 ]
Total events: 366 (Higher PUFA	A), 363 (Lower PUFA)				
Heterogeneity: $Tau^2 = 0.04$ ; Ch	ni <sup>2</sup> = 21.84, df = 15 (P =	= 0.11); 12 = 31%			
Test for overall effect: $Z = 0.17$	(P = 0.87)				
Test for subgroup differences: C	Chi <sup>2</sup> = 3.15, df = 3 (P =	0.37), I <sup>2</sup> =5%			
			0.05 0.2   5 20		
			urs higher PUFA Favours lower	0.154	

#### Analysis 2.13. Comparison 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes, Outcome **13 CARDIOVASCULAR EVENTS.**

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes

#### Outcome: 13 CARDIOVASCULAR EVENTS

Study or subgroup	Higher PUFA	Lower PUFA	Risk Ratio M-	Weight	Risk Ratio M
	n/N	n/N	H,Random,95% Cl		H,Random, C
AlphaOmega - ALA	319/2409	352/2428	•	18.8 %	0.91 [ 0.79, 1.05
Brox 2001	0/80	1/40		0.1 %	0.17 [ 0.01, 4.05
DART fat 1989	476/1018	478/1015	•	22.1 %	0.99 [ 0.91, 1.09
Doi 2014	/  9	24/119		2.8 %	0.46 [ 0.24, 0.89
EPIC-1 2008	1/188	0/186		0.1 %	2.97 [ 0.12, 72.40
EPOCH 2011	8/195	5/196		1.1 %	1.61 [ 0.54, 4.83
FAAT - Leaf 2005	31/200	39/202	-	5.8 %	0.80 [ 0.52, 1.23
GLAMT 1993	0/54	1/57	·	0.1 %	0.35 [ 0.01, 8.45
HARP- Sacks 1995	7/41	7/39	_	1.5 %	0.95 [ 0.37, 2.46
Kumar 2013	1/39	1/39		0.2 %	1.00 [ 0.06, 15.43
MRC 1968	62/199	74/194	-	10.8 %	0.82 [ 0.62, 1.07
NDHS Open 1st 1968	5/726	1/341	<u> </u>	0.3 %	2.35 [ 0.28, 20.02
Nodari 2011 HF	10/67	26/66		3.0 %	0.38 [ 0.20, 0.72
PREDIMED 2013	83/2454	96/2543	+	10.1 %	0.90 [ 0.67, 1.20
Proudman 2015	1/87	0/53		0.1 %	1.84 [ 0.08, 44.38
Puri 2005	1/60	0/61		0.1 %	3.05 [ 0.13, 73.40
Raitt 2005	2/100	5/100		0.5 %	0.40 [ 0.08, 2.01
Rose 1965	15/28	11/26		3.7 %	1.27 [ 0.72, 2.23
Sydney Diet-Heart 1978	37/221	25/237	-	5.0 %	1.59 [ 0.99, 2.55
Veterans Admin 1969	97/424	122/422	-	13.0 %	0.79 [ 0.63, 1.00
WAHA - Ros 2016	3/362	4/364	<b>-</b>	0.6 %	0.75 [ 0.17, 3.35
otal (95% CI)	9071	8728	•	100.0 %	0.89 [ 0.79, 1.01
tatal events: 1170 (Higher PUFA eterogeneity: Tau <sup>2</sup> = 0.01; Chi <sup>2</sup> est for overall effect: $Z = 1.87$ ( est for subgroup differences: No	P = 0.061)	,			

# Analysis 2.14. Comparison 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes, Outcome 14 CVD events - SA.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes

Outcome: 14 CVD events - SA

Study or subgroup	Higher PUFA	Lower PUFA	Risk Ratio M-	Weight	Risk Ratio M-
	n/N	n/N	H,Random,95% Cl		H,Random,95 Cl
Low risk of bias for allocation	n concealment				
AlphaOmega - ALA	319/2409	352/2428	-	80.9 %	0.91 [ 0.79, 1.05 ]
Brox 2001	0/80	1/40		0.2 %	0.17 [ 0.01, 4.05 ]
EPIC-1 2008	1/188	0/186		0.2 %	2.97 [ 0.12, 72.40 ]
EPOCH 2011	8/195	5/196	<del></del>	1.3 %	1.61 [ 0.54, 4.83 ]
FAAT - Leaf 2005	31/200	39/202	-	8.7 %	0.80 [ 0.52, 1.23 ]
Kumar 2013	1/39	1/39		0.2 %	1.00 [ 0.06, 15.43 ]
NDHS Open 1st 1968	5/726	1/341		0.3 %	2.35 [ 0.28, 20.02 ]
Proudman 2015	1/87	0/53		0.2 %	1.84 [ 0.08, 44.38 ]
Puri 2005	1/60	0/61		0.2 %	3.05 [ 0.13, 73.40 ]
Sydney Diet-Heart 1978	37/221	25/237	-	7.1 %	1.59 [ 0.99, 2.55 ]
WAHA - Ros 2016	3/362	4/364		0.7 %	0.75 [ 0.17, 3.35 ]
Subtotal (95% CI)	4567	4147	•	100.0 %	0.95 [ 0.84, 1.08 ]
Heterogeneity: Tau <sup>2</sup> = 0.0; Chi fest for overall effect: Z = 0.78 2. Low risk of bias for attention AlphaOmega - ALA	3 (P = 0.43)	0.50); l <sup>2</sup> =0.0% 352/2428		30.8 %	0.91 [ 0.79, 1.05
Brox 2001	0/80	1/40		0.2 %	0.17 [ 0.01, 4.05 ]
Doi 2014	11/119	24/119		4.5 %	0.46 [ 0.24, 0.89 ]
EPIC-1 2008	1/188	0/186		0.2 %	2.97 [ 0.12, 72.40]
EPOCH 2011	8/195	5/196		1.8 %	1.61 [ 0.54, 4.83
EPOCH 2011				9.5 %	0.80 [ 0.52, 1.23
FAAT - Leaf 2005	31/200	39/202	-	7.5 70	0.000 [ 0.002, 1.25
	31/200 0/54	39/202 1/57		0.2 %	0.35 [ 0.01, 8.45

0.01 0.1 1 10 100 Favours higher PUFA Favours lower PUFA

(Continued . . . )

Study or subgroup	Higher PUFA	Lower PUFA	Risk Ratio	Weight	( Continued Risk Ratio M-
	n/N	n/N	H,Random,95% Cl		H,Random,9 Cl
NDHS Open 1st 1968	5/726	1/341		0.5 %	2.35 [ 0.28, 20.02 ]
Nodari 2011 HF	10/67	26/66		4.8 %	0.38 [ 0.20, 0.72 ]
PREDIMED 2013	83/2454	96/2543	+	16.5 %	0.90 [ 0.67, 1.20 ]
Proudman 2015	1/87	0/53		0.2 %	1.84 [ 0.08, 44.38 ]
Puri 2005	1/60	0/61		0.2 %	3.05 [ 0.13, 73.40 ]
Raitt 2005	2/100	5/100		0.8 %	0.40 [ 0.08, 2.01 ]
Rose 1965	15/28	11/26	-	6.0 %	1.27 [ 0.72, 2.23 ]
Veterans Admin 1969	97/424	122/422	-	21.2 %	0.79 [ 0.63, 1.00 ]
ubtotal (95% CI)	7232	6879	•	100.0 %	0.83 [ 0.72, 0.97 ]
est for overall effect: Z = 2.36 Low risk of bias for complianc Brox 2001	. ,	1/40		0.3 %	0.17 [ 0.01, 4.05 ]
DART fat 1989	476/1018	478/1015	J	36.9 %	0.99 [ 0.91, 1.09 ]
MRC 1968	62/199	74/194	-	20.0 %	0.82 [ 0.62, 1.07 ]
NDHS Open 1st 1968	5/726	1/341		0.6 %	2.35 [ 0.28, 20.02 ]
Rose 1965	15/28	11/26	-	7.4 %	1.27 [ 0.72, 2.23 ]
Sydney Diet-Heart 1978	37/221	25/237	-	9.9 %	1.59 [ 0.99, 2.55 ]
Veterans Admin 1969	97/424	122/422	-	23.6 %	0.79 [ 0.63, 1.00 ]
WAHA - Ros 2016	3/362	4/364		1.3 %	0.75 [ 0.17, 3.35 ]
ubtotal (95% CI)	3058	2639	•	100.0 %	0.96 [ 0.81, 1.14 ]
otal events: 695 (Higher PUFA) leterogeneity: Tau <sup>2</sup> = 0.02; Chi est for overall effect: Z = 0.44 Low summary risk of bias	$f^{2} = 11.71$ , df = 7 (P = (P = 0.66)				
AlphaOmega - ALA	319/2409	352/2428	- T	57.4 %	0.91 [ 0.79, 1.05 ]
EPOCH 2011	8/195	5/196		8.6 %	1.61 [ 0.54, 4.83 ]
NDHS Open 1st 1968	5/726	1/341		2.5 %	2.35 [ 0.28, 20.02 ]
Proudman 2015	1/87	0/53		1.2 %	1.84 [ 0.08, 44.38 ]
Puri 2005	1/60	0/61		1.2 %	3.05 [ 0.13, 73.40 ]
Sydney Diet-Heart 1978	37/221	25/237	-	29.1 %	1.59 [ 0.99, 2.55 ]
Sydney Diet-Heart 1770		3316	_	100.0 %	1.18 [ 0.83, 1.67 ]

0.01 0.1 1 10 100

Favours higher PUFA Favours lower PUFA

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Study or subgroup	Higher PUFA	Lower PUFA	Risk Ratio M-	Weight	( Continued) Risk Ratio M-
	n/N	n/N	H,Random,95% Cl		H,Random,955 Cl
Test for overall effect: Z = 0.93	(P = 0.35)				
5 Trials registry or pre-2010 AlphaOmega - ALA	319/2409	352/2428	_	18.8 %	0.91 [ 0.79, 1.05 ]
				0.1 %	
Brox 2001	0/80	1/40			0.17 [ 0.01, 4.05 ]
DART fat 1989	476/1018	478/1015		22.1 %	0.99 [ 0.91, 1.09 ]
Doi 2014	/  9	24/119		2.8 %	0.46 [ 0.24, 0.89 ]
EPIC-1 2008	1/188	0/186		0.1 %	2.97 [ 0.12, 72.40 ]
EPOCH 2011	8/195	5/196		1.1 %	1.61 [ 0.54, 4.83 ]
FAAT - Leaf 2005	31/200	39/202	-	5.8 %	0.80 [ 0.52, 1.23 ]
GLAMT 1993	0/54	1/57		0.1 %	0.35 [ 0.01, 8.45 ]
HARP- Sacks 1995	7/41	7/39		1.5 %	0.95 [ 0.37, 2.46 ]
Kumar 2013	1/39	1/39		0.2 %	1.00 [ 0.06, 15.43 ]
MRC 1968	62/199	74/194	-	10.8 %	0.82 [ 0.62, 1.07 ]
NDHS Open 1st 1968	5/726	1/341		0.3 %	2.35 [ 0.28, 20.02 ]
Nodari 2011 HF	10/67	26/66		3.0 %	0.38 [ 0.20, 0.72 ]
PREDIMED 2013	83/2454	96/2543	+	10.1 %	0.90 [ 0.67, 1.20 ]
Proudman 2015	1/87	0/53		0.1 %	1.84 [ 0.08, 44.38 ]
Puri 2005	1/60	0/61		0.1 %	3.05 [ 0.13, 73.40 ]
Raitt 2005	2/100	5/100		0.5 %	0.40 [ 0.08, 2.01 ]
Rose 1965	15/28	11/26		3.7 %	1.27 [ 0.72, 2.23 ]
Sydney Diet-Heart 1978	37/221	25/237	-	5.0 %	1.59 [ 0.99, 2.55 ]
Veterans Admin 1969	97/424	22/422	-	13.0 %	0.79 [ 0.63, 1.00 ]
WAHA - Ros 2016	3/362	4/364		0.6 %	0.75 [ 0.17, 3.35 ]
Subtotal (95% CI)	9071	8728	•	100.0 %	0.89 [ 0.79, 1.01 ]
otal events: 1170 (Higher PUF, leterogeneity: Tau <sup>2</sup> = 0.01; Ch est for overall effect: Z = 1.87 No industry funding	i <sup>2</sup> = 28.7 I, df = 20 (P	,			
Brox 2001	0/80	1/40		1.4 %	0.17 [ 0.01, 4.05 ]
FAAT - Leaf 2005	31/200	39/202	-	29.7 %	0.80 [ 0.52, 1.23 ]
MRC 1968	62/199	74/194	-	38.5 %	0.82 [ 0.62, 1.07 ]
NDHS Open 1st 1968	5/726	1/341		2.9 %	2.35 [ 0.28, 20.02 ]
Sydney Diet-Heart 1978	37/221	25/237	-	27.5 %	1.59 [ 0.99, 2.55 ]
			0.01 0.1 I 10 100 rs higher PUFA Favours lower		(Continued

Study or subgroup	Higher PUFA	Lower PUFA	Risk Ratio M- H,Random,95%	Weight	( Continued) Risk Ratio M- H,Random,95:
	n/N	n/N	Ć	100.0.0/	Cl
Subtotal (95% CI) Total events: 135 (Higher PUFA Heterogeneity: Tau <sup>2</sup> = 0.08; Ch Test for overall effect: Z = 0.08 7 Randomised 100+ participant	$i^2 = 8.10, df = 4 (P = 0)$ (P = 0.93)	<b>1014</b> 0.09); I <sup>2</sup> =5 I %		100.0 %	0.98 [ 0.67, 1.44 ]
AlphaOmega - ALA	319/2409	352/2428	-	19.0 %	0.91 [ 0.79, 1.05 ]
Brox 2001	0/80	1/40		0.2 %	0.17 [ 0.01, 4.05 ]
DART fat 1989	476/1018	478/1015	-	21.7 %	0.99 [ 0.91, 1.09 ]
Doi 2014	/  9	24/119		3.3 %	0.46 [ 0.24, 0.89 ]
EPIC-1 2008	1/188	0/186		0.2 %	2.97 [ 0.12, 72.40 ]
EPOCH 2011	8/195	5/196		1.3 %	1.61 [ 0.54, 4.83 ]
FAAT - Leaf 2005	31/200	39/202	-	6.6 %	0.80 [ 0.52, 1.23 ]
GLAMT 1993	0/54	1/57		0.2 %	0.35 [ 0.01, 8.45 ]
MRC 1968	62/199	74/194	-	11.7 %	0.82 [ 0.62, 1.07 ]
NDHS Open 1st 1968	5/726	1/341	·	0.4 %	2.35 [ 0.28, 20.02 ]
Nodari 2011 HF	10/67	26/66		3.4 %	0.38 [ 0.20, 0.72 ]
PREDIMED 2013	83/2454	96/2543	+	11.0 %	0.90 [ 0.67, 1.20 ]
Proudman 2015	1/87	0/53		0.2 %	1.84 [ 0.08, 44.38 ]
Puri 2005	1/60	0/61		0.2 %	3.05 [ 0.13, 73.40 ]
Raitt 2005	2/100	5/100		0.6 %	0.40 [ 0.08, 2.01 ]
Sydney Diet-Heart 1978	37/221	25/237	-	5.7 %	1.59 [ 0.99, 2.55 ]
Veterans Admin 1969	97/424	122/422	-	13.8 %	0.79 [ 0.63, 1.00 ]
WAHA - Ros 2016	3/362	4/364		0.7 %	0.75 [ 0.17, 3.35 ]
Subtotal (95% CI) Total events: 1147 (Higher PUF, Heterogeneity: Tau <sup>2</sup> = 0.02; Ch Test for overall effect: Z = 2.00 8 Randomised 250+ participant	$i^2 = 27.55$ , df = 17 (P = (P = 0.045)	,	•	100.0 %	0.88 [ 0.77, 1.00 ]
AlphaOmega - ALA	319/2409	352/2428	-	24.4 %	0.91 [ 0.79, 1.05 ]
DART fat 1989	476/1018	478/1015	•	36.0 %	0.99 [ 0.91, 1.09 ]
EPIC-1 2008	1/188	0/186		0.1 %	2.97 [ 0.12, 72.40 ]
EPOCH 2011	8/195	5/196	+	0.7 %	1.61 [ 0.54, 4.83 ]
FAAT - Leaf 2005	31/200	39/202	-+	4.2 %	0.80 [ 0.52, 1.23 ]
MRC 1968	62/199	74/194	-	9.4 %	0.82 [ 0.62, 1.07 ]
			0.01 0.1 I 10 I Favours higher PUFA Favours low	00 er PUFA	(Continued

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Study or subgroup	Higher PUFA	Lower PUFA	Risk Ratio	Weight	( Continued) Risk Ratio M-
	n/N	n/N	H,Random,95% Cl		H,Random,95% Cl
NDHS Open 1st 1968	5/726	1/341		0.2 %	2.35 [ 0.28, 20.02 ]
PREDIMED 2013	83/2454	96/2543	+	8.6 %	0.90 [ 0.67, 1.20 ]
Sydney Diet-Heart 1978	37/221	25/237		3.5 %	1.59 [ 0.99, 2.55 ]
Veterans Admin 1969	97/424	122/422	-	12.5 %	0.79 [ 0.63, 1.00 ]
WAHA - Ros 2016	3/362	4/364		0.4 %	0.75 [ 0.17, 3.35 ]
Subtotal (95% CI)	8396	8128	•	100.0 %	0.93 [ 0.85, 1.02 ]
Total events: 1122 (Higher PUF	A), 1196 (Lower PUFA	)			
Heterogeneity: Tau <sup>2</sup> = 0.00; Ch	i <sup>2</sup> = 12.20, df = 10 (P =	= 0.27); I <sup>2</sup> = I 8%			
Test for overall effect: Z = 1.51	(P = 0.13)				
			0.01 0.1 1 10 100		

Favours higher PUFA Favours lower PUFA

#### Analysis 2.15. Comparison 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes, Outcome 15 CVD events - SA fixed-effect.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes

Outcome: 15 CVD events - SA fixed-effect

Study or subgroup	Higher PUFA n/N	Lower PUFA n/N	Risk Ratio M-H,Fixed,95% Cl	Weight	Risk Ratio M-H,Fixed,95% Cl
AlphaOmega - ALA	319/2409	352/2428	•	27.5 %	0.91 [ 0.79, 1.05 ]
Brox 200 l	0/80	1/40		0.2 %	0.17 [ 0.01, 4.05 ]
DART fat 1989	476/1018	478/1015	-	37.6 %	0.99 [ 0.91, 1.09 ]
Doi 2014	/  9	24/119		1.9 %	0.46 [ 0.24, 0.89 ]
EPIC-1 2008	1/188	0/186		0.0 %	2.97 [ 0.12, 72.40 ]
EPOCH 2011	8/195	5/196	_ <del></del>	0.4 %	1.61 [ 0.54, 4.83 ]
FAAT - Leaf 2005	31/200	39/202		3.0 %	0.80 [ 0.52, 1.23 ]
		Fave	0.01 0.1 1 10 100 Durs higher PUFA Favours lower PU	JFA	

(Continued . . . )

Study or subgroup	Higher PUFA n/N	Lower PUFA n/N	Risk Ratio M-H,Fixed,95% Cl	Weight	( Continued) Risk Ratio M-H,Fixed,95% Cl
GLAMT 1993	0/54	1/57	·	0.1 %	0.35 [ 0.01, 8.45 ]
HARP- Sacks 1995	7/41	7/39		0.6 %	0.95 [ 0.37, 2.46 ]
Kumar 2013	1/39	1/39		0.1 %	1.00 [ 0.06, 15.43 ]
MRC 1968	62/199	74/194	-	5.9 %	0.82 [ 0.62, 1.07 ]
NDHS Open 1st 1968	5/726	1/341		0.1 %	2.35 [ 0.28, 20.02 ]
Nodari 2011 HF	10/67	26/66		2.1 %	0.38 [ 0.20, 0.72 ]
PREDIMED 2013	83/2454	96/2543	+	7.4 %	0.90 [ 0.67, 1.20 ]
Proudman 2015	1/87	0/53		0.0 %	1.84 [ 0.08, 44.38 ]
Puri 2005	1/60	0/61		0.0 %	3.05 [ 0.13, 73.40 ]
Raitt 2005	2/100	5/100		0.4 %	0.40 [ 0.08, 2.01 ]
Rose 1965	15/28	11/26		0.9 %	1.27 [ 0.72, 2.23 ]
Sydney Diet-Heart 1978	37/221	25/237		1.9 %	1.59 [ 0.99, 2.55 ]
Veterans Admin 1969	97/424	122/422	-	9.6 %	0.79 [ 0.63, 1.00 ]
WAHA - Ros 2016	3/362	4/364		0.3 %	0.75 [ 0.17, 3.35 ]
<b>Cotal (95% CI)</b>	9071	8728	*	100.0 %	0.92 [ 0.86, 0.98 ]
otal events: 1170 (Higher PUF, leterogeneity: Chi <sup>2</sup> = 28.71, df est for overall effect: Z = 2.44 est for subgroup differences: N	$P = 20 (P = 0.09); I^2 = 3$ (P = 0.015)	,			

0.01 0.1 1 10 100

Favours higher PUFA Favours lower PUFA

#### Analysis 2.16. Comparison 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes, Outcome 16 CVD events - subgroup by PUFA dose.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes

Outcome: 16 CVD events - subgroup by PUFA dose

Study or subgroup	Higher PUFA	Lower PUFA	Risk Ratio M-	Weight	Risk Ratio M-
	n/N	n/N	H,Random,95% Cl		H,Random,9 Cl
I total PUFA < 1.0% E					
Doi 2014	/  9	24/119		2.8 %	0.46 [ 0.24, 0.89 ]
EPOCH 2011	8/195	5/196		1.1 %	1.61 [ 0.54, 4.83 ]
FAAT - Leaf 2005	31/200	39/202	-	5.8 %	0.80 [ 0.52, 1.23 ]
Kumar 2013	1/39	1/39		0.2 %	1.00 [ 0.06, 15.43 ]
Nodari 2011 HF	10/67	26/66		3.0 %	0.38 [ 0.20, 0.72 ]
Puri 2005	1/60	0/61		0.1 %	3.05 [ 0.13, 73.40 ]
Raitt 2005	2/100	5/100		0.5 %	0.40 [ 0.08, 2.01 ]
Subtotal (95% CI)	780	783	•	13.5 %	0.63 [ 0.42, 0.96 ]
2 total PUFA 1.0 to < 2.0% E AlphaOmega - ALA	319/2409	352/2428		18.8 %	0.91 [ 0.79, 1.05 ]
Heterogeneity: Tau <sup>2</sup> = 0.09; Chi Test for overall effect: Z = 2.14		<i>y</i> .			
AlphaOmega - ALA	319/2409	352/2428	-	18.8 %	0.91 [ 0.79, 1.05 ]
Brox 2001	0/80	1/40		0.1 %	0.17[0.01,4.05]
EPIC-1 2008	1/188	0/186		0.1 %	2.97 [ 0.12, 72.40 ]
EPIC-1 2008 PREDIMED 2013	1/188 83/2454	0/186 96/2543	*	0.1 %	2.97 [ 0.12, 72.40 ] 0.90 [ 0.67, 1.20 ]
PREDIMED 2013 Proudman 2015	83/2454	96/2543		10.1 %	0.90 [ 0.67, 1.20 ]
PREDIMED 2013 Proudman 2015 <b>Subtotal (95% CI)</b> Total events: 404 (Higher PUFA Heterogeneity: Tau <sup>2</sup> = 0.0; Chi <sup>2</sup> Test for overall effect: Z = 1.46 3 total PUFA 2.0 to $< 5.0\%$ E	83/2454 1/87 <b>5218</b> A), 449 (Lower PUFA) P = 1.81, df = 4 (P = 0.14) (P = 0.14)	96/2543 0/53 <b>5250</b> 777); I <sup>2</sup> =0.0%	•	10.1 % 0.1 % <b>29.3 %</b>	0.90 [ 0.67, 1.20 ] 1.84 [ 0.08, 44.38 ] <b>0.91 [ 0.80, 1.03 ]</b>
PREDIMED 2013 Proudman 2015 <b>Subtotal (95% CI)</b> Total events: 404 (Higher PUFA Heterogeneity: Tau <sup>2</sup> = 0.0; Chi <sup>2</sup> Test for overall effect: Z = 1.46 3 total PUFA 2.0 to < 5.0% E DART fat 1989	83/2454 1/87 <b>5218</b> a), 449 (Lower PUFA) <sup>2</sup> = 1.81, df = 4 (P = 0. (P = 0.14) 476/1018	96/2543 0/53 <b>5250</b> 77); I <sup>2</sup> =0.0% 478/1015	•	10.1 % 0.1 % <b>29.3 %</b> 22.1 %	0.90 [ 0.67, 1.20 ] 1.84 [ 0.08, 44.38 ] <b>0.91 [ 0.80, 1.03 ]</b> 0.99 [ 0.91, 1.09 ]
PREDIMED 2013 Proudman 2015 Subtotal (95% CI) Total events: 404 (Higher PUFA Heterogeneity: Tau <sup>2</sup> = 0.0; Chi <sup>2</sup> Test for overall effect: Z = 1.46 3 total PUFA 2.0 to < 5.0% E DART fat 1989 GLAMT 1993	83/2454 1/87 <b>5218</b> A), 449 (Lower PUFA) <sup>2</sup> = 1.81, df = 4 (P = 0.14) (P = 0.14) 476/1018 0/54	96/2543 0/53 <b>5250</b> 777); I <sup>2</sup> =0.0% 478/1015 1/57	•	10.1 % 0.1 % <b>29.3 %</b> 22.1 % 0.1 %	0.90 [ 0.67, 1.20 ] 1.84 [ 0.08, 44.38 ] <b>0.91 [ 0.80, 1.03 ]</b> 0.99 [ 0.91, 1.09 ] 0.35 [ 0.01, 8.45 ]
PREDIMED 2013 Proudman 2015 <b>Subtotal (95% CI)</b> Fotal events: 404 (Higher PUFA Heterogeneity: Tau <sup>2</sup> = 0.0; Chi <sup>2</sup> Fest for overall effect: Z = 1.46 B total PUFA 2.0 to < 5.0% E DART fat 1989	83/2454 1/87 <b>5218</b> a), 449 (Lower PUFA) <sup>2</sup> = 1.81, df = 4 (P = 0. (P = 0.14) 476/1018	96/2543 0/53 <b>5250</b> 77); I <sup>2</sup> =0.0% 478/1015		10.1 % 0.1 % <b>29.3 %</b> 22.1 %	0.90 [ 0.67, 1.20 ] 1.84 [ 0.08, 44.38 ] <b>0.91 [ 0.80, 1.03 ]</b> 0.99 [ 0.91, 1.09 ]

(Continued . . . )

( Continued Risk Ratio M- H,Random,9. Cl	Weight	Risk Ratio M- H,Random,95% Cl	Lower PUFA n/N	Higher PUFA n/N	Study or subgroup
			); I <sup>2</sup> =0.0%	= 0.42, df = 2 (P = 0.8	Heterogeneity: Tau <sup>2</sup> = 0.0; Chi <sup>2</sup> =
				P = 0.86)	Test for overall effect: $Z = 0.18$ (F
					4 total PUFA > 5.0% E
0.82 [ 0.62, 1.07 ]	10.8 %	1	74/194	62/199	MRC 1968
2.35 [ 0.28, 20.02 ]	0.3 %		1/341	5/726	NDHS Open 1st 1968
1.27 [ 0.72, 2.23 ]	3.7 %		11/26	15/28	Rose 1965
1.59 [ 0.99, 2.55 ]	5.0 %	-	25/237	37/221	Sydney Diet-Heart 1978
0.79 [ 0.63, 1.00 ]	13.0 %	-	122/422	97/424	Veterans Admin 1969
0.75 [ 0.17, 3.35 ]	0.6 %		4/364	3/362	WAHA - Ros 2016
0.99 [ 0.76, 1.29 ]	33.4 %	+	1584	1960	Subtotal (95% CI)
				· · · · ·	Total events: 219 (Higher PUFA),
			09); l <sup>2</sup> =47%		Heterogeneity: $Tau^2 = 0.04$ ; Chi <sup>2</sup>
	100.0.0/		0720	,	Test for overall effect: $Z = 0.09$ (F
0.89 [ 0.79, 1.01 ]	100.0 %	•	8728	9071	Total (95% CI)
				, , , ,	Total events: 1170 (Higher PUFA)
			$(0.09); 1^2 = 30\%$		Heterogeneity: Tau <sup>2</sup> = 0.01; Chi <sup>2</sup>
				,	Test for overall effect: $Z = 1.87$ (F
			0.17), l <sup>2</sup> =40%	$i^2 = 4.97, df = 3 (P = 0)$	Test for subgroup differences: Chi

Favours higher PUFA

Favours lower PUFA

### Analysis 2.17. Comparison 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes, Outcome 17 CVD events - subgroup by duration.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes

Outcome: 17 CVD events - subgroup by duration

Study or subgroup	Higher PUFA	Lower PUFA	Risk Ratio M-	Weight	Risk Ratic M-
	n/N	n/N	H,Random,95% Cl		H,Random, C
Medium duration I to < 2 year	ars				
Brox 2001	0/80	1/40		0.1 %	0.17 [ 0.01, 4.05
Doi 2014	/  9	24/119		2.8 %	0.46 [ 0.24, 0.89
EPIC-1 2008	1/188	0/186		0.1 %	2.97 [ 0.12, 72.40
EPOCH 2011	8/195	5/196	_ <b></b> -	1.1 %	1.61 [ 0.54, 4.83
FAAT - Leaf 2005	31/200	39/202	-	5.8 %	0.80 [ 0.52, 1.23
GLAMT 1993	0/54	1/57		0.1 %	0.35 [ 0.01, 8.45
Kumar 2013	1/39	1/39		0.2 %	1.00 [ 0.06, 15.43
NDHS Open 1st 1968	5/726	1/341		0.3 %	2.35 [ 0.28, 20.02
Nodari 2011 HF	10/67	26/66		3.0 %	0.38 [ 0.20, 0.72
Proudman 2015	1/87	0/53		0.1 %	1.84 [ 0.08, 44.38
Puri 2005	1/60	0/61		0.1 %	3.05 [ 0.13, 73.40
Subtotal (95% CI)	1815	1360	•	13.9 %	0.68 [ 0.47, 0.99
otal events: 69 (Higher PUFA), Heterogeneity: Tau <sup>2</sup> = 0.06; Chi Test for overall effect: Z = 2.03 Medium-long duration 2 to <	$^{2} = 11.75$ , df = 10 (P = (P = 0.042)	= 0.30); I <sup>2</sup> = I 5%			
AlphaOmega - ALA	319/2409	352/2428	-	18.8 %	0.91 [ 0.79, 1.05
DART fat 1989	476/1018	478/1015	-	22.1 %	0.99 [ 0.91, 1.09
HARP- Sacks 1995	7/41	7/39		1.5 %	0.95 [ 0.37, 2.46
Raitt 2005	2/100	5/100		0.5 %	0.40 [ 0.08, 2.01
Rose 1965	15/28	11/26		3.7 %	1.27 [ 0.72, 2.23
WAHA - Ros 2016	3/362	4/364		0.6 %	0.75 [ 0.17, 3.35
Subtotal (95% CI)	3958	3972	•	47.2 %	0.97 [ 0.90, 1.05
otal events: 822 (Higher PUFA)	), 857 (Lower PUFA) = 3.15, df = 5 (P = 0.6	68); I <sup>2</sup> =0.0%			

(Continued . . . )

Study or subgroup	Higher PUFA n/N	Lower PUFA n/N		sk Ratio M- dom,95%	Weight	( Continued) Risk Ratio M- H,Random,95%
3 Long duration 4+ years	11/15	n/in		CI		<u> </u>
MRC 1968	62/199	74/194	-		10.8 %	0.82 [ 0.62, 1.07 ]
PREDIMED 2013	83/2454	96/2543	+		10.1 %	0.90 [ 0.67, 1.20 ]
Sydney Diet-Heart 1978	37/221	25/237	-	-	5.0 %	1.59 [ 0.99, 2.55 ]
Veterans Admin 1969	97/424	122/422	-		13.0 %	0.79 [ 0.63, 1.00 ]
Subtotal (95% CI)	3298	3396	•		38.9 %	0.92 [ 0.73, 1.16 ]
Total events: 279 (Higher PUFA	.), 317 (Lower PUFA)					
Heterogeneity: Tau <sup>2</sup> = 0.03; Ch	$i^2 = 7.12$ , df = 3 (P = 0	0.07); l <sup>2</sup> =58%				
Test for overall effect: Z = 0.72	(P = 0.47)					
Total (95% CI)	9071	8728	•		100.0 %	0.89 [ 0.79, 1.01 ]
Total events: 1170 (Higher PUF	A), 1272 (Lower PUFA	)				
Heterogeneity: Tau <sup>2</sup> = 0.01; Ch	i <sup>2</sup> = 28.7 I, df = 20 (P =	= 0.09); I <sup>2</sup> =30%				
Test for overall effect: Z = 1.87	(P = 0.061)					
Test for subgroup differences: C	$Chi^2 = 3.48, df = 2 (P =$	0.18), l <sup>2</sup> =43%				
			0.01 0.1 1	10 100		
			Favours higher PUFA	Favours lower f	PUFA	

### Analysis 2.18. Comparison 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes, Outcome 18 CVD events - subgroup by primary or secondary prevention.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes

Outcome: 18 CVD events - subgroup by primary or secondary prevention

	Higher PUFA	Lower PUFA	Risk Ratio M- H,Random,95%	Weight	Risk Ratio M- H,Random,95
	n/N	n/N	Cl		Cl
Primary prevention of CVD					
Brox 200 l	0/80	1/40		0.1 %	0.17 [ 0.01, 4.05 ]
EPIC-1 2008	1/188	0/186		0.1 %	2.97 [ 0.12, 72.40 ]
EPOCH 2011	8/195	5/196		1.1 %	1.61 [ 0.54, 4.83 ]
GLAMT 1993	0/54	1/57		0.1 %	0.35 [ 0.01, 8.45 ]
NDHS Open 1st 1968	5/726	1/341		0.3 %	2.35 [ 0.28, 20.02 ]
PREDIMED 2013	83/2454	96/2543	+	10.1 %	0.90 [ 0.67, 1.20 ]
Proudman 2015	1/87	0/53		0.1 %	1.84 [ 0.08, 44.38 ]
Puri 2005	1/60	0/61		0.1 %	3.05 [ 0.13, 73.40 ]
	97/424	122/422	-	13.0 %	0.79 [ 0.63, 1.00 ]
Veterans Admin 1969	777727				
Veterans Admin 1969 WAHA - Ros 2016	3/362	4/364	<b>-</b>	0.6 %	0.75 [ 0.17, 3.35 ]
	3/362 <b>4630</b> A), 230 (Lower PUFA)	4263	•	0.6 % 25.8 %	0.75 [ 0.17, 3.35 ] 0.85 [ 0.72, 1.01 ]
WAHA - Ros 2016 <b>Subtotal (95% CI)</b> total events: 199 (Higher PUF, Heterogeneity: Tau <sup>2</sup> = 0.0; Ch est for overall effect: Z = 1.81 Secondary prevention of CV	3/362 <b>4630</b> A), 230 (Lower PUFA) i <sup>2</sup> = 5,43, df = 9 (P = 0.8 I (P = 0.070) D	<b>4263</b> 30); I <sup>2</sup> =0.0%	•	25.8 %	0.85 [ 0.72, 1.01 ]
WAHA - Ros 2016 <b>Subtotal (95% CI)</b> total events: 199 (Higher PUF, Heterogeneity: Tau <sup>2</sup> = 0.0; Ch est for overall effect: Z = 1.8	3/362 <b>4630</b> A), 230 (Lower PUFA) i <sup>2</sup> = 5.43, df = 9 (P = 0.8 I (P = 0.070)	4263	•		
WAHA - Ros 2016 <b>Subtotal (95% CI)</b> total events: 199 (Higher PUF, Heterogeneity: Tau <sup>2</sup> = 0.0; Ch est for overall effect: Z = 1.81 Secondary prevention of CV	3/362 <b>4630</b> A), 230 (Lower PUFA) i <sup>2</sup> = 5,43, df = 9 (P = 0.8 I (P = 0.070) D	<b>4263</b> 30); I <sup>2</sup> =0.0%	•	25.8 %	0.85 [ 0.72, 1.01 ]
WAHA - Ros 2016 <b>Subtotal (95% CI)</b> Total events: 199 (Higher PUF, Heterogeneity: Tau <sup>2</sup> = 0.0; Ch test for overall effect: Z = 1.81 Secondary prevention of CV AlphaOmega - ALA	3/362 <b>4630</b> A), 230 (Lower PUFA) i <sup>2</sup> = 5.43, df = 9 (P = 0.8 i (P = 0.070) 7D 319/2409	<b>4263</b> 30); I <sup>2</sup> =0.0% 352/2428	•	<b>25.8 %</b>	0.85 [ 0.72, 1.01 ]
WAHA - Ros 2016 <b>Subtotal (95% CI)</b> fotal events: 199 (Higher PUF, leterogeneity: Tau <sup>2</sup> = 0.0; Ch fest for overall effect: Z = 1.8 Secondary prevention of CV AlphaOmega - ALA DART fat 1989	3/362 <b>4630</b> A), 230 (Lower PUFA) $i^2 = 5.43$ , df = 9 (P = 0.8 1 (P = 0.070) 7D 319/2409 476/1018	<b>4263</b> 30); I <sup>2</sup> =0.0% 352/2428 478/1015		25.8 % 18.8 % 22.1 %	0.85 [ 0.72, 1.01 ] 0.91 [ 0.79, 1.05 ] 0.99 [ 0.91, 1.09 ]
WAHA - Ros 2016 <b>Subtotal (95% CI)</b> Total events: 199 (Higher PUF, deterogeneity: Tau <sup>2</sup> = 0.0; Ch est for overall effect: Z = 1.8 Secondary prevention of CV AlphaOmega - ALA DART fat 1989 Doi 2014	3/362 <b>4630</b> A), 230 (Lower PUFA) i <sup>2</sup> = 5.43, df = 9 (P = 0.8 I (P = 0.070) 7D 319/2409 476/1018 11/119	<b>4263</b> 30); I <sup>2</sup> =0.0% 352/2428 478/1015 24/119		25.8 % 18.8 % 22.1 % 2.8 %	0.85 [ 0.72, 1.01 ] 0.91 [ 0.79, 1.05 ] 0.99 [ 0.91, 1.09 ] 0.46 [ 0.24, 0.89 ]
WAHA - Ros 2016 <b>Subtotal (95% CI)</b> Total events: 199 (Higher PUF, Heterogeneity: Tau <sup>2</sup> = 0.0; Ch test for overall effect: Z = 1.81 Secondary prevention of CV AlphaOmega - ALA DART fat 1989 Doi 2014 FAAT - Leaf 2005	3/362 <b>4630</b> A), 230 (Lower PUFA) i <sup>2</sup> = 5.43, df = 9 (P = 0.8 1 (P = 0.070) 7D 319/2409 476/1018 11/119 31/200	<b>4263</b> 30); I <sup>2</sup> =0.0% 352/2428 478/1015 24/119 39/202		25.8 % 18.8 % 22.1 % 2.8 % 5.8 %	0.85 [ 0.72, 1.01 ] 0.91 [ 0.79, 1.05 ] 0.99 [ 0.91, 1.09 ] 0.46 [ 0.24, 0.89 ] 0.80 [ 0.52, 1.23 ]
WAHA - Ros 2016 <b>Subtotal (95% CI)</b> fotal events: 199 (Higher PUF, deterogeneity: Tau <sup>2</sup> = 0.0; Ch fest for overall effect: Z = 1.8 Secondary prevention of CV AlphaOmega - ALA DART fat 1989 Doi 2014 FAAT - Leaf 2005 HARP- Sacks 1995	3/362 <b>4630</b> A), 230 (Lower PUFA) i <sup>2</sup> = 5.43, df = 9 (P = 0.8 1 (P = 0.070) 'D 319/2409 476/1018 11/119 31/200 7/41	<b>4263</b> 30); I <sup>2</sup> =0.0% 352/2428 478/1015 24/119 39/202 7/39		25.8 % 18.8 % 22.1 % 2.8 % 5.8 % 1.5 %	0.85 [ 0.72, 1.01 ] 0.91 [ 0.79, 1.05 ] 0.99 [ 0.91, 1.09 ] 0.46 [ 0.24, 0.89 ] 0.80 [ 0.52, 1.23 ] 0.95 [ 0.37, 2.46 ]
WAHA - Ros 2016 <b>Subtotal (95% CI)</b> Total events: 199 (Higher PUF, Heterogeneity: Tau <sup>2</sup> = 0.0; Ch Test for overall effect: Z = 1.81 Secondary prevention of CV AlphaOmega - ALA DART fat 1989 Doi 2014 FAAT - Leaf 2005 HARP- Sacks 1995 Kumar 2013	3/362 <b>4630</b> A), 230 (Lower PUFA) i <sup>2</sup> = 5,43, df = 9 (P = 0.8 1 (P = 0.070) 7D 319/2409 476/1018 11/119 31/200 7/41 1/39	<b>4263</b> 30); l <sup>2</sup> =0.0% 352/2428 478/1015 24/119 39/202 7/39 1/39		25.8 % 18.8 % 22.1 % 2.8 % 5.8 % 1.5 % 0.2 %	0.85 [ 0.72, 1.01 ] 0.91 [ 0.79, 1.05 ] 0.99 [ 0.91, 1.09 ] 0.46 [ 0.24, 0.89 ] 0.80 [ 0.52, 1.23 ] 0.95 [ 0.37, 2.46 ] 1.00 [ 0.06, 15.43 ]
WAHA - Ros 2016 <b>Subtotal (95% CI)</b> fotal events: 199 (Higher PUF, Heterogeneity: Tau <sup>2</sup> = 0.0; Ch test for overall effect: Z = 1.81 Secondary prevention of CV AlphaOmega - ALA DART fat 1989 Doi 2014 FAAT - Leaf 2005 HARP- Sacks 1995 Kumar 2013 MRC 1968	3/362 <b>4630</b> A), 230 (Lower PUFA) $i^2 = 5.43$ , df = 9 (P = 0.8 1 (P = 0.070) D 319/2409 476/1018 11/119 31/200 7/41 1/39 62/199	<b>4263</b> 30); l <sup>2</sup> =0.0% 352/2428 478/1015 24/119 39/202 7/39 1/39 74/194		25.8 % 18.8 % 22.1 % 2.8 % 1.5 % 0.2 % 10.8 %	0.85 [ 0.72, 1.01 ] 0.91 [ 0.79, 1.05 ] 0.99 [ 0.91, 1.09 ] 0.46 [ 0.24, 0.89 ] 0.80 [ 0.52, 1.23 ] 0.95 [ 0.37, 2.46 ] 1.00 [ 0.06, 15.43 ] 0.82 [ 0.62, 1.07 ]

Favours higher PUFA Favours lower PUFA

(Continued ...)

Study or subgroup	Higher PUFA	Lower PUFA	Risk Ratio M- H,Random,95%	Weight	( Continued) Risk Ratio M- H.Random,95%
	n/N	n/N	Cl		Cl
Sydney Diet-Heart 1978	37/221	25/237		5.0 %	1.59 [ 0.99, 2.55 ]
Subtotal (95% CI)	4441	4465	•	74.2 %	0.89 [ 0.75, 1.05 ]
Total events: 971 (Higher PUFA	), 1042 (Lower PUFA)				
Heterogeneity: Tau <sup>2</sup> = 0.03; Ch	ni <sup>2</sup> = 22.10, df = 10 (P =	= 0.01); I <sup>2</sup> =55%			
Test for overall effect: $Z = 1.43$	(P = 0.15)				
Total (95% CI)	9071	8728	•	100.0 %	0.89 [ 0.79, 1.01 ]
Total events: 1170 (Higher PUF	A), 1272 (Lower PUFA	)			
Heterogeneity: Tau <sup>2</sup> = 0.01; Ch	m <sup>2</sup> = 28.7 I, df = 20 (P =	= 0.09); l <sup>2</sup> =30%			
Test for overall effect: $Z = 1.87$	(P = 0.061)				
Test for subgroup differences: C	$Chi^2 = 0.11, df = 1 (P = 1)$	0.74), l <sup>2</sup> =0.0%			

0.01 0.1 1 10 100

Favours higher PUFA Favours lower PUFA

### Analysis 2.19. Comparison 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes, Outcome 19 CVD events - subgroup by baseline PUFA dose.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes

Outcome: 19 CVD events - subgroup by baseline PUFA dose

Study or subgroup	Higher PUFA	Lower PUFA	Risk Ratio M-	Weight	Risk Ratio M-
	n/N	n/N	H,Random,95% Cl		H,Random,9 Cl
Baseline total PUFA < 6% E					
NDHS Open 1st 1968	5/726	1/341		0.3 %	2.35 [ 0.28, 20.02 ]
Veterans Admin 1969	97/424	122/422	-	13.0 %	0.79 [ 0.63, 1.00 ]
Subtotal (95% CI)	1150	763	•	13.3 %	0.80 [ 0.64, 1.01 ]
Total events: 102 (Higher PUFA	), 123 (Lower PUFA)				
Heterogeneity: Tau <sup>2</sup> = 0.0; Chi <sup>2</sup>	,	32); I <sup>2</sup> =0.0%			
Test for overall effect: $Z = 1.90$	· · · ·				
Baseline total PUFA 6 to < 11		470/1015		22 + 0/	
DART fat 1989	476/1018	478/1015	1	22.1 %	0.99 [ 0.91, 1.09 ]
PREDIMED 2013	83/2454	96/2543	*	10.1 %	0.90 [ 0.67, 1.20 ]
Sydney Diet-Heart 1978	37/221	25/237	•	5.0 %	1.59 [ 0.99, 2.55 ]
WAHA - Ros 2016	3/362	4/364		0.6 %	0.75 [ 0.17, 3.35 ]
Subtotal (95% CI)	4055	4159	•	37.9 %	1.02 [ 0.85, 1.22 ]
Test for overall effect: Z = 0.21 3 Baseline total PUFA 11+% E Subtotal (95% CI)	0	0			Not estimable
	0	0			N. 4 4!
Total events: 0 (Higher PUFA), (		Ū			i tot couniuble
Heterogeneity: not applicable					
Test for overall effect: not applic	able				
Baseline total PUFA unclear					
AlphaOmega - ALA	319/2409	352/2428	•	18.8 %	0.91 [ 0.79, 1.05 ]
Brox 2001	0/80	1/40		0.1 %	0.17 [ 0.01, 4.05 ]
Doi 2014	/  9	24/119		2.8 %	0.46 [ 0.24, 0.89 ]
EPIC-1 2008	1/188	0/186		0.1 %	2.97 [ 0.12, 72.40 ]
EPOCH 2011	8/195	5/196	- <del>  -</del>	1.1 %	1.61 [ 0.54, 4.83
FAAT - Leaf 2005	31/200	39/202	-	5.8 %	0.80 [ 0.52, 1.23 ]
GLAMT 1993	0/54	1/57		0.1 %	0.35 [ 0.01, 8.45
			0.01 0.1 1 10 100		
		F	0.01 0.1 1 10 100 Favours higher PUFA Favours lower F	PUFA	
					(Continued

( Continued) Risk Ratio M- H,Random,95	Weight	Risk Ratio M- H,Random,95%	Lower PUFA	Higher PUFA	Study or subgroup
CI	1.5 %		n/N 7/39	n/N 7/41	HARP- Sacks 1995
0.95 [ 0.37, 2.46 ]	1.5 %		//37	//41	MARE- JACKS 1773
1.00 [ 0.06, 15.43 ]	0.2 %		1/39	1/39	Kumar 2013
0.82 [ 0.62, 1.07 ]	10.8 %	-	74/194	62/199	MRC 1968
0.38 [ 0.20, 0.72 ]	3.0 %		26/66	10/67	Nodari 2011 HF
1.84 [ 0.08, 44.38 ]	0.1 %		0/53	1/87	Proudman 2015
3.05 [ 0.13, 73.40 ]	0.1 %		0/61	1/60	Puri 2005
0.40 [ 0.08, 2.01 ]	0.5 %		5/100	2/100	Raitt 2005
1.27 [ 0.72, 2.23 ]	3.7 %		11/26	15/28	Rose 1965
0.82 [ 0.69, 0.98 ]	48.8 %	•	3806	3866	Subtotal (95% CI)
				A), 546 (Lower PUFA)	Total events: 469 (Higher PUFA
			0.24); l <sup>2</sup> = l 9%	ni² = 17.24, df = 14 (P =	Heterogeneity: $Tau^2 = 0.02$ ; Ch
				(P = 0.030)	Test for overall effect: $Z = 2.17$
0.89 [ 0.79, 1.01 ]	100.0 %	•	8728	9071	Total (95% CI)
				A), 1272 (Lower PUFA)	Total events: 1170 (Higher PUF
			0.09); I <sup>2</sup> =30%	ni <sup>2</sup> = 28.71, df = 20 (P =	Heterogeneity: Tau <sup>2</sup> = 0.01; Ch
				(P = 0.061)	Test for overall effect: Z = 1.87
			0.15), I <sup>2</sup> =47%	Chi <sup>2</sup> = 3.78, df = 2 (P =	Test for subgroup differences: C

Favours higher PUFA

Favours lower PUFA

## Analysis 2.20. Comparison 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes, Outcome 20 CVD events - subgroup by replacement.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes

Outcome: 20 CVD events - subgroup by replacement

Study or subgroup	Higher PUFA	Lower PUFA	Risk Ratio M-	Weight	Risk Ratio M-
	n/N	n/N	H,Random,95% Cl		H,Random, C
PUFA replaced saturated fats					
DART fat 1989	476/1018	478/1015	•	39.3 %	0.99 [ 0.91, 1.09 ]
MRC 1968	62/199	74/194	-	21.9 %	0.82 [ 0.62, 1.07 ]
NDHS Open 1st 1968	5/726	1/341		0.7 %	2.35 [ 0.28, 20.02 ]
Sydney Diet-Heart 1978	37/221	25/237	-	11.0 %	1.59 [ 0.99, 2.55
Veterans Admin 1969	97/424	122/422	-	25.7 %	0.79 [ 0.63, 1.00 ]
WAHA - Ros 2016	3/362	4/364		1.4 %	0.75 [ 0.17, 3.35 ]
Subtotal (95% CI)	2950	2573	•	100.0 %	0.95 [ 0.79, 1.14 ]
Fotal events: 680 (Higher PUFA) Heterogeneity: Tau <sup>2</sup> = 0.02; Chi <sup>2</sup> Fest for overall effect: Z = 0.59 (	P = 9.66, df = 5 (P = 0 P = 0.56)	0.09); I <sup>2</sup> =48%			
2 PUFA replaced monounsatural		252/2420		242.04	
AlphaOmega - ALA	319/2409	352/2428	1	24.2 %	0.91 [ 0.79, 1.05
EPOCH 2011	8/195	5/196		2.3 %	1.61 [ 0.54, 4.83
FAAT - Leaf 2005	31/200	39/202	-	10.6 %	0.80 [ 0.52, 1.23 ]
HARP- Sacks 1995	7/41	7/39		3.0 %	0.95 [ 0.37, 2.46
NDHS Open 1st 1968	5/726	1/341		0.7 %	2.35 [ 0.28, 20.02 ]
Nodari 2011 HF	10/67	26/66		5.9 %	0.38 [ 0.20, 0.72 ]
PREDIMED 2013	83/2454	96/2543	-	16.2 %	0.90 [ 0.67, 1.20]
Proudman 2015	1/87	0/53		0.3 %	1.84 [ 0.08, 44.38 ]
Raitt 2005	2/100	5/100	<b>.</b>	1.1 %	0.40 [ 0.08, 2.01
Rose 1965	15/28	11/26	-	7.2 %	1.27 [ 0.72, 2.23
Sydney Diet-Heart 1978	37/221	25/237	-	9.3 %	1.59 [ 0.99, 2.55
Veterans Admin 1969	97/424	122/422	-	19.2 %	0.79 [ 0.63, 1.00
Subtotal (95% CI)	6952	6653	•	100.0 %	0.91 [ 0.76, 1.08
otal events: 615 (Higher PUFA) Heterogeneity: Tau <sup>2</sup> = 0.03; Chi <sup>2</sup>	, ,	= 0.07); I <sup>2</sup> =40%			

Favours higher PUFA Favours lower PUFA

(Continued ...)

Study or subgroup	Higher PUFA	Lower PUFA	Risk Ratio M- H,Random,95%	Weight	( Continued) Risk Ratio M- H.Random,95
	n/N	n/N	Cl		Cl
Test for overall effect: $Z = 1.10$	· ,				
3 PUFA replaced carbohydrate					
Rose 1965	15/28	11/26		87.4 %	1.27 [ 0.72, 2.23 ]
WAHA - Ros 2016	3/362	4/364		12.6 %	0.75 [ 0.17, 3.35 ]
Subtotal (95% CI)	390	390	•	100.0 %	1.19 [ 0.70, 2.01 ]
Total events: 18 (Higher PUFA	A), I5 (Lower PUFA)				
Heterogeneity: $Tau^2 = 0.0$ ; Ch	$m^2 = 0.43, df = 1 (P = 0.43)$	5 I ); I <sup>2</sup> =0.0%			
Test for overall effect: $Z = 0.62$	3 (P = 0.53)				
4 PUFA replaced protein			_		
MRC 1968	62/199	74/194		96.7 %	0.82 [ 0.62, 1.07 ]
WAHA - Ros 2016	3/362	4/364		3.3 %	0.75 [ 0.17, 3.35 ]
Subtotal (95% CI)	561	558	•	100.0 %	0.81 [ 0.62, 1.07 ]
Heterogeneity: $Tau^2 = 0.0$ ; Ch		92); I <sup>2</sup> =0.0%			
Heterogeneity: Tau <sup>2</sup> = 0.0; Ch Test for overall effect: Z = 1.4 <sup>r</sup> 5 PUFA replaced unclear Brox 2001	$hi^2 = 0.01$ , $df = 1$ (P = 0.	92); I <sup>2</sup> =0.0%		3.6 %	0.17 [ 0.01, 4.05 ]
Test for overall effect: Z = 1.4 5 PUFA replaced unclear Brox 2001	i <sup>2</sup> = 0.01, df = 1 (P = 0. 9 (P = 0.14) 0/80	1/40		3.6 % 81 0 %	0.17 [ 0.01, 4.05 ] 0.46 [ 0.24 0.89 ]
Test for overall effect: Z = 1.4 5 PUFA replaced unclear Brox 2001 Doi 2014	i <sup>2</sup> = 0.01, df = 1 (P = 0. 9 (P = 0.14) 0/80	1/40 24/119		81.0 %	0.46 [ 0.24, 0.89 ]
Test for overall effect: Z = 1.4 5 PUFA replaced unclear Brox 2001 Doi 2014 EPIC-1 2008	i <sup>2</sup> = 0.01, df = 1 (P = 0. 9 (P = 0.14) 0/80 11/119 1/188	1/40 24/119 0/186		81.0 % 3.5 %	0.46 [ 0.24, 0.89 ] 2.97 [ 0.12, 72.40 ]
Test for overall effect: Z = 1.4 5 PUFA replaced unclear Brox 2001 Doi 2014	i <sup>2</sup> = 0.01, df = 1 (P = 0. 9 (P = 0.14) 0/80	1/40 24/119		81.0 %	0.46 [ 0.24, 0.89 ]
Test for overall effect: Z = 1.4 5 PUFA replaced unclear Brox 2001 Doi 2014 EPIC-1 2008	i <sup>2</sup> = 0.01, df = 1 (P = 0. 9 (P = 0.14) 0/80 11/119 1/188	1/40 24/119 0/186		81.0 % 3.5 %	0.46 [ 0.24, 0.89 ] 2.97 [ 0.12, 72.40 ]
Test for overall effect: Z = 1.4 5 PUFA replaced unclear Brox 2001 Doi 2014 EPIC-1 2008 GLAMT 1993	i <sup>2</sup> = 0.01, df = 1 (P = 0. 9 (P = 0.14) 0/80 11/119 1/188 0/54	1/40 24/119 0/186 1/57		81.0 % 3.5 % 3.6 %	0.46 [ 0.24, 0.89 ] 2.97 [ 0.12, 72.40 ] 0.35 [ 0.01, 8.45 ]
Test for overall effect: Z = 1.4 5 PUFA replaced unclear Brox 2001 Doi 2014 EPIC-1 2008 GLAMT 1993 Kumar 2013	i <sup>2</sup> = 0.01, df = 1 (P = 0. 9 (P = 0.14) 0/80 11/119 1/188 0/54 1/39	1/40 24/119 0/186 1/57 1/39		81.0 % 3.5 % 3.6 % 4.8 %	0.46 [ 0.24, 0.89 ] 2.97 [ 0.12, 72.40 ] 0.35 [ 0.01, 8.45 ] 1.00 [ 0.06, 15.43 ]
Test for overall effect: Z = 1.4 5 PUFA replaced unclear Brox 2001 Doi 2014 EPIC-1 2008 GLAMT 1993 Kumar 2013 Puri 2005	si <sup>2</sup> = 0.01, df = 1 (P = 0. 9 (P = 0.14) 0/80 11/119 1/188 0/54 1/39 1/60 <b>540</b>	1/40 24/119 0/186 1/57 1/39 0/61		81.0 % 3.5 % 3.6 % 4.8 % 3.6 %	0.46 [ 0.24, 0.89 ] 2.97 [ 0.12, 72.40 ] 0.35 [ 0.01, 8.45 ] 1.00 [ 0.06, 15.43 ] 3.05 [ 0.13, 73.40 ]
Test for overall effect: Z = 1.4' 5 PUFA replaced unclear Brox 2001 Doi 2014 EPIC-1 2008 GLAMT 1993 Kumar 2013 Puri 2005 <b>Subtotal (95% CI)</b> Total events: 14 (Higher PUFA	si <sup>2</sup> = 0.01, df = 1 (P = 0. 9 (P = 0.14) 0/80 11/119 1/188 0/54 1/39 1/60 <b>540</b> A), 27 (Lower PUFA)	1/40 24/119 0/186 1/57 1/39 0/61 <b>502</b>		81.0 % 3.5 % 3.6 % 4.8 % 3.6 %	0.46 [ 0.24, 0.89 ] 2.97 [ 0.12, 72.40 ] 0.35 [ 0.01, 8.45 ] 1.00 [ 0.06, 15.43 ] 3.05 [ 0.13, 73.40 ]
Test for overall effect: Z = 1.4 5 PUFA replaced unclear Brox 2001 Doi 2014 EPIC-1 2008 GLAMT 1993 Kumar 2013 Puri 2005 Subtotal (95% CI)	$h^{2} = 0.01, df = 1 (P = 0.9)$ 9 (P = 0.14) 0/80 11/119 1/188 0/54 1/39 1/60 <b>540</b> A), 27 (Lower PUFA) $h^{2} = 3.24, df = 5 (P = 0.9)$ 4 (P = 0.033)	1/40 24/119 0/186 1/57 1/39 0/61 <b>502</b> 66); 1 <sup>2</sup> =0.0%		81.0 % 3.5 % 3.6 % 4.8 % 3.6 %	0.46 [ 0.24, 0.89 ] 2.97 [ 0.12, 72.40 ] 0.35 [ 0.01, 8.45 ] 1.00 [ 0.06, 15.43 ] 3.05 [ 0.13, 73.40 ]

0.01 0.1 I 10 100 Favours higher PUFA Favours lower PUFA

# Analysis 2.21. Comparison 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes, Outcome 21 CVD events - subgroup by sex.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes

Outcome: 21 CVD events - subgroup by sex

n/N 319/2409 476/1018 11/119 31/200 0/54 7/41 62/199	n/N 352/2428 478/1015 24/119 39/202 1/57 7/39	M- H,Random,95% Cl	18.8 % 22.1 % 2.8 % 5.8 %	M. H,Random, C 0.91 [ 0.79, 1.05 ] 0.99 [ 0.91, 1.09 ] 0.46 [ 0.24, 0.89 ]
476/1018 11/119 31/200 0/54 7/41	478/1015 24/119 39/202 1/57		22.1 % 2.8 %	0.99 [ 0.91, 1.09 ]
476/1018 11/119 31/200 0/54 7/41	478/1015 24/119 39/202 1/57		22.1 % 2.8 %	0.99 [ 0.91, 1.09 ]
11/119 31/200 0/54 7/41	24/119 39/202 1/57	 	2.8 %	0.46 [ 0.24, 0.89 ]
31/200 0/54 7/41	39/202 1/57			
0/54 7/41	1/57		5.8 %	
7/41				0.80 [ 0.52, 1.23 ]
	7/39		0.1 %	0.35 [ 0.01, 8.45
62/199		_	1.5 %	0.95 [ 0.37, 2.46
	74/194	-	10.8 %	0.82 [ 0.62, 1.07
5/726	1/341		0.3 %	2.35 [ 0.28, 20.02
10/67	26/66		3.0 %	0.38 [ 0.20, 0.72
2/100	5/100		0.5 %	0.40 [ 0.08, 2.01
37/221	25/237		5.0 %	1.59 [ 0.99, 2.55
97/424	122/422	-	13.0 %	0.79 [ 0.63, 1.00
5578	5220	•	83.7 %	0.86 [ 0.74, 1.00]
16, df = 11 (P =			0.1 %	1.84 [ 0.08, 44.38
87	53		0.1 %	1.84 [ 0.08, 44.38
0/80	1/40		0.1 %	0.17 [ 0.01, 4.05
1/188	0/186		0.1 %	2.97 [ 0.12, 72.40
		1		
1 7	2/100 37/221 97/424 <b>5578</b> H (Lower PUFA) 16, df = 11 (P = 048) 1/87 <b>87</b> r PUFA)	$2/100   5/100   37/221   25/237   97/424   122/422   5578   5220   4 (Lower PUFA)   16, df = 11 (P = 0.01); 1^2 = 54\%   148)   1/87   0/53   87   53   753   753   71)$	2/100 $5/100$ 37/221 $25/23797/424$ $122/4225578 52204$ (Lower PUFA) 16, df = 11 (P = 0.01); 1 <sup>2</sup> = 54% 1/87 0/53 <b>87 53</b> r PUFA) 71)	$2/100   5/100   0.5\%$ $37/221   25/237   5.0\%$ $97/424   122/422   13.0\%$ $5578   5220   83.7\%$ $4 (Lower PUFA)$ $16, df = 11 (P = 0.01); 1^2 = 54\%$ $1/87   0/53   0.1\%$ $87   53   0.1\%$ $r PUFA)$ $71)$

(Continued . . . )

Study or subgroup	Higher PUFA n/N	Lower PUFA	Risk Ratio M- H,Random,95%	Weight	( Continued) Risk Ratio M- H,Random,95%
PREDIMED 2013	83/2454	96/2543	+	10.1 %	0.90 [ 0.67, 1.20 ]
Puri 2005	1/60	0/61		0.1 %	3.05 [ 0.13, 73.40 ]
WAHA - Ros 2016	3/362	4/364		0.6 %	0.75 [ 0.17, 3.35 ]
Subtotal (95% CI)	3183	3233	•	11.3 %	0.90 [ 0.68, 1.18 ]
Heterogeneity: $Tau^2 = 0.0$ ; Ch Test for overall effect: $Z = 0.7$ 4 sex not reported		.82); I <sup>2</sup> =0.0%			
4 sex not reported EPOCH 2011	8/195	5/196		1.1 %	1.61 [ 0.54, 4.83 ]
Rose 1965	15/28	11/26		3.7 %	1.27 [ 0.72, 2.23 ]
Subtotal (95% CI)	223	222	•	<b>4.8</b> %	1.33 [ 0.80, 2.20 ]
Total events: 23 (Higher PUFA Heterogeneity: $Tau^2 = 0.0$ ; Ch Test for overall effect: $Z = 1.1$	$i^2 = 0.16$ , df = 1 (P = 0	.69); I <sup>2</sup> =0.0%			
Total (95% CI)	9071	8728	•	100.0 %	0.89 [ 0.79, 1.01 ]
Total events: 1170 (Higher PU	FA), 1272 (Lower PUFA	A)			
Heterogeneity: $Tau^2 = 0.01$ ; C	$hi^2 = 28.7 I$ , $df = 20$ (P	= 0.09); I <sup>2</sup> =30%			
Test for overall effect: $Z = 1.8$	7 (P = 0.061)				
Test for subgroup differences:	$Chi^2 = 2.88, df = 3 (P =$	= 0.41), 12 =0.0%			

0.01 0.1 1 10 100

Favours higher PUFA Favours lower PUFA

# Analysis 2.22. Comparison 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes, Outcome 22 CVD events - subgroup by age.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes

Outcome: 22 CVD events - subgroup by age

Study or subgroup	Higher PUFA	Lower PUFA	Risk Ratio M-	Weight	Risk Ratio M-
	n/N	n/N	H,Random,95% Cl		H,Random,9 Cl
I Mean age < 50 years					
EPIC-1 2008	1/188	0/186		0.1 %	2.97 [ 0.12, 72.40 ]
NDHS Open 1st 1968	5/726	1/341		0.3 %	2.35 [ 0.28, 20.02 ]
Puri 2005	1/60	0/61		0.1 %	3.05 [ 0.13, 73.40 ]
Sydney Diet-Heart 1978	37/221	25/237	-	5.0 %	1.59 [ 0.99, 2.55 ]
Subtotal (95% CI)	1195	825	•	5.6 %	1.66 [ 1.05, 2.61 ]
Total events: 44 (Higher PUFA), 2 Heterogeneity: Tau <sup>2</sup> = 0.0; Chi <sup>2</sup> = Test for overall effect: Z = 2.19 (F 2 Mean age 50 to < 65 years	= 0.41, df = 3 (P = 0. P = 0.029)	,			
Brox 2001	0/80	1/40		0.1 %	0.17 [ 0.01, 4.05 ]
DART fat 1989	476/1018	478/1015	•	22.1 %	0.99 [ 0.91, 1.09 ]
GLAMT 1993	0/54	1/57		0.1 %	0.35 [ 0.01, 8.45
HARP- Sacks 1995	7/41	7/39		1.5 %	0.95 [ 0.37, 2.46 ]
MRC 1968	62/199	74/194	-	10.8 %	0.82 [ 0.62, 1.07 ]
Nodari 2011 HF	10/67	26/66		3.0 %	0.38 [ 0.20, 0.72 ]
Proudman 2015	1/87	0/53		0.1 %	1.84 [ 0.08, 44.38 ]
Raitt 2005	2/100	5/100		0.5 %	0.40 [ 0.08, 2.01 ]
Rose 1965	15/28	11/26	-+	3.7 %	1.27 [ 0.72, 2.23 ]
Subtotal (95% CI)	1674	1590	•	42.0 %	0.84 [ 0.66, 1.08 ]
Total events: 573 (Higher PUFA), Heterogeneity: Tau <sup>2</sup> = 0.04; Chi <sup>2</sup> Test for overall effect: Z = 1.34 (F 3 Mean age 65+ years	= 13.75, df = 8 (P =	0.09); I <sup>2</sup> =42%			
AlphaOmega - ALA	319/2409	352/2428	-	18.8 %	0.91 [ 0.79, 1.05 ]
	/  9	24/119		2.8 %	0.46 [ 0.24, 0.89 ]
Doi 2014					

(Continued . . . )

udy or subgroup	Higher PUFA	Lower PUFA	Risk Ratio M- H,Random,95%	Weight	( Continued) Risk Ratio H- H,Random,95%
	n/N	n/N	Cl		Cl
mar 2013	1/39	1/39		0.2 %	1.00 [ 0.06, 15.43 ]
EDIMED 2013	83/2454	96/2543	+	10.1 %	0.90 [ 0.67, 1.20 ]
erans Admin 1969	97/424	122/422	-	13.0 %	0.79 [ 0.63, 1.00 ]
AHA - Ros 2016	3/362	4/364		0.6 %	0.75 [ 0.17, 3.35 ]
otal (95% CI)	6007	6117	*	51.3 %	0.86 [ 0.78, 0.96 ]
events: 545 (Higher PUFA), 6	638 (Lower PUFA)				
ogeneity: Tau <sup>2</sup> = 0.0; Chi <sup>2</sup> =	4.85, df = 6 (P = 0.	56); I <sup>2</sup> =0.0%			
or overall effect: Z = 2.77 (P	= 0.0056)				
n age unclear					
DCH 2011	8/195	5/196		1.1 %	1.61 [ 0.54, 4.83 ]
otal (95% CI)	195	196	-	1.1 %	1.61 [ 0.54, 4.83 ]
events: 8 (Higher PUFA), 5 (	Lower PUFA)				
ogeneity: not applicable					
or overall effect: Z = 0.85 (P	= 0.40)				
l (95% CI)	9071	8728	•	100.0 %	0.89 [ 0.79, 1.01 ]
events: 1170 (Higher PUFA),	, 1272 (Lower PUFA	)			
$a_{\text{consiture}} T_{\text{cu}}^2 = 0.01$ ; Chi <sup>2</sup>	= 28.71, df = 20 (P =	= 0.09); I <sup>2</sup> =30%			
Dgeneity. Tau – 0.01, Chi -	· · ·				
or overall effect: $Z = 1.87$ (P	= 0.061)				

0.01 0.1 1 10 100

Favours higher PUFA Favours lower PUFA

### Analysis 2.23. Comparison 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes, Outcome 23 CVD events - subgroup by statin use.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes

Outcome: 23 CVD events - subgroup by statin use

Study or subgroup	Higher PUFA	Lower PUFA	Risk Ratio M-	Weight	Risk Ratio M-
	n/N	n/N	H,Random,95% Cl		H,Random,9 Cl
I < 50% on statins					
Brox 2001	0/80	1/40		0.1 %	0.17 [ 0.01, 4.05 ]
DART fat 1989	476/1018	478/1015	•	22.1 %	0.99 [ 0.91, 1.09 ]
EPIC-1 2008	1/188	0/186		0.1 %	2.97 [ 0.12, 72.40 ]
EPOCH 2011	8/195	5/196		1.1 %	1.61 [ 0.54, 4.83 ]
GLAMT 1993	0/54	1/57		0.1 %	0.35 [ 0.01, 8.45 ]
HARP- Sacks 1995	7/41	7/39		1.5 %	0.95 [ 0.37, 2.46 ]
MRC 1968	62/199	74/194	-	10.8 %	0.82 [ 0.62, 1.07 ]
NDHS Open 1st 1968	5/726	1/341		0.3 %	2.35 [ 0.28, 20.02 ]
Nodari 2011 HF	10/67	26/66		3.0 %	0.38 [ 0.20, 0.72 ]
PREDIMED 2013	83/2454	96/2543	+	10.1 %	0.90 [ 0.67, 1.20 ]
Proudman 2015	1/87	0/53		0.1 %	1.84 [ 0.08, 44.38 ]
Puri 2005	1/60	0/61		0.1 %	3.05 [ 0.13, 73.40 ]
Raitt 2005	2/100	5/100		0.5 %	0.40 [ 0.08, 2.01 ]
Rose 1965	15/28	11/26		3.7 %	1.27 [ 0.72, 2.23 ]
Sydney Diet-Heart 1978	37/221	25/237	-	5.0 %	1.59 [ 0.99, 2.55 ]
Veterans Admin 1969	97/424	122/422	-	13.0 %	0.79 [ 0.63, 1.00 ]
Subtotal (95% CI)	5942	5576	•	71.8 %	0.92 [ 0.78, 1.08 ]
Total events: 805 (Higher PUFA) Heterogeneity: Tau <sup>2</sup> = 0.02; Chi Test for overall effect: Z = 1.02 2 50+% on statins	<sup>2</sup> = 23.36, df = 15 (P =	= 0.08); I <sup>2</sup> =36%			
AlphaOmega - ALA	319/2409	352/2428	•	18.8 %	0.91 [ 0.79, 1.05 ]
Doi 2014	/  9	24/119		2.8 %	0.46 [ 0.24, 0.89 ]
Kumar 2013	1/39	1/39		0.2 %	1.00 [ 0.06, 15.43 ]
Subtotal (95% CI)	2567	2586	•	21.8 %	0.73 [ 0.43, 1.25 ]

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Study or subgroup	Higher PUFA	Lower PUFA	Risk Ratio	Weight	( Continued) Risk Ratio
	n/N	n/N	M- H,Random,95% Cl		M- H,Random,95% Cl
Total events: 331 (Higher PUF	A), 377 (Lower PUFA)				
Heterogeneity: $Tau^2 = 0.11$ ; C	$Chi^2 = 3.94, df = 2 (P = 0)$	).   4);   <sup>2</sup> =49%			
Test for overall effect: $Z = 1.1$	5 (P = 0.25)				
3 Percentage on statins unclea	ır				
FAAT - Leaf 2005	31/200	39/202	-	5.8 %	0.80 [ 0.52, 1.23 ]
WAHA - Ros 2016	3/362	4/364		0.6 %	0.75 [ 0.17, 3.35 ]
Subtotal (95% CI)	562	566	•	6.5 %	0.80 [ 0.53, 1.21 ]
Total events: 34 (Higher PUFA	A), 43 (Lower PUFA)				
Heterogeneity: $Tau^2 = 0.0$ ; Ch	$m^2 = 0.01$ , $df = 1$ (P = 0.1)	94); I <sup>2</sup> =0.0%			
Test for overall effect: $Z = 1.0$	7 (P = 0.29)				
Total (95% CI)	9071	8728	•	100.0 %	0.89 [ 0.79, 1.01 ]
Total events: 1170 (Higher PU	IFA), 1272 (Lower PUFA	)			
Heterogeneity: $Tau^2 = 0.01$ ; C	2hi <sup>2</sup> = 28.7 I, df = 20 (P =	= 0.09); I <sup>2</sup> =30%			
Test for overall effect: $Z = 1.8$	7 (P = 0.061)				
Test for subgroup differences:	$Chi^2 = 0.95, df = 2 (P =$	0.62), I <sup>2</sup> =0.0%			
			0.01 0.1 1 10 100	)	

Favours higher PUFA Favours lower PUFA

#### Analysis 2.24. Comparison 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes, Outcome 24 CVD events - subgroup by intervention type.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes

Outcome: 24 CVD events - subgroup by intervention type

Study or subgroup	Higher PUFA	Lower PUFA	Risk Ratio M- H,Random,95%	Weight	Risk Ratio M- H,Random,9
	n/N	n/N	Cl		H,Random,93 Cl
Dietary advice					
DART fat 1989	476/1018	478/1015	•	22.1 %	0.99 [ 0.91, 1.09 ]
Subtotal (95% CI)	1018	1015	•	22.1 %	0.99 [ 0.91, 1.09 ]
Total events: 476 (Higher PUFA)	), 478 (Lower PUFA)				
Heterogeneity: not applicable Fest for overall effect: Z = 0.15	(P = 0.88)				
Supplemental foods % diet pro	· /				
AlphaOmega - ALA	319/2409	352/2428		18.8 %	0.91 [ 0.79, 1.05 ]
NDHS Open 1st 1968	5/726	1/341		0.3 %	2.35 [ 0.28, 20.02 ]
PREDIMED 2013	83/2454	96/2543	+	10.1 %	0.90 [ 0.67, 1.20 ]
Veterans Admin 1969	97/424	122/422	-	13.0 %	0.79 [ 0.63, 1.00 ]
	3/362	4/364		0.6 %	0.75 [ 0.17, 3.35 ]
WAHA - Ros 2016	5/502				
Subtotal (95% CI) Fotal events: 507 (Higher PUFA) Heterogeneity: Tau <sup>2</sup> = 0.0; Chi <sup>2</sup>	<b>6375</b> ), 575 (Lower PUFA) = 1.95, df = 4 (P = 0.7	<b>6098</b> 74); I <sup>2</sup> =0.0%	•	42.8 %	0.88 [ 0.79, 0.99 ]
WAHA - Ros 2016 Subtotal (95% CI) Total events: 507 (Higher PUFA) Heterogeneity: Tau <sup>2</sup> = 0.0; Chi <sup>2</sup> Test for overall effect: Z = 2.22	<b>6375</b> ), 575 (Lower PUFA) = 1.95, df = 4 (P = 0.7		•	42.8 %	0.88 [ 0.79, 0.99 ]
Subtotal (95% CI)         Total events: 507 (Higher PUFA)         Heterogeneity: Tau <sup>2</sup> = 0.0; Chi <sup>2</sup> Fest for overall effect: Z = 2.22         Supplements (capsules % unus	<b>6375</b> ), 575 (Lower PUFA) = 1.95, df = 4 (P = 0.2 (P = 0.026) sual foods)	74); I <sup>2</sup> =0.0%	•		
<b>Subtotal (95% CI)</b> Total events: 507 (Higher PUFA) Heterogeneity: Tau <sup>2</sup> = 0.0; Chi <sup>2</sup> Test for overall effect: Z = 2.22	<b>6375</b> ), 575 (Lower PUFA) = 1.95, df = 4 (P = 0.7 (P = 0.026)		•	<b>42.8 %</b> 0.1 %	
<b>Subtotal (95% CI)</b> Total events: 507 (Higher PUFA) Heterogeneity: Tau <sup>2</sup> = 0.0; Chi <sup>2</sup> Test for overall effect: $Z = 2.22$ Supplements (capsules % unus	<b>6375</b> ), 575 (Lower PUFA) = 1.95, df = 4 (P = 0.2 (P = 0.026) sual foods)	74); I <sup>2</sup> =0.0%	•		<b>0.88 [ 0.79, 0.99 ]</b> 0.17 [ 0.01, 4.05 ] 0.46 [ 0.24, 0.89 ]
<b>Subtotal (95% CI)</b> Total events: 507 (Higher PUFA) Heterogeneity: Tau <sup>2</sup> = 0.0; Chi <sup>2</sup> Test for overall effect: Z = 2.22 ( Supplements (capsules % unus Brox 2001	<b>6375</b> ), 575 (Lower PUFA) = 1.95, df = 4 (P = 0.7 (P = 0.026) sual foods) 0/80	74); I <sup>2</sup> =0.0%	•	0.1 %	0.17 [ 0.01, 4.05 ] 0.46 [ 0.24, 0.89 ]
<b>Subtotal (95% CI)</b> Total events: 507 (Higher PUFA) Heterogeneity: Tau <sup>2</sup> = 0.0; Chi <sup>2</sup> Test for overall effect: Z = 2.22 ( Supplements (capsules % unus Brox 2001 Doi 2014	<b>6375</b> ), 575 (Lower PUFA) = 1.95, df = 4 (P = 0.7 (P = 0.026) sual foods) 0/80 11/119	1/40 24/119	• 	0.1 % 2.8 %	0.17 [ 0.01, 4.05 ] 0.46 [ 0.24, 0.89 ] 2.97 [ 0.12, 72.40 ]
<b>Subtotal (95% CI)</b> Total events: 507 (Higher PUFA) Heterogeneity: Tau <sup>2</sup> = 0.0; Chi <sup>2</sup> Test for overall effect: Z = 2.22 ( Supplements (capsules % unus Brox 2001 Doi 2014 EPIC-1 2008	<b>6375</b> ), 575 (Lower PUFA) = 1.95, df = 4 (P = 0.3 (P = 0.026) sual foods) 0/80 11/119 1/188	74); l <sup>2</sup> =0.0% 1/40 24/119 0/186	•	0.1 % 2.8 % 0.1 %	0.17 [ 0.01, 4.05 ] 0.46 [ 0.24, 0.89 ] 2.97 [ 0.12, 72.40 ] 1.61 [ 0.54, 4.83 ]
<b>Subtotal (95% CI)</b> Total events: 507 (Higher PUFA) Heterogeneity: Tau <sup>2</sup> = 0.0; Chi <sup>2</sup> Test for overall effect: $Z = 2.22$ ( Supplements (capsules % unus Brox 2001 Doi 2014 EPIC-1 2008 EPOCH 2011	<b>6375</b> ), 575 (Lower PUFA) = 1.95, df = 4 (P = 0.1 (P = 0.026) sual foods) 0/80 11/119 1/188 8/195	74); l <sup>2</sup> =0.0% 1/40 24/119 0/186 5/196		0.1 % 2.8 % 0.1 % 1.1 %	0.17 [ 0.01, 4.05 ]
Gubtotal (95% CI) Total events: 507 (Higher PUFA) deterogeneity: Tau <sup>2</sup> = 0.0; Chi <sup>2</sup> est for overall effect: Z = 2.22 ( Supplements (capsules % unus Brox 2001 Doi 2014 EPIC-1 2008 EPOCH 2011 FAAT - Leaf 2005	6375 ), 575 (Lower PUFA) = 1.95, df = 4 (P = 0.7 (P = 0.026) sual foods) 0/80 11/119 1/188 8/195 31/200	74); l <sup>2</sup> =0.0% 1/40 24/119 0/186 5/196 39/202		0.1 % 2.8 % 0.1 % 1.1 % 5.8 %	0.17 [ 0.01, 4.05 ] 0.46 [ 0.24, 0.89 ] 2.97 [ 0.12, 72.40 ] 1.61 [ 0.54, 4.83 ] 0.80 [ 0.52, 1.23 ] 0.35 [ 0.01, 8.45 ]
Subtotal (95% CI) Total events: 507 (Higher PUFA) Heterogeneity: Tau <sup>2</sup> = 0.0; Chi <sup>2</sup> Test for overall effect: Z = 2.22 ( Supplements (capsules % unus Brox 2001 Doi 2014 EPIC-1 2008 EPOCH 2011 FAAT - Leaf 2005 GLAMT 1993	6375 6375 (Lower PUFA) = 1.95, df = 4 (P = 0.1 (P = 0.026) sual foods) 0/80 11/119 1/188 8/195 31/200 0/54	74); l <sup>2</sup> =0.0% 1/40 24/119 0/186 5/196 39/202 1/57		0.1 % 2.8 % 0.1 % 1.1 % 5.8 % 0.1 %	0.17 [ 0.01, 4.05 ] 0.46 [ 0.24, 0.89 ] 2.97 [ 0.12, 72.40 ] 1.61 [ 0.54, 4.83 ] 0.80 [ 0.52, 1.23 ]
Subtotal (95% CI) Total events: 507 (Higher PUFA) Heterogeneity: Tau <sup>2</sup> = 0.0; Chi <sup>2</sup> Test for overall effect: Z = 2.22 ( Supplements (capsules % unus Brox 2001 Doi 2014 EPIC-1 2008 EPOCH 2011 FAAT - Leaf 2005 GLAMT 1993 HARP- Sacks 1995	6375 ), 575 (Lower PUFA) = 1.95, df = 4 (P = 0. (P = 0.026) sual foods) 0/80 11/119 1/188 8/195 31/200 0/54 7/41	74); l <sup>2</sup> =0.0% 1/40 24/119 0/186 5/196 39/202 1/57 7/39		0.1 % 2.8 % 0.1 % 1.1 % 5.8 % 0.1 % 1.5 %	0.17 [ 0.01, 4.05 ] 0.46 [ 0.24, 0.89 ] 2.97 [ 0.12, 72.40 ] 1.61 [ 0.54, 4.83 ] 0.80 [ 0.52, 1.23 ] 0.35 [ 0.01, 8.45 ] 0.95 [ 0.37, 2.46 ]

(Continued . . . )

Study or subgroup	Higher PUFA	Lower PUFA	Risk Ratio M- H,Random,95% Cl	Weight	( Continued) Risk Ratio M- H,Random,95% Cl
Puri 2005	1/60	0/61		0.1 %	3.05 [ 0.13, 73.40 ]
Raitt 2005	2/100	5/100		0.5 %	0.40 [ 0.08, 2.01 ]
Rose 1965	15/28	11/26		3.7 %	1.27 [ 0.72, 2.23 ]
Subtotal (95% CI)	1258	1184	•	19.3 %	0.75 [ 0.54, 1.04 ]
Total events: 88 (Higher PUFA)	), 120 (Lower PUFA)				
Heterogeneity: $Tau^2 = 0.07$ ; Ch	$hi^2 = 15.43$ , df = 12 (P	= 0.22); I <sup>2</sup> =22%			
Test for overall effect: $Z = 1.70$					
4 Any combination	(				
MRC 1968	62/199	74/194	-	10.8 %	0.82 [ 0.62, 1.07 ]
Sydney Diet-Heart 1978	37/221	25/237	-	5.0 %	1.59 [ 0.99, 2.55 ]
Subtotal (95% CI)	420	431	+	15.8 %	1.11 [ 0.57, 2.13 ]
Total events: 99 (Higher PUFA)	), 99 (Lower PUFA)				
Heterogeneity: Tau <sup>2</sup> = 0.19; Cł	$hi^2 = 5.79, df = 1$ (P = 0	0.02); I <sup>2</sup> =83%			
Test for overall effect: $Z = 0.30$	(P = 0.76)				
Total (95% CI)	9071	8728	•	100.0 %	0.89 [ 0.79, 1.01 ]
Total events: 1170 (Higher PUF	A), 1272 (Lower PUFA	.)			
Heterogeneity: Tau <sup>2</sup> = 0.01; Cł	$hi^2 = 28.71$ , df = 20 (P	= 0.09); l <sup>2</sup> = 30%			
Test for overall effect: Z = 1.87	,	<i>,</i>			
Test for subgroup differences: (	· /	$(0.20)$ , $ ^2 = 35\%$			

0.01 0.1 1 10 100

Favours higher PUFA Favours lower PUFA

### Analysis 2.25. Comparison 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes, Outcome 25 CORONARY HEART DISEASE (CHD) MORTALITY.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes

Outcome: 25 CORONARY HEART DISEASE (CHD) MORTALITY

Study or subgroup	Higher PUFA	Lower PUFA	Risk Ratio M-	Weight	Risk Ratio M-
	n/N	n/N	H,Random,95% Cl		H,Random,95% Cl
AlphaOmega - ALA	66/2409	72/2428	+	22.5 %	0.92 [ 0.66, 1.28 ]
Brox 2001 (1)	0/80	1/40		0.2 %	0.17[0.01,4.05]
DART fat 1989	162/1018	178/1015	•	64.6 %	0.91 [ 0.75, 1.10 ]
Doi 2014 (2)	0/119	2/119		0.3 %	0.20 [ 0.01, 4.12 ]
FAAT - Leaf 2005 (3)	9/200	9/202		3.0 %	1.01 [ 0.41, 2.49 ]
HARP- Sacks 1995	0/41	1/39		0.2 %	0.32 [ 0.01, 7.57 ]
Raitt 2005	2/100	5/100		0.9 %	0.40 [ 0.08, 2.01 ]
Rose 1965	2/28	1/26		0.4 %	1.86 [ 0.18, 19.29 ]
Veterans Admin 1969	23/424	23/422	-	7.7 %	1.00 [ 0.57, 1.75 ]
Total (95% CI)	4419	4391	•	100.0 %	0.91 [ 0.78, 1.06 ]
Total events: 264 (Higher PU	IFA), 292 (Lower PUFA)	)			
Heterogeneity: Tau <sup>2</sup> = 0.0; C	$hi^2 = 3.98$ , df = 8 (P =	0.86); l <sup>2</sup> =0.0%			
Test for overall effect: $Z = 1.2$	23 (P = 0.22)				
Test for subgroup differences	: Not applicable				

Favours higher PUFA Favours lower PUFA

(I) Fatal MI

(2) Fatal MI/ sudden death

(3) Cardiac deaths

# Analysis 2.26. Comparison 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes, Outcome 26 CHD mortality - SA.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes

Outcome: 26 CHD mortality - SA

Study or subgroup	Higher PUFA	Lower PUFA	Risk Ratio M-	Weight	Risk Ratio M-
	n/N n/N	H,Random,95% Cl		H,Random,95 Cl	
I Low risk of bias for allocation	concealment				
AlphaOmega - ALA	66/2409	72/2428		87.4 %	0.92 [ 0.66, 1.28 ]
Brox 2001 (1)	0/80	1/40		0.9 %	0.17 [ 0.01, 4.05 ]
FAAT - Leaf 2005 (2)	9/200	9/202	-	11.6 %	1.01 [ 0.41, 2.49 ]
Subtotal (95% CI)	2689	2670	•	100.0 %	0.92 [ 0.68, 1.25 ]
Total events: 75 (Higher PUFA) Heterogeneity: Tau <sup>2</sup> = 0.0; Chi <sup>2</sup> Test for overall effect: Z = 0.54 2 Low risk of bias for attention	$^{2} = 1.14$ , df = 2 (P = 0	0.57); l <sup>2</sup> =0.0%			
AlphaOmega - ALA	66/2409	72/2428	•	63.7 %	0.92 [ 0.66, 1.28 ]
Brox 2001 (3)	0/80	1/40		0.7 %	0.17 [ 0.01, 4.05 ]
Doi 2014 (4)	0/119	2/119		0.8 %	0.20 [ 0.01, 4.12 ]
FAAT - Leaf 2005 (5)	9/200	9/202	_	8.5 %	1.01 [ 0.41, 2.49 ]
HARP- Sacks 1995	0/41	1/39		0.7 %	0.32 [ 0.01, 7.57 ]
Raitt 2005	2/100	5/100		2.6 %	0.40 [ 0.08, 2.01 ]
Rose 1965	2/28	1/26		1.3 %	1.86 [ 0.18, 19.29 ]
Veterans Admin 1969	23/424	23/422	-	21.8 %	1.00 [ 0.57, 1.75 ]
Subtotal (95% CI)	3401	3376	•	100.0 %	0.91 [ 0.70, 1.18 ]
Fotal events: 102 (Higher PUFA Heterogeneity: Tau <sup>2</sup> = 0.0; Chi <sup>2</sup> Fest for overall effect: Z = 0.74 B Low risk of bias for compliance Brox 2001 (6)	$P^{2} = 3.98$ , df = 7 (P = 0 (P = 0.46)	0.78); I <sup>2</sup> =0.0%		0.3 %	0.17 [ 0.01, 4.05 ]
			_		
DART fat 1989	162/1018	178/1015	<b>-</b>	88.5 %	0.91 [ 0.75, 1.10 ]
Rose 1965	2/28	1/26		0.6 %	1.86 [ 0.18, 19.29 ]
Veterans Admin 1969	23/424	23/422	+	10.6 %	1.00 [ 0.57, 1.75 ]
Subtotal (95% CI) Total events: 187 (Higher PUFA	<b>1550</b> A), 203 (Lower PUFA)	1503	+	100.0 %	0.92 [ 0.76, 1.10 ]

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Study or subgroup	Higher PUFA	Lower PUFA	Risk Ratio M-	Weight	( Continued Risk Ratio M-
	n/N	n/N	H,Random,95% Cl		H,Random,9 Cl
Heterogeneity: Tau <sup>2</sup> = 0.0; Ch					G
Test for overall effect: $Z = 0.9$	,				
4 Low summary risk of bias					
AlphaOmega - ALA	66/2409	72/2428		100.0 %	0.92 [ 0.66, 1.28 ]
Subtotal (95% CI)	2409	2428	•	100.0 %	0.92 [ 0.66, 1.28 ]
Total events: 66 (Higher PUFA	N), 72 (Lower PUFA)				
Heterogeneity: not applicable					
Test for overall effect: $Z = 0.4$	7 (P = 0.64)				
5 Trials registry or pre-2010 AlphaOmega - ALA	66/2409	72/2428	-	22.5 %	0.92 [ 0.66, 1.28 ]
Brox 2001 (7)	0/80	1/40		0.2 %	0.17 [ 0.01, 4.05 ]
DART fat 1989	162/1018	178/1015		64.6 %	0.91 [ 0.75, 1.10 ]
Doi 2014 (8)	0/119	2/119		0.3 %	0.20 [ 0.01, 4.12 ]
FAAT - Leaf 2005 (9)	9/200	9/202	+	3.0 %	1.01 [ 0.41, 2.49 ]
HARP- Sacks 1995	0/41	1/39		0.2 %	0.32 [ 0.01, 7.57 ]
Raitt 2005	2/100	5/100	<del></del>	0.9 %	0.40 [ 0.08, 2.01 ]
Rose 1965	2/28	1/26		0.4 %	1.86 [ 0.18, 19.29 ]
Veterans Admin 1969	23/424	23/422	-	7.7 %	1.00 [ 0.57, 1.75 ]
Subtotal (95% CI)	4419	4391	•	100.0 %	0.91 [ 0.78, 1.06 ]
Fotal events: 264 (Higher PUF Heterogeneity: Tau <sup>2</sup> = 0.0; Ch Fest for overall effect: Z = 1.2 5 No industry funding	$ii^2 = 3.98, df = 8 (P = 0)$	0.86); I <sup>2</sup> =0.0%			
Brox 2001 (10)	0/80	1/40		12.4 %	0.17 [ 0.01, 4.05 ]
FAAT - Leaf 2005 (11)	9/200	9/202	- <b></b> -	87.6 %	1.01 [ 0.41, 2.49 ]
Subtotal (95% CI)	280	242	-	100.0 %	0.81 [ 0.25, 2.58 ]
Fotal events: 9 (Higher PUFA) Heterogeneity: Tau <sup>2</sup> = 0.19; C Fest for overall effect: Z = 0.30 7 Randomised 100+ participal	$Chi^2 = 1.13$ , $df = 1$ (P = 6 (P = 0.72)	0.29); I <sup>2</sup> =12%			
AlphaOmega - ALA	66/2409	72/2428	+	22.7 %	0.92 [ 0.66, 1.28 ]
Brox 2001 (12)	0/80	1/40		0.2 %	0.17 [ 0.01, 4.05 ]
DART fat 1989	162/1018	178/1015	=	65.1 %	0.91 [ 0.75, 1.10 ]
Doi 2014 (13)	0/119	2/119		0.3 %	0.20 [ 0.01, 4.12 ]
FAAT - Leaf 2005 (14)	9/200	9/202	+	3.0 %	1.01 [ 0.41, 2.49 ]
Raitt 2005	2/100	5/100		0.9 %	0.40 [ 0.08, 2.01 ]
			0.01 0.1 1 10 100 rs higher PUFA Favours lower 1	PUFA	(Continued

(Continued . . . )

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Study or subgroup	Higher PUFA	Lower PUFA	Risk Ratio M-	Weight	( Continued) Risk Ratio M-
	n/N	n/N	H,Random,95% Cl		H,Random,95% Cl
Veterans Admin 1969	23/424	23/422	-	7.8 %	1.00 [ 0.57, 1.75 ]
Subtotal (95% CI)	4350	4326	•	100.0 %	0.91 [ 0.77, 1.06 ]
Total events: 262 (Higher PUF	A), 290 (Lower PUFA)				
Heterogeneity: Tau <sup>2</sup> = 0.0; Ch	ni <sup>2</sup> = 3.20, df = 6 (P = 0	0.78); I <sup>2</sup> =0.0%			
Test for overall effect: $Z = 1.2$	3 (P = 0.22)				
8 Randomised 250+ participa	nts				
AlphaOmega - ALA	66/2409	72/2428	+	23.0 %	0.92 [ 0.66, 1.28 ]
DART fat 1989	162/1018	178/1015	-	66.1 %	0.91 [ 0.75, 1.10 ]
FAAT - Leaf 2005 (15)	9/200	9/202		3.1 %	1.01 [ 0.41, 2.49 ]
Veterans Admin 1969	23/424	23/422	+	7.9 %	1.00 [ 0.57, 1.75 ]
Subtotal (95% CI)	4051	4067	•	100.0 %	0.92 [ 0.79, 1.08 ]
Total events: 260 (Higher PUF	A), 282 (Lower PUFA)				
Heterogeneity: Tau <sup>2</sup> = 0.0; Ch	$hi^2 = 0.14, df = 3 (P = 0.14)$	0.99); l <sup>2</sup> =0.0%			
Test for overall effect: $Z = 1.0$	2 (P = 0.31)				

Favours higher PUFA Favours lower PUFA

(I) Fatal MI

(2) Cardiac deaths

(3) Fatal MI

(4) Fatal MI/ sudden death

(5) Cardiac deaths

(6) Fatal MI

(7) Fatal MI

(8) Fatal MI/ sudden death

(9) Cardiac deaths

(10) Fatal MI

(II) Cardiac deaths

(12) Fatal MI

(13) Fatal MI/ sudden death

(14) Cardiac deaths

(15) Cardiac deaths

# Analysis 2.27. Comparison 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes, Outcome 27 CHD mortality - SA fixed-effect.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes

Outcome: 27 CHD mortality - SA fixed-effect

Study or subgroup	Higher PUFA n/N	Lower PUFA n/N	Risk Ratio M-H,Fixed,95% Cl	Weight	Risk Ratio M-H,Fixed,95% Cl
AlphaOmega - ALA	66/2409	72/2428	+	24.4 %	0.92 [ 0.66, 1.28 ]
Brox 2001 (1)	0/80	1/40		0.7 %	0.17[0.01,4.05]
DART fat 1989	162/1018	178/1015	=	60.6 %	0.91 [ 0.75, 1.10 ]
Doi 2014 (2)	0/119	2/119		0.9 %	0.20 [ 0.01, 4.12 ]
FAAT - Leaf 2005 (3)	9/200	9/202		3.0 %	1.01 [ 0.41, 2.49 ]
HARP- Sacks 1995	0/41	1/39		0.5 %	0.32 [ 0.01, 7.57 ]
Raitt 2005	2/100	5/100		1.7 %	0.40 [ 0.08, 2.01 ]
Rose 1965	2/28	1/26		0.4 %	1.86 [ 0.18, 19.29 ]
Veterans Admin 1969	23/424	23/422	+	7.8 %	1.00 [ 0.57, 1.75 ]
<b>Total (95% CI)</b> Total events: 264 (Higher PUF Heterogeneity: $Chi^2 = 3.98$ , d Test for overall effect: $Z = 1.2$ Test for subgroup differences:	$f = 8 (P = 0.86); I^2 = 0.00$ 9 (P = 0.20)	<b>4391</b>	•	100.0 %	0.90 [ 0.77, 1.05 ]
			0.01 0.1 1 10 100		

Favours higher PUFA

Favours lower PUFA

(I) Fatal MI

-

(2) Fatal MI/ sudden death

(3) Cardiac deaths

# Analysis 2.28. Comparison 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes, Outcome 28 CHD mortality - subgroup by PUFA dose.

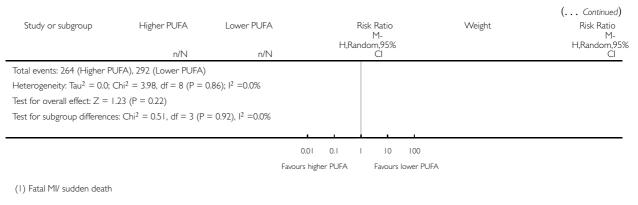
Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes

Outcome: 28 CHD mortality - subgroup by PUFA dose

	Higher PUFA	Lower PUFA	Risk Ratio M-	0	Μ
	n/N	n/N	H,Random,95% Cl		H,Random, C
l total PUFA < 1.0% E					
Doi 2014 (1)	0/119	2/119		0.3 %	0.20 [ 0.01, 4.12 ]
FAAT - Leaf 2005 (2)	9/200	9/202	<u> </u>	3.0 %	1.01 [ 0.41, 2.49
Raitt 2005	2/100	5/100	<del></del>	0.9 %	0.40 [ 0.08, 2.01
Subtotal (95% CI)	419	421	-	4.2 %	0.74 [ 0.35, 1.59
Total events: 11 (Higher PUF/ Heterogeneity: Tau <sup>2</sup> = 0.0; Cl	, , , ,	0.42); I <sup>2</sup> =0.0%			
Test for overall effect: $Z = 0.7$	· · · ·				
2 total PUFA 1.0 to < 2.0% E AlphaOmega - ALA	66/2409	72/2428	+	22.5 %	0.92 [ 0.66, 1.28
Brox 2001 (3)	0/80	1/40		0.2 %	0.17 [ 0.01, 4.05
Total events: 66 (Higher PUF) Heterogeneity: Tau <sup>2</sup> = 0.12; ( Test for overall effect: $Z = 0.4$	$Chi^2 = 1.09, df = 1 (P = 14 (P = 0.66))$	<b>2468</b> : 0.30); I <sup>2</sup> =8%	•	22.8 %	0.85   0.41, 1.76
Total events: 66 (Higher PUF)	A), 73 (Lower PUFA)		•	22.8 %	0.85 [ 0.41, 1.76
Total events: 66 (Higher PUF) Heterogeneity: Tau <sup>2</sup> = 0.12; ( Test for overall effect: $Z = 0.4$	A), 73 (Lower PUFA) Chi <sup>2</sup> = 1.09, df = 1 (P = 14 (P = 0.66)		•	22.8 %	0.85   0.41, 1.76
Total events: 66 (Higher PUF, Heterogeneity: Tau <sup>2</sup> = 0.12; ( Test for overall effect: Z = 0.4	A), 73 (Lower PUFA) Chi <sup>2</sup> = 1.09, df = 1 (P = 14 (P = 0.66)		•	<b>22.8 %</b> 64.6 %	
Total events: 66 (Higher PUF, Heterogeneity: Tau <sup>2</sup> = 0.12; 0 Test for overall effect: Z = 0.4 3 total PUFA 2.0 to < 5.0% E	A), 73 (Lower PUFA) Chi <sup>2</sup> = 1.09, df = 1 (P = 14 (P = 0.66)	0.30); I <sup>2</sup> =8%	•		0.91 [ 0.75, 1.10
Total events: 66 (Higher PUF, Heterogeneity: Tau <sup>2</sup> = 0.12; ( Test for overall effect: Z = 0.4 3 total PUFA 2.0 to < 5.0% E DART fat 1989 HARP- Sacks 1995	A), 73 (Lower PUFA) Chi <sup>2</sup> = 1.09, df = 1 (P = 14 (P = 0.66) 162/1018	0.30); l <sup>2</sup> =8%		64.6 %	0.91 [ 0.75, 1.10
Total events: 66 (Higher PUF, Heterogeneity: Tau <sup>2</sup> = 0.12; 0 Test for overall effect: Z = 0.4 3 total PUFA 2.0 to < 5.0% E DART fat 1989 HARP- Sacks 1995 Subtotal (95% CI) Total events: 162 (Higher PU	A), 73 (Lower PUFA) Chi <sup>2</sup> = 1.09, df = 1 (P = 44 (P = 0.66) 162/1018 0/41 <b>1059</b> FA), 179 (Lower PUFA)	0.30); l <sup>2</sup> =8% 178/1015 1/39 <b>1054</b>		64.6 % 0.2 %	0.91 [ 0.75, 1.10
Total events: 66 (Higher PUF, Heterogeneity: Tau <sup>2</sup> = 0.12; 0 Test for overall effect: Z = 0.4 3 total PUFA 2.0 to < 5.0% E DART fat 1989 HARP- Sacks 1995 <b>Subtotal (95% CI)</b> Total events: 162 (Higher PUI Heterogeneity: Tau <sup>2</sup> = 0.0; CI Test for overall effect: Z = 1.0	A), 73 (Lower PUFA) Chi <sup>2</sup> = 1.09, df = 1 (P = 14 (P = 0.66) 162/1018 0/41 <b>1059</b> FA), 179 (Lower PUFA) hi <sup>2</sup> = 0.42, df = 1 (P = 1)	0.30); l <sup>2</sup> =8% 178/1015 1/39 <b>1054</b>	•	64.6 % 0.2 %	0.91 [ 0.75, 1.10
Total events: 66 (Higher PUF, Heterogeneity: Tau <sup>2</sup> = 0.12; 0 Test for overall effect: Z = 0.4 3 total PUFA 2.0 to < 5.0% E DART fat 1989 HARP- Sacks 1995 <b>Subtotal (95% CI)</b> Total events: 162 (Higher PUI Heterogeneity: Tau <sup>2</sup> = 0.0; CI Test for overall effect: Z = 1.0	A), 73 (Lower PUFA) Chi <sup>2</sup> = 1.09, df = 1 (P = 14 (P = 0.66) 162/1018 0/41 <b>1059</b> FA), 179 (Lower PUFA) hi <sup>2</sup> = 0.42, df = 1 (P = 1)	0.30); l <sup>2</sup> =8% 178/1015 1/39 <b>1054</b>		64.6 % 0.2 %	0.91 [ 0.75, 1.10 0.32 [ 0.01, 7.57 <b>0.90 [ 0.74, 1.10</b>
Total events: 66 (Higher PUF, Heterogeneity: Tau <sup>2</sup> = 0.12; 0 Test for overall effect: Z = 0.4 3 total PUFA 2.0 to < 5.0% E DART fat 1989 HARP- Sacks 1995 <b>Subtotal (95% CI)</b> Total events: 162 (Higher PUI Heterogeneity: Tau <sup>2</sup> = 0.0; CI Test for overall effect: Z = 1.0 4 total PUFA > 5.0% E	A), 73 (Lower PUFA) Chi <sup>2</sup> = 1.09, df = 1 (P = 14 (P = 0.66) 162/1018 0/41 <b>1059</b> FA), 179 (Lower PUFA) hi <sup>2</sup> = 0.42, df = 1 (P = 1) 02 (P = 0.31)	178/1015 1/39 <b>1054</b> 0.52); l <sup>2</sup> =0.0%		64.6 % 0.2 % <b>64.9 %</b>	0.91 [ 0.75, 1.10 0.32 [ 0.01, 7.57 <b>0.90 [ 0.74, 1.10</b> 1.86 [ 0.18, 19.29
Total events: 66 (Higher PUF, Heterogeneity: Tau <sup>2</sup> = 0.12; 0 Test for overall effect: Z = 0.4 3 total PUFA 2.0 to < 5.0% E DART fat 1989 HARP- Sacks 1995 <b>Subtotal (95% CI)</b> Total events: 162 (Higher PUI Heterogeneity: Tau <sup>2</sup> = 0.0; CI Test for overall effect: Z = 1.0 4 total PUFA > 5.0% E Rose 1965 Veterans Admin 1969	A), 73 (Lower PUFA) Chi <sup>2</sup> = 1.09, df = 1 (P = 14 (P = 0.66) 162/1018 0/41 <b>1059</b> FA), 179 (Lower PUFA) hi <sup>2</sup> = 0.42, df = 1 (P = 0) 22 (P = 0.31) 2/28	178/1015 1/39 <b>1054</b> 0.52); I <sup>2</sup> =0.0%		64.6 % 0.2 % <b>64.9 %</b> 0.4 %	0.91 [ 0.75, 1.10 0.32 [ 0.01, 7.57 <b>0.90 [ 0.74, 1.10</b> 1.86 [ 0.18, 19.29 1.00 [ 0.57, 1.75
Total events: 66 (Higher PUF, Heterogeneity: Tau <sup>2</sup> = 0.12; 0 Test for overall effect: Z = 0.4 3 total PUFA 2.0 to < 5.0% E DART fat 1989 HARP- Sacks 1995 <b>Subtotal (95% CI)</b> Total events: 162 (Higher PUI Heterogeneity: Tau <sup>2</sup> = 0.0; CI Test for overall effect: Z = 1.0 4 total PUFA > 5.0% E Rose 1965 Veterans Admin 1969 <b>Subtotal (95% CI)</b> Total events: 25 (Higher PUF,	A), 73 (Lower PUFA) Chi <sup>2</sup> = 1.09, df = 1 (P = 14 (P = 0.66) 162/1018 0/41 <b>1059</b> FA), 179 (Lower PUFA) hi <sup>2</sup> = 0.42, df = 1 (P = 1) 2 (P = 0.31) 2/28 23/424 <b>452</b> A), 24 (Lower PUFA)	178/1015 1/39 <b>1054</b> 0.52); 1 <sup>2</sup> =0.0% 1/26 23/422 <b>448</b>		64.6 % 0.2 % <b>64.9 %</b> 0.4 % 7.7 %	0.91 [ 0.75, 1.10 0.32 [ 0.01, 7.57 <b>0.90 [ 0.74, 1.10</b> 1.86 [ 0.18, 19.29 1.00 [ 0.57, 1.75
HARP- Sacks 1995 <b>Subtotal (95% CI)</b> Total events: 162 (Higher PUI Heterogeneity: Tau <sup>2</sup> = 0.0; CI Test for overall effect: Z = 1.0 4 total PUFA > 5.0% E Rose 1965	A), 73 (Lower PUFA) Chi <sup>2</sup> = 1.09, df = 1 (P = 14 (P = 0.66) 162/1018 0/41 <b>1059</b> FA), 179 (Lower PUFA) hi <sup>2</sup> = 0.42, df = 1 (P = 1) 2/28 23/424 <b>452</b> A), 24 (Lower PUFA) hi <sup>2</sup> = 0.26, df = 1 (P = 1)	178/1015 1/39 <b>1054</b> 0.52); 1 <sup>2</sup> =0.0% 1/26 23/422 <b>448</b>		64.6 % 0.2 % <b>64.9 %</b> 0.4 % 7.7 %	0.85 [ 0.41, 1.76 0.91 [ 0.75, 1.10 0.32 [ 0.01, 7.57 0.90 [ 0.74, 1.10 1.86 [ 0.18, 19.29 1.00 [ 0.57, 1.75 1.03 [ 0.60, 1.78 0.91 [ 0.78, 1.06

(Continued . . . )



(2) Cardiac deaths

(3) Fatal MI

## Analysis 2.29. Comparison 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes, Outcome 29 CHD mortality - subgroup by duration.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes

Outcome: 29 CHD mortality - subgroup by duration

Study or subgroup	Higher PUFA	Lower PUFA	Risk Ratio	Weight	Risk Ratio M-
	n/N	n/N	H,Random,95% Cl		H,Random,95% Cl
I Medium duration I to < 2	years				
Brox 2001 (1)	0/80	1/40		0.2 %	0.17 [ 0.01, 4.05 ]
Doi 2014 (2)	0/119	2/119		0.3 %	0.20 [ 0.01, 4.12 ]
FAAT - Leaf 2005 (3)	9/200	9/202		3.0 %	1.01 [ 0.41, 2.49 ]
Subtotal (95% CI)	399	361	+	3.5 %	0.78 [ 0.34, 1.83 ]
Total events: 9 (Higher PUFA	A), 12 (Lower PUFA)				
Heterogeneity: $Tau^2 = 0.01$ ;	Chi <sup>2</sup> = 2.01, df = 2 (P =	: 0.37); l <sup>2</sup> = l %			
Test for overall effect: $Z = 0$ .	.56 (P = 0.57)				
2 Medium-long duration 2 to	o < 4 years				
AlphaOmega - ALA	66/2409	72/2428	+	22.5 %	0.92 [ 0.66, 1.28 ]
DART fat 1989	162/1018	178/1015	•	64.6 %	0.91 [ 0.75, 1.10 ]
			0.01 0.1 1 10 100		
			Favours higher PUFA Favours lower PUFA		

(Continued . . . )

( Continued) Risk Ratio H,Random,959 Cl	Weight	Risk Ratio M- H,Random,95%	Lower PUFA	Higher PUFA	Study or subgroup
0.32 [ 0.01, 7.57 ]	0.2 %		1/39	0/41	HARP- Sacks 1995
0.40 [ 0.08, 2.01 ]	0.9 %		5/100	2/100	Raitt 2005
1.86 [ 0.18, 19.29 ]	0.4 %	<b>.</b>	1/26	2/28	Rose 1965
0.90 [ 0.77, 1.07 ]	88.8 %	•	3608	3596	Subtotal (95% CI)
				A), 257 (Lower PUFA)	Total events: 232 (Higher PUF
			8); I <sup>2</sup> =0.0%	$mi^2 = 1.78$ , df = 4 (P = 0.1)	Heterogeneity: $Tau^2 = 0.0$ ; Ch
				9 (P = 0.23)	Test for overall effect: $Z = 1.1$
					3 Long duration 4+ years
1.00 [ 0.57, 1.75 ]	7.7 %	-	23/422	23/424	Veterans Admin 1969
1.00 [ 0.57, 1.75 ]	7.7 %	+	422	424	Subtotal (95% CI)
				A), 23 (Lower PUFA)	Total events: 23 (Higher PUFA
					Heterogeneity: not applicable
				2 (P = 0.99)	Test for overall effect: $Z = 0.0$
0.91 [ 0.78, 1.06 ]	100.0 %	•	4391	4419	Total (95% CI)
				FA), 292 (Lower PUFA)	Total events: 264 (Higher PUF
			6); l <sup>2</sup> =0.0%	$m^2 = 3.98$ , df = 8 (P = 0.1)	Heterogeneity: $Tau^2 = 0.0$ ; Ch
				3 (P = 0.22)	Test for overall effect: Z = 1.2
			0.90), I <sup>2</sup> =0.0%	Chi <sup>2</sup> = 0.22, df = 2 (P =	Test for subgroup differences:

0.01 0.1 1 10 10

Favours higher PUFA Favours lower PUFA

(I) Fatal MI

(2) Fatal MI/ sudden death

(3) Cardiac deaths

### Analysis 2.30. Comparison 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes, Outcome 30 CHD mortality - subgroup by primary or secondary prevention.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes

Outcome: 30 CHD mortality - subgroup by primary or secondary prevention

Study or subgroup	Higher PUFA	Lower PUFA	Risk Ratio M-	Weight	Risk Ratio
	n/N	n/N	H,Random,95% Cl		H,Random,959 Cl
I Primary prevention of CVD					
Brox 2001 (1)	0/80	1/40		0.2 %	0.17 [ 0.01, 4.05 ]
Veterans Admin 1969	23/424	23/422	+	7.7 %	1.00 [ 0.57, 1.75 ]
Subtotal (95% CI)	504	462	-	8.0 %	0.84 [ 0.30, 2.34 ]
Total events: 23 (Higher PUFA	A), 24 (Lower PUFA)				
Heterogeneity: Tau <sup>2</sup> = 0.22; (	$Chi^2 = 1.16, df = 1 (P = 1)$	= 0.28);   <sup>2</sup> =   4%			
Test for overall effect: $Z = 0.3$	4 (P = 0.74)				
2 Secondary prevention of C					
AlphaOmega - ALA	66/2409	72/2428	-	22.5 %	0.92 [ 0.66, 1.28 ]
DART fat 1989	162/1018	178/1015	•	64.6 %	0.91 [ 0.75, 1.10 ]
Doi 2014 (2)	0/119	2/119		0.3 %	0.20 [ 0.01, 4.12 ]
FAAT - Leaf 2005 (3)	9/200	9/202		3.0 %	1.01 [ 0.41, 2.49 ]
HARP- Sacks 1995	0/41	1/39		0.2 %	0.32 [ 0.01, 7.57 ]
Raitt 2005	2/100	5/100		0.9 %	0.40 [ 0.08, 2.01 ]
Rose 1965	2/28	1/26		0.4 %	1.86 [ 0.18, 19.29 ]
Subtotal (95% CI)	3915	3929	•	<b>92.0</b> %	0.90 [ 0.77, 1.06 ]
Total events: 241 (Higher PUF	FA), 268 (Lower PUFA)				
Heterogeneity: $Tau^2 = 0.0$ ; Ch	$hi^2 = 2.79, df = 6 (P =$	0.83); l <sup>2</sup> =0.0%			
Test for overall effect: $Z = 1.2$	( )				
Total (95% CI)	4419	4391	1	100.0 %	0.91 [ 0.78, 1.06 ]
Total events: 264 (Higher PUF	, , ,				
Heterogeneity: $Tau^2 = 0.0$ ; Ch		0.86); l <sup>2</sup> =0.0%			
Test for overall effect: Z = 1.2 Test for subgroup differences:	( )				

0.01 0.1 I 10 100 Favours higher PUFA Favours lower PUFA

(I) Fatal MI

(2) Fatal MI/ sudden death

(3) Cardiac deaths

# Analysis 2.31. Comparison 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes, Outcome 31 CHD mortality - subgroup by baseline PUFA dose.

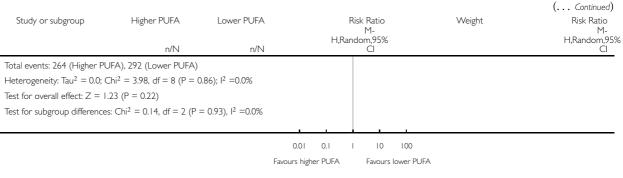
Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes

Outcome: 31 CHD mortality - subgroup by baseline PUFA dose

Study or subgroup	Higher PUFA	Lower PUFA	Risk Ratio M-	Weight	Risk Ratio M-
	n/N	n/N	H,Random,95% Cl		H,Random,S Cl
I Baseline total PUFA < 6% E					
Veterans Admin 1969	23/424	23/422	+	7.7 %	1.00 [ 0.57, 1.75 ]
Subtotal (95% CI)	424	422	+	7.7 %	1.00 [ 0.57, 1.75 ]
Total events: 23 (Higher PUFA	A), 23 (Lower PUFA)				
Heterogeneity: not applicable					
Test for overall effect: Z = 0.0 2 Baseline total PUFA 6 to <	( )				
DART fat 1989	162/1018	178/1015	-	64.6 %	0.91 [ 0.75, 1.10 ]
Subtotal (95% CI)	1018	1015	•	<b>64.6</b> %	0.91 [ 0.75, 1.10 ]
Total events: 162 (Higher PUF	FA), 178 (Lower PUFA)	-			
Heterogeneity: not applicable					
Test for overall effect: $Z = 0.9$	, ,				
3 Baseline total PUFA 11+% [		0			N
<b>Subtotal (95% CI)</b> Total events: 0 (Higher PUFA)		0			Not estimable
Heterogeneity: not applicable					
Test for overall effect: not app					
4 Baseline total PUFA unclear					
AlphaOmega - ALA	66/2409	72/2428	+	22.5 %	0.92 [ 0.66, 1.28 ]
Brox 2001 (1)	0/80	1/40		0.2 %	0.17 [ 0.01, 4.05 ]
Doi 2014 (2)	0/119	2/119		0.3 %	0.20 [ 0.01, 4.12 ]
FAAT - Leaf 2005 (3)	9/200	9/202		3.0 %	1.01 [ 0.41, 2.49 ]
HARP- Sacks 1995	0/41	1/39		0.2 %	0.32 [ 0.01, 7.57 ]
Raitt 2005	2/100	5/100		0.9 %	0.40 [ 0.08, 2.01 ]
Rose 1965	2/28	1/26	<b>·</b>	0.4 %	1.86 [ 0.18, 19.29 ]
Subtotal (95% CI)	2977	2954	+	27.6 %	0.88 [ 0.66, 1.19 ]
Total events: 79 (Higher PLIE)	A), 91 (Lower PUFA)				
	2 - 2 0 4 Jf - ( /D -	0.70); l <sup>2</sup> =0.0%			
Heterogeneity: Tau <sup>2</sup> = 0.0; Cf Test for overall effect: $Z = 0.8$					

(Continued . . . )



(I) Fatal MI

(2) Fatal MI/ sudden death

(3) Cardiac deaths

### Analysis 2.32. Comparison 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes, Outcome 32 CHD mortality - subgroup by replacement.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes

Outcome: 32 CHD mortality - subgroup by replacement

Study or subgroup	Higher PUFA	Lower PUFA	Risk Ratio M-	Weight	Risk Ratio M-
	n/N	n/N	H,Random,95% Cl		H,Random,95% Cl
I PUFA replaced saturated fa	ts				
DART fat 1989	162/1018	178/1015	+	89.3 %	0.91 [ 0.75, 1.10 ]
Veterans Admin 1969	23/424	23/422	+	10.7 %	1.00 [ 0.57, 1.75 ]
Subtotal (95% CI)	1442	1437	•	100.0 %	0.92 [ 0.76, 1.10 ]
Total events: 185 (Higher PU	FA), 201 (Lower PUFA)	)			
Heterogeneity: $Tau^2 = 0.0$ ; C	$hi^2 = 0.09, df = 1 (P =$	0.76); l <sup>2</sup> =0.0%			
Test for overall effect: $Z = 0.9$	93 (P = 0.35)				
2 PUFA replaced monounsat	urated fats				
AlphaOmega - ALA	66/2409	72/2428	-	64.6 %	0.92 [ 0.66, 1.28 ]
FAAT - Leaf 2005 (1)	9/200	9/202		8.6 %	1.01 [ 0.41, 2.49 ]
HARP- Sacks 1995	0/41	1/39		0.7 %	0.32 [ 0.01, 7.57 ]
			0.01 0.1 1 10 100		
		Fa	avours higher PUFA Favours lower	PUFA	(Continued)

(Continued . . . )

( Continued Risk Ratio	Weight	Risk Ratio	Lower PUFA	Higher PUFA	Study or subgroup	
M- H,Random,95 Cl		M- H,Random,95% Cl	n/N	H,Random,95%	n/N	
0.40 [ 0.08, 2.01 ]	2.7 %		5/100	2/100	Raitt 2005	
1.86 [ 0.18, 19.29 ]	1.3 %	<u> </u>	1/26	2/28	Rose 1965	
1.00 [ 0.57, 1.75 ]	22.2 %	+	23/422	23/424	Veterans Admin 1969	
0.93 [ 0.71, 1.21 ]	100.0 %	•	3217	3202	Subtotal (95% CI)	
				A), III (Lower PUFA)	Total events: 102 (Higher PUF/	
			.86); I <sup>2</sup> =0.0%	$hi^2 = 1.91, df = 5 (P = 0)$	Heterogeneity: $Tau^2 = 0.0$ ; Chi	
				6 (P = 0.57)	Test for overall effect: $Z = 0.56$	
				es	3 PUFA replaced carbohydrate	
1.86 [ 0.18, 19.29 ]	100.0 %		1/26	2/28	Rose 1965	
1.86 [ 0.18, 19.29 ]	100.0 %		26	28	Subtotal (95% CI)	
				, I (Lower PUFA)	Total events: 2 (Higher PUFA),	
					Heterogeneity: not applicable	
				2 (P = 0.60)	Test for overall effect: Z = 0.52	
					4 PUFA replaced protein	
Not estimable			0	0	Subtotal (95% CI)	
				, 0 (Lower PUFA)	Total events: 0 (Higher PUFA),	
					Heterogeneity: not applicable	
				licable	Test for overall effect: not appli	
					5 PUFA replaced unclear	
0.17 [ 0.01, 4.05 ]	47.5 %		1/40	0/80	Brox 2001 (2)	
0.20 [ 0.01, 4.12 ]	52.5 %		2/119	0/119	Doi 2014 (3)	
0.18 [ 0.02, 1.65 ]	100.0 %		159	199	Subtotal (95% CI)	
				, 3 (Lower PUFA)	Total events: 0 (Higher PUFA),	
			.94); I <sup>2</sup> =0.0%	$m^2 = 0.01$ , $df = 1$ (P = 0	Heterogeneity: $Tau^2 = 0.0$ ; Chi	
				I (P = 0.13)	Test for overall effect: $Z = 1.51$	
			= 0.49), I <sup>2</sup> =0.0%	$Chi^2 = 2.4I, df = 3 (P$	Test for subgroup differences: (	

0.01 0.1 I 10 100 Favours higher PUFA Favours lower PUFA

(I) Cardiac deaths

(2) Fatal MI

(3) Fatal MI/ sudden death

# Analysis 2.33. Comparison 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes, Outcome 33 CHD mortality - subgroup by sex.

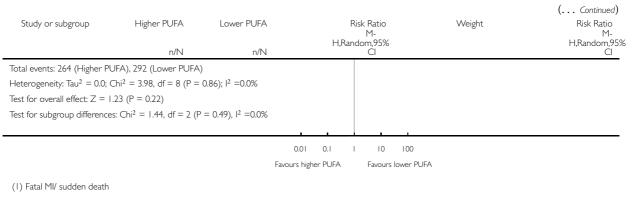
Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes

Outcome: 33 CHD mortality - subgroup by sex

Study or subgroup	Higher PUFA	Lower PUFA	Risk Ratio M-	Weight	Risk Ratio M-
	n/N	n/N	H,Random,95% Cl		H,Random,95 Cl
> 70% men					
AlphaOmega - ALA	66/2409	72/2428	+	22.5 %	0.92 [ 0.66, 1.28 ]
DART fat 1989	162/1018	178/1015	•	64.6 %	0.91 [ 0.75, 1.10 ]
Doi 2014 (1)	0/119	2/119		0.3 %	0.20 [ 0.01, 4.12 ]
FAAT - Leaf 2005 (2)	9/200	9/202	<u> </u>	3.0 %	1.01 [ 0.41, 2.49 ]
HARP- Sacks 1995	0/41	1/39		0.2 %	0.32 [ 0.01, 7.57 ]
Raitt 2005	2/100	5/100		0.9 %	0.40 [ 0.08, 2.01 ]
Veterans Admin 1969	23/424	23/422	+	7.7 %	1.00 [ 0.57, 1.75 ]
Subtotal (95% CI)	4311	4325	•	99.3 %	0.91 [ 0.78, 1.06 ]
Heterogeneity: Tau <sup>2</sup> = 0.0; Chi	<sup>2</sup> = 2.54, df = 6 (P =	0.86); l <sup>2</sup> =0.0%			
Test for overall effect: $Z = 1.21$	(P = 0.23)				
Test for overall effect: Z = 1.21 2 > 70% women <b>Subtotal (95% CI)</b> Total events: 0 (Higher PUFA), Heterogeneity: not applicable Test for overall effect: not appli	<b>0</b> 0 (Lower PUFA)	0			Not estimable
Test for overall effect: Z = 1.21 2 > 70% women Subtotal (95% CI) Total events: 0 (Higher PUFA), Heterogeneity: not applicable Test for overall effect: not appli 3 men % women Brox 2001 (3)	<b>0</b> 0 (Lower PUFA)	<b>0</b> 1/40		0.2 %	<b>Not estimable</b> 0.17 [ 0.01, 4.05 ]
Test for overall effect: Z = 1.21 2 > 70% women <b>Subtotal (95% CI)</b> Total events: 0 (Higher PUFA), Heterogeneity: not applicable Test for overall effect: not appli 3 men % women	0 0 (Lower PUFA) cable 0/80 <b>80</b> I (Lower PUFA)			0.2 % <b>0.2 %</b>	
Test for overall effect: Z = 1.21 2 > 70% women Subtotal (95% CI) Total events: 0 (Higher PUFA), Heterogeneity: not applicable Test for overall effect: not appli 3 men % women Brox 2001 (3) Subtotal (95% CI) Total events: 0 (Higher PUFA), Heterogeneity: not applicable Test for overall effect: Z = 1.10	0 0 (Lower PUFA) cable 0/80 <b>80</b> I (Lower PUFA)	1/40			0.17 [ 0.01, 4.05 ]
Test for overall effect: $Z = 1.21$ 2 > 70% women <b>Subtotal (95% CI)</b> Total events: 0 (Higher PUFA), Heterogeneity: not applicable Test for overall effect: not appli 3 men % women Brox 2001 (3) <b>Subtotal (95% CI)</b> Total events: 0 (Higher PUFA), Heterogeneity: not applicable Test for overall effect: $Z = 1.10$ 4 sex not reported	0 0 (Lower PUFA) cable 0/80 80 I (Lower PUFA) 2/28 28 I (Lower PUFA)	1/40 <b>40</b>		0.2 %	0.17 [ 0.01, 4.05 ] <b>0.17 [ 0.01, 4.05 ]</b>

(Continued . . . )



(2) Cardiac deaths

(3) Fatal MI

## Analysis 2.34. Comparison 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes, Outcome 34 CHD mortality - subgroup by age.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes

Outcome: 34 CHD mortality - subgroup by age

Study or subgroup	Higher PUFA	Lower PUFA	Risk Ratio M- H,Random,95%	Weight	Risk Ratio M- H,Random,95%
	n/N	n/N	CI		Cl
l Mean age < 50 years					
Subtotal (95% CI)	0	0			Not estimable
Total events: 0 (Higher PUFA	A), 0 (Lower PUFA)				
Heterogeneity: not applicabl	e				
Test for overall effect: not ap	oplicable				
2 Mean age 50 to < 65 year	rs				
Brox 2001 (1)	0/80	1/40		0.2 %	0.17 [ 0.01, 4.05 ]
DART fat 1989	162/1018	178/1015	-	64.6 %	0.91 [ 0.75, 1.10 ]
HARP- Sacks 1995	0/41	1/39		0.2 %	0.32 [ 0.01, 7.57 ]
Raitt 2005	2/100	5/100		0.9 %	0.40 [ 0.08, 2.01 ]
Rose 1965	2/28	1/26		0.4 %	1.86 [ 0.18, 19.29 ]
			0.01 0.1 1 10 100		
		Fav	vours higher PUFA Favours lower PU	IFA	
					(Continued)

(Continued . . . )

	Risk Ratio M- H,Random,95% Cl	Lower PUFA n/N	Higher PUFA n/N	Study or subgroup
66.5 %	•	1220	1267	Subtotal (95% CI)
			A), 186 (Lower PUFA)	Total events: 166 (Higher PUFA
		9); I <sup>2</sup> =0.0%	<sup>2</sup> = 2.82, df = 4 (P = 0.	Heterogeneity: Tau <sup>2</sup> = 0.0; Chi <sup>2</sup>
			(P = 0.24)	Test for overall effect: $Z = 1.16$
				3 Mean age 65+ years
22.5 %	+	72/2428	66/2409	AlphaOmega - ALA
0.3 %		2/119	0/119	Doi 2014 (2)
3.0 %		9/202	9/200	FAAT - Leaf 2005 (3)
7.7 %	+	23/422	23/424	Veterans Admin 1969
33.5 %	•	3171	3152	Subtotal (95% CI)
			), 106 (Lower PUFA)	Total events: 98 (Higher PUFA)
		8); I <sup>2</sup> =0.0%	$^{2} = 1.08$ , df = 3 (P = 0.7)	Heterogeneity: Tau <sup>2</sup> = 0.0; Chi <sup>2</sup>
			(P = 0.63)	Test for overall effect: $Z = 0.48$
100.0 %	•	4391	4419	Total (95% CI)
			A), 292 (Lower PUFA)	Total events: 264 (Higher PUFA
		6); I <sup>2</sup> =0.0%	<sup>2</sup> = 3.98, df = 8 (P = 0.8	Heterogeneity: Tau <sup>2</sup> = 0.0; Chi <sup>2</sup>
			(P = 0.22)	Test for overall effect: Z = 1.23
		0.78), I <sup>2</sup> =0.0%	$Chi^2 = 0.08, df = 1 (P =$	Test for subgroup differences: C
3.0 % 7.7 % <b>33.5 %</b>		9/202 23/422 <b>3171</b> 8); I <sup>2</sup> =0.0% <b>4391</b> 6); I <sup>2</sup> =0.0% 0.78), I <sup>2</sup> =0.0%	9/200 23/424 <b>3152</b> ), 106 (Lower PUFA) $^{2} = 1.08, df = 3 (P = 0.2)$ (P = 0.63) <b>4419</b> A), 292 (Lower PUFA) $^{2} = 3.98, df = 8 (P = 0.2)$ (P = 0.22)	-11 <sup>2</sup> -8 -7 -11 <sup>2</sup> -3

Favours higher PUFA Favours lower PUFA

(I) Fatal MI

(2) Fatal MI/ sudden death

(3) Cardiac deaths

#### Analysis 2.35. Comparison 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes, Outcome 35 CHD mortality - subgroup by statin use.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes

Outcome: 35 CHD mortality - subgroup by statin use

Study or subgroup	Higher PUFA	Lower PUFA	Risk Ratio M-	Weight	Risk Ratic M
	n/N	n/N	H,Random,95% Cl		H,Random, C
I < 50% on statins					
Brox 2001 (1)	0/80	1/40		0.2 %	0.17 [ 0.01, 4.05 ]
DART fat 1989	162/1018	178/1015	-	64.6 %	0.91 [ 0.75, 1.10]
HARP- Sacks 1995	0/41	1/39		0.2 %	0.32 [ 0.01, 7.57 ]
Raitt 2005	2/100	5/100		0.9 %	0.40 [ 0.08, 2.01 ]
Rose 1965	2/28	1/26		0.4 %	1.86 [ 0.18, 19.29 ]
Veterans Admin 1969	23/424	23/422	+	7.7 %	1.00 [ 0.57, 1.75
Subtotal (95% CI)	1691	1642	•	74.2 %	0.90 [ 0.75, 1.08 ]
Heterogeneity: Tau <sup>2</sup> = 0.0; Ch Test for overall effect: Z = 1.11 2 50+% on statins	I (P = 0.27)	<i>.</i>			
AlphaOmega - ALA	66/2409	72/2428	+	22.5 %	0.92 [ 0.66, 1.28
Doi 2014 (2)	0/119	2/119		0.3 %	0.20 [ 0.01, 4.12
Subtotal (95% CI)	2528	2547	•	22.8 %	0.91 [ 0.65, 1.26]
Total events: 66 (Higher PUFA Heterogeneity: Tau <sup>2</sup> = 0.0; Ch Test for overall effect: Z = 0.58 3 Percentage on statins unclea	$i^2 = 0.97$ , df = 1 (P = 3 (P = 0.56)	0.32); I <sup>2</sup> =0.0%			
FAAT - Leaf 2005 (3)	9/200	9/202		3.0 %	1.01 [ 0.41, 2.49
Subtotal (95% CI)	200	202	+	3.0 %	1.01 [ 0.41, 2.49 ]
Total events: 9 (Higher PUFA), Heterogeneity: not applicable Test for overall effect: Z = 0.02	· · · · · ·				
Total (95% CI)	4419	4391	•	100.0 %	0.91 [ 0.78, 1.06
Total events: 264 (Higher PUF, Heterogeneity: Tau <sup>2</sup> = 0.0; Ch Test for overall effect: Z = 1.23	$i^2 = 3.98$ , df = 8 (P = 3 (P = 0.22)				

(I) Fatal MI

(2) Fatal MI/ sudden death

(3) Cardiac deaths

## Analysis 2.36. Comparison 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes, Outcome 36 CHD mortality - subgroup by intervention type.

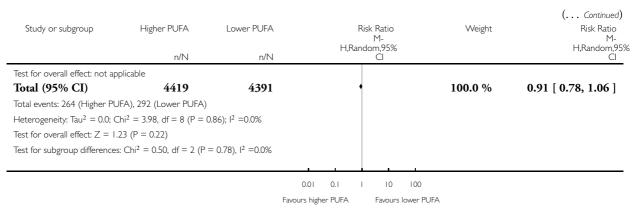
Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes

Outcome: 36 CHD mortality - subgroup by intervention type

Study or subgroup	Higher PUFA	Lower PUFA	Risk Ratio M-	Weight	Risk Ratio M-
	n/N	n/N	H,Random,95% Cl		H,Random,95 Cl
I Dietary advice					
DART fat 1989	162/1018	178/1015	-	64.6 %	0.91 [ 0.75, 1.10 ]
Subtotal (95% CI)	1018	1015	•	64.6 %	0.91 [ 0.75, 1.10 ]
Total events: 162 (Higher PU	IFA), 178 (Lower PUFA)				
Heterogeneity: not applicable	2				
Test for overall effect: $Z = 0.9$	98 (P = 0.33)				
2 Supplemental foods % diet					
AlphaOmega - ALA	66/2409	72/2428	-	22.5 %	0.92 [ 0.66, 1.28 ]
Veterans Admin 1969	23/424	23/422	+	7.7 %	1.00 [ 0.57, 1.75 ]
Subtotal (95% CI)	2833	2850	+	30.2 %	0.94 [ 0.71, 1.25 ]
Total events: 89 (Higher PUF	A), 95 (Lower PUFA)				
Heterogeneity: Tau <sup>2</sup> = 0.0; C	$2hi^2 = 0.05$ , $df = 1$ (P =	0.82); l <sup>2</sup> =0.0%			
Test for overall effect: $Z = 0.4$	41 (P = 0.68)				
3 Supplements (capsules % u	inusual foods)				
Brox 2001 (1)	0/80	1/40		0.2 %	0.17 [ 0.01, 4.05 ]
Doi 2014 (2)	0/119	2/119		0.3 %	0.20 [ 0.01, 4.12 ]
FAAT - Leaf 2005 (3)	9/200	9/202		3.0 %	1.01 [ 0.41, 2.49 ]
HARP- Sacks 1995	0/41	1/39		0.2 %	0.32 [ 0.01, 7.57 ]
Raitt 2005	2/100	5/100	<b>·</b>	0.9 %	0.40 [ 0.08, 2.01 ]
Rose 1965	2/28	1/26	<b>·</b>	0.4 %	1.86 [ 0.18, 19.29 ]
Subtotal (95% CI)	568	526	-	5.1 %	0.72 [ 0.36, 1.43 ]
Total events: 13 (Higher PUF	A), 19 (Lower PUFA)				
Heterogeneity: $Tau^2 = 0.0$ ; C	$Chi^2 = 3.45, df = 5 (P =$	0.63); l <sup>2</sup> =0.0%			
Test for overall effect: $Z = 0.9$	94 (P = 0.35)				
4 Any combination					
Subtotal (95% CI)	0	0			Not estimable
Total events: 0 (Higher PUFA	, , ,				
Heterogeneity: not applicable	5				
			0.01 0.1 1 10 100		
		Favou	rs higher PUFA Favours lower P	'UFA	

(Continued . . . )



(I) Fatal MI

(2) Fatal MI/ sudden death

(3) Cardiac deaths

#### Analysis 2.37. Comparison 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes, Outcome 37 MYOCARDIAL INFARCTION (MI) - fatal and non fatal.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes

Outcome: 37 MYOCARDIAL INFARCTION (MI) - fatal and non fatal

Study or subgroup	Higher PUFA	Lower PUFA	Risk Ratio M- H,Random,95%	Weight	Risk Ratio M- H,Random,95%
	n/N	n/N			Cl
AlphaOmega - ALA	90/2409	101/2428	•	19.4 %	0.90 [ 0.68, 1.19 ]
Brox 2001	0/80	1/40		0.1 %	0.17 [ 0.01, 4.05 ]
DART fat 1989	197/1018	225/1015	•	51.7 %	0.87 [ 0.74, 1.04 ]
Doi 2014	1/119	0/119		0.1 %	3.00 [ 0.12, 72.91 ]
EPOCH 2011	1/195	0/196		0.1 %	3.02 [ 0.12, 73.57 ]
GLAMT 1993	0/54	1/57		0.1 %	0.35 [ 0.01, 8.45 ]
HARP- Sacks 1995	1/41	3/39		0.3 %	0.32 [ 0.03, 2.92 ]
Houtsmuller 1979	0/51	6/5 I	· · · · · · · · · · · · · · · · · · ·	0.2 %	0.08 [ 0.00, 1.33 ]
		Fa	0.01 0.1 1 10 100 vours higher PUFA Favours lower PU	FA	

(Continued ...)

Study or subgroup	Higher PUFA	Lower PUFA			sk Ratio M- Jom,95%	Weight	( Continued) Risk Ratio M- H,Random,95%
	n/N	n/N			CI		Cl
MRC 1968	39/199	40/194		-		9.7 %	0.95 [ 0.64, 1.41 ]
NDHS Open 1st 1968	4/726	1/341			+	0.3 %	1.88 [ 0.21, 16.75 ]
PREDIMED 2013	31/2454	37/2543		-		6.7 %	0.87 [ 0.54, 1.39 ]
Proudman 2015	1/87	0/53			+	0.1 %	1.84 [ 0.08, 44.38 ]
Raitt 2005	1/100	3/100			_	0.3 %	0.33 [ 0.04, 3.15 ]
Rose 1965	9/28	7/26				2.2 %	1.19 [ 0.52, 2.74 ]
Veterans Admin 1969	36/424	44/422		-		8.5 %	0.81 [ 0.54, 1.24 ]
Total (95% CI)	7985	7624		•		100.0 %	0.88 [ 0.78, 0.99 ]
Total events: 411 (Higher PUF	FA), 469 (Lower PUFA)						
Heterogeneity: $Tau^2 = 0.0$ ; Ch	ni <sup>2</sup> = 8.36, df = 14 (P =	0.87); l <sup>2</sup> =0.0%					
Test for overall effect: Z = 2.0	6 (P = 0.040)						
Test for subgroup differences:	Not applicable						
			1				
			0.01	0.1 1	10 100		
			Favours high	er PUFA	Favours lower P	UFA	

# Analysis 2.38. Comparison 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes, Outcome 38 SUDDEN CARDIAC DEATH (SCD).

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes

Outcome: 38 SUDDEN CARDIAC DEATH (SCD)

Study or subgroup	Higher PUFA	Lower PUFA	Risk Ratio M-	Weight	Risk Ratio M-
	n/N	n/N	H,Random,95% Cl		H,Random,95% Cl_
Doi 2014	0/119	2/119		2.4 %	0.20 [ 0.01, 4.12 ]
MRC 1968	8/199	7/194		22.3 %	1.11 [ 0.41, 3.01 ]
Raitt 2005	2/100	0/100		2.4 %	5.00 [ 0.24, 102.85 ]
Rose 1965	3/28	2/26		7.6 %	1.39 [ 0.25, 7.68 ]
Veterans Admin 1969	18/424	27/422	-	65.3 %	0.66 [ 0.37, 1.19 ]
Total (95% CI)	870	861	•	100.0 %	0.80 [ 0.50, 1.29 ]
Total events: 31 (Higher PUI	FA), 38 (Lower PUFA)				
Heterogeneity: $Tau^2 = 0.0$ ; (	$Chi^2 = 3.45, df = 4 (P = 0)$	0.49); l <sup>2</sup> =0.0%			
Test for overall effect: $Z = 0$	.91 (P = 0.36)				
Test for subgroup difference	s: Not applicable				
			0.01 0.1 1 10 100		
		Favo	ours higher PUFA Favours lower P	UFA	

#### Analysis 2.39. Comparison 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes, Outcome 39 ATRIAL FIBRILLATION (AF) & ARRHYTHMIAS (including AF, ventricular tachycardia (VT), ventricular fibrillation(VF).

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes

Outcome: 39 ATRIAL FIBRILLATION (AF) % ARRHYTHMIAS (including AF, ventricular tachycardia (VT), ventricular fibrillation(VF)

Study or subgroup	Higher PUFA	Lower PUFA	Risk Ratio M-	Weight	Risk Ratio M-
	n/N	n/N	H,Random,95% Cl		H,Random,95 Cl
l Recurrent arrhythmia					
FAAT - Leaf 2005	60/200	79/202		15.9 %	0.77 [ 0.58, 1.01 ]
Kumar 2012	61/91	78/87	+	20.0 %	0.75 [ 0.64, 0.88 ]
Nodari 2011 AF	37/100	56/99		14.7 %	0.65 [ 0.48, 0.89 ]
Raitt 2005 (1)	65/100	59/100	-	18.0 %	1.10 [ 0.89, 1.37 ]
Subtotal (95% CI)	491	488	•	68.6 %	0.81 [ 0.65, 1.01 ]
Total events: 223 (Higher PL	IFA), 272 (Lower PUFA)				
Heterogeneity: $Tau^2 = 0.03$ ;	Chi <sup>2</sup> = 10.62, df = 3 (P	= 0.01); I <sup>2</sup> =72%			
Test for overall effect: $Z = 1$ .	89 (P = 0.059)				
2 New arrhythmia					
AlphaOmega - ALA	62/2409	79/2428		14.0 %	0.79 [ 0.57, 1.10 ]
EPIC-1 2008	1/188	0/186	<b>←</b>	0.4 %	2.97 [ 0.12, 72.40 ]
EPOCH 2011	2/195	1/196	·	0.6 %	2.01 [ 0.18, 21.99 ]
Nodari 2011 HF	1/67	4/66	••	0.8 %	0.25 [ 0.03, 2.15 ]
ORL 2013	0/171	1/165	· · · · · · · · · · · · · · · · · · ·	0.4 %	0.32 [ 0.01, 7.84 ]
PREDIMED 2013	92/2210	72/2292		14.9 %	1.33 [ 0.98, 1.79 ]
Proudman 2015	1/87	0/53	·	0.4 %	1.84 [ 0.08, 44.38 ]
Subtotal (95% CI)	5327	5386	+	31.4 %	1.01 [ 0.70, 1.46 ]
Total events: 159 (Higher PL	IFA), 157 (Lower PUFA)				
Heterogeneity: $Tau^2 = 0.05$ ;	Chi <sup>2</sup> = 8.19, df = 6 (P =	= 0.22); I <sup>2</sup> =27%			
Test for overall effect: $Z = 0$ .	06 (P = 0.95)				
Total (95% CI)	5818	5874	•	100.0 %	0.87 [ 0.72, 1.06 ]
Total events: 382 (Higher PL	IFA), 429 (Lower PUFA)				
Heterogeneity: $Tau^2 = 0.04$ ;		$P = 0.01$ ); $ ^2 = 57\%$			
Test for overall effect: $Z = 1$ .	· /				
Test for subgroup differences	$:: Chi^2 = 1.04, df = 1 (P)$	= 0.3 l ), l <sup>2</sup> =4%			
			0.2 0.5 I 2 5		

(1) ICD therapy for VT/VF

# Analysis 2.40. Comparison 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes, Outcome 40 AF - SA.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes

Outcome: 40 AF - SA

Study or subgroup	Higher PUFA	Lower PUFA	Risk Ratio M-	Weight	Risk Ratic M-
	n/N	n/N	H,Random,95% Cl		H,Random, C
Low risk of bias for allocation	on concealment				
AlphaOmega - ALA	62/2409	79/2428		27.6 %	0.79 [ 0.57, 1.10 ]
EPIC-1 2008	1/188	0/186	<b>←</b>	0.3 %	2.97 [ 0.12, 72.40 ]
EPOCH 2011	2/195	1/196		0.5 %	2.01 [ 0.18, 21.99
FAAT - Leaf 2005	60/200	79/202		39.8 %	0.77 [ 0.58, 1.01
Nodari 2011 AF	37/100	56/99		31.2 %	0.65 [ 0.48, 0.89
ORL 2013	0/171	1/165	·	0.3 %	0.32 [ 0.01, 7.84
Proudman 2015	1/87	0/53		0.3 %	1.84 [ 0.08, 44.38 ]
Subtotal (95% CI)	3350	3329	•	100.0 %	0.74 [ 0.63, 0.88]
AlphaOmega - ALA	62/2409	79/2428		17.6 %	
Heterogeneity: Tau <sup>2</sup> = 0.0; Cl Test for overall effect: $Z = 3.3$		3.65), 1 -0.0%			
Low risk of bias for attentic AlphaOmega - ALA		79/2428		17.6 %	0.79 [ 0.57, 1.10
EPIC-1 2008	1/188	0/186	• • • • • • • • • • • • • • • • • • • •	0.5 %	2.97 [ 0.12, 72.40
EPOCH 2011	2/195	1/196	·	0.9 %	2.01 [ 0.18, 21.99
FAAT - Leaf 2005	60/200	79/202		19.9 %	0.77 [ 0.58, 1.01
Nodari 2011 AF	37/100	56/99		18.4 %	0.65 [ 0.48, 0.89
Nodari 2011 HF	1/67	4/66	<b>4</b> +	1.0 %	0.25 [ 0.03, 2.15
Nodari 2011 HF ORL 2013	1/67 0/171	4/66	· · · · · · · · · · · · · · · · · · ·	1.0 % 0.5 %	0.25 [ 0.03, 2.15
			•		-
ORL 2013	0/171	1/165		0.5 %	0.32 [ 0.01, 7.84
ORL 2013 PREDIMED 2013	0/171 92/2210	1/165 72/2292		0.5 %	- 0.32 [ 0.01, 7.84 1.33 [ 0.98, 1.79
ORL 2013 PREDIMED 2013 Proudman 2015 Raitt 2005 (1)	0/171 92/2210 1/87	1/165 72/2292 0/53		0.5 % 18.6 % 0.5 %	0.32 [ 0.01, 7.84 1.33 [ 0.98, 1.79 1.84 [ 0.08, 44.38
ORL 2013 PREDIMED 2013 Proudman 2015	0/171 92/2210 1/87 65/100 <b>5727</b> FA), 351 (Lower PUFA) Chi <sup>2</sup> = 18.37, df = 9 (P	1/165 72/2292 0/53 59/100 <b>5787</b>		0.5 % 18.6 % 0.5 % 22.2 %	0.32 [ 0.01, 7.84 1.33 [ 0.98, 1.79 1.84 [ 0.08, 44.38 1.10 [ 0.89, 1.37

(Continued . . . )

Study or subgroup	Higher PUFA	Lower PUFA	Risk Ratio M-	Weight	( Continued Risk Ratio M-
	n/N	n/N	H,Random,95% Cl		H,Random,959 Cl
Low risk of bias for complia Subtotal (95% CI) Total events: 0 (Higher PUFA) Heterogeneity: not applicable Test for overall effect: not app	<b>0</b> ), 0 (Lower PUFA)	0			Not estimable
Low summary risk of bias AlphaOmega - ALA	62/2409	79/2428		97.1 %	0.79 [ 0.57, 1.10 ]
EPOCH 2011	2/195	1/196	·	1.8 %	2.01 [ 0.18, 21.99 ]
Proudman 2015	1/87	0/53	· · · · · ·	1.0 %	1.84 [ 0.08, 44.38 ]
Subtotal (95% CI)	2691	<b>26</b> 77		100.0 %	0.81 [ 0.59, 1.12 ]
Heterogeneity: Tau <sup>2</sup> = 0.0; Ch est for overall effect: Z = 1.2 Trials registry or pre-2010 AlphaOmega - ALA		0.66); l <sup>2</sup> =0.0% 79/2428	_	14.0 %	0.79 [ 0.57, 1.10 ]
EPIC-1 2008	1/188	0/186	·	0.4 %	2.97 [ 0.12, 72.40 ]
EPOCH 2011	2/195	1/196	· · · · · · · · · · · · · · · · · · ·	0.6 %	2.01 [ 0.18, 21.99 ]
FAAT - Leaf 2005	60/200	79/202		15.9 %	0.77 [ 0.58, 1.01 ]
Kumar 2012	61/91	78/87	-	20.0 %	0.75 [ 0.64, 0.88 ]
Nodari 2011 AF	37/100	56/99		14.7 %	0.65 [ 0.48, 0.89 ]
Nodari 2011 HF	1/67	4/66	••	0.8 %	0.25 [ 0.03, 2.15 ]
ORL 2013	0/171	1/165	· · · · · · · · · · · · · · · · · · ·	0.4 %	0.32 [ 0.01, 7.84 ]
PREDIMED 2013	92/2210	72/2292		14.9 %	1.33 [ 0.98, 1.79 ]
Proudman 2015	1/87	0/53	·	0.4 %	1.84 [ 0.08, 44.38 ]
Raitt 2005 (2)	65/100	59/100	-	18.0 %	1.10 [ 0.89, 1.37 ]
Subtotal (95% CI)	5818	5874		100.0 %	0.87 [ 0.72, 1.06 ]
Total events: 382 (Higher PUF Heterogeneity: Tau <sup>2</sup> = 0.04; C Test for overall effect: Z = 1.4 No industry funding FAAT - Leaf 2005	FA), 429 (Lower PUFA) $Chi^2 = 23.28$ , df = 10 (f	l i i i i i i i i i i i i i i i i i i i	-	56.1 %	0.77 [ 0.58, 1.01 ]
Nodari 2011 AF	37/100	56/99		43.9 %	0.65 [ 0.48, 0.89 ]
Subtotal (95% CI)	300	301	•	100.0 %	0.72 [ 0.58, 0.88 ]
botal events: 97 (Higher PUFA leterogeneity: Tau <sup>2</sup> = 0.0; CP est for overall effect: $Z = 3.2$ Randomised 100+ participa	A), 135 (Lower PUFA) $hi^2 = 0.58$ , df = 1 (P = 21 (P = 0.0013)				

UFA n/N	r subgroup Higher PUFA	Lower PUFA	Risk Ratio M- H,Random,95% Cl	Weight	( Continued) Risk Ratio M- H,Random,95 Cl
	mega - ALA 62/2409	79/2428		14.0 %	0.79 [ 0.57, 1.10 ]
/188	2008 1/188	0/186		0.4 %	2.97 [ 0.12, 72.40 ]
/195	2/195	1/196		0.6 %	2.01 [ 0.18, 21.99 ]
/200	Leaf 2005 60/200	79/202		15.9 %	0.77 [ 0.58, 1.01 ]
/9	2012 61/91	78/87	-	20.0 %	0.75 [ 0.64, 0.88 ]
/100	2011 AF 37/100	56/99		14.7 %	0.65 [ 0.48, 0.89 ]
1/67	2011 HF 1/67	4/66		0.8 %	0.25 [ 0.03, 2.15 ]
/171	0/171	1/165	<b>← · · · · · · · · · · · · · · · · · · ·</b>	0.4 %	0.32 [ 0.01, 7.84 ]
2210	1ED 2013 92/2210	72/2292		14.9 %	1.33 [ 0.98, 1.79 ]
1/87	an 2015 1/87	0/53	·	0.4 %	1.84 [ 0.08, 44.38 ]
/100	05 (3) 65/100	59/100		18.0 %	1.10 [ 0.89, 1.37 ]
er PUFA	<b>L (95% CI)</b> 5818 s: 382 (Higher PUFA), 429 (Lower P eity: Tau <sup>2</sup> = 0.04; Chi <sup>2</sup> = 23.28, df = erall effect: Z = 1.42 (P = 0.16) sed 250+ participants			100.0 %	0.87 [ 0.72, 1.06 ]
2409	mega - ALA 62/2409	79/2428		30.4 %	0.79 [ 0.57, 1.10 ]
/188	2008 1/188	0/186	·	0.9 %	2.97 [ 0.12, 72.40 ]
/195	2/195	1/196		1.6 %	2.01 [ 0.18, 21.99 ]
/200	Leaf 2005 60/200	79/202		34.1 %	0.77 [ 0.58, 1.01 ]
/171	0/171	1/165	·	0.9 %	0.32 [ 0.01, 7.84 ]
2210	1ED 2013 92/2210	72/2292		32.1 %	1.33 [ 0.98, 1.79 ]
	(95% CI) 5373	5469	-	100.0 %	0.94 [ 0.69, 1.28 ]

(1) ICD therapy for VT/VF

(2) ICD therapy for VT/VF

(3) ICD therapy for VT/VF

# Analysis 2.41. Comparison 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes, Outcome 41 AF - SA fixed-effect.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes

Outcome: 41 AF - SA fixed-effect

Study or subgroup	Higher PUFA n/N	Lower PUFA n/N	Risk Ratio M-H,Fixed,95% Cl	Weight	Risk Ratio M-H,Fixed,95% Cl
l Recurrent arrhythmia					
FAAT - Leaf 2005	60/200	79/202		18.3 %	0.77 [ 0.58, 1.01 ]
Kumar 2012	61/91	78/87	+	18.5 %	0.75 [ 0.64, 0.88 ]
Nodari 2011 AF	37/100	56/99		13.1 %	0.65 [ 0.48, 0.89 ]
Raitt 2005 (1)	65/100	59/100	-	13.7 %	1.10 [ 0.89, 1.37 ]
Subtotal (95% CI)	491	488	•	63.5 %	0.81 [ 0.72, 0.91 ]
Total events: 223 (Higher PUI Heterogeneity: Chi <sup>2</sup> = 10.62, Test for overall effect: Z = 3.4 2 New arrhythmia	df = 3 (P = 0.01); $I^2 =$				
AlphaOmega - ALA	62/2409	79/2428		18.3 %	0.79 [ 0.57, 1.10 ]
EPIC-1 2008	1/188	0/186	<u>← → </u>	0.1 %	2.97 [ 0.12, 72.40 ]
EPOCH 2011	2/195	1/196		0.2 %	2.01 [ 0.18, 21.99 ]
Nodari 2011 HF	1/67	4/66	<del> </del>	0.9 %	0.25 [ 0.03, 2.15 ]
ORL 2013	0/171	1/165	<u> </u>	0.4 %	0.32 [ 0.01, 7.84 ]
PREDIMED 2013	92/2210	72/2292		16.4 %	1.33 [ 0.98, 1.79 ]
Proudman 2015	1/87	0/53	·	0.1 %	1.84 [ 0.08, 44.38 ]
Subtotal (95% CI)	5327	5386	+	36.5 %	1.03 [ 0.83, 1.28 ]
Total events: 159 (Higher PU) Heterogeneity: $Chi^2 = 8.19$ , c	$ff = 6 (P = 0.22); I^2 = 2$				
Test for overall effect: Z = 0.2 <b>Total (95% CI)</b>	5818 (P = 0.78)	5874	•	100.0 %	0.89 [ 0.80, 1.00 ]
Total events: 382 (Higher PUI				100.0 /0	0.09 [ 0.00, 1.00 ]
Heterogeneity: $Chi^2 = 23.28$ ,	$df = 10 (P = 0.01); I^2 =$	=57%			
Test for overall effect: Z = 2.0	03 (P = 0.042)				
Test for subgroup differences:	$Chi^2 = 3.69, df = 1 (P$	= 0.05), I <sup>2</sup> =73%			

Favours higher PUFA Favours lower PUFA

(1) ICD therapy for VT/VF

# Analysis 2.42. Comparison 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes, Outcome 42 AF - subgroup by PUFA dose.

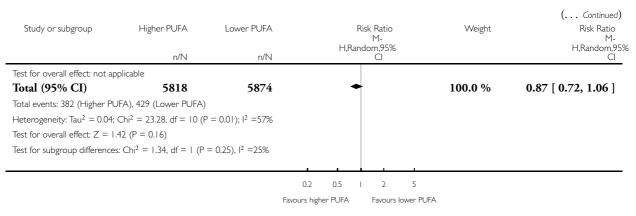
Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes

Outcome: 42 AF - subgroup by PUFA dose

Study or subgroup	Higher PUFA	Lower PUFA	Risk Ratio M-	Weight	Risk Ratio M-
	n/N	n/N	H,Random,95% Cl		H,Random,95 Cl
total PUFA < 1.0% E					
EPOCH 2011	2/195	1/196	· · · · · · · · · · · · · · · · · · ·	0.6 %	2.01 [ 0.18, 21.99 ]
FAAT - Leaf 2005	60/200	79/202		15.9 %	0.77 [ 0.58, 1.01 ]
Kumar 2012	61/91	78/87	+	20.0 %	0.75 [ 0.64, 0.88 ]
Nodari 2011 AF	37/100	56/99		4.7 %	0.65 [ 0.48, 0.89 ]
Nodari 2011 HF	1/67	4/66	<b>4</b>	0.8 %	0.25 [ 0.03, 2.15 ]
ORL 2013	0/171	1/165	• · · · · · · · · · · · · · · · · · · ·	0.4 %	0.32 [ 0.01, 7.84 ]
Raitt 2005 (1)	65/100	59/100	-	18.0 %	1.10 [ 0.89, 1.37 ]
Subtotal (95% CI)	924	915	•	70.4 %	0.80 [ 0.65, 0.99 ]
Total events: 226 (Higher PUF/	A), 278 (Lower PUFA)				
Heterogeneity: Tau <sup>2</sup> = 0.03; Cl	hi <sup>2</sup> = 12.69, df = 6 (P	= 0.05); I <sup>2</sup> =53%			
Test for overall effect: $Z = 2.07$	7 (P = 0.038)				
2 total PUFA 1.0 to < 2.0% E	· · · ·				
AlphaOmega - ALA	62/2409	79/2428		14.0 %	0.79 [ 0.57, 1.10 ]
EPIC-1 2008	1/188	0/186	<→	0.4 %	2.97 [ 0.12, 72.40 ]
PREDIMED 2013	92/2210	72/2292		14.9 %	1.33 [ 0.98, 1.79 ]
Proudman 2015	1/87	0/53		0.4 %	1.84 [ 0.08, 44.38 ]
Subtotal (95% CI)	4894	4959	-	29.6 %	1.06 [ 0.70, 1.60 ]
Total events: 156 (Higher PUF)	A), [5] (Lower PUFA)	1			
Heterogeneity: Tau <sup>2</sup> = 0.07; Cl	, , ,				
Test for overall effect: $Z = 0.27$					
3 total PUFA 2.0 to < 5.0% E	(				
Subtotal (95% CI)	0	0			Not estimable
Total events: 0 (Higher PUFA),	-	U			Not estimable
Heterogeneity: not applicable	0 (LOWER FOR A)				
Test for overall effect: not appli	icable				
4 total PUFA 5.0+% E					
Subtotal (95% CI)	0	0			Not estimable
Total events: 0 (Higher PUFA),	0 (Lower PUFA)				
Heterogeneity: not applicable	. ,				
<b>J J J J J J J J J J</b>					
			0.2 0.5 I 2 5		
			rs higher PUFA Favours lower PU		

(Continued . . . )



(1) ICD therapy for VT/VF

#### Analysis 2.43. Comparison 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes, Outcome 43 AF - subgroup by duration.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes

Outcome: 43 AF - subgroup by duration

Study or subgroup	Higher PUFA	Lower PUFA	Risk Ratio M-	Weight	Risk Ratio M-
	n/N	n/N	H,Random,95% Cl		H,Random,95% Cl
Medium duration   to < 2	years				
EPIC-1 2008	1/188	0/186	<b>←</b> →	0.4 %	2.97 [ 0.12, 72.40 ]
EPOCH 2011	2/195	1/196	· · · · · · · · · · · · · · · · · · ·	0.6 %	2.01 [ 0.18, 21.99 ]
FAAT - Leaf 2005	60/200	79/202		15.9 %	0.77 [ 0.58, 1.01 ]
Kumar 2012	61/91	78/87	-	20.0 %	0.75 [ 0.64, 0.88 ]
Nodari 2011 AF	37/100	56/99		14.7 %	0.65 [ 0.48, 0.89 ]
Nodari 2011 HF	1/67	4/66	<u>د،                                     </u>	0.8 %	0.25 [ 0.03, 2.15 ]
ORL 2013	0/171	1/165	• • • • • •	0.4 %	0.32 [ 0.01, 7.84 ]
Proudman 2015	1/87	0/53	←· →	0.4 %	1.84 [ 0.08, 44.38 ]
Subtotal (95% CI)	1099	1054	•	53.2 %	0.74 [ 0.65, 0.83 ]

(Continued . . . )

Study or subgroup	Higher PUFA n/N	Lower PUFA n/N	Risk Ratio M- H,Random,95% Cl	Weight	( Continued) Risk Ratio M- H,Random,95% Cl
Total events: 163 (Higher PUF	FA), 219 (Lower PUFA)				
Heterogeneity: $Tau^2 = 0.0$ ; Ch	$hi^2 = 3.66, df = 7 (P = 0)$	0.82); I <sup>2</sup> =0.0%			
Test for overall effect: $Z = 4.7$	78 (P < 0.00001)				
2 Medium-long duration 2 to	< 4 years				
AlphaOmega - ALA	62/2409	79/2428		14.0 %	0.79 [ 0.57, 1.10 ]
Raitt 2005 (1)	65/100	59/100	+	18.0 %	1.10 [ 0.89, 1.37 ]
Subtotal (95% CI)	2509	2528	-	32.0 %	0.95 [ 0.66, 1.36 ]
Total events: 127 (Higher PUF	FA), I 38 (Lower PUFA)				
Heterogeneity: $Tau^2 = 0.05$ ; C	$Chi^2 = 3.37, df = 1 (P =$	0.07); l <sup>2</sup> =70%			
Test for overall effect: $Z = 0.2$	27 (P = 0.79)				
3 Long duration 4+ years					
PREDIMED 2013	92/2210	72/2292		14.9 %	1.33 [ 0.98, 1.79 ]
Subtotal (95% CI)	2210	2292	•	14.9 %	1.33 [ 0.98, 1.79 ]
Total events: 92 (Higher PUFA	A), 72 (Lower PUFA)				
Heterogeneity: not applicable					
Test for overall effect: $Z = 1.8$	32 (P = 0.068)				
Total (95% CI)	5818	5874	•	100.0 %	0.87 [ 0.72, 1.06 ]
Total events: 382 (Higher PUF	FA), 429 (Lower PUFA)				
Heterogeneity: $Tau^2 = 0.04$ ; C	$Chi^2 = 23.28, df = 10 (F)$	$P = 0.01$ ); $I^2 = 57\%$			
Test for overall effect: $Z = 1.4$	12 (P = 0.16)				
Test for subgroup differences:	$Chi^2 = 13.13, df = 2$ (F	$P = 0.00$ ), $I^2 = 85\%$			
			0.2 0.5 I 2 5		
			Favours higher PUFA Favours lower PU	JFA	

(1) ICD therapy for VT/VF

# Analysis 2.44. Comparison 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes, Outcome 44 AF - subgroup by primary or secondary prevention.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes

Outcome: 44 AF - subgroup by primary or secondary prevention

Study or subgroup	Higher PUFA	Lower PUFA	Risk Ratio M-	Weight	Risk Ratio M-
	n/N	n/N	H,Random,95% Cl		H,Random,9 Cl
I Primary prevention of CVE	)				
EPIC-1 2008	1/188	0/186		0.4 %	2.97 [ 0.12, 72.40 ]
EPOCH 2011	2/195	1/196	· · · · · · · · · · · · · · · · · · ·	0.6 %	2.01 [ 0.18, 21.99 ]
ORL 2013	0/171	1/165	← → ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓	0.4 %	0.32 [ 0.01, 7.84 ]
PREDIMED 2013	92/2210	72/2292		14.9 %	1.33 [ 0.98, 1.79 ]
Proudman 2015	1/87	0/53	· · · · · · · · · · · · · · · · · · ·	0.4 %	1.84 [ 0.08, 44.38 ]
Subtotal (95% CI)	2851	2892	-	16.6 %	1.33 [ 0.99, 1.79 ]
Total events: 96 (Higher PUF,		0.00), 12 -0.09/			
Heterogeneity: $Tau^2 = 0.0$ ; C Test for overall effect: $Z = 1.8$		0.89); 12 =0.0%			
2 Secondary prevention of C	,				
AlphaOmega - ALA	62/2409	79/2428		14.0 %	0.79 [ 0.57, 1.10 ]
FAAT - Leaf 2005	60/200	79/202		15.9 %	0.77 [ 0.58, 1.01
Kumar 2012	61/91	78/87	-	20.0 %	0.75 [ 0.64, 0.88
Nodari 2011 AF	37/100	56/99		14.7 %	0.65 [ 0.48, 0.89
Nodari 2011 HF	1/67	4/66	•••	0.8 %	0.25 [ 0.03, 2.15
Raitt 2005 (1)	65/100	59/100	-	18.0 %	1.10 [ 0.89, 1.37 ]
Subtotal (95% CI)	2967	2982	•	83.4 %	0.80 [ 0.67, 0.96 ]
Total events: 286 (Higher PU	FA), 355 (Lower PUFA)				
Heterogeneity: $Tau^2 = 0.03$ ; (		= 0.04); l <sup>2</sup> =58%			
Test for overall effect: $Z = 2.4$	· /				
Total (95% CI)	5818	5874	•	100.0 %	0.87 [ 0.72, 1.06 ]
Total events: 382 (Higher PU	, , , ,				
Heterogeneity: $Tau^2 = 0.04$ ; (		$P = 0.01$ ); $I^2 = 57\%$			
Test for overall effect: Z = 1.4 Test for subgroup differences	,				

0.2 0.5 I 2 5 Favours higher PUFA Favours lower PUFA

(1) ICD therapy for VT/VF

### Analysis 2.45. Comparison 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes, Outcome 45 Atrial fibrillation - subgroup by baseline PUFA dose.

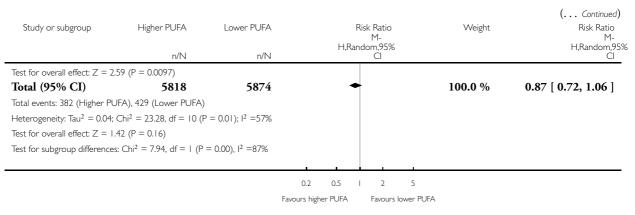
Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes

Outcome: 45 Atrial fibrillation - subgroup by baseline PUFA dose

Study or subgroup	Higher PUFA	Lower PUFA	Risk Ratio M-	Weight	Risk Ratio M-
	n/N	n/N	H,Random,95% Cl		H,Random,9 Cl
Baseline total PUFA < 6% E					
Subtotal (95% CI)	0	0			Not estimable
Fotal events: 0 (Higher PUFA)	, 0 (Lower PUFA)				
Heterogeneity: not applicable					
Fest for overall effect: not app					
2 Baseline total PUFA 6 to <		70/00.00	_		
PREDIMED 2013	92/2210	72/2292		14.9 %	1.33 [ 0.98, 1.79 ]
Subtotal (95% CI)	2210	2292	-	14.9 %	1.33 [ 0.98, 1.79 ]
Fotal events: 92 (Higher PUFA	A), 72 (Lower PUFA)				
Heterogeneity: not applicable					
Fest for overall effect: Z = 1.8 Baseline total PUFA 11+% E	,				
Subtotal (95% CI)	0	0			Not estimable
Fotal events: 0 (Higher PUFA)	-	v			Tot estimatic
Heterogeneity: not applicable	, , , , , , , , , , , , , , , , , , , ,				
Fest for overall effect: not app	licable				
Baseline total PUFA unclear					
AlphaOmega - ALA	62/2409	79/2428		14.0 %	0.79 [ 0.57, 1.10 ]
EPIC-1 2008	1/188	0/186	· · · · ·	0.4 %	2.97 [ 0.12, 72.40 ]
EPOCH 2011	2/195	1/196	· · · · · · · · · · · · · · · · · · ·	0.6 %	2.01 [ 0.18, 21.99 ]
FAAT - Leaf 2005	60/200	79/202		15.9 %	0.77 [ 0.58, 1.01 ]
Kumar 2012	61/91	78/87	-	20.0 %	0.75 [ 0.64, 0.88 ]
Nodari 2011 AF	37/100	56/99		14.7 %	0.65 [ 0.48, 0.89 ]
Nodari 2011 HF	1/67	4/66	<b>←</b>	0.8 %	0.25 [ 0.03, 2.15 ]
ORL 2013	0/171	1/165	• • • • • • • • • • • • • • • • • • •	0.4 %	0.32 [ 0.01, 7.84 ]
Proudman 2015	1/87	0/53		0.4 %	I.84 [ 0.08, 44.38 ]
Raitt 2005 (1)	65/100	59/100	-	18.0 %	1.10 [ 0.89, 1.37 ]
Subtotal (95% CI)	3608	3582	•	85.1 %	0.81 [ 0.69, 0.95 ]
Fotal events: 290 (Higher PUF	A), 357 (Lower PUFA)				
1 + 1 + 2 = 0.02	Chi <sup>2</sup> = 13.59, df = 9 (P	= 0.14); l <sup>2</sup> =34%			

(Continued . . . )



(1) ICD therapy for VT/VF

#### Analysis 2.46. Comparison 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes, Outcome 46 AF - subgroup by replacement.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes

Outcome: 46 AF - subgroup by replacement

	Higher PUFA	Lower PUFA	Risk Ratio M-	Weight	Risk Ratio
	n/N	n/N	H,Random,95% Cl		H,Random,95% Cl
PUFA replaced saturated fats	1				
Subtotal (95% CI)	0	0			Not estimable
Fotal events: 0 (Higher PUFA),	0 (Lower PUFA)				
Heterogeneity: not applicable					
Test for overall effect: not appli	cable				
2 PUFA replaced monounsatur	rated fats				
AlphaOmega - ALA	62/2409	79/2428		17.9 %	0.79 [ 0.57, 1.10 ]
EPOCH 2011	2/195	1/196	·	0.9 %	2.01 [ 0.18, 21.99 ]
FAAT - Leaf 2005	60/200	79/202		20.0 %	0.77 [ 0.58, 1.01 ]
Nodari 2011 AF	37/100	56/99		18.6 %	0.65 [ 0.48, 0.89 ]
Nodari 2011 HF	1/67	4/66	·	1.1 %	0.25 [ 0.03, 2.15 ]
PREDIMED 2013	92/2210	72/2292		18.8 %	1.33 [ 0.98, 1.79 ]

(Continued . . . )

( Continue) Risk Ratic M- H,Random,	Weight	Risk Ratio M- H,Random,95%	Lower PUFA	Higher PUFA	Study or subgroup
C		Cl	n/N	n/N	
1.84 [ 0.08, 44.38 ]	0.5 %	• • • •	0/53	1/87	Proudman 2015
1.10 [ 0.89, 1.37 ]	22.1 %	-	59/100	65/100	Raitt 2005 (1)
0.90 [ 0.71, 1.14 ]	100.0 %	•	5436	5368	Subtotal (95% CI)
				FA), 350 (Lower PUFA)	Total events: 320 (Higher PUF
			0.0 l ); l <sup>2</sup> =60%	Chi <sup>2</sup> = 17.44, df = 7 (P =	Heterogeneity: Tau <sup>2</sup> = 0.05; C
				8 (P = 0.38)	Test for overall effect: $Z = 0.8$
				es	3 PUFA replaced carbohydrate
Not estimable			0	0	Subtotal (95% CI)
				), 0 (Lower PUFA)	Total events: 0 (Higher PUFA)
					Heterogeneity: not applicable
				licable	Test for overall effect: not app
					4 PUFA replaced protein
Not estimable			0	0	Subtotal (95% CI)
				), 0 (Lower PUFA)	Total events: 0 (Higher PUFA)
					Heterogeneity: not applicable
				licable	Test for overall effect: not app
					5 PUFA replaced unclear
2.97 [ 0.12, 72.40 ]	0.3 %	<b>←</b>	0/186	1/188	EPIC-1 2008
0.75 [ 0.64, 0.88 ]	99.5 %	<b>—</b>	78/87	61/91	Kumar 2012
0.32 [ 0.01, 7.84 ]	0.3 %	• • • • • • •	1/165	0/171	ORL 2013
0.75 [ 0.64, 0.88 ]	100.0 %	•	438	450	Subtotal (95% CI)
				A), 79 (Lower PUFA)	Total events: 62 (Higher PUFA
			61); I <sup>2</sup> =0.0%	$mi^2 = 0.99$ , $df = 2$ (P = 0.	Heterogeneity: $Tau^2 = 0.0$ ; Ch
				4 (P = 0.00040)	Test for overall effect: $Z = 3.5$
			0.21), 12 =38%	$Chi^2 = 1.60, df = 1 (P = 1)$	Test for subgroup differences:

Favours higher PUFA Favours lower PUFA

(1) ICD therapy for VT/VF  $% \left( I\right) =\left( I\right) \left( I\right)$ 

## Analysis 2.47. Comparison 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes, Outcome 47 Atrial fibrillation - subgroup by sex.

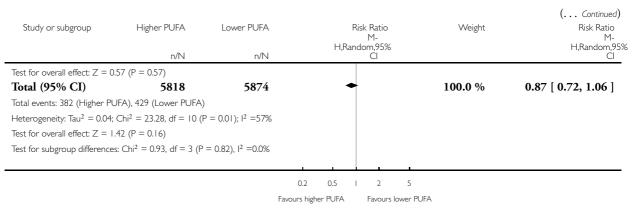
Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes

Outcome: 47 Atrial fibrillation - subgroup by sex

Study or subgroup	Higher PUFA	Lower PUFA	Risk Ratio M-	Weight	Risk Ratio M-
	n/N	n/N	H,Random,95% Cl		H,Random,S Cl
l > 70% men					
AlphaOmega - ALA	62/2409	79/2428		14.0 %	0.79 [ 0.57, 1.10 ]
FAAT - Leaf 2005	60/200	79/202		15.9 %	0.77 [ 0.58, 1.01 ]
Kumar 2012	61/91	78/87	-	20.0 %	0.75 [ 0.64, 0.88 ]
Nodari 2011 HF	1/67	4/66	••	0.8 %	0.25 [ 0.03, 2.15 ]
ORL 2013	0/171	1/165	← →	0.4 %	0.32 [ 0.01, 7.84 ]
Raitt 2005 (1)	65/100	59/100	-	18.0 %	1.10 [ 0.89, 1.37 ]
Subtotal (95% CI)	3038	3048	•	<b>69.1</b> %	0.83 [ 0.69, 1.01 ]
Total events: 249 (Higher PUF	FA), 300 (Lower PUFA	)			
Heterogeneity: $Tau^2 = 0.02$ ; C	Chi <sup>2</sup> = 10.09, df = 5 (P	= 0.07); l <sup>2</sup> =50%			
Test for overall effect: Z = 1.8	87 (P = 0.061)				
2 > 70% women	. ,				
Proudman 2015	1/87	0/53	·	0.4 %	1.84 [ 0.08, 44.38 ]
Subtotal (95% CI)	87	53		0.4 %	1.84 [ 0.08, 44.38 ]
Total events: I (Higher PUFA)	), 0 (Lower PUFA)				
Heterogeneity: not applicable					
Test for overall effect: $Z = 0.3$	88 (P = 0.71)				
3 men % women					
EPIC-1 2008	1/188	0/186	·	0.4 %	2.97 [ 0.12, 72.40 ]
Nodari 2011 AF	37/100	56/99		14.7 %	0.65 [ 0.48, 0.89 ]
PREDIMED 2013	92/2210	72/2292		14.9 %	1.33 [ 0.98, 1.79 ]
Subtotal (95% CI)	2498	2577		<b>29.9</b> %	0.98 [ 0.50, 1.93 ]
Total events: 130 (Higher PUF	FA), 128 (Lower PUFA	)			
Heterogeneity: $Tau^2 = 0.23$ ; C	Chi <sup>2</sup> = 11.48, df = 2 (P	= 0.003); l <sup>2</sup> =83%			
Test for overall effect: $Z = 0.0$	06 (P = 0.95)				
4 sex not reported	. ,				
EPOCH 2011	2/195	1/196	<b>←</b>	0.6 %	2.01 [ 0.18, 21.99 ]
Subtotal (95% CI)	195	196		0.6 %	2.01 [ 0.18, 21.99 ]
Total events: 2 (Higher PUFA)	), I (Lower PUFA)				
Heterogeneity: not applicable	,				
			0.2 0.5 1 2 5		
		Em	ours higher PUFA Favours lower PL	IFΔ	

(Continued . . . )



(1) ICD therapy for VT/VF

#### Analysis 2.48. Comparison 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes, Outcome 48 AF - subgroup by age.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes

Outcome: 48 AF - subgroup by age

Study or subgroup	Higher PUFA	Lower PUFA	Risk Ratio M-	Weight	Risk Ratio M-
	n/N	n/N	H,Random,95% Cl		H,Random,95% Cl
l Mean age < 50 years					
EPIC-1 2008	1/188	0/186	٠ <u>·</u>	0.4 %	2.97 [ 0.12, 72.40 ]
Subtotal (95% CI)	188	186		0.4 %	2.97 [ 0.12, 72.40 ]
Total events: I (Higher PUFA),	, 0 (Lower PUFA)				
Heterogeneity: not applicable					
Test for overall effect: $Z = 0.67$	7 (P = 0.50)				
2 Mean age 50 to < 65 years					
Kumar 2012	61/91	78/87	-	20.0 %	0.75 [ 0.64, 0.88 ]
Nodari 2011 HF	1/67	4/66	•••	0.8 %	0.25 [ 0.03, 2.15 ]
ORL 2013	0/171	1/165	· · · · · · · · · · · · · · · · · · ·	0.4 %	0.32 [ 0.01, 7.84 ]
Proudman 2015	1/87	0/53	· · · · · ·	0.4 %	1.84 [ 0.08, 44.38 ]
Raitt 2005 (1)	65/100	59/100	-	18.0 %	1.10 [ 0.89, 1.37 ]

(Continued . . . )

Study or subgroup	Higher PUFA n/N	Lower PUFA n/N	Risk Ratio M- H,Random,95% Cl	Weight	( Continued) Risk Ratio M-S H,Random,95% Cl
Subtotal (95% CI)	516	471	*	39.5 %	0.87 [ 0.62, 1.23 ]
Total events: 128 (Higher PU Heterogeneity: Tau <sup>2</sup> = 0.06; (	, ,	,			
Test for overall effect: $Z = 0.8$	80 (P = 0.42)				
3 Mean age 65+ years AlphaOmega - ALA	62/2409	79/2428		14.0 %	0.79 [ 0.57, 1.10 ]
FAAT - Leaf 2005	60/200	79/202		15.9 %	0.77 [ 0.58, 1.01 ]
Nodari 2011 AF	37/100	56/99		14.7 %	0.65 [ 0.48, 0.89 ]
PREDIMED 2013	92/2210	72/2292		14.9 %	1.33 [ 0.98, 1.79 ]
Subtotal (95% CI) Total events: 251 (Higher PU Heterogeneity: Tau <sup>2</sup> = 0.07; ( Test for overall effect: Z = 1.0 4 Mean age unclear EPOCH 2011	$Chi^2 = 12.11, df = 3 (P$	,		<b>59.5 %</b> 0.6 %	<b>0.85 [ 0.63, 1.15 ]</b> 2.01 [ 0.18, 21.99 ]
Subtotal (95% CI) Total events: 2 (Higher PUFA Heterogeneity: not applicable Test for overall effect: Z = 0.	2	196		0.6 %	2.01 [ 0.18, 21.99 ]
<b>Total (95% CI)</b> Total events: 382 (Higher PU Heterogeneity: Tau <sup>2</sup> = 0.04; ( Test for overall effect: $Z = 1$ . Test for subgroup differences	$Chi^2 = 23.28, df = 10 ($ 42 (P = 0.16)	P = 0.01); I <sup>2</sup> =57%	5	100.0 %	0.87 [ 0.72, 1.06 ]
			0.2 0.5 I 2 5 Favours higher PUFA Favours lower PUI	ĒA	

(1) ICD therapy for VT/VF

### Analysis 2.49. Comparison 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes, Outcome 49 AF - subgroup by statin use.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes

Outcome: 49 AF - subgroup by statin use

Study or subgroup	Higher PUFA	Lower PUFA	Risk Ratio M-	Weight	Risk Ratio M
	n/N	n/N	H,Random,95% Cl		H,Random, C
< 50% on statins					
EPIC-1 2008	1/188	0/186	<b>←</b>	0.4 %	2.97 [ 0.12, 72.40 ]
EPOCH 2011	2/195	1/196	← → ↓ → ↓	0.6 %	2.01 [ 0.18, 21.99 ]
Kumar 2012	61/91	78/87	-	20.0 %	0.75 [ 0.64, 0.88
Nodari 2011 AF	37/100	56/99		14.7 %	0.65 [ 0.48, 0.89
Nodari 2011 HF	1/67	4/66	<u> </u>	0.8 %	0.25 [ 0.03, 2.15
ORL 2013	0/171	1/165	· · · · · · · · · · · · · · · · · · ·	0.4 %	0.32 [ 0.01, 7.84
PREDIMED 2013	92/2210	72/2292		14.9 %	1.33 [ 0.98, 1.79
Proudman 2015	1/87	0/53	· · · · · · · · · · · · · · · · · · ·	0.4 %	1.84 [ 0.08, 44.38
Raitt 2005 (1)	65/100	59/100		18.0 %	1.10 [ 0.89, 1.37
Subtotal (95% CI)	3209	3244	+	70.1 %	0.91 [ 0.68, 1.21 ]
AlphaOmega - ALA <b>Subtotal (95% CI)</b> Total events: 62 (Higher PL)	62/2409 <b>2409</b> FA) 79 (Lower PUFA)	79/2428 <b>2428</b>	-	14.0 %	0.79 [ 0.57, 1.10 <b>0.79 [ 0.57, 1.10</b>
Total events: 62 (Higher PUI Heterogeneity: not applicabl Test for overall effect: Z = 1	FA), 79 (Lower PUFA) le	2420		14.0 /0	0.77 [ 0.97, 1.10
3 Percentage on statins uncl	, ,				
FAAT - Leaf 2005	60/200	79/202		15.9 %	0.77 [ 0.58, 1.01
Subtotal (95% CI) Total events: 60 (Higher PUI	, , ,	202	•	15.9 %	0.77 [ 0.58, 1.01
Test for overall effect: $Z = I$		5874	•	100.0 %	0.87 [ 0.72, 1.06
Test for overall effect: $Z = 1$ <b>Total (95% CI)</b> Total events: 382 (Higher PU Heterogeneity: Tau <sup>2</sup> = 0.04; Test for overall effect: $Z = 1$	.90 (P = 0.057) <b>5818</b> JFA), 429 (Lower PUFA) Chi <sup>2</sup> = 23.28, df = 10 (f .42 (P = 0.16)	$P = 0.01$ ); $ ^2 = 57\%$	•	100.0 %	0.87 [ 0.72, 1.06
Heterogeneity: not applicabl Test for overall effect: Z = 1 <b>Total (95% CI)</b> Total events: 382 (Higher PL Heterogeneity: Tau <sup>2</sup> = 0.04; Test for overall effect: Z = 1 Test for subgroup difference	.90 (P = 0.057) <b>5818</b> JFA), 429 (Lower PUFA) Chi <sup>2</sup> = 23.28, df = 10 (f .42 (P = 0.16)	$P = 0.01$ ); $ ^2 = 57\%$	•	100.0 %	0.87 [ 0.72, 1.06

(1) ICD therapy for VT/VF

# Analysis 2.50. Comparison 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes, Outcome 50 AF - subgroup by intervention type.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes

Outcome: 50 AF - subgroup by intervention type

Study or subgroup	Higher PUFA	Lower PUFA	Risk Ratio M-	Weight	Risk Ratio M-
	n/N	n/N	H,Random,95% Cl		H,Random,95 Cl
I Dietary advice					
Subtotal (95% CI)	0	0			Not estimable
Total events: 0 (Higher PUFA	, , ,				
Heterogeneity: not applicable Test for overall effect: not app					
2 Supplemental foods % diet					
AlphaOmega - ALA	62/2409	79/2428		14.0 %	0.79 [ 0.57, 1.10 ]
PREDIMED 2013	92/2210	72/2292		14.9 %	1.33 [ 0.98, 1.79 ]
Subtotal (95% CI)	4619	4720	-	28.9 %	1.03 [ 0.62, 1.70 ]
Total events: 154 (Higher PU Heterogeneity: Tau <sup>2</sup> = 0.11; ( Test for overall effect: $Z = 0$ .	$Chi^2 = 5.14, df = 1 (P = 1)$				
3 Supplements (capsules % u EPIC-1 2008	inusual foods) 1/188	0/186	<b>←</b> →	0.4 %	2.97 [ 0.12, 72.40 ]
EPOCH 2011	2/195	1/196		0.6 %	2.01 [ 0.18, 21.99 ]
FAAT - Leaf 2005	60/200	79/202		15.9 %	0.77 [ 0.58, 1.01 ]
Kumar 2012	61/91	78/87	-	20.0 %	0.75 [ 0.64, 0.88 ]
Nodari 2011 AF	37/100	56/99		14.7 %	0.65 [ 0.48, 0.89 ]
Nodari 2011 HF	1/67	4/66		0.8 %	0.25 [ 0.03, 2.15 ]
ORL 2013	0/171	1/165	· · · · · · · · · · · · · · · · · · ·	0.4 %	0.32 [ 0.01, 7.84 ]
Proudman 2015	1/87	0/53	·	0.4 %	1.84 [ 0.08, 44.38 ]
Raitt 2005 (1)	65/100	59/100	-	18.0 %	1.10 [ 0.89, 1.37 ]
Subtotal (95% CI)	1199	1154	•	71.1 %	0.81 [ 0.67, 0.98 ]
Total events: 228 (Higher PU Heterogeneity: Tau <sup>2</sup> = 0.02; ( Test for overall effect: Z = 2. 4 Any combination	Chi <sup>2</sup> = 13.55, df = 8 (P				
			0.2 0.5 I 2 5 rs higher PUFA Favours lower PU		

(Continued ...)

								( Continued)
Study or subgroup	Higher PUFA	Lower PUFA		F	Risk Ratio M-		Weight	Risk Ratio
				H,Rar	1ºI- ndom,95%			M- H,Random,95%
	n/N	n/N			Cl			Cl
Subtotal (95% CI)	0	0						Not estimable
Total events: 0 (Higher PUFA	A), 0 (Lower PUFA)							
Heterogeneity: not applicable	e							0.87 [ 0.72, 1.06 ]
Test for overall effect: not ap	plicable							
Total (95% CI)	5818	5874		+	-		100.0 %	
Total events: 382 (Higher PL	JFA), 429 (Lower PUFA)							
Heterogeneity: $Tau^2 = 0.04$ ;	Chi <sup>2</sup> = 23.28, df = 10 (F	$P = 0.01$ ); $I^2 = 57\%$						
Test for overall effect: $Z = I$ .	42 (P = 0.16)							
Test for subgroup differences	s: $Chi^2 = 0.73$ , $df = 1$ (P	= 0.39), l <sup>2</sup> =0.0%						
			0.2	0.5	1 2	5		
			Favours high	er PUFA	Favours le	ower PUFA		

(1) ICD therapy for VT/VF

# Analysis 2.51. Comparison 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes, Outcome 51 ANGINA.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes

Outcome: 51 ANGINA

Study or subgroup	Higher PUFA	Lower PUFA	Risk Ratio M- H,Random,95%	Weight	Risk Ratio M- H,Random,95%
FAAT - Leaf 2005 (1)	n/N 0/200	n/N 4/202	CI	3.7 %	0.11 [ 0.01, 2.07 ]
Houtsmuller 1979	8/51	24/51		23.4 %	0.33 [ 0.17, 0.67 ]
MRC 1968	1/199	4/194		6.1 %	0.24 [ 0.03, 2.16 ]
Nye 1990	5/36	/37		18.4 %	0.47 [ 0.18, 1.21 ]
Raitt 2005	10/100	7/100		18.9 %	1.43 [ 0.57, 3.60 ]
Rose 1965	3/28	2/26		9.0 %	1.39 [ 0.25, 7.68 ]
Veterans Admin 1969	11/424	10/422		20.4 %	1.09 [ 0.47, 2.55 ]
Total (95% CI)	1038	1032	•	100.0 %	0.64 [ 0.35, 1.16 ]
		Favo	0.01 0.1 1 10 100 Durs higher PUFA Favours lower P	UFA	

(Continued . . . )

						( Continued)
Study or subgroup	Higher PUFA	Lower PUFA		sk Ratio M-	Weight	Risk Ratio
	n/N	n/N	H,Ranc	lom,95% Cl		H,Random,95% Cl
Total events: 38 (Higher PU	FA), 62 (Lower PUFA)					
Heterogeneity: $Tau^2 = 0.27$	; Chi <sup>2</sup> = 11.12, df = 6 (P	= 0.08); l <sup>2</sup> =46%				
Test for overall effect: $Z = I$	.48 (P = 0.14)					
Test for subgroup difference	es: Not applicable					
			0.01 0.1 1	10 IC	00	
		Fav	ours higher PUFA	Favours lowe	r PUFA	

(1) Worsening angina

# Analysis 2.52. Comparison 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes, Outcome 52 HEART FAILURE.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes

Outcome: 52 HEART FAILURE

Study or subgroup	Higher PUFA	Lower PUFA	Risk Ratio M- H,Random,95%	Weight	Risk Ratio M- H,Random,95%
	n/N	n/N	Cl		Cl
DART fat 1989	3/1018	6/1015		12.0 %	0.50 [ 0.13, 1.99 ]
FAAT - Leaf 2005	6/200	8/202		16.5 %	0.76 [ 0.27, 2.14 ]
HARP- Sacks 1995	0/41	1/39		3.3 %	0.32 [ 0.01, 7.57 ]
MRC 1968	1/199	0/194		3.3 %	2.93 [ 0.12, 71.37 ]
Nodari 2011 HF	4/67	20/66		16.8 %	0.20 [ 0.07, 0.55 ]
PREDIMED 2013 (1)	33/10279	29/11737	<b>-</b>	26.2 %	1.30 [ 0.79, 2.14 ]
Raitt 2005	14/100	12/100		22.0 %	1.17 [ 0.57, 2.40 ]
Total (95% CI)	11904	13353	•	100.0 %	0.74 [ 0.40, 1.36 ]
Total events: 61 (Higher PUF	FA), 76 (Lower PUFA)				
Heterogeneity: Tau <sup>2</sup> = 0.30;	$Chi^2 = 13.00, df = 6 (P$	<sup>9</sup> = 0.04); l <sup>2</sup> =54%			
Test for overall effect: $Z = 0$ .	.98 (P = 0.33)				
Test for subgroup differences	s: Not applicable				
			0.01 0.1 1 10 100		
			Favours higher PUFA Favours lower PU	JFA	

# Analysis 2.53. Comparison 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes, Outcome 53 PERIPHERAL ARTERIAL DISEASE (PAD).

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes

Outcome: 53 PERIPHERAL ARTERIAL DISEASE (PAD)

Study or subgroup	Higher PUFA	Lower PUFA	Risk Ratio M-	Weight	Risk Ratio M-
	n/N	n/N	H,Random,95% Cl		H,Random,95% Cl_
DART fat 1989	0/1018	1/1015		1.5 %	0.33 [ 0.01, 8.15 ]
NDHS Open 1st 1968	1/726	0/341		1.5 %	1.41 [ 0.06, 34.55 ]
PREDIMED 2013	26/2452	18/2539		42.8 %	1.50 [ 0.82, 2.72 ]
Veterans Admin 1969	26/424	25/422	+	54.2 %	1.04 [ 0.61, 1.76 ]
Total (95% CI)	4620	4317	*	100.0 %	1.20 [ 0.81, 1.77 ]
Total events: 53 (Higher PUFA	A), 44 (Lower PUFA)				
Heterogeneity: $Tau^2 = 0.0$ ; Ch	$mi^2 = 1.45, df = 3 (P = 0)$	.69); l <sup>2</sup> =0.0%			
Test for overall effect: $Z = 0.96$	0 (P = 0.37)				
Test for subgroup differences:	Not applicable				
				1	
			0.01 0.1 1 10	100	

Favours higher PUFA Favours lower PUFA

# Analysis 2.54. Comparison 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes, Outcome 54 REVASCULARISATION - angioplasty and/or coronary artery bypass grafting.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 2 Higher PUFA vs lower PUFA - dichotomous secondary outcomes

Outcome: 54 REVASCULARISATION - angioplasty and/or coronary artery bypass grafting

Study or subgroup	Higher PUFA	Lower PUFA	Risk Ratio M-	Weight	Risk Ratio M-
	n/N	n/N	H,Random,95% Cl		H,Random,95% Cl
Doi 2014	9/119	15/119		52.9 %	0.60 [ 0.27, 1.32 ]
EPOCH 2011	2/195	2/196	••	8.6 %	1.01 [ 0.14, 7.06 ]
HARP- Sacks 1995	3/41	3/39		13.8 %	0.95 [ 0.20, 4.43 ]
Nye 1990	1/36	1/37	••	4.4 %	1.03 [ 0.07, 15.82 ]
Raitt 2005	2/100	4/100	• <b>•</b>	11.7 %	0.50 [ 0.09, 2.67 ]
Vijayakumar 2014	2/100	2/100	••	8.7 %	1.00 [ 0.14, 6.96 ]
Total (95% CI)	591	591	-	100.0 %	0.70 [ 0.40, 1.24 ]
Total events: 19 (Higher P Heterogeneity: Tau <sup>2</sup> = 0.0 Test for overall effect: Z =	; $Chi^2 = 0.79$ , $df = 5$ (P =	0.98); l <sup>2</sup> =0.0%			
Test for subgroup differen	ces: Not applicable				
		_	0.2 0.5 I 2 5		

Favours higher PUFA Favours lower PUFA

#### Analysis 3.1. Comparison 3 Higher PUFA vs lower PUFA - continuous secondary outcomes, Outcome I ADIPOSITY - BODY WEIGHT, kg.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 3 Higher PUFA vs lower PUFA - continuous secondary outcomes

Outcome: I ADIPOSITY - BODY WEIGHT, kg

Study or subgroup	Higher PUFA N	Mean(SD)	Lower PUFA N	Mean(SD)	Mean Difference IV,Random,95% Cl	Weight	Mean Difference IV,Random,95% Cl
Bassey 2000-Post	21	0.74 (2.2913)	21	0.74 (1.3748)		8.3 %	0.0 [ -1.14, 1.14 ]
Bassey 2000-Pre	19	0.37 (2.6589)	24	0.19 (1.5677)		6.7 %	0.18 [ -1.17, 1.53 ]
Black 1994	58	80 (0)	57	76.5 (0)			Not estimable
Dullaart 1992	16	77 (10)	20	76 (11.2) 🕇		<b>→</b> 0.4 %	1.00 [ -5.94, 7.94 ]
HARP- Sacks 1995	31	82 (14)	28	80 (15) 🕇	······	→ 0.3 %	2.00 [ -5.43, 9.43 ]
HERO-Tapsell 2009	18	92 (17.1)	17	92.3 (13.8) 🕇	•	→ 0.2 %	-0.30 [ -10.57, 9.97 ]
Ley 2004 (I)	70	0.59 (13.4702)	66	-3.32 (5.5243)		→ I.4 %	3.91 [ 0.48, 7.34 ]
MARINA - Sanders 2011 (2)	80	0.2 (1.8)	71	-0.3 (2.53)		13.2 %	0.50 [ -0.21, 1.21 ]
MRC 1968	88	0 (0)	89	-1.4 (0)			Not estimable
PREDIMED 2013 (3)	1062	-0.5 (7.5)	1236	-1 (6.3)		15.2 %	0.50 [ -0.07, 1.07 ]
PREDIMED 2013 (4)	662	0.02 (5.3)	663	-0.2 (5.9)		14.7 %	0.22 [ -0.38, 0.82 ]
PREDIMED 2013 (5)	54	-0.1 (0.37)	54	-1.3 (0.37)	-	20.5 %	1.20 [ 1.06, 1.34 ]
WAHA - Ros 2016	156	-0.29 (3.85)	156	-1.05 (3.85)		11.3 %	0.76 [ -0.09,  .6  ]
WELCOME 2015	47	94.1 (13)	48	90.4 (16.3)		•• 0.5 %	3.70 [ -2.22, 9.62 ]
WINS 2006 (6)	328	72.8 (14.8609)	840	70.6 (14.7661)		7.2 %	2.20 [ 0.92, 3.48 ]
Total (95% CI)	3710		3390		•	100.0 % 0	0.76 [ 0.34, 1.19 ]
Heterogeneity: $Tau^2 = 0.22$ ; Chi <sup>2</sup>	<sup>2</sup> = 29.28, df =	I 2 (P = 0.004);	l <sup>2</sup> =59%				
Test for overall effect: $Z = 3.52$ (	P = 0.00044)						
Test for subgroup differences: No	ot applicable						
						i	
				-4	-2 0 2	4	

(1) Change data, variance presented as SDs, but assumed to be SEs and converted

(2) 0.9g/d n3 vs placebo (as these arms were well balanced for weight at baseline)

(3) Babio CMAJ 2014 - Participants with metabolic syndrome at baseline, 5 year data

(4) Babio CMAJ 2014 participants without metabolic syndrome at baseline, 5 year data

(5) Barcelona hospital cohort at 5 years, Casa 2016

(6) One year data

# Analysis 3.2. Comparison 3 Higher PUFA vs lower PUFA - continuous secondary outcomes, Outcome 2 Body weight, kg - SA.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 3 Higher PUFA vs lower PUFA - continuous secondary outcomes

Outcome: 2 Body weight, kg - SA

$\begin{array}{c} 0.2 (1.8) \\ 71 \\ 74.1 (13) \\ 14.8609) \\ 840 \\ 1045 \\ 106); 1^2 = 55\% \\ (2.2913) \\ (2.6589) \\ 24 \\ 82 (14) \\ 28 \\ 92 (17.1) \\ 17 \\ 0.2 (1.8) \\ 71 \end{array}$	Mean(SD) 76 (11.2) ← -3.32 (5.5243) -0.3 (2.53) 90.4 (16.3) 70.6 (14.7661) 0.74 (1.3748) 0.19 (1.5677) 80 (15) ← 92.3 (13.8) ← -0.3 (2.53)	IV,Random,95% Cl	10.6 % 8.6 % → 0.4 % → 0.2 %	IV,Random,95% ( 1.00 [ -5.94, 7.94 3.91 [ 0.48, 7.34 0.50 [ -0.21, 1.21 3.70 [ -2.22, 9.62 2.20 [ 0.92, 3.48 <b>1.72 [ 0.29, 3.15</b> 0.0 [ -1.14, 1.14 0.18 [ -1.17, 1.53 2.00 [ -5.43, 9.43 -0.30 [ -10.57, 9.97
13.4702)       66         0.2 (1.8)       71         94.1 (13)       48         14.8609)       840         1045       1045         .06); 1² =55%       24         82 (14)       28         92 (17.1)       17         0.2 (1.8)       71	$\begin{array}{c} -3.32 \ (5.5243) \\ -0.3 \ (2.53) \\ 90.4 \ (16.3) \\ 70.6 \ (14.7661) \\ \end{array}$ $\begin{array}{c} 0.74 \ (1.3748) \\ 0.19 \ (1.5677) \\ 80 \ (15) \end{array}$		<ul> <li>12.8 %</li> <li>43.2 %</li> <li>5.2 %</li> <li>34.9 %</li> <li>100.0 %</li> <li>106.6 %</li> <li>8.6 %</li> <li>0.4 %</li> <li>0.2 %</li> </ul>	3.91 [ 0.48, 7.34 0.50 [ -0.21, 1.21 3.70 [ -2.22, 9.62 2.20 [ 0.92, 3.48 <b>1.72 [ 0.29, 3.15</b> 0.0 [ -1.14, 1.14 0.18 [ -1.17, 1.53 2.00 [ -5.43, 9.43 -0.30 [ -10.57, 9.97
13.4702)       66         0.2 (1.8)       71         94.1 (13)       48         14.8609)       840         1045       1045         .06); 1² =55%       24         82 (14)       28         92 (17.1)       17         0.2 (1.8)       71	$\begin{array}{c} -3.32 \ (5.5243) \\ -0.3 \ (2.53) \\ 90.4 \ (16.3) \\ 70.6 \ (14.7661) \\ \end{array}$ $\begin{array}{c} 0.74 \ (1.3748) \\ 0.19 \ (1.5677) \\ 80 \ (15) \end{array}$		<ul> <li>12.8 %</li> <li>43.2 %</li> <li>5.2 %</li> <li>34.9 %</li> <li>100.0 %</li> <li>106.6 %</li> <li>8.6 %</li> <li>0.4 %</li> <li>0.2 %</li> </ul>	3.91 [ 0.48, 7.34 0.50 [ -0.21, 1.21 3.70 [ -2.22, 9.62 2.20 [ 0.92, 3.48 <b>1.72 [ 0.29, 3.15</b> 0.0 [ -1.14, 1.14 0.18 [ -1.17, 1.53 2.00 [ -5.43, 9.43 -0.30 [ -10.57, 9.97
$\begin{array}{c} 0.2 (1.8) \\ 71 \\ 74.1 (13) \\ 14.8609) \\ 840 \\ 1045 \\ 106); 1^2 = 55\% \\ (2.2913) \\ (2.6589) \\ 24 \\ 82 (14) \\ 28 \\ 92 (17.1) \\ 17 \\ 0.2 (1.8) \\ 71 \end{array}$	-0.3 (2.53) 90.4 (16.3) 70.6 (14.7661) 0.74 (1.3748) 0.19 (1.5677) 80 (15) ← 92.3 (13.8) ←		432 % 5.2 % 34.9 % 100.0 % 10.6 % 8.6 % → 0.4 % → 0.2 %	0.50 [ -0.21, 1.21 3.70 [ -2.22, 9.62 2.20 [ 0.92, 3.48 <b>1.72 [ 0.29, 3.15</b> 0.0 [ -1.14, 1.14 0.18 [ -1.17, 1.53 2.00 [ -5.43, 9.43 -0.30 [ -10.57, 9.97
(1)       48         (4.8609)       840         1045       1045         (06); 1 <sup>2</sup> =55%       21         (2.2913)       21         (2.6589)       24         82 (14)       28         92 (17.1)       17         0.2 (1.8)       71	90.4 (16.3) 70.6 (14.7661) 0.74 (1.3748) 0.19 (1.5677) 80 (15) ↔ 92.3 (13.8) ↔		<ul> <li>5.2 %</li> <li>34.9 %</li> <li>100.0 %</li> <li>10.6 %</li> <li>8.6 %</li> <li>0.4 %</li> <li>0.2 %</li> </ul>	3.70 [ -2.22, 9.62 2.20 [ 0.92, 3.4£ <b>1.72 [ 0.29, 3.15</b> 0.0 [ -1.14, 1.14 0.18 [ -1.17, 1.53 2.00 [ -5.43, 9.43 -0.30 [ -10.57, 9.97
14.8609)       840         1045         .06); I <sup>2</sup> =55%         (2.2913)       21         (2.6589)       24         82 (14)       28         92 (17.1)       17         0.2 (1.8)       71	70.6 (14.7661) 0.74 (1.3748) 0.19 (1.5677) 80 (15) ← 92.3 (13.8) ←		34.9 % 100.0 % 106 % 8.6 % → 0.4 % → 0.2 %	2.20 [ 0.92, 3.48 <b>1.72 [ 0.29, 3.15</b> 0.0 [ -1.14, 1.14 0.18 [ -1.17, 1.53 2.00 [ -5.43, 9.43 -0.30 [ -10.57, 9.97
1045         1.06); 1 <sup>2</sup> =55%         (2.2913)       21         (2.6589)       24         82 (14)       28         92 (17.1)       17         0.2 (1.8)       71	0.74 (1.3748) 0.19 (1.5677) 80 (15) ↔ 92.3 (13.8) ↔		100.0 % 10.6 % 8.6 % → 0.4 % → 0.2 %	1.72 [ 0.29, 3.15 0.0 [ -1.14, 1.14 0.18 [ -1.17, 1.53 2.00 [ -5.43, 9.43 -0.30 [ -10.57, 9.97
(2.2913) 21 (2.6589) 24 82 (14) 28 92 (17.1) 17 0.2 (1.8) 71	0.19 (1.5677) 80 (15) ← 92.3 (13.8) ←		10.6 % 8.6 % → 0.4 % → 0.2 %	0.0 [ -1.14, 1.14 0.18 [ -1.17, 1.53 2.00 [ -5.43, 9.43 -0.30 [ -10.57, 9.97
(2.2913) 21 (2.6589) 24 82 (14) 28 92 (17.1) 17 0.2 (1.8) 71	0.19 (1.5677) 80 (15) ← 92.3 (13.8) ←	 	10.6 % 8.6 % → 0.4 % → 0.2 %	0.0 [ -1.14, 1.14 0.18 [ -1.17, 1.53 2.00 [ -5.43, 9.43 -0.30 [ -10.57, 9.97
(2.6589)     24       82 (14)     28       92 (17.1)     17       0.2 (1.8)     71	0.19 (1.5677) 80 (15) ← 92.3 (13.8) ←	<b>_</b>	8.6 % → 0.4 % → 0.2 %	0.18 [ -1.17, 1.5] 2.00 [ -5.43, 9.4] -0.30 [ -10.57, 9.9]
82 (14) 28 92 (17.1) 17 0.2 (1.8) 71	80 (15) ← 92.3 (13.8) ←	······································	<ul> <li>→ 0.4 %</li> <li>→ 0.2 %</li> </ul>	2.00 [ -5.43, 9.43 -0.30 [ -10.57, 9.97
92 (17.1) 17 0.2 (1.8) 71	92.3 (13.8) ←			-0.30 [ -10.57, 9.97
	-0.3 (2.53)			-
0.5 (7.5) 100(		T <b>-</b>	16.7 %	0.50 [ -0.21, 1.2
-0.5 (7.5)  236	-1 (6.3)		19.0 %	0.50 [ -0.07, 1.0]
).1 (0.37) 54	-1.3 (0.37)	-	25.3 %	1.20 [ 1.06, 1.3
0.02 (5.3) 663	-0.2 (5.9)		18.5 %	0.22 [ -0.38, 0.8
94.1 (13) 48	90.4 (16.3)		•• 0.7 %	3.70 [ -2.22, 9.6
<b>2162</b> 0.003); I <sup>2</sup> =65%		•	100.0 %	0.57 [ 0.08, 1.06
77 (10) 20	76 (11.2) ←		→ 5.6 %	1.00 [ -5.94, 7.94
	· · /		■ 18.8 %	3.91 [ 0.48, 7.3 <sup>,</sup>
0 (0) 89	-1.4 (0)			Not estimat
29 (3.85) 156	-1.05 (3.85)		68.2 %	0.76 [ -0.09, 1.6
)	.02 (5.3) 663 14.1 (13) 48 <b>2162</b> 0.003); l <sup>2</sup> =65% 77 (10) 20 13.4702) 66 0 (0) 89	$\begin{array}{c} .02 (5.3) & 663 & -0.2 (5.9) \\ 14.1 (13) & 48 & 90.4 (16.3) \\ 2162 \\ 0.003); 1^2 = 65\% \end{array}$ $\begin{array}{c} 77 (10) & 20 & 76 (11.2) \leftarrow \\ 13.4702) & 66 & -3.32 (5.5243) \\ 0 (0) & 89 & -1.4 (0) \\ 19 (3.85) & 156 & -1.05 (3.85) \end{array}$	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	$\begin{array}{cccccccccccccccccccccccccccccccccccc$

Mean Mean Study or subgroup Higher PUFA Lower PUFA Difference Weight Difference Ν Mean(SD) Ν Mean(SD) IV.Random.95% CI IV.Random.95% CI WELCOME 2015 47 48 3.70 [ -2.22, 9.62 ] 94.1 (13) 90.4 (16.3) 7.4 % Subtotal (95% CI) 379 100.0 % 1.59 [ -0.11, 3.28 ] 377 Heterogeneity: Tau<sup>2</sup> = 0.90; Chi<sup>2</sup> = 3.87, df = 3 (P = 0.28); I<sup>2</sup> = 23% Test for overall effect: Z = 1.84 (P = 0.066) 4 Low summary risk of bias Ley 2004 (9) 70 0.59 (13.4702) 66 -3.32 (5.5243) 14.6 % 3.91 [ 0.48, 7.34 ] MARINA - Sanders 2011 (10) 0.50 [ -0.21, 1.21 ] 80 0.2 (1.8) 71 -0.3 (2.53) 432 % WELCOME 2015 90.4 (16.3) 3.70 [ -2.22, 9.62 ] 47 94.1 (13) 48 6.2 % WINS 2006 (11) 1328 72.8 (14.8609) 840 70.6 (14.7661) 2.20 [ 0.92, 3.48 ] 361% Subtotal (95% CI) 1525 1025 100.0 % 1.81 [ 0.23, 3.38 ] Heterogeneity: Tau<sup>2</sup> = 1.37; Chi<sup>2</sup> = 8.86, df = 3 (P = 0.03); I<sup>2</sup> =66% Test for overall effect: Z = 2.25 (P = 0.024) 5 Trials registry or pre-2010 Bassey 2000-Post 21 0.74 (2.2913) 21 0.74 (1.3748) 83% 0.0 [ -1.14, 1.14 ] Bassey 2000-Pre 19 0.37 (2.6589) 24 0.19 (1.5677) 6.7 % 0.18 [ -1.17, 1.53 ] Black 1994 58 80 (0) 57 76.5 (0) Not estimable Dullaart 1992 76 (11.2) 0.4 % 1.00 [ -5.94, 7.94 ] 16 77 (10) 20 HARP- Sacks 1995 2.00 [ -5.43, 9.43 ] 31 82 (14) 80 (15) 03% 28 HERO-Tapsell 2009 -0.30 [ -10.57, 9.97 ] 18 92 (17.1) 17 92.3 (13.8) 0.2 % Ley 2004 (12) 70 0.59 (13.4702) 66 -3.32 (5.5243) 1.4 % 3.91 [ 0.48, 7.34 ] MARINA - Sanders 2011 (13) 0.2 (1.8) 0.50 [ -0.21, 1.21 ] 80 71 -0.3 (2.53) 132 % MRC 1968 88 0 (0) 89 -1.4 (0) Not estimable PREDIMED 2013 (14) 1062 -0.5 (7.5) 1236 -1 (6.3) 15.2 % 0.50 [ -0.07, 1.07 ] PREDIMED 2013 (15) H 20.5 % 1.20 [ 1.06, 1.34 ] 54 -0.1 (0.37) 54 -1.3 (0.37) PREDIMED 2013 (16) 662 0.02 (5.3) 663 -0.2 (5.9) 14.7 % 0.22 [ -0.38, 0.82 ] WAHA - Ros 2016 156 -0.29 (3.85) -1.05 (3.85) 11.3 % 0.76 [ -0.09, 1.61 ] 156 WELCOME 2015 3.70 [ -2.22, 9.62 ] 47 94.1 (13) 48 90.4 (16.3) 0.5 % WINS 2006 (17) 1328 72.8 (14.8609) 7.2 % 2.20 [ 0.92, 3.48 ] 840 70.6 (14.7661) 100.0 % 0.76 [ 0.34, 1.19 ] Subtotal (95% CI) 3710 3390 Heterogeneity: Tau<sup>2</sup> = 0.22; Chi<sup>2</sup> = 29.28, df = 12 (P = 0.004); I<sup>2</sup> = 59% Test for overall effect: Z = 3.52 (P = 0.00044) 6 No industry funding Black 1994 58 80 (0) 57 76.5 (0) Not estimable Dullaart 1992 76 (11.2) 1.00 [ -5.94, 7.94 ] 16 77 (10) 20 4.3 %

-4 -2 0 2 4

Favours higher PUFA Favours lower PUFA

(Continued . . . )

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Ley 2004 (18) MARINA - Sanders 2011 (19) MRC 1968	N 70 0 80	Mean(SD) 1.59 (13.4702)	N	Mean(SD)	IV,Random,95% CI		IV,Random,95% C
MARINA - Sanders 2011 (19) MRC 1968		.59 (13.4702)					
MRC 1968	80		66	-3.32 (5.5243)		■ I4.0 %	3.91 [ 0.48, 7.34
		0.2 (1.8)	71	-0.3 (2.53)		44.9 %	0.50 [ -0.21, 1.21
14/10/1C 2007 (20)	88	0 (0)	89	-1.4 (0)			Not estimabl
WINS 2006 (20)	1328 7	2.8 (14.8609)	840	70.6 (14.7661)		36.7 %	2.20 [ 0.92, 3.48
Subtotal (95% CI)	1640		1143		-	100.0 %	1.62 [ 0.11, 3.14
Heterogeneity: $Tau^2 = 1.19$ ; $Chi^2 = 8$ .	,	$P = 0.04$ ); $I^2 = 639$	%				
Test for overall effect: Z = 2.10 (P = 0 7 Randomised 100+ participants	).035)						
Black 1994	58	80 (0)	57	76.5 (0)			Not estimabl
Ley 2004 (21)	70 0	.59 (13.4702)	66	-3.32 (5.5243)		→ I.8 %	3.91 [ 0.48, 7.34
MARINA - Sanders 2011 (22)	80	0.2 (1.8)	71	-0.3 (2.53)		15.8 %	0.50 [ -0.21, 1.21
MRC 1968	88	0 (0)	89	-1.4 (0)			Not estimabl
PREDIMED 2013 (23)	54	-0.1 (0.37)	54	-1.3 (0.37)	-	23.7 %	1.20 [ 1.06, 1.34
PREDIMED 2013 (24)	662	0.02 (5.3)	663	-0.2 (5.9)		17.5 %	0.22 [ -0.38, 0.82
PREDIMED 2013 (25)	1062	-0.5 (7.5)	1236	-1 (6.3)	-	18.0 %	0.50 [ -0.07, 1.07
WAHA - Ros 2016	156	-0.29 (3.85)	156	-1.05 (3.85)		13.7 %	0.76 [ -0.09, 1.61
WELCOME 2015	47	94.1 (13)	48	90.4 (16.3)		•• 0.6 %	3.70 [ -2.22, 9.62
WINS 2006 (26)	1328 7	2.8 (14.8609)	840	70.6 (14.7661)		8.9 %	2.20 [ 0.92, 3.48
Subtotal (95% CI)	3605		3280		•	100.0 %	0.89 [ 0.41, 1.36
Heterogeneity: Tau <sup>2</sup> = 0.25; Chi <sup>2</sup> = 2 Test for overall effect: $Z = 3.62$ (P = 0		$(P = 0.001); I^2 = 1$	71%				
8 Randomised 250+ participants MARINA - Sanders 2011 (27)	80	0.2 (1.8)	71	-0.3 (2.53)	+	16.1 %	0.50 [ -0.21, 1.21
MRC 1968	88	0 (0)	89	-1.4 (0)			Not estimab
PREDIMED 2013 (28)	1062	-0.5 (7.5)	1236	-1 (6.3)		18.5 %	0.50 [ -0.07, 1.07
PREDIMED 2013 (29)	662	0.02 (5.3)	663	-0.2 (5.9)		17.9 %	0.22 [ -0.38, 0.82
PREDIMED 2013 (30)	54	-0.1 (0.37)	54	-1.3 (0.37)	-	24.8 %	1.20 [ 1.06, 1.34
WAHA - Ros 2016	156	-0.29 (3.85)	156	-1.05 (3.85)		13.9 %	0.76 [ -0.09, 1.61
WINS 2006 (31)	1328 7	2.8 (14.8609)	840	70.6 (14.7661)	<b>_</b>	8.9 %	2.20 [ 0.92, 3.48
Subtotal (95% CI) Heterogeneity: Tau <sup>2</sup> = 0.23; Chi <sup>2</sup> = 20 Test for overall effect: $Z = 3.36$ (P = 0		(P = 0.00098); I <sup>2</sup>	<b>3109</b> =76%		•	100.0 %	0.81 [ 0.34, 1.28

(1) Change data, variance presented as SDs, but assumed to be SEs and converted

(2) 0.9g/d n3 vs placebo (as these arms were well balanced for weight at baseline)

(3) One year data

(4) 0.9g/d n3 vs placebo (as these arms were well balanced for weight at baseline)

(5) Babio CMAJ 2014 - Participants with metabolic syndrome at baseline, 5 year data

(6) Barcelona hospital cohort at 5 years, Casa 2016

(7) Babio CMAJ 2014 participants without metabolic syndrome at baseline, 5 year data

(8) Change data, variance presented as SDs, but assumed to be SEs and converted

(9) Change data, variance presented as SDs, but assumed to be SEs and converted

(10) 0.9g/d n3 vs placebo (as these arms were well balanced for weight at baseline)

(II) One year data

(12) Change data, variance presented as SDs, but assumed to be SEs and converted

(13) 0.9g/d n3 vs placebo (as these arms were well balanced for weight at baseline)

(14) Babio CMAJ 2014 - Participants with metabolic syndrome at baseline, 5 year data

(15) Barcelona hospital cohort at 5 years, Casa 2016

(16) Babio CMAJ 2014 participants without metabolic syndrome at baseline, 5 year data

(17) One year data

- (18) Change data, variance presented as SDs, but assumed to be SEs and converted
- (19) 0.9g/d n3 vs placebo (as these arms were well balanced for weight at baseline)
- (20) One year data
- (21) Change data, variance presented as SDs, but assumed to be SEs and converted
- (22) 0.9g/d n3 vs placebo (as these arms were well balanced for weight at baseline)
- (23) Barcelona hospital cohort at 5 years, Casa 2016
- (24) Babio CMAJ 2014 participants without metabolic syndrome at baseline, 5 year data
- (25) Babio CMAJ 2014 Participants with metabolic syndrome at baseline, 5 year data
- (26) One year data

(27) 0.9g/d n3 vs placebo (as these arms were well balanced for weight at baseline)

(28) Babio CMAJ 2014 - Participants with metabolic syndrome at baseline, 5 year data

(29) Babio CMAJ 2014 participants without metabolic syndrome at baseline, 5 year data

- (30) Barcelona hospital cohort at 5 years, Casa 2016
- (31) One year data

#### Analysis 3.3. Comparison 3 Higher PUFA vs lower PUFA - continuous secondary outcomes, Outcome 3 Body weight, kg - SA fixed-effect.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 3 Higher PUFA vs lower PUFA - continuous secondary outcomes

Outcome: 3 Body weight, kg - SA fixed-effect

Mear Difference IV,Fixed,95% C	Weight	Mean fference æd,95% Cl	Mean(SD)	ver PUFA N	Mean(SD)	Higher PUFA N	Study or subgroup
0.0 [ -1.14, 1.14]	1.2 %		 0.74 (1.3748)	21	0.74 (2.2913)	21	Bassey 2000-Post
0.18 [ -1.17, 1.53 ]	0.9 %		 0.19 (1.5677)	24	0.37 (2.6589)	19	Bassey 2000-Pre
Not estimable			76.5 (0)	57	80 (0)	58	Black 1994
1.00 [ -5.94, 7.94	• 0.0 %		 76 (11.2)	20	77 (10)	16	Dullaart 1992
2.00 [ -5.43, 9.43	• 0.0 %		 80 (15)	28	82 (14)	31	HARP- Sacks 1995
-0.30 [ -10.57, 9.97	• 0.0 %	•	 92.3 (13.8)	17	92 (17.1)	18	HERO-Tapsell 2009
3.91 [ 0.48, 7.34	• 0.1 %		-3.32 (5.5243)	66	0.59 (13.4702)	70	Ley 2004 (1)
0.50 [ -0.21, 1.21	3.2 %	<b></b>	-0.3 (2.53)	71	0.2 (1.8)	80	MARINA - Sanders 2011 (2)
Not estimable			-1.4 (0)	89	0 (0)	88	MRC 1968
0.50 [ -0.07, 1.07	4.9 %		-1 (6.3)	1236	-0.5 (7.5)	1062	PREDIMED 2013 (3)
0.22 [ -0.38, 0.82	4.4 %		-0.2 (5.9)	663	0.02 (5.3)	662	PREDIMED 2013 (4)
1.20 [ 1.06, 1.34 ]	82.0 %	+	-1.3 (0.37)	54	-0.1 (0.37)	54	PREDIMED 2013 (5)
0.76 [ -0.09, 1.61	2.2 %		-1.05 (3.85)	156	-0.29 (3.85)	156	WAHA - Ros 2016
3.70 [ -2.22, 9.62 ]	• 0.0 %		 90.4 (16.3)	48	94.1 (13)	47	WELCOME 2015
2.20 [ 0.92, 3.48	1.0 %		70.6 (14.7661)	840	72.8 (14.8609)	328	WINS 2006 (6)
1.08 [ 0.96, 1.21 ]	100.0 %	•		3390	ł); l² =59%	<b>3710</b> = 12 (P = 0.004	<b>Fotal (95% CI)</b> Heterogeneity: Chi <sup>2</sup> = 29.28, df
						` '	est for overall effect: $Z = 16.78$
						ot applicable	est for subgroup differences: No

(1) Change data, variance presented as SDs, but assumed to be SEs and converted

- (2) 0.9g/d n3 vs placebo (as these arms were well balanced for weight at baseline)
- (3) Babio CMAJ 2014 Participants with metabolic syndrome at baseline, 5 year data
- (4) Babio CMAJ 2014 participants without metabolic syndrome at baseline, 5 year data
- (5) Barcelona hospital cohort at 5 years, Casa 2016
- (6) One year data

# Analysis 3.4. Comparison 3 Higher PUFA vs lower PUFA - continuous secondary outcomes, Outcome 4 Body weight, kg - subgroup by PUFA dose.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 3 Higher PUFA vs lower PUFA - continuous secondary outcomes

Outcome: 4 Body weight, kg - subgroup by PUFA dose

Me: Differen	Weight	Mean Difference		Lower PUFA		Higher PUFA	Study or subgroup
IV,Random,95%		IV,Random,95% Cl	Mean(SD)	N	Mean(SD)	N	
							l total PUFA < 1.0% E
3.91 [ 0.48, 7.34	• 1.4 %		-3.32 (5.5243)	66	0.59 (13.4702)	70	Ley 2004 (I)
0.50 [ -0.21, 1.21	13.2 %	+	-0.3 (2.53)	71	0.2 (1.8)	80	MARINA - Sanders 2011 (2)
.78 [ -1.46, 5.01	14.7 % 1			137		150	Subtotal (95% CI)
				73%	(P = 0.06); $I^2 =$		Heterogeneity: Tau <sup>2</sup> = 4.22; Chi
						(P = 0.28)	Test for overall effect: $Z = 1.08$
0.0 [ -1.14, 1.14	8.3 %		0.74 (1.3748)	21	0.74 (2.2913)	21	2 total PUFA 1.0 to < 2.0% E Bassey 2000-Post
2			. ,		. ,		,
0.18 [ -1.17, 1.53	6.7 %		0.19 (1.5677)	24	0.37 (2.6589)	19	Bassey 2000-Pre
0.22 [ -0.38, 0.82	14.7 %		-0.2 (5.9)	663	0.02 (5.3)	662	PREDIMED 2013 (3)
1.20 [ 1.06, 1.34	20.5 %	-	-1.3 (0.37)	54	-0.1 (0.37)	54	PREDIMED 2013 (4)
0.50 [ -0.07, 1.07	15.2 %		-1 (6.3)	1236	-0.5 (7.5)	1062	PREDIMED 2013 (5)
3.70 [ -2.22, 9.62	0.5 %		90.4 (16.3)	48	94.1 (13)	47	WELCOME 2015
2.20 [ 0.92, 3.48	7.2 %	_ <b></b>	70.6 (14.7661)	840	72.8 (14.8609)	328	WINS 2006 (6)
0.74 [ 0.18, 1.30	73.1 %	•		2886		3193	Subtotal (95% CI)
				$ ^2 = 74\%$	6 (P = 0.00071)	<sup>2</sup> = 23.28, df =	Heterogeneity: Tau <sup>2</sup> = 0.32; Chi
						(P = 0.0095)	Test for overall effect: $Z = 2.59$
<b>N</b> 1			745 (0)		00.00	50	3 total PUFA 2.0 to < 5.0% E
Not estimat			76.5 (0)	57	80 (0)	58	Black 1994
1.00 [ -5.94, 7.94	0.4 %		76 (11.2) ←	20	77 (10)	16	Dullaart 1992
2.00 [ -5.43, 9.43	0.3 %		80 (15) 🔶	28	82 (14)	31	HARP- Sacks 1995
.47 [ -3.60, 6.53	0.7 % 1			105		105	Subtotal (95% CI)
				0%	$(P = 0.85); I^2 = 0$	= 0.04, df = 1 (	Heterogeneity: Tau <sup>2</sup> = 0.0; Chi <sup>2</sup>
						(P = 0.57)	Test for overall effect: $Z = 0.57$
							4 total PUFA 5.0+% E
			92.3 (13.8) 🗕	17	92 (17.1)	18	HERO-Tapsell 2009
-0.30 [ -10.57, 9.97	0.2 %		( )				
-0.30 [ -10.57, 9.97 Not estimab	0.2 %		-1.4 (0)	89	0 (0)	88	MRC 1968
-	0.2 %		. ,	89 156	0 (0) -0.29 (3.85)	88 156	MRC 1968 WAHA - Ros 2016

								( Continued)
Study or subgroup	Higher PUFA	Lc	ower PUFA		D	Mean	Weight	Mean Difference
	Ν	Mean(SD)	Ν	Mean(SD)	IV,Rar	idom,95% Cl		IV,Random,95% Cl
Subtotal (95% CI)	262		262			•	11.5 %	0.75 [ -0.10, 1.60 ]
Heterogeneity: $Tau^2 = 0.0$ ; C	$hi^2 = 0.04, df = 1 (P$	= 0.84); l <sup>2</sup> =0.0%	Ś					
Test for overall effect: $Z = 1.7$	73 (P = 0.083)							
Total (95% CI)	3710		3390			•	100.0 %	0.76 [ 0.34, 1.19 ]
Heterogeneity: $Tau^2 = 0.22$ ;	$Chi^2 = 29.28, df = 12$	2 (P = 0.004); I <sup>2</sup> =	=59%					
Test for overall effect: $Z = 3.5$	52 (P = 0.00044)							
Test for subgroup differences	$Chi^2 = 0.46, df = 3$	(P = 0.93), I <sup>2</sup> =0.	.0%					
				-4	-2	0 2	4	

Favours higher PUFA Favours lower PUFA

(1) Change data, variance presented as SDs, but assumed to be SEs and converted

(2) 0.9g/d n3 vs placebo (as these arms were well balanced for weight at baseline)

(3) Babio CMAJ 2014 participants without metabolic syndrome at baseline, 5 year data

(4) Barcelona hospital cohort at 5 years, Casa 2016

(5) Babio CMAJ 2014 - Participants with metabolic syndrome at baseline, 5 year data

(6) One year data

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# Analysis 3.5. Comparison 3 Higher PUFA vs lower PUFA - continuous secondary outcomes, Outcome 5 Body weight, kg - subgroup by duration.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 3 Higher PUFA vs lower PUFA - continuous secondary outcomes

Outcome: 5 Body weight, kg - subgroup by duration

Mea Differenc	Weight	Mean Difference		Lower PUFA		Higher PUFA	Study or subgroup
IV,Random,95% (		IV,Random,95% CI	Mean(SD)	N	Mean(SD)	N	
	0.0.0/		074 (10740)	21	074 (0.0010)		I Medium duration I to < 2 ye
0.0 [ -1.14, 1.14	8.3 %	Ī	0.74 (1.3748)	21	0.74 (2.2913)	21	Bassey 2000-Post
0.18 [ -1.17, 1.53	6.7 %		0.19 (1.5677)	24	0.37 (2.6589)	19	Bassey 2000-Pre
-0.30 [ -10.57, 9.97	• 0.2 %		92.3 (  3.8)	17	92 (17.1)	18	HERO-Tapsell 2009
3.91 [ 0.48, 7.34	• 1.4 %		-3.32 (5.5243)	66	0.59 (13.4702)	70	Ley 2004 (I)
0.50 [ -0.21, 1.21	13.2 %		-0.3 (2.53)	71	0.2 (1.8)	.) 80	MARINA - Sanders 2011 (2
3.70 [ -2.22, 9.62	• 0.5 %		90.4 (16.3)	48	94.1 (13)	47	WELCOME 2015
0.47 [ -0.20, 1.14	30.4 %	•		247		255	Subtotal (95% CI)
						(P = 0.17) 4 years	Heterogeneity: Tau <sup>2</sup> = 0.11; Cl Test for overall effect: Z = 1.37 2 Medium-long duration 2 to <
Not estimab			76.5 (0)	57	80 (0)	58	Black 1994
1.00 [ -5.94, 7.94	• 0.4 %		76 (11.2) 🔶	20	77 (10)	16	Dullaart 1992
2.00 [ -5.43, 9.43	• 0.3 %		80 (15) 🔶	28	82 (14)	31	HARP- Sacks 1995
0.76 [ -0.09, 1.61	11.3 %		-1.05 (3.85)	156	-0.29 (3.85)	156	WAHA - Ros 2016
0.78 [ -0.06, 1.62	12.0 %	•		261		261	Subtotal (95% CI)
				0%	(P = 0.95); I <sup>2</sup> =0		Heterogeneity: Tau <sup>2</sup> = 0.0; Chi Test for overall effect: Z = 1.81 3 Long duration 4+ years
Not estimab			-1.4 (0)	89	0 (0)	88	MRC 1968
1.20 [ 1.06, 1.34	20.5 %	-	-1.3 (0.37)	54	-0.1 (0.37)	54	PREDIMED 2013 (3)
0.50 [ -0.07, 1.07	15.2 %		-1 (6.3)	1236	-0.5 (7.5)	1062	PREDIMED 2013 (4)
0.22 [ -0.38, 0.82	14.7 %		-0.2 (5.9)	663	0.02 (5.3)	662	PREDIMED 2013 (5)
2.20 [ 0.92, 3.48	7.2 %		70.6 (14.7661)	840	72.8 (14.8609)	1328	WINS 2006 (6)
0.90 [ 0.27, 1.54	57.6 %	•		<b>2882</b>   <sup>2</sup> =82%	3 (P = 0.00069);		Subtotal (95% CI) Heterogeneity: $Tau^2 = 0.31$ ; Cf
0.76 [ 0.34, 1.19	100.0 %	•		3390		(P = 0.0053) <b>3710</b>	Test for overall effect: Z = 2.79 Total (95% CI)
v./v [ v.J4, 1.19	100.0 70			5570		5/10	10tal (7570 CI)

(Continued . . . )

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Study or subgroup	Higher PUFA	Low	er PUFA		Mean Difference	Weight	Mean Difference
	Ν	Mean(SD)	Ν	Mean(SD)	IV,Random,95% CI		IV,Random,95% CI
Heterogeneity: Tau <sup>2</sup> = 0.22; C	Chi <sup>2</sup> = 29.28, df = 12	$P = 0.004$ ; $I^2 = 56$	9%				
Test for overall effect: $Z = 3.5$	2 (P = 0.00044)						
Test for subgroup differences:	Chi <sup>2</sup> = 0.87, df = 2	$(P = 0.65), I^2 = 0.09$	6				
				-4	-2 0 2 4	1	
				Favours hig	her PUFA Favours lowe	er PUFA	
(I) Change data, variance pre	esented as SDs, but a	assumed to be SEs a	and convert	ed			
(2) 0.9g/d n3 vs placebo (as t	these arms were wel	l balanced for weigh	nt at baselin	e)			
(3) Barcelona hospital cohor	t at 5 years, Casa 20	16					

(4) Babio CMAJ 2014 - Participants with metabolic syndrome at baseline, 5 year data

(5) Babio CMAJ 2014 participants without metabolic syndrome at baseline, 5 year data

(6) One year data

### Analysis 3.6. Comparison 3 Higher PUFA vs lower PUFA - continuous secondary outcomes, Outcome 6 Body weight, kg - subgroup by primary or secondary prevention.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 3 Higher PUFA vs lower PUFA - continuous secondary outcomes

Outcome: 6 Body weight, kg - subgroup by primary or secondary prevention

Study or subgroup H	ligher PUFA		Lower PUFA		Mean Difference	Weight	Mear Difference
	N	Mean(SD)	N	Mean(SD)	IV,Random,95% CI		IV,Random,95% C
Primary prevention of CVD	21	0.74 (2.201.2)	21	0.74 (1.2740)		0.2.9/	005 114 114
Bassey 2000-Post	21	0.74 (2.2913)	21	0.74 (1.3748)	L	8.3 %	0.0 [ -1.14, 1.14 ]
Bassey 2000-Pre	19	0.37 (2.6589)	24	0.19 (1.5677)		6.7 %	0.18 [ -1.17, 1.53 ]
Black 1994	58	80 (0)	57	76.5 (0)			Not estimable
Dullaart 1992	16	77 (10)	20	76 (11.2) ←		→ 0.4 %	1.00 [ -5.94, 7.94 ]
HERO-Tapsell 2009	18	92 (17.1)	17	92.3 (13.8) ←		→ 0.2 %	-0.30 [ -10.57, 9.97 ]
Ley 2004 (I)	70	0.59 (13.4702)	66	-3.32 (5.5243)		→ I.4 %	3.91 [ 0.48, 7.34 ]
MARINA - Sanders 2011 (2)	80	0.2 (1.8)	71	-0.3 (2.53)		13.2 %	0.50 [ -0.21, 1.21
PREDIMED 2013 (3)	1062	-0.5 (7.5)	1236	-1 (6.3)		15.2 %	0.50 [ -0.07, 1.07
PREDIMED 2013 (4)	54	-0.1 (0.37)	54	-1.3 (0.37)	-	20.5 %	1.20 [ 1.06, 1.34 ]
PREDIMED 2013 (5)	662	0.02 (5.3)	663	-0.2 (5.9)		14.7 %	0.22 [ -0.38, 0.82 ]
WAHA - Ros 2016	156	-0.29 (3.85)	156	-1.05 (3.85)		11.3 %	0.76 [ -0.09, 1.61
WELCOME 2015	47	94.1 (13)	48	90.4 (16.3)		•• 0.5 %	3.70 [ -2.22, 9.62
WINS 2006 (6)	1328	72.8 (14.8609)	840	70.6 (14.7661)		7.2 %	2.20 [ 0.92, 3.48
Subtotal (95% CI)	3591		3273		•	<b>99.</b> 7 %	0.76 [ 0.33, 1.19]
Heterogeneity: $Tau^2 = 0.24$ ; $Chi^2 = $ rest for overall effect: $Z = 3.44$ (P 2. Secondary prevention of CVD	= 0.00059)	. ,		00 (15) 🛨		→ 0.2.0%	2005 5 42 0 42
HARP- Sacks 1995	31	82 (14)	28	80 (15) ←		→ 0.3 %	2.00 [ -5.43, 9.43
MRC 1968	88	0 (0)	89	-1.4 (0)			Not estimable
Subtotal (95% CI) Heterogeneity: not applicable Test for overall effect: Z = 0.53 (P	<b>119</b> = 0.60)		117	_		0.3 %	2.00 [ -5.43, 9.43
Total (95% CI)	3710		3390		•	100.0 %	0.76 [ 0.34, 1.19
Heterogeneity: $Tau^2 = 0.22$ ; Chi <sup>2</sup> = Test for overall effect: Z = 3.52 (P		12 (P = 0.004);	l <sup>2</sup> =59%				
est for subgroup differences: $Chi^2$		(P = 0.74),   <sup>2</sup>	=0.0%				
5							

- (1) Change data, variance presented as SDs, but assumed to be SEs and converted
- (2) 0.9g/d n3 vs placebo (as these arms were well balanced for weight at baseline)
- (3) Babio CMAJ 2014 Participants with metabolic syndrome at baseline, 5 year data
- (4) Barcelona hospital cohort at 5 years, Casa 2016
- (5) Babio CMAJ 2014 participants without metabolic syndrome at baseline, 5 year data
- (6) One year data

#### Analysis 3.7. Comparison 3 Higher PUFA vs lower PUFA - continuous secondary outcomes, Outcome 7 Body weight, kg - subgroup by baseline PUFA dose.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 3 Higher PUFA vs lower PUFA - continuous secondary outcomes

Outcome: 7 Body weight, kg - subgroup by baseline PUFA dose

Study or subgroup	Higher PUFA		Lower PUFA		Mea Differenc		Mean Difference
	Ν	Mean(SD)	Ν	Mean(SD)	IV,Random,9	5% CI	IV,Random,95% CI
Baseline total PUFA < 6% E							
HERO-Tapsell 2009	18	92 (17.1)	17	92.3 (13.8)		0.2 %	-0.30 [ -10.57, 9.97 ]
Ley 2004 (I)	70	0.59 (13.4702)	66	-3.32 (5.5243)		• 1.4 %	3.91 [ 0.48, 7.34 ]
WINS 2006 (2)	1328	72.8 (14.8609)	840	70.6 (14.7661)	=	7.2 %	2.20 [ 0.92, 3.48 ]
Subtotal (95% CI) Heterogeneity: $Tau^2 = 0.0$ ; Chi <sup>2</sup> Test for overall effect: $Z = 3.91$ 2 Baseline total PUFA 6 to < 1	(P = 0.000093)	$(P = 0.58); I^2 = 0$	<b>923</b>			8.8 %	2.37 [ 1.18, 3.56 ]
Black 1994	58	80 (0)	57	76.5 (0)			Not estimable
Dullaart 1992	16	77 (10)	20	76 (11.2)		0.4 %	1.00 [ -5.94, 7.94 ]
MARINA - Sanders 2011 (3)	) 80	0.2 (1.8)	71	-0.3 (2.53)		13.2 %	0.50 [ -0.21, 1.21 ]
PREDIMED 2013 (4)	54	-0.1 (0.37)	54	-1.3 (0.37)		20.5 %	1.20 [ 1.06, 1.34 ]
PREDIMED 2013 (5)	662	0.02 (5.3)	663	-0.2 (5.9)		14.7 %	0.22 [ -0.38, 0.82 ]
PREDIMED 2013 (6)	1062	-0.5 (7.5)	1236	-1 (6.3)		15.2 %	0.50 [ -0.07, 1.07 ]
WAHA - Ros 2016	156	-0.29 (3.85)	156	-1.05 (3.85)		- 11.3 %	0.76 [ -0.09, 1.61 ]
				 Favours I		2 4 avours lower PUFA	

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							(··· Containaed)
Study or subgroup	Higher PUFA	La	ower PUFA		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	Ν	Mean(SD)	IV,Random,95% CI		IV,Random,95% CI
Subtotal (95% CI)	2088		2257		*	75.3 %	0.68 [ 0.21, 1.15 ]
Heterogeneity: $Tau^2 = 0.20$ ; C	Chi <sup>2</sup> = 17.69, df =	5 (P = 0.003); $I^2 =$	72%				
Test for overall effect: $Z = 2.8$	5 (P = 0.0043)						
3 Baseline total PUFA 11+% E	-						
Subtotal (95% CI)	0		0				Not estimable
Heterogeneity: not applicable							
Test for overall effect: not app	licable						
4 Baseline total PUFA unclear							
Bassey 2000-Post	21	0.74 (2.2913)	21	0.74 (1.3748)		8.3 %	0.0 [ -1.14, 1.14 ]
Bassey 2000-Pre	19	0.37 (2.6589)	24	0.19 (1.5677)		6.7 %	0.18 [ -1.17, 1.53 ]
HARP- Sacks 1995	31	82 (14)	28	80 (15) ←		→ 0.3 %	2.00 [ -5.43, 9.43 ]
MRC 1968	88	0 (0)	89	-1.4 (0)			Not estimable
WELCOME 2015	47	94.1 (13)	48	90.4 (16.3)		•• 0.5 %	3.70 [ -2.22, 9.62 ]
Subtotal (95% CI)	206		210		-	15.9 %	0.18 [ -0.68, 1.03 ]
Heterogeneity: Tau <sup>2</sup> = 0.0; Ch	$mi^2 = 1.68, df = 3$ (	$P = 0.64$ ; $I^2 = 0.0\%$	6				
Test for overall effect: $Z = 0.4$	0 (P = 0.69)						
Total (95% CI)	3710		3390		•	100.0 %	0.76 [ 0.34, 1.19 ]
Heterogeneity: Tau <sup>2</sup> = 0.22; C	$Chi^2 = 29.28$ , df =	2 (P = 0.004);   <sup>2</sup> =	=59%				
Test for overall effect: $Z = 3.5$	2 (P = 0.00044)						
Test for subgroup differences:	Chi <sup>2</sup> = 8.94, df =	2 (P = 0.01), I <sup>2</sup> =7	8%				
				-4	-2 0 2	4	
				Favours hig	her PUFA Favours Iov	wer PUFA	

(1) Change data, variance presented as SDs, but assumed to be SEs and converted

(2) One year data

(3) 0.9g/d n3 vs placebo (as these arms were well balanced for weight at baseline)

(4) Barcelona hospital cohort at 5 years, Casa 2016

(5) Babio CMAJ 2014 participants without metabolic syndrome at baseline, 5 year data

(6) Babio CMAJ 2014 - Participants with metabolic syndrome at baseline, 5 year data

# Analysis 3.8. Comparison 3 Higher PUFA vs lower PUFA - continuous secondary outcomes, Outcome 8 Body weight, kg - subgroup by replacement.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 3 Higher PUFA vs lower PUFA - continuous secondary outcomes

Outcome: 8 Body weight, kg - subgroup by replacement

		Lower PUFA		Higher PUFA	Study or subgroup
	Mean(SD)	N	Mean(SD)	N	
	74 (11.0)	20	77 (10)		I PUFA replaced saturated fats
	76 (11.2)	20	77 (10)	16	Dullaart 1992
•	92.3 (13.8)	17	92 (17.1)	18	HERO-Tapsell 2009
	-1.4 (0)	89	0 (0)	88	MRC 1968
		126		122	Subtotal (95% CI)
		0%	$(P = 0.84); I^2 = 0.$	P = 0.84)	Heterogeneity: Tau <sup>2</sup> = 0.0; Chi <sup>2</sup> Test for overall effect: Z = 0.20 2 PUFA replaced monounsatura
•	80 (15)	28	82 (14)	31	HARP- Sacks 1995
	-0.3 (2.53)	71	0.2 (1.8)	80	MARINA - Sanders 2011 (1)
	-0.2 (5.9)	663	0.02 (5.3)	662	PREDIMED 2013 (2)
	-1 (6.3)	1236	-0.5 (7.5)	1062	PREDIMED 2013 (3)
	-1.3 (0.37)	54	-0.1 (0.37)	54	PREDIMED 2013 (4)
	90.4 (16.3)	48	94.1 (13)	47	WELCOME 2015
		2100		1936	Subtotal (95% CI)
		=72%	5 (P = 0.003); I <sup>2</sup>		Heterogeneity: Tau <sup>2</sup> = 0.24; Ch Test for overall effect: Z = 2.51 3 PUFA replaced carbohydrates
	76.5 (0)	57	80 (0)	58	Black 1994
	-3.32 (5.5243)	66	0.59 (13.4702)	70	Ley 2004 (5)
	-0.3 (2.53)	71	0.2 (1.8)	80	MARINA - Sanders 2011 (6)
	-1.05 (3.85)	156	-0.29 (3.85)	156	WAHA - Ros 2016
	70.6 (14.7661)	840	72.8 (14.8609)	328	WINS 2006 (7)
		1190	D = 0.04 $P = 0.04$	<b>1692</b>	Subtotal (95% CI)
		04%	s (P - 0.04); P -		Heterogeneity: Tau~ – 0.54; Ch Test for overall effect: Z = 2.52
				01012)	4 PUFA replaced protein
•	92.3 (13.8)	17	92 (17.1)	18	HERO-Tapsell 2009
▲ 4 higher	92.3 (13.8)	840 <b>1190</b> %	64	72.8 (14.8609) $P(P = 0.04); I^2 = 64$	$ 328 \ 72.8 \ ( 4.8609)$ $1692$ $i^{2} = 8.26, df = 3 \ (P = 0.04); \  ^{2} = 64$ $(P = 0.012)$

Study or subgroup	Higher PUFA N	Lo Mean(SD)	wer PUFA N	Mean(SD)	Mean Difference IV.Random,95% Cl	Weight	( Continued) Mean Difference IV,Random,95% Cl
Ley 2004 (8)		0.59 (13.4702)		-3.32 (5.5243)		26.8 %	3.91 [ 0.48, 7.34 ]
MRC 1968	88	0 (0)	89	-1.4 (0)			Not estimable
WAHA - Ros 2016	156	-0.29 (3.85)	156	-1.05 (3.85)		68.9 %	0.76 [ -0.09, 1.61 ]
Subtotal (95% CI)	332		328			100.0 %	1.56 [ -0.64, 3.75 ]
Test for overall effect: Z = 1.39 5 unclear Bassey 2000-Post	(P = 0.16) 21	0.74 (2.2913)	21	0.74 (1.3748)	-	58.3 %	0.0 [ -1.14, 1.14 ]
Bassey 2000-Pre	19	0.37 (2.6589)	24	0.19 (1.5677)		41.7 %	0.18 [ -1.17, 1.53 ]
<b>Subtotal (95% CI)</b> Heterogeneity: Tau <sup>2</sup> = 0.0; Chi Test for overall effect: Z = 0.17 Test for subgroup differences: C	(P = 0.87)				-	100.0 %(	0.08 [ -0.80, 0.95 ]

Favours higher PUFA Favours lower PUFA

(1) 0.9g/d n3 vs placebo (as these arms were well balanced for weight at baseline)

(2) Babio CMAJ 2014 participants without metabolic syndrome at baseline, 5 year data

(3) Babio CMAJ 2014 - Participants with metabolic syndrome at baseline, 5 year data

(4) Barcelona hospital cohort at 5 years, Casa 2016

(5) Change data, variance presented as SDs, but assumed to be SEs and converted

(6) 0.9g/d n3 vs placebo (as these arms were well balanced for weight at baseline)

(7) One year data

(8) Change data, variance presented as SDs, but assumed to be SEs and converted

# Analysis 3.9. Comparison 3 Higher PUFA vs lower PUFA - continuous secondary outcomes, Outcome 9 Body weight, kg - subgroup by sex.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 3 Higher PUFA vs lower PUFA - continuous secondary outcomes

Outcome: 9 Body weight, kg - subgroup by sex

Study or subgroup	Higher PUFA		Lower PUFA		Mean Difference	Weight	Mear Difference
	N	Mean(SD)	Ν	Mean(SD)	IV,Random,95% CI		IV,Random,95% (
> 70% men							
Dullaart 1992	16	77 (10)	20	76 (11.2) ←	· ·	• 0.4 %	1.00 [ -5.94, 7.94
HARP- Sacks 1995	31	82 (14)	28	80 (15) ←		• 0.3 %	2.00 [ -5.43, 9.43
Ley 2004 (I)	70	0.59 (13.4702)	66	-3.32 (5.5243)		• 1.4 %	3.91 [ 0.48, 7.34
MRC 1968	88	0 (0)	89	-1.4 (0)			Not estimabl
Subtotal (95% CI)	205		203			2.1 %	3.14 [ 0.31, 5.98
Heterogeneity: $Tau^2 = 0.0$ ; Chi <sup>2</sup>	<sup>2</sup> = 0.65, df = 2	$(P = 0.72); I^2 = 0$	0.0%				
Test for overall effect: $Z = 2.17$	(P = 0.030)						
2 > 70% women	21	074 (22012)	21	0.74 (1.2740)		8.3 %	
Bassey 2000-Post	21		21	0.74 (1.3748)			0.0 [ -1.14, 1.14
Bassey 2000-Pre	19	0.37 (2.6589)	24	0.19 (1.5677)		6.7 %	0.18 [ -1.17, 1.53
WINS 2006 (2)	328	72.8 (14.8609)	840	70.6 (14.7661)	<b>_</b>	7.2 %	2.20 [ 0.92, 3.48
Subtotal (95% CI)	1368		885			22.3 %	0.78 [ -0.60, 2.17
3 men % women Black 1994	58	80 (0)	57	76.5 (0)			Not estimab
Black 1994	58	80 (0)	57	76.5 (0)			Not estimabl
MARINA - Sanders 2011 (3	) 80	0.2 (1.8)	71	-0.3 (2.53)		13.2 %	0.50 [ -0.21, 1.21
PREDIMED 2013 (4)	54	-0.1 (0.37)	54	-1.3 (0.37)	-	20.5 %	1.20 [ 1.06, 1.34
PREDIMED 2013 (5)	1062	-0.5 (7.5)	1236	-1 (6.3)	-	15.2 %	0.50 [ -0.07, 1.07
PREDIMED 2013 (6)	662	0.02 (5.3)	663	-0.2 (5.9)		14.7 %	0.22 [ -0.38, 0.82
WAHA - Ros 2016	156	-0.29 (3.85)	156	-1.05 (3.85)		11.3 %	0.76 [ -0.09, 1.61
WELCOME 2015	47	94.1 (13)	48	90.4 (16.3)		• 0.5 %	3.70 [ -2.22, 9.62
Subtotal (95% CI)	2119		2285		•	75.5 %	0.70 [ 0.22, 1.18
Heterogeneity: $Tau^2 = 0.21$ ; Ch		5 (P = 0.002); I	2 =73%				
Test for overall effect: $Z = 2.86$	(P = 0.0042)						
4 sex not reported HERO-Tapsell 2009	18	92 (17.1)	17	92.3 (13.8) ←		• 0.2 %	-0.30 [ -10.57, 9.97

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Study or subgroup	Higher PUFA	Low	ver PUFA		Diffe	Mean erence	Weight	( Continued) Mean Difference
	Ν	Mean(SD)	Ν	Mean(SD)	IV,Rand	om,95% Cl		IV,Random,95% CI
Subtotal (95% CI)	18		17				0.2 % -	0.30 [ -10.57, 9.97 ]
Heterogeneity: not applicable								
Test for overall effect: $Z = 0.06$	6 (P = 0.95)							
Total (95% CI)	3710		3390			•	100.0 %	0.76 [ 0.34, 1.19 ]
Heterogeneity: Tau <sup>2</sup> = 0.22; Cl	$hi^2 = 29.28, df = 1$	2 (P = 0.004); $I^2 = 1$	59%					
Test for overall effect: $Z = 3.52$	2 (P = 0.00044)							
Test for subgroup differences: (	Chi <sup>2</sup> = 2.82, df = 3	(P = 0.42), I <sup>2</sup> =0.0	1%					
				-4	-2	0 2	4	

Favours higher PUFA Favours lower PUFA

(1) Change data, variance presented as SDs, but assumed to be SEs and converted

(2) One year data

(3) 0.9g/d n3 vs placebo (as these arms were well balanced for weight at baseline)

(4) Barcelona hospital cohort at 5 years, Casa 2016

(5) Babio CMAJ 2014 - Participants with metabolic syndrome at baseline, 5 year data

(6) Babio CMAJ 2014 participants without metabolic syndrome at baseline, 5 year data

# Analysis 3.10. Comparison 3 Higher PUFA vs lower PUFA - continuous secondary outcomes, Outcome 10 Body weight, kg - subgroup by age.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 3 Higher PUFA vs lower PUFA - continuous secondary outcomes

Outcome: 10 Body weight, kg - subgroup by age

Study or subgroup	Higher PUFA		Lower PUFA		Mean Difference	Weight	Mear Difference
	Ν	Mean(SD)	Ν	Mean(SD)	IV,Random,95% CI		IV,Random,95% C
I Mean age < 50 years							
Bassey 2000-Pre	19	0.37 (2.6589)	24	0.19 (1.5677)		6.7 %	0.18 [ -1.17, 1.53
Dullaart 1992	16	77 (10)	20	76 (11.2) ←		→ 0.4 %	1.00 [ -5.94, 7.94
Subtotal (95% CI)	35		44		-	7.1 %	0.21 [ -1.12, 1.54
Heterogeneity: $Tau^2 = 0.0$ ; Chi <sup>2</sup> Test for overall effect: $Z = 0.31$ (		$P = 0.82$ ; $I^2 = 0.0$	)%				
2 Mean age 50 to $< 65$ years	0.70)						
Bassey 2000-Post	21	0.74 (2.2913)	21	0.74 (1.3748)		8.3 %	0.0 [ -1.14, 1.14
Black 1994	58	80 (0)	57	76.5 (0)			Not estimabl
HARP- Sacks 1995	31	82 (14)	28	80 (15) 🔶	·	→ 0.3 %	2.00 [ -5.43, 9.43
HERO-Tapsell 2009	18	92 (17.1)	17	92.3 (13.8) ←		→ 0.2 %	-0.30 [ -10.57, 9.97
Ley 2004 (I)	70	0.59 (13.4702)	66	-3.32 (5.5243)		→ I.4 %	3.91 [ 0.48, 7.34
MARINA - Sanders 2011 (2)	80	0.2 (1.8)	71	-0.3 (2.53)		13.2 %	0.50 [ -0.21, 1.21
MRC 1968	88	0 (0)	89	-1.4 (0)			Not estimabl
WELCOME 2015	47	94.1 (13)	48	90.4 (16.3)		•• 0.5 %	3.70 [ -2.22, 9.62
WINS 2006 (3)	1328	72.8 (14.8609)	840	70.6 (14.7661)	<b>_</b> _	7.2 %	2.20 [ 0.92, 3.48
Subtotal (95% CI)	1741		1237		-	31.2 %	1.15 [ 0.12, 2.18
Heterogeneity: $Tau^2 = 0.67$ ; Chi <sup>2</sup> Test for overall effect: $Z = 2.20$ (		6 (P = 0.08); I <sup>2</sup> =	47%				
3 Mean age 65+ years PREDIMED 2013 (4)	662	0.02 (5.3)	663	-0.2 (5.9)		14.7 %	0.22 [ -0.38, 0.82
PREDIMED 2013 (5)	1062	-0.5 (7.5)	1236	-1 (6.3)		15.2 %	0.50 [ -0.07, 1.07
PREDIMED 2013 (6)	54	-0.1 (0.37)	54	-1.3 (0.37)	-	20.5 %	1.20 [ 1.06, 1.34
WAHA - Ros 2016	156	-0.29 (3.85)	156	-1.05 (3.85)		11.3 %	0.76 [ -0.09, 1.61
Subtotal (95% CI)	1934		2109		•	61.7 %	0.71 [ 0.16, 1.26
Heterogeneity: Tau <sup>2</sup> = 0.24; Chi <sup>2</sup>		3 (P = 0.002); $I^2$ :	=80%				
Test for overall effect: $Z = 2.52$ (	,						
Total (95% CI)	3710		3390		•	100.0 %	0.76 [ 0.34, 1.19

(Continued ...)

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Study or subgroup	Higher PUFA	Lowe	er PUFA		∩ Differe	1ean ence	Weight	Mean Difference
	Ν	Mean(SD)	Ν	Mean(SD)	IV,Randon	n,95% Cl		IV,Random,95% CI
Heterogeneity: $Tau^2 = 0.22$ ; (	Chi <sup>2</sup> = 29.28, df = 12	$2 (P = 0.004); I^2 = 59$	1%					
Test for overall effect: $Z = 3.5$	52 (P = 0.00044)							
Test for subgroup differences	: $Chi^2 = 1.25$ , $df = 2$	$(P = 0.54), I^2 = 0.0\%$						
				-4	-2 0	2 4		
				Favours high	er PUFA	Favours lower	PUFA	
(I) Change data, variance pr	resented as SDs, but	assumed to be SEs a	nd convert	ed				
(2) 0.9g/d n3 vs placebo (as	these arms were we	I balanced for weigh	t at baselin	e)				
(3) One year data								

(4) Babio CMAJ 2014 participants without metabolic syndrome at baseline, 5 year data

(5) Babio CMAJ 2014 - Participants with metabolic syndrome at baseline, 5 year data

(6) Barcelona hospital cohort at 5 years, Casa 2016

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# Analysis 3.11. Comparison 3 Higher PUFA vs lower PUFA - continuous secondary outcomes, Outcome 11 Body weight, kg - subgroup by statin use.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 3 Higher PUFA vs lower PUFA - continuous secondary outcomes

Outcome: II Body weight, kg - subgroup by statin use

	Higher PUFA		Lower PUFA		Mean Difference	Weight	Mear Difference
	N	Mean(SD)	N	Mean(SD)	IV,Random,95% CI		IV,Random,95% C
I < 50% on statins Bassey 2000-Post	21	0.74 (2.2913)	21	0.74 (1.3748)		8.3 %	0.0 [ -1.14, 1.14
,	19	0.37 (2.6589)	24	0.19 (1.5677)		6.7 %	-
Bassey 2000-Pre		· · · ·		· · · ·		0.7 /0	0.18 [ -1.17, 1.53
Black 1994	58	80 (0)	57	76.5 (0)			Not estimabl
Dullaart 1992	16	77 (10)	20	76 (11.2) ←	•	→ 0.4 %	1.00 [ -5.94, 7.94
HARP- Sacks 1995	31	82 (14)	28	80 (15)		→ 0.3 %	2.00 [ -5.43, 9.43
MARINA - Sanders 2011 (1)	80	0.2 (1.8)	71	-0.3 (2.53)		13.2 %	0.50 [ -0.21, 1.21
MRC 1968	88	0 (0)	89	-1.4 (0)			Not estimabl
PREDIMED 2013 (2)	662	0.02 (5.3)	663	-0.2 (5.9)		14.7 %	0.22 [ -0.38, 0.82
PREDIMED 2013 (3)	1062	-0.5 (7.5)	1236	-1 (6.3)		15.2 %	0.50 [ -0.07, 1.07
PREDIMED 2013 (4)	54	-0.1 (0.37)	54	-1.3 (0.37)	-	20.5 %	1.20 [ 1.06, 1.34
						72.0/	220102240
WINS 2006 (5) Subtotal (95% CI)	3419	72.8 (14.8609)	3103	70.6 (14.7661)	•	7.2 % <b>86.6 %</b>	-
WINS 2006 (5)	<b>3419</b> = 25.30, df = 5		3103	70.6 (14.7661) 92.3 (13.8) ←	•		2.20 [ 0.92, 3.48 0.69 [ 0.21, 1.17 -0.30 [ -10.57, 9.97
WINS 2006 (5) <b>Subtotal (95% CI)</b> Heterogeneity: Tau <sup>2</sup> = 0.26; Chi <sup>2</sup> Test for overall effect: Z = 2.84 (P 2 50+% on statins	<b>3419</b> = 25.30, df = 2 P = 0.0045)	8 (P = 0.001); I <sup>2</sup>	<b>3103</b>	, <i>,</i>	•	86.6 %	<b>0.69 [ 0.21, 1.17</b>
WINS 2006 (5) <b>Subtotal (95% CI)</b> Heterogeneity: Tau <sup>2</sup> = 0.26; Chi <sup>2</sup> Test for overall effect: Z = 2.84 (P 2 50+% on statins HERO-Tapsell 2009 WELCOME 2015 <b>Subtotal (95% CI)</b> Heterogeneity: Tau <sup>2</sup> = 0.0; Chi <sup>2</sup> = Test for overall effect: Z = 1.03 (P 3 Percentage on statins unclear	<b>3419</b> = 25.30, df = 1 P = 0.0045) 18 47 <b>65</b> = 0.44, df = 1 ( P = 0.30)	8 (P = 0.001); l <sup>2</sup> 92 (17.1) 94.1 (13) P = 0.51); l <sup>2</sup> =0	<b>3103</b> = 68% 17 48 <b>65</b>	92.3 (13.8) ← 90.4 (16.3)	•	<ul> <li>86.6 %</li> <li>0.2 %</li> <li>0.5 %</li> <li>0.7 %</li> </ul>	0.69 [ 0.21, 1.17 -0.30 [ -10.57, 9.97 3.70 [ -2.22, 9.62 2.70 [ -2.43, 7.83
WINS 2006 (5) Subtotal (95% CI) Heterogeneity: Tau <sup>2</sup> = 0.26; Chi <sup>2</sup> Test for overall effect: Z = 2.84 (P 2 50+% on statins HERO-Tapsell 2009 WELCOME 2015 Subtotal (95% CI) Heterogeneity: Tau <sup>2</sup> = 0.0; Chi <sup>2</sup> = Test for overall effect: Z = 1.03 (P 3 Percentage on statins unclear Ley 2004 (6)	<b>3419</b> = 25.30, df = 1 2 = 0.0045) 18 47 <b>65</b> = 0.44, df = 1 ( 2 = 0.30) 70	$8 (P = 0.001);  ^{2}$ $92 (17.1)$ $94.1 (13)$ $P = 0.51);  ^{2} = 0$ $0.59 (13.4702)$	<b>3103</b> = 68% 17 48 <b>65</b> 00%	92.3 (13.8) ← 90.4 (16.3) -3.32 (5.5243)	•	<ul> <li>86.6 %</li> <li>0.2 %</li> <li>0.5 %</li> <li>0.7 %</li> <li>1.4 %</li> </ul>	0.69 [ 0.21, 1.17 -0.30 [ -10.57, 9.97 3.70 [ -2.22, 9.62 2.70 [ -2.43, 7.83 3.91 [ 0.48, 7.34
WINS 2006 (5) <b>Subtotal (95% CI)</b> Heterogeneity: Tau <sup>2</sup> = 0.26; Chi <sup>2</sup> Test for overall effect: $Z = 2.84$ (P 2 50+% on statins HERO-Tapsell 2009 WELCOME 2015 <b>Subtotal (95% CI)</b> Heterogeneity: Tau <sup>2</sup> = 0.0; Chi <sup>2</sup> = Test for overall effect: $Z = 1.03$ (P 3 Percentage on statins unclear Ley 2004 (6) WAHA - Ros 2016	<b>3419</b> = 25.30, df = 1 P = 0.0045) 18 47 <b>65</b> = 0.44, df = 1 ( P = 0.30) 70 156	8 (P = 0.001); l <sup>2</sup> 92 (17.1) 94.1 (13) P = 0.51); l <sup>2</sup> =0	<b>3103</b> = 68% 17 48 <b>65</b> .0% 66 156	92.3 (13.8) ← 90.4 (16.3)	• 	<ul> <li>■ 0.2 %</li> <li>■ 0.5 %</li> <li>■ 0.7 %</li> <li>■ 1.4 %</li> <li>□ 1.3 %</li> </ul>	0.69 [ 0.21, 1.17 -0.30 [ -10.57, 9.97 3.70 [ -2.22, 9.62 2.70 [ -2.43, 7.83 3.91 [ 0.48, 7.34 0.76 [ -0.09, 1.61
WINS 2006 (5) Subtotal (95% CI) Heterogeneity: Tau <sup>2</sup> = 0.26; Chi <sup>2</sup> Test for overall effect: Z = 2.84 (P 2 50+% on statins HERO-Tapsell 2009 WELCOME 2015 Subtotal (95% CI) Heterogeneity: Tau <sup>2</sup> = 0.0; Chi <sup>2</sup> = Test for overall effect: Z = 1.03 (P 3 Percentage on statins unclear Ley 2004 (6)	<b>3419</b> = 25.30, df = 1 2 = 0.0045) 18 47 <b>65</b> = 0.44, df = 1 ( 2 = 0.30) 70 156 <b>226</b> = 3.06, df = 1	$8 (P = 0.001); 1^{2}$ $92 (17.1)$ $94.1 (13)$ $P = 0.51); 1^{2} = 0$ $0.59 (13.4702)$ $-0.29 (3.85)$	<b>3103</b> = 68% 17 48 65 0.0% 66 156 <b>222</b>	92.3 (13.8) ← 90.4 (16.3) -3.32 (5.5243)	•	<ul> <li>■ 0.2 %</li> <li>■ 0.5 %</li> <li>■ 0.7 %</li> <li>■ 1.4 %</li> <li>□ 1.3 %</li> </ul>	0.69 [ 0.21, 1.17 -0.30 [ -10.57, 9.97 3.70 [ -2.22, 9.62 2.70 [ -2.43, 7.83

(... Continued)

Study or subgroup	Higher PUFA	Lowe	r PUFA		Diff	Mean erence	Weight	Mean Difference
	Ν	Mean(SD)	Ν	Mean(SD)	IV,Rand	om,95% Cl		IV,Random,95% Cl
Heterogeneity: $Tau^2 = 0.22$ ; 0	Chi <sup>2</sup> = 29.28, df = 12	$2 (P = 0.004); I^2 = 599$	%					
Test for overall effect: $Z = 3.5$	52 (P = 0.00044)							
Test for subgroup differences	:: $Chi^2 = 1.17$ , $df = 2$	$(P = 0.56), I^2 = 0.0\%$						
				-4	-2	0 2	4	
				Favours hig	ner PUFA	Favours Iov	wer PUFA	
(1) 0.9g/d n3 vs placebo (as	these arms were we	I balanced for weight	at baselir	ne)				
(2) Babio CMAJ 2014 partic	ipants without metab	olic syndrome at bas	eline, 5 ye	ear data				
(3) Babio CMAJ 2014 - Part	icipants with metabo	lic syndrome at baseli	ne, 5 year	- data				

(4) Barcelona hospital cohort at 5 years, Casa 2016

(5) One year data

(6) Change data, variance presented as SDs, but assumed to be SEs and converted

### Analysis 3.12. Comparison 3 Higher PUFA vs lower PUFA - continuous secondary outcomes, Outcome 12 Body weight, kg - subgroup by intervention type.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 3 Higher PUFA vs lower PUFA - continuous secondary outcomes

Outcome: 12 Body weight, kg - subgroup by intervention type

Study or subgroup	Higher PUFA		Lower PUFA		Mean Difference	Weight	Mear Difference
	Ν	Mean(SD)	Ν	Mean(SD)	IV,Random,95% CI		IV,Random,95% C
I Dietary advice							
Black 1994	58	80 (0)	57	76.5 (0)			Not estimabl
Dullaart 1992	16	77 (10)	20	76 (11.2) ←		• 0.4 %	1.00 [ -5.94, 7.94
Ley 2004 (I)	70	0.59 (13.4702)	66	-3.32 (5.5243)		• 1.4 %	3.91 [ 0.48, 7.34
WINS 2006 (2)	1328	72.8 (14.8609)	840	70.6 (14.7661)		7.2 %	2.20 [ 0.92, 3.48
Subtotal (95% CI)	1472		983		-	9.0 %	2.37 [ 1.19, 3.55
Heterogeneity: Tau <sup>2</sup> = 0.0; Chi <sup>2</sup>	= 0.99, df = 2	$(P = 0.6 I); I^2 = 0$	.0%				
Test for overall effect: $Z = 3.93$ (	· · · · · ·						
2 Supplemental foods % diet pro	ovided		17	022(120) +		• 0.2.%	0.201 1017 007
HERO-Tapsell 2009		92 (17.1)		92.3 (13.8) ←		• 0.2 %	-0.30 [ -10.57, 9.97
PREDIMED 2013 (3)	54	-0.1 (0.37)	54	-1.3 (0.37)	-	20.5 %	1.20 [ 1.06, 1.34
PREDIMED 2013 (4)	1062	-0.5 (7.5)	1236	-1 (6.3)		15.2 %	0.50 [ -0.07, 1.07
PREDIMED 2013 (5)	662	0.02 (5.3)	663	-0.2 (5.9)		14.7 %	0.22 [ -0.38, 0.82
WAHA - Ros 2016	156	-0.29 (3.85)	156	-1.05 (3.85)		11.3 %	0.76 [ -0.09, 1.61
Subtotal (95% CI)	1952		2126		•	61.9 %	0.71 [ 0.18, 1.25
Heterogeneity: Tau <sup>2</sup> = 0.22; Chi <sup>2</sup>	<sup>2</sup> = 15.03, df =	4 (P = 0.005); I <sup>2</sup>	=73%				
Test for overall effect: $Z = 2.61$ (	· /						
3 Supplements (capsules % unus	,	0.74 (2.2012)	21	0.74 (1.2740)		8.3 %	0.0 [ -1.14, 1.14
Bassey 2000-Post		0.74 (2.2913)		0.74 (1.3748)	T		-
Bassey 2000-Pre	19	0.37 (2.6589)	24	0.19 (1.5677)		6.7 %	0.18 [ -1.17, 1.53
HARP- Sacks 1995	31	82 (14)	28	80 (15) ←		• 0.3 %	2.00 [ -5.43, 9.43
MARINA - Sanders 2011 (6)	80	0.2 (1.8)	71	-0.3 (2.53)		13.2 %	0.50 [ -0.21, 1.21
WELCOME 2015	47	94.1 (13)	48	90.4 (16.3)		• 0.5 %	3.70 [ -2.22, 9.62
Subtotal (95% CI)	198		192		•	29.1 %	0.37 [ -0.18, 0.91
Heterogeneity: $Tau^2 = 0.0$ ; $Chi^2$	= 2.01, df = 4	$(P = 0.73); I^2 = 0$	.0%				
Test for overall effect: $Z = 1.32$ (	(P = 0.19)						
4 Any combination	~~	0.00	~~~				NT 1 11
MRC 1968	88	0 (0)	89	-1.4 (0)			Not estimabl

<sup>(</sup>Continued . . . )

								( Continued)
Study or subgroup	Higher PUFA	Lo	wer PUFA		Dif	Mean ference	Weight	Mean Difference
	Ν	Mean(SD)	Ν	Mean(SD)	IV,Rand	dom,95% Cl		IV,Random,95% CI
Subtotal (95% CI)	88		89					Not estimable
Heterogeneity: not applicable								
Test for overall effect: not appl	icable							
Total (95% CI)	3710		3390			•	100.0 %	0.76 [ 0.34, 1.19 ]
Heterogeneity: Tau <sup>2</sup> = 0.22; C	$hi^2 = 29.28, df = 12$	2 (P = 0.004); $I^2 =$	59%					
Test for overall effect: $Z = 3.52$	2 (P = 0.00044)							
Test for subgroup differences:	Chi <sup>2</sup> = 9.08, df = 2	(P = 0.01), I <sup>2</sup> =78	3%					
				-4	-2	0 2	4	

Favours higher PUFA Favours lower PUFA

(1) Change data, variance presented as SDs, but assumed to be SEs and converted

(2) One year data

(3) Barcelona hospital cohort at 5 years, Casa 2016

(4) Babio CMAJ 2014 - Participants with metabolic syndrome at baseline, 5 year data

(5) Babio CMAJ 2014 participants without metabolic syndrome at baseline, 5 year data

(6) 0.9g/d n3 vs placebo (as these arms were well balanced for weight at baseline)

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#### Analysis 3.13. Comparison 3 Higher PUFA vs lower PUFA - continuous secondary outcomes, Outcome 13 ADIPOSITY - Body Mass Index (BMI), kg/m2.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 3 Higher PUFA vs lower PUFA - continuous secondary outcomes

Outcome: 13 ADIPOSITY - Body Mass Index (BMI), kg/m2

Study or subgroup	Higher PUFA		Lower PUFA		Mean Difference	Weight	Mean Difference
	Ν	Mean(SD)	Ν	Mean(SD)	IV,Random,95% CI		IV,Random,95% CI
AlphaOmega - ALA (1)	630	0.07 (1.5)	630	-0.08 (1.8)	-	15.6 %	0.15 [ -0.03, 0.33 ]
Dodin 2005	85	25.9 (4.5)	94	27.4 (4.8)	•	2.8 %	-1.50 [ -2.86, -0.14 ]
Mita 2007	30	25.1 (5.3)	30	24.1 (3)		→ I.2 %	1.00 [ -1.18, 3.18 ]
Nodari 2011 HF	67	26 (0.4)	66	26 (0.6)	+	15.7 %	0.0 [ -0.17, 0.17 ]
PREDIMED 2013 (2)	51	28.7 (3.01)	42	28.6 (2.9)		3.4 %	0.10 [ -1.10, 1.30 ]
PREDIMED 2013 (3)	54	-0.02 (0.18)	54	-0.5 (0.37)	-	16.5 %	0.48 [ 0.37, 0.59 ]
PREDIMED 2013 (4)	102	-0.5 (2.04)	112	-0.5 (1.6)		10.1 %	0.0 [ -0.49, 0.49 ]
PREDIMED 2013 (5)	58	-0.1 (1.36)	59	-0.1 (1.18)		10.7 %	0.0 [ -0.46, 0.46 ]
Sydney Diet-Heart 1978	179	24.3 (1.5)	192	24.5 (2)		12.5 %	-0.20 [ -0.56, 0.16 ]
WELCOME 2015	47	33.4 (4.9)	48	30.8 (4.5)		→ I.5 %	2.60 [ 0.71, 4.49 ]
WINS 2006 (6)	1328	27.6 (5.5728)	840	26.8 (5.9064)	_ <b></b>	10.0 %	0.80 [ 0.30, 1.30 ]
Total (95% CI) Heterogeneity: Tau <sup>2</sup> = 0.09; Test for overall effect: $Z = I$ .		f = 10 (P<0.000	<b>2167</b> 01); I <sup>2</sup> =80%		•	100.0 %	0.17 [ -0.08, 0.42 ]
Test for subgroup differences	s: Not applicable	2				1	

-2 -1 0 1 2

Favours higher PUFA Favours lower PUFA

(1) Numer of participants equally divided between groups

(3) Barcelona hospital cohort at 5 years, Casa 2016

(4) Canaries subcohort, change from baseline to 1 year, Alvarez-Perez 2016

(5) Damasceno 2013, Barcelona North subcohort, I year data

(6) One year data

<sup>(2)</sup> Reus subcohort, 2 year data

# Analysis 3.14. Comparison 3 Higher PUFA vs lower PUFA - continuous secondary outcomes, Outcome 14 BMI, kg/m2 - SA.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 3 Higher PUFA vs lower PUFA - continuous secondary outcomes

Outcome: 14 BMI, kg/m2 - SA

Study or subgroup Hig	gher PUFA N	Mean(SD)	Lower PUFA N	Mean(SD)	Mean Difference IV,Random,95% Cl	Weight	Mean Difference IV,Random,95% CI
Low risk of bias for allocation c	oncealment	. ,		. ,			
AlphaOmega - ALA (1)	630	0.07 (1.5)	630	-0.08 (1.8)	-	35.2 %	0.15 [ -0.03, 0.33 ]
Sydney Diet-Heart 1978	179	24.3 (1.5)	192	24.5 (2)		31.3 %	-0.20 [ -0.56, 0.16 ]
WELCOME 2015	47	33.4 (4.9)	48	30.8 (4.5)		+ 6.2 %	2.60 [ 0.71, 4.49 ]
WINS 2006 (2)	1328	27.6 (5.5728)	840	26.8 (5.9064)		27.4 %	0.80 [ 0.30, 1.30 ]
Subtotal (95% CI)	2184		1710		-	100.0 %	0.37 [ -0.15, 0.88 ]
Heterogeneity: Tau <sup>2</sup> = 0.19; Chi <sup>2</sup>	<sup>2</sup> = 16.58, df	= 3 (P = 0.0008	36); I <sup>2</sup> =82%				
Test for overall effect: $Z = 1.41$ (F	P = 0.16)						
2 Low risk of bias for attention AlphaOmega - ALA (3)	630	0.07 (1.5)	630	-0.08 (1.8)		20.4 %	0.15 [ -0.03, 0.33 ]
Dodin 2005	85	25.9 (4.5)	94	· · · ·	<u></u>	3.3 %	-1.50 [ -2.86, -0.14 ]
				27.4 (4.8)			
Mita 2007	30	25.1 (5.3)	30	24.1 (3)		• 1.4 %	1.00 [ -1.18, 3.18 ]
Nodari 2011 HF	67	26 (0.4)	66	26 (0.6)	+	20.6 %	0.0 [ -0.17, 0.17 ]
PREDIMED 2013 (4)	51	28.7 (3.01)	42	28.6 (2.9)		4.1 %	0.10 [ -1.10, 1.30 ]
PREDIMED 2013 (5)	58	-0.1 (1.36)	59	-0.1 (1.18)		13.6 %	0.0 [ -0.46, 0.46 ]
PREDIMED 2013 (6)	54	-0.02 (0.18)	54	-0.5 (0.37)	-	21.7 %	0.48 [ 0.37, 0.59 ]
PREDIMED 2013 (7)	102	-0.5 (2.04)	112	-0.5 (1.6)	_ <b>-</b>	12.8 %	0.0 [ -0.49, 0.49 ]
WELCOME 2015	47	33.4 (4.9)	48	30.8 (4.5)		→ I.9 %	2.60 [ 0.71, 4.49 ]
Subtotal (95% CI) Heterogeneity: Tau <sup>2</sup> = 0.08; Chi <sup>2</sup>	<b>1124</b>	= 8 (P<0.00001	1135 ): 1 <sup>2</sup> =80%		•	100.0 %	0.15 [ -0.12, 0.42 ]
Test for overall effect: $Z = 1.10$ (F B Low risk of bias for compliance	P = 0.27)		),				
Mita 2007	30	25.1 (5.3)	30	24.1 (3)		→ 27.0 %	1.00 [ -1.18, 3.18 ]
Sydney Diet-Heart 1978	179	24.3 (1.5)	192	24.5 (2)		43.2 %	-0.20 [ -0.56, 0.16 ]
WELCOME 2015	47	33.4 (4.9)	48	30.8 (4.5)	<u> </u>	→ 29.8 %	2.60 [ 0.71, 4.49 ]
Subtotal (95% CI)	<b>256</b> = 9.07. df =	= 2 (P = 0.01); I <sup>2</sup>	<b>270</b>			- 100.0 %	0.96 [ -0.86, 2.78 ]

(Continued ...)

Study or subgroup	Higher PUFA N	Mean(SD)	Lower PUFA N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Test for overall effect: Z = 1.0	3 (P = 0.30)						
4 Low summary risk of bias	. ,						
AlphaOmega - ALA (8)	630	0.07 (1.5)	630	-0.08 (1.8)	-	35.2 %	0.15 [ -0.03, 0.33 ]
Sydney Diet-Heart 1978	179	24.3 (1.5)	192	24.5 (2)		31.3 %	-0.20 [ -0.56, 0.16 ]
WELCOME 2015	47	33.4 (4.9)	48	30.8 (4.5)		• 6.2 %	2.60 [ 0.71, 4.49 ]
WINS 2006 (9)	1328	27.6 (5.5728)	840	26.8 (5.9064)		27.4 %	0.80 [ 0.30, 1.30 ]
Subtotal (95% CI)	2184		1710		-	100.0 %	0.37 [ -0.15, 0.88 ]
Heterogeneity: $Tau^2 = 0.19$ ; C	$Chi^2 = 16.58$ , dt	F = 3 (P = 0.000	86); l <sup>2</sup> =82%				
Test for overall effect: $Z = 1.4$	I (P = 0.16)						
5 Trials registry or pre-2010							
AlphaOmega - ALA (10)	630	0.07 (1.5)	630	-0.08 (1.8)		15.6 %	0.15 [ -0.03, 0.33 ]
Dodin 2005	85	25.9 (4.5)	94	27.4 (4.8)		2.8 %	-1.50 [ -2.86, -0.14 ]
Mita 2007	30	25.1 (5.3)	30	24.1 (3)			1.00 [ -1.18, 3.18 ]
Nodari 2011 HF	67	26 (0.4)	66	26 (0.6)	+	15.7 %	0.0 [ -0.17, 0.17 ]
PREDIMED 2013 (11)	51	28.7 (3.01)	42	28.6 (2.9)		3.4 %	0.10 [ -1.10, 1.30 ]
PREDIMED 2013 (12)	58	-0.1 (1.36)	59	-0.  ( . 8)		10.7 %	0.0 [ -0.46, 0.46 ]
PREDIMED 2013 (13)	54	-0.02 (0.18)	54	-0.5 (0.37)	-	16.5 %	0.48 [ 0.37, 0.59 ]
PREDIMED 2013 (14)	102	-0.5 (2.04)	112	-0.5 (1.6)		10.1 %	0.0 [ -0.49, 0.49 ]
Sydney Diet-Heart 1978	179	24.3 (1.5)	192	24.5 (2)		12.5 %	-0.20 [ -0.56, 0.16 ]
WELCOME 2015	47	33.4 (4.9)	48	30.8 (4.5)			2.60 [ 0.71, 4.49 ]
WINS 2006 (15)	1328	27.6 (5.5728)	840	26.8 (5.9064)		10.0 %	0.80 [ 0.30, 1.30 ]
Subtotal (95% CI)	2631		2167		•	100.0 %	0.17 [ -0.08, 0.42 ]
Heterogeneity: Tau <sup>2</sup> = 0.09; C	:hi² = 51.21, df	F = 10 (P<0.000	01); I <sup>2</sup> =80%				
Test for overall effect: $Z = 1.3$	6 (P = 0.17)						
6 No industry funding							
Sydney Diet-Heart 1978	179	24.3 (1.5)	192	24.5 (2)		51.6 %	-0.20 [ -0.56, 0.16 ]
WINS 2006 (16)		27.6 (5.5728)	840	26.8 (5.9064)		48.4 %	0.80 [ 0.30, 1.30 ]
Subtotal (95% CI)	1507		1032			100.0 %	0.28 [ -0.70, 1.26 ]
Heterogeneity: Tau <sup>2</sup> = 0.45; C		f = 1 (P = 0.001)	); l <sup>2</sup> =90%				
Test for overall effect: $Z = 0.5$	` '						
7 Randomised 100+ participa AlphaOmega - ALA (17)	nts 630	0.07 (1.5)	630	-0.08 (1.8)		15.7 %	0.15 [ -0.03, 0.33 ]
		. ,	94	. ,			
Dodin 2005	85	25.9 (4.5)		27.4 (4.8)	<b>_</b>	2.8 %	-1.50 [ -2.86, -0.14 ]
Nodari 2011 HF	67	26 (0.4)	66	26 (0.6)	Ī	15.9 %	0.0 [ -0.17, 0.17 ]
PREDIMED 2013 (18)	58	-0.1 (1.36)	59	-0.1 (1.18)	_	10.8 %	0.0 [ -0.46, 0.46 ]
				-2	-1 0 1	2	
				2	· · ·	2	

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Mear Difference IV,Random,95% C	Weight	Mean Difference IV,Random,95% Cl	Mean(SD)	Lower PUFA N	Mean(SD)	Higher PUFA N	Study or subgroup
0.0 [ -0.49, 0.49 ]	10.3 %		-0.5 (1.6)	112	-0.5 (2.04)	102	PREDIMED 2013 (19)
0.48 [ 0.37, 0.59 ]	16.6 %	-	-0.5 (0.37)	54	-0.02 (0.18)	54	PREDIMED 2013 (20)
0.10 [ -1.10, 1.30 ]	3.4 %		28.6 (2.9)	42	28.7 (3.01)	51	PREDIMED 2013 (21)
-0.20 [ -0.56, 0.16 ]	12.7 %		24.5 (2)	192	24.3 (1.5)	179	Sydney Diet-Heart 1978
2.60 [ 0.71, 4.49 ]	· 1.6 %		30.8 (4.5)	48	33.4 (4.9)	47	WELCOME 2015
0.80 [ 0.30, 1.30 ]	10.2 %		26.8 (5.9064)	840	27.6 (5.5728)	1328	WINS 2006 (22)
0.16 [ -0.09, 0.41 ]	100.0 %	•		<b>2137</b> ); I <sup>2</sup> =82%	F = 9 (P<0.0000)	27 (P = 0.20)	Subtotal (95% CI) Heterogeneity: Tau <sup>2</sup> = 0.09; Test for overall effect: Z = 1. 8 Randomised 250+ particip
0.15 [ -0.03, 0.33 ]	20.7 %	-	-0.08 (1.8)	630	0.07 (1.5)	630	AlphaOmega - ALA (23)
0.10 [ -1.10, 1.30 ]	3.7 %		28.6 (2.9)	42	28.7 (3.01)	51	PREDIMED 2013 (24)
0.0 [ -0.46, 0.46 ]	13.1 %	_	-0.1 (1.18)	59	-0.1 (1.36)	58	PREDIMED 2013 (25)
0.48 [ 0.37, 0.59 ]	22.3 %	-	-0.5 (0.37)	54	-0.02 (0.18)	54	PREDIMED 2013 (26)
0.0 [ -0.49, 0.49 ]	12.3 %	_	-0.5 (1.6)	112	-0.5 (2.04)	102	PREDIMED 2013 (27)
-0.20 [ -0.56, 0.16 ]	15.8 %		24.5 (2)	192	24.3 (1.5)	179	Sydney Diet-Heart 1978
0.80 [ 0.30, 1.30 ]	12.1 %	— <b>—</b>	26.8 (5.9064)	840	27.6 (5.5728)	1328	WINS 2006 (28)
0.21 [ -0.04, 0.46 ]	100.0 %	•		<b>1929</b> 19); 1 <sup>2</sup> =77%	F = 6 (P = 0.000		Subtotal (95% CI) Heterogeneity: Tau <sup>2</sup> = 0.07; Test for overall effect: $Z = 1$ .

Favours higher PUFA

Favours lower PUFA

(... Continued)

- (1) Numer of participants equally divided between groups
- (2) One year data
- (3) Numer of participants equally divided between groups
- (4) Reus subcohort, 2 year data
- (5) Damasceno 2013, Barcelona North subcohort, I year data
- (6) Barcelona hospital cohort at 5 years, Casa 2016
- (7) Canaries subcohort, change from baseline to 1 year, Alvarez-Perez 2016
- (8) Numer of participants equally divided between groups
- (9) One year data
- (10) Numer of participants equally divided between groups
- (11) Reus subcohort, 2 year data
- (12) Damasceno 2013, Barcelona North subcohort, 1 year data
- (13) Barcelona hospital cohort at 5 years, Casa 2016
- (14) Canaries subcohort, change from baseline to 1 year, Alvarez-Perez 2016
- (15) One year data
- (16) One year data
- (17) Numer of participants equally divided between groups
- (18) Damasceno 2013, Barcelona North subcohort, 1 year data
- (19) Canaries subcohort, change from baseline to 1 year, Alvarez-Perez 2016
- (20) Barcelona hospital cohort at 5 years, Casa 2016
- (21) Reus subcohort, 2 year data
- (22) One year data
- (23) Numer of participants equally divided between groups
- (24) Reus subcohort, 2 year data
- (25) Damasceno 2013, Barcelona North subcohort, I year data
- (26) Barcelona hospital cohort at 5 years, Casa 2016
- (27) Canaries subcohort, change from baseline to 1 year, Alvarez-Perez 2016
- (28) One year data

#### Analysis 3.15. Comparison 3 Higher PUFA vs lower PUFA - continuous secondary outcomes, Outcome 15 BMI, kg/m2 - SA fixed-effect.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 3 Higher PUFA vs lower PUFA - continuous secondary outcomes

Outcome: 15 BMI, kg/m2 - SA fixed-effect

Study or subgroup	Higher PUFA		Lower PUFA		Mean Difference	Weight	Mean Difference
	Ν	Mean(SD)	Ν	Mean(SD)	IV,Fixed,95% CI		IV,Fixed,95% CI
AlphaOmega - ALA (I)	630	0.07 (1.5)	630	-0.08 (1.8)	-	17.7 %	0.15 [ -0.03, 0.33 ]
Dodin 2005	85	25.9 (4.5)	94	27.4 (4.8)	<del></del>	0.3 %	-1.50 [ -2.86, -0.14 ]
Mita 2007	30	25.1 (5.3)	30	24.1 (3)		→ 0.1 %	1.00 [ -1.18, 3.18 ]
Nodari 2011 HF	67	26 (0.4)	66	26 (0.6)	+	19.7 %	0.0 [ -0.17, 0.17 ]
PREDIMED 2013 (2)	102	-0.5 (2.04)	112	-0.5 (1.6)		2.4 %	0.0 [ -0.49, 0.49 ]
PREDIMED 2013 (3)	54	-0.02 (0.18)	54	-0.5 (0.37)		49.3 %	0.48 [ 0.37, 0.59 ]
PREDIMED 2013 (4)	58	-0.1 (1.36)	59	-0.1 (1.18)		2.8 %	0.0 [ -0.46, 0.46 ]
PREDIMED 2013 (5)	51	28.7 (3.01)	42	28.6 (2.9)		0.4 %	0.10 [ -1.10, 1.30 ]
Sydney Diet-Heart 1978	179	24.3 (1.5)	192	24.5 (2)		4.6 %	-0.20 [ -0.56, 0.16 ]
WELCOME 2015	47	33.4 (4.9)	48	30.8 (4.5)		→ 0.2 %	2.60 [ 0.71, 4.49
WINS 2006 (6)	328	27.6 (5.5728)	840	26.8 (5.9064)		2.4 %	0.80 [ 0.30, 1.30 ]
Total (95% CI)	2631		2167		•	100.0 %	0.27 [ 0.20, 0.35 ]
Heterogeneity: Chi <sup>2</sup> = 51.21,	df = 10 (P<0.0	00001); l <sup>2</sup> =80%					
Test for overall effect: Z = 6.9	98 (P < 0.0000	)					
Test for subgroup differences:	Not applicable	1					

Favours higher PUFA Favours lower PUFA

(1) Numer of participants equally divided between groups

(2) Canaries subcohort, change from baseline to 1 year, Alvarez-Perez 2016

(3) Barcelona hospital cohort at 5 years, Casa 2016

(4) Damasceno 2013, Barcelona North subcohort, I year data

(5) Reus subcohort, 2 year data

(6) One year data

# Analysis 3.16. Comparison 3 Higher PUFA vs lower PUFA - continuous secondary outcomes, Outcome 16 BMI, kg/m2 - subgroup by PUFA dose.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 3 Higher PUFA vs lower PUFA - continuous secondary outcomes

Outcome: 16 BMI, kg/m2 - subgroup by PUFA dose

Study or subgroup	Higher PUFA		Lower PUFA		Mean Difference	Weight	Mea Differenc
	N	Mean(SD)	N	Mean(SD)	IV,Random,95% Cl		IV,Random,95% (
I total PUFA < 1.0% E							
Mita 2007	30	25.1 (5.3)	30	24.1 (3)		→ I.2 %	1.00 [ -1.18, 3.18
Nodari 2011 HF	67	26 (0.4)	66	26 (0.6)	+	15.7 %	0.0 [ -0.17, 0.17
Subtotal (95% CI)	97		96		+	16.9 %	0.01 [ -0.17, 0.18
Heterogeneity: $Tau^2 = 0.0$ ; Cl	ni² = 0.80, df =	I (P = 0.37); I <sup>2</sup>	=0.0%				
Test for overall effect: $Z = 0.0$	` '						
2 total PUFA 1.0 to < 2.0% E					_		
AlphaOmega - ALA (1)	630	0.07 (1.5)	630	-0.08 (1.8)		15.6 %	0.15 [ -0.03, 0.33
Dodin 2005	85	25.9 (4.5)	94	27.4 (4.8)		2.8 %	-1.50 [ -2.86, -0.14
PREDIMED 2013 (2)	102	-0.5 (2.04)	112	-0.5 (1.6)		10.1 %	0.0 [ -0.49, 0.49
PREDIMED 2013 (3)	54	-0.02 (0.18)	54	-0.5 (0.37)	-	16.5 %	0.48 [ 0.37, 0.59
PREDIMED 2013 (4)	58	-0.1 (1.36)	59	-0.  ( . 8)	_	10.7 %	0.0 [ -0.46, 0.46
PREDIMED 2013 (5)	51	28.7 (3.01)	42	28.6 (2.9)		3.4 %	0.10 [ -1.10, 1.30
WELCOME 2015	47	33.4 (4.9)	48	30.8 (4.5)		→ I.5 %	2.60 [ 0.71, 4.49
WINS 2006 (6)	1328	27.6 (5.5728)	840	26.8 (5.9064)	_ <b></b>	10.0 %	0.80 [ 0.30, 1.30
Subtotal (95% CI)	2355		1879		•	70.6 %	0.26 [ -0.03, 0.55
Heterogeneity: $Tau^2 = 0.09$ ; (	$Chi^2 = 29.63, dt$	f = 7 (P = 0.000	)  );   <sup>2</sup> =76%				
Test for overall effect: $Z = 1.7$	78 (P = 0.076)						
3 total PUFA 2.0 to < 5.0% E							
Subtotal (95% CI)	0		0				Not estimabl
Heterogeneity: not applicable							
Test for overall effect: not app	olicable						
4 total PUFA 5.0+% E Sydney Diet-Heart 1978	179	24.3 (1.5)	192	24.5 (2)		12.5 %	-0.20 [ -0.56, 0.16
Subtotal (95% CI)	179	()	192	(_)	•		-0.20 [ -0.56, 0.16
Heterogeneity: not applicable			1/2			12.9 /0	0.20 [ 0.90, 0.10
Test for overall effect: $Z = 1.0$							
Total (95% CI)	2631		2167		•	100.0 %	0.17 [ -0.08, 0.42
Heterogeneity: $Tau^2 = 0.09$ ; (	Chi <sup>2</sup> = 51.21, dt	f= 10 (P<0.000	001); I <sup>2</sup> =80%				
Test for overall effect: $Z = 1.3$	86 (P = 0.17)						
Test for subgroup differences:	Chi <sup>2</sup> = 4.13, d	f = 2 (P = 0.13)	, l <sup>2</sup> =52%				
				I			

- (1) Numer of participants equally divided between groups
- (2) Canaries subcohort, change from baseline to 1 year, Alvarez-Perez 2016
- (3) Barcelona hospital cohort at 5 years, Casa 2016
- (4) Damasceno 2013, Barcelona North subcohort, I year data
- (5) Reus subcohort, 2 year data
- (6) One year data

#### Analysis 3.17. Comparison 3 Higher PUFA vs lower PUFA - continuous secondary outcomes, Outcome 17 BMI, kg/m2 - subgroup by duration.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 3 Higher PUFA vs lower PUFA - continuous secondary outcomes

Outcome: 17 BMI, kg/m2 - subgroup by duration

Study or subgroup	Higher PUFA		Lower PUFA		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	Ν	Mean(SD)	IV,Random,95% CI	-	IV,Random,95% CI
Medium duration   to <	2 years						
Dodin 2005	85	25.9 (4.5)	94	27.4 (4.8)	<b>←</b> →	2.8 %	-1.50 [ -2.86, -0.14 ]
Nodari 2011 HF	67	26 (0.4)	66	26 (0.6)	+	15.7 %	0.0 [ -0.17, 0.17 ]
WELCOME 2015	47	33.4 (4.9)	48	30.8 (4.5)			2.60 [ 0.71, 4.49 ]
Subtotal (95% CI)	199		208			20.0 %	0.21 [ -1.40, 1.81 ]
Heterogeneity: $Tau^2 = 1.6$	I; Chi <sup>2</sup> = 11.90, df	= 2 (P = 0.003)	); I <sup>2</sup> =83%				
Test for overall effect: Z =	0.25 (P = 0.80)						
2 Medium-long duration 2	to < 4 years						
AlphaOmega - ALA (1)	630	0.07 (1.5)	630	-0.08 (1.8)	-	15.6 %	0.15 [ -0.03, 0.33 ]
Mita 2007	30	25.1 (5.3)	30	24.1 (3)		• 1.2 %	1.00 [ -1.18, 3.18 ]
Subtotal (95% CI)	660		660		<b>•</b>	16.8 %	0.16 [ -0.03, 0.34 ]
Heterogeneity: $Tau^2 = 0.0$ ;	$Chi^2 = 0.58, df =$	I (P = 0.45); I <sup>2</sup>	=0.0%				
Test for overall effect: $Z =$	I.68 (P = 0.094)						
3 Long duration 4+ years							
PREDIMED 2013 (2)	51	28.7 (3.01)	42	28.6 (2.9)		3.4 %	0.10 [ -1.10, 1.30 ]
PREDIMED 2013 (3)	102	-0.5 (2.04)	112	-0.5 (1.6)		10.1 %	0.0 [ -0.49, 0.49 ]
PREDIMED 2013 (4)	54	-0.02 (0.18)	54	-0.5 (0.37)	-	16.5 %	0.48 [ 0.37, 0.59 ]
					-2 -1 0 1	2	
					s higher PUFA Favours low		
				i avours	singlici rorra i avours iow	GIUNA	

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					Maar		( Continued)
Study or subgroup	Higher PUFA		Lower PUFA		Mean Difference	Weight	Mean Difference
	Ν	Mean(SD)	Ν	Mean(SD)	IV,Random,95% CI		IV,Random,95% CI
PREDIMED 2013 (5)	58	-0.1 (1.36)	59	-0.  ( . 8)		10.7 %	0.0 [ -0.46, 0.46 ]
Sydney Diet-Heart 1978	179	24.3 (1.5)	192	24.5 (2)		12.5 %	-0.20 [ -0.56, 0.16 ]
WINS 2006 (6)	1328	27.6 (5.5728)	840	26.8 (5.9064)		10.0 %	0.80 [ 0.30, 1.30 ]
Subtotal (95% CI)	1772		1299		•	63.2 %	0.22 [ -0.12, 0.55 ]
Heterogeneity: $Tau^2 = 0.11$ ;	$Chi^2 = 20.92, d$	f = 5 (P = 0.000	84); I <sup>2</sup> =76%				
Test for overall effect: $Z = I$	.27 (P = 0.20)						
Total (95% CI)	2631		2167		•	100.0 %	0.17 [ -0.08, 0.42 ]
Heterogeneity: $Tau^2 = 0.09$ ;	Chi <sup>2</sup> = 51.21, d	f = 10 (P<0.000	01); I <sup>2</sup> =80%				
Test for overall effect: $Z = I$	.36 (P = 0.17)						
Test for subgroup difference	s: Chi <sup>2</sup> = 0.10, d	f = 2 (P = 0.95)	I <sup>2</sup> =0.0%				
						i	

-2 -1 0 I 2 Favours higher PUFA Favours lower PUFA

(1) Numer of participants equally divided between groups

(2) Reus subcohort, 2 year data

(3) Canaries subcohort, change from baseline to 1 year, Alvarez-Perez 2016

(4) Barcelona hospital cohort at 5 years, Casa 2016

(5) Damasceno 2013, Barcelona North subcohort, 1 year data

(6) One year data

#### Analysis 3.18. Comparison 3 Higher PUFA vs lower PUFA - continuous secondary outcomes, Outcome 18 BMI, kg/m2 - subgroup by primary or secondary prevention.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 3 Higher PUFA vs lower PUFA - continuous secondary outcomes

Outcome: 18 BMI, kg/m2 - subgroup by primary or secondary prevention

Study or subgroup	Higher PUFA N	Mean(SD)	Lower PUFA N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
I Primary prevention of CV	D						
Dodin 2005	85	25.9 (4.5)	94	27.4 (4.8)	<b>←</b> →───	2.8 %	-1.50 [ -2.86, -0.14 ]
Mita 2007	30	25.1 (5.3)	30	24.1 (3)		• 1.2 %	1.00 [ -1.18, 3.18 ]
PREDIMED 2013 (1)	58	-0.1 (1.36)	59	-0.1 (1.18)		10.7 %	0.0 [ -0.46, 0.46 ]
PREDIMED 2013 (2)	51	28.7 (3.01)	42	28.6 (2.9)	<u>,</u>	3.4 %	0.10 [ -1.10, 1.30 ]
PREDIMED 2013 (3)	102	-0.5 (2.04)	112	-0.5 (1.6)	_ <b>_</b>	10.1 %	0.0 [ -0.49, 0.49 ]
PREDIMED 2013 (4)	54	-0.02 (0.18)	54	-0.5 (0.37)	-	16.5 %	0.48 [ 0.37, 0.59 ]
WELCOME 2015	47	33.4 (4.9)	48	30.8 (4.5)		• 1.5 %	2.60 [ 0.71, 4.49 ]
WINS 2006 (5)	1328	27.6 (5.5728)	840	26.8 (5.9064)	_ <b></b>	10.0 %	0.80 [ 0.30, 1.30 ]
Subtotal (95% CI)	1755		1279		-	56.2 %	0.30 [ -0.09, 0.69 ]
Heterogeneity: $Tau^2 = 0.15$ ;	$Chi^2 = 22.38, d$	f = 7 (P = 0.002	); l <sup>2</sup> =69%				
Test for overall effect: $Z = I$	.53 (P = 0.13)						
2 Secondary prevention of 0	CVD						
AlphaOmega - ALA (6)	630	0.07 (1.5)	630	-0.08 (1.8)	-	15.6 %	0.15 [ -0.03, 0.33 ]
Nodari 2011 HF	67	26 (0.4)	66	26 (0.6)	+	15.7 %	0.0 [ -0.17, 0.17 ]
Sydney Diet-Heart 1978	179	24.3 (1.5)	192	24.5 (2)		12.5 %	-0.20 [ -0.56, 0.16 ]
Subtotal (95% CI)	876		888		+	43.8 %	0.03 [ -0.13, 0.19 ]
Heterogeneity: $Tau^2 = 0.01$ ;	$Chi^2 = 3.32$ , df	= 2 (P = 0.19); I	$ ^2 = 40\%$				
Test for overall effect: $Z = 0$	.34 (P = 0.74)						
Total (95% CI)	2631		2167		•	100.0 %	0.17 [ -0.08, 0.42 ]
Heterogeneity: $Tau^2 = 0.09$ ;		f = 10 (P<0.000	01); l <sup>2</sup> =80%				
Test for overall effect: $Z = I$	· /						
Test for subgroup difference	s: Chi <sup>2</sup> = 1.63, c	If = I (P = 0.20)	, I <sup>2</sup> =39%				
						1	

-2 -1 0 I 2 Favours higher PUFA Favours lower PUFA

(1) Damasceno 2013, Barcelona North subcohort, 1 year data

(2) Reus subcohort, 2 year data

(3) Canaries subcohort, change from baseline to 1 year, Alvarez-Perez 2016

(4) Barcelona hospital cohort at 5 years, Casa 2016

(5) One year data

(6) Numer of participants equally divided between groups

## Analysis 3.19. Comparison 3 Higher PUFA vs lower PUFA - continuous secondary outcomes, Outcome 19 BMI, kg/m2 - subgroup by baseline PUFA dose.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 3 Higher PUFA vs lower PUFA - continuous secondary outcomes

Outcome: 19 BMI, kg/m2 - subgroup by baseline PUFA dose

Study or subgroup	Higher PUFA		Lower PUFA		Mean Difference	Weight	Mear Difference
	Ν	Mean(SD)	N	Mean(SD)	IV,Random,95% CI		IV,Random,95% (
I Baseline total PUFA < 6% E							
Dodin 2005	85	25.9 (4.5)	94	27.4 (4.8)	<b>←</b> +	2.8 %	-1.50 [ -2.86, -0.14
WINS 2006 (1)	1328	27.6 (5.5728)	840	26.8 (5.9064)		10.0 %	0.80 [ 0.30, 1.30
Subtotal (95% CI)	1413		934			12.8 %	-0.26 [ -2.51, 1.99
Heterogeneity: Tau <sup>2</sup> = 2.37; (	$Chi^2 = 9.65, df$	= I (P = 0.002)	); l <sup>2</sup> =90%				
Test for overall effect: $Z = 0.2$	23 (P = 0.82)						
2 Baseline total PUFA 6 to <	11% E						
PREDIMED 2013 (2)	102	-0.5 (2.04)	112	-0.5 (1.6)		10.1 %	0.0 [ -0.49, 0.49
PREDIMED 2013 (3)	58	-0.1 (1.36)	59	-0.  ( . 8)	-	10.7 %	0.0 [ -0.46, 0.46
PREDIMED 2013 (4)	54	-0.02 (0.18)	54	-0.5 (0.37)	-	16.5 %	0.48 [ 0.37, 0.59
PREDIMED 2013 (5)	51	28.7 (3.01)	42	28.6 (2.9)		3.4 %	0.10 [ -1.10, 1.30
Sydney Diet-Heart 1978	179	24.3 (1.5)	192	24.5 (2)		12.5 %	-0.20 [ -0.56, 0.16
Subtotal (95% CI)	444		459		-	53.2 %	0.10 [ -0.27, 0.47
Heterogeneity: $Tau^2 = 0.12$ ; (	Chi <sup>2</sup> = 18.34, d	f = 4 (P = 0.00)	I); I <sup>2</sup> =78%				
Test for overall effect: Z = 0.5	52 (P = 0.60)						
3 Baseline total PUFA 11+%	E						
Subtotal (95% CI)	0		0				Not estimable
Heterogeneity: not applicable							
Test for overall effect: not app	olicable						
4 Baseline total PUFA unclear							
AlphaOmega - ALA (6)	630	0.07 (1.5)	630	-0.08 (1.8)	-	15.6 %	0.15 [ -0.03, 0.33
Mita 2007	30	25.1 (5.3)	30	24.1 (3)		• 1.2 %	1.00 [ -1.18, 3.18
Nodari 2011 HF	67	26 (0.4)	66	26 (0.6)	+	15.7 %	0.0 [ -0.17, 0.17
WELCOME 2015	47	33.4 (4.9)	48	30.8 (4.5)		• 1.5 %	2.60 [ 0.71, 4.49
Subtotal (95% CI)	774		774		•	34.0 %	0.16 [ -0.16, 0.48
Heterogeneity: $Tau^2 = 0.05$ ; (	$Chi^2 = 8.86, df$	= 3 (P = 0.03);	$ ^2 = 66\%$				
Test for overall effect: $Z = 0.9$	99 (P = 0.32)						
						ı	
				-	2 -1 0 1	2	

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Study or subgroup	Higher PUFA	Lc	ower PUFA		l	Mean Difference		Weight	Mean Difference
	Ν	Mean(SD)	Ν	Mean(SD)	IV,Ra	andom,95%	CI		IV,Random,95% Cl
Total (95% CI)	2631		2167			•		100.0 %	0.17 [ -0.08, 0.42 ]
Heterogeneity: $Tau^2 = 0.0$	9; Chi <sup>2</sup> = 51.21, df	= 10 (P<0.00001);	l <sup>2</sup> =80%						
Test for overall effect: Z =	1.36 (P = 0.17)								
Test for subgroup difference	ces: $Chi^2 = 0.18$ , df	= 2 (P = 0.91), I <sup>2</sup>	=0.0%						
				-2	-1	0 1	2	!	
				Favours hi	gher PUFA	Favo	urs lowe	r PUFA	

(I) One year data

(2) Canaries subcohort, change from baseline to 1 year, Alvarez-Perez 2016

(3) Damasceno 2013, Barcelona North subcohort, I year data

(4) Barcelona hospital cohort at 5 years, Casa 2016

(5) Reus subcohort, 2 year data

(6) Numer of participants equally divided between groups

## Analysis 3.20. Comparison 3 Higher PUFA vs lower PUFA - continuous secondary outcomes, Outcome 20 BMI, kg/m2 - subgroup by replacement.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 3 Higher PUFA vs lower PUFA - continuous secondary outcomes

Outcome: 20 BMI, kg/m2 - subgroup by replacement

Study or subgroup	Higher PUFA		Lower PUFA		Mean Difference	Weight	Mear Difference
	N	Mean(SD)	Ν	Mean(SD)	IV,Random,95% CI		IV,Random,95% C
I PUFA replaced saturated f Sydney Diet-Heart 1978	fats 179	24.3 (1.5)	192	24.5 (2)	-	100.0 %	-0.20 [ -0.56, 0.16
, ,		21.5 (1.5)		2113 (2)			-
Subtotal (95% CI) Heterogeneity: not applicabl	179		192			100.0 %	-0.20 [ -0.56, 0.16
Test for overall effect: $Z = 1$							
2 PUFA replaced monounsa	· · · ·						
AlphaOmega - ALA (I)	630	0.07 (1.5)	630	-0.08 (1.8)	-	18.5 %	0.15 [ -0.03, 0.33
Nodari 2011 HF	67	26 (0.4)	66	26 (0.6)	-	18.7 %	0.0 [ -0.17, 0.17
PREDIMED 2013 (2)	54	-0.02 (0.18)	54	-0.5 (0.37)	-	19.8 %	0.48 [ 0.37, 0.59
PREDIMED 2013 (3)	58	-0.1 (1.36)	59	-0.  ( . 8)	_	12.1 %	0.0 [ -0.46, 0.46
PREDIMED 2013 (4)	102	-0.5 (2.04)	112	-0.5 (1.6)	_	11.4 %	0.0 [ -0.49, 0.49
PREDIMED 2013 (5)	51	28.7 (3.01)	42	28.6 (2.9)		3.6 %	0.10 [ -1.10, 1.30
Sydney Diet-Heart 1978	179	24.3 (1.5)	192	24.5 (2)		14.4 %	-0.20 [ -0.56, 0.16
WELCOME 2015	47	33.4 (4.9)	48	30.8 (4.5)		→ I.6 %	2.60 [ 0.71, 4.49
Subtotal (95% CI)	1188		1203		•	100.0 %	0.14 [ -0.11, 0.39
Heterogeneity: Tau <sup>2</sup> = 0.08; Test for overall effect: Z = 1 3 PUFA replaced carbohydra Dodin 2005	.09 (P = 0.28)	f = 7 (P<0.0000) 25.9 (4.5)	); I <sup>2</sup> =82% 94	27.4 (4.8)	·-	46.0 %	-1.50 [ -2.86, -0.14
WINS 2006 (6)	1328	27.6 (5.5728)	840	26.8 (5.9064)		54.0 %	0.80 [ 0.30, 1.30
Subtotal (95% CI)	1413		934			- 100.0 %	-0.26 [ -2.51, 1.99
Heterogeneity: Tau <sup>2</sup> = 2.37; Test for overall effect: $Z = 0$ 4 PUFA replaced protein	$Chi^2 = 9.65, df$	= I (P = 0.002);				10000 /0	
Subtotal (95% CI)	0		0				Not estimabl
Heterogeneity: not applicabl	e						
Test for overall effect: not ap	plicable						
5 PUFA replaced unclear							
Mita 2007	30	25.1 (5.3)	30	24.1 (3)		→ 100.0 %	1.00 [ -1.18, 3.18
					-2 -1 0 I s higher PUFA Favours Iov	2 wer PUFA	
					<u> </u>		(Continued

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Study or subgroup	Higher PUFA	Lo	wer PUFA		C	Mean Difference	Weight	Mean Difference
	Ν	Mean(SD)	Ν	Mean(SD)	IV,Ra	ndom,95% Cl		IV,Random,95% CI
Subtotal (95% CI)	30		30				100.0 %	1.00 [ -1.18, 3.18 ]
Heterogeneity: not applical	ole							
Test for overall effect: $Z =$	0.90 (P = 0.37)							
Test for subgroup difference	es: Chi <sup>2</sup> = 3.14, df	= 3 (P = 0.37), I <sup>2</sup> =	=4%					
							1	
				-2	- 1	0 I	2	
				Favours	nigher PUFA	Favours lo	wer PUFA	

(1) Numer of participants equally divided between groups

(2) Barcelona hospital cohort at 5 years, Casa 2016

(3) Damasceno 2013, Barcelona North subcohort, I year data

(4) Canaries subcohort, change from baseline to 1 year, Alvarez-Perez 2016

(5) Reus subcohort, 2 year data

(6) One year data

# Analysis 3.21. Comparison 3 Higher PUFA vs lower PUFA - continuous secondary outcomes, Outcome 21 BMI, kg/m2 - subgroup by sex.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 3 Higher PUFA vs lower PUFA - continuous secondary outcomes

Outcome: 21 BMI, kg/m2 - subgroup by sex

Study or subgroup	Higher PUFA N	Mean(SD)	Lower PUFA N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
> 70% men		. ,		. ,			
AlphaOmega - ALA (1)	630	0.07 (1.5)	630	-0.08 (1.8)	-	15.6 %	0.15 [ -0.03, 0.33 ]
Nodari 2011 HF	67	26 (0.4)	66	26 (0.6)	+	15.7 %	0.0 [ -0.17, 0.17 ]
Sydney Diet-Heart 1978	179	24.3 (1.5)	192	24.5 (2)		12.5 %	-0.20 [ -0.56, 0.16 ]
Subtotal (95% CI)	876		888		+	43.8 %	0.03 [ -0.13, 0.19 ]
Heterogeneity: Tau <sup>2</sup> = 0.01; Test for overall effect: $Z = 0$ . 2 > 70% women		= 2 (P = 0.19);	12 =40%				
Dodin 2005	85	25.9 (4.5)	94	27.4 (4.8)		2.8 %	-1.50 [ -2.86, -0.14 ]
WINS 2006 (2)	1328	27.6 (5.5728)	840	26.8 (5.9064)		10.0 %	0.80 [ 0.30, 1.30 ]
Subtotal (95% CI)	1413		934			12.8 %	-0.26 [ -2.51, 1.99 ]
Test for overall effect: Z = 0. 3 men % women Mite 2007	× ,	25   (5 2)	20	24   (2)		→ 12 °	
3 men % women Mita 2007	30	25.1 (5.3)	30	24.1 (3)		→ 1.2 %	1.00 [ -1.18, 3.18 ]
PREDIMED 2013 (3)	54	-0.02 (0.18)	54	-0.5 (0.37)	-	16.5 %	0.48 [ 0.37, 0.59 ]
PREDIMED 2013 (4)	51	28.7 (3.01)	42	28.6 (2.9)		3.4 %	0.10 [ -1.10, 1.30 ]
PREDIMED 2013 (5)	58	-0.1 (1.36)	59	-0.  ( . 8)	_	10.7 %	0.0 [ -0.46, 0.46 ]
PREDIMED 2013 (6)	102	-0.5 (2.04)	112	-0.5 (1.6)		10.1 %	0.0 [ -0.49, 0.49 ]
WELCOME 2015	47	33.4 (4.9)	48	30.8 (4.5)		→ I.5 %	2.60 [ 0.71, 4.49 ]
Subtotal (95% CI) Heterogeneity: Tau <sup>2</sup> = 0.11; Test for overall effect: $Z = 1$ .		f = 5 (P = 0.03)	<b>345</b> ; I <sup>2</sup> =60%		•	43.4 %	0.31 [ -0.08, 0.71 ]
Total (95% CI)	2631		2167		•	100.0 %	0.17 [ -0.08, 0.42 ]
Heterogeneity: $Tau^2 = 0.09;$		f = 10 (P<0.000				10000 /0	
Test for overall effect: $Z = 1$ .	36 (P = 0.17)						
Test for subgroup differences	: $Chi^2 = 1.82$ , c	f = 2 (P = 0.40)	, l <sup>2</sup> =0.0%				
				Favour	-2 -1 0 1 s higher PUFA Favours	2 Iower PUFA	

- (1) Numer of participants equally divided between groups
- (2) One year data
- (3) Barcelona hospital cohort at 5 years, Casa 2016
- (4) Reus subcohort, 2 year data
- (5) Damasceno 2013, Barcelona North subcohort, I year data
- (6) Canaries subcohort, change from baseline to 1 year, Alvarez-Perez 2016

#### Analysis 3.22. Comparison 3 Higher PUFA vs lower PUFA - continuous secondary outcomes, Outcome 22 BMI, kg/m2 - subgroup by age.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 3 Higher PUFA vs lower PUFA - continuous secondary outcomes

Outcome: 22 BMI, kg/m2 - subgroup by age

Study or subgroup	Higher PUFA		Lower PUFA		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	Ν	Mean(SD)	IV,Random,95% CI		IV,Random,95% Cl
Mean age < 50 years							
Sydney Diet-Heart 1978	3 179	24.3 (1.5)	192	24.5 (2)		12.5 %	-0.20 [ -0.56, 0.16 ]
Subtotal (95% CI)	179		192		•	12.5 %	-0.20 [ -0.56, 0.16 ]
Heterogeneity: not applicab	ble						
Test for overall effect: Z =	1.09 (P = 0.27)						
2 Mean age 50 to < 65 yea	irs						
Dodin 2005	85	25.9 (4.5)	94	27.4 (4.8)	•	2.8 %	-1.50 [ -2.86, -0.14 ]
Mita 2007	30	25.1 (5.3)	30	24.1 (3)		→ I.2 %	1.00 [ -1.18, 3.18 ]
Nodari 2011 HF	67	26 (0.4)	66	26 (0.6)	+	15.7 %	0.0 [ -0.17, 0.17 ]
WELCOME 2015	47	33.4 (4.9)	48	30.8 (4.5)		→ I.5 %	2.60 [ 0.71, 4.49 ]
WINS 2006 (I)	1328	27.6 (5.5728)	840	26.8 (5.9064)		10.0 %	0.80 [ 0.30, 1.30 ]
Subtotal (95% CI)	1557		1078			31.2 %	0.38 [ -0.42, 1.18 ]
Heterogeneity: $Tau^2 = 0.5 I$	; Chi <sup>2</sup> = 21.45, c	If = 4 (P = 0.000)	026); I <sup>2</sup> =81%				
Test for overall effect: $Z = 0$	0.93 (P = 0.35)						
3 Mean age 65+ years							
AlphaOmega - ALA (2)	630	0.07 (1.5)	630	-0.08 (1.8)	-	15.6 %	0.15 [ -0.03, 0.33 ]
PREDIMED 2013 (3)	102	-0.5 (2.04)	112	-0.5 (1.6)		10.1 %	0.0 [ -0.49, 0.49 ]
					-2 -1 0 1	2	
				Favour	s higher PUFA Favours lo	wer PUFA	

(Continued ...)

							( Continued)
Study or subgroup	Higher PUFA	L	ower PUFA		Mean Difference	Weight	Mean Difference
	Ν	Mean(SD)	Ν	Mean(SD)	IV,Random,95% CI		IV,Random,95% CI
PREDIMED 2013 (4)	51	28.7 (3.01)	42	28.6 (2.9)		3.4 %	0.10 [ -1.10, 1.30 ]
PREDIMED 2013 (5)	58	-0.1 (1.36)	59	-0.1 (1.18)	_+_	10.7 %	0.0 [ -0.46, 0.46 ]
PREDIMED 2013 (6)	54	-0.02 (0.18)	54	-0.5 (0.37)	-	16.5 %	0.48 [ 0.37, 0.59 ]
Subtotal (95% CI)	895		897		•	56.2 %	0.21 [ -0.04, 0.47 ]
Heterogeneity: $Tau^2 = 0.05$	$5; Chi^2 = 14.20, df$	$= 4 (P = 0.01); I^2$	=72%				
Test for overall effect: Z =	I.66 (P = 0.098)						
Total (95% CI)	2631		2167		•	100.0 %	0.17 [ -0.08, 0.42 ]
Heterogeneity: $Tau^2 = 0.09$	9; Chi <sup>2</sup> = 51.21, df	= 10 (P<0.00001)	); l <sup>2</sup> =80%				
Test for overall effect: Z =	I.36 (P = 0.17)						
Test for subgroup difference	es: Chi <sup>2</sup> = 3.93, dt	$F = 2 (P = 0.14), I^2$	=49%				

-2 -1 0 1 2

Favours higher PUFA Favours lower PUFA

(I) One year data

(2) Numer of participants equally divided between groups

(3) Canaries subcohort, change from baseline to 1 year, Alvarez-Perez 2016

(4) Reus subcohort, 2 year data

(5) Damasceno 2013, Barcelona North subcohort, 1 year data

(6) Barcelona hospital cohort at 5 years, Casa 2016

## Analysis 3.23. Comparison 3 Higher PUFA vs lower PUFA - continuous secondary outcomes, Outcome 23 BMI, kg/m2 - subgroup by statin use.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 3 Higher PUFA vs lower PUFA - continuous secondary outcomes

Outcome: 23 BMI, kg/m2 - subgroup by statin use

Study or subgroup	Higher PUFA N	Mean(SD)	Lower PUFA N	Mean(SD)	M Differe IV,Random		Weight	Mean Difference IV,Random,95% CI
< 50% on statins		(ob)		110011(02)		,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,		
Dodin 2005	85	25.9 (4.5)	94	27.4 (4.8)	•		2.8 %	-1.50 [ -2.86, -0.14 ]
Mita 2007	30	25.1 (5.3)	30	24.1 (3)		<b>·</b> •	1.2 %	1.00 [ -1.18, 3.18 ]
Nodari 2011 HF	67	26 (0.4)	66	26 (0.6)	+		15.7 %	0.0 [ -0.17, 0.17 ]
PREDIMED 2013 (1)	51	28.7 (3.01)	42	28.6 (2.9)			3.4 %	0.10 [ -1.10, 1.30 ]
PREDIMED 2013 (2)	102	-0.5 (2.04)	112	-0.5 (1.6)	_	_	10.1 %	0.0 [ -0.49, 0.49 ]
PREDIMED 2013 (3)	54	-0.02 (0.18)	54	-0.5 (0.37)			16.5 %	0.48 [ 0.37, 0.59 ]
PREDIMED 2013 (4)	58	-0.1 (1.36)	59	-0.1 (1.18)	_	-	10.7 %	0.0 [ -0.46, 0.46 ]
Sydney Diet-Heart 1978	179	24.3 (1.5)	192	24.5 (2)			12.5 %	-0.20 [ -0.56, 0.16 ]
WINS 2006 (5)		27.6 (5.5728)	840	26.8 (5.9064)			10.0 %	0.80 [ 0.30, 1.30 ]
Subtotal (95% CI)	1954	27.0 (3.3720)	1489	20.0 (3.7007)				0.12 [ -0.17, 0.42 ]
Test for overall effect: Z = 0.8 2 50+% on statins AlphaOmega - ALA (6)	630	0.07 (1.5)	630	-0.08 (1.8)	-		15.6 %	0.15 [ -0.03, 0.33 ]
WELCOME 2015	47	33.4 (4.9)	48	30.8 (4.5)			1.5 %	2.60 [ 0.71, 4.49 ]
Subtotal (95% CI) Heterogeneity: Tau <sup>2</sup> = 2.53; C Test for overall effect: $Z = 0.9$		=   (P = 0.01);	<b>678</b> <sup>12</sup> =84%				17.1 %	1.19 [ -1.19, 3.56 ]
3 Percentage on statins unclear <b>Subtotal (95% CI)</b> Heterogeneity: not applicable Test for overall effect: not app	0		0					Not estimable
Total (95% CI)	2631		2167		•		100.0 %	0.17 [ -0.08, 0.42 ]
Heterogeneity: $Tau^2 = 0.09$ ; C	Chi <sup>2</sup> = 51.21, d	f = 10 (P<0.000	01); I <sup>2</sup> =80%					
Test for overall effect: $Z = 1.3$	86 (P = 0.17)							
Test for subgroup differences:	$Chi^2 = 0.76, d$	f =   (P = 0.38)	, l <sup>2</sup> =0.0%					
							L	
					-2 -1 0	I 2	2	
				Favours	higher PUFA	Favours lowe	er PUFA	

- (1) Reus subcohort, 2 year data
- (2) Canaries subcohort, change from baseline to 1 year, Alvarez-Perez 2016
- (3) Barcelona hospital cohort at 5 years, Casa 2016
- (4) Damasceno 2013, Barcelona North subcohort, I year data
- (5) One year data
- (6) Numer of participants equally divided between groups

#### Analysis 3.24. Comparison 3 Higher PUFA vs lower PUFA - continuous secondary outcomes, Outcome 24 BMI, kg/m2 - subgroup by intervention type.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 3 Higher PUFA vs lower PUFA - continuous secondary outcomes

Outcome: 24 BMI, kg/m2 - subgroup by intervention type

Study or subgroup	Higher PUFA		Lower PUFA		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	Ν	Mean(SD)	IV,Random,95% CI		IV,Random,95% CI
I Dietary advice							
WINS 2006 (1)	328	27.6 (5.5728)	840	26.8 (5.9064)		10.0 %	0.80 [ 0.30, 1.30 ]
Subtotal (95% CI)	1328		840		•	10.0 %	0.80 [ 0.30, 1.30 ]
Heterogeneity: not applicabl	e						
Test for overall effect: $Z = 3$	.14 (P = 0.0017)	)					
2 Supplemental foods % die	t provided						
AlphaOmega - ALA (2)	630	0.07 (1.5)	630	-0.08 (1.8)	-	15.6 %	0.15 [ -0.03, 0.33 ]
PREDIMED 2013 (3)	51	28.7 (3.01)	42	28.6 (2.9)		3.4 %	0.10 [ -1.10, 1.30 ]
PREDIMED 2013 (4)	54	-0.02 (0.18)	54	-0.5 (0.37)	-	16.5 %	0.48 [ 0.37, 0.59 ]
PREDIMED 2013 (5)	102	-0.5 (2.04)	2	-0.5 (1.6)	_+_	10.1 %	0.0 [ -0.49, 0.49 ]
PREDIMED 2013 (6)	58	-0.1 (1.36)	59	-0.  ( . 8)	_+_	10.7 %	0.0 [ -0.46, 0.46 ]
Subtotal (95% CI)	895		<b>89</b> 7		•	56.2 %	0.21 [ -0.04, 0.47 ]
Heterogeneity: $Tau^2 = 0.05$ ;	Chi <sup>2</sup> = 14.20, d	f = 4 (P = 0.01)	; I <sup>2</sup> =72%				
Test for overall effect: $Z = I$	.66 (P = 0.098)						
3 Supplements (capsules %	unusual foods)						
Dodin 2005	85	25.9 (4.5)	94	27.4 (4.8)		2.8 %	-1.50 [ -2.86, -0.14 ]
Mita 2007	30	25.1 (5.3)	30	24.1 (3)		→ I.2 %	1.00 [ -1.18, 3.18 ]
					-2 -1 0 1 rs higher PUFA Favours Io	2 Ner PLIEA	

(Continued  $\dots$ )

Study or subgroup	Higher PUFA N	l Mean(SD)	.ower PUFA N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	( Continued) Mean Difference IV,Random,95% Cl
Nodari 2011 HF	67	26 (0.4)	66	26 (0.6)	-	15.7 %	0.0 [ -0.17, 0.17 ]
WELCOME 2015	47	33.4 (4.9)	48	30.8 (4.5)		→ I.5 %	2.60 [ 0.71, 4.49 ]
<b>Subtotal (95% CI)</b> Heterogeneity: Tau <sup>2</sup> = 1.26; Test for overall effect: Z = 0. 4 Any combination Sydney Diet-Heart 1978		= 3 (P = 0.01); I <sup>2</sup> 24.3 (1.5)	<b>238</b> =76%	24.5 (2)	-	<b>21.2 %</b>	<b>0.33 [ -0.99, 1.64 ]</b> -0.20 [ -0.56, 0.16 ]
Subtotal (95% CI) Heterogeneity: not applicable Test for overall effect: Z = 1.			192		•	12.5 %	-0.20 [ -0.56, 0.16 ]
<b>Total (95% CI)</b> Heterogeneity: Tau <sup>2</sup> = 0.09; Test for overall effect: Z = 1. Test for subgroup differences	<b>2631</b> Chi <sup>2</sup> = 51.21, df 36 (P = 0.17)	,		-2	-1 0 1	<b>100.0 %</b>	0.17 [ -0.08, 0.42 ]

Favours higher PUFA Favours lower PUFA

(I) One year data

(2) Numer of participants equally divided between groups

(3) Reus subcohort, 2 year data

(4) Barcelona hospital cohort at 5 years, Casa 2016

(5) Canaries subcohort, change from baseline to 1 year, Alvarez-Perez 2016

(6) Damasceno 2013, Barcelona North subcohort, I year data

#### Analysis 3.25. Comparison 3 Higher PUFA vs lower PUFA - continuous secondary outcomes, Outcome 25 Adiposity - waist circumference, cm.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 3 Higher PUFA vs lower PUFA - continuous secondary outcomes

Outcome: 25 Adiposity - waist circumference, cm

Study or subgroup	Higher PUFA		Lower PUFA		Me Differer		Weight	Mean Difference
	Ν	Mean(SD)	Ν	Mean(SD)	IV,Random,	95% CI		IV,Random,95% CI
ORL 2013	168	0.1 (2.9)	165	-0.6 (4.1)	-	⊢	51.4 %	0.70 [ -0.06, 1.46 ]
PREDIMED 2013 (1)	63	-0.23 (3.6)	65	-0.63 (4.76)			15.1 %	0.40 [ -1.06, 1.86 ]
PREDIMED 2013 (2)	102	-2.3 (5.6)	112	-1.1 (6.41)			12.5 %	-1.20 [ -2.81, 0.41 ]
PREDIMED 2013 (3)	54	-1.6 (4.76)	54	-1.2 (4.76)		_	10.1 %	-0.40 [ -2.20, 1.40 ]
PREDIMED 2013	55	-2.8 (5.5)	55	-3.2 (5.5)			7.7 %	0.40 [ -1.66, 2.46 ]
PREDIMED 2013 (4)	51	102.7 (7.8)	42	103 (7.8)			3.2 %	-0.30 [ -3.49, 2.89 ]
WAHA - Ros 2016	156	2.25 (0)	156	1.94 (0)				Not estimable
Total (95% CI)	649		649		•		100.0 %	0.25 [ -0.32, 0.83 ]
Heterogeneity: $Tau^2 = 0$ .	.02; Chi <sup>2</sup> = 5.13, d	f = 5 (P = 0.40);	l <sup>2</sup> =2%					
Test for overall effect: Z	= 0.86 (P = 0.39)							
Test for subgroup differen	nces: Not applicab	le						
				-	4 -2 0	2 4	1	
				Favours	higher PUFA	Favours lowe	er PUFA	

(1) AP-UNAV centre, 3 year data

(2) Canaries cohort, change to 1 year, Alvarez-Perez 2016

(3) Barcelona hospital cohort at 5 years, Casa 2016

(4) Reus subcohort, 2 year data

## Analysis 3.26. Comparison 3 Higher PUFA vs lower PUFA - continuous secondary outcomes, Outcome 26 Adiposity - % body fat.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 3 Higher PUFA vs lower PUFA - continuous secondary outcomes

Outcome: 26 Adiposity - % body fat

-

-

Study or subgroup	Higher PUFA		Lower PUFA			Mean Difference	Weight	Mean Difference
	Ν	Mean(SD)	Ν	Mean(SD)	IV,R	andom,95% Cl		IV,Random,95% CI
PREDIMED 2013 (1)	102	0.6 (4.58)	112	-0.2 (4.27)		-	70.3 %	0.80 [ -0.39, 1.99 ]
WELCOME 2015	47	33.5 (9.6)	48	29 (13.8)		-	- 29.7 %	4.50 [ -0.27, 9.27 ]
Total (95% CI)	149		160			-	100.0 %	1.90 [ -1.41, 5.21 ]
Heterogeneity: $Tau^2 = 3$	.70; $Chi^2 = 2.17$ , df	F =   (P = 0. 4)	; I <sup>2</sup> =54%					
Test for overall effect: Z	= 1.12 (P = 0.26)							
Test for subgroup differe	nces: Not applicabl	e						
							i	
					-10 -5	0 5	10	
				Favour	s higher PUFA	A Favours Io	wer PUFA	

(1) Canaries cohort, change to 1 year, Alvarez-Perez 2016

#### Analysis 3.27. Comparison 3 Higher PUFA vs lower PUFA - continuous secondary outcomes, Outcome 27 Adiposity - body fat, kg.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 3 Higher PUFA vs lower PUFA - continuous secondary outcomes

Outcome: 27 Adiposity - body fat, kg

Study or subgroup	Higher PUFA		Lower PUFA				Mean erence	Weight	Mean Difference
	Ν	Mean(SD)	Ν	Mean(SD)		IV,Rando	om,95% Cl		IV,Random,95% CI
PREDIMED 2013 (1)	102	-0.1 (4.0729)	112	-0.1 (4.2726)		-		100.0 %	0.0 [ -1.12, 1.12 ]
Total (95% CI)	102		112			•	•	100.0 %	0.0 [ -1.12, 1.12 ]
Heterogeneity: not appli	cable								
Test for overall effect: Z	= 0.0 (P = 1.0)								
Test for subgroup differe	nces: Not applical	ble							
					-10	-5 (	5 5	10	
				Favou	rs higher	PUFA	Favours	lower PUFA	

#### Analysis 3.28. Comparison 3 Higher PUFA vs lower PUFA - continuous secondary outcomes, Outcome 28 Serum TOTAL CHOLESTEROL (TC, mmoL/L).

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 3 Higher PUFA vs lower PUFA - continuous secondary outcomes

Outcome: 28 Serum TOTAL CHOLESTEROL (TC, mmoL/L)

Study or subgroup	Higher PUFA		Lower PUFA		Mean Difference	Weight	Mean Difference
, 0 ,	N	Mean(SD)	Ν	Mean(SD)	IV,Random,95% CI	0	IV,Random,95% CI
Ahn 2016	38	3.6 (0.74)	36	3.75 (0.67)		3.6 %	-0.15 [ -0.47, 0.17 ]
AlphaOmega - ALA	605	-0.3 (0.98)	605	-0.28 (0.98)	+	5.4 %	-0.02 [ -0.13, 0.09 ]
Brox 2001 (1)	67	7.8896 (0.8168)	37	7.9 (0.8)		3.6 %	-0.01 [ -0.33, 0.31 ]
DART fat 1989	855	6.29 (1.13)	860	6.55 (1.1)	-	5.5 %	-0.26 [ -0.37, -0.15 ]
DIPP-Tokudome 2015 (2)	91	5.52 (0.9)	75	5.4 (0.79)		4.2 %	0.12 [ -0.14, 0.38 ]
Dodin 2005	85	5.66 (0.72)	94	5.96 (0.72)		4.6 %	-0.30 [ -0.51, -0.09 ]
HARP- Sacks 1995	31	5.02 (0.96)	28	4.99 (0.62)		3.0 %	0.03 [ -0.38, 0.44 ]
HERO-Tapsell 2009	8	4.9 (0.8)	17	4.6 (1)		1.9 %	0.30 [ -0.30, 0.90 ]
Houtsmuller 1979	48	6.43 (0.65)	48	6.9 (0.81)		3.9 %	-0.47 [ -0.76, -0.18 ]
Ley 2004 (3)	70	-0.05 (1.4223)	66	-0.15 (0.7312)		3.2 %	0.10 [ -0.28, 0.48 ]
MARINA - Sanders 2011 (4	) 80	0.2 (0.8987)	71	0.1 (0.63)		4.3 %	0.10 [ -0.15, 0.35 ]
Mendis 2001	26	-0.42 (0.5447)	28	-0.58 (0.7221)		3.5 %	0.16 [ -0.18, 0.50 ]
Mita 2007	30	5.15 (0.83)	30	5.27 (0.99)		2.6 %	-0.12 [ -0.58, 0.34 ]
MRC 1968	88	-1.11 (0)	89	-0.47 (0)			Not estimable
NDHS Faribault 1968 (5)	4	-0.9901 (0.6366)	51	-0.18 (0.5713)	<b>_</b>	4.8 %	-0.81 [ -1.00, -0.62 ]
NDHS Open 1st 1968 (6)	653	-0.6663 (0.693)	309	-0.25 (0.5274)	+	5.6 %	-0.42 [ -0.50, -0.34 ]
Nodari 2011 HF	67	4.8 (0.62)	66	4.9 (0.62)		4.6 %	-0.10[-0.31, 0.11]
Nye 1990	12	6.83 (I)	12	6.2 (1.31)		• 1.0 %	0.63 [ -0.30, 1.56 ]
PREDIMED 2013 (7)	58	-0.35 (0.9)	59	-0.3 (0.89)		3.6 %	-0.05 [ -0.37, 0.27 ]
PREDIMED 2013 (8)	54	-1.01 (0.92)	54	-0.8 (0.99)		3.3 %	-0.21 [ -0.57, 0.15 ]
				-	I -0.5 0 0.5		

Favours higher PUFA Favours lower PUFA

(Continued ...)

Study or subgroup	Higher PUFA N	Mean(SD)	Lower PUFA N	Mean(SD)	Mean Difference IV,Random,95%	Weight	( Continued) Mean Difference IV,Random,95% CI
PREDIMED 2013 (9)	51	5.I7 (I)	42	5.02 (0.94)		3.0 %	0.15 [ -0.25, 0.55 ]
Rose 1965	13	-0.51 (1.25)	13	-0.02 (0.94) 🕇		1.1 %	-0.49 [ -1.34, 0.36 ]
Rossing 1996	4	5.51 (1.12)	15	5.2 (1.16)		→ I.2 %	0.31 [ -0.52, 1.14 ]
Simon 1997	38	5.21 (1.11)	34	4.87 (0.87)		2.6 %	0.34 [ -0.12, 0.80 ]
Sydney Diet-Heart 1978	221	6.5 (1.2)	237	6.8 (1.1)		4.6 %	-0.30 [ -0.51, -0.09 ]
Veterans Admin 1969	423	4.93 (3.72)	420	5.3 (1.87)		3.0 %	-0.37 [ -0.77, 0.03 ]
Vijayakumar 2014	94	3.92 (1.15)	96	3.86 (0.74)		4.0 %	0.06 [ -0.22, 0.34 ]
WAHA - Ros 2016	260	-0.19 (0.65)	254	-0.01 (0.64)		5.4 %	-0.18 [ -0.29, -0.07 ]
WELCOME 2015	47	4.7 (1.1)	48	4.8 (1)		2.9 %	-0.10 [ -0.52, 0.32 ]
Total (95% CI)	4278		3794		•	100.0 %	-0.12 [ -0.23, -0.02 ]
Heterogeneity: $Tau^2 = 0.04$ ; C	$hi^2 = 127.08$ , df =	27 (P<0.0001);	l <sup>2</sup> =79%				
Test for overall effect: $Z = 2.44$	+ (P = 0.015)						
Test for subgroup differences: I	Not applicable						
						_	

-I -0.5 0 0.5 I

Favours higher PUFA Favours lower PUFA

(1) 14 month data, cod liver oil % seal oil combined

(2) 2 year data

(3) Change data

(4) G2 arm data used

(5) Arms A, B % E combined vs D (control), 52 week data, change data

(6) Arms A, B % X combined vs D (control), 52 week data, change data

(7) Damasceno 2013, Barcelona North subcohort, I year data

(8) Barcelona hospital cohort at 5 years, Casas 2016

(9) Fernandez-Real 2012, Reus subcohort, 2 year data

# Analysis 3.29. Comparison 3 Higher PUFA vs lower PUFA - continuous secondary outcomes, Outcome 29 TC, mmoL/L - SA.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 3 Higher PUFA vs lower PUFA - continuous secondary outcomes

Outcome: 29 TC, mmoL/L - SA

Study or subgroup	Higher PUFA N	Mean(SD)	Lower PUFA N	Mean(SD)	Mean Difference IV,Random,95% Cl	Weight	Mean Difference IV,Random,95% CI
I Low risk of bias for allocatio	n concealment						
Ahn 2016	38	3.6 (0.74)	36	3.75 (0.67)		9.2 %	-0.15 [ -0.47, 0.17 ]
AlphaOmega - ALA	605	-0.3 (0.98)	605	-0.28 (0.98)	-	11.7 %	-0.02 [ -0.13, 0.09 ]
Brox 2001 (1)	67	7.8896 (0.8168)	37	7.9 (0.8)	_ <b>+</b> _	9.1 %	-0.0  [ -0.33, 0.3  ]
DIPP-Tokudome 2015 (2)	91	5.52 (0.9)	75	5.4 (0.79)		10.1 %	0.12 [ -0.14, 0.38 ]
Ley 2004 (3)	70	-0.05 (1.4223)	66	-0.15 (0.7312)		8.4 %	0.10 [ -0.28, 0.48 ]
MARINA - Sanders 2011	80	0.2 (0.8987)	71	0.1 (0.63)		10.2 %	0.10 [ -0.15, 0.35 ]
NDHS Faribault 1968	4	-0.99 (0.637)	51	-0.18 (0.571) -	-	11.0 %	-0.81 [ -1.00, -0.62 ]
NDHS Open 1st 1968	653	-0.666 (0.69)	309	-0.25 (0.527)		12.0 %	-0.42 [ -0.50, -0.34 ]
Sydney Diet-Heart 1978	221	6.5 (1.2)	237	6.8 (1.1)	— <b>—</b>	10.7 %	-0.30 [ -0.51, -0.09 ]
WELCOME 2015	47	4.7 ( . )	48	4.8 (1)		7.7 %	-0.10 [ -0.52, 0.32 ]
Subtotal (95% CI)	2013		1535		-	100.0 %	-0.16 [ -0.36, 0.03 ]
Test for overall effect: $7 = 1.6$	6 (P = 0.097)						
Test for overall effect: $Z = 1.6$	,						
2 Low risk of bias for attention	n	-0.3 (0.98)	605	-0.28 (0.98)	+	6.8 %	-0.02 [ -0.13, 0.09 ]
2 Low risk of bias for attention AlphaOmega - ALA	n 605	-0.3 (0.98) 7 8896 (0.8168)	605	-0.28 (0.98)	+	6.8 %	
2 Low risk of bias for attention AlphaOmega - ALA Brox 2001	n 605 67	7.8896 (0.8168)	37	7.9 (0.8)	* -*-	5.1 %	-0.02 [ -0.13, 0.09 ] -0.01 [ -0.33, 0.31 ]
2 Low risk of bias for attention AlphaOmega - ALA Brox 2001 DIPP-Tokudome 2015 (4)	n 605 67 91	7.8896 (0.8168) 5.52 (0.9)	37 75	7.9 (0.8) 5.4 (0.79)	+	5.1 % 5.7 %	-0.01 [ -0.33, 0.31 ] 0.12 [ -0.14, 0.38 ]
2 Low risk of bias for attention AlphaOmega - ALA Brox 2001 DIPP-Tokudome 2015 (4) Dodin 2005	n 605 67 91 85	7.8896 (0.8168) 5.52 (0.9) 5.66 (0.72)	37 75 94	7.9 (0.8) 5.4 (0.79) 5.96 (0.72)	+ -+ -+	5.1 % 5.7 % 6.1 %	-0.01 [ -0.33, 0.31 ] 0.12 [ -0.14, 0.38 ] -0.30 [ -0.51, -0.09 ]
2 Low risk of bias for attention AlphaOmega - ALA Brox 2001 DIPP-Tokudome 2015 (4) Dodin 2005 HARP- Sacks 1995	n 605 67 91 85 31	7.8896 (0.8168) 5.52 (0.9) 5.66 (0.72) 5.02 (0.96)	37 75 94 28	7.9 (0.8) 5.4 (0.79) 5.96 (0.72) 4.99 (0.62)		5.1 % 5.7 % 6.1 % 4.4 %	-0.01 [ -0.33, 0.31 ] 0.12 [ -0.14, 0.38 ] -0.30 [ -0.51, -0.09 ] 0.03 [ -0.38, 0.44 ]
2 Low risk of bias for attention AlphaOmega - ALA Brox 2001 DIPP-Tokudome 2015 (4) Dodin 2005	n 605 67 91 85	7.8896 (0.8168) 5.52 (0.9) 5.66 (0.72)	37 75 94	7.9 (0.8) 5.4 (0.79) 5.96 (0.72)	+ -+- 	5.1 % 5.7 % 6.1 %	
2 Low risk of bias for attention AlphaOmega - ALA Brox 2001 DIPP-Tokudome 2015 (4) Dodin 2005 HARP- Sacks 1995	n 605 67 91 85 31	7.8896 (0.8168) 5.52 (0.9) 5.66 (0.72) 5.02 (0.96)	37 75 94 28	7.9 (0.8) 5.4 (0.79) 5.96 (0.72) 4.99 (0.62)		5.1 % 5.7 % 6.1 % 4.4 %	-0.01 [ -0.33, 0.31 ] 0.12 [ -0.14, 0.38 ] -0.30 [ -0.51, -0.09 ] 0.03 [ -0.38, 0.44 ]
2 Low risk of bias for attention AlphaOmega - ALA Brox 2001 DIPP-Tokudome 2015 (4) Dodin 2005 HARP- Sacks 1995 HERO-Tapsell 2009	n 605 67 91 85 31 18	7.8896 (0.8168) 5.52 (0.9) 5.66 (0.72) 5.02 (0.96) 4.9 (0.8)	37 75 94 17 71	7.9 (0.8) 5.4 (0.79) 5.96 (0.72) 4.99 (0.62) 4.6 (1)		5.1 % 5.7 % 6.1 % 4.4 %	-0.01 [ -0.33, 0.31 ] 0.12 [ -0.14, 0.38 ] -0.30 [ -0.51, -0.09 ] 0.03 [ -0.38, 0.44 ] 0.30 [ -0.30, 0.90 ]
2 Low risk of bias for attention AlphaOmega - ALA Brox 2001 DIPP-Tokudome 2015 (4) Dodin 2005 HARP- Sacks 1995 HERO-Tapsell 2009 MARINA - Sanders 2011	n 605 67 91 85 31 18 80	7.8896 (0.8168) 5.52 (0.9) 5.66 (0.72) 5.02 (0.96) 4.9 (0.8) 0.2 (0.8987)	37 75 94 17 71	7.9 (0.8) 5.4 (0.79) 5.96 (0.72) 4.99 (0.62) 4.6 (1) 0.1 (0.63)		5.1 % 5.7 % 6.1 % 4.4 % 3.0 % 5.8 %	-0.01 [ -0.33, 0.31 ] 0.12 [ -0.14, 0.38 ] -0.30 [ -0.51, -0.09 ] 0.03 [ -0.38, 0.44 ] 0.30 [ -0.30, 0.90 ] 0.10 [ -0.15, 0.35 ]
2 Low risk of bias for attention AlphaOmega - ALA Brox 2001 DIPP-Tokudome 2015 (4) Dodin 2005 HARP- Sacks 1995 HERO-Tapsell 2009 MARINA - Sanders 2011 Mendis 2001	n 605 67 91 85 31 18 80 26	7.8896 (0.8168) 5.52 (0.9) 5.66 (0.72) 5.02 (0.96) 4.9 (0.8) 0.2 (0.8987) -0.42 (0.5447)	37 75 94 17 17 28	7.9 (0.8) 5.4 (0.79) 5.96 (0.72) 4.99 (0.62) 4.6 (1) 0.1 (0.63) -0.58 (0.7221)	* -*- -*- -*-  *-	5.1 % 5.7 % 6.1 % 4.4 % 5.8 % 5.0 %	-0.01 [ -0.33, 0.31 ] 0.12 [ -0.14, 0.38 ] -0.30 [ -0.51, -0.09 ] 0.03 [ -0.38, 0.44 ] 0.30 [ -0.30, 0.90 ] 0.10 [ -0.15, 0.35 ] 0.16 [ -0.18, 0.50 ]

Favours higher PUFA Favours lower PUFA

(Continued ...)

Study or subgroup	Higher PUFA N	L Mean(SD)	.ower PUFA N	Mean(SD)	Mean Difference IV,Random,95% Cl	Weight	( Continue Mea Difference IV,Random,95% C
Nodari 2011 HF	67	4.8 (0.62)	66	4.9 (0.62)		6.1 %	-0.10 [ -0.31, 0.11
Nye 1990	12	6.83 (1)	12	6.2 (1.31)		→ I.7 %	0.63 [ -0.30, 1.56
PREDIMED 2013 (5)	51	5.17 (1)	42	5.02 (0.94)		4.5 %	0.15 [ -0.25, 0.55
PREDIMED 2013 (6)	58	-0.35 (0.9)	59	-0.3 (0.89)		5.1 %	-0.05 [ -0.37, 0.27
PREDIMED 2013 (7)	54	-1.01 (0.92)	54	-0.8 (0.99)		4.8 %	-0.21 [ -0.57, 0.15
Rose 1965	13	-0.51 (1.25)	13	-0.02 (0.94) 🕇		1.9 %	-0.49 [ -1.34, 0.36
Rossing 1996	14	5.51 (1.12)	15	5.2 (1.16)		→ 2.0 %	0.31 [ -0.52, 1.14
Veterans Admin 1969	423	4.93 (3.72)	420	5.3 (1.87)		4.5 %	-0.37 [ -0.77, 0.03
Vijayakumar 2014	94	3.92 (1.15)	96	3.86 (0.74)		5.6 %	0.06 [ -0.22, 0.34
WELCOME 2015	47	4.7 ( . )	48	4.8 (1)		4.3 %	-0.10 [ -0.52, 0.32
Subtotal (95% CI) Heterogeneity: Tau <sup>2</sup> = 0.07; Ch Test for overall effect: Z = 1.36 3 Low risk of bias for complianc	(P = 0.17)	= 20 (P<0.00001)	<b>2170</b> ; I <sup>2</sup> =82%		•	100.0 %	-0.10 [ -0.23, 0.04
Ahn 2016	e 38	3.6 (0.74)	36	3.75 (0.67)		6.5 %	-0.15 [ -0.47, 0.17
Brox 2001	67	7.8896 (0.8168)	37	7.9 (0.8)	_	6.5 %	-0.01 [ -0.33, 0.31
DART fat 1989	855	6.29 (1.13)	860	6.55 (1.1)		10.8 %	-0.26 [ -0.37, -0.15
Houtsmuller 1979	48	6.43 (0.65)	48	6.9 (0.81)	<b>e</b>	7.0 %	-0.47 [ -0.76, -0.18
Ley 2004 (8)	70	-0.05 (1.4223)	66	-0.15 (0.7312)		5.6 %	0.10 [ -0.28, 0.48
Mita 2007	30	5.15 (0.83)	30	5.27 (0.99)		4.4 %	-0.12 [ -0.58, 0.34
MRC 1968	88	- .   (0)	89	-0.47 (0)			Not estimab
NDHS Faribault 1968	4	-0.99 (0.637)	51	-0.18 (0.571) -		9.2 %	-0.81 [ -1.00, -0.62
NDHS Open 1st 1968	653	-0.666 (0.69)	309	-0.25 (0.527)	-	11.2 %	-0.42 [ -0.50, -0.34
Rose 1965	13	-0.5  (1.25)	13	-0.02 (0.94) 🕇		1.8 %	-0.49 [ -1.34, 0.36
Sydney Diet-Heart 1978	221	6.5 (1.2)	237	6.8 (1.1)	— <b>—</b>	8.7 %	-0.30 [ -0.51, -0.09
Veterans Admin 1969	423	4.93 (3.72)	420	5.3 (1.87)		5.3 %	-0.37 [ -0.77, 0.03
Vijayakumar 2014	94	3.92 (1.15)	96	3.86 (0.74)		7.4 %	0.06 [ -0.22, 0.34
WAHA - Ros 2016	260	-0.19 (0.65)	254	-0.01 (0.64)		10.7 %	-0.18 [ -0.29, -0.07
WELCOME 2015	47	4.7 ( . )	48	4.8 (1)		4.9 %	-0.10 [ -0.52, 0.32
Subtotal (95% CI) Heterogeneity: Tau <sup>2</sup> = 0.03; Ch Fest for overall effect: Z = 4.26 How summary risk of bias		· · · · · ·	<b>2594</b> I <sup>2</sup> =78%		•	100.0 % -	-0.27 [ -0.39, -0.14

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Me Differen IV,Random,95%	Weight	Mean Difference IV,Random,95% Cl	Mean(SD)	Lower PUFA N	Mean(SD)	Higher PUFA N	Study or subgroup
-0.02 [ -0.13, 0.09	16.3 %	-	-0.28 (0.98)	605	-0.3 (0.98)	605	AlphaOmega - ALA
0.10 [ -0.28, 0.48	11.8 %		-0.15 (0.7312)	66	-0.05 (1.4223)	70	Ley 2004 (9)
0.10 [ -0.15, 0.35	14.3 %		0.1 (0.63)	71	0.2 (0.8987)	80	MARINA - Sanders 2011
-0.81 [ -1.00, -0.62	15.2 %	•	-0.18 (0.571) —	51	-0.99 (0.637)	4	NDHS Faribault 1968
-0.42 [ -0.50, -0.34	16.6 %	+	-0.25 (0.527)	309	-0.666 (0.69)	653	NDHS Open 1st 1968
-0.30 [ -0.51, -0.09	14.9 %	<b></b>	6.8 (1.1)	237	6.5 (1.2)	221	Sydney Diet-Heart 1978
-0.10 [ -0.52, 0.32	10.9 %		4.8 (1)	48	4.7 (1.1)	47	WELCOME 2015
-0.23 [ -0.46, 0.01	100.0 %	•		<b>1387</b> I <sup>2</sup> =92%	= 6 (P<0.00001);		Subtotal (95% CI) Heterogeneity: Tau <sup>2</sup> = 0.08; C est for overall effect: Z = 1.8
-0.02 [ -0.13, 0.09	5.8 %	-	-0.28 (0.98)	605	-0.3 (0.98)	605 ° (1 – 0.080)	Trials registry or pre-2010 AlphaOmega - ALA
-0.01 [ -0.33, 0.3	3.9 %		7.9 (0.8)	37	7.8896 (0.8168)	67	Brox 200 I
-0.26 [ -0.37, -0.15	5.9 %		6.55 (1.1)	860	6.29 (1.13)	855	DART fat 1989
0.12 [ -0.14, 0.38	4.5 %		5.4 (0.79)	75	5.52 (0.9)	) 91	DIPP-Tokudome 2015 (10
-0.30 [ -0.5  , -0.02	5.0 %		5.96 (0.72)	94	5.66 (0.72)	85	Dodin 2005
0.03 [ -0.38, 0.44	3.2 %		4.99 (0.62)	28	5.02 (0.96)	31	HARP- Sacks 1995
0.30 [ -0.30, 0.90	2.0 %		4.6 (1)	17	4.9 (0.8)	18	HERO-Tapsell 2009
-0.47 [ -0.76, -0.18	4.2 %		6.9 (0.81)	48	6.43 (0.65)	48	Houtsmuller 1979
0.10 [ -0.28, 0.48	3.5 %	<u> </u>	-0.15 (0.7312)	66	-0.05 (1.4223)	70	Ley 2004 (11)
0.10 [ -0.15, 0.3	4.7 %	_ <del></del>	0.1 (0.63)	71	0.2 (0.8987)	80	MARINA - Sanders 2011
0.16 [ -0.18, 0.50	3.8 %		-0.58 (0.7221)	28	-0.42 (0.5447)	26	Mendis 2001
-0.12 [ -0.58, 0.34	2.8 %	<b>_</b>	5.27 (0.99)	30	5.15 (0.83)	30	Mita 2007
Not estimat			-0.47 (0)	89	- .   (0)	88	MRC 1968
-0.81 [ -1.00, -0.62	5.2 %	•	-0.18 (0.571) —	51	-0.99 (0.637)	4	NDHS Faribault 1968
-0.42 [ -0.50, -0.34	6.0 %	+	-0.25 (0.527)	309	-0.666 (0.69)	653	NDHS Open 1st 1968
-0.10 [ -0.31, 0.1	5.0 %	<del>_</del> _	4.9 (0.62)	66	4.8 (0.62)	67	Nodari 2011 HF
0.63 [ -0.30, 1.56	1.1 %		6.2 (1.31)	12	6.83 (1)	12	Nye 1990
0.15 [ -0.25, 0.5	3.3 %	<del></del> +	5.02 (0.94)	42	5.17 (1)	51	PREDIMED 2013 (12)
-0.21 [ -0.57, 0.15	3.6 %	<b>.</b>	-0.8 (0.99)	54	-1.01 (0.92)	54	PREDIMED 2013 (13)
-0.05 [ -0.37, 0.2]	3.9 %		-0.3 (0.89)	59	-0.35 (0.9)	58	PREDIMED 2013 (14)
-0.49 [ -1.34, 0.36	1.2 %		-0.02 (0.94) 🔶	3	-0.5  (1.25)	13	Rose 1965

(Continued . . . )

Study or subgroup	Higher PUFA		Lower PUFA		Mean Difference	Weight	Mea Differenc
, , ,	N	Mean(SD)	Ν	Mean(SD)	IV,Random,95% CI	Ũ	IV,Random,95% (
Rossing 1996	14	5.51 (1.12)	15	5.2 (1.16)		→ I.3 %	0.3  [ -0.52, 1.14
Simon 1997	38	5.21 (1.11)	34	4.87 (0.87)		2.9 %	0.34 [ -0.12, 0.80
Sydney Diet-Heart 1978	221	6.5 (1.2)	237	6.8 (1.1)		5.0 %	-0.30 [ -0.51, -0.09
Veterans Admin 1969	423	4.93 (3.72)	420	5.3 (1.87)		3.3 %	-0.37 [ -0.77, 0.03
WAHA - Ros 2016	260	-0.19 (0.65)	254	-0.01 (0.64)	-#-	5.8 %	-0.18 [ -0.29, -0.07
WELCOME 2015	47	4.7 ( . )	48	4.8 (1)		3.1 %	-0.10 [ -0.52, 0.32
Subtotal (95% CI) Heterogeneity: Tau <sup>2</sup> = 0.05; Ch Test for overall effect: Z = 2.45 6 No industry funding		T = 25 (P<0.00001	<b>3662</b> ); I <sup>2</sup> =80%		•	100.0 %	-0.13 [ -0.24, -0.03
Ahn 2016	38	3.6 (0.74)	36	3.75 (0.67)		9.3 %	-0.15 [ -0.47, 0.17
Brox 2001	67	7.8896 (0.8168)	37	7.9 (0.8)		9.3 %	-0.01 [ -0.33, 0.31
DIPP-Tokudome 2015 (15)	91	5.52 (0.9)	75	5.4 (0.79)		10.2 %	0.12 [ -0.14, 0.38
Houtsmuller 1979	48	6.43 (0.65)	48	6.9 (0.81)	<b>_</b>	9.7 %	-0.47 [ -0.76, -0.18
Ley 2004 (16)	70	-0.05 (1.4223)	66	-0.15 (0.7312)		8.5 %	0.10 [ -0.28, 0.48
MARINA - Sanders 2011	80	0.2 (0.8987)	71	0.1 (0.63)		10.3 %	0.10 [ -0.15, 0.35
Mendis 2001	26	-0.42 (0.5447)	28	-0.58 (0.7221)		9.0 %	0.16 [ -0.18, 0.50
MRC 1968	88	- .   (0)	89	-0.47 (0)			Not estimat
NDHS Faribault 1968	4	-0.99 (0.637)	51	-0.18 (0.571) -		11.0 %	-0.81 [ -1.00, -0.62
NDHS Open 1st 1968	653	-0.666 (0.69)	309	-0.25 (0.527)	-	12.0 %	-0.42 [ -0.50, -0.34
Sydney Diet-Heart 1978	221	6.5 (1.2)	237	6.8 (1.1)	— <b>—</b> —	10.8 %	-0.30 [ -0.51, -0.09
Subtotal (95% CI)	1523		1047		-	100.0 %	-0.19 [ -0.39, 0.01
Heterogeneity: Tau <sup>2</sup> = 0.08; Ch est for overall effect: Z = 1.83 Randomised 100+ participan AlphaOmega - ALA	(P = 0.068)	= 9 (P<0.00001); -0.3 (0.98)	<sup>2</sup> =87% 605	-0.28 (0.98)	+	6.6 %	-0.02 [ -0.13, 0.09
Brox 2001	67	7.8896 (0.8168)	37	7.9 (0.8)		4.4 %	-0.01 [ -0.33, 0.31
DART fat 1989	855	6.29 (1.13)	860	6.55 (1.1)		6.6 %	-0.26 [ -0.37, -0.15
DIPP-Tokudome 2015 (17)	91	5.52 (0.9)	75	5.4 (0.79)	+	5.1 %	0.12 [ -0.14, 0.38
Dodin 2005	85	5.66 (0.72)	94	5.96 (0.72)		5.6 %	-0.30 [ -0.51, -0.09
Houtsmuller 1979	48	6.43 (0.65)	48	6.9 (0.81)		4.7 %	-0.47 [ -0.76, -0.18
Ley 2004 (18)	70	-0.05 (1.4223)	66	-0.15 (0.7312)		3.9 %	0.10 [ -0.28, 0.48
MARINA - Sanders 2011	80	0.2 (0.8987)	71	0.1 (0.63)		5.2 %	0.10 [ -0.15, 0.35

(Continued . . . )

Mea Differenc IV,Random,95% (	Weight	Difference IV,Random,95% Cl	Mean(SD)	Lower PUFA N	Mean(SD)	Higher PUFA N	Study or subgroup
Not estimab			-0.47 (0)	89	-1.11 (0)	88	MRC 1968
-0.8  [ -1.00, -0.62	5.9 %	_	-0.18 (0.571)	51	-0.99 (0.637)	141	NDHS Faribault 1968
-0.42 [ -0.50, -0.34	6.8 %	+	-0.25 (0.527)	309	-0.666 (0.69)	653	NDHS Open 1st 1968
-0.10[-0.31,0.11	5.6 %		4.9 (0.62)	66	4.8 (0.62)	67	Nodari 2011 HF
-0.05 [ -0.37, 0.27	4.4 %	<u> </u>	-0.3 (0.89)	59	-0.35 (0.9)	58	PREDIMED 2013 (19)
-0.21 [ -0.57, 0.15	4.0 %		-0.8 (0.99)	54	-1.01 (0.92)	54	PREDIMED 2013 (20)
0.15 [ -0.25, 0.55	3.7 %		5.02 (0.94)	42	5.17 (1)	51	PREDIMED 2013 (21)
0.34 [ -0.12, 0.80	3.2 %	- <b></b>	4.87 (0.87)	34	5.21 (1.11)	38	Simon 1997
-0.30 [ -0.51, -0.09	5.6 %		6.8 (1.1)	237	6.5 (1.2)	221	Sydney Diet-Heart 1978
-0.37 [ -0.77, 0.03	3.7 %		5.3 (1.87)	420	4.93 (3.72)	423	Veterans Admin 1969
0.06 [ -0.22, 0.34	4.9 %		3.86 (0.74)	96	3.92 (1.15)	94	Vijayakumar 2014
-0.18 [ -0.29, -0.07	6.6 %		-0.01 (0.64)	254	-0.19 (0.65)	260	WAHA - Ros 2016
-0.10 [ -0.52, 0.32	3.5 %		4.8 (1)	48	4.7 (1.1)	47	WELCOME 2015
				, i =05%	- 17 (1 <0.0000	37 (P = 0.0041)	Heterogeneity: Tau <sup>2</sup> = 0.04; ( Test for overall effect: Z = 2.8 Randomised 250+ participa
-0.02 [ -0.13, 0.09	13.3 %	_	-0.28 (0.98)	605	-0.3 (0.98)	ants 605	3 Randomised 250+ participa AlphaOmega - ALA
-0.26 [ -0.37, -0.15	13.5 %		6.55 (1.1)	860	6.29 (1.13)	855	DART fat 1989
0.10 [ -0.15, 0.35	9.4 %		0.1 (0.63)	71	0.2 (0.8987)	80	MARINA - Sanders 2011
- Not estimab			-0.47 (0)	89	-1.11 (0)	88	MRC 1968
	14.1 %	+	-0.25 (0.527)	309	-0.666 (0.69)	653	NDHS Open 1st 1968
-0.42 [ -0.50, -0.34					-0.35 (0.9)	58	PREDIMED 2013 (22)
-0.42 [ -0.50, -0.34 -0.05 [ -0.37, 0.27	7.4 %		-0.3 (0.89)	59			
-	7.4 % 6.6 %	<b>_</b>	-0.3 (0.89) -0.8 (0.99)	59 54	-1.01 (0.92)	54	PREDIMED 2013 (23)
-0.05 [ -0.37, 0.27		 	. ,		. ,	54 51	PREDIMED 2013 (23) PREDIMED 2013 (24)
-0.05 [ -0.37, 0.27 -0.21 [ -0.57, 0.15	6.6 %	 	-0.8 (0.99)	54	-1.01 (0.92)		
-0.05 [ -0.37, 0.27 -0.21 [ -0.57, 0.15 0.15 [ -0.25, 0.55	6.6 % 6.0 %	 	-0.8 (0.99) 5.02 (0.94)	54 42	-1.01 (0.92) 5.17 (1)	51	PREDIMED 2013 (24)
-0.05 [ -0.37, 0.27 -0.21 [ -0.57, 0.15 0.15 [ -0.25, 0.55 -0.30 [ -0.51, -0.09	6.6 % 6.0 % 10.4 %		-0.8 (0.99) 5.02 (0.94) 6.8 (1.1)	54 42 237	-1.01 (0.92) 5.17 (1) 6.5 (1.2)	51 221	PREDIMED 2013 (24) Sydney Diet-Heart 1978

(I) I4 month data

- (2) 2-year data
- (3) Change data
- (4) 2-year data
- (5) Fernandez-Real 2012, Reus subcohort, 2 year data
- (6) Damasceno 2013, Barcelona North subcohort, I year data
- (7) Barcelona hospital cohort at 5 years, Casas 2016
- (8) Change data
- (9) Change data
- (10) 2-year data
- (11) Change data
- (12) Fernandez-Real 2012, Reus subcohort, 2 year data
- (13) Barcelona hospital cohort at 5 years, Casas 2016
- (14) Damasceno 2013, Barcelona North subcohort, 1 year data
- (15) 2-year data
- (16) Change data
- (17) 2-year data
- (18) Change data
- (19) Damasceno 2013, Barcelona North subcohort, 1 year data
- (20) Barcelona hospital cohort at 5 years, Casas 2016
- (21) Fernandez-Real 2012, Reus subcohort, 2 year data
- (22) Damasceno 2013, Barcelona North subcohort, I year data
- (23) Barcelona hospital cohort at 5 years, Casas 2016
- (24) Fernandez-Real 2012, Reus subcohort, 2 year data

# Analysis 3.30. Comparison 3 Higher PUFA vs lower PUFA - continuous secondary outcomes, Outcome 30 TC, mmoL/L - SA fixed-effect.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 3 Higher PUFA vs lower PUFA - continuous secondary outcomes

Outcome: 30 TC, mmoL/L - SA fixed-effect

Study or subgroup	Higher PUFA N	Mean(SD)	Lower PUFA N	Mean(SD)	Mean Difference IV,Fixed,95% Cl	Weight	Mean Difference IV,Fixed,95% Cl
Ahn 2016	38	3.6 (0.74)	36	3.75 (0.67)		1.5 %	-0.15 [ -0.47, 0.17 ]
AlphaOmega - ALA	605	-0.3 (0.98)	605	-0.28 (0.98)		12.5 %	-0.02 [ -0.13, 0.09 ]
Brox 2001	67	7.8896 (0.8168)	37	7.9 (0.8)		1.5 %	-0.01 [ -0.33, 0.31 ]
DART fat 1989	855	6.29 (1.13)	860	6.55 (1.1)		13.7 %	-0.26 [ -0.37, -0.15 ]
DIPP-Tokudome 2015 (1)	91	5.52 (0.9)	75	5.4 (0.79)		2.3 %	0.12 [ -0.14, 0.38 ]
Dodin 2005	85	5.66 (0.72)	94	5.96 (0.72)	•	3.4 %	-0.30 [ -0.51, -0.09 ]
HARP- Sacks 1995	31	5.02 (0.96)	28	4.99 (0.62)		0.9 %	0.03 [ -0.38, 0.44 ]
HERO-Tapsell 2009	18	4.9 (0.8)	17	4.6 (1)		• 0.4 %	0.30 [ -0.30, 0.90 ]
Houtsmuller 1979	48	6.43 (0.65)	48	6.9 (0.81)		1.8 %	-0.47 [ -0.76, -0.18 ]
Ley 2004 (2)	70	-0.05 (1.4223)	66	-0.15 (0.7312)		· I.I %	0.10 [ -0.28, 0.48 ]
MARINA - Sanders 2011	80	0.2 (0.8987)	71	0.1 (0.63)		2.5 %	0.10 [ -0.15, 0.35 ]
Mendis 2001	26	-0.42 (0.5447)	28	-0.58 (0.7221)		- 1.3 %	0.16 [ -0.18, 0.50 ]
Mita 2007	30	5.15 (0.83)	30	5.27 (0.99)	· · · · · · · · · · · · · · · · · · ·	0.7 %	-0.12 [ -0.58, 0.34 ]
MRC 1968	88	-1.11 (0)	89	-0.47 (0)			Not estimable
NDHS Faribault 1968	4	-0.99 (0.637)	51	-0.18 (0.571)		4.3 %	-0.81 [ -1.00, -0.62 ]
NDHS Open 1st 1968	653	-0.666 (0.69)	309	-0.25 (0.527)		24.4 %	-0.42 [ -0.50, -0.34 ]
Nodari 2011 HF	67	4.8 (0.62)	66	4.9 (0.62)		3.4 %	-0.10 [ -0.31, 0.11 ]
Nye 1990	12	6.83 (I)	12	6.2 (1.31)		• 0.2 %	0.63 [ -0.30, 1.56 ]
PREDIMED 2013 (3)	54	-1.01 (0.92)	54	-0.8 (0.99)	•	1.2 %	-0.21 [ -0.57, 0.15 ]
PREDIMED 2013 (4)	58	-0.35 (0.9)	59	-0.3 (0.89)		1.4 %	-0.05 [ -0.37, 0.27 ]
PREDIMED 2013 (5)	51	5.17 (1)	42	5.02 (0.94)		• I.0 %	0.15 [ -0.25, 0.55 ]
Rose 1965	13	-0.51 (1.25)	13	-0.02 (0.94)	•	0.2 %	-0.49 [ -1.34, 0.36 ]
Rossing 1996	14	5.51 (1.12)	15	5.2 (1.16)	• • •	• 0.2 %	0.31 [ -0.52, 1.14 ]
Simon 1997	38	5.21 (1.11)	34	4.87 (0.87)	· · · · · ·	• 0.7 %	0.34 [ -0.12, 0.80 ]

-0.5 -0.25 0 0.25 0.5 Favours higher PUFA Favours lower PUFA

(Continued . . . )

							( Continued)
Study or subgroup	Higher PUFA	l	Lower PUFA		Mean Difference	Weight	Mean Difference
	Ν	Mean(SD)	Ν	Mean(SD)	IV,Fixed,95% C	1	IV,Fixed,95% CI
Sydney Diet-Heart 1978	221	6.5 (1.2)	237	6.8 (Ⅰ.Ⅰ) ←	[	3.4 %	-0.30 [ -0.5  , -0.09 ]
Veterans Admin 1969	423	4.93 (3.72)	420	5.3 (1.87) ←		1.0 %	-0.37 [ -0.77, 0.03 ]
Vijayakumar 2014	94	3.92 (1.15)	96	3.86 (0.74)		- 2.0 %	0.06 [ -0.22, 0.34 ]
WAHA - Ros 2016	260	-0.19 (0.65)	254	-0.01 (0.64)		12.2 %	-0.18 [ -0.29, -0.07 ]
WELCOME 2015	47	4.7 ( . )	48	4.8 (∣) ←		- 0.9 %	-0.10 [ -0.52, 0.32 ]
Total (95% CI)	4278		3794		•	100.0 %	-0.22 [ -0.26, -0.18 ]
Heterogeneity: Chi <sup>2</sup> = 127.1	2, df = 27 (P<0.00	0001); I <sup>2</sup> =79%					
Test for overall effect: $Z = 1$	1.21 (P < 0.00001)	)					
Test for subgroup differences	: Not applicable						

-0.5 -0.25 0 0.25 0.5

Favours higher PUFA Favours lower PUFA

(I) 2 year data

(2) Change data

(3) Barcelona hospital cohort at 5 years, Casas 2016

(4) Damasceno 2013, Barcelona North subcohort, I year data

(5) Fernandez-Real 2012, Reus subcohort, 2 year data

# Analysis 3.31. Comparison 3 Higher PUFA vs lower PUFA - continuous secondary outcomes, Outcome 31 TC, mmoL/L - subgroup by PUFA dose.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 3 Higher PUFA vs lower PUFA - continuous secondary outcomes

Outcome: 31 TC, mmoL/L - subgroup by PUFA dose

Mea Differenc IV,Random,95% (	Weight	Mean Difference IV,Random,95% Cl	Mean(SD)	Lower PUFA N	Mean(SD)	Higher PUFA N	Study or subgroup
14,14110011,2270 0		TV, Naridoni, 7576 Ci	r icali(SD)	14	r icari(5D)		total PUFA < 1.0% E
0.10 [ -0.28, 0.48	3.2 %		-0.15 (0.7312)	66	-0.05 (1.4223)	70	Ley 2004 (I)
0.10 [ -0.15, 0.35	4.3 %		0.1 (0.63)	71	0.2 (0.8987)	80	MARINA - Sanders 2011
-0.12 [ -0.58, 0.34	2.6 %		5.27 (0.99) 🗲	30	5.15 (0.83)	30	Mita 2007
-0.10 [ -0.31, 0.11	4.6 %		4.9 (0.62)	66	4.8 (0.62)	67	Nodari 2011 HF
-0.01 [ -0.15, 0.13	14.7 %	-		233		247	Subtotal (95% CI)
				).0%	3 (P = 0.57); I <sup>2</sup> =	2 (P = 0.90)	Heterogeneity: $Tau^2 = 0.0$ ; C Test for overall effect: Z = 0.1 2 total PUFA 1.0 to < 2.0% E
-0.15 [ -0.47, 0.17	3.6 %		3.75 (0.67) -	36	3.6 (0.74)	38	Ahn 2016
-0.02 [ -0.13, 0.09	5.4 %	-	-0.28 (0.98)	605	-0.3 (0.98)	605	AlphaOmega - ALA
-0.01 [ -0.33, 0.31	3.6 %		7.9 (0.8)	37	7.8896 (0.8168)	67	Brox 2001 (2)
0.12 [ -0.14, 0.38	4.2 %		5.4 (0.79)	75	5.52 (0.9)	91	DIPP-Tokudome 2015 (3)
-0.30 [ -0.51, -0.09	4.6 %	<del></del>	5.96 (0.72) ←	94	5.66 (0.72)	85	Dodin 2005
0.63 [ -0.30, 1.56	1.0 %		6.2 (1.31)	12	6.83 (1)	12	Nye 1990
-0.05 [ -0.37, 0.27	3.6 %		-0.3 (0.89)	59	-0.35 (0.9)	58	PREDIMED 2013 (4)
0.15 [ -0.25, 0.55	3.0 %		5.02 (0.94)	42	5.17 (1)	51	PREDIMED 2013 (5)
-0.21 [ -0.57, 0.15	3.3 %		-0.8 (0.99) ←	54	-1.01 (0.92)	54	PREDIMED 2013 (6)
-0.10 [ -0.52, 0.32	2.9 %		4.8 (∣) ←	48	4.7 ( . )	47	WELCOME 2015
-0.06 [ -0.16, 0.04	35.3 %	-		<b>1062</b> =22%	= 9 (P = 0.24); I <sup>2</sup>	4 (P = 0.25)	Subtotal (95% CI) Heterogeneity: Tau <sup>2</sup> = 0.01; ( Test for overall effect: Z = 1. 3 total PUFA 2.0 to < 5.0% E
-0.26 [ -0.37, -0.15	5.5 %	_ <b>.</b> _	6.55 (1.1)	860	6.29 (1.13)	855	DART fat 1989
0.03 [ -0.38, 0.44	3.0 %		4.99 (0.62)	28	5.02 (0.96)	31	HARP- Sacks 1995
0.16 [ -0.18, 0.50	3.5 %		-0.58 (0.7221)	28	-0.42 (0.5447)	26	Mendis 2001
0.31 [ -0.52, 1.14	1.2 %		5.2 (1.16) ←	15	5.51 (1.12)	14	Rossing 1996

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								( Continued
Study or subgroup	Higher PUFA		Lower PUFA			Mean rence	Weight	Mean Difference
, , ,	N	Mean(SD)	Ν	Mean(SD)	IV,Rando	m,95% Cl	5	IV,Random,95% C
Subtotal (95% CI)	926		931				13.0 %	-0.03 [ -0.31, 0.25 ]
Heterogeneity: $Tau^2 = 0.05$ ;	Chi <sup>2</sup> = 8.22, df =	3 (P = 0.04); I <sup>2</sup> =	=64%					
Test for overall effect: $Z = 0$	.20 (P = 0.84)							
4 total PUFA 5.0+% E								
HERO-Tapsell 2009	18	4.9 (0.8)	17	4.6 (1)			→ I.9 %	0.30 [ -0.30, 0.90 ]
Houtsmuller 1979	48	6.43 (0.65)	48	6.9 (0.81)			3.9 %	-0.47 [ -0.76, -0.18 ]
MRC 1968	88	-1.11 (0)	89	-0.47 (0)				Not estimable
NDHS Faribault 1968	4	-0.99 (0.637)	51	-0.18 (0.571)	•		4.8 %	-0.81 [ -1.00, -0.62 ]
NDHS Open 1st 1968	653	-0.666 (0.69)	309	-0.25 (0.527)			5.6 %	-0.42 [ -0.50, -0.34 ]
Rose 1965	13	-0.51 (1.25)	13	-0.02 (0.94)	•		1.1 %	-0.49 [ -1.34, 0.36 ]
Simon 1997	38	5.21 (1.11)	34	4.87 (0.87)			→ 2.6 %	0.34 [ -0.12, 0.80 ]
Sydney Diet-Heart 1978	221	6.5 (1.2)	237	6.8 (1.1)	•		4.6 %	-0.30 [ -0.51, -0.09 ]
Veterans Admin 1969	423	4.93 (3.72)	420	5.3 (1.87)	•		3.0 %	-0.37 [ -0.77, 0.03 ]
Vijayakumar 2014	94	3.92 (1.15)	96	3.86 (0.74)			4.0 %	0.06 [ -0.22, 0.34 ]
WAHA - Ros 2016	260	-0.19 (0.65)	254	-0.01 (0.64)			5.4 %	-0.18 [ -0.29, -0.07 ]
Subtotal (95% CI)	1997		1568				37.0 %	-0.28 [ -0.45, -0.10 ]
Heterogeneity: $Tau^2 = 0.05;$	$Chi^2 = 57.08, df$	= 9 (P<0.00001);	l <sup>2</sup> =84%					
Test for overall effect: $Z = 3$	( )							
Total (95% CI)	4278		3794		•		100.0 %	-0.12 [ -0.23, -0.02 ]
Heterogeneity: $Tau^2 = 0.04;$		f = 27 (P<0.0000	l); l <sup>2</sup> =79%					
Test for overall effect: $Z = 2$	· ,							
Test for subgroup difference	s: Chi <sup>2</sup> = 5.96, df	$= 3 (P = 0.11), 1^{2}$	=50%					
						I	1	

Favours higher PUFA Favo

Favours lower PUFA

(I) Change data

(2) 14 month data

(3) 2-year data

(4) Damasceno 2013, Barcelona North subcohort, I year data

(5) Fernandez-Real 2012, Reus subcohort, 2 year data

(6) Barcelona hospital cohort at 5 years, Casas 2016

# Analysis 3.32. Comparison 3 Higher PUFA vs lower PUFA - continuous secondary outcomes, Outcome 32 TC, mmoL/L - subgroup by duration.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 3 Higher PUFA vs lower PUFA - continuous secondary outcomes

Outcome: 32 TC, mmoL/L - subgroup by duration

Mei Differen	Weight	Mean Difference		Lower PUFA		Higher PUFA	Study or subgroup
IV,Random,95%		IV,Random,95% Cl	Mean(SD)	N	Mean(SD)	N	
	3.6 %			36	3.6 (0.74)	years 38	I Medium duration I to < 2 Ahn 2016
-0.15 [ -0.47, 0.17			3.75 (0.67)		. ,		
-0.01 [ -0.33, 0.31	3.6 %		7.9 (0.8)	37	7.8896 (0.8168)		Brox 2001 (1)
-0.30 [ -0.51, -0.09	4.6 %		5.96 (0.72)	94	5.66 (0.72)	85	Dodin 2005
0.30 [ -0.30, 0.90	1.9 %		4.6 (1)	17	4.9 (0.8)	18	HERO-Tapsell 2009
0.10 [ -0.28, 0.48	3.2 %		-0.15 (0.7312)	66	-0.05 (1.4223)	70	Ley 2004 (2)
0.10 [ -0.15, 0.35	4.3 %		0.1 (0.63)	71	0.2 (0.8987)	80	MARINA - Sanders 2011
0.16 [ -0.18, 0.50	3.5 %		-0.58 (0.7221)	28	-0.42 (0.5447)	26	Mendis 2001
-0.81 [ -1.00, -0.62	4.8 %		-0.18 (0.571)	51	-0.99 (0.637)	4	NDHS Faribault 1968
-0.42 [ -0.50, -0.34	5.6 %	_	-0.25 (0.527) —	309	-0.666 (0.69)	653	NDHS Open 1st 1968
-0.10[-0.31,0.11	4.6 %		4.9 (0.62)	66	4.8 (0.62)	67	Nodari 2011 HF
0.63 [ -0.30, 1.56	1.0 %		6.2 (1.31)	12	6.83 (1)	12	Nye 1990
0.3  [ -0.52,  . 4	1.2 %		5.2 (1.16) ←	15	5.51 (1.12)	14	Rossing 1996
-0.10 [ -0.52, 0.32	2.9 %		4.8 (I) <b>-</b>	48	4.7 (1.1)	47	WELCOME 2015
0.11 [ -0.30, 0.08	<b>44.</b> 7 %			850		1318	Subtotal (95% CI)
				); I <sup>2</sup> =84%	= 12 (P<0.00001	5 (P = 0.25)	Heterogeneity: $Tau^2 = 0.08$ ; Test for overall effect: $Z = 1$ . 2 Medium-long duration 2 to
-0.02 [ -0.13, 0.09	5.4 %		-0.28 (0.98)	605	-0.3 (0.98)	605	AlphaOmega - ALA
-0.26 [ -0.37, -0.15	5.5 %	_ <b></b>	6.55 (1.1)	860	6.29 (1.13)	855	DART fat 1989
0.12 [ -0.14, 0.38	4.2 %		5.4 (0.79)	75	5.52 (0.9)	91	DIPP-Tokudome 2015 (3)
0.03 [ -0.38, 0.44	3.0 %		4.99 (0.62)	28	5.02 (0.96)	31	HARP- Sacks 1995
-0.12 [ -0.58, 0.34	2.6 %		5.27 (0.99) ←	30	5.15 (0.83)	30	Mita 2007
			-0.02 (0.94)	13	-0.51 (1.25)	13	Rose 1965
-0.49 [ -1.34, 0.36	1.1 %						
-0.49 [ -1.34, 0.36 0.34 [ -0.12, 0.80	1.1 % 2.6 %		4.87 (0.87)	34	5.21 (1.11)	38	Simon 1997

Favours higher PUFA Favours lower PUFA

(Continued ...)

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<b>(</b> )								
Mea Differenc	Weight	Mean Difference			Lower PUFA	L	Higher PUFA	Study or subgroup
IV,Random,95% (	-	Random,95% Cl	IV,	Mean(SD)	Ν	Mean(SD)	N	,
-0.18 [ -0.29, -0.07	5.4 %	-		-0.01 (0.64)	254	-0.19 (0.65)	260	WAHA - Ros 2016
6 -0.07 [ -0.19, 0.05	33.8 %	•			1995		2017	Subtotal (95% CI)
					=62%	8 (P = 0.01); l <sup>2</sup>	Chi <sup>2</sup> = 21.11, df =	Heterogeneity: $Tau^2 = 0.02;$
							12 (P = 0.26)	Test for overall effect: $Z = I$
								3 Long duration 4+ years
-0.47 [ -0.76, -0.18	3.9 %	-	4	6.9 (0.81)	48	6.43 (0.65)	48	Houtsmuller 1979
Not estimabl				-0.47 (0)	89	-1.11 (0)	88	MRC 1968
% -0.05 [ -0.37, 0.27	3.6 %			-0.3 (0.89)	59	-0.35 (0.9)	58	PREDIMED 2013 (4)
% 0.15 [ -0.25, 0.55	3.0 %		_	5.02 (0.94)	42	5.17 (1)	51	PREDIMED 2013 (5)
% -0.21 [ -0.57, 0.15	3.3 %		•	-0.8 (0.99)	54	-1.01 (0.92)	54	PREDIMED 2013 (6)
% -0.30 [ -0.5  , -0.09	4.6 %	—	•	6.8 ( . )	237	6.5 (1.2)	221	Sydney Diet-Heart 1978
% -0.37 [ -0.77, 0.03	3.0 %		<b>4</b>	5.3 (1.87)	420	4.93 (3.72)	423	Veterans Admin 1969
6 -0.23 [ -0.40, -0.06	21.5 %		-		949		943	Subtotal (95% CI)
•					39%	5 (P = 0.15); $I^2 =$	Chi <sup>2</sup> = 8.16, df =	Heterogeneity: $Tau^2 = 0.02;$
							7I (P = 0.0067)	Test for overall effect: $Z = 2$
6 -0.12 [ -0.23, -0.02	100.0 %	•	-		3794		4278	Total (95% CI)
					); l <sup>2</sup> =79%	= 27 (P<0.00001	$Chi^2 = 127.12$ , df	Heterogeneity: $Tau^2 = 0.04;$
							44 (P = 0.015)	Test for overall effect: $Z = 2$
					=18%	= 2 (P = 0.30), I <sup>2</sup> =	s: Chi <sup>2</sup> = 2.44, df =	Test for subgroup difference

-0.5 -0.25 0 0.25 0.5 Favours higher PUFA Favours lower PUFA

(I) I4 month data

(2) Change data

(3) 2 year data

(4) Damasceno 2013, Barcelona North subcohort, I year data

(5) Fernandez-Real 2012, Reus subcohort, 2 year data

(6) Barcelona hospital cohort at 5 years, Casas 2016

#### Analysis 3.33. Comparison 3 Higher PUFA vs lower PUFA - continuous secondary outcomes, Outcome 33 TC, mmoL/L - subgroup by primary or secondary prevention.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 3 Higher PUFA vs lower PUFA - continuous secondary outcomes

Outcome: 33 TC, mmoL/L - subgroup by primary or secondary prevention

Mea Differenc	Weight	Mean Difference			Lower PUFA		Higher PUFA	Study or subgroup
IV,Random,95% (		Random,95% Cl	IV,F	Mean(SD)	N	Mean(SD)	N	
-0.01 [ -0.33, 0.31	3.6 %			7.9 (0.8)	37	7.8896 (0.8168)	(7	I Primary prevention of CVD Brox 2001 (1)
-	4.2 %			. ,	75	, ,		
0.12 [ -0.14, 0.38				5.4 (0.79)		5.52 (0.9)	91	DIPP-Tokudome 2015 (2)
-0.30 [ -0.51, -0.09	4.6 %	_	•	5.96 (0.72)	94	5.66 (0.72)	85	Dodin 2005
0.30 [ -0.30, 0.90	1.9 %			4.6 (1)	17	4.9 (0.8)	18	HERO-Tapsell 2009
-0.47 [ -0.76, -0.18	3.9 %		4	6.9 (0.81)	48	6.43 (0.65)	48	Houtsmuller 1979
0.10 [ -0.28, 0.48	3.2 %			-0.15 (0.7312)	66	-0.05 (1.4223)	70	Ley 2004 (3)
0.10 [ -0.15, 0.35	4.3 %			0.1 (0.63)	71	0.2 (0.8987)	80	MARINA - Sanders 2011
0.16 [ -0.18, 0.50	3.5 %			-0.58 (0.7221)	28	-0.42 (0.5447)	26	Mendis 2001
-0.12 [ -0.58, 0.34	2.6 %		•	5.27 (0.99)	30	5.15 (0.83)	30	Mita 2007
-0.81 [ -1.00, -0.62	4.8 %		4	-0.18 (0.571)	51	-0.99 (0.637)	4	NDHS Faribault 1968
-0.42 [ -0.50, -0.34	5.6 %			-0.25 (0.527)	309	-0.666 (0.69)	653	NDHS Open 1st 1968
-0.05 [ -0.37, 0.27	3.6 %			-0.3 (0.89)	59	-0.35 (0.9)	58	PREDIMED 2013 (4)
0.15 [ -0.25, 0.55	3.0 %		_	5.02 (0.94)	42	5.17 (1)	51	PREDIMED 2013 (5)
-0.21 [ -0.57, 0.15	3.3 %		•	-0.8 (0.99)	54	-1.01 (0.92)	54	PREDIMED 2013 (6)
0.31 [ -0.52, 1.14	1.2 %		•	5.2 (1.16)	15	5.51 (1.12)	14	Rossing 1996
0.34 [ -0.12, 0.80	2.6 %			4.87 (0.87)	34	5.21 (1.11)	38	Simon 1997
-0.37 [ -0.77, 0.03	3.0 %		<del>• • • • • • • • • • • • • • • • • • • </del>	5.3 (1.87)	420	4.93 (3.72)	423	Veterans Admin 1969
-0.18 [ -0.29, -0.07	5.4 %	<u></u>	—	-0.01 (0.64)	254	-0.19 (0.65)	260	WAHA - Ros 2016
-0.10 [ -0.52, 0.32	2.9 %		•	4.8 (1)	48	4.7 (1.1)	47	WELCOME 2015
-0.12 [ -0.26, 0.02	67.2 %				1752		2254	Subtotal (95% CI)
					); I <sup>2</sup> =82%	= 18 (P<0.0000)		Heterogeneity: Tau <sup>2</sup> = 0.06; C Test for overall effect: Z = $1.7$
							′D	2 Secondary prevention of C
-0.15 [ -0.47, 0.17	3.6 %	•		3.75 (0.67)	36	3.6 (0.74)	38	Ahn 2016
-0.02 [ -0.13, 0.09	5.4 %			-0.28 (0.98)	605	-0.3 (0.98)	605	AlphaOmega - ALA

Favours higher PUFA Favours lower PUFA

(Continued ...)

								( Continued)
Study or subgroup	Higher PUFA	Le	ower PUFA		Mea Differend		Weight	Mean Difference
	Ν	Mean(SD)	Ν	Mean(SD)	IV,Random,9	5% CI		IV,Random,95% CI
DART fat 1989	855	6.29 (1.13)	860	6.55 (1.1)			5.5 %	-0.26 [ -0.37, -0.15 ]
HARP- Sacks 1995	31	5.02 (0.96)	28	4.99 (0.62)			3.0 %	0.03 [ -0.38, 0.44 ]
MRC 1968	88	-1.11 (0)	89	-0.47 (0)				Not estimable
Nodari 2011 HF	67	4.8 (0.62)	66	4.9 (0.62)			4.6 %	-0.10 [ -0.31, 0.11 ]
Nye 1990	12	6.83 (1)	12	6.2 (1.31)			• 1.0 %	0.63 [ -0.30, 1.56 ]
Rose 1965	13	-0.51 (1.25)	13	-0.02 (0.94)	•		1.1 %	-0.49 [ -1.34, 0.36 ]
Sydney Diet-Heart 1978	221	6.5 (1.2)	237	6.8 (1.1)	•		4.6 %	-0.30 [ -0.51, -0.09 ]
Vijayakumar 2014	94	3.92 (1.15)	96	3.86 (0.74)			4.0 %	0.06 [ -0.22, 0.34 ]
Subtotal (95% CI)	2024		2042		-		32.8 %	-0.12 [ -0.24, 0.00 ]
Heterogeneity: $Tau^2 = 0.01$ ; (	$Chi^2 = 17.80, df =$	8 (P = 0.02); I <sup>2</sup> =	55%					
Test for overall effect: $Z = 2.0$	) (P = 0.044)							
Total (95% CI)	4278		3794		-		100.0 %	-0.12 [ -0.23, -0.02 ]
Heterogeneity: $Tau^2 = 0.04$ ; (	$Chi^2 = 127.12$ , df	= 27 (P<0.00001)	; I <sup>2</sup> =79%					
Test for overall effect: $Z = 2.4$	14 (P = 0.015)							
Test for subgroup differences	$Chi^2 = 0.00, df =$	= I (P = 0.98), I <sup>2</sup> =	=0.0%					

-0.5 -0.25 0 0.25 0.5

Favours higher PUFA Favours lower PUFA

(I) I4 month data

(2) 2 year data

(3) Change data

(4) Damasceno 2013, Barcelona North subcohort, I year data

(5) Fernandez-Real 2012, Reus subcohort, 2 year data

(6) Barcelona hospital cohort at 5 years, Casas 2016

# Analysis 3.34. Comparison 3 Higher PUFA vs lower PUFA - continuous secondary outcomes, Outcome 34 TC, mmoL/L - subgroup by baseline PUFA dose.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 3 Higher PUFA vs lower PUFA - continuous secondary outcomes

Outcome: 34 TC, mmoL/L - subgroup by baseline PUFA dose

Study or subgroup	Higher PUFA N	Mean(SD)	Lower PUFA	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mear Difference IV,Random,95% C
Baseline total PUFA < 6% E		Fiedri(SD)	11	Mean(SD)	TV,I\andoin,25% CI		1V,IVaIId0III,7578 C
Dodin 2005	85	5.66 (0.72)	94	5.96 (0.72)	•	4.6 %	-0.30 [ -0.51, -0.09
HERO-Tapsell 2009	18	4.9 (0.8)	17	4.6 (1)		→ I.9 %	0.30 [ -0.30, 0.90
Ley 2004 (I)	70	-0.05 (1.4223)	66	-0.15 (0.7312)		3.2 %	0.10 [ -0.28, 0.48
NDHS Faribault 1968	4	-0.99 (0.637)	51	-0.18 (0.571)	•	4.8 %	-0.8  [ -1.00, -0.62
NDHS Open 1st 1968	653	-0.666 (0.69)	309	-0.25 (0.527)		5.6 %	-0.42 [ -0.50, -0.34
Veterans Admin 1969	423	4.93 (3.72)	420	5.3 (1.87)	• • • • • • • • • • • • • • • • • • • •	3.0 %	-0.37 [ -0.77, 0.03
Subtotal (95% CI)	1390		957			23.1 %	-0.33 [ -0.56, -0.09
est for overall effect: $Z = 2.7$ Baseline total PUFA 6 to <	11% E						
DART fat 1989	855	6.29 (1.13)	860	6.55 (1.1)		5.5 %	-0.26 [ -0.37, -0.15
DIPP-Tokudome 2015 (2)	91	5.52 (0.9)	75	5.4 (0.79)		4.2 %	0.12 [ -0.14, 0.38
MARINA - Sanders 2011	80	0.2 (0.8987)	71	0.1 (0.63)		4.3 %	0.10 [ -0.15, 0.35
PREDIMED 2013 (3)	54	-1.01 (0.92)	54	-0.8 (0.99)	• • • • • • • • • • • • • • • • • • •	3.3 %	-0.21 [ -0.57, 0.15
PREDIMED 2013 (4)	58	-0.35 (0.9)	59	-0.3 (0.89)		3.6 %	-0.05 [ -0.37, 0.27
PREDIMED 2013 (5)	51	5.17 (1)	42	5.02 (0.94)		→ 3.0 %	0.15 [ -0.25, 0.55
Simon 1997	38	5.21 (1.11)	34	4.87 (0.87)		2.6 %	0.34 [ -0.12, 0.80
Sydney Diet-Heart 1978	221	6.5 (1.2)	237	6.8 (1.1)	<b>←</b>	4.6 %	-0.30 [ -0.51, -0.09
WAHA - Ros 2016	260	-0.19 (0.65)	254	-0.01 (0.64)	<b></b>	5.4 %	-0.18 [ -0.29, -0.07
Subtotal (95% CI)	1708		1686		-	36.6 %	-0.09 [ -0.21, 0.04
leterogeneity: Tau <sup>2</sup> = 0.02; C est for overall effect: Z = 1.3 Baseline total PUFA 11+% E	8 (P = 0.17)	= 8 (P = 0.01); I <sup>2</sup>	2 =63%				
Subtotal (95% CI)	0		0				Not estimabl
leterogeneity: not applicable							
est for overall effect: not app Baseline total PUFA unclear							
				-0	.5 -0.25 0 0.25	0.5	

Higher PUFA	1	ower PUFA		Mean Difference	Weight	Mear Difference
N	Mean(SD)	N		IV,Random,95% Cl		IV,Random,95% C
38	3.6 (0.74)	36	3.75 (0.67) -	· ·	3.6 %	-0.15 [ -0.47, 0.17
605	-0.3 (0.98)	605	-0.28 (0.98)		5.4 %	-0.02 [ -0.13, 0.09 ]
67	7.8896 (0.8168)	37	7.9 (0.8)		3.6 %	-0.01 [ -0.33, 0.31
31	5.02 (0.96)	28	4.99 (0.62)		3.0 %	0.03 [ -0.38, 0.44
48	6.43 (0.65)	48	6.9 (0.81) 🗯		3.9 %	-0.47 [ -0.76, -0.18
26	-0.42 (0.5447)	28	-0.58 (0.7221)		- 3.5 %	0.16 [ -0.18, 0.50
30	5.15 (0.83)	30	5.27 (0.99) ←		2.6 %	-0.12 [ -0.58, 0.34
88	-1.11 (0)	89	-0.47 (0)			Not estimabl
67	4.8 (0.62)	66	4.9 (0.62)		4.6 %	-0.10 [ -0.31, 0.11
12	6.83 (1)	12	6.2 (1.31)		→ I.0 %	0.63 [ -0.30, 1.56
13	-0.51 (1.25)	13	-0.02 (0.94) 👉		1.1 %	-0.49 [ -1.34, 0.36
4	5.51 (1.12)	15	5.2 (1.16) ←		→ I.2 %	0.31 [ -0.52, 1.14
94	3.92 (1.15)	96	3.86 (0.74)	<b>+</b>	4.0 %	0.06 [ -0.22, 0.34
47	4.7 ( . )	48	4.8 (∣) ←		2.9 %	-0.10 [ -0.52, 0.32
1180		1151		-	40.3 %	-0.06 [ -0.16, 0.04
i <sup>2</sup> = 14.94, df	$= 12 (P = 0.24); I^{2}$	=20%				
(P = 0.23)						
4278		3794		-	100.0 %	-0.12 [ -0.23, -0.02 ]
i <sup>2</sup> = 127.12, d	f = 27 (P<0.00001	); I <sup>2</sup> =79%				
(P = 0.015)						
$Chi^2 = 4.24$ , df	= 2 (P = 0.12), 1 <sup>2</sup>	=53%				
	$\begin{array}{c} 38\\ 605\\ 67\\ 31\\ 48\\ 26\\ 30\\ 88\\ 67\\ 12\\ 13\\ 14\\ 94\\ 47\\ 1180\\ i^2 = 14.94, df\\ (P = 0.23)\\ 4278\\ i^2 = 127.12, d\\ (P = 0.015)\end{array}$	$\begin{array}{c} 38 & 3.6 (0.74) \\ 605 & -0.3 (0.98) \\ 67 & 7.8896 (0.8168) \\ 31 & 5.02 (0.96) \\ 48 & 6.43 (0.65) \\ 26 & -0.42 (0.5447) \\ 30 & 5.15 (0.83) \\ 88 & -1.11 (0) \\ 67 & 4.8 (0.62) \\ 12 & 6.83 (1) \\ 13 & -0.51 (1.25) \\ 14 & 5.51 (1.12) \\ 94 & 3.92 (1.15) \\ 47 & 4.7 (1.1) \\ \begin{array}{c} 1180 \\ \mathbf{i}^2 = 14.94,  df = 12 (P = 0.24); 1^2 \\ (P = 0.23) \\ 4278 \\ \mathbf{i}^2 = 127.12,  df = 27 (P < 0.00001 \\ (P = 0.015) \end{array}$	38         3.6 (0.74)         36           605         -0.3 (0.98)         605           67         7.8896 (0.8168)         37           31         5.02 (0.96)         28           48         6.43 (0.65)         48           26         -0.42 (0.5447)         28           30         5.15 (0.83)         30           88         -1.11 (0)         89           67         4.8 (0.62)         66           12         6.83 (1)         12           13         -0.51 (1.25)         13           14         5.51 (1.12)         15           94         3.92 (1.15)         96           47         4.7 (1.1)         48 <b>1180 1151</b> $i^2 = 14.94$ , df = 12 (P = 0.24); $i^2 = 20\%$ (P = 0.23) <b>3794</b> $i^2 = 127.12$ , df = 27 (P<0.00001); $i^2 = 79\%$	38 $3.6 (0.74)$ $36$ $3.75 (0.67)$ 605 $-0.3 (0.98)$ $605$ $-0.28 (0.98)$ 67 $7.8896 (0.8168)$ $37$ $7.9 (0.8)$ 31 $5.02 (0.96)$ $28$ $4.99 (0.62)$ 48 $6.43 (0.65)$ $48$ $6.9 (0.81)$ 26 $-0.42 (0.5447)$ $28$ $-0.58 (0.7221)$ 30 $5.15 (0.83)$ $30$ $5.27 (0.99)$ 88 $-1.11 (0)$ $89$ $-0.47 (0)$ 67 $4.8 (0.62)$ $66$ $4.9 (0.62)$ 12 $6.83 (1)$ 12 $62 (1.31)$ 13 $-0.51 (1.25)$ 13 $-0.02 (0.94)$ 14 $5.51 (1.12)$ 15 $5.2 (1.16)$ 94 $3.92 (1.15)$ $96$ $3.86 (0.74)$ $47$ $4.7 (1.1)$ $48$ $4.8 (1)$ $4278$ $3794$ $i^2 = 127.12, df = 27 (P<0.00001); 1^2 = 79\%$ $i^2 = 127.12, df = 27 (P<0.00001); 1^2 = 79\%$ $(P = 0.015)$	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	$\begin{array}{c ccccccccccccccccccccccccccccccccccc$

Favours higher PUFA

Favours lower PUFA

(I) Change data

(2) 2 year data

(3) Barcelona hospital cohort at 5 years, Casas 2016

(4) Damasceno 2013, Barcelona North subcohort, 1 year data

(5) Fernandez-Real 2012, Reus subcohort, 2 year data

(6) 14 month data

# Analysis 3.35. Comparison 3 Higher PUFA vs lower PUFA - continuous secondary outcomes, Outcome 35 TC, mmoL/L - subgroup by replacement.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 3 Higher PUFA vs lower PUFA - continuous secondary outcomes

Outcome: 35 TC, mmoL/L - subgroup by replacement

Study or subgroup	Higher PUFA		Lower PUFA		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	Ν	Mean(SD)	IV,Random,95% Cl		IV,Random,95% Cl
I PUFA replaced saturated fa							
DART fat 1989	855	6.29 (1.13)	860	6.55 (1.1)		18.7 %	-0.26 [ -0.37, -0.15 ]
HERO-Tapsell 2009	18	4.9 (0.8)	17	4.6 (1)		→ 6.2 %	0.30 [ -0.30, 0.90 ]
MRC 1968	88	-1.11 (0)	89	-0.47 (0)			Not estimable
NDHS Faribault 1968	4	-0.99 (0.637)	51	-0.18 (0.571)	•	16.4 %	-0.81 [ -1.00, -0.62 ]
NDHS Open 1st 1968	653	-0.666 (0.69)	309	-0.25 (0.527) -		19.2 %	-0.42 [ -0.50, -0.34 ]
Sydney Diet-Heart 1978	221	6.5 (1.2)	237	6.8 ( . )	•	15.7 %	-0.30 [ -0.51, -0.09 ]
Veterans Admin 1969	423	4.93 (3.72)	420	5.3 (1.87) 🕇	• <b>B</b>	10.2 %	-0.37 [ -0.77, 0.03 ]
Vijayakumar 2014	94	3.92 (1.15)	96	3.86 (0.74)		13.6 %	0.06 [ -0.22, 0.34 ]
Subtotal (95% CI)	2493		2079	-		100.0 % -0	.32 [ -0.50, -0.14 ]
Test for overall effect: Z = 3.4	16 (P = 0.00053)						
2 PUFA replaced monounsatu		-0.3 (0.98)	605	-0.28 (0.98)	_	9.6 %	-0.02 [ -0.13. 0.09 ]
2 PUFA replaced monounsatu AlphaOmega - ALA	605	-0.3 (0.98)	605 28	-0.28 (0.98)	_	9.6 %	L .
2 PUFA replaced monounsatu AlphaOmega - ALA HARP- Sacks 1995	605 31	5.02 (0.96)	28	4.99 (0.62)		- 6.2 %	0.03 [ -0.38, 0.44
2 PUFA replaced monounsatu AlphaOmega - ALA HARP- Sacks 1995 MARINA - Sanders 2011	605 31 80	5.02 (0.96) 0.2 (0.8987)	28 71	4.99 (0.62) 0.1 (0.63)		- 6.2 % 8.2 %	0.03 [ -0.38, 0.44 ]
2 PUFA replaced monounsatu AlphaOmega - ALA HARP- Sacks 1995 MARINA - Sanders 2011 NDHS Faribault 1968	605 31 80 141	5.02 (0.96) 0.2 (0.8987) -0.99 (0.637)	28 71 51	4.99 (0.62) 0.1 (0.63) -0.18 (0.571)		- 6.2 % 8.2 % 8.8 %	0.03 [ -0.38, 0.44 ] 0.10 [ -0.15, 0.35 ] -0.81 [ -1.00, -0.62 ]
2 PUFA replaced monounsatu AlphaOmega - ALA HARP- Sacks 1995 MARINA - Sanders 2011 NDHS Faribault 1968 NDHS Open 1st 1968	605 31 80 141 653	5.02 (0.96) 0.2 (0.8987) -0.99 (0.637) -0.666 (0.69)	28 71 51 309	4.99 (0.62) 0.1 (0.63) -0.18 (0.571)		- 6.2 % 8.2 % 8.8 % 9.8 %	-0.02 [ -0.13, 0.09 ] 0.03 [ -0.38, 0.44 ] 0.10 [ -0.15, 0.35 ] -0.81 [ -1.00, -0.62 ] -0.42 [ -0.50, -0.34 ]
2 PUFA replaced monounsatu AlphaOmega - ALA HARP- Sacks 1995 MARINA - Sanders 2011 NDHS Faribault 1968	605 31 80 141	5.02 (0.96) 0.2 (0.8987) -0.99 (0.637)	28 71 51	4.99 (0.62) 0.1 (0.63) -0.18 (0.571)		- 6.2 % 8.2 % 8.8 %	0.03 [ -0.38, 0.44 ] 0.10 [ -0.15, 0.35 ] -0.81 [ -1.00, -0.62 ]
2 PUFA replaced monounsatu AlphaOmega - ALA HARP- Sacks 1995 MARINA - Sanders 2011 NDHS Faribault 1968 NDHS Open 1st 1968	605 31 80 141 653	5.02 (0.96) 0.2 (0.8987) -0.99 (0.637) -0.666 (0.69)	28 71 51 309	4.99 (0.62) 0.1 (0.63) -0.18 (0.571)		- 6.2 % 8.2 % 8.8 % 9.8 %	0.03 [ -0.38, 0.44 0.10 [ -0.15, 0.35 -0.81 [ -1.00, -0.62 -0.42 [ -0.50, -0.34
2 PUFA replaced monounsatu AlphaOmega - ALA HARP- Sacks 1995 MARINA - Sanders 2011 NDHS Faribault 1968 NDHS Open 1st 1968 Nodari 2011 HF	605 31 80 141 653 67	5.02 (0.96) 0.2 (0.8987) -0.99 (0.637) -0.666 (0.69) 4.8 (0.62)	28 71 51 309 66	4.99 (0.62) 0.1 (0.63) -0.18 (0.571) • -0.25 (0.527) = 4.9 (0.62)		- 6.2 % 8.2 % 8.8 % 9.8 % 8.6 %	0.03 [ -0.38, 0.44 0.10 [ -0.15, 0.35 -0.81 [ -1.00, -0.62 -0.42 [ -0.50, -0.34 -0.10 [ -0.31, 0.11 0.63 [ -0.30, 1.56
2 PUFA replaced monounsatu AlphaOmega - ALA HARP- Sacks 1995 MARINA - Sanders 2011 NDHS Faribault 1968 NDHS Open 1st 1968 Nodari 2011 HF Nye 1990	605 31 80 141 653 67 12	5.02 (0.96) 0.2 (0.8987) -0.99 (0.637) -0.666 (0.69) 4.8 (0.62) 6.83 (1)	28 71 51 309 66 12	4.99 (0.62) 0.1 (0.63) -0.18 (0.571) -0.25 (0.527) 4.9 (0.62) 6.2 (1.31)		- 6.2 % 8.2 % 8.8 % 9.8 % 8.6 % 2.4 %	0.03 [ -0.38, 0.44 0.10 [ -0.15, 0.35 -0.81 [ -1.00, -0.62 -0.42 [ -0.50, -0.34 -0.10 [ -0.31, 0.11 0.63 [ -0.30, 1.56 0.15 [ -0.25, 0.55
2 PUFA replaced monounsatu AlphaOmega - ALA HARP- Sacks 1995 MARINA - Sanders 2011 NDHS Faribault 1968 NDHS Open 1st 1968 Nodari 2011 HF Nye 1990 PREDIMED 2013 (1)	605 31 80 141 653 67 12 51	5.02 (0.96) 0.2 (0.8987) -0.99 (0.637) -0.666 (0.69) 4.8 (0.62) 6.83 (1) 5.17 (1)	28 71 51 309 66 12 42	4.99 (0.62) 0.1 (0.63) -0.18 (0.571) -0.25 (0.527) 4.9 (0.62) 6.2 (1.31) 5.02 (0.94)		- 6.2 % 8.2 % 8.8 % 9.8 % 8.6 % - 2.4 % - 6.3 %	0.03 [ -0.38, 0.44 0.10 [ -0.15, 0.35 -0.81 [ -1.00, -0.62 -0.42 [ -0.50, -0.34 -0.10 [ -0.31, 0.11 0.63 [ -0.30, 1.56 0.15 [ -0.25, 0.55 -0.05 [ -0.37, 0.27
2 PUFA replaced monounsatu AlphaOmega - ALA HARP- Sacks 1995 MARINA - Sanders 2011 NDHS Faribault 1968 NDHS Open 1st 1968 Nodari 2011 HF Nye 1990 PREDIMED 2013 (1) PREDIMED 2013 (2)	605 31 80 141 653 67 12 51 58	5.02 (0.96) 0.2 (0.8987) -0.99 (0.637) -0.666 (0.69) 4.8 (0.62) 6.83 (1) 5.17 (1) -0.35 (0.9)	28 71 309 66 12 42 59	4.99 (0.62) 0.1 (0.63) -0.18 (0.571) -0.25 (0.527) 4.9 (0.62) 6.2 (1.31) 5.02 (0.94) -0.3 (0.89)		<ul> <li>- 6.2 %</li> <li>8.2 %</li> <li>8.8 %</li> <li>9.8 %</li> <li>8.6 %</li> <li>→ 2.4 %</li> <li>→ 6.3 %</li> <li>7.2 %</li> </ul>	0.03 [ -0.38, 0.44 ] 0.10 [ -0.15, 0.35 ] -0.81 [ -1.00, -0.62 ] -0.42 [ -0.50, -0.34 ] -0.10 [ -0.31, 0.11 ]
2 PUFA replaced monounsatu AlphaOmega - ALA HARP- Sacks 1995 MARINA - Sanders 2011 NDHS Faribault 1968 NDHS Open 1st 1968 Nodari 2011 HF Nye 1990 PREDIMED 2013 (1) PREDIMED 2013 (2) PREDIMED 2013 (3)	605 31 80 141 653 67 12 51 58 54	5.02 (0.96) 0.2 (0.8987) -0.99 (0.637) -0.666 (0.69) 4.8 (0.62) 6.83 (1) 5.17 (1) -0.35 (0.9) -1.01 (0.92)	28 71 51 309 66 12 42 59 54	4.99 (0.62) 0.1 (0.63) -0.18 (0.571) -0.25 (0.527) 4.9 (0.62) 6.2 (1.31) 5.02 (0.94) -0.3 (0.89) -0.8 (0.99)		<ul> <li>- 6.2 %</li> <li>8.2 %</li> <li>8.8 %</li> <li>9.8 %</li> <li>8.6 %</li> <li>- 2.4 %</li> <li>- 6.3 %</li> <li>7.2 %</li> <li>6.7 %</li> </ul>	0.03 [ -0.38, 0.44 0.10 [ -0.15, 0.35 -0.81 [ -1.00, -0.62 -0.42 [ -0.50, -0.34 -0.10 [ -0.31, 0.11] 0.63 [ -0.30, 1.56 0.15 [ -0.25, 0.55 -0.05 [ -0.37, 0.27 -0.21 [ -0.57, 0.15

Favours higher PUFA Favours lower PUFA

(Continued ...)

Study or subgroup	Higher PUFA N	Mean(SD)	Lower PUFA N	Mean(SD)	Mean Difference IV,Random,95% Cl	Weight	Mear Difference IV,Random,95% C
Veterans Admin 1969	423	4.93 (3.72)	420	5.3 (1.87) ←	•	6.3 %	-0.37 [ -0.77, 0.03
WELCOME 2015	47	4.7 (1.1)	48	4.8 (1) ←		6.0 %	-0.10 [ -0.52, 0.32
Subtotal (95% CI)	2470		2030				-0.17 [ -0.33, 0.00
Heterogeneity: $Tau^2 = 0.07$ ; Cł Test for overall effect: $Z = 1.98$ 3 PUFA replaced carbohydrate	$hi^2 = 90.40$ , df 8 (P = 0.047)	= 14 (P<0.0000					, [,
DIPP-Tokudome 2015 (4)	91	5.52 (0.9)	75	5.4 (0.79)		12.9 %	0.12 [ -0.14, 0.38
Dodin 2005	85	5.66 (0.72)	94	5.96 (0.72) ←	_ <b></b>	14.4 %	-0.30 [ -0.51, -0.09
Houtsmuller 1979	48	6.43 (0.65)	48	6.9 (0.81) 🖷		11.7 %	-0.47 [ -0.76, -0.18
Ley 2004 (5)	70	-0.05 (1.4223)	66	-0.15 (0.7312)		- 9.3 %	0.10 [ -0.28, 0.48
MARINA - Sanders 2011	80	0.2 (0.8987)	71	0.1 (0.63)		13.3 %	0.10 [ -0.15, 0.35
Mendis 2001	26	-0.42 (0.5447)	28	-0.58 (0.7221)		- 10.3 %	0.16 [ -0.18, 0.50
Rose 1965	13	-0.51 (1.25)	13	-0.02 (0.94) 🔶		3.0 %	-0.49 [ -1.34, 0.36
Simon 1997	38	5.21 (1.11)	34	4.87 (0.87)		→ 7.5 %	0.34 [ -0.12, 0.80
WAHA - Ros 2016	260	-0.19 (0.65)	254	-0.01 (0.64)	_ <b>_</b>	17.6 %	-0.18 [ -0.29, -0.07
Heterogeneity: $Tau^2 = 0.03$ ; Ch	ni² = 24.30, df	= 8 (P = 0.002);	$1^2 = 67\%$				
Test for overall effect: Z = 0.79 4 PUFA replaced protein HERO-Tapsell 2009	P (P = 0.43)	4.9 (0.8)	17	4.6 (1)		→ 15.3 %	0.30 [ -0.30, 0.90
4 PUFA replaced protein HERO-Tapsell 2009	· · ·			4.6 (1) -0.15 (0.7312)		→ 15.3 % - 28.2 %	-
4 PUFA replaced protein	18	-0.05 (1.4223)		4.6 (1) -0.15 (0.7312) -0.47 (0)			0.10 [ -0.28, 0.48
4 PUFA replaced protein HERO-Tapsell 2009 Ley 2004 (6)	18		66	-0.15 (0.7312)	•		0.10 [ -0.28, 0.48 Not estimab
4 PUFA replaced protein HERO-Tapsell 2009 Ley 2004 (6) MRC 1968	18 70 88 260 <b>436</b> $h^{2} = 4.10, df =$	-0.05 (1.4223) -1.11 (0) -0.19 (0.65)	66 89 254 <b>426</b>	-0.15 (0.7312) -0.47 (0)		- 28.2 % 56.5 %	0.30 [ -0.30, 0.90 0.10 [ -0.28, 0.48 Not estimabl -0.18 [ -0.29, -0.07 <b>-0.03 [ -0.30, 0.24</b> -0.15 [ -0.47, 0.17
4 PUFA replaced protein HERO-Tapsell 2009 Ley 2004 (6) MRC 1968 WAHA - Ros 2016 Subtotal (95% CI) Heterogeneity: Tau <sup>2</sup> = 0.03; CH Test for overall effect: Z = 0.20 5 PUFA replaced unclear	$18 \\ 70 \\ 88 \\ 260 \\ 436 \\ ni^2 = 4.10, df = 0 (P = 0.84) \\ 38 \\ 38 \\ 38 \\ 38 \\ 38 \\ 38 \\ 38 \\ 3$	-0.05 (1.4223) -1.11 (0) -0.19 (0.65) = 2 (P = 0.13); I <sup>2</sup>	66 89 254 <b>426</b> =51%	-0.15 (0.7312) -0.47 (0) -0.01 (0.64)		<ul> <li>28.2 %</li> <li>56.5 %</li> <li>100.0 %</li> </ul>	0.10 [ -0.28, 0.48 Not estimab -0.18 [ -0.29, -0.07 -0.03 [ -0.30, 0.24
4 PUFA replaced protein HERO-Tapsell 2009 Ley 2004 (6) MRC 1968 WAHA - Ros 2016 Subtotal (95% CI) Heterogeneity: Tau <sup>2</sup> = 0.03; CH Test for overall effect: Z = 0.20 5 PUFA replaced unclear Ahn 2016	$18 \\ 70 \\ 88 \\ 260 \\ 436 \\ ni^2 = 4.10, df = 0 (P = 0.84) \\ 38 \\ 38 \\ 38 \\ 38 \\ 38 \\ 38 \\ 38 \\ 3$	-0.05 (1.4223) -1.11 (0) -0.19 (0.65) = 2 (P = 0.13); I <sup>2</sup> 3.6 (0.74)	66 89 254 <b>426</b> =51%	-0.15 (0.7312) -0.47 (0) -0.01 (0.64) 3.75 (0.67)		<ul> <li>28.2 %</li> <li>56.5 %</li> <li>100.0 %</li> <li>40.5 %</li> </ul>	-0.10 [ -0.28, 0.48 Not estimab -0.18 [ -0.29, -0.07 -0.03 [ -0.30, 0.24 -0.15 [ -0.47, 0.17

- (1) Fernandez-Real 2012, Reus subcohort, 2 year data
- (2) Damasceno 2013, Barcelona North subcohort, I year data
- (3) Barcelona hospital cohort at 5 years, Casas 2016
- (4) 2 year data
- (5) Change data
- (6) Change data

(7) 14 month data

## Analysis 3.36. Comparison 3 Higher PUFA vs lower PUFA - continuous secondary outcomes, Outcome 36 TC, mmoL/L - subgroup by sex.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 3 Higher PUFA vs lower PUFA - continuous secondary outcomes

Outcome: 36 TC, mmoL/L - subgroup by sex

Study or subgroup	Higher PUFA		Lower PUFA		Mean Difference	Weight	Mean Difference
	Ν	Mean(SD)	Ν	Mean(SD)	IV,Random,95% CI		IV,Random,95% CI
> 70% men							
Ahn 2016	38	3.6 (0.74)	36	3.75 (0.67)		3.6 %	-0.15 [ -0.47, 0.17 ]
AlphaOmega - ALA	605	-0.3 (0.98)	605	-0.28 (0.98)		5.4 %	-0.02 [ -0.13, 0.09 ]
DART fat 1989	855	6.29 ( . 3)	860	6.55 (1.1)		5.5 %	-0.26 [ -0.37, -0.15 ]
DIPP-Tokudome 2015 (1)	91	5.52 (0.9)	75	5.4 (0.79)		4.2 %	0.12 [ -0.14, 0.38 ]
HARP- Sacks 1995	31	5.02 (0.96)	28	4.99 (0.62)		- 3.0 %	0.03 [ -0.38, 0.44 ]
Ley 2004 (2)	70	-0.05 (1.4223)	66	-0.15 (0.7312)		3.2 %	0.10 [ -0.28, 0.48 ]
Mendis 2001	26	-0.42 (0.5447)	28	-0.58 (0.7221)		3.5 %	0.16 [ -0.18, 0.50 ]
MRC 1968	88	-1.11 (0)	89	-0.47 (0)			Not estimable
NDHS Faribault 1968	4	-0.99 (0.637)	51	-0.18 (0.571)	•	4.8 %	-0.81 [ -1.00, -0.62 ]
NDHS Open 1st 1968	653	-0.666 (0.69)	309	-0.25 (0.527)		5.6 %	-0.42 [ -0.50, -0.34 ]
Nodari 2011 HF	67	4.8 (0.62)	66	4.9 (0.62)		4.6 %	-0.10 [ -0.31, 0.11 ]
Nye 1990	12	6.83 (1)	12	6.2 (1.31)		→ I.0 %	0.63 [ -0.30, 1.56 ]
				_(	0.5 -0.25 0 0.25	0.5	

Favours higher PUFA Favours lower PUFA

(Continued ...)

Study or subgroup	Higher PUFA N	Lo Mean(SD)	ower PUFA N	Mean(SD)	Mean Difference IV,Random,95% Cl	Weight	Mea Differenc IV,Random,95% (
Sydney Diet-Heart 1978	221	6.5 (1.2)	237	6.8 (1.1) ←		4.6 %	-0.30 [ -0.51, -0.09
, ,				. ,			-
Veterans Admin 1969	423	4.93 (3.72)	420	5.3 (1.87) ←		3.0 %	-0.37 [ -0.77, 0.03
Vijayakumar 2014	94	3.92 (1.15)	96	3.86 (0.74)		4.0 %	0.06 [ -0.22, 0.34
Subtotal (95% CI) Heterogeneity: $Tau^2 = 0.06$ ; C Test for overall effect: $Z = 2.0$ 2 > 70% women		= 13 (P<0.00001);	<b>2978</b> 1 <sup>2</sup> =87%		-	56.0 %	-0.15 [ -0.30, -0.01
Dodin 2005	85	5.66 (0.72)	94	5.96 (0.72) ←		4.6 %	-0.30 [ -0.51, -0.09
Simon 1997	38	5.21 (1.11)	34	4.87 (0.87)		→ 2.6 %	0.34 [ -0.12, 0.80
Subtotal (95% CI)	123		128	_		- 7.2 %	-0.01 [ -0.64, 0.61
Heterogeneity: $Tau^2 = 0.17$ ; C Test for overall effect: $Z = 0.0$ 3 men % women		$  (P = 0.01);  ^2 = 8$	4%				
Brox 2001 (3)	67 7	.8896 (0.8168)	37	7.9 (0.8)		3.6 %	-0.01 [ -0.33, 0.31
Houtsmuller 1979	48	6.43 (0.65)	48	6.9 (0.81) 🖛		3.9 %	-0.47 [ -0.76, -0.18
MARINA - Sanders 2011	80	0.2 (0.8987)	71	0.1 (0.63)		4.3 %	0.10 [ -0.15, 0.35
Mita 2007	30	5.15 (0.83)	30	5.27 (0.99) ←		2.6 %	-0.12 [ -0.58, 0.34
PREDIMED 2013 (4)	58	-0.35 (0.9)	59	-0.3 (0.89)		3.6 %	-0.05 [ -0.37, 0.27
PREDIMED 2013 (5)	54	-1.01 (0.92)	54	-0.8 (0.99) ←		3.3 %	-0.21 [ -0.57, 0.15
PREDIMED 2013 (6)	51	5.17 (1)	42	5.02 (0.94)		→ 3.0 %	0.15 [ -0.25, 0.55
Rossing 1996	14	5.51 (1.12)	15	5.2 (1.16) ←		→ I.2 %	0.31 [ -0.52, 1.14
WAHA - Ros 2016	260	-0.19 (0.65)	254	-0.01 (0.64)	_ <b></b>	5.4 %	-0.18 [ -0.29, -0.07
WELCOME 2015	47	4.7 (1.1)	48	4.8 (1) ←		2.9 %	-0.10 [ -0.52, 0.32
Subtotal (95% CI) Heterogeneity: Tau <sup>2</sup> = 0.01; C Test for overall effect: Z = 1.7 4 sex not reported		= 9 (P = 0.15); l <sup>2</sup> =	<b>658</b> 32%		•	33.8 %	-0.11 [ -0.22, 0.01
HERO-Tapsell 2009	18	4.9 (0.8)	17	4.6 (1)		→ I.9 %	0.30 [ -0.30, 0.90
Rose 1965	13	-0.5  (1.25)	13	-0.02 (0.94) 👉		1.1 %	-0.49 [ -1.34, 0.36
<b>Subtotal (95% CI)</b> Heterogeneity: Tau <sup>2</sup> = 0.17; C Test for overall effect: Z = 0.0		$  (P = 0.14);  ^2 = 5$	<b>30</b> 5%	_		- 3.0 %	-0.04 [ -0.80, 0.73
<b>Total (95% CI)</b> Heterogeneity: Tau <sup>2</sup> = 0.04; C Test for overall effect: $Z = 2.4$ Test for subgroup differences:	<b>4278</b> Chi <sup>2</sup> = 127.12, df 14 (P = 0.015)				•	100.0 %	-0.12 [ -0.23, -0.02

(I) 2 year data

(2) Change data

(3) 14 month data

(4) Damasceno 2013, Barcelona North subcohort, I year data

(5) Barcelona hospital cohort at 5 years, Casas 2016

(6) Fernandez-Real 2012, Reus subcohort, 2 year data

## Analysis 3.37. Comparison 3 Higher PUFA vs lower PUFA - continuous secondary outcomes, Outcome 37 TC, mmoL/L - subgroup by age.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 3 Higher PUFA vs lower PUFA - continuous secondary outcomes

Outcome: 37 TC, mmoL/L - subgroup by age

Study or subgroup	Higher PUFA		Lower PUFA		Diff	Mean erence	Weight	Mean Difference
	Ν	Mean(SD)	Ν	Mean(SD)	IV,Rand	om,95% Cl		IV,Random,95% Cl
Mean age < 50 years								
NDHS Faribault 1968	4	-0.99 (0.637)	51	-0.18 (0.571)	•		4.8 %	-0.81 [ -1.00, -0.62 ]
NDHS Open 1st 1968	653	-0.666 (0.69)	309	-0.25 (0.527)			5.6 %	-0.42 [ -0.50, -0.34 ]
Rossing 1996	14	5.51 (1.12)	15	5.2 (1.16)	•		1.2 %	0.31 [ -0.52, 1.14 ]
Simon 1997	38	5.21 (1.11)	34	4.87 (0.87)			2.6 %	0.34 [ -0.12, 0.80 ]
Sydney Diet-Heart 1978	221	6.5 (1.2)	237	6.8 (1.1)	←		4.6 %	-0.30 [ -0.51, -0.09 ]
Subtotal (95% CI)	1067		646				18.8 %	-0.30 [ -0.59, -0.02 ]
Heterogeneity: Tau <sup>2</sup> = 0.08;	$Chi^2 = 31.04$ , d	f = 4 (P<0.00001)	); l <sup>2</sup> =87%					
Test for overall effect: $Z = 2$	.IO (P = 0.036)							
2 Mean age 50 to < 65 year	^S							
Brox 2001 (1)	67	7.8896 (0.8168)	37	7.9 (0.8)			3.6 %	-0.01 [ -0.33, 0.31 ]
DART fat 1989	855	6.29 (1.13)	860	6.55 (1.1)			5.5 %	-0.26 [ -0.37, -0.15 ]
DIPP-Tokudome 2015 (2	2) 91	5.52 (0.9)	75	5.4 (0.79)			4.2 %	0.12 [ -0.14, 0.38 ]
Dodin 2005	85	5.66 (0.72)	94	5.96 (0.72)	•		4.6 %	-0.30 [ -0.51, -0.09 ]
HARP- Sacks 1995	31	5.02 (0.96)	28	4.99 (0.62)			3.0 %	0.03 [ -0.38, 0.44 ]
					0.5 -0.25	0 0.25 0	).5	

Favours higher PUFA Favours lower PUFA

(Continued . . . )

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Study or subgroup H	igher PUFA N	Mean(SD)	Lower PUFA N	Mean(SD)	Mean Difference IV,Random,95% Cl	Weight	Mean Difference IV,Random,95% Cl
HERO-Tapsell 2009	18	4.9 (0.8)	17	4.6 (1)		→ I.9 %	0.30 [ -0.30, 0.90
Ley 2004 (3)	70	-0.05 (1.4223)	66	-0.15 (0.7312)		- 3.2 %	0.10 [ -0.28, 0.48 ]
MARINA - Sanders 2011	80	0.2 (0.8987)	71	0.1 (0.63)		4.3 %	0.10 [ -0.15, 0.35
Mita 2007	30	5.15 (0.83)	30	5.27 (0.99)	·	2.6 %	
		. ,		. ,		2.0 /0	-0.12 [ -0.58, 0.34 ]
MRC 1968	88	-1.11 (0)	89	-0.47 (0)			Not estimable
Nodari 2011 HF	67	4.8 (0.62)	66	4.9 (0.62)		4.6 %	-0.10 [ -0.31, 0.11 ]
Nye 1990	12	6.83 (1)	12	6.2 (1.31)		→ I.0 %	0.63 [ -0.30, 1.56 ]
Rose 1965	13	-0.51 (1.25)	13	-0.02 (0.94)	•	1.1 %	-0.49 [ -1.34, 0.36 ]
Vijayakumar 2014	94	3.92 (1.15)	96	3.86 (0.74)		4.0 %	0.06 [ -0.22, 0.34 ]
WELCOME 2015	47	4.7 (1.1)	48	4.8 (1)	••	2.9 %	-0.10 [ -0.52, 0.32 ]
Subtotal (95% CI) Heterogeneity: Tau <sup>2</sup> = 0.02; Chi <sup>2</sup> Test for overall effect: $Z = 0.93$ (		= 13 (P = 0.02);	<b>1602</b>   <sup>2</sup> =48%		-	46.4 %	-0.05 [ -0.17, 0.06 ]
3 Mean age 65+ years AlphaOmega - ALA	605	-0.3 (0.98)	605	-0.28 (0.98)		5.4 %	-0.02 [ -0.13, 0.09 ]
PREDIMED 2013 (4)	51	5.17 (1)	42	5.02 (0.94)		→ 3.0 %	0.15 [ -0.25, 0.55 ]
PREDIMED 2013 (5)	58	-0.35 (0.9)	59	-0.3 (0.89)		3.6 %	-0.05 [ -0.37, 0.27 ]
PREDIMED 2013 (6)	54	-1.01 (0.92)	54	-0.8 (0.99)	· · · · ·	3.3 %	-0.21 [ -0.57, 0.15 ]
Veterans Admin 1969		. ,		. ,	• • • • • • • • • • • • • • • • • • •		
	423	4.93 (3.72)	420	5.3 (1.87)	_	3.0 %	-0.37 [ -0.77, 0.03 ]
WAHA - Ros 2016	260	-0.19 (0.65)	254	-0.01 (0.64)		5.4 %	-0.18 [ -0.29, -0.07 ]
Subtotal (95% CI) Heterogeneity: Tau <sup>2</sup> = 0.01; Chi <sup>-</sup> Test for overall effect: Z = 1.88 ( 4 Mean age unclear		= 5 (P = 0.17); I <sup>2</sup>	1434 =36%			<b>23.8</b> %	-0.10 [ -0.21, 0.00 ]
Ahn 2016	38	3.6 (0.74)	36	3.75 (0.67)		3.6 %	-0.15 [ -0.47, 0.17 ]
Houtsmuller 1979	48	6.43 (0.65)	48	6.9 (0.81)	<del></del>	3.9 %	-0.47 [ -0.76, -0.18
Mendis 2001	26	-0.42 (0.5447)	28	-0.58 (0.7221)		- 3.5 %	0.16 [ -0.18, 0.50 ]
Subtotal (95% CI) Heterogeneity: $Tau^2 = 0.07$ ; Chi <sup>2</sup> Test for overall effect: $Z = 0.88$ ( Total (95% CI) Heterogeneity: $Tau^2 = 0.04$ ; Chi <sup>2</sup> Test for overall effect: $Z = 2.44$ ( Test for subgroup differences: Cf	(P = 0.38) <b>4278</b> $P^2 = 127.12, d$ (P = 0.015)	f = 27 (P<0.000	<b>3794</b> 01); I <sup>2</sup> =79%		-		-0.16 [ -0.52, 0.20 ]

(I) I4 month data

(2) 2 year data

(3) Change data

-

-

- (4) Fernandez-Real 2012, Reus subcohort, 2 year data
- (5) Damasceno 2013, Barcelona North subcohort, I year data
- (6) Barcelona hospital cohort at 5 years, Casas 2016

#### Analysis 3.38. Comparison 3 Higher PUFA vs lower PUFA - continuous secondary outcomes, Outcome 38 TC, mmoL/L - subgroup by statin use.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 3 Higher PUFA vs lower PUFA - continuous secondary outcomes

Outcome: 38 TC, mmoL/L - subgroup by statin use

Study or subgroup	Higher PUFA		Lower PUFA		Mean Difference	Weight	Mean Difference
	Ν	Mean(SD)	Ν	Mean(SD)	IV,Random,95% CI		IV,Random,95% CI
I < 50% on statins							
Brox 2001 (1)	67	7.8896 (0.8168)	37	7.9 (0.8)		3.6 %	-0.01 [ -0.33, 0.31 ]
DART fat 1989	855	6.29 (1.13)	860	6.55 (1.1)	+	5.5 %	-0.26 [ -0.37, -0.15 ]
DIPP-Tokudome 2015 (2)	91	5.52 (0.9)	75	5.4 (0.79)		4.2 %	0.12 [ -0.14, 0.38 ]
Dodin 2005	85	5.66 (0.72)	94	5.96 (0.72)		4.6 %	-0.30 [ -0.51, -0.09 ]
HARP- Sacks 1995	31	5.02 (0.96)	28	4.99 (0.62)	<u> </u>	3.0 %	0.03 [ -0.38, 0.44 ]
Houtsmuller 1979	48	6.43 (0.65)	48	6.9 (0.81)		3.9 %	-0.47 [ -0.76, -0.18 ]
MARINA - Sanders 2011	80	0.2 (0.8987)	71	0.1 (0.63)		4.3 %	0.10 [ -0.15, 0.35 ]
Mendis 2001	26	-0.42 (0.5447)	28	-0.58 (0.7221)		3.5 %	0.16 [ -0.18, 0.50 ]
Mita 2007	30	5.15 (0.83)	30	5.27 (0.99)		2.6 %	-0.12 [ -0.58, 0.34 ]
MRC 1968	88	- .   (0)	89	-0.47 (0)			Not estimable
NDHS Faribault 1968	4	-0.99 (0.637)	51	-0.18 (0.571)	<u> </u>	4.8 %	-0.81 [ -1.00, -0.62 ]
NDHS Open 1st 1968	653	-0.666 (0.69)	309	-0.25 (0.527)	+	5.6 %	-0.42 [ -0.50, -0.34 ]
Nodari 2011 HF	67	4.8 (0.62)	66	4.9 (0.62)	_+_	4.6 %	-0.10 [ -0.31, 0.11 ]
				-	I -0.5 0 0.5	1	

Favours higher PUFA Favours lower PUFA

(Continued ...)

Mean Difference Mean Difference Study or subgroup Higher PUFA Lower PUFA Weight Mean(SD) Mean(SD) IV.Random.95% CI IV,Random,95% CI Ν Ν Nye 1990 12 6.83(1) 12 6.2 (1.31) 1.0 % 0.63 [ -0.30, 1.56 ] PREDIMED 2013 (3) 51 5.17(1) 42 5.02 (0.94) 3.0 % 0.15 [ -0.25, 0.55 ] -0.21 [ -0.57, 0.15 ] PREDIMED 2013 (4) 54 -1.01 (0.92) 54 -0.8 (0.99) 3.3 % PREDIMED 2013 (5) 58 -0.35 (0.9) 59 -0.3 (0.89) 3.6 % -0.05 [ -0.37, 0.27 ] Rose 1965 13 -0.51 (1.25) 13 -0.02 (0.94) 1.1% -0.49 [ -1.34, 0.36 ] Rossing 1996 14 5.51 (1.12) 15 5.2 (1.16) 1.2 % 0.3| [-0.52, 1.14] Simon 1997 0.34 [ -0.12, 0.80 ] 38 5.21 (1.11) 34 4.87 (0.87) 2.6 % Sydney Diet-Heart 1978 221 6.5 (1.2) 237 6.8 (1.1) 4.6 % -0.30 [ -0.51, -0.09 ] Veterans Admin 1969 423 4.93 (3.72) 420 5.3 (1.87) 3.0 % -0.37 [ -0.77, 0.03 ] Subtotal (95% CI) 3146 2672 73.6 % -0.15 [ -0.28, -0.03 ] Heterogeneity: Tau<sup>2</sup> = 0.05; Chi<sup>2</sup> = 96.16, df = 20 (P<0.00001); l<sup>2</sup> = 79% Test for overall effect: Z = 2.45 (P = 0.014) 2 50+% on statins Ahn 2016 38 3.6 (0.74) 3.75 (0.67) 3.6 % -0.15 [ -0.47, 0.17 ] 36 AlphaOmega - ALA 605 -0.3 (0.98) 605 -0.28 (0.98) 5.4 % -0.02 [ -0.13, 0.09 ] HERO-Tapsell 2009 0.30 [ -0.30, 0.90 ] 18 4.9 (0.8) 17 4.6 (1) 1.9 % Vijayakumar 2014 3.92 (1.15) 3.86 (0.74) 4.0 % 0.06 [ -0.22, 0.34 ] 94 96 WELCOME 2015 47 4.7 (1.1) 48 4.8 (1) 2.9 % -0.10 [ -0.52, 0.32 ] Subtotal (95% CI) 802 802 17.8 % -0.02 [ -0.11, 0.08 ] Heterogeneity: Tau<sup>2</sup> = 0.0; Chi<sup>2</sup> = 2.17, df = 4 (P = 0.70); l<sup>2</sup> = 0.0% Test for overall effect: Z = 0.37 (P = 0.71) 3 Percentage on statins unclear Ley 2004 (6) 70 -0.05 (1.4223) 66 -0.15 (0.7312) 3.2 % 0.10 [ -0.28, 0.48 ] WAHA - Ros 2016 -0.18 [ -0.29, -0.07 ] 260 -0.19 (0.65) 254 -0.01 (0.64) 5.4 % Subtotal (95% CI) 330 320 8.6 % -0.10 [ -0.35, 0.15 ] Heterogeneity: Tau<sup>2</sup> = 0.02; Chi<sup>2</sup> = 1.95, df = 1 (P = 0.16); l<sup>2</sup> =49% Test for overall effect: Z = 0.79 (P = 0.43) Total (95% CI) 4278 3794 100.0 % -0.12 [ -0.23, -0.02 ] Heterogeneity: Tau<sup>2</sup> = 0.04; Chi<sup>2</sup> = 127.12, df = 27 (P<0.00001); l<sup>2</sup> = 79% Test for overall effect: Z = 2.44 (P = 0.015) Test for subgroup differences:  $Chi^2 = 3.03$ , df = 2 (P = 0.22),  $I^2 = 34\%$ - | -0.5 0 0.5 ī. Favours higher PUFA Favours lower PUFA

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(I) I4 month data

- (2) 2 year data
- (3) Fernandez-Real 2012, Reus subcohort, 2 year data
- (4) Barcelona hospital cohort at 5 years, Casas 2016
- (5) Damasceno 2013, Barcelona North subcohort, I year data
- (6) Change data

#### Analysis 3.39. Comparison 3 Higher PUFA vs lower PUFA - continuous secondary outcomes, Outcome 39 TC, mmoL/L - subgroup by intervention type.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 3 Higher PUFA vs lower PUFA - continuous secondary outcomes

Outcome: 39 TC, mmoL/L - subgroup by intervention type

Study or subgroup	Higher PUFA		Lower PUFA		Diffe	Mean erence	Weight	Mean Difference
	Ν	Mean(SD)	Ν	Mean(SD)	IV,Rando	om,95% Cl		IV,Random,95% CI
Dietary advice								
DART fat 1989	855	6.29 (1.13)	860	6.55 (1.1)			5.5 %	-0.26 [ -0.37, -0.15 ]
Houtsmuller 1979	48	6.43 (0.65)	48	6.9 (0.81)	*		3.9 %	-0.47 [ -0.76, -0.18 ]
Ley 2004 (I)	70	-0.05 (1.4223)	66	-0.15 (0.7312)			3.2 %	0.10 [ -0.28, 0.48 ]
Simon 1997	38	5.21 (1.11)	34	4.87 (0.87)			2.6 %	0.34 [ -0.12, 0.80 ]
Subtotal (95% CI)	1011		1008				15.1 %	-0.13 [ -0.41, 0.15 ]
Heterogeneity: $Tau^2 = 0.06$	5; Chi <sup>2</sup> = 11.75, df	= 3 (P = 0.01); I	<sup>2</sup> =74%					
Test for overall effect: Z =	0.88 (P = 0.38)							
2 Supplemental foods % di	et provided							
AlphaOmega - ALA	605	-0.3 (0.98)	605	-0.28 (0.98)		<b></b>	5.4 %	-0.02 [ -0.13, 0.09 ]
HERO-Tapsell 2009	18	4.9 (0.8)	17	4.6 (1)			1.9 %	0.30 [ -0.30, 0.90 ]
NDHS Faribault 1968	4	-0.99 (0.637)	51	-0.18 (0.571)	•		4.8 %	-0.81 [ -1.00, -0.62 ]
NDHS Open 1st 1968	653	-0.666 (0.69)	309	-0.25 (0.527)			5.6 %	-0.42 [ -0.50, -0.34 ]
PREDIMED 2013 (2)	58	-0.35 (0.9)	59	-0.3 (0.89)			3.6 %	-0.05 [ -0.37, 0.27 ]
PREDIMED 2013 (3)	51	5.17 (1)	42	5.02 (0.94)		· · · · ·	3.0 %	0.15 [ -0.25, 0.55 ]
					).5 -0.25 ( higher PUFA	0 0.25 0 Favours lowe		
				Favours	nighter FUFA	Favour's 10W6	STIUFA	

(Continued . . . )

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Study or subgroup	Higher PUFA N	Maan/SD)	Lower PUFA N	Maan (SD)	Mean Difference IV,Random,95% Cl	Weight	Mean Difference IV,Random,95% CI
	54	Mean(SD) -1.01 (0.92)	54	Mean(SD)		3.3 %	
PREDIMED 2013 (4)				-0.8 (0.99)			-0.21 [ -0.57, 0.15 ]
Veterans Admin 1969	423	4.93 (3.72)	420	5.3 (1.87) ←		3.0 %	-0.37 [ -0.77, 0.03 ]
Vijayakumar 2014	94	3.92 (1.15)	96	3.86 (0.74)		4.0 %	0.06 [ -0.22, 0.34 ]
WAHA - Ros 2016	260	-0.19 (0.65)	254	-0.01 (0.64)		5.4 %	-0.18 [ -0.29, -0.07 ]
Subtotal (95% CI)	2357		1907			40.2 %	-0.19 [ -0.37, -0.01 ]
Heterogeneity: $Tau^2 = 0.06;$		= 9 (P<0.00001	); l <sup>2</sup> =89%				
Test for overall effect: $Z = 2.0$ 3 Supplements (capsules % u	· · · ·						
Ahn 2016	38	3.6 (0.74)	36	3.75 (0.67) -		3.6 %	-0.15 [ -0.47, 0.17 ]
Brox 2001 (5)	67	7.8896 (0.8168)	37	7.9 (0.8)		3.6 %	-0.01 [ -0.33, 0.31 ]
Dodin 2005	85	5.66 (0.72)	94	5.96 (0.72) ←		4.6 %	-0.30 [ -0.51, -0.09 ]
HARP- Sacks 1995	31	5.02 (0.96)	28	4.99 (0.62)		- 3.0 %	0.03 [ -0.38, 0.44 ]
		· · · ·					
MARINA - Sanders 2011	80	0.2 (0.8987)	71	0.1 (0.63)		4.3 %	0.10 [ -0.15, 0.35 ]
Mita 2007	30	5.15 (0.83)	30	5.27 (0.99) ←		2.6 %	-0.12 [ -0.58, 0.34 ]
Nodari 2011 HF	67	4.8 (0.62)	66	4.9 (0.62)		4.6 %	-0.10 [ -0.31, 0.11 ]
Nye 1990	12	6.83 (1)	12	6.2 (1.31)		→ I.0 %	0.63 [ -0.30, 1.56 ]
Rose 1965	13	-0.51 (1.25)	13	-0.02 (0.94) 🗲		1.1 %	-0.49 [ -1.34, 0.36 ]
Rossing 1996	14	5.51 (1.12)	15	5.2 (1.16) ←		→ I.2 %	0.31 [ -0.52, 1.14 ]
WELCOME 2015	47	4.7 (1.1)	48	4.8 (I) <b>+</b>		2.9 %	-0.10 [ -0.52, 0.32 ]
Subtotal (95% CI)	484		450		-	32.4 %	-0.09 [ -0.19, 0.02 ]
Heterogeneity: $Tau^2 = 0.00$ ; Test for overall effect: $Z = 1$ . 4 Any combination	62 (P = 0.11)	、 <i>、</i> ,					
DIPP-Tokudome 2015 (6)	) 91	5.52 (0.9)	75	5.4 (0.79)		4.2 %	0.12 [ -0.14, 0.38 ]
Mendis 2001	26	-0.42 (0.5447)	28	-0.58 (0.7221)	+	- 3.5 %	0.16 [ -0.18, 0.50 ]
MRC 1968	88	-1.11 (0)	89	-0.47 (0)			Not estimable
Sydney Diet-Heart 1978	221	6.5 (1.2)	237	6.8 (1.1) ←		4.6 %	-0.30 [ -0.51, -0.09 ]
Subtotal (95% CI)	426		429			12.3 %	-0.02 [ -0.34, 0.29 ]
Heterogeneity: $Tau^2 = 0.06$ ; Test for overall effect: $Z = 0$ .		= 2 (P = 0.01); I <sup>2</sup>	=76%				
<b>Total (95% CI)</b> Heterogeneity: Tau <sup>2</sup> = 0.04; Test for overall effect: Z = 2: Test for subgroup differences	<b>4278</b> Chi <sup>2</sup> = 127.12, c 44 (P = 0.015)		*		•	100.0 %	-0.12 [ -0.23, -0.02 ]
				-0.5 Favours hi	-0.25 0 0.25 gher PUFA Favours lo	0.5 wer PUFA	

(I) Change data

- (2) Damasceno 2013, Barcelona North subcohort, I year data
- (3) Fernandez-Real 2012, Reus subcohort, 2 year data
- (4) Barcelona hospital cohort at 5 years, Casas 2016
- (5) 14 month data
- (6) 2 year data

# Analysis 3.40. Comparison 3 Higher PUFA vs lower PUFA - continuous secondary outcomes, Outcome 40 Serum fasting TRIGLYCERIDE (TG, mmoL/L).

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 3 Higher PUFA vs lower PUFA - continuous secondary outcomes

Outcome: 40 Serum fasting TRIGLYCERIDE (TG, mmoL/L)

Mear Difference IV,Random,95% C	Weight	Mean Difference IV,Random,95% Cl	Mean(SD)	Lower PUFA	Mean(SD)	Higher PUFA N	Study or subgroup
-0.06 [ -0.17, 0.05	9.0 %		-0.05 (0.98)	605	-0.11 (0.98)	605	AlphaOmega - ALA
-0.13 [ -0.54, 0.27	2.9 %	•	2.2 (0.89)	37	2.0657 (1.1999)	67	Brox 2001
0.01 [ -0.28, 0.30	4.5 %		1.44 (0.81)	71	1.45 (1.05)	90	DIPP-Tokudome 2015
-0.02 [ -0.20, 0.16	6.9 %		1.17 (0.72)	94	1.15 (0.53)	85	Dodin 2005
-0.50 [ -1.64, 0.64	0.5 %	14	1.8 (2.24)	20	1.3 (1.2)	16	Dullaart 1992
-0.47 [ -0.81, -0.13	3.6 %	*	1.61 (0.76)	28	1.14 (0.56)	31	HARP- Sacks 1995
0.30 [ -0.39, 0.99	1.2 %		1.8 (0.7)	17	2.1 (1.3)	18	HERO-Tapsell 2009
-0.26 [ -0.50, -0.02	5.5 %	<b>_</b>	1.05 (0.6)	48	0.79 (0.6)	48	Houtsmuller 1979
0.04 [ -0.42, 0.50	2.3 %		0.03 (0.8936)	66	0.07 (1.757)	70	Ley 2004 (I)
-0.30 [ -0.48, -0.12	7.1 %	<b>_</b>	0.1 (0.63)	71	-0.2 (0.45)	80	MARINA - Sanders 2011
0.58 [ 0.17, 0.99	2.8 %		-0.23 (0.98)	28	0.35 (0.5199)	26	Mendis 2001
0.26 [ -0.24, 0.76	2.1 %		1.51 (0.9)	30	1.77 (1.07)	30	Mita 2007
-0.14 [ -0.36, 0.08	5.9 %		1.75 (0.78)	66	1.61 (0.51)	67	Nodari 2011 HF
-0.40 [ -0.85, 0.05	2.4 %	••••	1.8 (0.55)	12	1.4 (0.58)	12	Nye 1990

Favours higher PUFA Favours lower PUFA

(Continued ...)

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ORL 2013       170       -0.78 (0.9)       165       -0.4 (0.87)       67 %       -0.38 [         PREDIMED 2013 (2)       58       -0.18 (0.58)       59       -0.04 (0.58)       62 %       -0.14 [         PREDIMED 2013 (3)       54       -0.28 (0.77)       54       -0.25 (0.84)       42 %       -0.03 [         PREDIMED 2013 (4)       51       1.27 (0.58)       42       1.4 (0.7)       49 %       -0.13 [         Simon 1997       37       1.25 (0.61)       34       1.35 (1.05)       29 %       -0.10 [         Sydney Diet-Heart 1978       221       1.6 (0.9)       237       1.7 (0.9)       7.4 %       -0.10 [         Vijayakumar 2014       94       1.27 (0.51)       96       1.23 (0.53)       7.9 %       0.04 [         WELCOME 2015       47       1.5 (1.2)       48       1.8 (0.6)       3.1 %       -0.30 [	Higher PUFA		Lower PUFA		Mean Difference	Weight	( Continued Mean Difference
PREDIMED 2013 (2)       58       -0.18 (0.58)       59       -0.04 (0.58)       62 %       -0.14 [         PREDIMED 2013 (3)       54       -0.28 (0.77)       54       -0.25 (0.84)       42 %       -0.03 [         PREDIMED 2013 (4)       51       1.27 (0.58)       42       1.4 (0.7)       49 %       -0.13 [         Simon 1997       37       1.25 (0.61)       34       1.35 (1.05)       29 %       -0.10 [         Sydney Diet-Heart 1978       221       1.6 (0.9)       237       1.7 (0.9)       7.4 %       -0.10 [         Vijayakumar 2014       94       1.27 (0.51)       96       1.23 (0.53)       7.9 %       0.04 [         WELCOME 2015       47       1.5 (1.2)       48       1.8 (0.6)       3.1 %       -0.30 [	N	Mean(SD)	Ν	Mean(SD)	IV,Random,95% CI	0	IV,Random,95% CI
PREDIMED 2013 (3)       54       -0.28 (0.77)       54       -0.25 (0.84)       42 %       -0.03 [         PREDIMED 2013 (4)       51       1.27 (0.58)       42       1.4 (0.7)       49 %       -0.13 [         Simon 1997       37       1.25 (0.61)       34       1.35 (1.05)       2.9 %       -0.10 [         Sydney Diet-Heart 1978       221       1.6 (0.9)       237       1.7 (0.9)       7.4 %       -0.10 [         Vijayakumar 2014       94       1.27 (0.51)       96       1.23 (0.53)       7.9 %       0.04 [         WELCOME 2015       47       1.5 (1.2)       48       1.8 (0.6)       3.1 %       -0.30 [	170	-0.78 (0.9)	165	-0.4 (0.87)	•	6.7 %	-0.38 [ -0.57, -0.19 ]
PREDIMED 2013 (4)       51       1.27 (0.58)       42       1.4 (0.7)       4.9 %       -0.13 [         Simon 1997       37       1.25 (0.61)       34       1.35 (1.05)       2.9 %       -0.10 [         Sydney Diet-Heart 1978       221       1.6 (0.9)       237       1.7 (0.9)       7.4 %       -0.10 [         Vijayakumar 2014       94       1.27 (0.51)       96       1.23 (0.53)       7.9 %       0.04 [         WELCOME 2015       47       1.5 (1.2)       48       1.8 (0.6)       3.1 %       -0.30 [	58	-0.18 (0.58)	59	-0.04 (0.58)		6.2 %	-0.14 [ -0.35, 0.07 ]
Simon 1997       37       1.25 (0.61)       34       1.35 (1.05)       2.9 %       -0.10 [         Sydney Diet-Heart 1978       221       1.6 (0.9)       237       1.7 (0.9)       7.4 %       -0.10 [         Vijayakumar 2014       94       1.27 (0.51)       96       1.23 (0.53)       7.9 %       0.04 [         WELCOME 2015       47       1.5 (1.2)       48       1.8 (0.6)       3.1 %       -0.30 [	54	-0.28 (0.77)	54	-0.25 (0.84)		4.2 %	-0.03 [ -0.33, 0.27 ]
Sydney Diet-Heart 1978       221       1.6 (0.9)       237       1.7 (0.9)       •       7.4 %       -0.10 [         Vijayakumar 2014       94       1.27 (0.51)       96       1.23 (0.53)       •       7.9 %       0.04 [         WELCOME 2015       47       1.5 (1.2)       48       1.8 (0.6)       •       3.1 %       -0.30 [	51	1.27 (0.58)	42	1.4 (0.7)	<b>i</b>	4.9 %	-0.13 [ -0.39, 0.13 ]
Vijayakumar 2014       94       1.27 (0.51)       96       1.23 (0.53)       -       7.9 %       0.04 [         WELCOME 2015       47       1.5 (1.2)       48       1.8 (0.6)       -       3.1 %       -0.30 [	37	1.25 (0.61)	34	1.35 (1.05)	· · · · ·	2.9 %	-0.10 [ -0.50, 0.30 ]
WELCOME 2015 47 1.5 (1.2) 48 1.8 (0.6) - 3.1 % -0.30 [	221	1.6 (0.9)	237	1.7 (0.9)		7.4 %	-0.10 [ -0.26, 0.06 ]
	94	1.27 (0.51)	96	1.23 (0.53)		7.9 %	0.04 [ -0.11, 0.19 ]
	47	1.5 (1.2)	48	1.8 (0.6)	•	3.1 %	-0.30 [ -0.68, 0.08 ]
<b>Fotal (95% CI)</b> 1977 1928  → 100.0 % -0.12 [ -0.2	1977		1928		•	100.0 % ·	-0.12 [ -0.20, -0.04 ]
	· · · · · ·						
. ,		N 170 58 54 51 37 221 94 47 <b>1977</b> Chi <sup>2</sup> = 42.24, df =	$\begin{tabular}{ c c c c c } \hline N & Mean(SD) \\ \hline 170 & -0.78 & (0.9) \\ \hline 58 & -0.18 & (0.58) \\ \hline 54 & -0.28 & (0.77) \\ \hline 51 & 1.27 & (0.58) \\ \hline 37 & 1.25 & (0.61) \\ \hline 221 & 1.6 & (0.9) \\ \hline 94 & 1.27 & (0.51) \\ \hline 47 & 1.5 & (1.2) \\ \hline 1977 \\ Chi^2 = 42.24, df = 21 & (P = 0.004); \\ B4 & (P = 0.0046) \\ \hline \end{tabular}$	N         Mean(SD)         N           170         -0.78 (0.9)         165           58         -0.18 (0.58)         59           54         -0.28 (0.77)         54           51         1.27 (0.58)         42           37         1.25 (0.61)         34           221         1.6 (0.9)         237           94         1.27 (0.51)         96           47         1.5 (1.2)         48 <b>1977 1928</b> Chi <sup>2</sup> = 42.24, df = 21 (P = 0.004); l <sup>2</sup> = 50%         84 (P = 0.0046)	N         Mean(SD)         N         Mean(SD)           170         -0.78 (0.9)         165         -0.4 (0.87)           58         -0.18 (0.58)         59         -0.04 (0.58)           54         -0.28 (0.77)         54         -0.25 (0.84)           51         1.27 (0.58)         42         1.4 (0.7)           37         1.25 (0.61)         34         1.35 (1.05)           221         1.6 (0.9)         237         1.7 (0.9)           94         1.27 (0.51)         96         1.23 (0.53)           47         1.5 (1.2)         48         1.8 (0.6)           1977         1928           Chi <sup>2</sup> = 42.24, df = 21 (P = 0.004); I <sup>2</sup> = 50%         84 (P = 0.0046)	Higher PUFA       Lower PUFA       Difference         N       Mean(SD)       N       Mean(SD)       IV,Random,95% CI         170       -0.78 (0.9)       165       -0.4 (0.87)       IV         58       -0.18 (0.58)       59       -0.04 (0.58)       IV         54       -0.28 (0.77)       54       -0.25 (0.84)       IV         51       1.27 (0.58)       42       1.4 (0.7)       IV         37       1.25 (0.61)       34       1.35 (1.05)       IV         221       1.6 (0.9)       237       1.7 (0.9)       IV         94       1.27 (0.51)       96       1.23 (0.53)       IV         47       1.5 (1.2)       48       1.8 (0.6)       IV         Chi <sup>2</sup> = 42.24, df = 21 (P = 0.004); 1 <sup>2</sup> = 50%       H       IV       IV         84 (P = 0.0046)       IV       IV       IV       IV	Higher PUFA       Lower PUFA       Difference       Weight         N       Mean(SD)       N       Mean(SD)       IV,Random,95% CI         170       -0.78 (0.9)       165       -0.4 (0.87)       6.7 %         58       -0.18 (0.58)       59       -0.04 (0.58)       6.2 %         54       -0.28 (0.77)       54       -0.25 (0.84)       4.2 %         51       1.27 (0.58)       42       1.4 (0.7)       4.9 %         37       1.25 (0.61)       34       1.35 (1.05)       2.9 %         221       1.6 (0.9)       237       1.7 (0.9)       7.4 %         94       1.27 (0.51)       96       1.23 (0.53)       7.9 %         47       1.5 (1.2)       48       1.8 (0.6)       3.1 %         1977       1928        100.0 %       100.0 %         Chi <sup>2</sup> = 42.24, df = 21 (P = 0.004); 1 <sup>2</sup> =50%       84 (P = 0.0046)        100.0 %

-0.5 -0.25 0 0.25 0.5

Favours higher PUFA Favours lower PUFA

(I) Change data

(2) Damasceno 2013, Barcelona North subcohort, I year data

(3) Barcelona hospital cohort at 5 years, Casas 2016

(4) Fernandez-Real 2012, Reus subcohort, 2 year data

## Analysis 3.41. Comparison 3 Higher PUFA vs lower PUFA - continuous secondary outcomes, Outcome 41 TG, mmoL/L - SA.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 3 Higher PUFA vs lower PUFA - continuous secondary outcomes

Outcome: 41 TG, mmoL/L - SA

Study or subgroup	Higher PUFA		Lower PUFA		Mean Difference	Weight	Mear Difference
	N	Mean(SD)	N	Mean(SD)	IV,Random,95% Cl		IV,Random,95% C
Low risk of bias for allocati	ion concealmen <sup>.</sup> 605					22.0.9/	
AlphaOmega - ALA		-0.11 (0.98)	605	-0.05 (0.98)	_	23.0 %	-0.06 [ -0.17, 0.05 ]
Brox 2001	67	2.0657 (1.1999)	37	2.2 (0.89) +	•	5.7 %	-0.13 [ -0.54, 0.27 ]
DIPP-Tokudome 2015	90	1.45 (1.05)	71	1.44 (0.81)		9.6 %	0.01 [ -0.28, 0.30 ]
Dullaart 1992	16	1.3 (1.2)	20	I.8 (2.24) 🗕		+ 0.9 %	-0.50 [ -1.64, 0.64
Ley 2004 (I)	70	0.07 (1.757)	66	0.03 (0.8936)		- 4.6 %	0.04 [ -0.42, 0.50 ]
MARINA - Sanders 2011	80	-0.2 (0.45)	71	0.1 (0.63) -		16.7 %	-0.30 [ -0.48, -0.12 ]
ORL 2013	170	-0.78 (0.9)	165	-0.4 (0.87) +		15.6 %	-0.38 [ -0.57, -0.19
Sydney Diet-Heart 1978	221	1.6 (0.9)	237	1.7 (0.9)		17.7 %	-0.10 [ -0.26, 0.06
WELCOME 2015	47	1.5 (1.2)	48	I.8 (0.6) <b>+</b>		6.3 %	-0.30 [ -0.68, 0.08
Subtotal (95% CI)	1366		1320		•	100.0 % -	0.17 [ -0.28, -0.06
Heterogeneity: $Tau^2 = 0.01$ ; Test for overall effect: $Z = 3.0$	.08 (P = 0.0021)	, ,	- =43%				
0 ,		, ,	- =43%				
0 ,	.08 (P = 0.0021)	, ,	<sup>2</sup> =43% 605	-0.05 (0.98)		10.1 %	-0.06 [ -0.17, 0.05
Test for overall effect: $Z = 3$ . 2 Low risk of bias for attention	08 (P = 0.0021) on 605	-0.11 (0.98)		-0.05 (0.98) 2.2 (0.89) ←		10.1 %	L
Test for overall effect: Z = 3. 2 Low risk of bias for attentio AlphaOmega - ALA	08 (P = 0.0021) on 605	)	605	· · /			-0.13 [ -0.54, 0.27
Test for view of bias for attention 2 Low risk of bias for attention AlphaOmega - ALA Brox 2001	08 (P = 0.0021) on 605 67	-0.11 (0.98) 2.0657 (1.1999)	605 37	2.2 (0.89) +		3.8 %	-0.13 [ -0.54, 0.27 0.01 [ -0.28, 0.30
Test for overall effect: Z = 3. 2 Low risk of bias for attention AlphaOmega - ALA Brox 2001 DIPP-Tokudome 2015	08 (P = 0.0021) on 605 67 90	-0.11 (0.98) 2.0657 (1.1999) 1.45 (1.05)	605 37 71	2.2 (0.89) + 1.44 (0.81)		3.8 % 5.7 %	-0.13 [ -0.54, 0.27 0.01 [ -0.28, 0.30 -0.02 [ -0.20, 0.16
Test for overall effect: Z = 3: 2 Low risk of bias for attention AlphaOmega - ALA Brox 2001 DIPP-Tokudome 2015 Dodin 2005	08 (P = 0.0021) on 605 67 90 85	-0.11 (0.98) 2.0657 (1.1999) 1.45 (1.05) 1.15 (0.53)	605 37 71 94	2.2 (0.89) + 1.44 (0.81) 1.17 (0.72)		3.8 % 5.7 % 8.2 %	-0.13 [ -0.54, 0.27 0.01 [ -0.28, 0.30 -0.02 [ -0.20, 0.16 -0.47 [ -0.81, -0.13
Test for overall effect: Z = 3. 2 Low risk of bias for attention AlphaOmega - ALA Brox 2001 DIPP-Tokudome 2015 Dodin 2005 HARP- Sacks 1995	08 (P = 0.0021) on 605 67 90 85 31	-0.11 (0.98) 2.0657 (1.1999) 1.45 (1.05) 1.15 (0.53) 1.14 (0.56)	605 37 71 94 28	2.2 (0.89) + 1.44 (0.81) 1.17 (0.72) 1.61 (0.76) +		3.8 % 5.7 % 8.2 % 4.7 %	-0.06 [ -0.17, 0.05 -0.13 [ -0.54, 0.27 0.01 [ -0.28, 0.30 -0.02 [ -0.20, 0.16 -0.47 [ -0.81, -0.13 0.30 [ -0.39, 0.99 -0.30 [ -0.48, -0.12
Test for overall effect: Z = 3. 2 Low risk of bias for attention AlphaOmega - ALA Brox 2001 DIPP-Tokudome 2015 Dodin 2005 HARP- Sacks 1995 HERO-Tapsell 2009	08 (P = 0.0021) on 605 67 90 85 31 18	-0.11 (0.98) 2.0657 (1.1999) 1.45 (1.05) 1.15 (0.53) 1.14 (0.56) 2.1 (1.3)	605 37 71 94 28 17	2.2 (0.89) ← 1.44 (0.81) 1.17 (0.72) 1.61 (0.76) ← 1.8 (0.7)		3.8 % 5.7 % 8.2 % 4.7 % ↓ 1.7 %	-0.13 [ -0.54, 0.27 0.01 [ -0.28, 0.30 -0.02 [ -0.20, 0.16 -0.47 [ -0.81, -0.13 0.30 [ -0.39, 0.99 -0.30 [ -0.48, -0.12
Test for overall effect: Z = 3. 2 Low risk of bias for attention AlphaOmega - ALA Brox 2001 DIPP-Tokudome 2015 Dodin 2005 HARP- Sacks 1995 HERO-Tapsell 2009 MARINA - Sanders 2011	08 (P = 0.0021) on 605 67 90 85 31 18 80	-0.11 (0.98) 2.0657 (1.1999) 1.45 (1.05) 1.15 (0.53) 1.14 (0.56) 2.1 (1.3) -0.2 (0.45)	605 37 71 94 28 17 71	2.2 (0.89) ← 1.44 (0.81) 1.17 (0.72) 1.61 (0.76) ← 1.8 (0.7) 0.1 (0.63) ←		3.8 % 5.7 % 8.2 % 4.7 % 1.7 % 8.4 %	-0.13 [ -0.54, 0.27 0.01 [ -0.28, 0.30 -0.02 [ -0.20, 0.16 -0.47 [ -0.81, -0.13 0.30 [ -0.39, 0.99 -0.30 [ -0.48, -0.12 0.58 [ 0.17, 0.99
Test for overall effect: Z = 3. 2 Low risk of bias for attention AlphaOmega - ALA Brox 2001 DIPP-Tokudome 2015 Dodin 2005 HARP- Sacks 1995 HERO-Tapsell 2009 MARINA - Sanders 2011 Mendis 2001	08 (P = 0.0021) on 605 67 90 85 31 18 80 26	-0.11 (0.98) 2.0657 (1.1999) 1.45 (1.05) 1.15 (0.53) 1.14 (0.56) 2.1 (1.3) -0.2 (0.45) 0.35 (0.5199)	605 37 94 28 17 71 28	2.2 (0.89) + 1.44 (0.81) 1.17 (0.72) 1.61 (0.76) + 1.8 (0.7) 0.1 (0.63) - -0.23 (0.98)		3.8 % 5.7 % 8.2 % 4.7 % + 1.7 % 8.4 % + 3.7 %	-0.13 [ -0.54, 0.27 0.01 [ -0.28, 0.30 -0.02 [ -0.20, 0.16 -0.47 [ -0.81, -0.13 0.30 [ -0.39, 0.99 -0.30 [ -0.48, -0.12 0.58 [ 0.17, 0.99 0.26 [ -0.24, 0.76
Test for overall effect: Z = 3: 2 Low risk of bias for attention AlphaOmega - ALA Brox 2001 DIPP-Tokudome 2015 Dodin 2005 HARP- Sacks 1995 HERO-Tapsell 2009 MARINA - Sanders 2011 Mendis 2001 Mita 2007	08 (P = 0.0021) on 605 67 90 85 31 18 80 26 30	-0.11 (0.98) 2.0657 (1.1999) 1.45 (1.05) 1.15 (0.53) 1.14 (0.56) 2.1 (1.3) -0.2 (0.45) 0.35 (0.5199) 1.77 (1.07)	605 37 71 94 28 17 71 28 30	2.2 (0.89) ← 1.44 (0.81) 1.17 (0.72) 1.61 (0.76) ← 1.8 (0.7) 0.1 (0.63) ← -0.23 (0.98) 1.51 (0.9)		3.8 % 5.7 % 8.2 % 4.7 % → 1.7 % 8.4 % → 3.7 % → 2.8 %	-0.13 [ -0.54, 0.27 0.01 [ -0.28, 0.30 -0.02 [ -0.20, 0.16 -0.47 [ -0.81, -0.13 0.30 [ -0.39, 0.99

Favours higher PUFA Favours lower PUFA

(Continued ...)

Study or subgroup	Higher PUFA		Lower PUFA		Mean Difference	Weight	Mear Difference
, , ,	N	Mean(SD)	Ν	Mean(SD)	IV,Random,95% Cl	0	IV,Random,95% C
PREDIMED 2013 (2)	51	1.27 (0.58)	42	1.4 (0.7)		6.2 %	-0.13 [ -0.39, 0.13
PREDIMED 2013 (3)	54	-0.28 (0.77)	54	-0.25 (0.84)		5.4 %	-0.03 [ -0.33, 0.27
PREDIMED 2013 (4)	58	-0.18 (0.58)	59	-0.04 (0.58)		7.5 %	-0.14 [ -0.35, 0.07
Vijayakumar 2014	94	1.27 (0.51)	96	1.23 (0.53)		9.1 %	0.04 [ -0.11, 0.19
WELCOME 2015	47	1.5 (1.2)	48	1.8 (0.6) ←		4.1 %	-0.30 [ -0.68, 0.08 ]
Subtotal (95% CI)	1585		1523		-	100.0 %	-0.11 [ -0.20, -0.01 ]
Heterogeneity: Tau <sup>2</sup> = 0.02; Test for overall effect: $Z = 2$ 3 Low risk of bias for compl	.19 (P = 0.029)	If = 16 (P = 0.000	81); I <sup>2</sup> =60%				
Brox 2001		2.0657 (1.1999)	37	2.2 (0.89) ←		6.7 %	-0.13 [ -0.54, 0.27 ]
Dullaart 1992	16	1.3 (1.2)	20	I.8 (2.24) 🖛		→ 0.9 %	-0.50 [ -1.64, 0.64 ]
Houtsmuller 1979	48	0.79 (0.6)	48	1.05 (0.6) —		16.3 %	-0.26 [ -0.50, -0.02 ]
Ley 2004 (5)	70	0.07 (1.757)	66	0.03 (0.8936)		- 5.3 %	0.04 [ -0.42, 0.50 ]
Mita 2007	30	1.77 (1.07)	30	1.51 (0.9)		→ 4.6 %	0.26 [ -0.24, 0.76 ]
Sydney Diet-Heart 1978	221	1.6 (0.9)	237	1.7 (0.9)		27.5 %	-0.10 [ -0.26, 0.06 ]
Vijayakumar 2014	94	1.27 (0.51)	96	1.23 (0.53)	_ <b>_</b> _	31.2 %	0.04 [ -0.11, 0.19 ]
WELCOME 2015	47	1.5 (1.2)	48	1.8 (0.6) ←		7.5 %	-0.30 [ -0.68, 0.08 ]
Subtotal (95% CI)	593		582		-	100.0 %	-0.08 [ -0.19, 0.03 ]
Heterogeneity: $Tau^2 = 0.00;$		$= 7 (P = 0.28); I^2$	=18%				
Test for overall effect: $Z = I$ 4 Low summary risk of bias	.41 (P = 0.16)						
AlphaOmega - ALA	605	-0.11 (0.98)	605	-0.05 (0.98)		36.8 %	-0.06 [ -0.17, 0.05
Ley 2004 (6)	70	0.07 (1.757)	66	0.03 (0.8936)		- 5.5 %	0.04 [ -0.42, 0.50 ]
MARINA - Sanders 2011	80	-0.2 (0.45)	71	0.1 (0.63) -	<b></b>	24.0 %	-0.30 [ -0.48, -0.12 ]
Sydney Diet-Heart 1978	221	1.6 (0.9)	237	1.7 (0.9)		25.9 %	-0.10 [ -0.26, 0.06 ]
WELCOME 2015	47	1.5 (1.2)	48	1.8 (0.6) ←		7.7 %	-0.30 [ -0.68, 0.08 ]
Subtotal (95% CI)	1023		1027		-	100.0 %	-0.14 [ -0.26, -0.03 ]
Heterogeneity: Tau <sup>2</sup> = 0.01; Fest for overall effect: Z = 2 5 Trials registry or pre-2010		$= 4 (P = 0.17); 1^2$	=38%				
AlphaOmega - ALA	605	-0.11 (0.98)	605	-0.05 (0.98)		10.0 %	-0.06 [ -0.17, 0.05 ]
Brox 2001	67	2.0657 (1.1999)	37	2.2 (0.89) ←		3.1 %	-0.13 [ -0.54, 0.27 ]
DIPP-Tokudome 2015	90	1.45 (1.05)	71	1.44 (0.81)		4.9 %	0.01 [ -0.28, 0.30]
Dodin 2005	85	1.15 (0.53)	94	1.17 (0.72)		7.5 %	-0.02 [ -0.20, 0.16

Favours higher PUFA Favours lower PUFA

(Continued . . . )

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Mea Differenc	Weight	Mean Difference		Lower PUFA		Higher PUFA	Study or subgroup
IV,Random,95% (		IV,Random,95% CI	Mean(SD)	Ν	Mean(SD)	Ν	
-0.50 [ -1.64, 0.64	0.5 %		1.8 (2.24)	20	1.3 (1.2)	16	Dullaart 1992
-0.47 [ -0.81, -0.13	3.9 %		1.61 (0.76) 🗕	28	1.14 (0.56)	31	HARP- Sacks 1995
0.30 [ -0.39, 0.99	1.3 %		1.8 (0.7)	17	2.1 (1.3)	18	HERO-Tapsell 2009
-0.26 [ -0.50, -0.02	6.0 %		1.05 (0.6) -	48	0.79 (0.6)	48	Houtsmuller 1979
0.04 [ -0.42, 0.50	2.5 %		0.03 (0.8936)	66	0.07 (1.757)	70	Ley 2004 (7)
-0.30 [ -0.48, -0.12	7.8 %		0.1 (0.63) -	71	-0.2 (0.45)	80	MARINA - Sanders 2011
0.58 [ 0.17, 0.99	3.0 %		-0.23 (0.98)	28	0.35 (0.5199)	26	Mendis 2001
0.26 [ -0.24, 0.76	2.2 %		1.51 (0.9)	30	1.77 (1.07)	30	Mita 2007
-0.14 [ -0.36, 0.08	6.4 %		1.75 (0.78)	66	1.61 (0.51)	67	Nodari 2011 HF
-0.40 [ -0.85, 0.05	2.6 %		1.8 (0.55) ←	12	1.4 (0.58)	12	Nye 1990
-0.38 [ -0.57, -0.19	7.4 %	•	-0.4 (0.87) 🔶	165	-0.78 (0.9)	170	ORL 2013
-0.13 [ -0.39, 0.13	5.4 %		1.4 (0.7)	42	1.27 (0.58)	51	PREDIMED 2013 (8)
-0.03 [ -0.33, 0.27	4.6 %		-0.25 (0.84)	54	-0.28 (0.77)	54	PREDIMED 2013 (9)
-0.14 [ -0.35, 0.07	6.8 %		-0.04 (0.58)	59	-0.18 (0.58)	58	PREDIMED 2013 (10)
-0.10 [ -0.50, 0.30	3.1 %		1.35 (1.05) —	34	1.25 (0.61)	37	Simon 1997
-0.10 [ -0.26, 0.06	8.1 %		1.7 (0.9)	237	1.6 (0.9)	221	Sydney Diet-Heart 1978
-0.30 [ -0.68, 0.08	3.3 %		1.8 (0.6) ←	48	1.5 (1.2)	47	WELCOME 2015
0.13 [ -0.21, -0.05	100.0 %	•		1832		1883	Subtotal (95% CI)
-0.13 [ -0.54, 0.27	10.2 %	<b>-</b>	2.2 (0.89)	<sup>2</sup> =47% 37	= 20 (P = 0.01); 2.0657 (1.1999)	08 (P = 0.0020)	Heterogeneity: $Tau^2 = 0.01$ ; 4 Fest for overall effect: $Z = 3.05$ 5 No industry funding Brox 2001
0.01 [ -0.28, 0.30	14.3 %	<b>#</b>	1.44 (0.81)	71	1.45 (1.05)	90	DIPP-Tokudome 2015
-0.50 [ -1.64, 0.64	2.0 %		I.8 (2.24) 🛏	20	1.3 (1.2)	16	Dullaart 1992
-0.26 [ -0.50, -0.02	16.3 %		1.05 (0.6) -	48	0.79 (0.6)	48	Houtsmuller 1979
0.04 [ -0.42, 0.50	8.6 %		0.03 (0.8936)	66	0.07 (1.757)	70	Ley 2004 (11)
-0.30 [ -0.48, -0.12	19.1 %		0.1 (0.63) -	71	-0.2 (0.45)	80	MARINA - Sanders 2011
0.58 [ 0.17, 0.99	9.9 %	·	-0.23 (0.98)	28	0.35 (0.5199)	26	Mendis 2001
-0.10 [ -0.26, 0.06	19.6 %	_ <b>e</b>	1.7 (0.9)	237	1.6 (0.9)	221	Sydney Diet-Heart 1978
2	100.0 %			578		618	Subtotal (95% CI) Heterogeneity: Tau <sup>2</sup> = 0.03;

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Study or subgroup H	ligher PUFA N	Mean(SD)	Lower PUFA N	Mean(SD)	Mean Difference IV,Random,95% Cl	Weight	Mea Differenc IV,Random,95% C
AlphaOmega - ALA	605	-0.11 (0.98)	605	-0.05 (0.98)	IV,Random,95% CI	13.7 %	-0.06 [ -0.17, 0.05
		. ,					2
Brox 2001		2.0657 (1.1999)	37	2.2 (0.89) +		2.4 %	-0.13 [ -0.54, 0.27
DIPP-Tokudome 2015	90	1.45 (1.05)	71	1.44 (0.81)	-	4.3 %	0.01 [ -0.28, 0.30
Dodin 2005	85	1.15 (0.53)	94	1.17 (0.72)		8.2 %	-0.02 [ -0.20, 0.16
Houtsmuller 1979	48	0.79 (0.6)	48	1.05 (0.6) -		5.7 %	-0.26 [ -0.50, -0.02
Ley 2004 (12)	70	0.07 (1.757)	66	0.03 (0.8936)		- 1.9 %	0.04 [ -0.42, 0.50
MARINA - Sanders 2011	80	-0.2 (0.45)	71	0.1 (0.63)		8.7 %	-0.30 [ -0.48, -0.12
Nodari 2011 HF	67	1.61 (0.51)	66	1.75 (0.78)		6.3 %	-0.14 [ -0.36, 0.08
ORL 2013	170	-0.78 (0.9)	165	-0.4 (0.87) +		7.9 %	-0.38 [ -0.57, -0.19
PREDIMED 2013 (13)	58	-0.18 (0.58)	59	-0.04 (0.58)		6.9 %	-0.14 [ -0.35, 0.07
PREDIMED 2013 (14)	54	-0.28 (0.77)	54	-0.25 (0.84)		4.0 %	-0.03 [ -0.33, 0.27
PREDIMED 2013 (15)	51	1.27 (0.58)	42	1.4 (0.7)		4.9 %	-0.13 [ -0.39, 0.13
Simon 1997	37	1.25 (0.61)	34	1.35 (1.05) -		2.4 %	-0.10 [ -0.50, 0.30
Sydney Diet-Heart 1978	221	1.6 (0.9)	237	1.7 (0.9)		9.4 %	-0.10 [ -0.26, 0.06
Vijayakumar 2014	94	1.27 (0.51)	96	1.23 (0.53)		10.6 %	0.04 [ -0.11, 0.19
WELCOME 2015	47	1.5 (1.2)	48	1.8 (0.6)		2.7 %	-0.30 [ -0.68, 0.08
Subtotal (95% CI)	1844		1793		•	100.0 % -0	.12 [ -0.19, -0.06
Heterogeneity: Tau <sup>2</sup> = 0.01; Ch Fest for overall effect: Z = 3.66 8 Randomised 250+ participant	(P = 0.0002	,	;  2 =31%				
AlphaOmega - ALA	605	-0.11 (0.98)	605	-0.05 (0.98)		22.2 %	-0.06 [ -0.17, 0.05
MARINA - Sanders 2011	80	-0.2 (0.45)	71	0.1 (0.63)		15.7 %	-0.30 [ -0.48, -0.12
ORL 2013	170	-0.78 (0.9)	165	-0.4 (0.87) +		14.6 %	-0.38 [ -0.57, -0.19
PREDIMED 2013 (16)	54	-0.28 (0.77)	54	-0.25 (0.84)		8.0 %	-0.03 [ -0.33, 0.27
PREDIMED 2013 (17)	51	1.27 (0.58)	42	1.4 (0.7)		9.8 %	-0.13 [ -0.39, 0.13
PREDIMED 2013 (18)	58	-0.18 (0.58)	59	-0.04 (0.58)		13.0 %	-0.14 [ -0.35, 0.07
Sydney Diet-Heart 1978	221	1.6 (0.9)	237	1.7 (0.9)		16.7 %	-0.10 [ -0.26, 0.06
Sydney Bleet leare 1770			1233		•	100.0 % -0	.17 [ -0.27, -0.07

(I) Change data

- (2) Fernandez-Real 2012, Reus subcohort, 2 year data
- (3) Barcelona hospital cohort at 5 years, Casas 2016
- (4) Damasceno 2013, Barcelona North subcohort, I year data
- (5) Change data
- (6) Change data
- (7) Change data
- (8) Fernandez-Real 2012, Reus subcohort, 2 year data
- (9) Barcelona hospital cohort at 5 years, Casas 2016
- (10) Damasceno 2013, Barcelona North subcohort, I year data
- (11) Change data
- (12) Change data
- (13) Damasceno 2013, Barcelona North subcohort, 1 year data
- (14) Barcelona hospital cohort at 5 years, Casas 2016
- (15) Fernandez-Real 2012, Reus subcohort, 2 year data
- (16) Barcelona hospital cohort at 5 years, Casas 2016
- (17) Fernandez-Real 2012, Reus subcohort, 2 year data
- (18) Damasceno 2013, Barcelona North subcohort, 1 year data

## Analysis 3.42. Comparison 3 Higher PUFA vs lower PUFA - continuous secondary outcomes, Outcome 42 TG, mmoL/L - SA fixed-effect.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 3 Higher PUFA vs lower PUFA - continuous secondary outcomes

Outcome: 42 TG, mmoL/L - SA fixed-effect

Mea Differenc IV,Fixed,95% (	Weight	Mean Difference IV,Fixed,95% CI	Mean(SD)	Lower PUFA N	Mean(SD)	Higher PUFA N	Study or subgroup
-0.06 [ -0.17, 0.05	20.5 %		-0.05 (0.98)	605	-0.11 (0.98)	605	AlphaOmega - ALA
-0.13 [ -0.54, 0.27	1.5 %		2.2 (0.89)	37	2.0657 (1.1999)	67	Brox 2001
0.01 [ -0.28, 0.30	3.0 %		1.44 (0.81)	71	1.45 (1.05)	90	DIPP-Tokudome 2015
-0.02 [ -0.20, 0.16	7.4 %	<b>_</b>	1.17 (0.72)	94	1.15 (0.53)	85	Dodin 2005
-0.50 [ -1.64, 0.64	• 0.2 %		I.8 (2.24) <b>'</b>	20	1.3 (1.2)	16	Dullaart 1992
-0.47 [ -0.81, -0.13	2.1 %		1.61 (0.76)	28	1.14 (0.56)	31	HARP- Sacks 1995
0.30 [ -0.39, 0.99	• 0.5 %		1.8 (0.7)	17	2.1 (1.3)	18	HERO-Tapsell 2009
-0.26 [ -0.50, -0.02	4.3 %		1.05 (0.6)	48	0.79 (0.6)	48	Houtsmuller 1979
0.04 [ -0.42, 0.50	- 1.2 %		0.03 (0.8936)	66	0.07 (1.757)	70	Ley 2004 (I)
-0.30 [ -0.48, -0.12	8.0 %		0.1 (0.63)	71	-0.2 (0.45)	80	MARINA - Sanders 2011
0.58 [ 0.17, 0.99	• 1.5 %		-0.23 (0.98)	28	0.35 (0.5199)	26	Mendis 2001
0.26 [ -0.24, 0.76	• 1.0 %		1.51 (0.9)	30	1.77 (1.07)	30	Mita 2007
-0.14 [ -0.36, 0.08	5.0 %		1.75 (0.78)	66	1.61 (0.51)	67	Nodari 2011 HF
-0.40 [ -0.85, 0.05	1.2 %		I.8 (0.55)	12	1.4 (0.58)	12	Nye 1990
-0.38 [ -0.57, -0.19	6.9 %	•	-0.4 (0.87)	165	-0.78 (0.9)	170	ORL 2013
-0.14 [ -0.35, 0.07	5.6 %		-0.04 (0.58)	59	-0.18 (0.58)	58	PREDIMED 2013 (2)
-0.13 [ -0.39, 0.13	3.6 %		1.4 (0.7)	42	1.27 (0.58)	51	PREDIMED 2013 (3)
-0.03 [ -0.33, 0.27	2.7 %		-0.25 (0.84)	54	-0.28 (0.77)	54	PREDIMED 2013 (4)
-0.10 [ -0.50, 0.30	1.5 %		1.35 (1.05)	34	1.25 (0.61)	37	Simon 1997
-0.10 [ -0.26, 0.06	9.2 %		1.7 (0.9)	237	1.6 (0.9)	221	Sydney Diet-Heart 1978
0.04 [ -0.11, 0.19	11.4 %		1.23 (0.53)	96	1.27 (0.51)	94	Vijayakumar 2014
-0.30 [ -0.68, 0.08	1.7 %		1.8 (0.6)	48	1.5 (1.2)	47	WELCOME 2015
0.11 [ -0.16, -0.06	100.0 % -	•		1928		1977	Total (95% CI)
					2)	37 (P = 0.0000)	eterogeneity: $Chi^2 = 42.24$ est for overall effect: $Z = 4$ .

- (I) Change data
- (2) Damasceno 2013, Barcelona North subcohort, I year data
- (3) Fernandez-Real 2012, Reus subcohort, 2 year data
- (4) Barcelona hospital cohort at 5 years, Casas 2016

#### Analysis 3.43. Comparison 3 Higher PUFA vs lower PUFA - continuous secondary outcomes, Outcome 43 TG, mmoL/L - subgroup by PUFA dose.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 3 Higher PUFA vs lower PUFA - continuous secondary outcomes

Outcome: 43 TG, mmoL/L - subgroup by PUFA dose

Study or subgroup	Higher PUFA		Lower PUFA		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	Ν	Mean(SD)	IV,Random,95% Cl	-	IV,Random,95% CI
total PUFA < 1.0% E							
Ley 2004 (I)	70	0.07 (1.757)	66	0.03 (0.8936)		2.3 %	0.04 [ -0.42, 0.50 ]
MARINA - Sanders 2011	80	-0.2 (0.45)	71	0.1 (0.63)		7.1 %	-0.30 [ -0.48, -0.12 ]
Mita 2007	30	1.77 (1.07)	30	1.51 (0.9)		→ 2.1 %	0.26 [ -0.24, 0.76 ]
Nodari 2011 HF	67	1.61 (0.51)	66	1.75 (0.78)		5.9 %	-0.14 [ -0.36, 0.08 ]
ORL 2013	170	-0.78 (0.9)	165	-0.4 (0.87)	<b>←</b> ∎	6.7 %	-0.38 [ -0.57, -0.19 ]
Subtotal (95% CI) Heterogeneity: Tau <sup>2</sup> = 0.02; Test for overall effect: $Z = 2$ . 2 total PUFA 1.0 to $< 2.0\%$	24 (P = 0.025)	= 4 (P = 0.07); I <sup>2</sup>	<b>398</b> =53%			24.1 %	-0.20 [ -0.37, -0.02 ]
AlphaOmega - ALA	- 605	-0.11 (0.98)	605	-0.05 (0.98)		9.0 %	-0.06 [ -0.17, 0.05 ]
Brox 2001	67	2.0657 (1.1999)	37	2.2 (0.89)	<b>٠</b>	2.9 %	-0.13 [ -0.54, 0.27 ]
DIPP-Tokudome 2015	90	1.45 (1.05)	71	1.44 (0.81)		4.5 %	0.01 [ -0.28, 0.30 ]
Dodin 2005	85	1.15 (0.53)	94	1.17 (0.72)		6.9 %	-0.02 [ -0.20, 0.16 ]
Nye 1990	12	1.4 (0.58)	12	1.8 (0.55)	<b>←</b> +	2.4 %	-0.40 [ -0.85, 0.05 ]
PREDIMED 2013 (2)	54	-0.28 (0.77)	54	-0.25 (0.84)		4.2 %	-0.03 [ -0.33, 0.27 ]
PREDIMED 2013 (3)	51	1.27 (0.58)	42	1.4 (0.7)		4.9 %	-0.13 [ -0.39, 0.13 ]
					0.5 -0.25 0 0.25 higher PUFA Favours lo	0.5 wer PUFA	

(Continued  $\dots$ )

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( Contini Me Differen	Weight	Mean			Lower PUFA		Higher PUFA	Study or subgroup
IV,Random,95%	VVCigite	om,95% Cl		Mean(SD)	N	Mean(SD)	N	study of subgroup
-0.14 [ -0.35, 0.07	6.2 %	_		-0.04 (0.58)	59	-0.18 (0.58)	58	PREDIMED 2013 (4)
-0.30 [ -0.68, 0.08	3.1 %	_	• •	1.8 (0.6)	48	1.5 (1.2)	47	WELCOME 2015
-0.08 [ -0.15, -0.01	44.2 %		•		1022		1069	Subtotal (95% CI)
					0.0%	8 (P = 0.79); I <sup>2</sup> =	Chi <sup>2</sup> = 4.72, df =	Heterogeneity: $Tau^2 = 0.0$ ; (
							( )	Test for overall effect: Z = 2 3 total PUFA 2.0 to < 5.0%
-0.50 [ -1.64, 0.64	0.5 %	,	•	1.8 (2.24)	20	1.3 (1.2)	16	Dullaart 1992
-0.47 [ -0.81, -0.13	3.6 %		•	1.61 (0.76)	28	1.14 (0.56)	31	HARP- Sacks 1995
0.58 [ 0.17, 0.99	2.8 %			-0.23 (0.98)	28	0.35 (0.5199)	26	Mendis 2001
-0.08 [ -0.91, 0.75	6.8 %				76		73	Subtotal (95% CI)
					)); I <sup>2</sup> =87%	= 2 (P = 0.0005	Chi <sup>2</sup> = 15.20, df	Heterogeneity: $Tau^2 = 0.43$ ;
							.19 (P = 0.85)	Test for overall effect: $Z = C$
								4 total PUFA 5.0+% E
0.30 [ -0.39, 0.99	· I.2 %			1.8 (0.7)	17	2.1 (1.3)	18	HERO-Tapsell 2009
-0.26 [ -0.50, -0.02	5.5 %			1.05 (0.6)	48	0.79 (0.6)	48	Houtsmuller 1979
-0.10 [ -0.50, 0.30	2.9 %			1.35 (1.05)	34	1.25 (0.61)	37	Simon 1997
-0.10 [ -0.26, 0.06	7.4 %	_		1.7 (0.9)	237	1.6 (0.9)	221	Sydney Diet-Heart 1978
0.04 [ -0.11, 0.19	7.9 %			1.23 (0.53)	96	1.27 (0.51)	94	Vijayakumar 2014
-0.07 [ -0.20, 0.06	24.9 %	-	-		432		418	Subtotal (95% CI)
					=30%	: 4 (P = 0.22); I <sup>2</sup>	Chi <sup>2</sup> = 5.74, df =	Heterogeneity: $Tau^2 = 0.01$ ;
							.05 (P = 0.29)	Test for overall effect: $Z = I$
-0.12 [ -0.20, -0.04	100.0 %		•		1928		1977	Total (95% CI)
					; I <sup>2</sup> =50%	= 21 (P = 0.004)	Chi <sup>2</sup> = 42.24, df	Heterogeneity: $Tau^2 = 0.02$ ;
							.84 (P = 0.0046)	Test for overall effect: $Z = 2$
					2 =0.0%	= 3 (P = 0.65), I	s: $Chi^2 = 1.62$ , df	Test for subgroup difference

Favours higher PUFA Favou

A Favours lower PUFA

(I) Change data

(2) Barcelona hospital cohort at 5 years, Casas 2016

(3) Fernandez-Real 2012, Reus subcohort, 2 year data

(4) Damasceno 2013, Barcelona North subcohort, I year data

## Analysis 3.44. Comparison 3 Higher PUFA vs lower PUFA - continuous secondary outcomes, Outcome 44 TG, mmoL/L - subgroup by duration.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 3 Higher PUFA vs lower PUFA - continuous secondary outcomes

Outcome: 44 TG, mmoL/L - subgroup by duration

Study or subgroup	Higher PUFA		Lower PUFA		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Random,95% CI		IV,Random,95% CI
Medium duration   to < 2	,						
Brox 2001		2.0657 (1.1999)	37	2.2 (0.89) +		2.9 %	-0.13 [ -0.54, 0.27 ]
Dodin 2005	85	1.15 (0.53)	94	1.17 (0.72)		6.9 %	-0.02 [ -0.20, 0.16 ]
HERO-Tapsell 2009	18	2.1 (1.3)	17	1.8 (0.7)		• 1.2 %	0.30 [ -0.39, 0.99 ]
Ley 2004 (I)	70	0.07 (1.757)	66	0.03 (0.8936)		- 2.3 %	0.04 [ -0.42, 0.50 ]
MARINA - Sanders 2011	80	-0.2 (0.45)	71	0.1 (0.63)		7.1 %	-0.30 [ -0.48, -0.12 ]
Mendis 2001	26	0.35 (0.5199)	28	-0.23 (0.98)		• 2.8 %	0.58 [ 0.17, 0.99 ]
Nodari 2011 HF	67	1.61 (0.51)	66	1.75 (0.78)		5.9 %	-0.14 [ -0.36, 0.08 ]
Nye 1990	12	1.4 (0.58)	12	I.8 (0.55) <b>*</b>		2.4 %	-0.40 [ -0.85, 0.05 ]
ORL 2013	170	-0.78 (0.9)	165	-0.4 (0.87) +		6.7 %	-0.38 [ -0.57, -0.19 ]
	47	1.5 (1.2)	48	I.8 (0.6) <b>+</b>	<b>·</b>	3.1 %	-0.30 [ -0.68, 0.08 ]
WELCOME 2015	17						
Subtotal (95% CI) Heterogeneity: $Tau^2 = 0.04$ ;	<b>642</b> Chi <sup>2</sup> = 26.05, d	f = 9 (P = 0.002);	<b>604</b>   <sup>2</sup> =65%		-	41.3 %	-0.12 [ -0.28, 0.04 ]
Subtotal (95% CI)	<b>642</b> Chi <sup>2</sup> = 26.05, d .50 (P = 0.13)	f = 9 (P = 0.002);			-	41.3 %	-0.12 [ -0.28, 0.04 ]
<b>Subtotal (95% CI)</b> Heterogeneity: Tau <sup>2</sup> = 0.04; Test for overall effect: Z = 1	<b>642</b> Chi <sup>2</sup> = 26.05, d .50 (P = 0.13)	f = 9 (P = 0.002); -0.11 (0.98)		-0.05 (0.98)	_	<b>41.3 %</b> 9.0 %	-0.12 [ -0.28, 0.04 ] -0.06 [ -0.17, 0.05 ]
<b>Subtotal (95% CI)</b> Heterogeneity: Tau <sup>2</sup> = 0.04; Test for overall effect: Z = 1 2 Medium-long duration 2 t	<b>642</b> Chi <sup>2</sup> = 26.05, d .50 (P = 0.13) o < 4 years	, , , , , , , , , , , , , , , , , , ,	l <sup>2</sup> =65%	-0.05 (0.98) 1.44 (0.81)	-		-0.06 [ -0.17, 0.05 ]
Subtotal (95% CI) Heterogeneity: Tau <sup>2</sup> = 0.04; Test for overall effect: Z = 1 2 Medium-long duration 2 t AlphaOmega - ALA	<b>642</b> Chi <sup>2</sup> = 26.05, d .50 (P = 0.13) o < 4 years 605	-0.11 (0.98)	l <sup>2</sup> =65%	~ /		9.0 %	
Subtotal (95% CI) Heterogeneity: Tau <sup>2</sup> = 0.04; Test for overall effect: Z = 1 2 Medium-long duration 2 t AlphaOmega - ALA DIPP-Tokudome 2015	<b>642</b> Chi <sup>2</sup> = 26.05, d .50 (P = 0.13) o < 4 years 605 90	-0.11 (0.98) 1.45 (1.05)	<sup>2</sup> =65% 605 7	1.44 (0.81)		9.0 % 4.5 %	-0.06 [ -0.17, 0.05 ] 0.01 [ -0.28, 0.30 ]
Subtotal (95% CI) Heterogeneity: Tau <sup>2</sup> = 0.04; Test for overall effect: Z = 1 2 Medium-long duration 2 t AlphaOmega - ALA DIPP-Tokudome 2015 Dullaart 1992	<b>642</b> Chi <sup>2</sup> = 26.05, d .50 (P = 0.13) o < 4 years 605 90 16	-0.11 (0.98) 1.45 (1.05) 1.3 (1.2)	l <sup>2</sup> =65% 605 7 l 20	I.44 (0.81) I.8 (2.24) **		9.0 % 4.5 % ► 0.5 %	-0.06 [ -0.17, 0.05 ] 0.01 [ -0.28, 0.30 ] -0.50 [ -1.64, 0.64 ]
Subtotal (95% CI) Heterogeneity: Tau <sup>2</sup> = 0.04; Test for overall effect: Z = 1 2 Medium-long duration 2 t AlphaOmega - ALA DIPP-Tokudome 2015 Dullaart 1992 HARP- Sacks 1995	<b>642</b> Chi <sup>2</sup> = 26.05, d .50 (P = 0.13) o < 4 years 605 90 16 31	-0.11 (0.98) 1.45 (1.05) 1.3 (1.2) 1.14 (0.56)	l <sup>2</sup> =65% 605 71 20 28	.44 (0.8 )  .8 (2.24)  .6  (0.76) <b></b> ♣		9.0 % 4.5 % • 0.5 % 3.6 %	-0.06 [ -0.17, 0.05 ] 0.01 [ -0.28, 0.30 ] -0.50 [ -1.64, 0.64 ] -0.47 [ -0.81, -0.13 ]
Subtotal (95% CI) Heterogeneity: Tau <sup>2</sup> = 0.04; Test for overall effect: Z = 1 2 Medium-long duration 2 t AlphaOmega - ALA DIPP-Tokudome 2015 Dullaart 1992 HARP- Sacks 1995 Mita 2007	642 Chi <sup>2</sup> = 26.05, d .50 (P = 0.13) o < 4 years 605 90 16 31 30	-0.11 (0.98) 1.45 (1.05) 1.3 (1.2) 1.14 (0.56) 1.77 (1.07)	<sup>2</sup> =65% 605 71 20 28 30	1.44 (0.81) 1.8 (2.24) * 1.61 (0.76) * 1.51 (0.9)		90% 4.5% • 0.5% 3.6% • 2.1%	-0.06 [ -0.17, 0.05 ] 0.01 [ -0.28, 0.30 ] -0.50 [ -1.64, 0.64 ] -0.47 [ -0.81, -0.13 ] 0.26 [ -0.24, 0.76 ]
Subtotal (95% CI) Heterogeneity: Tau <sup>2</sup> = 0.04; Test for overall effect: Z = 1 2 Medium-long duration 2 t AlphaOmega - ALA DIPP-Tokudome 2015 Dullaart 1992 HARP- Sacks 1995 Mita 2007 Simon 1997	642 Chi <sup>2</sup> = 26.05, d .50 (P = 0.13) o < 4 years 605 90 16 31 30 37	-0.11 (0.98) 1.45 (1.05) 1.3 (1.2) 1.14 (0.56) 1.77 (1.07) 1.25 (0.61)	1 <sup>2</sup> =65% 605 71 20 28 30 34	I.44 (0.81) I.8 (2.24) ** I.61 (0.76) ** I.51 (0.9) I.35 (1.05) *		9.0 % 4.5 % 0.5 % 3.6 % 2.1 % 2.9 %	-0.06 [ -0.17, 0.05 ] 0.01 [ -0.28, 0.30 ] -0.50 [ -1.64, 0.64 ] -0.47 [ -0.81, -0.13 ] 0.26 [ -0.24, 0.76 ] -0.10 [ -0.50, 0.30 ] 0.04 [ -0.11, 0.19 ]
Subtotal (95% CI) Heterogeneity: Tau <sup>2</sup> = 0.04; Test for overall effect: Z = 1 2 Medium-long duration 2 t AlphaOmega - ALA DIPP-Tokudome 2015 Dullaart 1992 HARP- Sacks 1995 Mita 2007 Simon 1997 Vijayakumar 2014	642 Chi <sup>2</sup> = 26.05, d .50 (P = 0.13) o < 4 years 605 90 16 31 30 37 94 903	-0.11 (0.98) 1.45 (1.05) 1.3 (1.2) 1.14 (0.56) 1.77 (1.07) 1.25 (0.61) 1.27 (0.51)	<ul> <li>I<sup>2</sup> =65%</li> <li>605</li> <li>71</li> <li>20</li> <li>28</li> <li>30</li> <li>34</li> <li>96</li> <li>884</li> </ul>	I.44 (0.81) I.8 (2.24) ** I.61 (0.76) ** I.51 (0.9) I.35 (1.05) *		9.0 % 4.5 % 0.5 % 3.6 % 2.1 % 2.9 % 7.9 %	-0.06 [ -0.17, 0.05 ] 0.01 [ -0.28, 0.30 ] -0.50 [ -1.64, 0.64 ] -0.47 [ -0.81, -0.13 ] 0.26 [ -0.24, 0.76 ] -0.10 [ -0.50, 0.30 ] 0.04 [ -0.11, 0.19 ]
Subtotal (95% CI) Heterogeneity: Tau <sup>2</sup> = 0.04; Test for overall effect: Z = 1 2 Medium-long duration 2 t AlphaOmega - ALA DIPP-Tokudome 2015 Dullaart 1992 HARP- Sacks 1995 Mita 2007 Simon 1997 Vijayakumar 2014 Subtotal (95% CI) Heterogeneity: Tau <sup>2</sup> = 0.01; Test for overall effect: Z = 0	642 Chi <sup>2</sup> = 26.05, d .50 (P = 0.13) o < 4 years 605 90 16 31 30 37 94 903 Chi <sup>2</sup> = 9.46, df	-0.11 (0.98) 1.45 (1.05) 1.3 (1.2) 1.14 (0.56) 1.77 (1.07) 1.25 (0.61) 1.27 (0.51)	<ul> <li>I<sup>2</sup> =65%</li> <li>605</li> <li>71</li> <li>20</li> <li>28</li> <li>30</li> <li>34</li> <li>96</li> <li>884</li> </ul>	I.44 (0.81) I.8 (2.24) ** I.61 (0.76) ** I.51 (0.9) I.35 (1.05) *		9.0 % 4.5 % 0.5 % 3.6 % 2.1 % 2.9 % 7.9 %	-0.06 [ -0.17, 0.05 ] 0.01 [ -0.28, 0.30 ] -0.50 [ -1.64, 0.64 ] -0.47 [ -0.81, -0.13 ] 0.26 [ -0.24, 0.76 ] -0.10 [ -0.50, 0.30 ] 0.04 [ -0.11, 0.19 ]
Subtotal (95% CI) Heterogeneity: Tau <sup>2</sup> = 0.04; Test for overall effect: Z = 1 2 Medium-long duration 2 t AlphaOmega - ALA DIPP-Tokudome 2015 Dullaart 1992 HARP- Sacks 1995 Mita 2007 Simon 1997 Vijayakumar 2014 Subtotal (95% CI) Heterogeneity: Tau <sup>2</sup> = 0.01;	642 Chi <sup>2</sup> = 26.05, d .50 (P = 0.13) o < 4 years 605 90 16 31 30 37 94 903 Chi <sup>2</sup> = 9.46, df	-0.11 (0.98) 1.45 (1.05) 1.3 (1.2) 1.14 (0.56) 1.77 (1.07) 1.25 (0.61) 1.27 (0.51)	<ul> <li>I<sup>2</sup> =65%</li> <li>605</li> <li>71</li> <li>20</li> <li>28</li> <li>30</li> <li>34</li> <li>96</li> <li>884</li> </ul>	I.44 (0.81) I.8 (2.24) ** I.61 (0.76) ** I.51 (0.9) I.35 (1.05) *		9.0 % 4.5 % 0.5 % 3.6 % 2.1 % 2.9 % 7.9 %	-0.06 [ -0.17, 0.05 ] 0.01 [ -0.28, 0.30 ] -0.50 [ -1.64, 0.64 ] -0.47 [ -0.81, -0.13 ] 0.26 [ -0.24, 0.76 ] -0.10 [ -0.50, 0.30 ]

(Continued . . . )

Study or subgroup	Higher PUFA N	l Mean(SD)	Lower PUFA	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	( Continued) Mean Difference IV,Random,95% Cl
PREDIMED 2013 (2)	58	-0.18 (0.58)	59	-0.04 (0.58)		6.2 %	-0.14 [ -0.35, 0.07 ]
PREDIMED 2013 (3)	54	-0.28 (0.77)	54	-0.25 (0.84)		4.2 %	-0.03 [ -0.33, 0.27 ]
PREDIMED 2013 (4)	51	1.27 (0.58)	42	1.4 (0.7)		4.9 %	-0.13 [ -0.39, 0.13 ]
Sydney Diet-Heart 1978	221	1.6 (0.9)	237	1.7 (0.9)		7.4 %	-0.10 [ -0.26, 0.06 ]
Subtotal (95% CI) Heterogeneity: Tau <sup>2</sup> = 0.0; C Test for overall effect: $Z = 2$		$+$ (P = 0.80); $ ^2 = 0$	<b>440</b>		•	28.3 % -0	.13 [ -0.23, -0.03 ]
<b>Total (95% CI)</b> Heterogeneity: $Tau^2 = 0.02$ ; Test for overall effect: $Z = 2$ Test for subgroup difference	.84 (P = 0.0046)				•	100.0 % -0	.12 [ -0.20, -0.04 ]

-0.5 -0.25 0 0.25 0.5 Favours higher PUFA Favours lower PUFA

(I) Change data

(2) Damasceno 2013, Barcelona North subcohort, I year data

(3) Barcelona hospital cohort at 5 years, Casas 2016

(4) Fernandez-Real 2012, Reus subcohort, 2 year data

#### Analysis 3.45. Comparison 3 Higher PUFA vs lower PUFA - continuous secondary outcomes, Outcome 45 TG, mmoL/L - subgroup by primary or secondary prevention.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 3 Higher PUFA vs lower PUFA - continuous secondary outcomes

Outcome: 45 TG, mmoL/L - subgroup by primary or secondary prevention

Study or subgroup	Higher PUFA		Lower PUFA		Mean Difference	Weight	Mea Difference
	Ν	Mean(SD)	Ν	Mean(SD)	IV,Random,95% CI		IV,Random,95% C
I Primary prevention of CV							
Brox 2001	67	2.0657 (1.1999)	37	2.2 (0.89)	· · · · ·	2.9 %	-0.13 [ -0.54, 0.27
DIPP-Tokudome 2015	90	1.45 (1.05)	71	1.44 (0.81)		4.5 %	0.01 [ -0.28, 0.30
Dodin 2005	85	1.15 (0.53)	94	1.17 (0.72)		6.9 %	-0.02 [ -0.20, 0.16
Dullaart 1992	16	1.3 (1.2)	20	1.8 (2.24)	H		-0.50 [ -1.64, 0.64
HERO-Tapsell 2009	18	2.1 (1.3)	17	1.8 (0.7)		+ Ⅰ.2 %	0.30 [ -0.39, 0.99
Houtsmuller 1979	48	0.79 (0.6)	48	1.05 (0.6)		5.5 %	-0.26 [ -0.50, -0.02
Ley 2004 (I)	70	0.07 (1.757)	66	0.03 (0.8936)	·	- 2.3 %	0.04 [ -0.42, 0.50
MARINA - Sanders 2011	80	-0.2 (0.45)	71	0.1 (0.63)	<b>n</b>	7.1 %	-0.30 [ -0.48, -0.12
Mendis 2001	26	0.35 (0.5199)	28	-0.23 (0.98)			0.58 [ 0.17, 0.99
Mita 2007	30	1.77 (1.07)	30	1.51 (0.9)			0.26 [ -0.24, 0.76
ORL 2013	170	-0.78 (0.9)	165	-0.4 (0.87)	<b>←∎</b>	6.7 %	-0.38 [ -0.57, -0.19
PREDIMED 2013 (2)	54	-0.28 (0.77)	54	-0.25 (0.84)		4.2 %	-0.03 [ -0.33, 0.27
PREDIMED 2013 (3)	58	-0.18 (0.58)	59	-0.04 (0.58)		6.2 %	-0.14 [ -0.35, 0.07
PREDIMED 2013 (4)	51	1.27 (0.58)	42	1.4 (0.7)	<b>·</b>	4.9 %	-0.13 [ -0.39, 0.13
Simon 1997	37	1.25 (0.61)	34	1.35 (1.05)		2.9 %	-0.10 [ -0.50, 0.30
WELCOME 2015	47	1.5 (1.2)	48	1.8 (0.6)		3.1 %	-0.30 [ -0.68, 0.08
Subtotal (95% CI) Heterogeneity: Tau <sup>2</sup> = 0.02;	<b>947</b> Chi <sup>2</sup> = 30.75, d	f = 15 (P = 0.01);	<b>884</b>   <sup>2</sup> =51%		-	63.8 %	-0.10 [ -0.21, 0.01
Test for overall effect: $Z = 1$	.84 (P = 0.065)						
2 Secondary prevention of 0							
AlphaOmega - ALA	605	-0.11 (0.98)	605	-0.05 (0.98)		9.0 %	-0.06 [ -0.17, 0.05
HARP- Sacks 1995	31	1.14 (0.56)	28	1.61 (0.76)		3.6 %	-0.47 [ -0.81, -0.13
Nodari 2011 HF	67	1.61 (0.51)	66	1.75 (0.78)		5.9 %	-0.14 [ -0.36, 0.08
Nye 1990	12	1.4 (0.58)	12	1.8 (0.55)	•••	2.4 %	-0.40 [ -0.85, 0.05
Sydney Diet-Heart 1978	221	1.6 (0.9)	237	1.7 (0.9)		7.4 %	-0.10 [ -0.26, 0.06
Sydney Diet-Heart 1978	221	I.6 (0.9)	237		0.5 -0.25 0 0.25 0 i higher PUFA Favours low	0.5	-0.10 [ -0.26, 0.

(Continued ...)

							( Continued)
Study or subgroup	Higher PUFA	Lo	wer PUFA		Mean Difference	Weight	Mean Difference
	Ν	Mean(SD)	Ν	Mean(SD)	IV,Random,95% CI		IV,Random,95% CI
Vijayakumar 2014	94	1.27 (0.51)	96	1.23 (0.53)		7.9 %	0.04 [ -0.11, 0.19 ]
Subtotal (95% CI)	1030		1044		-	36.2 %	-0.11 [ -0.22, 0.00 ]
Heterogeneity: $Tau^2 = 0.01$	; Chi <sup>2</sup> = 9.86, df =	5 (P = 0.08); $I^2 = 4$	9%				
Test for overall effect: Z =	1.91 (P = 0.056)						
Total (95% CI)	1977		1928		•	100.0 %	-0.12 [ -0.20, -0.04 ]
Heterogeneity: $Tau^2 = 0.02$	2; Chi <sup>2</sup> = 42.24, df =	= 2 I (P = 0.004); I <sup>2</sup>	=50%				
Test for overall effect: $Z = 2$	2.84 (P = 0.0046)						
Test for subgroup difference	es: Chi <sup>2</sup> = 0.01, df	= I (P = 0.94), I <sup>2</sup> =	0.0%				
						1	
				0.5	0.25 0 0.25	0.F	

-0.5 -0.25 0 0.25 0.5

Favours higher PUFA Favours lower PUFA

(I) Change data

(2) Barcelona hospital cohort at 5 years, Casas 2016

(3) Damasceno 2013, Barcelona North subcohort, 1 year data

(4) Fernandez-Real 2012, Reus subcohort, 2 year data

#### Analysis 3.46. Comparison 3 Higher PUFA vs lower PUFA - continuous secondary outcomes, Outcome 46 TG, mmoL/L - subgroup by baseline PUFA dose.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 3 Higher PUFA vs lower PUFA - continuous secondary outcomes

Outcome: 46 TG, mmoL/L - subgroup by baseline PUFA dose

Mean(SD) 1.15 (0.53) 2.1 (1.3) 0.07 (1.757) 2 (P = 0.67); l <sup>2</sup> =0.0 1.45 (1.05) 1.3 (1.2) -0.2 (0.45) 1.27 (0.58) -0.18 (0.58) -0.28 (0.77) 1.25 (0.61)	177	Mean(SD) 1.17 (0.72) 1.8 (0.7) 0.03 (0.8936) 1.44 (0.81) 1.8 (2.24) 0.1 (0.63) -0.1 (0.63) -1.4 (0.7) -0.04 (0.58) -0.25 (0.84)	IV,Random,95% CI	6.9 % 1.2 % 2.3 % 10.4 % 4.5 % 0.5 % 7.1 % 4.9 % 6.2 % 4.2 %	IV,Random,95% C -0.02 [ -0.20, 0.16 0.30 [ -0.39, 0.99 0.04 [ -0.42, 0.50 <b>0.01 [ -0.16, 0.17</b> 0.01 [ -0.28, 0.30 -0.50 [ -1.64, 0.64 -0.30 [ -0.48, -0.12 -0.13 [ -0.39, 0.13 -0.14 [ -0.35, 0.07
$2.1 (1.3)$ $0.07 (1.757)$ $2 (P = 0.67); I^{2} = 0.0$ $1.45 (1.05)$ $1.3 (1.2)$ $-0.2 (0.45)$ $1.27 (0.58)$ $-0.18 (0.58)$ $-0.28 (0.77)$	17 66 <b>177</b> % 71 20 71 42 59	1.8 (0.7) 0.03 (0.8936) 1.44 (0.81) 1.8 (2.24) ← 0.1 (0.63) − 1.4 (0.7) -0.04 (0.58)		<ul> <li>1.2 %</li> <li>2.3 %</li> <li>10.4 %</li> <li>4.5 %</li> <li>0.5 %</li> <li>7.1 %</li> <li>4.9 %</li> <li>6.2 %</li> </ul>	0.30 [ -0.39, 0.99 0.04 [ -0.42, 0.50 <b>0.01 [ -0.16, 0.17</b> 0.01 [ -0.28, 0.30 -0.50 [ -1.64, 0.64 -0.30 [ -0.48, -0.12 -0.13 [ -0.39, 0.13 -0.14 [ -0.35, 0.07
$2.1 (1.3)$ $0.07 (1.757)$ $2 (P = 0.67); I^{2} = 0.0$ $1.45 (1.05)$ $1.3 (1.2)$ $-0.2 (0.45)$ $1.27 (0.58)$ $-0.18 (0.58)$ $-0.28 (0.77)$	17 66 <b>177</b> % 71 20 71 42 59	1.8 (0.7) 0.03 (0.8936) 1.44 (0.81) 1.8 (2.24) ← 0.1 (0.63) − 1.4 (0.7) -0.04 (0.58)		<ul> <li>1.2 %</li> <li>2.3 %</li> <li>10.4 %</li> <li>4.5 %</li> <li>0.5 %</li> <li>7.1 %</li> <li>4.9 %</li> <li>6.2 %</li> </ul>	0.30 [ -0.39, 0.99 0.04 [ -0.42, 0.50 <b>0.01 [ -0.16, 0.17</b> 0.01 [ -0.28, 0.30 -0.50 [ -1.64, 0.64 -0.30 [ -0.48, -0.12 -0.13 [ -0.39, 0.13 -0.14 [ -0.35, 0.07
$0.07 (1.757)$ $2 (P = 0.67); l^{2} = 0.0$ $1.45 (1.05)$ $1.3 (1.2)$ $-0.2 (0.45)$ $1.27 (0.58)$ $-0.18 (0.58)$ $-0.28 (0.77)$	66 <b>177</b> % 71 20 71 42 59	0.03 (0.8936) 1.44 (0.81) 1.8 (2.24) - 0.1 (0.63) - 1.4 (0.7) -0.04 (0.58)		<ul> <li>2.3 %</li> <li>10.4 %</li> <li>4.5 %</li> <li>0.5 %</li> <li>7.1 %</li> <li>4.9 %</li> <li>6.2 %</li> </ul>	0.04 [ -0.42, 0.50 0.01 [ -0.16, 0.17 0.01 [ -0.28, 0.30 -0.50 [ -1.64, 0.64 -0.30 [ -0.48, -0.12 -0.13 [ -0.39, 0.13 -0.14 [ -0.35, 0.07
2 (P = 0.67); I <sup>2</sup> =0.0 1.45 (1.05) 1.3 (1.2) -0.2 (0.45) 1.27 (0.58) -0.18 (0.58) -0.28 (0.77)	177 % 71 20 71 42 59	1.44 (0.81) 1.8 (2.24) ← 0.1 (0.63) − 1.4 (0.7) -0.04 (0.58)		10.4 % 4.5 % 0.5 % 7.1 % 4.9 % 6.2 %	0.01 [ -0.16, 0.17 0.01 [ -0.28, 0.30 -0.50 [ -1.64, 0.64 -0.30 [ -0.48, -0.12 -0.13 [ -0.39, 0.13 -0.14 [ -0.35, 0.07
1.45 (1.05) 1.3 (1.2) -0.2 (0.45) 1.27 (0.58) -0.18 (0.58) -0.28 (0.77)	71 20 71 42 59	1.8 (2.24) ← 0.1 (0.63) − 1.4 (0.7) -0.04 (0.58)		4.5 % 0.5 % 7.1 % 4.9 % 6.2 %	0.01 [ -0.28, 0.30 -0.50 [ -1.64, 0.64 -0.30 [ -0.48, -0.12 -0.13 [ -0.39, 0.13 -0.14 [ -0.35, 0.07
1.45 (1.05) 1.3 (1.2) -0.2 (0.45) 1.27 (0.58) -0.18 (0.58) -0.28 (0.77)	71 20 71 42 59	1.8 (2.24) ← 0.1 (0.63) − 1.4 (0.7) -0.04 (0.58)		• 0.5 % 7.1 % 4.9 % 6.2 %	-0.50 [ -1.64, 0.64 -0.30 [ -0.48, -0.12 -0.13 [ -0.39, 0.13 -0.14 [ -0.35, 0.07
1.3 (1.2) -0.2 (0.45) 1.27 (0.58) -0.18 (0.58) -0.28 (0.77)	20 71 42 59	1.8 (2.24) ← 0.1 (0.63) − 1.4 (0.7) -0.04 (0.58)		• 0.5 % 7.1 % 4.9 % 6.2 %	-0.50 [ -1.64, 0.64 -0.30 [ -0.48, -0.12 -0.13 [ -0.39, 0.13 -0.14 [ -0.35, 0.07
1.3 (1.2) -0.2 (0.45) 1.27 (0.58) -0.18 (0.58) -0.28 (0.77)	20 71 42 59	1.8 (2.24) ← 0.1 (0.63) − 1.4 (0.7) -0.04 (0.58)		• 0.5 % 7.1 % 4.9 % 6.2 %	-0.50 [ -1.64, 0.64 -0.30 [ -0.48, -0.12 -0.13 [ -0.39, 0.13 -0.14 [ -0.35, 0.07
1.3 (1.2) -0.2 (0.45) 1.27 (0.58) -0.18 (0.58) -0.28 (0.77)	20 71 42 59	1.8 (2.24) ← 0.1 (0.63) − 1.4 (0.7) -0.04 (0.58)		• 0.5 % 7.1 % 4.9 % 6.2 %	-0.50 [ -1.64, 0.64 -0.30 [ -0.48, -0.12 -0.13 [ -0.39, 0.13 -0.14 [ -0.35, 0.07
-0.2 (0.45) 1.27 (0.58) -0.18 (0.58) -0.28 (0.77)	71 42 59	0.1 (0.63) - 1.4 (0.7) -0.04 (0.58)	-•	7.1 % 4.9 % 6.2 %	-0.13 [ -0.39, 0.12 -0.13 [ -0.39, 0.13 -0.14 [ -0.35, 0.07
1.27 (0.58) -0.18 (0.58) -0.28 (0.77)	42 59	I.4 (0.7) -0.04 (0.58)		4.9 % 6.2 %	-0.13 [ -0.39, 0.13 -0.14 [ -0.35, 0.07
-0.18 (0.58) -0.28 (0.77)	59	-0.04 (0.58)		6.2 %	-0.14 [ -0.35, 0.07
-0.28 (0.77)					-
× /	54	-0.25 (0.84)		4.2 %	
125 (061)					-0.03 [ -0.33, 0.27
1.23 (0.01)	34	I.35 (I.05) —		2.9 %	-0.10 [ -0.50, 0.30
1.6 (0.9)	237	1.7 (0.9)		7.4 %	-0.10 [ -0.26, 0.06
	588		•	37.8 %	-0.14 [ -0.23, -0.06
7 (P = 0.62); l <sup>2</sup> =0.0	)%				
	0				Not estimabl
-0.11 (0.98)	605	-0.05 (0.98)		9.0 %	-0.06 [ -0.17, 0.05
2.0657 (1.1999)	37	2.2 (0.89) ←		2.9 %	-0.13 [ -0.54, 0.27
1.14 (0.56)	28	1.61 (0.76) 🔸		3.6 %	-0.47 [ -0.81, -0.13
0.79 (0.6)	48	1.05 (0.6) -		5.5 %	-0.26 [ -0.50, -0.02
0	10			0.0 /0	0.20 [ 0.00, 0.02
	.0657 (1.1999)	.0657 (1.1999) 37 1.14 (0.56) 28	-0.11 (0.98) 605 -0.05 (0.98) .0657 (1.1999) 37 2.2 (0.89) ← 1.14 (0.56) 28 1.61 (0.76) ← 0.79 (0.6) 48 1.05 (0.6) −	-0.11 (0.98) 605 -0.05 (0.98) .0657 (1.1999) 37 2.2 (0.89) 1.14 (0.56) 28 1.61 (0.76) 0.79 (0.6) 48 1.05 (0.6)	-0.11 (0.98)       605       -0.05 (0.98)       9.0 %         .0657 (1.1999)       37       2.2 (0.89)       2.9 %         1.14 (0.56)       28       1.61 (0.76)       3.6 %         0.79 (0.6)       48       1.05 (0.6)       5.5 %

(Continued . . . )

Study or subgroup	Higher PUFA N	L Mean(SD)	_ower PUFA N	Mean(SD)	Mean Difference IV,Random,95% Cl	Weight	( Continued) Mean Difference IV,Random,95% Cl
Mendis 2001	26	0.35 (0.5199)	28	-0.23 (0.98)		→ 2.8 %	0.58 [ 0.17, 0.99 ]
Mita 2007	30	1.77 (1.07)	30	1.51 (0.9)		→ 2.1 %	0.26 [ -0.24, 0.76 ]
Nodari 2011 HF	67	1.61 (0.51)	66	1.75 (0.78)		5.9 %	-0.14 [ -0.36, 0.08 ]
Nye 1990	12	1.4 (0.58)	12	1.8 (0.55)	<b>←</b> →	2.4 %	-0.40 [ -0.85, 0.05 ]
ORL 2013	170	-0.78 (0.9)	165	-0.4 (0.87)	<b>←</b> ∎──	6.7 %	-0.38 [ -0.57, -0.19 ]
Vijayakumar 2014	94	1.27 (0.51)	96	1.23 (0.53)		7.9 %	0.04 [ -0.11, 0.19 ]
WELCOME 2015	47	1.5 (1.2)	48	1.8 (0.6)	<b>٠</b>	3.1 %	-0.30 [ -0.68, 0.08 ]
Subtotal (95% CI)	1197		1163		-	51.8 %	-0.13 [ -0.27, 0.01 ]
Heterogeneity: $Tau^2 = 0.03$	8; Chi <sup>2</sup> = 33.61, df	= 10 (P = 0.00021	); I <sup>2</sup> =70%				
Test for overall effect: Z =	I.83 (P = 0.067)						
Total (95% CI)	1977		1928		•	100.0 %	-0.12 [ -0.20, -0.04 ]
Heterogeneity: $Tau^2 = 0.02$	; Chi <sup>2</sup> = 42.24, df	= 21 (P = 0.004);	$ ^2 = 50\%$				
Test for overall effect: $Z = $	2.84 (P = 0.0046)						
Test for subgroup difference	es: Chi <sup>2</sup> = 2.54, df	= 2 (P = 0.28), I <sup>2</sup>	=21%				

-0.5 -0.25 0 0.25 0.5

Favours higher PUFA Favours lower PUFA

(I) Change data

(2) Fernandez-Real 2012, Reus subcohort, 2 year data

(3) Damasceno 2013, Barcelona North subcohort, 1 year data

(4) Barcelona hospital cohort at 5 years, Casas 2016

#### Analysis 3.47. Comparison 3 Higher PUFA vs lower PUFA - continuous secondary outcomes, Outcome 47 TG, mmoL/L - subgroup by replacement.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 3 Higher PUFA vs lower PUFA - continuous secondary outcomes

Outcome: 47 TG, mmoL/L - subgroup by replacement

Mea Difference	Weight	Mean Difference		Lower PUFA		Higher PUFA	Study or subgroup
IV,Random,95% (		IV,Random,95% CI	Mean(SD)	Ν	Mean(SD)	Ν	
						ats	I PUFA replaced saturated f
-0.50 [ -1.64, 0.64	• 0.9 %		I.8 (2.24) <b>*</b>	20	1.3 (1.2)	16	Dullaart 1992
0.30 [ -0.39, 0.99			1.8 (0.7)	17	2.1 (1.3)	18	HERO-Tapsell 2009
-0.10 [ -0.26, 0.06	43.2 %		1.7 (0.9)	237	1.6 (0.9)	221	Sydney Diet-Heart 1978
0.04 [ -0.11, 0.19	53.3 %	_ <b></b>	1.23 (0.53)	96	1.27 (0.51)	94	Vijayakumar 2014
-0.02 [ -0.13, 0.09	100.0 %	-		370		349	Subtotal (95% CI)
				=2%	3 (P = 0.38); I <sup>2</sup> :	Chi <sup>2</sup> = 3.05, df =	Heterogeneity: $Tau^2 = 0.00;$
						.33 (P = 0.74)	Test for overall effect: $Z = 0$ .
		_					2 PUFA replaced monounsa
-0.06 [ -0.17, 0.05	25.1 %		-0.05 (0.98)	605	-0.11 (0.98)	605	AlphaOmega - ALA
-0.47 [ -0.81, -0.13	4.7 %	•	1.61 (0.76) 🕇	28	1.14 (0.56)	31	HARP- Sacks 1995
-0.30 [ -0.48, -0.12	14.1 %		0.1 (0.63)	71	-0.2 (0.45)	80	MARINA - Sanders 2011
-0.14 [ -0.36, 0.08	9.8 %		1.75 (0.78)	66	1.61 (0.51)	67	Nodari 2011 HF
-0.40 [ -0.85, 0.05	2.8 %		I.8 (0.55) 🕇	12	1.4 (0.58)	12	Nye 1990
-0.13 [ -0.39, 0.13	7.4 %		1.4 (0.7)	42	1.27 (0.58)	51	PREDIMED 2013 (1)
-0.14 [ -0.35, 0.07	10.9 %		-0.04 (0.58)	59	-0.18 (0.58)	58	PREDIMED 2013 (2)
-0.03 [ -0.33, 0.27	5.8 %		-0.25 (0.84)	54	-0.28 (0.77)	54	PREDIMED 2013 (3)
-0.10 [ -0.26, 0.06	15.5 %		1.7 (0.9)	237	1.6 (0.9)	221	Sydney Diet-Heart 1978
-0.30 [ -0.68, 0.08	3.9 %	·	1.8 (0.6)	48	1.5 (1.2)	47	WELCOME 2015
0.16 [ -0.24, -0.08	100.0 %	•		1222		1226	Subtotal (95% CI)
				=21%	= 9 (P = 0.25); $I^2$	$Chi^2 = 11.37, df$	Heterogeneity: $Tau^2 = 0.00$ ;
					)		Test for overall effect: $Z = 3$ .
							3 PUFA replaced carbohydra
0.01 [ -0.28, 0.30	14.8 %		1.44 (0.81)	71	1.45 (1.05)	90	DIPP-Tokudome 2015
-0.02 [ -0.20, 0.16	18.7 %		1.17 (0.72)	94	1.15 (0.53)	85	Dodin 2005
-0.26 [ -0.50, -0.02	16.6 %		1.05 (0.6) -	48	0.79 (0.6)	48	Houtsmuller 1979
	- 9.4 %		0.03 (0.8936)	66	0.07 (1.757)	70	Ley 2004 (4)

(Continued ...)

Study or subgroup	Higher PUFA N	L Mean(SD)	ower PUFA. N		Mean Difference IV,Random,95% CI	Weight	( Continuec Mean Difference IV,Random,95% CI
MARINA - Sanders 2011	80	-0.2 (0.45)	71	0.1 (0.63)		19.0 %	-0.30 [ -0.48, -0.12 ]
Mendis 2001	26	0.35 (0.5199)	28	-0.23 (0.98)		→ I0.7 %	0.58 [ 0.17, 0.99 ]
Simon 1997	37	1.25 (0.61)	34	I.35 (I.05) -		10.9 %	-0.10 [ -0.50, 0.30 ]
Subtotal (95% CI)	436		412			100.0 %	-0.05 [ -0.23, 0.14 ]
Heterogeneity: $Tau^2 = 0.04$ ; ( Test for overall effect: $Z = 0.5$ 4 PUFA replaced protein		= 6 (P = 0.005); I <sup>2</sup>	=68%				
HERO-Tapsell 2009	18	2.1 (1.3)	17	1.8 (0.7)		→ 31.4 %	0.30 [ -0.39, 0.99 ]
Ley 2004 (5)	70	0.07 (1.757)	66	0.03 (0.8936)		- 68.6 %	0.04 [ -0.42, 0.50 ]
Subtotal (95% CI)	88		83			- 100.0 %	0.12 [ -0.26, 0.51 ]
Heterogeneity: Tau <sup>2</sup> = 0.0; C	hi <sup>2</sup> = 0.38, df =	I (P = 0.54); I <sup>2</sup> =0	.0%				
Test for overall effect: $Z = 0.6$	62 (P = 0.54)						
5 PUFA replaced unclear							
Brox 2001	67 3	2.0657 (1.1999)	37	2.2 (0.89) +		30.5 %	-0.13 [ -0.54, 0.27 ]
Mita 2007	30	1.77 (1.07)	30	1.51 (0.9)		→ 25.3 %	0.26 [ -0.24, 0.76 ]
ORL 2013	170	-0.78 (0.9)	165	-0.4 (0.87) +	•	44.2 %	-0.38 [ -0.57, -0.19 ]
Subtotal (95% CI)	267		232	-		100.0 %	-0.14 [ -0.50, 0.21 ]
Heterogeneity: Tau <sup>2</sup> = 0.07; ( Test for overall effect: Z = 0.7 Test for subgroup differences	79 (P = 0.43)	· · · ·					

Favours higher PUFA Favours lower PUFA

(1) Fernandez-Real 2012, Reus subcohort, 2 year data

(2) Damasceno 2013, Barcelona North subcohort, 1 year data

(3) Barcelona hospital cohort at 5 years, Casas 2016

(4) Change data

(5) Change data

## Analysis 3.48. Comparison 3 Higher PUFA vs lower PUFA - continuous secondary outcomes, Outcome 48 TG, mmoL/L - subgroup by sex.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 3 Higher PUFA vs lower PUFA - continuous secondary outcomes

Outcome: 48 TG, mmoL/L - subgroup by sex

Study or subgroup	Higher PUFA		Lower PUFA		Mean Difference	Weight	Mean Difference
	Ν	Mean(SD)	Ν	Mean(SD)	IV,Random,95% CI		IV,Random,95% CI
> 70% men							
AlphaOmega - ALA	605	-0.11 (0.98)	605	-0.05 (0.98)		9.0 %	-0.06 [ -0.17, 0.05 ]
DIPP-Tokudome 2015	90	1.45 (1.05)	71	1.44 (0.81)		4.5 %	0.01 [ -0.28, 0.30 ]
Dullaart 1992	16	1.3 (1.2)	20	1.8 (2.24)	H	• 0.5 %	-0.50 [ -1.64, 0.64 ]
HARP- Sacks 1995	31	1.14 (0.56)	28	1.61 (0.76)	4	3.6 %	-0.47 [ -0.81, -0.13 ]
Ley 2004 (I)	70	0.07 (1.757)	66	0.03 (0.8936)		- 2.3 %	0.04 [ -0.42, 0.50 ]
Mendis 2001	26	0.35 (0.5199)	28	-0.23 (0.98)	,	• 2.8 %	0.58 [ 0.17, 0.99 ]
Nodari 2011 HF	67	1.61 (0.51)	66	1.75 (0.78)		5.9 %	-0.14 [ -0.36, 0.08 ]
Nye 1990	12	1.4 (0.58)	12	1.8 (0.55)	• · · · · · · · · · · · · · · · · · · ·	2.4 %	-0.40 [ -0.85, 0.05 ]
ORL 2013	170	-0.78 (0.9)	165	-0.4 (0.87)	<b>←</b> ∎──	6.7 %	-0.38 [ -0.57, -0.19 ]
Sydney Diet-Heart 1978	221	1.6 (0.9)	237	1.7 (0.9)		7.4 %	-0.10 [ -0.26, 0.06 ]
Vijayakumar 2014	94	1.27 (0.51)	96	1.23 (0.53)		7.9 %	0.04 [ -0.11, 0.19
Subtotal (95% CI)	1402		1394		-	53.1 %	-0.10 [ -0.23, 0.03 ]
Heterogeneity: $Tau^2 = 0.03$ ;		T = 10 (P = 0.0007	'8); I <sup>2</sup> =67%				
Test for overall effect: $Z = I$	.58 (P = 0.12)						
2 > 70% women Dodin 2005	85	1.15 (0.53)	94	1.17 (0.72)		6.9 %	-0.02 [ -0.20, 0.16
Simon 1997	37	1.25 (0.61)	34	1.35 (1.05)		2.9 %	-0.10 [ -0.50, 0.30
Subtotal (95% CI)	122		128	. ,		<b>9.8</b> %	-0.03 [ -0.20, 0.13 ]
Heterogeneity: $Tau^2 = 0.0$ ; C	$Chi^2 = 0.12, df =$	I (P = 0.72); I <sup>2</sup> =	0.0%				
Test for overall effect: $Z = 0$	.39 (P = 0.69)						
3 men % women Brox 2001	(7		37	2.2 (0.00)		2.9 %	
		2.0657 (1.1999)		2.2 (0.89)			-0.13 [ -0.54, 0.27
Houtsmuller 1979	48	0.79 (0.6)	48	1.05 (0.6)		5.5 %	-0.26 [ -0.50, -0.02
MARINA - Sanders 2011	80	-0.2 (0.45)	71	0.1 (0.63)		7.1 %	-0.30 [ -0.48, -0.12 ]
Mita 2007	30	1.77 (1.07)	30	1.51 (0.9)		► 2.1 %	0.26 [ -0.24, 0.76 ]
PREDIMED 2013 (2)	54	-0.28 (0.77)	54	-0.25 (0.84)		4.2 %	-0.03 [ -0.33, 0.27 ]

(Continued ...)

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								(
Study or subgroup	Higher PUFA	L	ower PUFA		Mea Difference		Weight	Mean Difference
,	N	Mean(SD)	Ν	Mean(SD)	IV,Random,9	5% CI	0	IV,Random,95% CI
PREDIMED 2013 (3)	58	-0.18 (0.58)	59	-0.04 (0.58)			6.2 %	-0.14 [ -0.35, 0.07 ]
PREDIMED 2013 (4)	51	1.27 (0.58)	42	1.4 (0.7)			4.9 %	-0.13 [ -0.39, 0.13 ]
WELCOME 2015	47	1.5 (1.2)	48	I.8 (0.6) <b>*</b>			3.1 %	-0.30 [ -0.68, 0.08 ]
Subtotal (95% CI)	435		389		•	36	<b>5.0</b> %	-0.19 [ -0.28, -0.09 ]
Heterogeneity: $Tau^2 = 0.0$ ; (	Chi <sup>2</sup> = 6.79, df = 7	✓ (P = 0.45); I <sup>2</sup> =0.	0%					
Test for overall effect: $Z = 3$	.91 (P = 0.000092	)						
4 sex not reported								
HERO-Tapsell 2009	18	2.1 (1.3)	17	1.8 (0.7)			1.2 %	0.30 [ -0.39, 0.99 ]
Subtotal (95% CI)	18		17			1	.2 %	0.30 [ -0.39, 0.99 ]
Heterogeneity: not applicabl	e							
Test for overall effect: $Z = 0$	.86 (P = 0.39)							
Total (95% CI)	1977		1928		•	100	.0 %	-0.12 [ -0.20, -0.04 ]
Heterogeneity: Tau <sup>2</sup> = 0.02;	Chi <sup>2</sup> = 42.24, df =	= 21 (P = 0.004); I	<sup>2</sup> =50%					
Test for overall effect: $Z = 2$	.84 (P = 0.0046)							
Test for subgroup difference	s: Chi <sup>2</sup> = 4.34, df	= 3 (P = 0.23), I <sup>2</sup> =	=31%					
				-0.	5 -0.25 0	0.25 0.5		
				Favours h	nigher PUFA F	avours lower PUFA		
				Favours h	nigher PUFA F	avours lower PUFA	<b>`</b>	

(I) Change data

(2) Barcelona hospital cohort at 5 years, Casas 2016

(3) Damasceno 2013, Barcelona North subcohort, I year data

(4) Fernandez-Real 2012, Reus subcohort, 2 year data

## Analysis 3.49. Comparison 3 Higher PUFA vs lower PUFA - continuous secondary outcomes, Outcome 49 TG, mmoL/L - subgroup by age.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 3 Higher PUFA vs lower PUFA - continuous secondary outcomes

Outcome: 49 TG, mmoL/L - subgroup by age

y or subgroup Hig	gher PUFA	L	ower PUFA		Mean Difference	Weight	Mear Difference
	Ν	Mean(SD)	Ν	Mean(SD)	IV,Random,95% Cl		IV,Random,95% C
ge < 50 years							
rt 1992	16	1.3 (1.2)	20	I.8 (2.24) 🗯		0.5 %	-0.50 [ -1.64, 0.64
1997	37	1.25 (0.61)	34	I.35 (I.05) —		2.9 %	-0.10 [ -0.50, 0.30
v Diet-Heart 1978	221	1.6 (0.9)	237	1.7 (0.9)		7.4 %	-0.10 [ -0.26, 0.06
al (95% CI)	274		291		-	10.8 %	-0.11 [ -0.26, 0.04
neity: $Tau^2 = 0.0$ ; Chi <sup>2</sup>	= 0.46, df = 2	2 (P = 0.79); $I^2 = 0$	.0%				
verall effect: $Z = 1.39$ (	P = 0.17)						
ge 50 to < 65 years							
001	67 2	2.0657 (1.1999)	37	2.2 (0.89) 🔶		2.9 %	-0.13 [ -0.54, 0.27
Tokudome 2015	90	1.45 (1.05)	71	1.44 (0.81)		4.5 %	0.01 [ -0.28, 0.30
2005	85	1.15 (0.53)	94	1.17 (0.72)		6.9 %	-0.02 [ -0.20, 0.16
- Sacks 1995	31	1.14 (0.56)	28	I.6I (0.76) <b>*</b> -		3.6 %	-0.47 [ -0.81, -0.13
-Tapsell 2009	18	2.1 (1.3)	17	1.8 (0.7)		1.2 %	0.30 [ -0.39, 0.99
004 (I)	70	0.07 (1.757)	66	0.03 (0.8936)		2.3 %	0.04 [ -0.42, 0.50
NA - Sanders 2011	80	-0.2 (0.45)	71	0.1 (0.63) -		7.1 %	-0.30 [ -0.48, -0.12
007	30	1.77 (1.07)	30	1.51 (0.9)		2.1 %	0.26 [ -0.24, 0.76
i 2011 HF	67	1.61 (0.51)	66	1.75 (0.78)		5.9 %	-0.14 [ -0.36, 0.08
990	12	1.4 (0.58)	12	I.8 (0.55) 🔶	•	2.4 %	-0.40 [ -0.85, 0.05
013	170	-0.78 (0.9)	165	-0.4 (0.87) 🔶		6.7 %	-0.38 [ -0.57, -0.19
umar 2014	94	1.27 (0.51)	96	1.23 (0.53)		7.9 %	0.04 [ -0.11, 0.19
COME 2015	47	1.5 (1.2)	48	1.8 (0.6) ←		3.1 %	-0.30 [ -0.68, 0.08
al (95% CI)	861		801		•	56.6 %	-0.15 [ -0.26, -0.03
neity: Tau <sup>2</sup> = 0.02; Chi <sup>2</sup>	<sup>2</sup> = 27.78, df	= 12 (P = 0.01); 1 <sup>2</sup>	=57%				
verall effect: $Z = 2.39$ (	P = 0.017)						
ge 65+ years							
Omega - ALA	605	-0.11 (0.98)	605	-0.05 (0.98)		9.0 %	-0.06 [ -0.17, 0.05
MED 2013 (2)	54	-0.28 (0.77)	54	-0.25 (0.84)		4.2 %	-0.03 [ -0.33, 0.27

Favours higher PUFA Favours lower PUFA

(Continued ...)

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							(
Study or subgroup	Higher PUFA	L	ower PUFA		Mear Difference		Mean Difference
, , ,	N	Mean(SD)	Ν	Mean(SD)	IV,Random,95	% CI	IV,Random,95% CI
PREDIMED 2013 (3)	51	1.27 (0.58)	42	1.4 (0.7)		4.9 %	-0.13 [ -0.39, 0.13 ]
PREDIMED 2013 (4)	58	-0.18 (0.58)	59	-0.04 (0.58)		6.2 %	-0.14 [ -0.35, 0.07 ]
Subtotal (95% CI)	768		760		-	24.4 %	-0.08 [ -0.17, 0.01 ]
Heterogeneity: $Tau^2 = 0.0;$	$Chi^2 = 0.68$ , df =	3 (P = 0.88); I <sup>2</sup> =0	.0%				
Test for overall effect: Z =	I.77 (P = 0.077)						
4 Mean age unclear							
Houtsmuller 1979	48	0.79 (0.6)	48	I.05 (0.6) -		5.5 %	-0.26 [ -0.50, -0.02 ]
Mendis 2001	26	0.35 (0.5199)	28	-0.23 (0.98)	-	2.8 %	0.58 [ 0.17, 0.99 ]
Subtotal (95% CI)	74		76	-		8.2 %	0.14 [ -0.68, 0.96 ]
Heterogeneity: Tau <sup>2</sup> = 0.32	2; Chi <sup>2</sup> = 11.82, df	= I (P = 0.00059)	; I <sup>2</sup> =92%				
Test for overall effect: Z =	0.34 (P = 0.73)						
Total (95% CI)	1977		1928		•	100.0 %	-0.12 [ -0.20, -0.04 ]
Heterogeneity: Tau <sup>2</sup> = 0.02	2; Chi <sup>2</sup> = 42.24, df	= 21 (P = 0.004);	l <sup>2</sup> =50%				
Test for overall effect: Z =	2.84 (P = 0.0046)						
Test for subgroup difference	es: Chi <sup>2</sup> = 1.11, df	$P = 3 (P = 0.78),  ^2$	=0.0%				
				1		1 1	
				-0.5	-0.25 0	0.25 0.5	
				Favours h	gher PUFA Fa	vours lower PUFA	

(I) Change data

(2) Barcelona hospital cohort at 5 years, Casas 2016

(3) Fernandez-Real 2012, Reus subcohort, 2 year data

(4) Damasceno 2013, Barcelona North subcohort, 1 year data

#### Analysis 3.50. Comparison 3 Higher PUFA vs lower PUFA - continuous secondary outcomes, Outcome 50 TG, mmoL/L - subgroup by statin use.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 3 Higher PUFA vs lower PUFA - continuous secondary outcomes

Outcome: 50 TG, mmoL/L - subgroup by statin use

gher PUFA		Lower PUFA		Mean Difference	Weight	Mean Difference
Ν	Mean(SD)	Ν	Mean(SD)	IV,Random,95% CI		IV,Random,95% CI
( <b>7</b> )		27			2.0.0/	
	, ,		~ /			-0.13 [ -0.54, 0.27 ]
90	1.45 (1.05)	71	1.44 (0.81)		4.5 %	0.01 [ -0.28, 0.30 ]
85	1.15 (0.53)	94	1.17 (0.72)		6.9 %	-0.02 [ -0.20, 0.16 ]
16	1.3 (1.2)	20	I.8 (2.24) <b>*</b>	•	• 0.5 %	-0.50 [ -1.64, 0.64 ]
31	1.14 (0.56)	28	1.61 (0.76)	<del></del>	3.6 %	-0.47 [ -0.81, -0.13 ]
48	0.79 (0.6)	48	1.05 (0.6)	<b>e</b>	5.5 %	-0.26 [ -0.50, -0.02 ]
80	-0.2 (0.45)	71	0.1 (0.63)		7.1 %	-0.30 [ -0.48, -0.12 ]
26	0.35 (0.5199)	28	-0.23 (0.98)		► 2.8 %	0.58 [ 0.17, 0.99 ]
30	1.77 (1.07)	30	1.51 (0.9)		• 2.1 %	0.26 [ -0.24, 0.76 ]
67	1.61 (0.51)	66	1.75 (0.78)		5.9 %	-0.14 [ -0.36, 0.08 ]
12	1.4 (0.58)	12	I.8 (0.55)	· · · · · · · · · · · · · · · · · · ·	2.4 %	-0.40 [ -0.85, 0.05 ]
170	-0.78 (0.9)	165	-0.4 (0.87)	•_ <b>_</b>	6.7 %	-0.38 [ -0.57, -0.19 ]
51	1.27 (0.58)	42	1.4 (0.7)		4.9 %	-0.13 [ -0.39, 0.13 ]
58	-0.18 (0.58)	59	-0.04 (0.58)		6.2 %	-0.14 [ -0.35, 0.07 ]
54	-0.28 (0.77)	54	-0.25 (0.84)		4.2 %	-0.03 [ -0.33, 0.27 ]
37	1.25 (0.61)	34	I.35 (I.05) <sup>-</sup>		2.9 %	-0.10 [ -0.50, 0.30 ]
221	1.6 (0.9)	237	1.7 (0.9)		7.4 %	-0.10 [ -0.26, 0.06 ]
1143		1096		•	76.4 % -	0.14 [ -0.24, -0.04 ]
	= 16 (P = 0.01);	$ ^2 = 5  \%$				
P = 0.0042)						
605	-0.11 (0.98)	605	-0.05 (0.98)		9.0 %	-0.06 [ -0.17, 0.05 ]
18	2.1 (1.3)	17	1.8 (0.7)		• 1.2 %	0.30 [ -0.39, 0.99 ]
94	1.27 (0.51)	96	1.23 (0.53)		7.9 %	0.04 [ -0.11, 0.19 ]
47	1.5 (1.2)	48	1.8 (0.6)	••	3.1 %	-0.30 [ -0.68, 0.08 ]
	$\begin{array}{c} & N \\ & 67 & 2 \\ & 90 \\ & 85 \\ & 16 \\ & 31 \\ & 48 \\ & 80 \\ & 26 \\ & 30 \\ & 67 \\ & 12 \\ & 170 \\ & 51 \\ & 54 \\ & 37 \\ & 221 \\ & 1143 \\ & 54 \\ & 37 \\ & 221 \\ & 1143 \\ & e = 32.73,  df \\ P = 0.0042) \\ & 605 \\ & 18 \\ & 94 \end{array}$	N         Mean(SD)           67         2.0657 (1.1999)           90         1.45 (1.05)           85         1.15 (0.53)           16         1.3 (1.2)           31         1.14 (0.56)           48         0.79 (0.6)           80         -0.2 (0.45)           26         0.35 (0.5199)           30         1.77 (1.07)           67         1.61 (0.51)           12         1.4 (0.58)           170         -0.78 (0.9)           51         1.27 (0.58)           58         -0.18 (0.58)           54         -0.28 (0.77)           37         1.25 (0.61)           221         1.6 (0.9)           1143         2 $e32.73$ , df = 16 (P = 0.01);           P = 0.0042)         605           605         -0.11 (0.98)           18         2.1 (1.3)           94         1.27 (0.51)	N         Mean(SD)         N           67         2.0657 (1.1999)         37           90         1.45 (1.05)         71           85         1.15 (0.53)         94           16         1.3 (1.2)         20           31         1.14 (0.56)         28           48         0.79 (0.6)         48           80         -0.2 (0.45)         71           26         0.35 (0.5199)         28           30         1.77 (1.07)         30           67         1.61 (0.51)         66           12         1.4 (0.58)         12           170         -0.78 (0.9)         1.65           51         1.27 (0.58)         42           58         -0.18 (0.58)         59           54         -0.28 (0.77)         54           37         1.25 (0.61)         34           221         1.6 (0.9)         237           1143         1096         23 $P = 0.0042)$ 605         -0.11 (0.98)         605           18         2.1 (1.3)         17           94         1.27 (0.51)         96	N         Mean(SD)         N         Mean(SD)           67         2.0657 (1.1999)         37         2.2 (0.89)         90           90         1.45 (1.05)         71         1.44 (0.81)           85         1.15 (0.53)         94         1.17 (0.72)           16         1.3 (1.2)         20         1.8 (2.24)           31         1.14 (0.56)         28         1.61 (0.76)           48         0.79 (0.6)         48         1.05 (0.6)           80         -0.2 (0.45)         71         0.1 (0.63)           26         0.35 (0.5199)         28         -0.23 (0.98)           30         1.77 (1.07)         30         1.51 (0.9)           67         1.61 (0.51)         66         1.75 (0.78)           12         1.4 (0.58)         12         1.8 (0.57)           51         1.27 (0.58)         42         1.4 (0.7)           58         -0.18 (0.58)         59         -0.04 (0.58)           54         -0.28 (0.77)         54         -0.25 (0.84)           37         1.25 (0.61)         34         1.35 (1.05)           221         1.6 (0.9)         237         1.7 (0.9)           1143         10	N         Mean(SD)         N         Mean(SD)         IV.Random,95% CI           67         2.0657 (1.1999)         37         2.2 (0.89)	N         Mean(SD)         N         Mean(SD)         IVRandom,95% CI           67         2.0657 (1.1999)         37         2.2 (0.89)         2.9 %           90         1.45 (1.05)         71         1.44 (0.81)         4.5 %           85         1.15 (0.53)         94         1.17 (0.72)         6.9 %           16         1.3 (1.2)         20         1.8 (2.24)         0.5 %           31         1.14 (0.56)         28         1.61 (0.76)         3.6 %           48         0.79 (0.6)         48         1.05 (0.6)         5.5 %           80         -0.2 (0.45)         71         0.1 (0.63)         71.1 %           26         0.35 (0.5199)         28         -0.23 (0.98)         2.8 %           30         1.77 (1.07)         30         1.51 (0.9)         2.1 %           12         1.4 (0.58)         12         1.8 (0.55)         2.4 %           170         -0.78 (0.9)         1.65         -0.4 (0.87)         6.7 %           51         1.27 (0.58)         42         1.4 (0.7)         4.9 %           58         -0.18 (0.58)         59         -0.04 (0.58)         2.9 %           221         1.6 (0.9)         237

Favours higher PUFA Favours lower PUFA

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							(
Study or subgroup	Higher PUFA	Lo	wer PUFA		Mean Difference	Weight	Mean Difference
	Ν	Mean(SD)	Ν	Mean(SD)	IV,Random,95% Cl		IV,Random,95% CI
Subtotal (95% CI)	764		766		-	21.2 %	-0.03 [ -0.15, 0.08 ]
Heterogeneity: $Tau^2 = 0.00$	; Chi <sup>2</sup> = 3.94, df =	3 (P = 0.27); I <sup>2</sup> =24	1%				
Test for overall effect: $Z = 0$	0.56 (P = 0.58)						
3 Percentage on statins unc	lear						
Ley 2004 (4)	70	0.07 (1.757)	66	0.03 (0.8936)		2.3 %	0.04 [ -0.42, 0.50 ]
Subtotal (95% CI)	70		66			2.3 %	0.04 [ -0.42, 0.50 ]
Heterogeneity: not applicab	ble						
Test for overall effect: $Z = 0$	0.17 (P = 0.87)						
Total (95% CI)	1977		1928		•	100.0 %	-0.12 [ -0.20, -0.04 ]
Heterogeneity: Tau <sup>2</sup> = 0.02	; Chi <sup>2</sup> = 42.24, df =	= 21 (P = 0.004); l <sup>2</sup>	=50%				
Test for overall effect: $Z = 2$	2.84 (P = 0.0046)						
Test for subgroup difference	es: $Chi^2 = 2.32$ , df	= 2 (P = 0.3 I), $I^2 =$	14%				
				1			
				-0.	5 -0.25 0 0.25	0.5	

Favours higher PUFA Favours lower PUFA

(1) Fernandez-Real 2012, Reus subcohort, 2 year data

(2) Damasceno 2013, Barcelona North subcohort, 1 year data

(3) Barcelona hospital cohort at 5 years, Casas 2016

(4) Change data

#### Analysis 3.51. Comparison 3 Higher PUFA vs lower PUFA - continuous secondary outcomes, Outcome 51 TG, mmoL/L - subgroup by intervention type.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 3 Higher PUFA vs lower PUFA - continuous secondary outcomes

Outcome: 51 TG, mmoL/L - subgroup by intervention type

Weight	Mean Difference		ver PUFA	Lc	Higher PUFA	Study or subgroup
	IV,Random,95% CI	Mean(SD)	Ν	Mean(SD)	Ν	
						I Dietary advice
0.5 %	•	I.8 (2.24) 🗯	20	1.3 (1.2)	16	Dullaart 1992
5.5 %		1.05 (0.6) —	48	0.79 (0.6)	48	Houtsmuller 1979
2.3 %		0.03 (0.8936)	66	0.07 (1.757)	70	Ley 2004 (I)
2.9 %		I.35 (I.05) —	34	1.25 (0.61)	37	Simon 1997
11.1 %	-		168		171	Subtotal (95% CI)
			6	P = 0.63; $P = 0.63$ ; $P = 0.03$	Chi <sup>2</sup> = 1.74, df =	Heterogeneity: $Tau^2 = 0.0;$
					. ,	Test for overall effect: $Z =$
0.0%		0.0E (0.00)	(0E	011 (000)		2 Supplemental foods % die AlphaOmega - ALA
		· · ·				
1.2 %		1.8 (0.7)	17	2.1 (1.3)	18	HERO-Tapsell 2009
4.9 %		1.4 (0.7)	42	1.27 (0.58)	51	PREDIMED 2013 (2)
4.2 %		-0.25 (0.84)	54	-0.28 (0.77)	54	PREDIMED 2013 (3)
6.2 %		-0.04 (0.58)	59	-0.18 (0.58)	58	PREDIMED 2013 (4)
7.9 %		1.23 (0.53)	96	1.27 (0.51)	94	Vijayakumar 2014
33.5 %	-		873		880	Subtotal (95% CI)
			6	5 (P = 0.62); $I^2 = 0.0$	Chi <sup>2</sup> = 3.50, df =	Heterogeneity: $Tau^2 = 0.0;$
					· · · ·	Test for overall effect: $Z =$
2.0.00		2.2 (0.00) <del>+</del>	77		,	3 Supplements (capsules %
		· · ·		· · ·		Brox 2001
6.9 %		1.17 (0.72)	94	1.15 (0.53)	85	Dodin 2005
3.6 %		I.6I (0.76) 🗯	28	1.14 (0.56)	31	HARP- Sacks 1995
7.1 %		0.1 (0.63) -	71	-0.2 (0.45)	I 80	MARINA - Sanders 201
2.1 %		1.51 (0.9)	30	1.77 (1.07)	30	Mita 2007
5.9 %		1.75 (0.78)	66	1.61 (0.51)	67	Nodari 2011 HF
2.4 %	•	I.8 (0.55) 🔶	12	1.4 (0.58)	12	Nye 1990
6.7 %		-0.4 (0.87) +	165	-0.78 (0.9)	170	ORL 2013
	<ul> <li>0.5 %</li> <li>5.5 %</li> <li>2.3 %</li> <li>2.9 %</li> <li>11.1 %</li> <li>9.0 %</li> <li>1.2 %</li> <li>4.9 %</li> <li>4.2 %</li> <li>6.2 %</li> <li>7.9 %</li> <li>33.5 %</li> <li>2.9 %</li> <li>6.9 %</li> <li>3.6 %</li> <li>7.1 %</li> <li>2.1 %</li> <li>5.9 %</li> </ul>	Difference Weight IV,Random,95% CI	Difference     Weight       Mean(SD)     IV,Random,95% CI       I.8 (2.24)     0.5 %       I.05 (0.6)     5.5 %       003 (0.8936)     2.3 %       I.35 (1.05)     2.9 %       I.1.1 %     11.1 %       -0.05 (0.98)     9.0 %       I.8 (0.7)     1.2 %       I.4 (0.7)     4.9 %       -0.25 (0.84)     6.2 %       I.23 (0.53)     7.9 %       33.5 %     33.5 %       2.2 (0.89)     2.9 %       I.17 (0.72)     6.9 %       I.61 (0.76)     3.6 %       0.1 (0.63)     7.1 %       I.51 (0.9)     2.1 %       I.75 (0.78)     5.9 %	N         Mean(SD)         Difference         Weight           20         1.8 (2.24)         0.5 %           48         1.05 (0.6)         5.5 %           66         0.03 (0.8936)         2.3 %           34         1.35 (1.05)         2.9 %           168         11.1 %           605         -0.05 (0.98)         9.0 %           17         1.8 (0.7)         1.2 %           42         1.4 (0.7)         4.9 %           54         -0.25 (0.84)         4.2 %           59         -0.04 (0.58)         6.2 %           96         1.23 (0.53)         7.9 %           873         33.5 % $^{76}$ 3.6 %           71         0.1 (0.63)         7.1 %           30         1.51 (0.9)         2.1 %           66         1.75 (0.78)         5.9 %	Lower PUFA       Difference       Weight         Mean(SD)       N       Mean(SD)       IV,Random,95% CI         1.3 (1.2)       20       1.8 (2.24)       0.5 %         0.79 (0.6)       48       1.05 (0.6)       5.5 %         0.07 (1.757)       66       0.03 (0.8936)       2.3 %         1.25 (0.61)       34       1.35 (1.05)       2.9 %         168       11.1 %       2.9 %         -0.11 (0.98)       605       -0.05 (0.98)       9.0 %         2.1 (1.3)       17       1.8 (0.7)       1.2 %         1.27 (0.58)       42       1.4 (0.7)       4.9 %         -0.18 (0.58)       59       -0.04 (0.58)       6.2 %         1.27 (0.51)       96       1.23 (0.53)       7.9 %         87.3       33.5 %       5 (P = 0.62); I <sup>2</sup> = 0.0%       33.5 %         5 (P = 0.62); I <sup>2</sup> = 0.0%       1.17 (0.72)       6.9 %         1.14 (0.56)       28       1.61 (0.76)       3.6 %         -0.2 (0.45)       71       0.1 (0.63)       7.1 %         1.77 (1.07)       30       1.51 (0.9)       2.1 %         1.61 (0.51)       66       1.75 (0.78)       5.9 %	Higher PUFA       Lower PUFA       Difference       Weight         N       Mean(SD)       N       Mean(SD)       IVRandom,95% CI         16       1.3 (1.2)       20       1.8 (2.24)       0.5 %         48       0.79 (0.6)       48       1.05 (0.6)       55 %         70       0.07 (1.757)       66       0.03 (0.8936)       2.3 %         37       1.25 (0.61)       34       1.35 (1.05)       2.9 % <b>171 168 11.1</b> %         Ch <sup>2</sup> = 0.052)       11 <b>168 11.1</b> %         et provided       605       -0.011 (0.98)       605       -0.05 (0.98)       9.0 %         18       2.1 (1.3)       17       1.8 (0.7)       1.2 %         51       1.27 (0.58)       42       1.4 (0.7)       4.9 %         54       -0.28 (0.77)       54       -0.25 (0.84)       42 %         58       -0.18 (0.58)       59       -0.04 (0.58)       62 %         94       1.27 (0.51)       96       1.23 (0.53)       7.9 % <b>880 87.3 33.5</b> % <b>33.5</b> %         Ch <sup>2</sup> = 0.25 unusual foods)       67       2.0657 (1.1999)       37       2.2 (0.89)

Favours higher PUFA Favours lower PUFA

(Continued ...)

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(... Continued)

Study or subgroup	Higher PUFA	L	ower PUFA		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	Ν	Mean(SD)	IV,Random,95% C	:1	IV,Random,95% CI
WELCOME 2015	47	1.5 (1.2)	48	1.8 (0.6) ←		3.1 %	-0.30 [ -0.68, 0.08 ]
Subtotal (95% CI)	589		551		-	40.6 %	-0.22 [ -0.35, -0.10 ]
Heterogeneity: $Tau^2 = 0.02$	; $Chi^2 = 15.05$ , df	= 8 (P = 0.06); l <sup>2</sup> =	=47%				
Test for overall effect: $Z = 3$	3.47 (P = 0.00052	)					
Any combination							
DIPP-Tokudome 2015	90	1.45 (1.05)	71	1.44 (0.81)		4.5 %	0.01 [ -0.28, 0.30 ]
Mendis 2001	26	0.35 (0.5199)	28	-0.23 (0.98)		2.8 %	0.58 [ 0.17, 0.99 ]
Sydney Diet-Heart 1978	221	1.6 (0.9)	237	1.7 (0.9)		7.4 %	-0.10 [ -0.26, 0.06 ]
Subtotal (95% CI)	337		336			14.7 %	0.12 [ -0.22, 0.46 ]
Heterogeneity: Tau <sup>2</sup> = 0.07	; Chi <sup>2</sup> = 8.94, df =	= 2 (P = 0.01); I <sup>2</sup> =	78%				
Test for overall effect: $Z = 0$	0.68 (P = 0.50)						
Total (95% CI)	1977		1928		•	100.0 %	-0.12 [ -0.20, -0.04 ]
Heterogeneity: Tau <sup>2</sup> = 0.02	; Chi <sup>2</sup> = 42.24, df	= 21 (P = 0.004); I	<sup>2</sup> =50%				
Test for overall effect: $Z = 2$	2.84 (P = 0.0046)						
Fest for subgroup difference	es: $Chi^2 = 8.16$ , df	$r = 3 (P = 0.04), I^2 =$	=63%				
				-0.5	-0.25 0 0.25	0.5	
				Favours hig	gher PUFA Favours	s lower PUFA	

(I) Change data

(2) Fernandez-Real 2012, Reus subcohort, 2 year data

(3) Barcelona hospital cohort at 5 years, Casas 2016

(4) Damasceno 2013, Barcelona North subcohort, I year data

## Analysis 3.52. Comparison 3 Higher PUFA vs lower PUFA - continuous secondary outcomes, Outcome 52 Serum HIGH DENSITY LIPOPROTEIN (HDL, mmoL/L).

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 3 Higher PUFA vs lower PUFA - continuous secondary outcomes

Outcome: 52 Serum HIGH DENSITY LIPOPROTEIN (HDL, mmoL/L)

Study or subgroup	Higher PUFA N	Mean(SD)	Lower PUFA N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Ahn 2016	38	1.19 (0.31)	36	1.14 (0.33)		- 1.2 %	0.05 [ -0.10, 0.20 ]
AlphaOmega - ALA	605	0.13 (0.25)	605	0.15 (0.25)		33.2 %	-0.02 [ -0.05, 0.01 ]
Brox 2001	67	1.3448 (0.3596)	37	1.3 (0.3)		1.6 %	0.04 [ -0.08, 0.17 ]
DART fat 1989	855	1.04 (0.29)	860	1.05 (0.28)		36.2 %	-0.01 [ -0.04, 0.02 ]
DIPP-Tokudome 2015	89	1.43 (0.36)	73	1.46 (0.33)		2.3 %	-0.03 [ -0.14, 0.08 ]
Dodin 2005	85	1.68 (0.35)	94	1.77 (0.38)		2.3 %	-0.09 [ -0.20, 0.02 ]
Dullaart 1992	16	1.28 (0.37)	20	1.29 (0.37)	•	→ 0.4 %	-0.01 [ -0.25, 0.23 ]
HARP- Sacks 1995	31	1.09 (0.28)	28	1.09 (0.34)		1.0 %	0.0 [ -0.16, 0.16 ]
HERO-Tapsell 2009	18	1.5 (0.4)	17	1.4 (0.4)		→ 0.4 %	0.10 [ -0.17, 0.37 ]
Ley 2004 (I)	70	0.01 (0.4183)	66	-0.02 (0.1625)	·	2.4 %	0.03 [ -0.08, 0.14 ]
MARINA - Sanders 2011	80	0 (0.45)	71	0 (0.21)		2.2 %	0.0 [ -0.11, 0.11 ]
Mendis 2001	26	0.26 (0.1981)	28	0.27 (0.2063)		2.3 %	-0.01 [ -0.12, 0.10 ]
Mita 2007	30	1.51 (0.59)	30	1.44 (0.37)		→ 0.4 %	0.07 [ -0.18, 0.32 ]
Nye 1990	12	1.38 (0.43)	12	1.45 (0.38)	• • •	→ 0.2 %	-0.07 [ -0.39, 0.25 ]
PREDIMED 2013 (2)	54	0.19 (0.37)	54	0.11 (0.38)		→ I.3 %	0.08 [ -0.06, 0.22 ]
PREDIMED 2013 (3)	51	1.33 (0.29)	42	1.33 (0.38)		1.3 %	0.0 [ -0.14, 0.14 ]
PREDIMED 2013 (4)	58	0.05 (0.2)	59	0.02 (0.17)		5.8 %	0.03 [ -0.04, 0.10 ]
Simon 1997	38	1.56 (0.55)	34	1.44 (0.58)		→ 0.4 %	0.12 [ -0.14, 0.38 ]
Vijayakumar 2014	94	1.15 (0.42)	96	1.12 (0.28)		2.5 %	0.03 [ -0.07, 0.13 ]
WELCOME 2015	47	1.1 (0.3)	48	1.1 (0.2)		2.5 %	0.0 [ -0.10, 0.10 ]
Total (95% CI)	2364		2310		•	100.0 %	-0.01 [ -0.02, 0.01 ]
Heterogeneity: $Tau^2 = 0.0$ ; C Test for overall effect: $Z = 0.4$ Test for subgroup differences	BI (P = 0.42)	~ /	2 =0.0%				
					.		
					).2 -0.1 0 0.1 higher PUFA Favours lov	0.2	
				i avoul s			

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- (I) Change data
- (2) Barcelona hospital cohort at 5 years, Casa 2016
- (3) Fernandez-Real 2012, Reus subcohort, 2 year data
- (4) Damasceno 2013, Barcelona North subcohort, I year data

## Analysis 3.53. Comparison 3 Higher PUFA vs lower PUFA - continuous secondary outcomes, Outcome 53 HDL, mmoL/L - SA.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 3 Higher PUFA vs lower PUFA - continuous secondary outcomes

Outcome: 53 HDL, mmoL/L - SA

Study or subgroup	Higher PUFA N	Mean(SD)	Lower PUFA N	Mean(SD)	Mean Difference IV,Random,95%	Weight	Mean Difference IV,Random,95% CI
I Low risk of bias for allocati	ion concealment						
Ahn 2016	38	1.19 (0.31)	36	1.14 (0.33)		2.7 %	0.05 [ -0.10, 0.20 ]
AlphaOmega - ALA	605	0.13 (0.25)	605	0.15 (0.25)	-	72.5 %	-0.02 [ -0.05, 0.01 ]
Brox 2001	67	1.345 (0.36)	37	1.3 (0.3)		3.4 %	0.04 [ -0.08, 0.17 ]
DIPP-Tokudome 2015	89	1.43 (0.36)	73	1.46 (0.33)		5.1 %	-0.03 [ -0.14, 0.08 ]
Dullaart 1992	16	1.28 (0.37)	20	1.29 (0.37)	•	1.0 %	-0.01 [ -0.25, 0.23 ]
Ley 2004 (I)	70	0.01 (0.4183)	66	-0.02 (0.1625)		- 5.2 %	0.03 [ -0.08, 0.14 ]
MARINA - Sanders 2011	80	0 (0.45)	71	0 (0.21)		4.7 %	0.0 [ -0.11, 0.11 ]
WELCOME 2015	47	1.1 (0.3)	48	1.1 (0.2)		5.4 %	0.0 [ -0.10, 0.10 ]
Subtotal (95% CI)	1012		956		•	100.0 %	-0.01 [ -0.04, 0.01 ]
Heterogeneity: $Tau^2 = 0.0$ ; C	$Chi^2 = 2.56, df =$	7 (P = 0.92); I <sup>2</sup>	=0.0%				
Test for overall effect: $Z = 0$ .	.95 (P = 0.34)						
2 Low risk of bias for attention	on						
AlphaOmega - ALA	605	0.13 (0.25)	605	0.15 (0.25)		55.8 %	-0.02 [ -0.05, 0.01 ]
Brox 2001	67	1.345 (0.36)	37	1.3 (0.3)		2.6 %	0.04 [ -0.08, 0.17 ]
DIPP-Tokudome 2015	89	1.43 (0.36)	73	1.46 (0.33)		3.9 %	-0.03 [ -0.14, 0.08 ]
Dodin 2005	85	1.68 (0.35)	94	1.77 (0.38)		3.9 %	-0.09 [ -0.20, 0.02 ]
HARP- Sacks 1995	31	1.09 (0.28)	28	1.09 (0.34)		1.7 %	0.0 [ -0.16, 0.16 ]
					0.2 -0.1 0 0.1 s higher PUFA Favou	I 0.2 urs lower PUFA	

(Continued . . . )

Study or subgroup	Higher PUFA		Lower PUFA		Mean Difference	Weight	( Continue Mea Differenc
Study of subgroup	N	Mean(SD)	N	Mean(SD)	IV,Random,95% Cl	V Velgili	IV,Random,95% (
HERO-Tapsell 2009	18	1.5 (0.4)	17	1.4 (0.4)		• 0.6 %	0.10 [ -0.17, 0.37
MARINA - Sanders 2011	80	0 (0.45)	71	0 (0.21)		3.7 %	0.0 [ -0.11, 0.11
Mendis 2001	26	0.26 (0.1981)	28	0.27 (0.2063)		3.8 %	-0.01 [ -0.12, 0.10
Mita 2007	30	1.51 (0.59)	30	1.44 (0.37)		• 0.7 %	0.07 [ -0.18, 0.32
Nye 1990	12	1.38 (0.43)	12	1.45 (0.38)	• • •	• 0.4 %	-0.07 [ -0.39, 0.25
PREDIMED 2013 (2)	58	0.05 (0.2)	59	0.02 (0.17)		9.8 %	0.03 [ -0.04, 0.10
PREDIMED 2013 (3)	51	1.33 (0.29)	42	1.33 (0.38)		2.3 %	0.0 [ -0.14, 0.14
PREDIMED 2013 (4)	54	0.19 (0.37)	54	0.11 (0.38)		• 2.2 %	0.08 [ -0.06, 0.22
Vijayakumar 2014	94	1.15 (0.42)	96	1.12 (0.28)		4.3 %	0.03 [ -0.07, 0.13
WELCOME 2015	47	1.1 (0.3)	48	1.1 (0.2)		4.2 %	0.0 [ -0.10, 0.10
<b>Subtotal (95% CI)</b> Heterogeneity: Tau <sup>2</sup> = 0.0; CP Test for overall effect: Z = 0.7 Low risk of bias for complia	6 (P = 0.45)	14 (P = 0.88);	<b>1294</b> 1 <sup>2</sup> =0.0%		•	100.0 %	-0.01 [ -0.03, 0.01
Ahn 2016	38	1.19 (0.31)	36	1.14 (0.33)		- 2.6 %	0.05 [ -0.10, 0.20
Brox 2001	67	1.345 (0.36)	37	1.3 (0.3)		3.3 %	0.04 [ -0.08, 0.17
DART fat 1989	855	1.04 (0.29)	860	1.05 (0.28)	-	76.6 %	-0.01 [ -0.04, 0.02
Dullaart 1992	16	1.28 (0.37)	20	1.29 (0.37)		• 0.9 %	-0.01 [ -0.25, 0.23
Ley 2004 (5)	70	0.01 (0.4183)	66	-0.02 (0.1625)		5.0 %	0.03 [ -0.08, 0.14
Mita 2007	30	1.51 (0.59)	30	1.44 (0.37)		• 0.9 %	0.07 [ -0.18, 0.32
Vijayakumar 2014	94	1.15 (0.42)	96	1.12 (0.28)		5.4 %	0.03 [ -0.07, 0.13
WELCOME 2015	47	1.1 (0.3)	48	1.1 (0.2)		5.3 %	0.0 [ -0.10, 0.10
<b>Subtotal (95% CI)</b> Heterogeneity: Tau <sup>2</sup> = 0.0; CP Test for overall effect: Z = 0.1 Low summary risk of bias AlphaOmega - ALA		7 (P = 0.94); I <sup>2</sup> 0.13 (0.25)	<b>1193</b> =0.0%	0.15 (0.25)	•	<b>100.0 %</b> 82.5 %	<b>0.00 [ -0.02, 0.02</b>
Ley 2004 (6)		0.01 (0.4183)		-0.02 (0.1625)		5.9 %	0.03 [ -0.08, 0.14
MARINA - Sanders 2011	80	0 (0.45)	71	0 (0.21)		5.4 %	0.0 [ -0.1 1, 0.1 1
WELCOME 2015	47	1.1 (0.3)	48	1.1 (0.2)		6.2 %	0.0 [ -0.10, 0.10
<b>Subtotal (95% CI)</b> leterogeneity: Tau <sup>2</sup> = 0.0; Ch est for overall effect: $Z = 1.1$	<b>802</b> hi <sup>2</sup> = 0.97, df =		790	. ()	-		-0.01 [ -0.04, 0.01

Mea Difference	Weight	Mean Difference		Lower PUFA		Higher PUFA	Study or subgroup
IV,Random,95% ( -0.02 [ -0.05, 0.01	34.5 %	IV,Random,95% Cl	Mean(SD) 0.15 (0.25)	N 605	Mean(SD) 0.13 (0.25)	N 605	AlphaOmega - ALA
0.04 [ -0.08, 0.17	1.6 %		1.3 (0.3)	37	1.345 (0.36)	67	Brox 2001
-0.01 [ -0.04, 0.02	37.6 %		1.05 (0.28)	860	1.04 (0.29)	855	DART fat 1989
-0.03 [ -0.14, 0.08	2.4 %		. ,	73	. ,	89	DIPP-Tokudome 2015
-			1.46 (0.33)		1.43 (0.36)		
-0.09 [ -0.20, 0.02	2.4 %		1.77 (0.38) -	94	1.68 (0.35)	85	Dodin 2005
-0.01 [ -0.25, 0.23	0.5 %		1.29 (0.37)	20	1.28 (0.37)	16	Dullaart 1992
0.0 [ -0.16, 0.16	1.1 %		1.09 (0.34)	28	1.09 (0.28)	31	HARP- Sacks 1995
0.10 [ -0.17, 0.37	0.4 %		1.4 (0.4)	17	1.5 (0.4)	18	HERO-Tapsell 2009
0.03 [ -0.08, 0.14	2.5 %		-0.02 (0.1625)	66	0.01 (0.4183)	70	Ley 2004 (7)
0.0 [ -0.11, 0.11	2.3 %		0 (0.21)	71	0 (0.45)	80	MARINA - Sanders 2011
-0.01 [ -0.12, 0.10	2.4 %		0.27 (0.2063)	28	0.26 (0.1981)	26	Mendis 2001
0.07 [ -0.18, 0.32	0.4 %		1.44 (0.37)	30	1.51 (0.59)	30	Mita 2007
-0.07 [ -0.39, 0.25	0.3 %		I.45 (0.38) 🔶	12	1.38 (0.43)	12	Nye 1990
0.08 [ -0.06, 0.22	1.4 %		0.11 (0.38)	54	0.19 (0.37)	54	PREDIMED 2013 (8)
0.0 [ -0.14, 0.14	1.4 %		1.33 (0.38)	42	1.33 (0.29)	51	PREDIMED 2013 (9)
0.03 [ -0.04, 0.10	6.0 %		0.02 (0.17)	59	0.05 (0.2)	58	PREDIMED 2013 (10)
0.12 [ -0.14, 0.38	0.4 %		1.44 (0.58)	34	1.56 (0.55)	38	Simon 1997
0.0 [ -0.10, 0.10	2.6 %		1.1 (0.2)	48	1.1 (0.3)	47	WELCOME 2015
-0.01 [ -0.02, 0.01	100.0 %	•		<b>2178</b> <sup>2</sup> =0.0%	17 (P = 0.94); I		Subtotal (95% CI)         Heterogeneity: Tau <sup>2</sup> = 0.0; C         Fest for overall effect: Z = 1.         No industry funding
0.05 [ -0.10, 0.20	10.0 %		1.14 (0.33)	36	1.19 (0.31)	38	Ahn 2016
0.04 [ -0.08, 0.17	12.7 %		1.3 (0.3)	37	1.345 (0.36)	67	Brox 2001
-0.03 [ -0.14, 0.08	18.8 %		1.46 (0.33)	73	1.43 (0.36)	89	DIPP-Tokudome 2015
-0.01 [ -0.25, 0.23	3.6 %		I.29 (0.37) 🕇	20	1.28 (0.37)	16	Dullaart 1992
0.03 [ -0.08, 0.14	19.1 %		-0.02 (0.1625)	66	0.01 (0.4183)	70	Ley 2004 (11)
0.0 [ -0.11, 0.11	17.6 %		0 (0.21)	71	0 (0.45)	80	MARINA - Sanders 2011
-0.01 [ -0.12, 0.10	18.3 %		0.27 (0.2063)	28	0.26 (0.1981)	26	Mendis 2001
0.01 [ -0.04, 0.05	100.0 %	-		<b>331</b> =0.0%	6 (P = 0.96); I <sup>2</sup>	37 (P = 0.71)	<b>Subtotal (95% CI)</b> Heterogeneity: Tau <sup>2</sup> = 0.0; C est for overall effect: Z = 0. Randomised 100+ particip

(Continued . . . )

N 605 67 855	Mean(SD) 0.13 (0.25) 1.345 (0.36)	N 605	Mean(SD) 0.15 (0.25)	IV,Random,95% CI	35.3 %	IV,Random,95% CI
	1.345 (0.36)				JJ.J /0	-0.02 [ -0.05, 0.01 ]
855	()	37	1.3 (0.3)		1.7 %	0.04 [ -0.08, 0.17 ]
	1.04 (0.29)	860	1.05 (0.28)	-	38.5 %	-0.01 [ -0.04, 0.02 ]
89	1.43 (0.36)	73	1.46 (0.33)		2.5 %	-0.03 [ -0.14, 0.08 ]
85	1.68 (0.35)	94	I.77 (0.38)		2.4 %	-0.09 [ -0.20, 0.02 ]
70	0.01 (0.4183)	66	-0.02 (0.1625)		2.5 %	0.03 [ -0.08, 0.14 ]
80	0 (0.45)	71	0 (0.21)		2.3 %	0.0 [ -0.11, 0.11 ]
54	0.19 (0.37)	54	0.11 (0.38)		→ I.4 %	0.08 [ -0.06, 0.22 ]
51	1.33 (0.29)	42	1.33 (0.38)		1.4 %	0.0 [ -0.14, 0.14 ]
58	0.05 (0.2)	59	0.02 (0.17)		6.2 %	0.03 [ -0.04, 0.10 ]
38	1.56 (0.55)	34	1.44 (0.58)		→ 0.4 %	0.12 [ -0.14, 0.38
94	1.15 (0.42)	96	1.12 (0.28)		2.7 %	0.03 [ -0.07, 0.13 ]
47	1.1 (0.3)	48	1.1 (0.2)		2.7 %	0.0 [ -0.10, 0.10 ]
2193		2139		•	100.0 %	-0.01 [ -0.02, 0.01 ]
	12 (P = 0.74); 0.13 (0.25)	l <sup>2</sup> =0.0% 605	0.15 (0.25)		41.5 %	-0.02 [ -0.05, 0.01 ]
855	1.04 (0.29)	860	1.05 (0.28)	-	45.2 %	-0.01 [ -0.04, 0.02 ]
80	0 (0.45)	71	0 (0.21)		2.7 %	0.0 [ -0.11, 0.11]
58	0.05 (0.2)	59	0.02 (0.17)		7.3 %	0.03 [ -0.04, 0.10 ]
54	0.19 (0.37)	54	0.11 (0.38)		→ I.6 %	0.08 [ -0.06, 0.22 ]
51	1.33 (0.29)	42	1.33 (0.38)		1.7 %	0.0 [ -0.14, 0.14 ]
4, df =	5 (P = 0.63); I <sup>2</sup>	<b>1691</b> ==0.0%		•	100.0 %	-0.01 [ -0.03, 0.01 ]
	70 80 54 51 58 38 94 47 <b>2193</b> 0.0, df = 0.34) 605 855 80 58 54 51 <b>1703</b>	70 $0.01$ $(0.4183)$ 80       0 $(0.45)$ 54 $0.19$ $(0.37)$ 51 $1.33$ $(0.29)$ 58 $0.05$ $(0.2)$ 38 $1.56$ $(0.55)$ 94 $1.15$ $(0.42)$ 47 $1.1$ $(0.3)$ 2193 $0.04f = 12$ $(P = 0.74)$ ; $1$ $0.04f = 12$ $(P = 0.74)$ ; $1$ $0.34$ $0.13$ $(0.25)$ 855 $1.04$ $(0.29)$ 80 $0$ $(0.45)$ 58 $0.05$ $(0.2)$ 54 $0.19$ $(0.37)$ 51 $1.33$ $(0.29)$ 14, df = 5 $(P = 0.63)$ ; $1^2$	70 $0.01$ $(0.4183)$ 66         80       0 $(0.45)$ 71         54 $0.19$ $(0.37)$ 54         51 $1.33$ $(0.29)$ 42         58 $0.05$ $(0.2)$ 59         38 $1.56$ $(0.55)$ 34         94 $1.15$ $(0.42)$ 96         47 $1.1$ $(0.3)$ 48 <b>2193 2139 2139</b> $0.df = 12$ $(P = 0.74)$ ; $I^2 = 0.0\%$ 234)         605 $0.13$ $(0.25)$ 605         855 $1.04$ $(0.29)$ 860         80 $0$ $(0.45)$ 71         58 $0.05$ $0.2$ 59         54 $0.19$ $0.37$ 54         51 $1.33$ $0.29$ 42         4703 $1691$ $4.4$ $4f = 5$	70       0.01 $(0.4183)$ 66 $-0.02$ $(0.1625)$ 80       0 $(0.45)$ 71       0 $(0.21)$ 54       0.19 $(0.37)$ 54       0.11 $(0.38)$ 51       1.33 $(0.29)$ 42       1.33 $(0.38)$ 58       0.05 $(0.2)$ 59 $0.02$ $(0.17)$ 38       1.56 $(0.55)$ 34       1.44 $(0.58)$ 94       1.15 $(0.42)$ 96       1.12 $(0.28)$ 47       1.1 $(0.3)$ 48       1.1 $(0.2)$ 2193       2139       2139 $0.04 = 12$ $(P = 0.74)$ ; $P = 0.0\%$ 0.0 df = 12 $(P = 0.74)$ ; $P = 0.0\%$ $860$ $1.05$ $(0.28)$ 80       0 $(0.45)$ 71 $0$ $(0.21)$ 58 $0.05$ $0.2$ $59$ $0.02$ $(0.17)$ 54 $0.19$ $(0.37)$ $54$ $0.111$ $(0.38)$ 51 $1.33$ $(0.29)$ $42$ $1.33$ $(0.38)$	$70 \ 0.01 \ (0.4183)$ $66 \ -0.02 \ (0.1625)$ $80 \ 0 \ (0.45)$ $71 \ 0 \ (0.21)$ $54 \ 0.19 \ (0.37)$ $54 \ 0.11 \ (0.38)$ $51 \ 1.33 \ (0.29)$ $42 \ 1.33 \ (0.38)$ $58 \ 0.05 \ (0.2)$ $59 \ 0.02 \ (0.17)$ $38 \ 1.56 \ (0.55)$ $34 \ 1.44 \ (0.58)$ $94 \ 1.15 \ (0.42)$ $96 \ 1.12 \ (0.28)$ $47 \ 1.1 \ (0.3)$ $48 \ 1.1 \ (0.2)$ $2193 \ 2139$ $0.0df = 12 \ (P = 0.74); \ I^2 = 0.0\%$ $0.df = 12 \ (P = 0.74); \ I^2 = 0.0\%$ $80 \ 0 \ (0.45)$ $71 \ 0 \ (0.21)$ $80 \ 0 \ (0.45)$ $71 \ 0 \ (0.21)$ $58 \ 0.05 \ (0.2)$ $59 \ 0.02 \ (0.17)$ $80 \ 0 \ (0.45)$ $71 \ 0 \ (0.21)$ $58 \ 0.05 \ (0.2)$ $59 \ 0.02 \ (0.17)$ $54 \ 0.19 \ (0.37)$ $54 \ 0.11 \ (0.38)$ $51 \ 1.33 \ (0.29)$ $42 \ 1.33 \ (0.38)$ $51 \ 1.33 \ (0.29)$ $42 \ 1.33 \ (0.38)$	70 $0.01 (0.4183)$ $66 -0.02 (0.1625)$ 2.5 %         80 $0 (0.45)$ 71 $0 (0.21)$ 2.3 %         54 $0.19 (0.37)$ 54 $0.11 (0.38)$ 1.4 %         51 $1.33 (0.29)$ 42 $1.33 (0.38)$ 1.4 %         58 $0.05 (0.2)$ 59 $0.02 (0.17)$ 62 %         38 $1.56 (0.55)$ 34 $1.44 (0.58)$ 0.4 %         94 $1.15 (0.42)$ 96 $1.12 (0.28)$ 2.7 %         47 $1.1 (0.3)$ 48 $1.1 (0.2)$ 2.7 %         2193       2139       100.0 %       0.0 df = 12 (P = 0.74); l <sup>2</sup> = 0.0%       41.5 %         855 $1.04 (0.29)$ $860$ $1.05 (0.28)$ 452 %         80 $0 (0.45)$ 71 $0 (0.21)$ 2.7 %         58 $0.05 (0.2)$ 59 $0.02 (0.17)$ 7.3 %         54 $0.19 (0.37)$ 54 $0.11 (0.38)$ 1.6 %         51 $1.33 (0.29)$ 42 $1.33 (0.38)$ 1.7 %         1703       1691       41691       100.0 %       4100.0 %

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(I) Change data

- (2) Damasceno 2013, Barcelona North subcohort, I year data
- (3) Fernandez-Real 2012, Reus subcohort, 2 year data
- (4) Barcelona hospital cohort at 5 years, Casa 2016
- (5) Change data
- (6) Change data
- (7) Change data
- (8) Barcelona hospital cohort at 5 years, Casa 2016
- (9) Fernandez-Real 2012, Reus subcohort, 2 year data
- (10) Damasceno 2013, Barcelona North subcohort, 1 year data
- (11) Change data
- (12) Change data
- (13) Barcelona hospital cohort at 5 years, Casa 2016
- (14) Fernandez-Real 2012, Reus subcohort, 2 year data
- (15) Damasceno 2013, Barcelona North subcohort, 1 year data
- (16) Damasceno 2013, Barcelona North subcohort, 1 year data
- (17) Barcelona hospital cohort at 5 years, Casa 2016
- (18) Fernandez-Real 2012, Reus subcohort, 2 year data

# Analysis 3.54. Comparison 3 Higher PUFA vs lower PUFA - continuous secondary outcomes, Outcome 54 HDL, mmoL/L - SA fixed-effect.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 3 Higher PUFA vs lower PUFA - continuous secondary outcomes

Outcome: 54 HDL, mmoL/L - SA fixed-effect

Mea Different IV,Fixed,95% (	Weight	Mean Difference IV,Fixed,95% Cl	Mean(SD)	Lower PUFA N	Mean(SD)	Higher PUFA N	Study or subgroup
0.05 [ -0.10, 0.20	1.2 %		1.14 (0.33)	36	1.19 (0.31)	38	Ahn 2016
-0.02 [ -0.05, 0.01	33.2 %		0.15 (0.25)	605	0.13 (0.25)	605	AlphaOmega - ALA
0.04 [ -0.08, 0.17	1.6 %		1.3 (0.3)	37	1.345 (0.36)	67	Brox 2001
-0.01 [ -0.04, 0.02	36.2 %	-	1.05 (0.28)	860	1.04 (0.29)	855	DART fat 1989
-0.03 [ -0.14, 0.08	2.3 %		1.46 (0.33)	73	1.43 (0.36)	89	DIPP-Tokudome 2015
-0.09 [ -0.20, 0.02	2.3 %		I.77 (0.38) <sup>–</sup>	94	1.68 (0.35)	85	Dodin 2005
-0.01 [ -0.25, 0.23	0.4 %	•	1.29 (0.37)	20	1.28 (0.37)	16	Dullaart 1992
0.0 [ -0.16, 0.16	1.0 %		1.09 (0.34)	28	1.09 (0.28)	31	HARP- Sacks 1995
0.10 [ -0.17, 0.37	0.4 %		1.4 (0.4)	17	1.5 (0.4)	18	HERO-Tapsell 2009
0.03 [ -0.08, 0.14	2.4 %		-0.02 (0.1625)	66	0.01 (0.4183)	70	Ley 2004 (I)
0.0 [ -0.11, 0.11	2.2 %		0 (0.21)	71	0 (0.45)	80	MARINA - Sanders 2011
-0.01 [ -0.12, 0.10	2.3 %		0.27 (0.2063)	28	0.26 (0.1981)	26	Mendis 2001
0.07 [ -0.18, 0.32	0.4 %	· ·	1.44 (0.37)	30	1.51 (0.59)	30	Mita 2007
-0.07 [ -0.39, 0.25	0.2 %		I.45 (0.38) 🕇	12	1.38 (0.43)	12	Nye 1990
0.08 [ -0.06, 0.22	1.3 %		0.11 (0.38)	54	0.19 (0.37)	54	PREDIMED 2013 (2)
0.0 [ -0.14, 0.14	1.3 %		1.33 (0.38)	42	1.33 (0.29)	51	PREDIMED 2013 (3)
0.03 [ -0.04, 0.10	5.8 %		0.02 (0.17)	59	0.05 (0.2)	58	PREDIMED 2013 (4)
0.12 [ -0.14, 0.38	0.4 %		1.44 (0.58)	34	1.56 (0.55)	38	Simon 1997
0.03 [ -0.07, 0.13	2.5 %		1.12 (0.28)	96	1.15 (0.42)	94	Vijayakumar 2014
0.0 [ -0.10, 0.10	2.5 %		1.1 (0.2)	48	1.1 (0.3)	47	WELCOME 2015
-0.01 [ -0.02, 0.01	100.0 %	•		2310		2364	Total (95% CI)
					<i>y.</i>	81 (P = 0.42)	Heterogeneity: $Chi^2 = 10.25$ Fest for overall effect: $Z = 0$ . Fest for subgroup differences

- (I) Change data
- (2) Barcelona hospital cohort at 5 years, Casa 2016
- (3) Fernandez-Real 2012, Reus subcohort, 2 year data
- (4) Damasceno 2013, Barcelona North subcohort, I year data

#### Analysis 3.55. Comparison 3 Higher PUFA vs lower PUFA - continuous secondary outcomes, Outcome 55 HDL, mmoL/L - subgroup by PUFA dose.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 3 Higher PUFA vs lower PUFA - continuous secondary outcomes

Outcome: 55 HDL, mmoL/L - subgroup by PUFA dose

Study or subgroup	Higher PUFA		Lower PUFA		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	Ν	Mean(SD)	IV,Random,95% CI		IV,Random,95% CI
total PUFA < 1.0% E							
Ley 2004 (I)	70	0.01 (0.4183)	66	-0.02 (0.1625)		2.4 %	0.03 [ -0.08, 0.14 ]
MARINA - Sanders 2011	80	0 (0.45)	71	0 (0.21)		2.2 %	0.0 [ -0.11, 0.11 ]
Mita 2007	30	1.51 (0.59)	30	1.44 (0.37)		• 0.4 %	0.07 [ -0.18, 0.32 ]
Subtotal (95% CI)	180		167		-	5.0 %	0.02 [ -0.05, 0.09 ]
Heterogeneity: $Tau^2 = 0.0$ ; (	Chi <sup>2</sup> = 0.32, df =	2 (P = 0.85); l <sup>2</sup>	=0.0%				
Test for overall effect: $Z = 0$	.55 (P = 0.59)						
2 total PUFA 1.0 to $< 2.0\%$	E						
Ahn 2016	38	1.19 (0.31)	36	1.14 (0.33)	· · · · ·	- 1.2 %	0.05 [ -0.10, 0.20 ]
AlphaOmega - ALA	605	0.13 (0.25)	605	0.15 (0.25)		33.2 %	-0.02 [ -0.05, 0.01 ]
Brox 2001	67	1.345 (0.36)	37	1.3 (0.3)		1.6 %	0.04 [ -0.08, 0.17 ]
DIPP-Tokudome 2015	89	1.43 (0.36)	73	1.46 (0.33)		2.3 %	-0.03 [ -0.14, 0.08 ]
Dodin 2005	85	1.68 (0.35)	94	1.77 (0.38)		2.3 %	-0.09 [ -0.20, 0.02 ]
Nye 1990	12	1.38 (0.43)	12	1.45 (0.38)		• 0.2 %	-0.07 [ -0.39, 0.25 ]
PREDIMED 2013 (2)	54	0.19 (0.37)	54	0.11 (0.38)		• 1.3 %	0.08 [ -0.06, 0.22 ]
PREDIMED 2013 (3)	51	1.33 (0.29)	42	1.33 (0.38)		1.3 %	0.0 [ -0.14, 0.14 ]
PREDIMED 2013 (4)	58	0.05 (0.2)	59	0.02 (0.17)	<b>=</b>	5.8 %	0.03 [ -0.04, 0.10 ]
					<u> </u>	1	
				-	0.2 -0.1 0 0.1 0	0.2	
				Favours	higher PUFA Favours low	er PUFA	

(Continued  $\dots$ )

(... Continued)

Study or subgroup	Higher PUFA		Lower PUFA		Mean Difference	Weight	Mean Difference
	Ν	Mean(SD)	Ν	Mean(SD)	IV,Random,95% CI		IV,Random,95% CI
WELCOME 2015	47	1.1 (0.3)	48	1.1 (0.2)		2.5 %	0.0 [ -0.10, 0.10 ]
Subtotal (95% CI)	1106		1060		•	51.8 %	-0.01 [ -0.03, 0.01 ]
Heterogeneity: $Tau^2 = 0.0;$	Chi <sup>2</sup> = 7.21, df =	9 (P = 0.62); I <sup>2</sup>	=0.0%				
Test for overall effect: $Z =$	0.92 (P = 0.36)						
3 total PUFA 2.0 to < 5.0%	Ε						
DART fat 1989	855	1.04 (0.29)	860	1.05 (0.28)	-	36.2 %	-0.01 [ -0.04, 0.02 ]
Dullaart 1992	16	1.28 (0.37)	20	I.29 (0.37) 🕇	•	• 0.4 %	-0.01 [ -0.25, 0.23 ]
HARP- Sacks 1995	31	1.09 (0.28)	28	1.09 (0.34)		1.0 %	0.0 [ -0.16, 0.16 ]
Mendis 2001	26	0.26 (0.1981)	28	0.27 (0.2063)		2.3 %	-0.01 [ -0.12, 0.10 ]
Subtotal (95% CI)	928		936		•	<b>39.9</b> %	-0.01 [ -0.04, 0.02 ]
Heterogeneity: $Tau^2 = 0.0$ ;							. , ,
Therefogeneity. Tau $-0.0$ ,	$Chi^2 = 0.01, df =$	$3 (P = 1.00); I^2$	=0.0%				
Test for overall effect: $Z = 1$		$3 (P = 1.00); I^2$	=0.0%				
σ,		3 (P = 1.00); I <sup>2</sup>	=0.0%				
Test for overall effect: $Z =$		1.5 (0.4)	=0.0%	1.4 (0.4)		• 0.4 %	0.10 [ -0.17, 0.37 ]
Test for overall effect: Z = 4 total PUFA 5.0+% E	0.74 (P = 0.46)			I.4 (0.4) I.44 (0.58)		+ 0.4 % + 0.4 %	
Test for overall effect: Z = 4 4 total PUFA 5.0+% E HERO-Tapsell 2009	0.74 (P = 0.46)	1.5 (0.4)	17				0.12 [ -0.14, 0.38 ]
Test for overall effect: Z = 4 4 total PUFA 5.0+% E HERO-Tapsell 2009 Simon 1997	0.74 (P = 0.46) 18 38	I.5 (0.4) I.56 (0.55)	17 34	1.44 (0.58)		• 0.4 %	0.12 [ -0.14, 0.38 ] 0.03 [ -0.07, 0.13 ]
Test for overall effect: Z = 4 4 total PUFA 5.0+% E HERO-Tapsell 2009 Simon 1997 Vijayakumar 2014	0.74 (P = 0.46) 18 38 94 <b>150</b>	I.5 (0.4) I.56 (0.55) I.15 (0.42)	17 34 96 <b>147</b>	1.44 (0.58)		• 0.4 % 2.5 %	0.12 [ -0.14, 0.38 ] 0.03 [ -0.07, 0.13 ]
Test for overall effect: Z = 4 4 total PUFA 5.0+% E HERO-Tapsell 2009 Simon 1997 Vijayakumar 2014 Subtotal (95% CI)	0.74 (P = 0.46) 18 38 94 <b>150</b> Chi <sup>2</sup> = 0.56, df =	I.5 (0.4) I.56 (0.55) I.15 (0.42)	17 34 96 <b>147</b>	1.44 (0.58)		• 0.4 % 2.5 %	0.12 [ -0.14, 0.38 ] 0.03 [ -0.07, 0.13 ]
Test for overall effect: Z = 4 4 total PUFA 5.0+% E HERO-Tapsell 2009 Simon 1997 Vijayakumar 2014 <b>Subtotal (95% CI)</b> Heterogeneity: Tau <sup>2</sup> = 0.0;	0.74 (P = 0.46) 18 38 94 <b>150</b> Chi <sup>2</sup> = 0.56, df =	I.5 (0.4) I.56 (0.55) I.15 (0.42)	17 34 96 <b>147</b>	1.44 (0.58)		<ul> <li>0.4 %</li> <li>2.5 %</li> <li>3.3 %</li> </ul>	0.12 [ -0.14, 0.38 ] 0.03 [ -0.07, 0.13 ] 0.05 [ -0.04, 0.14 ]
Test for overall effect: Z = 4 4 total PUFA 5.0+% E HERO-Tapsell 2009 Simon 1997 Vijayakumar 2014 <b>Subtotal (95% CI)</b> Heterogeneity: Tau <sup>2</sup> = 0.0; Test for overall effect: Z =	0.74 (P = 0.46) 18 38 94 <b>150</b> Chi <sup>2</sup> = 0.56, df = 1.06 (P = 0.29) <b>2364</b>	1.5 (0.4) 1.56 (0.55) 1.15 (0.42) 2 (P = 0.76); I <sup>2</sup>	17 34 96 147 =0.0% 2310	1.44 (0.58)		<ul> <li>0.4 %</li> <li>2.5 %</li> <li>3.3 %</li> </ul>	0.12 [ -0.14, 0.38 ] 0.03 [ -0.07, 0.13 ] 0.05 [ -0.04, 0.14 ]
Test for overall effect: Z = 4 4 total PUFA 5.0+% E HERO-Tapsell 2009 Simon 1997 Vijayakumar 2014 Subtotal (95% CI) Heterogeneity: Tau <sup>2</sup> = 0.0; Test for overall effect: Z = Total (95% CI)	0.74 (P = 0.46) 18 38 94 <b>150</b> Chi <sup>2</sup> = 0.56, df = 1.06 (P = 0.29) <b>2364</b> Chi <sup>2</sup> = 10.25, df 0.81 (P = 0.42)	I.5 (0.4) I.56 (0.55) I.15 (0.42) 2 (P = 0.76); I <sup>2</sup> = I9 (P = 0.95);	17 34 96 <b>147</b> =0.0% <b>2310</b> 1 <sup>2</sup> =0.0%	1.44 (0.58)		<ul> <li>0.4 %</li> <li>2.5 %</li> <li>3.3 %</li> </ul>	0.10 [ -0.17, 0.37 ] 0.12 [ -0.14, 0.38 ] 0.03 [ -0.07, 0.13 ] 0.05 [ -0.04, 0.14 ] -0.01 [ -0.02, 0.01 ]

-0.2 -0.1 0 0.1 0.2

Favours higher PUFA Favours lower PUFA

(I) Change data

(2) Barcelona hospital cohort at 5 years, Casa 2016

(3) Fernandez-Real 2012, Reus subcohort, 2 year data

(4) Damasceno 2013, Barcelona North subcohort, I year data

# Analysis 3.56. Comparison 3 Higher PUFA vs lower PUFA - continuous secondary outcomes, Outcome 56 HDL, mmoL/L - subgroup by duration.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 3 Higher PUFA vs lower PUFA - continuous secondary outcomes

Outcome: 56 HDL, mmoL/L - subgroup by duration

Study or subgroup	Higher PUFA		Lower PUFA	M (CD)	Mean Difference	Weight	Mean Difference
	Ν	Mean(SD)	N	Mean(SD)	IV,Random,95% Cl		IV,Random,95% CI
I Medium duration I to < 2 Ahn 2016	years 38	1.19 (0.31)	36	1.14 (0.33)		1.2 %	0.05 [ -0.10, 0.20 ]
		. ,		· · ·			
Brox 2001	67	1.345 (0.36)	37	1.3 (0.3)		1.6 %	0.04 [ -0.08, 0.17 ]
Dodin 2005	85	1.68 (0.35)	94	1.77 (0.38)		2.3 %	-0.09 [ -0.20, 0.02 ]
HERO-Tapsell 2009	18	1.5 (0.4)	17	1.4 (0.4)		0.4 %	0.10 [ -0.17, 0.37 ]
Ley 2004 (I)	70	0.01 (0.4183)	66	-0.02 (0.1625)		2.4 %	0.03 [ -0.08, 0.14 ]
MARINA - Sanders 2011	80	0 (0.45)	71	0 (0.21)		2.2 %	0.0 [ -0.11, 0.11 ]
Mendis 2001	26	0.26 (0.1981)	28	0.27 (0.2063)		2.3 %	-0.01 [ -0.12, 0.10 ]
Nye 1990	12	1.38 (0.43)	12	1.45 (0.38)	·	0.2 %	-0.07 [ -0.39, 0.25 ]
WELCOME 2015	47	1.1 (0.3)	48	1.1 (0.2)		2.5 %	0.0 [ -0.10, 0.10 ]
Subtotal (95% CI)	443		409		+	15.0 %	0.00 [ -0.04, 0.04 ]
Heterogeneity: $Tau^2 = 0.0$ ; C	Chi <sup>2</sup> = 4.70, df =	8 (P = 0.79); I <sup>2</sup>	=0.0%			-	
Test for overall effect: $Z = 0$ .	02 (P = 0.98)						
2 Medium-long duration 2 to	o < 4 years						
AlphaOmega - ALA	605	0.13 (0.25)	605	0.15 (0.25)		33.2 %	-0.02 [ -0.05, 0.01 ]
DART fat 1989	855	1.04 (0.29)	860	1.05 (0.28)		36.2 %	-0.01 [ -0.04, 0.02 ]
DIPP-Tokudome 2015	89	1.43 (0.36)	73	1.46 (0.33)		2.3 %	-0.03 [ -0.14, 0.08 ]
Dullaart 1992	16	1.28 (0.37)	20	1.29 (0.37)	••	0.4 %	-0.01 [ -0.25, 0.23 ]
HARP- Sacks 1995	31	1.09 (0.28)	28	1.09 (0.34)		1.0 %	0.0 [ -0.16, 0.16 ]
Mita 2007	30	1.51 (0.59)	30	1.44 (0.37)		0.4 %	0.07 [ -0.18, 0.32 ]
Simon 1997	38	1.56 (0.55)	34	1.44 (0.58)		0.4 %	0.12 [ -0.14, 0.38 ]
Vijayakumar 2014	94	1.15 (0.42)	96	1.12 (0.28)		2.5 %	0.03 [ -0.07, 0.13 ]
Subtotal (95% CI)	1758		1746		•	7 <b>6.5</b> %	-0.01 [ -0.03, 0.01 ]
Heterogeneity: $Tau^2 = 0.0$ ; C	2hi <sup>2</sup> = 2.5 I, df =	7 (P = 0.93); I <sup>2</sup>	=0.0%				
Test for overall effect: $Z = I$ .	31 (P = 0.19)						
3 Long duration 4+ years							
PREDIMED 2013 (2)	51	1.33 (0.29)	42	1.33 (0.38)		1.3 %	0.0 [ -0.14, 0.14 ]

(Continued  $\dots$ )

							( Continued)
Study or subgroup	Higher PUFA		Lower PUFA		Mean Difference	Weight	Mean Difference
	Ν	Mean(SD)	Ν	Mean(SD)	IV,Random,95% CI		IV,Random,95% CI
PREDIMED 2013 (3)	54	0.19 (0.37)	54	0.11 (0.38)		► I.3 %	0.08 [ -0.06, 0.22 ]
PREDIMED 2013 (4)	58	0.05 (0.2)	59	0.02 (0.17)		5.8 %	0.03 [ -0.04, 0.10 ]
Subtotal (95% CI)	163		155		-	8.5 %	0.03 [ -0.02, 0.09 ]
Heterogeneity: $Tau^2 = 0.0$ ;	Chi <sup>2</sup> = 0.65, df = 2	2 (P = 0.72); I <sup>2</sup>	=0.0%				
Test for overall effect: Z =	I.I6 (P = 0.25)						
Total (95% CI)	2364		2310		•	100.0 %	-0.01 [ -0.02, 0.01 ]
Heterogeneity: $Tau^2 = 0.0$ ;	Chi <sup>2</sup> = 10.25, df =	= 19 (P = 0.95);	$ ^2 = 0.0\%$				
Test for overall effect: $Z = 0$	0.81 (P = 0.42)						
Test for subgroup difference	es: Chi <sup>2</sup> = 2.39, df	= 2 (P = 0.30),	$ ^2 =  6\%$				

-0.2 -0.1

Favours higher PUFA

0

0.1 0.2

Favours lower PUFA

(I) Change data

(2) Fernandez-Real 2012, Reus subcohort, 2 year data

(3) Barcelona hospital cohort at 5 years, Casa 2016

(4) Damasceno 2013, Barcelona North subcohort, 1 year data

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# Analysis 3.57. Comparison 3 Higher PUFA vs lower PUFA - continuous secondary outcomes, Outcome 57 HDL, mmoL/L - subgroup by primary or secondary prevention.

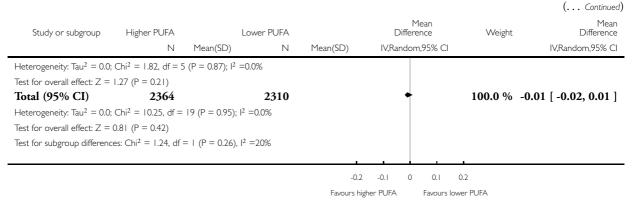
Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 3 Higher PUFA vs lower PUFA - continuous secondary outcomes

Outcome: 57 HDL, mmoL/L - subgroup by primary or secondary prevention

Me. Differen	Weight	Mean Difference		Lower PUFA		Higher PUFA	Study or subgroup
IV,Random,95%		IV,Random,95% CI	Mean(SD)	Ν	Mean(SD)	Ν	
						C	I Primary prevention of CVI
0.04 [ -0.08, 0.17	1.6 %		1.3 (0.3)	37	1.345 (0.36)	67	Brox 2001
-0.03 [ -0.14, 0.08	2.3 %		1.46 (0.33)	73	1.43 (0.36)	89	DIPP-Tokudome 2015
-0.09 [ -0.20, 0.02	2.3 %		I.77 (0.38) -	94	1.68 (0.35)	85	Dodin 2005
-0.01 [ -0.25, 0.23	0.4 %		1.29 (0.37)	20	1.28 (0.37)	16	Dullaart 1992
0.10 [ -0.17, 0.37	0.4 %		1.4 (0.4)	17	1.5 (0.4)	18	HERO-Tapsell 2009
0.03 [ -0.08, 0.14	2.4 %		-0.02 (0.1625)	66	0.01 (0.4183)	70	Ley 2004 (I)
0.0 [ -0.1 1, 0.1	2.2 %		0 (0.21)	71	0 (0.45)	80	MARINA - Sanders 2011
-0.01 [ -0.12, 0.10	2.3 %		0.27 (0.2063)	28	0.26 (0.1981)	26	Mendis 2001
0.07 [ -0.18, 0.32	0.4 %		1.44 (0.37)	30	1.51 (0.59)	30	Mita 2007
0.08 [ -0.06, 0.22	1.3 %		0.11 (0.38)	54	0.19 (0.37)	54	PREDIMED 2013 (2)
0.03 [ -0.04, 0.10	5.8 %	<b></b>	0.02 (0.17)	59	0.05 (0.2)	58	PREDIMED 2013 (3)
0.0 [ -0.14, 0.14	1.3 %		1.33 (0.38)	42	1.33 (0.29)	51	PREDIMED 2013 (4)
0.12 [ -0.14, 0.38	0.4 %		1.44 (0.58)	34	1.56 (0.55)	38	Simon 1997
0.0 [ -0.10, 0.10	2.5 %		1.1 (0.2)	48	1.1 (0.3)	47	WELCOME 2015
0.01 [ -0.02, 0.04	25.6 %	+		673		729	Subtotal (95% CI)
				2 =0.0%	3 (P = 0.89);	55 (P = 0.58)	Heterogeneity: Tau <sup>2</sup> = 0.0; C Fest for overall effect: $Z = 0.2$ 2 Secondary prevention of C
0.05 [ -0.10, 0.20	· I.2 %		1.14 (0.33)	36	1.19 (0.31)	38	Ahn 2016
-0.02 [ -0.05, 0.0	33.2 %		0.15 (0.25)	605	0.13 (0.25)	605	AlphaOmega - ALA
-0.01 [ -0.04, 0.02	36.2 %		1.05 (0.28)	860	1.04 (0.29)	855	DART fat 1989
0.0 [ -0.16, 0.16	1.0 %		1.09 (0.34)	28	1.09 (0.28)	31	HARP- Sacks 1995
-0.07 [ -0.39, 0.25	0.2 %		1.45 (0.38)	12	1.38 (0.43)	12	Nye 1990
0.03 [ -0.07, 0.13	2.5 %		1.12 (0.28)	96	1.15 (0.42)	94	Vijayakumar 2014
-0.01 [ -0.03, 0.01	74.4 %	•		1637		1635	Subtotal (95% CI)

(Continued . . . )



(I) Change data

(2) Barcelona hospital cohort at 5 years, Casa 2016

(3) Damasceno 2013, Barcelona North subcohort, I year data

(4) Fernandez-Real 2012, Reus subcohort, 2 year data

# Analysis 3.58. Comparison 3 Higher PUFA vs lower PUFA - continuous secondary outcomes, Outcome 58 HDL, mmoL/L - subgroup by baseline PUFA dose.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 3 Higher PUFA vs lower PUFA - continuous secondary outcomes

Outcome: 58 HDL, mmoL/L - subgroup by baseline PUFA dose

Study or subgroup	Higher PUFA		Lower PUFA		Mean Difference	Weight	Mea Difference
	Ν	Mean(SD)	Ν	Mean(SD)	IV,Random,95% CI		IV,Random,95% C
Baseline total PUFA < 6%	E						
Dodin 2005	85	1.68 (0.35)	94	1.77 (0.38)		2.3 %	-0.09 [ -0.20, 0.02
HERO-Tapsell 2009	18	1.5 (0.4)	17	1.4 (0.4)		• 0.4 %	0.10 [ -0.17, 0.37
Ley 2004 (I)	70	0.01 (0.4183)	66	-0.02 (0.1625)		2.4 %	0.03 [ -0.08, 0.14
Subtotal (95% CI)	173		177			5.0 %	-0.01 [ -0.11, 0.09
Heterogeneity: $Tau^2 = 0.00$ ; Test for overall effect: $Z = 0$ 2 Baseline total PUFA 6 to <	.26 (P = 0.79)	= 2 (P = 0.19);	l <sup>2</sup> =39%				
DART fat 1989	855	1.04 (0.29)	860	1.05 (0.28)		36.2 %	-0.01 [ -0.04, 0.02
DIPP-Tokudome 2015	89	1.43 (0.36)	73	1.46 (0.33)		2.3 %	-0.03 [ -0.14, 0.08
Dullaart 1992	16	1.28 (0.37)	20	1.29 (0.37)	• •	• 0.4 %	-0.01 [ -0.25, 0.23
MARINA - Sanders 2011	80	0 (0.45)	71	0 (0.21)		2.2 %	0.0 [ -0.1 1, 0.1 1
PREDIMED 2013 (2)	51	1.33 (0.29)	42	1.33 (0.38)		1.3 %	0.0 [ -0.14, 0.14
PREDIMED 2013 (3)	58	0.05 (0.2)	59	0.02 (0.17)	<b>=</b>	5.8 %	0.03 [ -0.04, 0.10
PREDIMED 2013 (4)	54	0.19 (0.37)	54	0.11 (0.38)		• 1.3 %	0.08 [ -0.06, 0.22
Simon 1997	38	1.56 (0.55)	34	1.44 (0.58)		• 0.4 %	0.12 [ -0.14, 0.38
Subtotal (95% CI)	1241		1213		•	50.0 %	0.00 [ -0.03, 0.02
Heterogeneity: Tau <sup>2</sup> = 0.0; G est for overall effect: Z = 0 Baseline total PUFA 11+%	.19 (P = 0.85)	7 (P = 0.82); I <sup>2</sup>	2 =0.0%				
Subtotal (95% CI) Heterogeneity: not applicabl Fest for overall effect: not ap Baseline total PUFA unclea	oplicable		0				Not estimable
Ahn 2016	38	1.19 (0.31)	36	1.14 (0.33)		- 1.2 %	0.05 [ -0.10, 0.20
AlphaOmega - ALA	605	0.13 (0.25)	605	0.15 (0.25)		33.2 %	-0.02 [ -0.05, 0.01
Brox 2001	67	1.345 (0.36)	37	1.3 (0.3)		1.6 %	0.04 [ -0.08, 0.17
HARP- Sacks 1995	31	1.09 (0.28)	28	1.09 (0.34)		1.0 %	0.0 [ -0.16, 0.16
95		. ,		1.09 (0.34)	0.2 -0.1 0 0.1 ( higher PUFA Favours low	I.0 %	0.04 [ -0.08, 0.17 0.0 [ -0.16, 0.16

							( Continued)
Study or subgroup	Higher PUFA		Lower PUFA		Mean Difference	Weight	Mean Difference
	Ν	Mean(SD)	Ν	Mean(SD)	IV,Random,95% C	1	IV,Random,95% Cl
Mendis 2001	26	0.26 (0.1981)	28	0.27 (0.2063)		2.3 %	-0.01 [ -0.12, 0.10 ]
Mita 2007	30	1.51 (0.59)	30	1.44 (0.37)		0.4 %	0.07 [ -0.18, 0.32 ]
Nye 1990	12	1.38 (0.43)	12	1.45 (0.38)	• •	0.2 %	-0.07 [ -0.39, 0.25 ]
Vijayakumar 2014	94	1.15 (0.42)	96	1.12 (0.28)	+•	2.5 %	0.03 [ -0.07, 0.13 ]
WELCOME 2015	47	1.1 (0.3)	48	1.1 (0.2)		2.5 %	0.0 [ -0.10, 0.10 ]
Subtotal (95% CI)	950		920		•	45.0 %	-0.01 [ -0.03, 0.01 ]
Heterogeneity: $Tau^2 = 0.0$ ;	Chi <sup>2</sup> = 3.00, df =	8 (P = 0.93); I <sup>2</sup>	=0.0%				
Test for overall effect: $Z =$	0.84 (P = 0.40)						
Total (95% CI)	2364		2310		•	100.0 %	-0.01 [ -0.02, 0.01 ]
Heterogeneity: Tau <sup>2</sup> = 0.0;	$Chi^2 = 10.25, df$	= 19 (P = 0.95)	; I <sup>2</sup> =0.0%				
Test for overall effect: Z =	0.81 (P = 0.42)						
Test for subgroup difference	es: Chi <sup>2</sup> = 0.25, d	f = 2 (P = 0.88)	, l <sup>2</sup> =0.0%				

-0.2 -0.1 0 0.1 0.2 Favours higher PUFA Favours lower PUFA

(I) Change data

(2) Fernandez-Real 2012, Reus subcohort, 2 year data

(3) Damasceno 2013, Barcelona North subcohort, 1 year data

(4) Barcelona hospital cohort at 5 years, Casa 2016

# Analysis 3.59. Comparison 3 Higher PUFA vs lower PUFA - continuous secondary outcomes, Outcome 59 HDL, mmoL/L - subgroup by replacement.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 3 Higher PUFA vs lower PUFA - continuous secondary outcomes

Outcome: 59 HDL, mmoL/L - subgroup by replacement

Study or subgroup H	ligher PUFA N	Maan(SD)	Lower PUFA N	Mean(SD)	Mean Difference IV,Random,95% Cl	Weight	Mea Differenc IV,Random,95% C
	IN	Mean(SD)	IN	(SD)	TV,Rahdom,75% Ci		IV,Nandom,75% C
PUFA replaced saturated fats DART fat 1989	855	1.04 (0.29)	860	1.05 (0.28)	-	91.5 %	-0.01 [ -0.04, 0.02
Dullaart 1992	16	1.28 (0.37)	20	1.29 (0.37)		• I.I %	-0.01 [ -0.25, 0.23
HERO-Tapsell 2009	18	1.5 (0.4)	17	1.4 (0.4)		→ 0.9 %	0.10 [ -0.17, 0.37
Vijayakumar 2014	94	( )	96	. ,			-
,,,		1.15 (0.42)		1.12 (0.28)		6.4 %	0.03 [ -0.07, 0.13
<b>btotal (95% CI)</b> terogeneity: Tau <sup>2</sup> = 0.0; Chi <sup>2</sup>	983	2(D - 0.7(), 1)	<b>993</b>		•	100.0 %	-0.01 [ -0.03, 0.02
the overall effect: $Z = 0.48$		5 (F – 0.76); F	-0.0%				
PUFA replaced monounsatura	` '						
AlphaOmega - ALA	605	0.13 (0.25)	605	0.15 (0.25)	-	69.7 %	-0.02 [ -0.05, 0.01
HARP- Sacks 1995	31	1.09 (0.28)	28	1.09 (0.34)		2.2 %	0.0 [ -0.16, 0.16
MARINA - Sanders 2011	80	0 (0.45)	71	0 (0.21)		4.6 %	0.0 [ -0.1 1, 0.1 1
Nye 1990	12	1.38 (0.43)	12	I.45 (0.38) 🗕		→ 0.5 %	-0.07 [ -0.39, 0.25
PREDIMED 2013 (1)	58	0.05 (0.2)	59	0.02 (0.17)	_ <b>_</b>	12.2 %	0.03 [ -0.04, 0.10
PREDIMED 2013 (2)	54	0.19 (0.37)	54	0.11 (0.38)		• 2.8 %	0.08 [ -0.06, 0.22
PREDIMED 2013 (3)	51	1.33 (0.29)	42	1.33 (0.38)		2.8 %	0.0 [ -0.14, 0.14
WELCOME 2015	47	1.1 (0.3)	48	1.1 (0.2)	<b>+</b>	5.2 %	0.0 [ -0.10, 0.10
lbtotal (95% CI)	938		919		•	100.0 %	-0.01 [ -0.03, 0.02
terogeneity: $Tau^2 = 0.0$ ; Chi <sup>2</sup> it for overall effect: $Z = 0.70$ PUFA replaced carbohydrates	(P = 0.48)	7 (P = 0.82); l <sup>2</sup>	=0.0%				
DIPP-Tokudome 2015	89	1.43 (0.36)	73	1.46 (0.33)		19.7 %	-0.03 [ -0.14, 0.08
Dodin 2005	85	1.68 (0.35)	94	1.77 (0.38) -		19.5 %	-0.09 [ -0.20, 0.02
Ley 2004 (4)	70	0.01 (0.4183)	66	-0.02 (0.1625)		20.0 %	0.03 [ -0.08, 0.14
MARINA - Sanders 2011	80	0 (0.45)	71	0 (0.21)		18.4 %	0.0 [ -0.1 1, 0.1 1
Mendis 2001	26	0.26 (0.1981)	28	0.27 (0.2063)		19.2 %	-0.01 [ -0.12, 0.10
I*iendis 2001							

(Continued  $\dots$ )

(... Continued)

Study or subgroup	Higher PUFA		Lower PUFA		Mean Difference	Weight	Mean Difference
	Ν	Mean(SD)	Ν	Mean(SD)	IV,Random,95% Cl		IV,Random,95% CI
Subtotal (95% CI)	388		366		•	100.0 %	-0.02 [ -0.06, 0.03 ]
Heterogeneity: $Tau^2 = 0.0;$	Chi <sup>2</sup> = 3.76, df =	5 (P = 0.58); I <sup>2</sup>	=0.0%				
Test for overall effect: $Z =$	0.64 (P = 0.52)						
4 PUFA replaced protein							
HERO-Tapsell 2009	18	1.5 (0.4)	17	1.4 (0.4)		→ I 3.7 %	0.10 [ -0.17, 0.37 ]
Ley 2004 (5)	70	0.01 (0.4183)	66	-0.02 (0.1625)		86.3 %	0.03 [ -0.08, 0.14 ]
Subtotal (95% CI)	88		83			100.0 %	0.04 [ -0.06, 0.14 ]
Heterogeneity: $Tau^2 = 0.0$ ;	Chi <sup>2</sup> = 0.23, df =	I (P = 0.63); I <sup>2</sup>	=0.0%				
Test for overall effect: Z =	0.79 (P = 0.43)						
5 PUFA replaced unclear							
Ahn 2016	38	1.19 (0.31)	36	1.14 (0.33)		- 38.2 %	0.05 [ -0.10, 0.20 ]
Brox 2001	67	1.345 (0.36)	37	1.3 (0.3)		48.6 %	0.04 [ -0.08, 0.17 ]
Mita 2007	30	1.51 (0.59)	30	1.44 (0.37)		→ I3.I%	0.07 [ -0.18, 0.32 ]
Subtotal (95% CI)	135		103			100.0 %	0.05 [ -0.04, 0.14 ]
Heterogeneity: Tau <sup>2</sup> = 0.0;	Chi <sup>2</sup> = 0.03, df =	2 (P = 0.98); I <sup>2</sup>	=0.0%				
Test for overall effect: Z =	1.09 (P = 0.28)						
Test for overall effect. $Z =$	( )						

-0.2 -0.1 0 0.1 0.2

Favours higher PUFA Favours lower PUFA

(1) Damasceno 2013, Barcelona North subcohort, 1 year data

(2) Barcelona hospital cohort at 5 years, Casa 2016

(3) Fernandez-Real 2012, Reus subcohort, 2 year data

(4) Change data

(5) Change data

# Analysis 3.60. Comparison 3 Higher PUFA vs lower PUFA - continuous secondary outcomes, Outcome 60 HDL, mmoL/L - subgroup by sex.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 3 Higher PUFA vs lower PUFA - continuous secondary outcomes

Outcome: 60 HDL, mmoL/L - subgroup by sex

Study or subgroup H	Higher PUFA		Lower PUFA		Mean Difference	Weight	Mear Difference
	Ν	Mean(SD)	Ν	Mean(SD)	IV,Random,95% CI		IV,Random,95% C
l > 70% men							
Ahn 2016	38	1.19 (0.31)	36	1.14 (0.33)		1.2 %	0.05 [ -0.10, 0.20
AlphaOmega - ALA	605	0.13 (0.25)	605	0.15 (0.25)		33.2 %	-0.02 [ -0.05, 0.01
DART fat 1989	855	1.04 (0.29)	860	1.05 (0.28)		36.2 %	-0.01 [ -0.04, 0.02
DIPP-Tokudome 2015	89	1.43 (0.36)	73	1.46 (0.33)		2.3 %	-0.03 [ -0.14, 0.08
Dullaart 1992	16	1.28 (0.37)	20	I.29 (0.37) 🔶		0.4 %	-0.01 [ -0.25, 0.23
HARP- Sacks 1995	31	1.09 (0.28)	28	1.09 (0.34)		1.0 %	0.0 [ -0.16, 0.16
Ley 2004 (I)	70	0.01 (0.4183)	66	-0.02 (0.1625)		2.4 %	0.03 [ -0.08, 0.14
Mendis 2001	26	0.26 (0.1981)	28	0.27 (0.2063)		2.3 %	-0.01 [ -0.12, 0.10
Nye 1990	12	1.38 (0.43)	12	1.45 (0.38) ←		0.2 %	-0.07 [ -0.39, 0.25
	94	1.15 (0.42)	96	1.12 (0.28)		2.5 %	0.03 [ -0.07, 0.13
Vijayakumar 2014							
Subtotal (95% CI) Heterogeneity: Tau <sup>2</sup> = 0.0; Chi <sup>2</sup> Test for overall effect: Z = 1.24		9 (P = 0.98); I <sup>2</sup>	<b>1824</b> =0.0%		•	81.8 %	-0.01 [ -0.03, 0.01
Subtotal (95% CI) Heterogeneity: Tau <sup>2</sup> = 0.0; Chi <sup>2</sup> Test for overall effect: Z = 1.24 2 > 70% women	e = 2.54, df = (P = 0.21)		=0.0%	77 (0 38) —	•		-0.01 [ -0.03, 0.01
Subtotal (95% CI) Heterogeneity: Tau <sup>2</sup> = 0.0; Chi <sup>2</sup> Test for overall effect: Z = 1.24	<sup>2</sup> = 2.54, df =	9 (P = 0.98); I <sup>2</sup> I.68 (0.35) I.56 (0.55)		I.77 (0.38) — I.44 (0.58)	• 	<b>81.8 %</b> 2.3 % 0.4 %	-0.01 [ -0.03, 0.01 -0.09 [ -0.20, 0.02 0.12 [ -0.14, 0.38
Subtotal (95% CI) Heterogeneity: Tau <sup>2</sup> = 0.0; Chi <sup>2</sup> Test for overall effect: Z = 1.24 2 > 70% women Dodin 2005 Simon 1997 Subtotal (95% CI) Heterogeneity: Tau <sup>2</sup> = 0.01; Chi Test for overall effect: Z = 0.21	<sup>2</sup> = 2.54, df = (P = 0.21) 85 38 <b>123</b> i <sup>2</sup> = 2.12, df =	I.68 (0.35) I.56 (0.55)	=0.0% 94 34 <b>128</b>	× /		2.3 % 0.4 %	-0.09 [ -0.20, 0.02
Subtotal (95% CI) Heterogeneity: Tau <sup>2</sup> = 0.0; Chi <sup>2</sup> Test for overall effect: Z = 1.24 2 > 70% women Dodin 2005 Simon 1997 Subtotal (95% CI) Heterogeneity: Tau <sup>2</sup> = 0.01; Chi Test for overall effect: Z = 0.21	<sup>2</sup> = 2.54, df = (P = 0.21) 85 38 <b>123</b> i <sup>2</sup> = 2.12, df =	I.68 (0.35) I.56 (0.55)	=0.0% 94 34 <b>128</b>	× /	• • • •	2.3 % 0.4 %	-0.09 [ -0.20, 0.02 0.12 [ -0.14, 0.38
Subtotal (95% CI) Heterogeneity: Tau <sup>2</sup> = 0.0; Chi <sup>2</sup> Test for overall effect: Z = 1.24 2 > 70% women Dodin 2005 Simon 1997 Subtotal (95% CI) Heterogeneity: Tau <sup>2</sup> = 0.01; Chi Test for overall effect: Z = 0.21 3 men % women	$e^2 = 2.54$ , df = (P = 0.21) 85 38 <b>123</b> $h^2 = 2.12$ , df = (P = 0.84)	I.68 (0.35) I.56 (0.55) = I (P = 0.15);	=0.0% 94 34 <b>128</b> <sup>12</sup> =53%	I.44 (0.58) —		2.3 % 0.4 % <b>2.7 %</b>	-0.09 [ -0.20, 0.02 0.12 [ -0.14, 0.38 - <b>0.02 [ -0.21, 0.17</b>
Subtotal (95% CI) Heterogeneity: Tau <sup>2</sup> = 0.0; Chi <sup>2</sup> Test for overall effect: Z = 1.24 2 > 70% women Dodin 2005 Simon 1997 Subtotal (95% CI) Heterogeneity: Tau <sup>2</sup> = 0.01; Chi Test for overall effect: Z = 0.21 3 men % women Brox 2001	$e^2 = 2.54, df = (P = 0.21)$ 85 38 <b>123</b> $i^2 = 2.12, df = (P = 0.84)$ 67	I.68 (0.35) I.56 (0.55) = I (P = 0.15); I.345 (0.36)	=0.0% 94 34 <b>128</b> <sup>12</sup> =53% 37	I.44 (0.58)		2.3 % 0.4 % <b>2.7 %</b>	-0.09 [ -0.20, 0.02 0.12 [ -0.14, 0.38 <b>-0.02 [ -0.21, 0.17</b> 0.04 [ -0.08, 0.17 0.0 [ -0.11, 0.11
Subtotal (95% CI) Heterogeneity: Tau <sup>2</sup> = 0.0; Chi <sup>2</sup> Test for overall effect: Z = 1.24 2 > 70% women Dodin 2005 Simon 1997 Subtotal (95% CI) Heterogeneity: Tau <sup>2</sup> = 0.01; Chi Test for overall effect: Z = 0.21 3 men % women Brox 2001 MARINA - Sanders 2011	2 = 2.54, df = (P = 0.21) 85 38 <b>123</b> i <sup>2</sup> = 2.12, df : (P = 0.84) 67 80	I.68 (0.35) I.56 (0.55) = I (P = 0.15); I.345 (0.36) 0 (0.45)	=0.0% 94 34 <b>128</b> <sup>12</sup> =53% 37 71	I.44 (0.58) I.3 (0.3) 0 (0.21)		2.3 % 0.4 % <b>2.7 %</b> 1.6 % 2.2 %	-0.09 [ -0.20, 0.02 0.12 [ -0.14, 0.38 <b>-0.02 [ -0.21, 0.17</b> 0.04 [ -0.08, 0.17
Subtotal (95% CI) Heterogeneity: Tau <sup>2</sup> = 0.0; Chi <sup>2</sup> Test for overall effect: Z = 1.24 2 > 70% women Dodin 2005 Simon 1997 Subtotal (95% CI) Heterogeneity: Tau <sup>2</sup> = 0.01; Chi Test for overall effect: Z = 0.21 3 men % women Brox 2001 MARINA - Sanders 2011 Mita 2007	2 = 2.54, df = (P = 0.21) 85 38 <b>123</b> i <sup>2</sup> = 2.12, df : (P = 0.84) 67 80 30	I.68 (0.35) I.56 (0.55) = I (P = 0.15); I.345 (0.36) 0 (0.45) I.51 (0.59)	=0.0% 94 34 <b>128</b> <sup>12</sup> =53% 37 71 30	I.44 (0.58) I.3 (0.3) 0 (0.21) I.44 (0.37)		2.3 % 0.4 % <b>2.7 %</b> 1.6 % 2.2 % 0.4 %	-0.09 [ -0.20, 0.02 0.12 [ -0.14, 0.38 -0.02 [ -0.21, 0.17 0.04 [ -0.08, 0.17 0.0 [ -0.11, 0.11 0.07 [ -0.18, 0.32

(Continued . . . )

(... Continued) Mean Difference Mean Difference Study or subgroup Higher PUFA Lower PUFA Weight Ν Mean(SD) Ν Mean(SD) IV.Random.95% CI IV,Random,95% Cl 0.0 [ -0.10, 0.10 ] WELCOME 2015 47 1.1 (0.3) 48 1.1 (0.2) 2.5 % Subtotal (95% CI) 387 341 15.1 % 0.03 [ -0.02, 0.07 ] Heterogeneity:  $Tau^2 = 0.0$ ;  $Chi^2 = 1.37$ , df = 6 (P = 0.97);  $I^2 = 0.0\%$ Test for overall effect: Z = 1.18 (P = 0.24) 4 sex not reported HERO-Tapsell 2009 0.10 [ -0.17, 0.37 ] 18 1.5 (0.4) 17 1.4 (0.4) 0.4 % Subtotal (95% CI) 18 17 0.4 % 0.10 [ -0.17, 0.37 ] Heterogeneity: not applicable Test for overall effect: Z = 0.74 (P = 0.46) Total (95% CI) 2364 2310 100.0 % -0.01 [ -0.02, 0.01 ] Heterogeneity: Tau<sup>2</sup> = 0.0; Chi<sup>2</sup> = 10.25, df = 19 (P = 0.95); l<sup>2</sup> =0.0% Test for overall effect: Z = 0.81 (P = 0.42) Test for subgroup differences:  $Chi^2 = 3.11$ , df = 3 (P = 0.37),  $I^2 = 4\%$ 

> -0.2 -0.1 0 0.1 0.2 Favours higher PUFA Favours lower PUFA

(I) Change data

(2) Damasceno 2013, Barcelona North subcohort, I year data

(3) Barcelona hospital cohort at 5 years, Casa 2016

(4) Fernandez-Real 2012, Reus subcohort, 2 year data

# Analysis 3.61. Comparison 3 Higher PUFA vs lower PUFA - continuous secondary outcomes, Outcome 61 HDL, mmoL/L - subgroup by age.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 3 Higher PUFA vs lower PUFA - continuous secondary outcomes

Outcome: 61 HDL, mmoL/L - subgroup by age

Study or subgroup	Higher PUFA		Lower PUFA		Mean Difference	Weight	Mear Difference
	Ν	Mean(SD)	Ν	Mean(SD)	IV,Random,95% CI		IV,Random,95% C
I Mean age < 50 years							
Dullaart 1992	16	1.28 (0.37)	20	1.29 (0.37)	• • •	→ 0.4 %	-0.01 [ -0.25, 0.23
Simon 1997	38	1.56 (0.55)	34	1.44 (0.58)		→ 0.4 %	0.12 [ -0.14, 0.38
Subtotal (95% CI)	54		54			- 0.8 %	0.05 [ -0.13, 0.23
Heterogeneity: $Tau^2 = 0.0;$		I (P = 0.48); I <sup>2</sup>	2 =0.0%				
Test for overall effect: $Z = 0$	· /						
2 Mean age 50 to < 65 yea Brox 2001	rs 67	1.345 (0.36)	37	1.3 (0.3)		1.6 %	0.04 [ -0.08, 0.17
DART fat 1989	855	1.04 (0.29)	860	1.05 (0.28)		36.2 %	-0.01 [ -0.04, 0.02
DIPP-Tokudome 2015	89	. ,	73	· · · ·		2.3 %	-
		1.43 (0.36)		1.46 (0.33)			-0.03 [ -0.14, 0.08
Dodin 2005	85	1.68 (0.35)	94	1.77 (0.38)		2.3 %	-0.09 [ -0.20, 0.02
HARP- Sacks 1995	31	1.09 (0.28)	28	1.09 (0.34)		1.0 %	0.0 [ -0.16, 0.16
HERO-Tapsell 2009	18	1.5 (0.4)	17	1.4 (0.4)	· · · ·	→ 0.4 %	0.10 [ -0.17, 0.37
Ley 2004 (I)	70	0.01 (0.4183)	66	-0.02 (0.1625)		2.4 %	0.03 [ -0.08, 0.14
MARINA - Sanders 201	80	0 (0.45)	71	0 (0.21)		2.2 %	0.0 [ -0.1  , 0.1
Mita 2007	30	1.51 (0.59)	30	1.44 (0.37)		→ 0.4 %	0.07 [ -0.18, 0.32
Nye 1990	12	1.38 (0.43)	12	1.45 (0.38)	• • •	→ 0.2 %	-0.07 [ -0.39, 0.25
Vijayakumar 2014	94	1.15 (0.42)	96	1.12 (0.28)	<u> </u>	2.5 %	0.03 [ -0.07, 0.13
WELCOME 2015	47	1.1 (0.3)	48	1.1 (0.2)		2.5 %	0.0 [ -0.10, 0.10
Subtotal (95% CI) Heterogeneity: $Tau^2 = 0.0$ ;	<b>1478</b> Chi <sup>2</sup> = 5.32, df =	II (P = 0.9I);	1432   <sup>2</sup> =0.0%		•	54.0 %	-0.01 [ -0.03, 0.02
Test for overall effect: $Z = 0$	0.61 (P = 0.54)						
3 Mean age 65+ years AlphaOmega - ALA	605	0.13 (0.25)	605	0.15 (0.25)		33.2 %	-0.02 [ -0.05, 0.01
PREDIMED 2013 (2)	51	1.33 (0.29)	42	1.33 (0.38)		1.3 %	0.0 [ -0.14, 0.14
PREDIMED 2013 (2)	54	0.19 (0.37)	54	0.11 (0.38)		→ 1.3 %	0.08 [ -0.06, 0.22
							-
PREDIMED 2013 (4)	58	0.05 (0.2)	59	0.02 (0.17)		5.8 %	0.03 [ -0.04, 0.10
				-0.	2 -0.1 0 0.1	0.2	
				Favours I	nigher PUFA Favours lov	ver PUFA	

(... Continued)

ner PUFA				Mean		Mean
	Lo	ower PUFA		Difference	Weight	Difference
Ν	Mean(SD)	Ν	Mean(SD)	IV,Random,95% Cl		IV,Random,95% CI
768		760		+	41.7 %	0.00 [ -0.04, 0.03 ]
= 3.41, df =	3 (P = 0.33); I <sup>2</sup> =	12%				
= 0.83)						
38	1.19 (0.31)	36	1.14 (0.33)		- 1.2 %	0.05 [ -0.10, 0.20 ]
26	0.26 (0.1981)	28	0.27 (0.2063)		2.3 %	-0.01 [ -0.12, 0.10 ]
64		64			3.5 %	0.01 [ -0.08, 0.10 ]
0.42, df =	$  (P = 0.52);  ^2 = 0$	).0%				
= 0.80)						
2364		2310		•	100.0 %	-0.01 [ -0.02, 0.01 ]
10.25, df =	19 (P = 0.95); I <sup>2</sup>	=0.0%				
= 0.42)						
= 0.53, df	$= 3 (P = 0.9 I), I^2$	=0.0%				
	<b>768</b> = 3.41, df = = 0.83) 38 26 <b>64</b> 0.42, df = 1 = 0.80) <b>2364</b> = 10.25, df = = 0.42)	<b>768</b> = 3.41, df = 3 (P = 0.33); $l^2$ = = 0.83) 38 1.19 (0.31) 26 0.26 (0.1981) <b>64</b> 0.42, df = 1 (P = 0.52); $l^2$ = 0 = 0.80) <b>2364</b> 10.25, df = 19 (P = 0.95); $l^2$ = 0.42)	768 $760$ = 3.41, df = 3 (P = 0.33); l <sup>2</sup> = 12%       =         = 0.83)       38       1.19 (0.31)       36         26       0.26 (0.1981)       28       64       64         0.42, df = 1 (P = 0.52); l <sup>2</sup> = 0.0%       =       0.80)       2364       2310         10.25, df = 19 (P = 0.95); l <sup>2</sup> = 0.0%       =       0.95); l <sup>2</sup> = 0.0%	768       760         = 3.41, df = 3 (P = 0.33); l <sup>2</sup> = 12%       =         = 0.83)       38       1.19 (0.31)       36       1.14 (0.33)         26       0.26 (0.1981)       28       0.27 (0.2063)         64       64       64         0.42, df = 1 (P = 0.52); l <sup>2</sup> = 0.0%       =       0.80)         2364       2310         10.25, df = 19 (P = 0.95); l <sup>2</sup> = 0.0%       =       0.42)	768       760 $= 3.41, df = 3 (P = 0.33); l^2 = 12\%$ $= 0.83$ )         38 $1.19 (0.31)$ 38 $1.19 (0.31)$ 26 $0.26 (0.1981)$ 28 $0.27 (0.2063)$ 64       64         0.42, df = 1 (P = 0.52); l^2 = 0.0% $= 0.80$ )         2364       2310 $= 10.25, df = 19 (P = 0.95); l^2 = 0.0\%$ $= 0.42$ )	$768$ $760$ $41.7 \%$ $= 3.41, df = 3 (P = 0.33); l^2 = l2\%$ $= 0.83$ ) $1.19 (0.31)$ $36  l.14 (0.33)$ $38  l.19 (0.31)$ $36  l.14 (0.33)$ $1.2 \%$ $26  0.26 (0.1981)$ $28  0.27 (0.2063)$ $2.3 \%$ $64$ $64$ $3.5 \%$ $0.42, df = 1 (P = 0.52); l^2 = 0.0\%$ $100.0 \%$ $= 0.80)$ $2364$ $2310$ $2364$ $2310$ $100.0 \%$ $= 0.42)$ $= 0.42$ $= 0.90$ ; l <sup>2</sup> = 0.0%

-0.2 -0.1 0 0.1 0.2 Favours higher PUFA Favours lower PUFA

(I) Change data

(2) Fernandez-Real 2012, Reus subcohort, 2 year data

(3) Barcelona hospital cohort at 5 years, Casa 2016

(4) Damasceno 2013, Barcelona North subcohort, I year data

# Analysis 3.62. Comparison 3 Higher PUFA vs lower PUFA - continuous secondary outcomes, Outcome 62 HDL, mmoL/L - subgroup by statin use.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 3 Higher PUFA vs lower PUFA - continuous secondary outcomes

Outcome: 62 HDL, mmoL/L - subgroup by statin use

Study or subgroup	Higher PUFA		Lower PUFA		Mean Difference	Weight	Mear Difference
	Ν	Mean(SD)	Ν	Mean(SD)	IV,Random,95% Cl		IV,Random,95% C
I < 50% on statins							
Brox 2001	67	1.345 (0.36)	37	1.3 (0.3)		1.6 %	0.04 [ -0.08, 0.17
DART fat 1989	855	1.04 (0.29)	860	1.05 (0.28)		36.2 %	-0.01 [ -0.04, 0.02
DIPP-Tokudome 2015	89	1.43 (0.36)	73	1.46 (0.33)		2.3 %	-0.03 [ -0.14, 0.08
Dodin 2005	85	1.68 (0.35)	94	1.77 (0.38) -		2.3 %	-0.09 [ -0.20, 0.02
Dullaart 1992	16	1.28 (0.37)	20	I.29 (0.37) 🔶		0.4 %	-0.01 [ -0.25, 0.23
HARP- Sacks 1995	31	1.09 (0.28)	28	1.09 (0.34)		1.0 %	0.0 [ -0.16, 0.16
MARINA - Sanders 2011	80	0 (0.45)	71	0 (0.21)		2.2 %	0.0 [ -0.11, 0.11
Mendis 2001	26	0.26 (0.1981)	28	0.27 (0.2063)		2.3 %	-0.01 [ -0.12, 0.10
Mita 2007	30	1.51 (0.59)	30	1.44 (0.37)		0.4 %	0.07 [ -0.18, 0.32
Nye 1990	12	1.38 (0.43)	12	I.45 (0.38) ←		0.2 %	-0.07 [ -0.39, 0.25
PREDIMED 2013 (1)	51	1.33 (0.29)	42	1.33 (0.38)		1.3 %	0.0 [ -0.14, 0.14
PREDIMED 2013 (2)	54	0.19 (0.37)	54	0.11 (0.38)		· I.3 %	0.08 [ -0.06, 0.22
PREDIMED 2013 (3)	58	0.05 (0.2)	59	0.02 (0.17)		5.8 %	0.03 [ -0.04, 0.10
Simon 1997	38	1.56 (0.55)	34	1.44 (0.58)		0.4 %	0.12 [ -0.14, 0.38
Subtotal (95% CI) Heterogeneity: Tau <sup>2</sup> = 0.0; Chi Test for overall effect: Z = 0.41 2 50+% on statins		I 3 (P = 0.89);	<b>1442</b> <sup>2</sup> =0.0%		+	57.8 %	0.00 [ -0.03, 0.02
Ahn 2016	38	1.19 (0.31)	36	1.14 (0.33)		1.2 %	0.05 [ -0.10, 0.20
AlphaOmega - ALA	605	0.13 (0.25)	605	0.15 (0.25)		33.2 %	-0.02 [ -0.05, 0.01
HERO-Tapsell 2009	18	1.5 (0.4)	17	1.4 (0.4)		0.4 %	0.10 [ -0.17, 0.37
Vijayakumar 2014	94	1.15 (0.42)	96	1.12 (0.28)		2.5 %	0.03 [ -0.07, 0.13
WELCOME 2015	47	1.1 (0.3)	48	1.1 (0.2)		2.5 %	0.0 [ -0.10, 0.10
Subtotal (95% CI) Heterogeneity: Tau <sup>2</sup> = 0.0; Chi	<b>802</b> <sup>2</sup> = 2.39, df =	4 (P = 0.66); I <sup>2</sup>	<b>802</b> =0.0%		-	39.8 %	-0.01 [ -0.04, 0.01

<sup>(</sup>Continued . . . )

								( Continued)
Study or subgroup	Higher PUFA		Lower PUFA			Mean rence	Weight	Mean Difference
	Ν	Mean(SD)	Ν	Mean(SD)	IV,Rando	om,95% Cl		IV,Random,95% CI
Test for overall effect: $Z = C$	).93 (P = 0.35)							
3 Percentage on statins uncl	ear							
Ley 2004 (4)	70	0.01 (0.4183)	66	-0.02 (0.1625)			2.4 %	0.03 [ -0.08, 0.14 ]
Subtotal (95% CI)	70		66				2.4 %	0.03 [ -0.08, 0.14 ]
Heterogeneity: not applicab	le							
Test for overall effect: $Z = C$	).56 (P = 0.58)							
Total (95% CI)	2364		2310		•	•	100.0 %	-0.01 [ -0.02, 0.01 ]
Heterogeneity: $Tau^2 = 0.0$ ; (	$Chi^2 = 10.25, df$	= 19 (P = 0.95);	l <sup>2</sup> =0.0%					
Test for overall effect: $Z = C$	0.81 (P = 0.42)							
Test for subgroup difference	es: Chi <sup>2</sup> = 0.69, d	f = 2 (P = 0.71)	, l <sup>2</sup> =0.0%					
				-0	.2 -0.1 0	0.1	0.2	

Favours higher PUFA Favours lower PUFA

(1) Fernandez-Real 2012, Reus subcohort, 2 year data

(2) Barcelona hospital cohort at 5 years, Casa 2016

(3) Damasceno 2013, Barcelona North subcohort, 1 year data

(4) Change data

#### Analysis 3.63. Comparison 3 Higher PUFA vs lower PUFA - continuous secondary outcomes, Outcome 63 HDL, mmoL/L - subgroup by intervention type.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 3 Higher PUFA vs lower PUFA - continuous secondary outcomes

Outcome: 63 HDL, mmoL/L - subgroup by intervention type

Study or subgroup High	ner PUFA		Lower PUFA		Mean Difference	Weight	Mear Difference
	N	Mean(SD)	Ν	Mean(SD)	IV,Random,95% Cl		IV,Random,95% C
tary advice ART fat 1989	855	1.04 (0.29)	860	1.05 (0.28)		36.2 %	-0.01 [ -0.04, 0.02
				· · ·			-
ullaart 1992	16	1.28 (0.37)	20	1.29 (0.37)		0.4 %	-0.01 [ -0.25, 0.23
y 2004 (I)	70	0.01 (0.4183)	66	-0.02 (0.1625)		2.4 %	0.03 [ -0.08, 0.14
non 1997	38	1.56 (0.55)	34	1.44 (0.58)		0.4 %	0.12 [ -0.14, 0.38
total (95% CI)	979		980		•	39.4 %	-0.01 [ -0.03, 0.02
rogeneity: Tau <sup>2</sup> = 0.0; Chi <sup>2</sup> =	1.42, df =	3 (P = 0.70); I <sup>2</sup>	=0.0%				
for overall effect: $Z = 0.48$ (P							
plemental foods % diet provi					_		
phaOmega - ALA	605	0.13 (0.25)	605	0.15 (0.25)	-	33.2 %	-0.02 [ -0.05, 0.01
ERO-Tapsell 2009	18	1.5 (0.4)	17	1.4 (0.4)		0.4 %	0.10 [ -0.17, 0.37
REDIMED 2013 (2)	58	0.05 (0.2)	59	0.02 (0.17)		5.8 %	0.03 [ -0.04, 0.10
REDIMED 2013 (3)	54	0.19 (0.37)	54	0.11 (0.38)		· I.3 %	0.08 [ -0.06, 0.22
REDIMED 2013 (4)	51	1.33 (0.29)	42	1.33 (0.38)		1.3 %	0.0 [ -0.14, 0.14
ayakumar 2014	94	1.15 (0.42)	96	1.12 (0.28)		2.5 %	0.03 [ -0.07, 0.13
total (95% CI)	880		873		•	44.6 %	-0.01 [ -0.03, 0.02
rogeneity: Tau <sup>2</sup> = 0.0; Chi <sup>2</sup> =	4.57, df =	5 (P = 0.47); I <sup>2</sup>	=0.0%				
for overall effect: $Z = 0.49$ (P	= 0.63)						
plements (capsules % unusua	ıl foods)						
nn 2016	38	1.19 (0.31)	36	1.14 (0.33)		1.2 %	0.05 [ -0.10, 0.20
ox 2001	67	1.345 (0.36)	37	1.3 (0.3)		1.6 %	0.04 [ -0.08, 0.17
odin 2005	85	1.68 (0.35)	94	1.77 (0.38) -		2.3 %	-0.09 [ -0.20, 0.02
ARP- Sacks 1995	31	1.09 (0.28)	28	1.09 (0.34)		1.0 %	0.0 [ -0.16, 0.16
ARINA - Sanders 2011	80	0 (0.45)	71	0 (0.21)		2.2 %	0.0 [ -0.11, 0.11
ta 2007	30	1.51 (0.59)	30	1.44 (0.37)		0.4 %	0.07 [ -0.18, 0.32
ye 1990	12	1.38 (0.43)	12	I.45 (0.38) 🗧		0.2 %	-0.07 [ -0.39, 0.25
	47	1.1 (0.3)	48	1.1 (0.2)		2.5 %	0.0 [ -0.10, 0.10

(Continued ...)

(... Continued)

Study or subgroup	Higher PUFA		Lower PUFA		Mean Difference	Weight	Mean Difference
	Ν	Mean(SD)	Ν	Mean(SD)	IV,Random,95% Cl		IV,Random,95% CI
Subtotal (95% CI)	390		356		+	11.5 %	-0.01 [ -0.05, 0.04 ]
Heterogeneity: $Tau^2 = 0.0$ ;	Chi <sup>2</sup> = 4.07, df =	7 (P = 0.77); $I^2 =$	=0.0%				
Test for overall effect: $Z = 0$	0.22 (P = 0.82)						
4 Any combination							
DIPP-Tokudome 2015	89	1.43 (0.36)	73	1.46 (0.33)		2.3 %	-0.03 [ -0.14, 0.08 ]
Mendis 2001	26	0.26 (0.1981)	28	0.27 (0.2063)		2.3 %	-0.01 [ -0.12, 0.10 ]
Subtotal (95% CI)	115		101			4.6 %	-0.02 [ -0.10, 0.06 ]
Heterogeneity: $Tau^2 = 0.0$ ;	$Chi^2 = 0.07, df =$	$  (P = 0.80);  ^2 =$	=0.0%				
Test for overall effect: $Z = 0$	0.52 (P = 0.60)						
Total (95% CI)	2364		2310		•	100.0 %	-0.01 [ -0.02, 0.01 ]
Heterogeneity: $Tau^2 = 0.0$ ;	Chi <sup>2</sup> = 10.25, df =	= 19 (P = 0.95); I	2 =0.0%				
Test for overall effect: $Z = 0$	0.81 (P = 0.42)						
Test for subgroup difference	es: Chi <sup>2</sup> = 0.13, df	= 3 (P = 0.99),	$ ^2 = 0.0\%$				
				-	<u> </u>	-	

-0.2 -0.1 0 0.1 0.2 Favours higher PUFA Favours lower PUFA

(I) Change data

(2) Damasceno 2013, Barcelona North subcohort, 1 year data

(3) Barcelona hospital cohort at 5 years, Casa 2016

(4) Fernandez-Real 2012, Reus subcohort, 2 year data

#### Analysis 3.64. Comparison 3 Higher PUFA vs lower PUFA - continuous secondary outcomes, Outcome 64 Serum LOW DENSITY LIPOPROTEIN (LDL, mmoL/L).

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 3 Higher PUFA vs lower PUFA - continuous secondary outcomes

Outcome: 64 Serum LOW DENSITY LIPOPROTEIN (LDL, mmoL/L)

Study or subgroup	Higher PUFA		Lower PUFA		Mean Difference	Weight	Mean Difference
, , ,	N	Mean(SD)	Ν	Mean(SD)	IV,Random,95% CI	0	IV,Random,95% CI
Ahn 2016	38	2.23 (1.33)	36	2.07 (0.13)		• 2.8 %	0.16 [ -0.26, 0.58 ]
AlphaOmega - ALA	562	-0.38 (0.71)	562	-0.39 (0.71)		14.5 %	0.01 [ -0.07, 0.09 ]
Dodin 2005	85	3.45 (0.67)	94	3.64 (0.67)		8.2 %	-0.19 [ -0.39, 0.01 ]
HARP- Sacks 1995	31	3.41 (0.78)	28	3.16 (0.62)		• 3.7 %	0.25 [ -0.11, 0.61 ]
HERO-Tapsell 2009	16	2.4 (0.6)	16	2.5 (0.8)	• • • • • • • • • • • • • • • • • • • •	2.2 %	-0.10 [ -0.59, 0.39 ]
Ley 2004 (I)	70	-0.02 (1.255)	66	-0.18 (0.7312)		- 3.9 %	0.16 [ -0.18, 0.50 ]
MARINA - Sanders 2011	80	0.2 (0.8987)	71	0.2 (0.4225)		7.2 %	0.0 [ -0.22, 0.22 ]
Mendis 2001	26	-0.65 (0.718)	28	-0.58 (0.9284)	• • • • • • • • • • • • • • • • • • • •	2.6 %	-0.07 [ -0.51, 0.37 ]
ORL 2013	170	0.08 (0.68)	165	-0.01 (0.6)		11.3 %	0.09 [ -0.04, 0.23 ]
PREDIMED 2013 (2)	54	-1.14 (0.95)	54	-0.62 (0.92)	·	3.7 %	-0.52 [ -0.87, -0.17 ]
PREDIMED 2013 (3)	58	-0.32 (0.76)	59	-0.3 (0.76)		5.4 %	-0.02 [ -0.30, 0.26 ]
PREDIMED 2013 (4)	51	3.26 (0.86)	42	3.07 (0.7)		• 4.4 %	0.19 [ -0.13, 0.51 ]
Rossing 1996	14	3.52 (0.9)	15	3.4 (0.97)	• •	• 1.2 %	0.12 [ -0.56, 0.80 ]
Simon 1997	38	3.09 (0.99)	34	2.79 (0.82)		• 2.8 %	0.30 [ -0.12, 0.72 ]
Vijayakumar 2014	94	2.32 (0.75)	96	2.35 (0.56)		8.5 %	-0.03 [ -0.22, 0.16 ]
WAHA - Ros 2016 (5)	260	-0.18 (0.48)	254	-0.03 (0.64)		13.6 %	-0.15 [ -0.25, -0.05 ]
WELCOME 2015	47	2.8 (0.9)	48	2.8 (0.8)		3.9 %	0.0 [ -0.34, 0.34 ]
Total (95% CI)	1694		1668		+	100.0 %	-0.01 [ -0.09, 0.06 ]
Heterogeneity: $Tau^2 = 0.01$ ; (		f = 16 (P = 0.02)	3); I <sup>2</sup> =44%				
Test for overall effect: $Z = 0.2$	( /						
Test for subgroup differences	Not applicable						
						1	
				-	0.5 -0.25 0 0.25 0	).5	

Favours higher PUFA Favours lower PUFA

(I) Change data

-

-

(2) Barcelona hospital cohort at 5 years, Casa 2016

(3) Damasceno 2013, Barcelona North subcohort, I year data

(4) Fernandez-Real 2012, Reus subcohort, 2 year data

(5) change from baseline

# Analysis 3.65. Comparison 3 Higher PUFA vs lower PUFA - continuous secondary outcomes, Outcome 65 LDL, mmoL/L - SA.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 3 Higher PUFA vs lower PUFA - continuous secondary outcomes

Outcome: 65 LDL, mmoL/L - SA

Mea Differenc	Weight	Mean Difference		Lower PUFA		Higher PUFA	Study or subgroup
IV,Random,95% (		IV,Random,95% Cl	Mean(SD)	Ν	Mean(SD)	N	
						on concealment	I Low risk of bias for allocati
0.16 [ -0.26, 0.58			2.07 (0.13)	36	2.23 (1.33)	38	Ahn 2016
0.01 [ -0.07, 0.09	60.1 %	-	-0.39 (0.71)	562	-0.38 (0.71)	562	AlphaOmega - ALA
0.16 [ -0.18, 0.50	- 3.5 %		-0.18 (0.7312)	66	-0.02 (1.255)	70	Ley 2004 (I)
0.0 [ -0.22, 0.22	8.6 %	<b>_</b>	0.2 (0.4225)	71	0.2 (0.8987)	80	MARINA - Sanders 2011
0.09 [ -0.04, 0.23	22.0 %		-0.01 (0.6)	165	0.08 (0.68)	170	ORL 2013
0.0 [ -0.34, 0.34	3.5 %		2.8 (0.8)	48	2.8 (0.9)	47	WELCOME 2015
0.04 [ -0.03, 0.10	100.0 %	•		948		<b>96</b> 7	Subtotal (95% CI)
				=0.0%	5 (P = 0.84); I <sup>2</sup>	hi <sup>2</sup> = 2.04, df =	Heterogeneity: $Tau^2 = 0.0$ ; C
						0 (P = 0.27)	Test for overall effect: $Z = I$ .
						n	2 Low risk of bias for attentio
0.01 [ -0.07, 0.09	22.1 %		-0.39 (0.71)	562	-0.38 (0.71)	562	AlphaOmega - ALA
-0.19 [ -0.39, 0.01	10.5 %		3.64 (0.67)	94	3.45 (0.67)	85	Dodin 2005
0.25 [ -0.11, 0.61	• 4.2 %		3.16 (0.62)	28	3.41 (0.78)	31	HARP- Sacks 1995
-0.10 [ -0.59, 0.39	2.4 %	•	2.5 (0.8)	16	2.4 (0.6)	16	HERO-Tapsell 2009
0.0 [ -0.22, 0.22	9.1 %		0.2 (0.4225)	71	0.2 (0.8987)	80	MARINA - Sanders 2011
-0.07 [ -0.51, 0.37	2.9 %	•	-0.58 (0.9284)	28	-0.65 (0.718)	26	Mendis 2001
0.09 [ -0.04, 0.23	15.6 %		-0.01 (0.6)	165	0.08 (0.68)	170	ORL 2013
0.19 [ -0.13, 0.51	→ 5.2 %		3.07 (0.7)	42	3.26 (0.86)	51	PREDIMED 2013 (2)
-0.52 [ -0.87, -0.17	4.4 %	•	-0.62 (0.92)	54	-1.14 (0.95)	54	PREDIMED 2013 (3)
-0.02 [ -0.30, 0.26	6.5 %		-0.3 (0.76)	59	-0.32 (0.76)	58	PREDIMED 2013 (4)
0.12 [ -0.56, 0.80		• • •	3.4 (0.97)	15	3.52 (0.9)	14	Rossing 1996
-0.03 [ -0.22, 0.16	11.1 %		2.35 (0.56)	96	2.32 (0.75)	94	Vijayakumar 2014
0.0 [ -0.34, 0.34	4.6 %		2.8 (0.8)	48	2.8 (0.9)	47	WELCOME 2015
-0.01 [ -0.09, 0.07	100.0 %	+		1278		1288	Subtotal (95% CI)

-0.5 -0.25 0 0.25 0.5 Favours higher PUFA Favours lower PUFA

(Continued ...)

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Study or subgroup	Higher PUFA N	Mean(SD)	Lower PUFA N	Mean(SD)	Mean Difference IV,Random,95% Cl	Weight	Mea Differenc IV,Random,95% (
Heterogeneity: $Tau^2 = 0.01;$		. ,		cur(5D)			, and on, 270
Test for overall effect: $Z = 0.2$		(	-,,				
3 Low risk of bias for complia							
Ahn 2016	38	2.23 (1.33)	36	2.07 (0.13)		• 6.8 %	0.16 [ -0.26, 0.58
Ley 2004 (5)	70	-0.02 (1.255)	66	-0.18 (0.7312)		- 10.0 %	0.16 [ -0.18, 0.50
Vijayakumar 2014	94	2.32 (0.75)	96	2.35 (0.56)		25.1 %	-0.03 [ -0.22, 0.16
WAHA - Ros 2016 (6)	260	-0.18 (0.48)	254	-0.03 (0.64)		48.1 %	-0.15 [ -0.25, -0.05
WELCOME 2015	47	2.8 (0.9)	48	2.8 (0.8)		10.0 %	0.0 [ -0.34, 0.34
Subtotal (95% CI)	509		500		-	100.0 %	-0.05 [ -0.17, 0.06
Heterogeneity: $Tau^2 = 0.00;$		= 4 (P = 0.24);	$ ^2 = 27\%$				
Test for overall effect: Z = 0.1 4 Low summary risk of bias	89 (P = 0.37)						
AlphaOmega - ALA	562	-0.38 (0.71)	562	-0.39 (0.71)	+	79.4 %	0.01 [ -0.07, 0.09
Ley 2004 (7)	70	-0.02 (1.255)	66	-0.18 (0.7312)		- 4.7 %	0.16 [ -0.18, 0.50
MARINA - Sanders 2011	80	0.2 (0.8987)	71	0.2 (0.4225)		11.3 %	0.0 [ -0.22, 0.22
WELCOME 2015	47	2.8 (0.9)	48	2.8 (0.8)		4.7 %	0.0 [ -0.34, 0.34
Subtotal (95% CI)	759		747		*	100.0 %	0.02 [ -0.06, 0.09
	41 (P = 0.68)						
	562	-0.38 (0.71)	562	-0.39 (0.71)		15.3 %	0.01 [ -0.07, 0.09
Trials registry or pre-2010	× ,	-0.38 (0.71) 3.45 (0.67)	562 94	-0.39 (0.71) 3.64 (0.67)		15.3 % 9.3 %	0.01 [ -0.07, 0.09 -0.19 [ -0.39, 0.01
5 Trials registry or pre-2010 AlphaOmega - ALA	562	. ,					-0.19 [ -0.39, 0.01
7 Trials registry or pre-2010 AlphaOmega - ALA Dodin 2005	562 85	3.45 (0.67)	94	3.64 (0.67)		9.3 %	2
5 Trials registry or pre-2010 AlphaOmega - ALA Dodin 2005 HARP- Sacks 1995	562 85 31	3.45 (0.67) 3.41 (0.78)	94 28	3.64 (0.67) 3.16 (0.62) 2.5 (0.8)		9.3 % • 4.4 %	-0.19 [ -0.39, 0.01 0.25 [ -0.11, 0.61
5 Trials registry or pre-2010 AlphaOmega - ALA Dodin 2005 HARP- Sacks 1995 HERO-Tapsell 2009	562 85 31 16	3.45 (0.67) 3.41 (0.78) 2.4 (0.6)	94 28 16	3.64 (0.67) 3.16 (0.62) 2.5 (0.8)		9.3 % + 4.4 % 2.6 %	-0.19 [ -0.39, 0.01 0.25 [ -0.11, 0.61 -0.10 [ -0.59, 0.39
5 Trials registry or pre-2010 AlphaOmega - ALA Dodin 2005 HARP- Sacks 1995 HERO-Tapsell 2009 Ley 2004 (8)	562 85 31 16 70	3.45 (0.67) 3.41 (0.78) 2.4 (0.6) -0.02 (1.255)	94 28 16 66	3.64 (0.67) 3.16 (0.62) 2.5 (0.8) -0.18 (0.7312)		9.3 % • 4.4 % 2.6 % - 4.7 %	-0.19 [ -0.39, 0.01 0.25 [ -0.11, 0.61 -0.10 [ -0.59, 0.39 0.16 [ -0.18, 0.50
5 Trials registry or pre-2010 AlphaOmega - ALA Dodin 2005 HARP- Sacks 1995 HERO-Tapsell 2009 Ley 2004 (8) MARINA - Sanders 2011	562 85 31 16 70 80	3.45 (0.67) 3.41 (0.78) 2.4 (0.6) -0.02 (1.255) 0.2 (0.8987)	94 28 16 66 71	3.64 (0.67) 3.16 (0.62) 2.5 (0.8) -0.18 (0.7312) 0.2 (0.4225)		9.3 % + 4.4 % 2.6 % - 4.7 % 8.2 %	-0.19 [ -0.39, 0.01 0.25 [ -0.11, 0.61 -0.10 [ -0.59, 0.39 0.16 [ -0.18, 0.50 0.0 [ -0.22, 0.22 -0.07 [ -0.51, 0.37
5 Trials registry or pre-2010 AlphaOmega - ALA Dodin 2005 HARP- Sacks 1995 HERO-Tapsell 2009 Ley 2004 (8) MARINA - Sanders 2011 Mendis 2001	562 85 31 16 70 80 26	3.45 (0.67) 3.41 (0.78) 2.4 (0.6) -0.02 (1.255) 0.2 (0.8987) -0.65 (0.718)	94 28 16 66 71 28	3.64 (0.67) 3.16 (0.62) 2.5 (0.8) -0.18 (0.7312) 0.2 (0.4225) -0.58 (0.9284) -0.01 (0.6)		9.3 % + 4.4 % 2.6 % - 4.7 % 8.2 % 3.1 %	-0.19 [ -0.39, 0.01 0.25 [ -0.11, 0.61 -0.10 [ -0.59, 0.39 0.16 [ -0.18, 0.50 0.0 [ -0.22, 0.22 -0.07 [ -0.51, 0.37 0.09 [ -0.04, 0.23
<ul> <li>Trials registry or pre-2010</li> <li>AlphaOmega - ALA</li> <li>Dodin 2005</li> <li>HARP- Sacks 1995</li> <li>HERO-Tapsell 2009</li> <li>Ley 2004 (8)</li> <li>MARINA - Sanders 2011</li> <li>Mendis 2001</li> <li>ORL 2013</li> </ul>	562 85 31 16 70 80 26 170	3.45 (0.67) 3.41 (0.78) 2.4 (0.6) -0.02 (1.255) 0.2 (0.8987) -0.65 (0.718) 0.08 (0.68)	94 28 66 71 28 165	3.64 (0.67) 3.16 (0.62) 2.5 (0.8) -0.18 (0.7312) 0.2 (0.4225) -0.58 (0.9284) -0.01 (0.6)		<ul> <li>9.3 %</li> <li>4.4 %</li> <li>2.6 %</li> <li>4.7 %</li> <li>8.2 %</li> <li>3.1 %</li> <li>12.3 %</li> </ul>	-0.19 [ -0.39, 0.01 0.25 [ -0.11, 0.61 -0.10 [ -0.59, 0.39 0.16 [ -0.18, 0.50 0.0 [ -0.22, 0.22 -0.07 [ -0.51, 0.37 0.09 [ -0.04, 0.23 -0.52 [ -0.87, -0.17
<ul> <li>Trials registry or pre-2010</li> <li>AlphaOmega - ALA</li> <li>Dodin 2005</li> <li>HARP- Sacks 1995</li> <li>HERO-Tapsell 2009</li> <li>Ley 2004 (8)</li> <li>MARINA - Sanders 2011</li> <li>Mendis 2001</li> <li>ORL 2013</li> <li>PREDIMED 2013 (9)</li> </ul>	562 85 31 16 70 80 26 170 54	3.45 (0.67) 3.41 (0.78) 2.4 (0.6) -0.02 (1.255) 0.2 (0.8987) -0.65 (0.718) 0.08 (0.68) -1.14 (0.95)	94 28 66 71 28 165 54	3.64 (0.67) 3.16 (0.62) 2.5 (0.8) -0.18 (0.7312) 0.2 (0.4225) -0.58 (0.9284) -0.01 (0.6) -0.62 (0.92)		<ul> <li>9.3 %</li> <li>4.4 %</li> <li>2.6 %</li> <li>4.7 %</li> <li>8.2 %</li> <li>3.1 %</li> <li>12.3 %</li> <li>4.5 %</li> </ul>	-0.19 [ -0.39, 0.01 0.25 [ -0.11, 0.61 -0.10 [ -0.59, 0.39 0.16 [ -0.18, 0.50 0.0 [ -0.22, 0.22
<ul> <li>Trials registry or pre-2010</li> <li>AlphaOmega - ALA</li> <li>Dodin 2005</li> <li>HARP- Sacks 1995</li> <li>HERO-Tapsell 2009</li> <li>Ley 2004 (8)</li> <li>MARINA - Sanders 2011</li> <li>Mendis 2001</li> <li>ORL 2013</li> <li>PREDIMED 2013 (9)</li> <li>PREDIMED 2013 (10)</li> </ul>	562 85 31 16 70 80 26 170 54 51	3.45 (0.67) 3.41 (0.78) 2.4 (0.6) -0.02 (1.255) 0.2 (0.8987) -0.65 (0.718) 0.08 (0.68) -1.14 (0.95) 3.26 (0.86)	94 28 16 66 71 28 165 54 42	3.64 (0.67) 3.16 (0.62) 2.5 (0.8) -0.18 (0.7312) 0.2 (0.4225) -0.58 (0.9284) -0.01 (0.6) -0.62 (0.92) 3.07 (0.7)		<ul> <li>9.3 %</li> <li>4.4 %</li> <li>2.6 %</li> <li>4.7 %</li> <li>8.2 %</li> <li>3.1 %</li> <li>12.3 %</li> <li>4.5 %</li> <li>5.2 %</li> </ul>	-0.19 [ -0.39, 0.01 0.25 [ -0.11, 0.61 -0.10 [ -0.59, 0.39 0.16 [ -0.18, 0.50 0.0 [ -0.22, 0.22 -0.07 [ -0.51, 0.37 0.09 [ -0.51, 0.23 -0.52 [ -0.87, -0.17 0.19 [ -0.13, 0.51
<ul> <li>Trials registry or pre-2010</li> <li>AlphaOmega - ALA</li> <li>Dodin 2005</li> <li>HARP- Sacks 1995</li> <li>HERO-Tapsell 2009</li> <li>Ley 2004 (8)</li> <li>MARINA - Sanders 2011</li> <li>Mendis 2001</li> <li>ORL 2013</li> <li>PREDIMED 2013 (9)</li> <li>PREDIMED 2013 (11)</li> </ul>	562 85 31 16 70 80 26 170 54 51 58	3.45 (0.67) 3.41 (0.78) 2.4 (0.6) -0.02 (1.255) 0.2 (0.8987) -0.65 (0.718) 0.08 (0.68) -1.14 (0.95) 3.26 (0.86) -0.32 (0.76)	94 28 16 66 71 28 165 54 42 59	3.64 (0.67) 3.16 (0.62) 2.5 (0.8) -0.18 (0.7312) 0.2 (0.4225) -0.58 (0.9284) -0.01 (0.6) -0.62 (0.92) 3.07 (0.7) -0.3 (0.76)		<ul> <li>9.3 %</li> <li>4.4 %</li> <li>2.6 %</li> <li>4.7 %</li> <li>8.2 %</li> <li>3.1 %</li> <li>12.3 %</li> <li>4.5 %</li> <li>5.2 %</li> <li>6.3 %</li> </ul>	-0.19 [-0.39, 0.01 0.25 [-0.11, 0.61 -0.10 [-0.59, 0.39 0.16 [-0.18, 0.50 0.0 [-0.22, 0.22 -0.07 [-0.51, 0.37 0.09 [-0.04, 0.23 -0.52 [-0.87, -0.17 0.19 [-0.13, 0.51 -0.02 [-0.30, 0.26

(... Continued)

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Study or subgroup	Higher PUFA		Lower PUFA		Mean Difference	Weight	Mear Difference
	Ν	Mean(SD)	Ν	Mean(SD)	IV,Random,95% CI		IV,Random,95% C
WELCOME 2015	47	2.8 (0.9)	48	2.8 (0.8)		4.7 %	0.0 [ -0.34, 0.34
Subtotal (95% CI)	1562		1536		•	100.0 %	-0.02 [ -0.10, 0.07 ]
Heterogeneity: $Tau^2 = 0.01$ ; ( Test for overall effect: $Z = 0.3$		F = 14 (P = 0.0)	1); I <sup>2</sup> =50%				
6 No industry funding	JS (1 = 0.75)						
Ahn 2016	38	2.23 (1.33)	36	2.07 (0.13)		• 13.9 %	0.16 [ -0.26, 0.58
Ley 2004 (13)	70	-0.02 (1.255)	66	-0.18 (0.7312)		21.4 %	0.16 [ -0.18, 0.50 ]
MARINA - Sanders 2011	80	0.2 (0.8987)	71	0.2 (0.4225)		51.8 %	0.0 [ -0.22, 0.22 ]
Mendis 2001	26	-0.65 (0.718)	28	-0.58 (0.9284)	•	12.9 %	-0.07 [ -0.51, 0.37
Subtotal (95% CI)	214		201		-	100.0 %	0.05 [ -0.11, 0.21
Heterogeneity: $Tau^2 = 0.0$ ; C Test for overall effect: $Z = 0.5$	59 (P = 0.56)	3 (P = 0.77); I	2 =0.0%				
7 Randomised 100+ participa AlphaOmega - ALA	ants 562	-0.38 (0.71)	562	-0.39 (0.71)	-	15.7 %	0.01 [ -0.07, 0.09
Dodin 2005	85	3.45 (0.67)	94	3.64 (0.67)		9.4 %	-0.19 [ -0.39, 0.01
Ley 2004 (14)	70	-0.02 (1.255)	66	-0.18 (0.7312)		- 4.8 %	0.16 [ -0.18, 0.50
MARINA - Sanders 2011	80	0.2 (0.8987)	71	0.2 (0.4225)		8.4 %	0.0 [ -0.22, 0.22
ORL 2013	170	0.08 (0.68)	165	-0.01 (0.6)		12.5 %	0.09 [ -0.04, 0.23
PREDIMED 2013 (15)	51	3.26 (0.86)	42	3.07 (0.7)		• 5.3 %	0.19 [ -0.13, 0.51
PREDIMED 2013 (16)	54	-1.14 (0.95)	54	-0.62 (0.92)	•	4.6 %	-0.52 [ -0.87, -0.17
PREDIMED 2013 (17)	58	-0.32 (0.76)	59	-0.3 (0.76)		6.4 %	-0.02 [ -0.30, 0.26
Simon 1997	38	3.09 (0.99)	34	2.79 (0.82)		→ 3.5 %	0.30 [ -0.12, 0.72
Vijayakumar 2014	94	2.32 (0.75)	96	2.35 (0.56)		9.8 %	-0.03 [ -0.22, 0.16
WAHA - Ros 2016 (18)	260	-0.18 (0.48)	254	-0.03 (0.64)	_ <b>_</b>	14.8 %	-0.15 [ -0.25, -0.05
WELCOME 2015	47	2.8 (0.9)	48	2.8 (0.8)		4.8 %	0.0 [ -0.34, 0.34
Subtotal (95% CI)	1569		1545		•	100.0 %	-0.03 [ -0.11, 0.06
Heterogeneity: Tau <sup>2</sup> = 0.01; ( Test for overall effect: $Z = 0.6$ 8 Randomised 250+ participa	60 (P = 0.55)	F = II (P = 0.0	I); I <sup>2</sup> =56%				
AlphaOmega - ALA	562	-0.38 (0.71)	562	-0.39 (0.71)	-	22.0 %	0.01 [ -0.07, 0.09
MARINA - Sanders 2011	80	0.2 (0.8987)	71	0.2 (0.4225)		12.9 %	0.0 [ -0.22, 0.22
ORL 2013	170	0.08 (0.68)	165	-0.01 (0.6)	+	18.3 %	0.09 [ -0.04, 0.23
PREDIMED 2013 (19)	54	-1.14 (0.95)	54	-0.62 (0.92)	←──── │	7.3 %	-0.52 [ -0.87, -0.17
PREDIMED 2013 (20)	51	3.26 (0.86)	42	3.07 (0.7)		• 8.5 %	0.19 [ -0.13, 0.51

(Continued . . . )

Study or subgroup	Higher PUFA		Lower PUFA		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Random,95% CI		IV,Random,95% CI
PREDIMED 2013 (21)	58	-0.32 (0.76)	59	-0.3 (0.76)		10.1 %	-0.02 [ -0.30, 0.26 ]
WAHA - Ros 2016 (22)	260	-0.18 (0.48)	254	-0.03 (0.64)		21.0 %	-0.15 [ -0.25, -0.05 ]
Subtotal (95% CI)	1235		1207		-	100.0 %	-0.04 [ -0.15, 0.08 ]
Heterogeneity: $Tau^2 = 0.01$ ;	Chi <sup>2</sup> = 19.12, df	= 6 (P = 0.004)	; I <sup>2</sup> =69%				
Test for overall effect: $Z = 0$ .	62 (P = 0.53)						

-0.5 -0.25 0 0.25 0.5

Favours higher PUFA Favours lower PUFA

- (I) Change data
- (2) Fernandez-Real 2012, Reus subcohort, 2 year data
- (3) Barcelona hospital cohort at 5 years, Casa 2016
- (4) Damasceno 2013, Barcelona North subcohort, I year data
- (5) Change data
- (6) change from baseline
- (7) Change data
- (8) Change data
- (9) Barcelona hospital cohort at 5 years, Casa 2016
- (10) Fernandez-Real 2012, Reus subcohort, 2 year data
- (11) Damasceno 2013, Barcelona North subcohort, 1 year data
- (12) change from baseline
- (13) Change data
- (14) Change data
- (15) Fernandez-Real 2012, Reus subcohort, 2 year data
- (16) Barcelona hospital cohort at 5 years, Casa 2016
- (17) Damasceno 2013, Barcelona North subcohort, I year data
- (18) change from baseline
- (19) Barcelona hospital cohort at 5 years, Casa 2016
- (20) Fernandez-Real 2012, Reus subcohort, 2 year data
- (21) Damasceno 2013, Barcelona North subcohort, 1 year data
- (22) change from baseline

(... Continued)

#### Analysis 3.66. Comparison 3 Higher PUFA vs lower PUFA - continuous secondary outcomes, Outcome 66 LDL, mmoL/L - SA fixed-effect.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 3 Higher PUFA vs lower PUFA - continuous secondary outcomes

Outcome: 66 LDL, mmoL/L - SA fixed-effect

Me Differen	Weight	Mean Difference			Lower PUFA		Higher PUFA	Study or subgroup
IV,Fixed,95%	-	IV,Fixed,95% CI		Mean(SD)	Ν	Mean(SD)	N	
0.16 [ -0.26, 0.58	1.2 %			2.07 (0.13)	36	2.23 (1.33)	38	Ahn 2016
0.01 [ -0.07, 0.09	31.8 %			-0.39 (0.71)	562	-0.38 (0.71)	562	AlphaOmega - ALA
-0.19 [ -0.39, 0.0	5.7 %	-	_	3.64 (0.67)	94	3.45 (0.67)	85	Dodin 2005
0.25 [ -0.11, 0.6	1.7 %			3.16 (0.62)	28	3.41 (0.78)	31	HARP- Sacks 1995
-0.10 [ -0.59, 0.39	0.9 %		•	2.5 (0.8)	16	2.4 (0.6)	16	HERO-Tapsell 2009
0.16 [ -0.18, 0.50	1.9 %			-0.18 (0.7312)	66	-0.02 (1.255)	70	Ley 2004 (I)
0.0 [ -0.22, 0.22	4.5 %			0.2 (0.4225)	71	0.2 (0.8987)	80	MARINA - Sanders 2011
-0.07 [ -0.51, 0.3]	1.1 %		•	-0.58 (0.9284)	28	-0.65 (0.718)	26	Mendis 2001
0.09 [ -0.04, 0.2]	11.7 %			-0.01 (0.6)	165	0.08 (0.68)	170	ORL 2013
-0.52 [ -0.87, -0.1]	1.8 %	_	•	-0.62 (0.92)	54	-1.14 (0.95)	54	PREDIMED 2013 (2)
0.19 [ -0.13, 0.5	2.2 %			3.07 (0.7)	42	3.26 (0.86)	51	PREDIMED 2013 (3)
-0.02 [ -0.30, 0.26	2.9 %			-0.3 (0.76)	59	-0.32 (0.76)	58	PREDIMED 2013 (4)
0.12 [ -0.56, 0.8	0.5 %		•	3.4 (0.97)	15	3.52 (0.9)	14	Rossing 1996
0.30 [ -0.12, 0.72	1.3 %			2.79 (0.82)	34	3.09 (0.99)	38	Simon 1997
-0.03 [ -0.22, 0.16	6.2 %			2.35 (0.56)	96	2.32 (0.75)	94	Vijayakumar 2014
-0.15 [ -0.25, -0.0	22.9 %			-0.03 (0.64)	254	-0.18 (0.48)	260	WAHA - Ros 2016 (5)
0.0 [ -0.34, 0.34	1.9 %		_	2.8 (0.8)	48	2.8 (0.9)	47	WELCOME 2015
-0.03 [ -0.07, 0.02	100.0 %	•			1668		1694	otal (95% CI)
						03); I <sup>2</sup> =44%	df = 16 (P = 0.	eterogeneity: Chi <sup>2</sup> = 28.67,
							II (P = 0.27)	est for overall effect: $Z = I$ .
							Not applicable	est for subgroup differences

Favours higher PUFA Favours lower PUFA

(I) Change data

(2) Barcelona hospital cohort at 5 years, Casa 2016

(3) Fernandez-Real 2012, Reus subcohort, 2 year data

(4) Damasceno 2013, Barcelona North subcohort, I year data

(5) change from baseline

# Analysis 3.67. Comparison 3 Higher PUFA vs lower PUFA - continuous secondary outcomes, Outcome 67 LDL, mmoL/L - subgroup by PUFA dose.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 3 Higher PUFA vs lower PUFA - continuous secondary outcomes

Outcome: 67 LDL, mmoL/L - subgroup by PUFA dose

Study or subgroup	Higher PUFA N	Mara (CD)	Lower PUFA N	Mara (CD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
	IN	Mean(SD)	IN	Mean(SD)	IV,Random,95% CI		IV,Random,95% C
I total PUFA < 1.0% E Ley 2004 (1)	70	-0.02 (1.255)	66	-0.18 (0.7312)		- 3.9 %	0.16 [ -0.18, 0.50 -
MARINA - Sanders 2011	80	0.2 (0.8987)	71	0.2 (0.4225)		7.2 %	0.0 [ -0.22, 0.22
		· · · ·		. ,			
ORL 2013	170	0.08 (0.68)	165	-0.01 (0.6)	-	11.3 %	0.09 [ -0.04, 0.23 ]
Subtotal (95% CI)	320		302			22.4 %	0.08 [ -0.03, 0.19 ]
Heterogeneity: $Tau^2 = 0.0$ ; C		2 (P = 0.69); I	2 =0.0%				
Test for overall effect: $Z = 1$ . 2 total PUFA 1.0 to < 2.0% I	· /						
2 total POFA 1.0 to < 2.0% t Ahn 2016	= 38	2.23 (1.33)	36	2.07 (0.13)			0.16 [ -0.26, 0.58 ]
AlphaOmega - ALA	562	-0.38 (0.71)	562	-0.39 (0.71)		14.5 %	0.01 [ -0.07, 0.09 ]
Dodin 2005	85	3.45 (0.67)	94	3.64 (0.67)		8.2 %	-0.19 [ -0.39, 0.01
PREDIMED 2013 (2)	58	-0.32 (0.76)	59	-0.3 (0.76)		5.4 %	-0.02 [ -0.30, 0.26
		. ,					
PREDIMED 2013 (3)	54	-1.14 (0.95)	54	-0.62 (0.92)		3.7 %	-0.52 [ -0.87, -0.17 ]
PREDIMED 2013 (4)	51	3.26 (0.86)	42	3.07 (0.7)		<b>→</b> 4.4 %	0.19 [ -0.13, 0.51 ]
WELCOME 2015	47	2.8 (0.9)	48	2.8 (0.8)		3.9 %	0.0 [ -0.34, 0.34 ]
Subtotal (95% CI)	895		895		-	43.0 %	-0.05 [ -0.19, 0.09 ]
Heterogeneity: $Tau^2 = 0.02;$	$Chi^2 = 13.47, df$	= 6 (P = 0.04)	); l <sup>2</sup> =55%				
Test for overall effect: $Z = 0$ .	· /						
3 total PUFA 2.0 to < 5.0% E		2.41.(0.70)	20	214 (0 (2)		+ 270/	
HARP- Sacks 1995	31	3.41 (0.78)	28	3.16 (0.62)		→ 3.7 %	0.25 [ -0.11, 0.61 ]
Mendis 2001	26	-0.65 (0.718)	28	-0.58 (0.9284)	• •	2.6 %	-0.07 [ -0.51, 0.37 ]
Rossing 1996	14	3.52 (0.9)	15	3.4 (0.97)	+ +		0.12 [ -0.56, 0.80 ]
Subtotal (95% CI)	71		71			7.5 %	0.12 [ -0.13, 0.38 ]
Heterogeneity: $Tau^2 = 0.0$ ; C	2hi <sup>2</sup> = 1.22, df =	2 (P = 0.54); I	2 =0.0%				
Test for overall effect: $Z = 0$ .	93 (P = 0.35)						
4 total PUFA 5.0+% E							
HERO-Tapsell 2009	16	2.4 (0.6)	16	2.5 (0.8)	· · · · · · · · · · · · · · · · · · ·	2.2 %	-0.10 [ -0.59, 0.39 ]
						0.5	
				Favour	s higher PUFA Favours Iow	ver PUFA	(Continued

							( Continued)
Study or subgroup	Higher PUFA	I	_ower PUFA		Mean Difference	Weight	Mean Difference
	Ν	Mean(SD)	Ν	Mean(SD)	IV,Random,95% CI		IV,Random,95% Cl
Simon 1997	38	3.09 (0.99)	34	2.79 (0.82)		• 2.8 %	0.30 [ -0.12, 0.72 ]
Vijayakumar 2014	94	2.32 (0.75)	96	2.35 (0.56)		8.5 %	-0.03 [ -0.22, 0.16 ]
WAHA - Ros 2016 (5)	260	-0.18 (0.48)	254	-0.03 (0.64)		13.6 %	-0.15 [ -0.25, -0.05 ]
Subtotal (95% CI)	408		400		-	27.2 %	-0.06 [ -0.21, 0.09 ]
Heterogeneity: $Tau^2 = 0.01$ ;	$Chi^2 = 5.02, df =$	= 3 (P = 0.17); I <sup>2</sup>	=40%				
Test for overall effect: $Z = 0$	0.82 (P = 0.41)						
Total (95% CI)	1694		1668		+	100.0 %	-0.01 [ -0.09, 0.06 ]
Heterogeneity: $Tau^2 = 0.01$	$Chi^2 = 28.67$ , df	= 16 (P = 0.03);	$ ^2 = 44\%$				
Test for overall effect: $Z = 0$	0.33 (P = 0.74)						
Test for subgroup difference	es: Chi² = 3.86, dt	= 3 (P = 0.28), I	<sup>2</sup> =22%				
						i	

-0.5 -0.25 0 0.25 0.5

Favours higher PUFA Favours lower PUFA

(I) Change data

(2) Damasceno 2013, Barcelona North subcohort, I year data

(3) Barcelona hospital cohort at 5 years, Casa 2016

(4) Fernandez-Real 2012, Reus subcohort, 2 year data

(5) change from baseline

# Analysis 3.68. Comparison 3 Higher PUFA vs lower PUFA - continuous secondary outcomes, Outcome 68 LDL, mmoL/L - subgroup by duration.

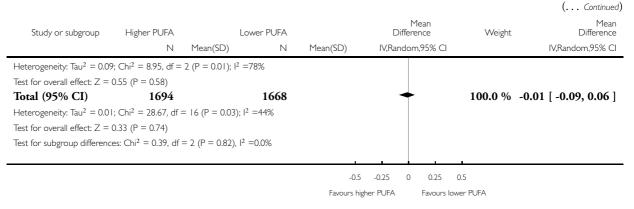
Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 3 Higher PUFA vs lower PUFA - continuous secondary outcomes

Outcome: 68 LDL, mmoL/L - subgroup by duration

Study or subgroup	Higher PUFA N	Mean(SD)	Lower PUFA N	Mean(SD)	Mean Difference IV,Random,95% Cl	Weight	Mean Difference IV,Random,95% Cl
Medium duration   to < 2		110411(02)		(ob)			
Ahn 2016	38	2.23 (1.33)	36	2.07 (0.13)		2.8 %	0.16 [ -0.26, 0.58 ]
Dodin 2005	85	3.45 (0.67)	94	3.64 (0.67)		8.2 %	-0.19 [ -0.39, 0.01 ]
HERO-Tapsell 2009	16	2.4 (0.6)	16	2.5 (0.8)	· · · · · · · · · · · · · · · · · · ·	2.2 %	-0.10 [ -0.59, 0.39 ]
Ley 2004 (I)	70	-0.02 (1.255)	66	-0.18 (0.7312)		3.9 %	0.16 [ -0.18, 0.50 ]
MARINA - Sanders 2011	80	0.2 (0.8987)	71	0.2 (0.4225)		7.2 %	0.0 [ -0.22, 0.22 ]
Mendis 2001	26	-0.65 (0.718)	28	-0.58 (0.9284)	·	2.6 %	-0.07 [ -0.51, 0.37 ]
ORL 2013	170	0.08 (0.68)	165	-0.01 (0.6)		11.3 %	0.09 [ -0.04, 0.23 ]
Rossing 1996	14	3.52 (0.9)	15	3.4 (0.97)		1.2 %	0.12 [ -0.56, 0.80 ]
WELCOME 2015	47	2.8 (0.9)	48	2.8 (0.8)		3.9 %	0.0 [ -0.34, 0.34 ]
Subtotal (95% CI)	546		539	()	•	43.2 %	0.01 [ -0.07, 0.10 ]
Heterogeneity: $Tau^2 = 0.0$ ; (		$8 (P = 0.53) \cdot 1^{-2}$				43.2 70	0.01 [ -0.0/ , 0.10 ]
Test for overall effect: $Z = 0$		0 (1 0100)) 1	01070				
2 Medium-long duration 2 to	o < 4 years						
AlphaOmega - ALA	562	-0.38 (0.71)	562	-0.39 (0.71)	-	14.5 %	0.01 [ -0.07, 0.09 ]
HARP- Sacks 1995	31	3.41 (0.78)	28	3.16 (0.62)		3.7 %	0.25 [ -0.11, 0.61 ]
Simon 1997	38	3.09 (0.99)	34	2.79 (0.82)		2.8 %	0.30 [ -0.12, 0.72 ]
Vijayakumar 2014	94	2.32 (0.75)	96	2.35 (0.56)		8.5 %	-0.03 [ -0.22, 0.16 ]
WAHA - Ros 2016 (2)	260	-0.18 (0.48)	254	-0.03 (0.64)		13.6 %	-0.15 [ -0.25, -0.05 ]
Subtotal (95% CI)	985		974		-	43.2 %	0.00 [ -0.13, 0.12 ]
Heterogeneity: Tau <sup>2</sup> = 0.01;	$Chi^2 = 11.30, d$	f = 4 (P = 0.02)	; I <sup>2</sup> =65%				
Test for overall effect: $Z = 0$	.07 (P = 0.95)						
3 Long duration 4+ years							
PREDIMED 2013 (3)	54	-1.14 (0.95)	54	-0.62 (0.92)	·	3.7 %	-0.52 [ -0.87, -0.17 ]
PREDIMED 2013 (4)	51	3.26 (0.86)	42	3.07 (0.7)		4.4 %	0.19 [ -0.13, 0.51 ]
PREDIMED 2013 (5)	58	-0.32 (0.76)	59	-0.3 (0.76)		5.4 %	-0.02 [ -0.30, 0.26 ]
Subtotal (95% CI)	163		155			13.6 %	-0.11 [ -0.49, 0.28 ]
				-	0.5 -0.25 0 0.25 0	.5	
PREDIMED 2013 (5)	58	. ,	59	-0.3 (0.76)	0.5 -0.25 0 0.25 0 higher PUFA Favours lowe	5.4 % <b>13.6 %</b>	-0.02 [ -0.30, 0.

(Continued ...)



(I) Change data

(2) change from baseline

(3) Barcelona hospital cohort at 5 years, Casa 2016

(4) Fernandez-Real 2012, Reus subcohort, 2 year data

(5) Damasceno 2013, Barcelona North subcohort, I year data

# Analysis 3.69. Comparison 3 Higher PUFA vs lower PUFA - continuous secondary outcomes, Outcome 69 LDL, mmoL/L - subgroup by primary or secondary prevention.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 3 Higher PUFA vs lower PUFA - continuous secondary outcomes

Outcome: 69 LDL, mmoL/L - subgroup by primary or secondary prevention

Study or subgroup	Higher PUFA N	Mean(SD)	Lower PUFA N	Mean(SD)	Mean Difference IV,Random,95% Cl	Weight	Mean Difference IV,Random,95% CI
I Primary prevention of CV					_		
Dodin 2005	85	3.45 (0.67)	94	3.64 (0.67)		8.2 %	-0.19 [ -0.39, 0.01 ]
HERO-Tapsell 2009	16	2.4 (0.6)	16	2.5 (0.8)	• • •	2.2 %	-0.10 [ -0.59, 0.39 ]
Ley 2004 (I)	70	-0.02 (1.255)	66	-0.18 (0.7312)		- 3.9 %	0.16 [ -0.18, 0.50 ]
MARINA - Sanders 201	80	0.2 (0.8987)	71	0.2 (0.4225)	<b>_</b>	7.2 %	0.0 [ -0.22, 0.22 ]
Mendis 2001	26	-0.65 (0.718)	28	-0.58 (0.9284)	•	2.6 %	-0.07 [ -0.51, 0.37 ]
ORL 2013	170	0.08 (0.68)	165	-0.01 (0.6)		11.3 %	0.09 [ -0.04, 0.23 ]
PREDIMED 2013 (2)	54	-1.14 (0.95)	54	-0.62 (0.92)	•	3.7 %	-0.52 [ -0.87, -0.17 ]
PREDIMED 2013 (3)	51	3.26 (0.86)	42	3.07 (0.7)		→ 4.4 %	0.19 [ -0.13, 0.51 ]
PREDIMED 2013 (4)	58	-0.32 (0.76)	59	-0.3 (0.76)	<b>_</b>	5.4 %	-0.02 [ -0.30, 0.26 ]
Rossing 1996	14	3.52 (0.9)	15	3.4 (0.97)	• •	→ I.2 %	0.12 [ -0.56, 0.80 ]
Simon 1997	38	3.09 (0.99)	34	2.79 (0.82)		→ 2.8 %	0.30 [ -0.12, 0.72 ]
WAHA - Ros 2016 (5)	260	-0.18 (0.48)	254	-0.03 (0.64)		13.6 %	-0.15 [ -0.25, -0.05 ]
WELCOME 2015	47	2.8 (0.9)	48	2.8 (0.8)		3.9 %	0.0 [ -0.34, 0.34 ]
Subtotal (95% CI)	969	. ,	946	. ,	-	70.5 %	-0.03 [ -0.14, 0.07 ]
Heterogeneity: $Tau^2 = 0.01$ ;		r = 12 (P = 0.02)				,,	
Test for overall effect: $Z = C$	0.61 (P = 0.54)						
2 Secondary prevention of							
Ahn 2016	38	2.23 (1.33)	36	2.07 (0.13)		→ 2.8 %	0.16 [ -0.26, 0.58 ]
AlphaOmega - ALA	562	-0.38 (0.71)	562	-0.39 (0.71)		14.5 %	0.01 [ -0.07, 0.09 ]
HARP- Sacks 1995	31	3.41 (0.78)	28	3.16 (0.62)		→ 3.7 %	0.25 [ -0.11, 0.61 ]
Vijayakumar 2014	94	2.32 (0.75)	96	2.35 (0.56)		8.5 %	-0.03 [ -0.22, 0.16 ]
Subtotal (95% CI)	725		722		•	29.5 %	0.02 [ -0.05, 0.09 ]
Heterogeneity: $Tau^2 = 0.0$ ; (	Chi <sup>2</sup> = 2.33, df =	3 (P = 0.5 I); I <sup>2</sup>	2 =0.0%				
Test for overall effect: $Z = 0$	· /						
Total (95% CI)	1694		1668		•	100.0 %	-0.01 [ -0.09, 0.06 ]
Heterogeneity: $Tau^2 = 0.01$ ;		f = 16 (P = 0.0)	3); I <sup>2</sup> =44%				
Test for overall effect: $Z = C$ Test for subgroup difference	· /	f = 1 (P - 0.42)	$ ^{2} = 0.0\%$				
lest for subgroup difference	.s. chi = 0.02, d	i = i (i = 0.15	), 1 =0.078				
				,	).5 -0.25 0 0.25	0.5	
					higher PUFA Favours Iov		

(I) Change data

- (2) Barcelona hospital cohort at 5 years, Casa 2016
- (3) Fernandez-Real 2012, Reus subcohort, 2 year data
- (4) Damasceno 2013, Barcelona North subcohort, I year data

(5) change from baseline

# Analysis 3.70. Comparison 3 Higher PUFA vs lower PUFA - continuous secondary outcomes, Outcome 70 LDL, mmoL/L - subgroup by baseline PUFA dose.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 3 Higher PUFA vs lower PUFA - continuous secondary outcomes

Outcome: 70 LDL, mmoL/L - subgroup by baseline PUFA dose

Study or subgroup	Higher PUFA		Lower PUFA			Mean rence	Weight	Mean Difference	
	N	Mean(SD)	Ν	Mean(SD)	IV,Rando	om,95% Cl		IV,Random,95% CI	
I Baseline total PUFA < 6%	έE								
Dodin 2005	85	3.45 (0.67)	94	3.64 (0.67)			8.2 %	-0.19 [ -0.39, 0.01 ]	
HERO-Tapsell 2009	16	2.4 (0.6)	16	2.5 (0.8)	• •		2.2 %	-0.10 [ -0.59, 0.39 ]	
Ley 2004 (I)	70	-0.02 (1.255)	66	-0.18 (0.7312)			- 3.9 %	0.16 [ -0.18, 0.50 ]	
Subtotal (95% CI)	171		176				14.3 %	-0.07 [ -0.30, 0.15 ]	
Heterogeneity: Tau <sup>2</sup> = 0.01	; Chi <sup>2</sup> = 3.01, df :	= 2 (P = 0.22);	l <sup>2</sup> =34%						
Test for overall effect: $Z = 0$	0.64 (P = 0.52)								
2 Baseline total PUFA 6 to	< 11%E								
MARINA - Sanders 201	I 80	0.2 (0.8987)	71	0.2 (0.4225)		<u> </u>	7.2 %	0.0 [ -0.22, 0.22 ]	
PREDIMED 2013 (2)	54	-1.14 (0.95)	54	-0.62 (0.92)	•		3.7 %	-0.52 [ -0.87, -0.17 ]	
PREDIMED 2013 (3)	58	-0.32 (0.76)	59	-0.3 (0.76)			5.4 %	-0.02 [ -0.30, 0.26 ]	
PREDIMED 2013 (4)	51	3.26 (0.86)	42	3.07 (0.7)		,	4.4 %	0.19 [ -0.13, 0.51 ]	
Simon 1997	38	3.09 (0.99)	34	2.79 (0.82)			2.8 %	0.30 [ -0.12, 0.72 ]	
WAHA - Ros 2016 (5)	260	-0.18 (0.48)	254	-0.03 (0.64)			13.6 %	-0.15 [ -0.25, -0.05 ]	
Subtotal (95% CI)	541		514			-	37.3 %	-0.05 [ -0.22, 0.12 ]	
Heterogeneity: $Tau^2 = 0.03$		f = 5 (P = 0.01)	$  ^2 = 65\%$						
Test for overall effect: $Z = 0$	0.58 (P = 0.56)								
						i			
				-	0.5 -0.25 0	0.25 0	).5		
				Favours	higher PUFA	Favours lowe	er PUFA		

(Continued . . . )

(... Continued)

							( continue
Study or subgroup	Higher PUFA		Lower PUFA		Mean Difference	Weight	Mear Difference
,	N	Mean(SD)	Ν	Mean(SD)	IV,Random,95% CI	-	IV,Random,95% C
3 Baseline total PUFA 11+9	6 E						
Subtotal (95% CI)	0		0				Not estimable
Heterogeneity: not applicab	le						
Test for overall effect: not a							
4 Baseline total PUFA uncle							
Ahn 2016	38	2.23 (1.33)	36	2.07 (0.13)		→ 2.8 %	0.16 [ -0.26, 0.58
AlphaOmega - ALA	562	-0.38 (0.71)	562	-0.39 (0.71)	-	14.5 %	0.01 [ -0.07, 0.09
HARP- Sacks 1995	31	3.41 (0.78)	28	3.16 (0.62)		→ 3.7 %	0.25 [ -0.11, 0.61
Mendis 2001	26	-0.65 (0.718)	28	-0.58 (0.9284)	•	2.6 %	-0.07 [ -0.51, 0.37
ORL 2013	170	0.08 (0.68)	165	-0.01 (0.6)		11.3 %	0.09 [ -0.04, 0.23
Rossing 1996	14	3.52 (0.9)	15	3.4 (0.97)	• • • •	→ I.2 %	0.12 [ -0.56, 0.80
Vijayakumar 2014	94	2.32 (0.75)	96	2.35 (0.56)		8.5 %	-0.03 [ -0.22, 0.16
WELCOME 2015	47	2.8 (0.9)	48	2.8 (0.8)		3.9 %	0.0 [ -0.34, 0.34
Subtotal (95% CI)	982		978		•	48.5 %	0.03 [ -0.03, 0.10
Heterogeneity: $Tau^2 = 0.0;$	Chi <sup>2</sup> = 3.55, df =	7 (P = 0.83); I <sup>2</sup>	=0.0%				
Test for overall effect: $Z = 1$	I.02 (P = 0.31)						
Total (95% CI)	1694		1668		+	100.0 %	-0.01 [ -0.09, 0.06 ]
Heterogeneity: Tau <sup>2</sup> = 0.01	; Chi <sup>2</sup> = 28.67, df	= 16 (P = 0.03	); I <sup>2</sup> =44%				
Test for overall effect: $Z = 0$	0.33 (P = 0.74)						
Test for subgroup difference	es: Chi <sup>2</sup> = 1.46, df	f = 2 (P = 0.48)	, l <sup>2</sup> =0.0%				

Favours higher PUFA Favours lower PUFA

(I) Change data

(2) Barcelona hospital cohort at 5 years, Casa 2016

(3) Damasceno 2013, Barcelona North subcohort, I year data

(4) Fernandez-Real 2012, Reus subcohort, 2 year data

(5) change from baseline

# Analysis 3.71. Comparison 3 Higher PUFA vs lower PUFA - continuous secondary outcomes, Outcome 71 LDL, mmoL/L - subgroup by replacement.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 3 Higher PUFA vs lower PUFA - continuous secondary outcomes

Outcome: 71 LDL, mmoL/L - subgroup by replacement

Study or subgroup H	igher PUFA N	Mean(SD)	Lower PUFA N	Mean(SD)	Mean Difference IV,Random,95% Cl	Weight	Mear Difference IV,Random,95% C
I PUFA replaced saturated fats				. ,			
HERO-Tapsell 2009	16	2.4 (0.6)	16	2.5 (0.8)		12.9 %	-0.10 [ -0.59, 0.39
Vijayakumar 2014	94	2.32 (0.75)	96	2.35 (0.56)		87.1 %	-0.03 [ -0.22, 0.16
Subtotal (95% CI)	110		112		-	100.0 %	-0.04 [ -0.21, 0.14
Heterogeneity: $Tau^2 = 0.0$ ; $Chi^2$	= 0.07, df =	(P = 0.79);	2 =0.0%				
Test for overall effect: $Z = 0.43$ (	· /						
2 PUFA replaced monounsatura							
AlphaOmega - ALA	562	-0.38 (0.71)	562	-0.39 (0.71)		30.4 %	0.01 [ -0.07, 0.09
HARP- Sacks 1995	31	3.41 (0.78)	28	3.16 (0.62)		+ 8.8 %	0.25 [ -0.11, 0.61
MARINA - Sanders 2011	80	0.2 (0.8987)	71	0.2 (0.4225)		16.5 %	0.0 [ -0.22, 0.22
PREDIMED 2013 (1)	58	-0.32 (0.76)	59	-0.3 (0.76)		12.6 %	-0.02 [ -0.30, 0.26
PREDIMED 2013 (2)	54	-1.14 (0.95)	54	-0.62 (0.92) 🔶		9.0 %	-0.52 [ -0.87, -0.17
PREDIMED 2013 (3)	51	3.26 (0.86)	42	3.07 (0.7)		→ I0.5 %	0.19 [ -0.13, 0.51
Rossing 1996	14	3.52 (0.9)	15	3.4 (0.97)		→ 3.0 %	0.12 [ -0.56, 0.80
WELCOME 2015	47	2.8 (0.9)	48	2.8 (0.8)		9.3 %	0.0 [ -0.34, 0.34
Subtotal (95% CI) Heterogeneity: Tau <sup>2</sup> = 0.01; Chi <sup>2</sup> Test for overall effect: $Z = 0.01$ (		F = 7 (P = 0.11)	<b>879</b> ;;   <sup>2</sup> =4   %		-	1 <b>00.0</b> %	0.00 [ -0.12, 0.12
3 PUFA replaced carbohydrates Dodin 2005	85	3.45 (0.67)	94	3.64 (0.67)		21.3 %	-0.19 [ -0.39, 0.01
Ley 2004 (4)	70	-0.02 (1.255)	66	-0.18 (0.7312)		- 10.2 %	0.16 [ -0.18, 0.50
MARINA - Sanders 2011	80	0.2 (0.8987)	71	0.2 (0.4225)	<b>_</b>	18.8 %	0.0 [ -0.22, 0.22
Mendis 2001	26	-0.65 (0.718)	28	-0.58 (0.9284) ←		6.7 %	-0.07 [ -0.5  , 0.37
Simon 1997	38	3.09 (0.99)	34	2.79 (0.82)		→ 7.4 %	0.30 [ -0.12, 0.72
WAHA - Ros 2016 (5)	260	-0.18 (0.48)	254	-0.03 (0.64)		35.6 %	-0.15 [ -0.25, -0.05
<b>Subtotal (95% CI)</b> Heterogeneity: Tau <sup>2</sup> = 0.01; Chi <sup>2</sup>	<b>559</b> <sup>2</sup> = 8.32, df =	= 5 (P = 0.14);	<b>547</b>   <sup>2</sup> =40%		•	100.0 %	-0.06 [ -0.18, 0.06

Favours higher PUFA Favours lower PUFA

(Continued . . . )

.60	2.4 (0.6) -0.02 (1.255) -0.18 (0.48)	16 66 254	2.5 (0.8) -0.18 (0.7312) -0.03 (0.64)	· · · · · · · · · · · · · · · · · · ·	II.8	0 % 0.16 [ -0.18, C	-
70 .60	-0.02 (1.255)	66	-0.18 (0.7312)	· •	21.0	0 % 0.16 [ -0.18, C	-
70 .60	-0.02 (1.255)	66	-0.18 (0.7312)		21.0	0 % 0.16 [ -0.18, C	-
.60	. ,		, , , , , , , , , , , , , , , , , , ,	-			).50 ]
	-0.18 (0.48)	254	-0.03 (0.64)				
			( )	_	67.2	2 % -0.15 [ -0.25, -0	).05 ]
¥6		336		-	100.0	% -0.08 [ -0.26, 0.2	10]
df =	= 2 (P = 0.23);	$ ^2 = 3 \%$					
)							
38	2.23 (1.33)	36	2.07 (0.13)		9.4	4 % 0.16 [ -0.26, 0	).58 ]
70	0.08 (0.68)	165	-0.01 (0.6)		90.6	6 % 0.09 [ -0.04, C	).23]
)8		201			<b>•</b> 100.0	% 0.10 [ -0.03, 0.2	23 ]
df =	$I (P = 0.77); I^2$	2 =0.0%					
)							
4, df	= 4 (P = 0.40)	), $ ^2 =  \% $					
, 9 1 ( 3	9) 38 170 <b>08</b> df = 3)	, df = 2 (P = 0.23); 9) 38 2.23 (1.33) 170 0.08 (0.68) <b>08</b> df = 1 (P = 0.77); F 3)	, df = 2 (P = 0.23); $l^2 = 31\%$ 9) 38 2.23 (1.33) 36 170 0.08 (0.68) 165 08 201 df = 1 (P = 0.77); $l^2 = 0.0\%$	, df = 2 (P = 0.23); $l^2 = 31\%$ 9) 38 2.23 (1.33) 36 2.07 (0.13) 170 0.08 (0.68) 165 -0.01 (0.6) 08 201 df = 1 (P = 0.77); $l^2 = 0.0\%$ 3)	, df = 2 (P = 0.23); $ ^2 = 31\%$ 9) 38 2.23 (1.33) 36 2.07 (0.13) 170 0.08 (0.68) 165 -0.01 (0.6) <b>08 201</b> df = 1 (P = 0.77); $ ^2 = 0.0\%$ 3)	$ \begin{array}{c} df = 2 \ (P = 0.23); \ l^2 = 31\% \\ 9) \\ 38  2.23 \ (1.33) \\ 170  0.08 \ (0.68) \\ 165  -0.01 \ (0.6) \\ \hline \end{array}  \begin{array}{c} \bullet \\ 90. \\ \hline \end{array}  \begin{array}{c} \bullet \\ 100.0 \\ \hline \end{array} $	$\begin{array}{c} df = 2 \ (P = 0.23); \ l^2 = 31\% \\ 9) \\ 38  2.23 \ (1.33) \\ 170  0.08 \ (0.68) \\ 165  -0.01 \ (0.6) \\ \hline \end{array} \begin{array}{c} 9.4 \ \% \\ 90.6 \ \% \\ 0.09 \ [-0.04, C] \\ 90.6 \ \% \\ 0.10 \ [-0.03, 0.2] \\ 100.0 \ \% \\ 0.10 \ [-0.03, 0.2] \\ 3) \end{array}$

-0.5 -0.25 0 0.25 0.5

Favours higher PUFA Favours lower PUFA

(1) Damasceno 2013, Barcelona North subcohort, 1 year data

(2) Barcelona hospital cohort at 5 years, Casa 2016

(3) Fernandez-Real 2012, Reus subcohort, 2 year data

(4) Change data

(5) change from baseline

(6) Change data

(7) change from baseline

# Analysis 3.72. Comparison 3 Higher PUFA vs lower PUFA - continuous secondary outcomes, Outcome 72 LDL, mmoL/L - subgroup by sex.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 3 Higher PUFA vs lower PUFA - continuous secondary outcomes

Outcome: 72 LDL, mmoL/L - subgroup by sex

I > 70% men Ahn 2016 AlphaOmega - ALA HARP- Sacks 1995 Ley 2004 (1) Mendis 2001 ORL 2013 Vijayakumar 2014	N 38 562 31 70 26 170	Mean(SD) 2.23 (1.33) -0.38 (0.71) 3.41 (0.78) -0.02 (1.255) -0.65 (0.718)	N 36 562 28 66	Mean(SD) 2.07 (0.13) -0.39 (0.71) 3.16 (0.62)	IV,Random,95% Cl	2.8 %	IV,Random,95% C 0.16 [ -0.26, 0.58 0.01 [ -0.07, 0.09
Ahn 2016 AlphaOmega - ALA HARP- Sacks 1995 Ley 2004 (1) Mendis 2001 ORL 2013	562 31 70 26	-0.38 (0.71) 3.41 (0.78) -0.02 (1.255)	562 28	-0.39 (0.71)			-
AlphaOmega - ALA HARP- Sacks 1995 Ley 2004 (1) Mendis 2001 ORL 2013	562 31 70 26	-0.38 (0.71) 3.41 (0.78) -0.02 (1.255)	562 28	-0.39 (0.71)			-
HARP- Sacks 1995 Ley 2004 (1) Mendis 2001 ORL 2013	31 70 26	3.41 (0.78) -0.02 (1.255)	28			14.5 %	0.0  [ -0.07. 0.09
Ley 2004 (1) Mendis 2001 ORL 2013	70 26	-0.02 (1.255)		3.16 (0.62)			L 0.07, 0.07
Mendis 2001 ORL 2013	26	· · · ·	66			3.7 %	0.25 [ -0.11, 0.61
ORL 2013		-0.65 (0.718)		-0.18 (0.7312)		3.9 %	0.16 [ -0.18, 0.50
	170		28	-0.58 (0.9284) ←		2.6 %	-0.07 [ -0.51, 0.37
Vijayakumar 2014		0.08 (0.68)	165	-0.01 (0.6)		11.3 %	0.09 [ -0.04, 0.23
	94	2.32 (0.75)	96	2.35 (0.56)		8.5 %	-0.03 [ -0.22, 0.16
Subtotal (95% CI)	991		981		-	47.3 %	0.04 [ -0.03, 0.10
Heterogeneity: $Tau^2 = 0.0$ ; $Chi^2 = 3$	8.96, df =	6 (P = 0.68); I <sup>2</sup>	=0.0%				
Test for overall effect: $Z = 1.16$ (P =	= 0.25)						
2 > 70% women							
Dodin 2005	85	3.45 (0.67)	94	3.64 (0.67)		8.2 %	-0.19 [ -0.39, 0.01
Simon 1997	38	3.09 (0.99)	34	2.79 (0.82)		2.8 %	0.30 [ -0.12, 0.72
Subtotal (95% CI)	123		128			11.0 %	0.02 [ -0.46, 0.49
Heterogeneity: $Tau^2 = 0.09$ ; Chi <sup>2</sup> =	4.32, df =	= I (P = 0.04); I	<sup>2</sup> =77%				
Test for overall effect: $Z = 0.08$ (P =	= 0.94)						
3 men % women							
MARINA - Sanders 2011	80	0.2 (0.8987)	71	0.2 (0.4225)		7.2 %	0.0 [ -0.22, 0.22
PREDIMED 2013 (2)	54	-1.14 (0.95)	54	-0.62 (0.92) ←		3.7 %	-0.52 [ -0.87, -0.17
PREDIMED 2013 (3)	58	-0.32 (0.76)	59	-0.3 (0.76)		5.4 %	-0.02 [ -0.30, 0.26
PREDIMED 2013 (4)	51	3.26 (0.86)	42	3.07 (0.7)		4.4 %	0.19 [ -0.13, 0.51
Rossing 1996	14	3.52 (0.9)	15	3.4 (0.97)		1.2 %	0.12 [ -0.56, 0.80
WAHA - Ros 2016 (5)	260	-0.18 (0.48)	254	-0.03 (0.64)		13.6 %	-0.15 [ -0.25, -0.05
WELCOME 2015	47	2.8 (0.9)	48	2.8 (0.8)		3.9 %	0.0 [ -0.34, 0.34
Subtotal (95% CI)	564		543			39.5 %	-0.07 [ -0.21, 0.06

-0.5 -0.25 0 0.25 0.5

Favours higher PUFA Favours lower PUFA

(Continued . . . )

							( Continued)
Study or subgroup	Higher PUFA	Lo	wer PUFA		Mean Difference	Weight	Mean Difference
	Ν	Mean(SD)	Ν	Mean(SD)	IV,Random,95% CI		IV,Random,95% CI
Test for overall effect: Z =	1.05 (P = 0.29)						
4 sex not reported							
HERO-Tapsell 2009	16	2.4 (0.6)	16	2.5 (0.8) 🕇		2.2 %	-0.10 [ -0.59, 0.39 ]
Subtotal (95% CI)	16		16	_		2.2 %	-0.10 [ -0.59, 0.39 ]
Heterogeneity: not applicab	ble						
Test for overall effect: $Z = 0$	0.40 (P = 0.69)						
Total (95% CI)	1694		1668		+	100.0 %	-0.01 [ -0.09, 0.06 ]
Heterogeneity: $Tau^2 = 0.01$	; Chi <sup>2</sup> = 28.67, df	= 16 (P = 0.03); 1 <sup>2</sup>	=44%				
Test for overall effect: $Z = 0$	0.33 (P = 0.74)						
Test for subgroup difference	es: Chi <sup>2</sup> = 2.28, df	= 3 (P = 0.52), I <sup>2</sup>	=0.0%				
				1		Ĩ	
				-0.5	-0.25 0 0.25	0.5	

Favours higher PUFA Favours lower PUFA

(I) Change data

(2) Barcelona hospital cohort at 5 years, Casa 2016

(3) Damasceno 2013, Barcelona North subcohort, 1 year data

(4) Fernandez-Real 2012, Reus subcohort, 2 year data

(5) change from baseline

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# Analysis 3.73. Comparison 3 Higher PUFA vs lower PUFA - continuous secondary outcomes, Outcome 73 LDL, mmoL/L - subgroup by age.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 3 Higher PUFA vs lower PUFA - continuous secondary outcomes

Outcome: 73 LDL, mmoL/L - subgroup by age

Study or subgroup	Higher PUFA		Lower PUFA		Mean Difference	Weight	Mear Difference
	Ν	Mean(SD)	Ν	Mean(SD)	IV,Random,95% CI		IV,Random,95% C
I Mean age < 50 years							
Rossing 1996	14	3.52 (0.9)	15	3.4 (0.97)	• •		0.12 [ -0.56, 0.80
Simon 1997	38	3.09 (0.99)	34	2.79 (0.82)			0.30 [ -0.12, 0.72
Subtotal (95% CI)	52		49			- 4.0 %	0.25 [ -0.11, 0.61
Heterogeneity: $Tau^2 = 0.0$ ; (	$Chi^2 = 0.20, df =$	$  (P = 0.66);  ^2$	=0.0%				
Test for overall effect: $Z = I$	· /						
2 Mean age 50 to < 65 year					_		
Dodin 2005	85	3.45 (0.67)	94	3.64 (0.67)		8.2 %	-0.19 [ -0.39, 0.01
HARP- Sacks 1995	31	3.41 (0.78)	28	3.16 (0.62)		• 3.7 %	0.25 [ -0.11, 0.61
HERO-Tapsell 2009	16	2.4 (0.6)	16	2.5 (0.8)	· · · · · · · · · · · · · · · · · · ·	2.2 %	-0.10 [ -0.59, 0.39
Ley 2004 (I)	70	-0.02 (1.255)	66	-0.18 (0.7312)		- 3.9 %	0.16 [ -0.18, 0.50
MARINA - Sanders 2011	80	0.2 (0.8987)	71	0.2 (0.4225)	<b>+</b>	7.2 %	0.0 [ -0.22, 0.22
ORL 2013	170	0.08 (0.68)	165	-0.01 (0.6)		11.3 %	0.09 [ -0.04, 0.23
Vijayakumar 2014	94	2.32 (0.75)	96	2.35 (0.56)		8.5 %	-0.03 [ -0.22, 0.16
WELCOME 2015	47	2.8 (0.9)	48	2.8 (0.8)		3.9 %	0.0 [ -0.34, 0.34
Subtotal (95% CI)	593		584		+	<b>48.8</b> %	0.01 [ -0.08, 0.10
Heterogeneity: $Tau^2 = 0.00;$	$Chi^2 = 8.25, df$	= 7 (P = 0.3 I);	$ ^2 =  5\% $				
Test for overall effect: $Z = 0$	.24 (P = 0.81)						
3 Mean age 65+ years							
AlphaOmega - ALA	562	-0.38 (0.71)	562	-0.39 (0.71)		14.5 %	0.01 [ -0.07, 0.09
PREDIMED 2013 (2)	58	-0.32 (0.76)	59	-0.3 (0.76)		5.4 %	-0.02 [ -0.30, 0.26
PREDIMED 2013 (3)	51	3.26 (0.86)	42	3.07 (0.7)		► 4.4 %	0.19 [ -0.13, 0.51
PREDIMED 2013 (4)	54	-1.14 (0.95)	54	-0.62 (0.92)	·	3.7 %	-0.52 [ -0.87, -0.17
WAHA - Ros 2016 (5)	260	-0.18 (0.48)	254	-0.03 (0.64)		13.6 %	-0.15 [ -0.25, -0.05
Subtotal (95% CI)	985		971		-	41.8 %	-0.08 [ -0.23, 0.07
Heterogeneity: $Tau^2 = 0.02$ ;	Chi <sup>2</sup> = 14.98, df	r = 4 (P = 0.005)	5); I <sup>2</sup> =73%				
Test for overall effect: $Z = I$	.04 (P = 0.30)						
4 Mean age unclear							
						1	
				-(	0.5 -0.25 0 0.25 (	0.5	

(Continued ...)

								( Continued)
Study or subgroup	Higher PUFA		Lower PUFA			Mean rence	Weight	Mean Difference
	Ν	Mean(SD)	Ν	Mean(SD)	IV,Rando	m,95% Cl		IV,Random,95% CI
Ahn 2016	38	2.23 (1.33)	36	2.07 (0.13)		+		0.16 [ -0.26, 0.58 ]
Mendis 2001	26	-0.65 (0.718)	28	-0.58 (0.9284)	•	<u> </u>	2.6 %	-0.07 [ -0.51, 0.37 ]
Subtotal (95% CI)	64		64				5.4 %	0.05 [ -0.26, 0.36 ]
Heterogeneity: $Tau^2 = 0.0;$	Chi <sup>2</sup> = 0.54, df =	I (P = 0.46); I <sup>2</sup>	=0.0%					
Test for overall effect: $Z = 0$	0.32 (P = 0.75)							
Total (95% CI)	1694		1668		-	•	100.0 %	-0.01 [ -0.09, 0.06 ]
Heterogeneity: $Tau^2 = 0.01$	$Chi^2 = 28.67, df$	= 16 (P = 0.03	3); I <sup>2</sup> =44%					
Test for overall effect: $Z = 0$	0.33 (P = 0.74)							
Test for subgroup difference	es: Chi <sup>2</sup> = 3.14, dt	f = 3 (P = 0.37)	, l <sup>2</sup> =4%					

-0.5 -0.25 0 0.25 0.5 Favours higher PUFA Favours lower PUFA

(I) Change data

(2) Damasceno 2013, Barcelona North subcohort, I year data

(3) Fernandez-Real 2012, Reus subcohort, 2 year data

(4) Barcelona hospital cohort at 5 years, Casa 2016

(5) change from baseline

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## Analysis 3.74. Comparison 3 Higher PUFA vs lower PUFA - continuous secondary outcomes, Outcome 74 LDL, mmoL/L - subgroup by statin use.

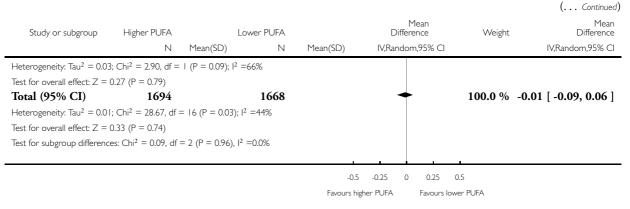
Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 3 Higher PUFA vs lower PUFA - continuous secondary outcomes

Outcome: 74 LDL, mmoL/L - subgroup by statin use

Study or subgroup	Higher PUFA		Lower PUFA		Mean Difference	Weight	Mear Difference
	Ν	Mean(SD)	Ν	Mean(SD)	IV,Random,95% CI		IV,Random,95% C
I < 50% on statins							
Dodin 2005	85	3.45 (0.67)	94	3.64 (0.67)		8.2 %	-0.19 [ -0.39, 0.01
HARP- Sacks 1995	31	3.41 (0.78)	28	3.16 (0.62)		• 3.7 %	0.25 [ -0.11, 0.61
MARINA - Sanders 2011	80	0.2 (0.8987)	71	0.2 (0.4225)		7.2 %	0.0 [ -0.22, 0.22
Mendis 2001	26	-0.65 (0.718)	28	-0.58 (0.9284)	·	2.6 %	-0.07 [ -0.51, 0.37
ORL 2013	170	0.08 (0.68)	165	-0.01 (0.6)		11.3 %	0.09 [ -0.04, 0.23
PREDIMED 2013 (1)	51	3.26 (0.86)	42	3.07 (0.7)		4.4 %	0.19 [ -0.13, 0.51
PREDIMED 2013 (2)	54	-1.14 (0.95)	54	-0.62 (0.92) 🕇	·	3.7 %	-0.52 [ -0.87, -0.17
PREDIMED 2013 (3)	58	-0.32 (0.76)	59	-0.3 (0.76)		5.4 %	-0.02 [ -0.30, 0.26
Rossing 1996	14	3.52 (0.9)	15	3.4 (0.97)		• 1.2 %	0.12 [ -0.56, 0.80
Simon 1997	38	3.09 (0.99)	34	2.79 (0.82)		• 2.8 %	0.30 [ -0.12, 0.72
						50 5 0/	0.00 [ -0.13, 0.13
Heterogeneity: $Tau^2 = 0.02$ ; (		7 = 9 (P = 0.02)	<b>590</b> ; I <sup>2</sup> =53%			50.5 %	0.00 [ -0.13, 0.13
<b>Subtotal (95% CI)</b> Heterogeneity: Tau <sup>2</sup> = 0.02; G Test for overall effect: Z = 0.0 2 50+% on statins	$Chi^2 = 19.18, df$	F = 9 (P = 0.02)				50.5 %	0.00 [ -0.13, 0.13
Heterogeneity: Tau <sup>2</sup> = 0.02; ( Test for overall effect: $Z = 0.0$	$Chi^2 = 19.18, df$	F = 9 (P = 0.02) 2.23 (1.33)		2.07 (0.13)		<b>50.5 %</b>	
Heterogeneity: Tau <sup>2</sup> = 0.02; 0 Test for overall effect: $Z = 0.0$ 2 50+% on statins	$Chi^2 = 19.18, df$ 02 (P = 0.98)	, , , , , , , , , , , , , , , , , , ,	; I <sup>2</sup> =53%	2.07 (0.13) -0.39 (0.71)			0.16 [ -0.26, 0.58
Heterogeneity: Tau <sup>2</sup> = 0.02; ( Test for overall effect: Z = 0.0 2 50+% on statins Ahn 2016	Chi <sup>2</sup> = 19.18, df )2 (P = 0.98) 38	2.23 (1.33)	; l <sup>2</sup> =53% 36	· · · ·		• 2.8 %	0.16 [ -0.26, 0.58
Heterogeneity: Tau <sup>2</sup> = 0.02; 6 Test for overall effect: Z = 0.6 2 50+% on statins Ahn 2016 AlphaOmega - ALA	Chi <sup>2</sup> = 19.18, df 02 (P = 0.98) 38 562	2.23 (1.33) -0.38 (0.71)	; I <sup>2</sup> =53% 36 562	-0.39 (0.71)		• 2.8 % 14.5 %	0.16 [ -0.26, 0.58 0.01 [ -0.07, 0.09 -0.10 [ -0.59, 0.39
Heterogeneity: Tau <sup>2</sup> = 0.02; ( Test for overall effect: Z = 0.0 2 50+% on statins Ahn 2016 AlphaOmega - ALA HERO-Tapsell 2009	Chi <sup>2</sup> = 19.18, df )2 (P = 0.98) 38 562 16	2.23 (1.33) -0.38 (0.71) 2.4 (0.6)	;   <sup>2</sup> =53% 36 562 16	-0.39 (0.71) 2.5 (0.8)		• 2.8 % 14.5 % 2.2 %	0.16 [ -0.26, 0.58 0.01 [ -0.07, 0.09 -0.10 [ -0.59, 0.39 -0.03 [ -0.22, 0.16
Heterogeneity: Tau <sup>2</sup> = 0.02; 0 Test for overall effect: Z = 0.0 2 50+% on statins Ahn 2016 AlphaOmega - ALA HERO-Tapsell 2009 Vijayakumar 2014 WELCOME 2015 <b>Subtotal (95% CI)</b> Heterogeneity: Tau <sup>2</sup> = 0.0; C Test for overall effect: Z = 0.1	Chi <sup>2</sup> = 19.18, df )2 (P = 0.98) 38 562 16 94 47 <b>757</b> hi <sup>2</sup> = 0.83, df = 5 (P = 0.88)	2.23 (1.33) -0.38 (0.71) 2.4 (0.6) 2.32 (0.75) 2.8 (0.9)	;   <sup>2</sup> =53% 36 562 16 96 48 <b>758</b>	-0.39 (0.71) 2.5 (0.8) + 2.35 (0.56)		• 2.8 % 14.5 % 2.2 % 8.5 %	0.16 [ -0.26, 0.58 0.01 [ -0.07, 0.09 -0.10 [ -0.59, 0.39 -0.03 [ -0.22, 0.16 0.0 [ -0.34, 0.34 <b>0.01 [ -0.07, 0.08</b>
Heterogeneity: Tau <sup>2</sup> = 0.02; 0 Test for overall effect: Z = 0.0 2 50+% on statins Ahn 2016 AlphaOmega - ALA HERO-Tapsell 2009 Vijayakumar 2014 WELCOME 2015 <b>Subtotal (95% CI)</b> Heterogeneity: Tau <sup>2</sup> = 0.0; C	Chi <sup>2</sup> = 19.18, df (P = 0.98) 38 562 16 94 47 <b>757</b> hi <sup>2</sup> = 0.83, df = 5 (P = 0.88) ar	2.23 (1.33) -0.38 (0.71) 2.4 (0.6) 2.32 (0.75) 2.8 (0.9)	;   <sup>2</sup> =53% 36 562 16 96 48 <b>758</b> =0.0%	-0.39 (0.71) 2.5 (0.8) + 2.35 (0.56)		• 2.8 % 14.5 % 2.2 % 8.5 % 3.9 %	0.16 [ -0.26, 0.58 0.01 [ -0.07, 0.09 -0.10 [ -0.59, 0.39 -0.03 [ -0.22, 0.16 0.0 [ -0.34, 0.34
Heterogeneity: Tau <sup>2</sup> = 0.02; 0 Test for overall effect: Z = 0.0 2 50+% on statins Ahn 2016 AlphaOmega - ALA HERO-Tapsell 2009 Vijayakumar 2014 WELCOME 2015 <b>Subtotal (95% CI)</b> Heterogeneity: Tau <sup>2</sup> = 0.0; C Test for overall effect: Z = 0. 3 Percentage on statins uncle	Chi <sup>2</sup> = 19.18, df (P = 0.98) 38 562 16 94 47 <b>757</b> hi <sup>2</sup> = 0.83, df = 5 (P = 0.88) ar	2.23 (1.33) -0.38 (0.71) 2.4 (0.6) 2.32 (0.75) 2.8 (0.9) 4 (P = 0.93); I <sup>2</sup>	;   <sup>2</sup> =53% 36 562 16 96 48 <b>758</b> =0.0%	-0.39 (0.71) 2.5 (0.8) • 2.35 (0.56) 2.8 (0.8)		<ul> <li>2.8 %</li> <li>14.5 %</li> <li>2.2 %</li> <li>8.5 %</li> <li>3.9 %</li> <li>31.9 %</li> </ul>	0.16 [ -0.26, 0.58 0.01 [ -0.07, 0.09 -0.10 [ -0.59, 0.39 -0.03 [ -0.22, 0.16 0.0 [ -0.34, 0.34 <b>0.01 [ -0.07, 0.08</b>

(Continued ...)



(1) Fernandez-Real 2012, Reus subcohort, 2 year data

(2) Barcelona hospital cohort at 5 years, Casa 2016

(3) Damasceno 2013, Barcelona North subcohort, I year data

(4) Change data

(5) change from baseline

## Analysis 3.75. Comparison 3 Higher PUFA vs lower PUFA - continuous secondary outcomes, Outcome 75 LDL, mmoL/L - subgroup by intervention type.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 3 Higher PUFA vs lower PUFA - continuous secondary outcomes

Outcome: 75 LDL, mmoL/L - subgroup by intervention type

Study or subgroup	Higher PUFA		Lower PUFA		Mean Difference	Weight	Mear Difference
	N	Mean(SD)	Ν	Mean(SD)	IV,Random,95% CI		IV,Random,95% C
I Dietary advice							
Ley 2004 (I)	70	-0.02 (1.255)	66	-0.18 (0.7312)		3.9 %	0.16 [ -0.18, 0.50
Simon 1997	38	3.09 (0.99)	34	2.79 (0.82)		2.8 %	0.30 [ -0.12, 0.72
Subtotal (95% CI)	108		100			6.8 %	0.22 [ -0.05, 0.48
Heterogeneity: $Tau^2 = 0.0$ ; (	Chi <sup>2</sup> = 0.26, df =	(P = 0.6 );   <sup>2</sup>	2 =0.0%				
Test for overall effect: $Z = I$	.60 (P = 0.11)						
2 Supplemental foods % die	t provided						
AlphaOmega - ALA	562	-0.38 (0.71)	562	-0.39 (0.71)		14.5 %	0.01 [ -0.07, 0.09
HERO-Tapsell 2009	16	2.4 (0.6)	16	2.5 (0.8)	· · · · · · · · · · · · · · · · · · ·	2.2 %	-0.10 [ -0.59, 0.39
PREDIMED 2013 (2)	58	-0.32 (0.76)	59	-0.3 (0.76)		5.4 %	-0.02 [ -0.30, 0.26
PREDIMED 2013 (3)	54	-1.14 (0.95)	54	-0.62 (0.92) 🕇		3.7 %	-0.52 [ -0.87, -0.17
PREDIMED 2013 (4)	51	3.26 (0.86)	42	3.07 (0.7)		4.4 %	0.19 [ -0.13, 0.51
Vijayakumar 2014	94	2.32 (0.75)	96	2.35 (0.56)		8.5 %	-0.03 [ -0.22, 0.16
WAHA - Ros 2016 (5)	260	-0.18 (0.48)	254	-0.03 (0.64)		13.6 %	-0.15 [ -0.25, -0.05
Subtotal (95% CI)	1095		1083		-	52.5 %	-0.07 [ -0.18, 0.05
Heterogeneity: $Tau^2 = 0.01$ ;	$Chi^2 = 15.09, dt$	f = 6 (P = 0.02)	); I <sup>2</sup> =60%				
Test for overall effect: $Z = I$	I9 (P = 0.23)						
3 Supplements (capsules % (	unusual foods)						
Ahn 2016	38	2.23 (1.33)	36	2.07 (0.13)		2.8 %	0.16 [ -0.26, 0.58
Dodin 2005	85	3.45 (0.67)	94	3.64 (0.67)		8.2 %	-0.19 [ -0.39, 0.01
HARP- Sacks 1995	31	3.41 (0.78)	28	3.16 (0.62)		3.7 %	0.25 [ -0.11, 0.61
MARINA - Sanders 2011	80	0.2 (0.8987)	71	0.2 (0.4225)		7.2 %	0.0 [ -0.22, 0.22
ORL 2013	170	0.08 (0.68)	165	-0.01 (0.6)	+	11.3 %	0.09 [ -0.04, 0.23
Rossing 1996	14	3.52 (0.9)	15	3.4 (0.97)		1.2 %	0.12 [ -0.56, 0.80
WELCOME 2015	47	2.8 (0.9)	48	2.8 (0.8)		3.9 %	0.0 [ -0.34, 0.34
Subtotal (95% CI)	465		457		-	38.2 %	0.02 [ -0.09, 0.13

-0.5 -0.25 0 0.25 0.5

Favours higher PUFA Favours lower PUFA

(Continued ...)

								( Continued)
Study or subgroup	Higher PUFA		Lower PUFA			Mean erence	Weight	Mean Difference
	Ν	Mean(SD)	Ν	Mean(SD)	IV,Rando	om,95% Cl		IV,Random,95% CI
Test for overall effect: $Z = 0$	0.43 (P = 0.67)							
4 Any combination								
Mendis 2001	26	-0.65 (0.718)	28	-0.58 (0.9284)	•		2.6 %	-0.07 [ -0.51, 0.37 ]
Subtotal (95% CI)	26		28				2.6 %	-0.07 [ -0.51, 0.37 ]
Heterogeneity: not applicab	ble							
Test for overall effect: $Z = 0$	0.31 (P = 0.76)							
Total (95% CI)	1694		1668		-	•	100.0 %	-0.01 [ -0.09, 0.06 ]
Heterogeneity: $Tau^2 = 0.01$	; Chi <sup>2</sup> = 28.67, df	= 16 (P = 0.03	3); l <sup>2</sup> =44%					
Test for overall effect: $Z = 0$	0.33 (P = 0.74)							
Test for subgroup difference	es: Chi <sup>2</sup> = 4.24, d	f = 3 (P = 0.24)	, I <sup>2</sup> =29%					
				-	0.5 -0.25 (	0.25	0.5	

Favours higher PUFA Favours lower PUFA

(I) Change data

(2) Damasceno 2013, Barcelona North subcohort, I year data

(3) Barcelona hospital cohort at 5 years, Casa 2016

(4) Fernandez-Real 2012, Reus subcohort, 2 year data

(5) change from baseline

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# Analysis 4.1. Comparison 4 Higher PUFA vs lower PUFA intake - tertiary outcomes, Outcome I SYSTOLIC BLOOD PRESSURE (sBP, mmHg).

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 4 Higher PUFA vs lower PUFA intake - tertiary outcomes

Outcome: I SYSTOLIC BLOOD PRESSURE (sBP, mmHg)

Study or subgroup	Higher PUFA		Lower PUFA		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	Ν	Mean(SD)	IV,Random,95% CI	-	IV,Random,95% CI
AlphaOmega - ALA	632	-0.24 (20)	632	-2.29 (21.3)		19.8 %	2.05 [ -0.23, 4.33 ]
Dodin 2005	85	120.6 (14.4)	94	120.8 (17.1)		9.6 %	-0.20 [ -4.82, 4.42 ]
HARP- Sacks 1995	31	129 (16)	28	137 (29)	<b>←</b> →	1.9 %	-8.00 [ -20.13, 4.13 ]
Ley 2004 (I)	70	3.37 (26.8568)	66	-4.1 (16.1668)		→ 4.6 %	7.47 [ 0.07, 14.87 ]
MARINA - Sanders 2011	80	8.3 ( 2. )	71	22.  ( 2.7)		11.7 %	-3.80 [ -7.77, 0.17 ]
MRC 1968	88	2 (0)	89	0 (0)			Not estimable
PREDIMED 2013 (2)	2367	-0.9 (21.6)	2441	0.42 (22.2)		26.1 %	-1.32 [ -2.56, -0.08 ]
Rossing 1996	14	42 ( 8.7)	15	144 (15.5)		→ I.8 %	-2.00 [ -14.55, 10.55 ]
Sydney Diet-Heart 1978	221	36.8 ( 6. )	237	37.9 ( 6. )		16.1 %	-1.10 [ -4.05, 1.85 ]
WELCOME 2015	47	33.3 ( 3.7)	48	33.9 (  .3)		8.4 %	-0.60 [ -5.66, 4.46 ]
Total (95% CI)	3635		3721		•	100.0 %	-0.47 [ -2.20, 1.26 ]
Heterogeneity: $Tau^2 = 2.59$ ;	Chi <sup>2</sup> = 15.13, d	f = 8 (P = 0.06);	$ ^2 = 47\%$				
Test for overall effect: $Z = 0$ .	53 (P = 0.59)						
Test for subgroup differences	: Not applicable	2					
						1	
				-	10 -5 0 5	10	
				Favours	higher PUFA Favours lov	wer PUFA	

(I) change data

(2) Toledo BMC Med 2013

# Analysis 4.2. Comparison 4 Higher PUFA vs lower PUFA intake - tertiary outcomes, Outcome 2 DIASTOLIC BLOOD PRESSURE (dBP, mmHg).

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 4 Higher PUFA vs lower PUFA intake - tertiary outcomes

Outcome: 2 DIASTOLIC BLOOD PRESSURE (dBP, mmHg)

Mean(SD) -1.79 (10.3) 75.5 (10.9) 77 (7) 2.11 (17.4862) -1.2 (6.1652) -1 (0)	N 632 94 28 66 71 89	Mean(SD) -2.75 (10.3) 76.1 (11.9) 77 (7) -1.73 (12.2673) 72.9 (6.3372) 3 (0)	IV,Random,95% CI	23.5 % 5.0 % 4.4 % - 2.3 % 11.6 %	-0.60 [ -3.94, 2.74 ] 0.0 [ -3.58, 3.58 ] 3.84 [ -1.21, 8.89 ] -1.70 [ -3.70, 0.30 ]
75.5 (10.9) 77 (7) 2.11 (17.4862) 71.2 (6.1652)	94 28 66 71	76.1 (11.9) 77 (7) -1.73 (12.2673) 72.9 (6.3372)		5.0 % 4.4 % - 2.3 %	-0.60 [ -3.94, 2.74 ] 0.0 [ -3.58, 3.58 ] 3.84 [ -1.21, 8.89 ] -1.70 [ -3.70, 0.30 ]
77 (7) 2.11 (17.4862) 71.2 (6.1652)	28 66 71	77 (7) -1.73 (12.2673) 72.9 (6.3372)	 	4.4 % - 2.3 %	0.0 [ -3.58, 3.58 ] 3.84 [ -1.21, 8.89 ] -1.70 [ -3.70, 0.30 ]
2.11 (17.4862) 71.2 (6.1652)	66 71	-1.73 (12.2673) 72.9 (6.3372)		- 2.3 %	3.84 [ -1.21, 8.89 ] -1.70 [ -3.70, 0.30 ]
71.2 (6.1652)	71	72.9 (6.3372)			-1.70 [ -3.70, 0.30 ]
· · · · ·		, ,		11.6 %	
-1 (0)	89	3 (0)			
					Not estimable
-0.61 (12.8)	2441	-1.41 (12.7)	-	33.1 %	0.80 [ 0.08, 1.52 ]
88.4 (9.4)	237	88.7 (9.6)		14.1 %	-0.30 [ -2.04, 1.44 ]
81.7 (8.2)	48	82.9 (6.5)		6.1 %	-1.20 [ -4.18, 1.78 ]
	<b>3706</b>   <sup>2</sup> =3  %		•	100.0 %	0.24 [ -0.55, 1.02 ]
e					
	7 81.7 (8.2)	7 81.7 (8.2) 48 <b>3706</b> df = 7 (P = 0.18); I <sup>2</sup> = 31%	7 81.7 (8.2) 48 82.9 (6.5) 3706 df = 7 (P = 0.18); l <sup>2</sup> = 31%	7 81.7 (8.2) 48 82.9 (6.5) 3706 df = 7 (P = 0.18); $l^2 = 31\%$ le	7       81.7 (8.2)       48       82.9 (6.5)       6.1 %

Favours higher PUFA Favours lower PUFA

(I) Change data

(2) Toledo BMC MED 2013

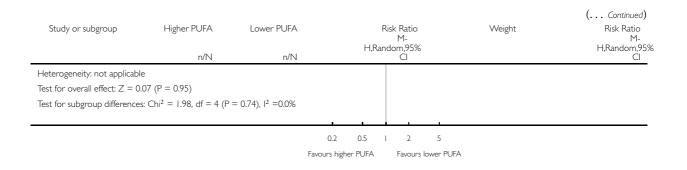
## Analysis 4.3. Comparison 4 Higher PUFA vs lower PUFA intake - tertiary outcomes, Outcome 3 SERIOUS ADVERSE EVENTS (SAEs).

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 4 Higher PUFA vs lower PUFA intake - tertiary outcomes

Outcome: 3 SERIOUS ADVERSE EVENTS (SAEs)

Study or subgroup	Higher PUFA	Lower PUFA	Ris	k Ratio M-	Weight	Risk Ratio M-
	n/N	n/N	H,Rand	om,95% Cl		H,Random,9 Cl
I Pulmonary embolism						
DART fat 1989	4/1018	2/1015		<mark>,</mark>	77.6 %	1.99 [ 0.37, 10.86 ]
Rose 1965	1/28	0/26	4	<b></b>	22.4 %	2.79 [ 0.12, 65.66 ]
Subtotal (95% CI)	1046	1041			100.0 %	2.15 [ 0.48, 9.57 ]
Total events: 5 (Higher PUFA)	, 2 (Lower PUFA)					
Heterogeneity: $Tau^2 = 0.0$ ; Ch	$hi^2 = 0.03$ , $df = 1$ (P =	0.85); l <sup>2</sup> =0.0%				
Test for overall effect: $Z = 1.00$	0 (P = 0.32)					
2 Multiple Sclerosis worsened	or had acute attack - (	GLA supplement				
Bates 1977	24/76	21/76		<b></b>	9.8 %	1.14 [ 0.70, 1.87 ]
Bates 1978	51/58	46/58			90.2 %	.   [ 0.94,  .30 ]
Subtotal (95% CI)	134	134	•	•	100.0 %	1.11 [ 0.95, 1.30 ]
Total events: 75 (Higher PUFA		2				
Heterogeneity: $Tau^2 = 0.0$ ; Ch		0.89); l <sup>2</sup> =0.0%				
Test for overall effect: $Z = 1.3$	5 (P = 0.18)					
3 Bleeding			_			
EPIC-1 2008	0/187	2/184	-		7.7 %	0.20 [ 0.01, 4.07 ]
EPIC-2 2008	9/189	10/188			92.3 %	0.90 [ 0.37, 2.15 ]
Subtotal (95% CI)	376	372			100.0 %	0.80 [ 0.34, 1.85 ]
Total events: 9 (Higher PUFA)	, 12 (Lower PUFA)					
Heterogeneity: $Tau^2 = 0.0$ ; Ch	$m^2 = 0.90$ , df = 1 (P =	0.34); l <sup>2</sup> =0.0%				
Test for overall effect: $Z = 0.52$	3 (P = 0.60)					
4 GI hospitalisation				_		
Raitt 2005	7/100	4/100		- <mark></mark> +	100.0 %	1.75 [ 0.53, 5.79 ]
Subtotal (95% CI)	100	100			100.0 %	1.75 [ 0.53, 5.79 ]
Total events: 7 (Higher PUFA)	, 4 (Lower PUFA)					
Heterogeneity: not applicable						
Test for overall effect: $Z = 0.92$	2 (P = 0.36)					
5 Retinopathy						
PREDIMED 2013	20/1142	22/1282			100.0 %	1.02 [ 0.56, 1.86 ]
Subtotal (95% CI)	1142	1282	-		100.0 %	1.02 [ 0.56, 1.86 ]
Total events: 20 (Higher PUFA	A), 22 (Lower PUFA)					
			0.2 0.5 1	2 5		
			Favours higher PUFA	Favours lower Pl	JFA	
						(Continued



# Analysis 4.4. Comparison 4 Higher PUFA vs lower PUFA intake - tertiary outcomes, Outcome 4 DROPOUTS.

Review: Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease

Comparison: 4 Higher PUFA vs lower PUFA intake - tertiary outcomes

Outcome: 4 DROPOUTS

-

Study or subgroup	Higher PUFA	Lower PUFA	Risk Ratio M- H,Random,95%	Weight	Risk Ratio M- H,Random,95%
	n/N	n/N	Cl		Cl
AlphaOmega - ALA	189/1197	191/1236		10.0 %	1.02 [ 0.85, 1.23 ]
Bates 1978 (1)	3/29	6/29	H <del></del>	0.9 %	0.50 [ 0.14, 1.81 ]
Bates 1978 (2)	0/29	1/29	←	0.2 %	0.33 [ 0.01, 7.86 ]
Bates 1989	10/155	10/157	·	2.0 %	1.01 [ 0.43, 2.37 ]
Black 1994	28/66	28/66		5.8 %	1.00 [ 0.67, 1.49 ]
Brox 2001	13/80	3/40		1.1 %	2.17 [ 0.65, 7.17 ]
DIPP-Tokudome 2015	3/104	5/101	← → →	0.8 %	0.58 [ 0.14, 2.37 ]
Dodin 2005	26/101	17/98		3.9 %	1.48 [ 0.86, 2.56 ]
Dullaart 1992	2/20	4/20	₩	0.6 %	0.50 [ 0.10, 2.43 ]
EPIC-1 2008	80/188	91/186		9.2 %	0.87 [ 0.70, 1.09 ]
EPIC-2 2008	4/ 89	112/190	_ <b>-</b>	10.5 %	1.02 [ 0.87, 1.21 ]
FAAT - Leaf 2005	73/200	69/202		8.3 %	1.07 [ 0.82, 1.39 ]
GLAMT 1993	10/54	17/57	<u>← ,                                    </u>	2.8 %	0.62 [ 0.31, 1.23 ]
		Fav	0.5 0.7 I I.5 2 vours higher PUFA Favours lower PU	JFA	

(Continued . . . )

( Continuec Risk Ratio M-	Weight	Risk Ratio M-	Lower PUFA	Higher PUFA	Study or subgroup
H,Random,9 Cl		H,Random,95% Cl	n/N	n/N	
0.86 [ 0.41, 1.80 ]	2.5 %		11/39	10/41	HARP- Sacks 1995
1.29 [ 0.47, 3.53 ]	1.5 %		5/24	7/26	HERO-Tapsell 2009
0.99 [ 0.57, 1.73 ]	3.8 %		19/85	20/90	Ley 2004
0.71 [ 0.42, 1.19 ]	4.2 %		17/88	38/279	MARINA - Sanders 2011
2.00 [ 0.40, 10.11 ]	0.6 %	и	2/30	4/30	Mendis 2001
0.93 [ 0.45, 1.95 ]	2.5 %		/4	10/40	Mita 2007
1.19 [ 0.37, 3.77 ]	1.1 %	· · · · · · · · · · · · · · · · · · ·	5/99	6/100	Nodari 2011 AF
0.52 [ 0.29, 0.92 ]	3.7 %		21/167	22/336	ORL 2013
0.65 [ 0.38, 1.13 ]	3.9 %		26/100	17/100	Raitt 2005
0.56 [ 0.15, 2.10 ]	0.9 %	· · · · · · · · · · · · · · · · · · ·	5/26	3/28	Rose 1965
1.33 [ 0.35, 5.13 ]	0.9 %		3/18	4/18	Rossing 1996
0.82 [ 0.50, 1.36 ]	4.4 %		26/98	21/96	Simon 1997
2.01 [ 1.51, 2.67 ]	7.8 %		58/422	7/424	Veterans Admin 1969
1.50 [ 0.44, 5.15 ]	1.0 %		4/99	6/99	Vijayakumar 2014
1.07 [ 0.69, 1.66 ]	5.2 %		34/346	38/362	WAHA - Ros 2016
0.99 [ 0.87, 1.13 ]	100.0 %	+	4093	<b>4481</b> 301 (Lower PUFA)	<b>Fotal (95% CI)</b> otal events: 874 (Higher PUFA), 8
			0.01);  2 =41%	= 45.54, df = 27 (P =	leterogeneity: Tau <sup>2</sup> = 0.03; Chi <sup>2</sup> =
				= 0.89)	Test for overall effect: $Z = 0.13$ (P
				applicable	est for subgroup differences: Not

(1) Arms C vs D, both given spread

(2) Arms A vs B, both given capsules

# ADDITIONAL TABLES

Table 1. Risk of bias assessment - detailed assessment methods

Risk of bias element	Criteria for low risk of bias	Criteria for unclear	Criteria for high risk of bias
Selection bias: random se- quence generation	to generate the allocation se-	The trial authors have not de- scribed their method in suffi- cient detail for the assessment of whether it would produce	assessed as not truly random, and may not produce compara-

	low an assessment of whether it should produce comparable groups. For example "the ran- domisation sequence was com- puter-generated". We allowed that a good method of randomi- sation was strongly implied if the trial authors discussed stratification and/or blocking. Therefore, if they were not ex- plicit about their randomisa- tion method but did describe stratification or blocking we as- sessed this as low risk	comparable groups. For exam- ple, the trial authors state "the trial was randomised" and pro- vide no further information	
Selection bias: allocation con- cealment	The trial authors needed to have described the method used to conceal allocation sequence in sufficient detail to determine whether the allocations could have been foreseen in advance of, or during, enrolment. Good methods included putting allo- cation codes in opaque, sealed envelopes (ideally prepared by someone outside the treatment or assessment teams and se- quentially numbered), using a telephone allocation system af- ter the participants had con- sented to participate or provid- ing a random number that links to a specific set of capsules pre- pared and distributed centrally or by an arms-length pharma- cist	The authors gave insufficient detail as to method.	The allocation was known in advance of participants con- senting to take part in the trial
Performance bias: blinding of participants and personnel		Insufficient methodological de- tails were provided e.g. "the trial was blinded."	The trial was unblinded or where blinding was broken, e. g. "the capsules were visually identical but the participants re- ported a strong fishy flavour in the intervention group only."

	" However if the trial authors did not provide information on whether the blinding was ef- fective, but sufficient detail was given on a good method of blinding, then it was assumed that the blinding was effective and the risk of bias was low		
Detection bias: blinding of outcome assessment	Trial authors needed to have described measures used, if any, to blind outcome asses- sors from knowledge of which intervention a participant re- ceived. Ideally, they should also have provided information re- lating to whether the intended blinding was effective. For ex- ample, the authors could say "the outcome assessors had no knowledge of the group alloca- tion, and both the intervention and placebo capsules looked and tasted the same so the self-assessment scales were also blinded." However if the trial authors did not provide infor- mation on whether the blinding was effective, but sufficient de- tail was given on a good method of blinding of the assessors, then it was assumed that the blind- ing was effective and the risk of bias is low. All biochemical as- sessment (lipids, glucose, CRP, insulin, PSA etc.) were consid- ered at low risk of detection bias if outcome assessor blinding or double blinding was stated	tails were provided e.g. "the trial	The trial was unblinded or blinding was broken, e.g. for a self-assessment measure "the capsules were visually identical but the participants reported a strong fishy flavour in the inter- vention group only." (Because the level of blinding could vary by outcome assess- ment of risk of bias was based on blinding of the review's pri- mary outcome(s). Where pri- mary outcomes had different assessments we opted for the higher risk of bias but noted that risk of bias was lower for other outcomes
Attrition bias: incomplete outcome data	The trial authors needed to de- scribe the completeness of out- come data for each main out- come, including attrition and exclusions from the analysis. They needed to report the num- ber of attrition/exclusions, the numbers in each group at each time point, reasons for attri-	The trial authors didn't state reasons for attrition/exclusion, or were unclear about the num- bers lost to attrition/exclusion in each trial arm	The trial authors demonstrated a substantial difference in the rates of attrition/ exclusions be- tween the trial arms and/or > 20% of the baseline sample was lost over a year (> 10% over 6 months)

	tion/exclusion and any re-inclu- sions in analyses. Ideally, they would report how they imputed any missing data e.g. last obser- vation carried forward. There needed to be a reasonable bal- ance of attrition/exclusions be- tween trial arms and $\leq 20\%$ of the sample should be lost over a year		
Reporting bias: selective out- come reporting	The trial authors needed to have published their trial protocol or trials registry entry before the end of the trial's recruitment period i.e. prospectively. They needed to have reported on all of the primary and secondary outcomes listed in the protocol/ registry entry. Reporting addi- tional secondary outcomes in the results paper(s), although not ideal, was deemed to still be low risk	No trial protocol or trials reg- istry entry was found, it was registered retrospectively, or the dates of registration and partic- ipant recruitment were unclear	The trial authors did not re- port at least one primary or sec- ondary outcome listed in the protocol/registry entry OR the results paper(s) reported a pri- mary outcome that was not listed at all in the protocol or not listed as a primary outcome in the protocol
Other sources of bias: Atten- tion bias	The trial authors needed to have reported that participants in all trial arms received the same amount of attention and time from researchers and clinical teams. For example, "All partic- ipants attended the clinic for a baseline assessment which took 2 hours. They were then fol- lowed with monthly telephone calls, and finally attended for a 6 month assessment at the clinic which took 1 hour." If the trial only differed by the content of the capsules, and the assessment schedule was not stated to dif- fer between the two arms, it was assumed to be at low risk	The trial authors did not state the attention each arm received	Participants in different arms received different amounts of attention. For example, "The intervention group only at- tended for additional assess- ments at months 2, 4, and 6" or "the rates of relapse dif- fered substantially between the groups which led to differing amounts of treatment time and attention," or "the intervention group received a 40 minute di- etary education session."
Other sources of bias: limited compliance	to demonstrate an increase in PUFA fats over control in a	Biomarker data not reported or not in a way that could be inter- preted. Where lipid biomarker and TC contradicted each other we chose unclear	reported but did not suggest higher total PUFA in the appro-

	ponents of PUFA), or greater reduction in TC in the higher PUFA arm	
Other sources of bias: other	In the absence of any additional issues this item was coded "low risk of bias"	If fraud concerns had been raised and the paper had been withdrawn, or the trial author had been found guilty of fraud by a legal or medical entity the paper was excluded from the re- view. However if fraud concerns were raised, but the journal had not withdrawn the paper, and the trial author had not been formally sanctioned; then the trial was included in the review, but concerns were raised here, and the risk of bias for this item was high

LA: linoleic acid; PUFA: polyunsaturated fatty acids; TC: total cholesterol

# APPENDICES

#### Appendix I. Searches run for this review, to 27 April 2017

These searches have each been run from database inception, then de-duplicated with each other. The RCT filter for MEDLINE is the Cochrane sensitivity and precision-maximising RCT filter, and for Embase, terms as recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* have been applied (Lefebvre 2011).

# CENTRAL

#1 MeSH descriptor: [Fatty Acids, Essential] explode all trees

- #2 MeSH descriptor: [Fatty Acids, Unsaturated] this term only
- #3 ((polyunsaturat\* or poly-unsaturat\*) near/3 fat\*)
- #4 (poly\* adj4 unsat\* near/4 fatty acid\*)
- #5 PUFA
- #6 MeSH descriptor: [Fatty Acids, Omega-6] explode all trees
- #7 omega-6
- #8 (n-6 near/4 acid\*) or ("n 6" near/4 acid\*)
- #9 linoleic acid\*
- #10 MeSH descriptor: [Corn Oil] this term only
- #11 MeSH descriptor: [Cottonseed Oil] this term only
- #12 MeSH descriptor: [Olive Oil] this term only
- #13 MeSH descriptor: [Safflower Oil] this term only
- #14 MeSH descriptor: [Sesame Oil] this term only
- #15 MeSH descriptor: [Soybean Oil] this term only

#16 ((corn or maize or mazola) near/4 oil\*) #17 (cottonseed\* or (cotton next seed\*)) #18 (olive near/4 oil\*) #19 (safflower near/4 oil\*) #20 (sesame near/4 oil\*) #21 ((soy bean or soybean) near/4 (oil\* or fat\*)) #22 (so?a near/4 oil\*) #23 so?aoil\* #24 (soy near/4 oil\*) #25 (sunflower near/4 oil\*) #26 helianth\* #27 (grapeseed near/4 oil\*) #28 (canola near/4 oil\*) #29 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or # 20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 **MEDLINE Ovid** 1. exp fatty acids, essential/ 2. fatty acids, unsaturated/ 3. ((polyunsaturat\* or poly-unsaturat\*) adj3 fat\*).ti,ab. 4. (poly\* adj4 unsat\* adj4 fatty acid\*).ti,ab. 5. PUFA.ti,ab. 6. exp fatty acids, omega-6/ 7. omega-6.ti,ab. 8. (n-6 adj4 acid\*).ti,ab. 9. linoleic acid\*.ti.ab. 10. corn oil/ or cottonseed oil/ or olive oil/ or safflower oil/ or sesame oil/ or soybean oil/ 11. ((corn or maize or mazola) adj4 oil\*).ti,ab. 12. (cottonseed\* or (cotton adj seed\*)).ti,ab. 13. (olive adj4 oil\*).ti,ab. 14. (safflower adj4 oil\*).ti,ab. 15. (sesame adj4 oil\*).ti,ab. 16. ((soy bean or soybean) adj4 (oil\* or fat\*)).ti,ab. 17. (so?a adj4 oil\*).ti,ab. 18. so?aoil\*.ti,ab. 19. (soy adj4 oil\*).ti,ab. 20. (sunflower adj4 oil\*).ti,ab. 21. helianth\*.ti,ab. 22. (grapeseed adj4 oil\*).ti,ab. 23. (canola adj4 oil\*).ti,ab. 24. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 25. randomized controlled trial.pt. 26. controlled clinical trial.pt. 27. randomized.ab. 28. placebo.ab. 29. clinical trials as topic.sh. 30. randomly.ab. 31. trial.ti. 32. 25 or 26 or 27 or 28 or 29 or 30 or 31 33. exp animals/ not humans.sh. 34. 32 not 33 35. 24 and 34 **Embase** Ovid 1. exp essential fatty acid/

2. unsaturated fatty acid/ or docosapentaenoic acid/ or omega 6 fatty acid/ or polyunsaturated fatty acid/

3. ((polyunsaturat\* or poly-unsaturat\*) adj3 fat\*).ti,ab.

4. (poly\* adj4 unsat\* adj4 fatty acid\*).ti,ab.

5. PUFA.ti,ab.

6. omega-6.ti,ab.

7. (n-6 adj4 acid\*).ti,ab.

8. linoleic acid\*.ti,ab.

9. edible oil/ or canola oil/ or corn oil/ or cotton seed oil/ or olive oil/ or safflower oil/ or safflower oil plus soybean oil/ or sesame seed oil/ or soybean oil/ or sunflower oil/

10. ((corn or maize or mazola) adj4 oil\*).ti,ab.

11. (cottonseed\* or (cotton adj seed\*)).ti,ab.

- 12. (olive adj4 oil\*).ti,ab.
- 13. (safflower adj4 oil\*).ti,ab.
- 14. (sesame adj4 oil\*).ti,ab.
- 15. ((soy bean or soybean) adj4 (oil\* or fat\*)).ti,ab.
- 16. (so?a adj4 oil\*).ti,ab.
- 17. so?aoil\*.ti,ab.
- 18. (soy adj4 oil\*).ti,ab.
- 19. (sunflower adj4 oil\*).ti,ab.
- 20. helianth\*.ti,ab.
- 21. (grapeseed adj4 oil\*).ti,ab.
- 22. (canola adj4 oil\*).ti,ab.
- 23. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22
- 24. double blind procedure/
- 25. single blind procedure/
- 26. randomized controlled trial/
- 27. ((double\* or single\*) adj blind\*).ti,ab.
- 28. (random\* or placebo\*).ti,ab.
- 29. 24 or 25 or 26 or 27 or 28
- 30. (animal/ or nonhuman/) not human/
- 31. 29 not 30
- 32. 23 and 31

#### Appendix 2. Searches run for the allied review, to 27 April 2017

The searches for the omega-3 review (Abdelhamid 2018) were last run in 20 February 2002. We have updated the search strategies and have now re-run the searches to identify any records added to the databases since the last search. We applied date limits to the terms from the original strategies so that only new records would be found, but have not applied date limits to the newly added terms. The RCT filter for MEDLINE is the Cochrane sensitivity and precision-maximising RCT filter, and for Embase, we have applied terms as recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (Lefebvre 2011).

#### CENTRAL

- #1 MeSH descriptor: [Fish Oils] explode all trees
- #2 MeSH descriptor: [Linseed Oil] this term only
- #3 MeSH descriptor: [Linolenic Acids] this term only
- #4 MeSH descriptor: [Fatty Acids, Omega-3] explode all trees
- #5 (fish near/3 oil\*)
- #6 (oil\* near/3 (cod\* or marin\*))
- #7 (omega-3 or omega3 or (omega\* near/5 fat\*))
- #8 eicosapentaen\*
- #9 docosahexaen\*
- #10 (oil\* near/3 (flax\* or rapeseed\* or canola\*))
- #11 (Linolen\* or alpha-linolen\* or alphalinolen\*)

#12 (perilla\* or linseed\* or maxepa\*) #13 (oil\* near/3 (rape or colza)) #14 (marin\* near/3 lipid\*) #15 (naudicelle\* or herring\* or sild) #16 (clupe\* near/3 hareng\*) #17 (whitebait or sardine\* or sardina\* or pilchard\* or sprat\* or brisling\*) #18 (salmo\* near/3 trut\*) #19 (trout or bloater or kipper\* or salmon or mackerel\* or scomb\* or conger\* or tuna or tunny or tunafish or tuna-fish) #20 (thunnus\* or swordfish\* or xiphias\* or dogfish or scyliorrhinus\*) #21 (crab or crabs or (cancer pagarus)) #22 (DHA or EPA) #23 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or # 20 or #21 or #22 Publication Year from 2002 to 2016 #24 MeSH descriptor: [Salmoniformes] explode all trees #25 MeSH descriptor: [Tuna] this term only #26 MeSH descriptor: [alpha-Linolenic Acid] this term only #27 MeSH descriptor: [Flax] this term only #28 (fish near/3 (diet\* or capsul\* or nutrit\* or supplement\*)) #29 (icosapentaen\* or docosapentaen\*) #30 (oil\* near/3 (purslane or mustard\* or candlenut\* or stillingia or walnut\*)) #31 (laks or lax) #32 (ALA or DPA) #33 (algal near oil\*) #34 #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 #35 #23 or #34 **MEDLINE Ovid** 1. exp Fish Oils/ 2. Linseed Oil/ 3. linolenic acids/ or alpha-linolenic acid/ 4. Flax/ 5. exp Fatty Acids, Omega-3/ 6. (fish adj3 (diet\* or nutrit\* or oil\* or supplement\*)).ti,ab. 7. (oil\* adj3 (cod\* or marin\*)).ti,ab. 8. (omega-3 or omega3 or (omega\* adj5 fat\*)).ti,ab. 9. eicosapentaen\*.ti,ab. 10. docosahexaen\*.ti,ab. 11. (oil\* adj3 (flax\* or rapeseed\* or canola\*)).ti,ab. 12. (Linolen\* or alpha-linolen\* or alphalinolen\*).ti,ab. 13. (perilla\* or linseed\* or maxepa\*).ti,ab. 14. (oil\* adj3 (rape or colza)).ti,ab. 15. (marin\* adj3 lipid\*).ti,ab. 16. (naudicelle\* or herring\* or sild).ti,ab. 17. (clupe\* adj3 hareng\*).ti,ab. 18. (whitebait or sardine\* or sardina\* or pilchard\* or sprat\* or brisling\*).ti,ab. 19. (salmo\* adj3 trut\*).ti,ab. 20. (trout or bloater or kipper\* or salmon or mackerel\* or scomb\* or conger\* or tuna or tunny or tunafish or tuna-fish).ti,ab. 21. (thunnus\* or swordfish\* or xiphias\* or dogfish or scyliorrhinus\* or laks or lax).ti,ab. 22. (crab or crabs or cancer pagarus).ti,ab. 23. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 24. randomized controlled trial.pt. 25. controlled clinical trial.pt.

- 26. randomized.ab.
- 27. placebo.ab.

28. clinical trials as topic.sh. 29. randomly.ab. 30. trial.ti. 31. 24 or 25 or 26 or 27 or 28 or 29 or 30 32. exp animals/ not humans.sh. 33. 31 not 32 34. 23 and 33 35. limit 34 to ed=20020201-20160721 36. exp salmoniformes/ or tuna/ 37. (fish adj3 capsul\*).ti,ab. 38. icosapentaen\*.ti,ab. 39. docosapentaen\*.ti,ab. 40. (oil\* adj3 (purslane or mustard\* or candlenut\* or stillingia or walnut\*)).ti,ab. 41. 36 or 37 or 38 or 39 or 40 42. 33 and 41 43. 35 or 42 **Embase Ovid** 1. exp salmoniformes/ or tuna/ 2. fish oil/ 3. linseed oil/ 4. linolenic acid/ 5. Flax/ 6. omega 3 fatty acid/ 7. (fish adj3 (diet\* or nutrit\* or oil\* or supplement\*)).ti,ab. 8. (oil\* adj3 (cod\* or marin\*)).ti,ab. 9. (omega-3 or omega3 or (omega\* adj5 fat\*)).ti,ab. 10. (eicosapentaen\* or icosapentaen\*).ti,ab. 11. docosahexaen\*.ti,ab. 12. (oil\* adj3 (flax\* or rapeseed\* or canola\*)).ti,ab. 13. (Linolen\* or alpha-linolen\* or alphalinolen\*).ti,ab. 14. (perilla\* or linseed\* or maxepa\*).ti,ab. 15. (marin\* adj3 lipid\*).ti,ab. 16. (naudicelle\* or herring\* or sild).ti,ab. 17. (clupe\* adj3 hareng\*).ti,ab. 18. (whitebait or sardine\* or sardina\* or pilchard\* or sprat\* or brisling\*).ti,ab. 19. (salmo\* adj3 trut\*).ti,ab. 20. (trout or bloater or kipper\* or salmon or mackerel\* or scomb\* or conger\* or tuna or tunny or tunafish or tuna-fish).ti,ab. 21. (thunnus\* or swordfish\* or xiphias\* or dogfish or scyliorrhinus\* or laks or lax).ti,ab. 22. (crab or crabs or (cancer adj3 pagarus)).ti,ab. 23. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 24. random\$.tw. 25. placebo\$.tw. 26. (doubl\$ adj blind\$).tw. 27. (singl\$ adj blind\$).tw. 28. double blind procedure/ 29. randomized controlled trial/ 30. single blind procedure/ 31. 24 or 25 or 26 or 27 or 28 or 29 or 30 32. (animal/ or nonhuman/) not human/ 33. 31 not 32 34. 23 and 33 35. (2002\* or 2003\* or 2004\* or 2005\* or 2006\* or 2007\* or 2008\* or 2009\* or 2010\* or 2011\* or 2012\* or 2013\* or 2014\* or 2015\* or 2016\*).dd,em.

36. 34 and 35
37. exp salmonine/
38. (fish adj3 capsul\*).ti,ab.
39. docosapentaen\*.ti,ab.
40. (ALA or DHA or DPA or EPA).ti,ab.
41. (algal adj oil\*).ti,ab.
42. 37 or 38 or 39 or 40 or 41
43. 33 and 42
44. 36 or 43

## CONTRIBUTIONS OF AUTHORS

LH conceived this review and wrote the first draft of the protocol; LH drafted the searches, which were developed, refined, run and deduplicated by CB. ASA, NM, CB, XW, JSB, TJB, SH, OFJ, SMAA, FS, KHOD and LH screened titles and abstracts; ASA, JSB, SMAA, SH, NM, XW and LH assessed full-text papers for inclusion; LH, SH and JSB searched trials registers and assessed entries for inclusion; XW, NM, LH and ASA located full texts, LH and ASA managed assessment and collection of titles, abstracts and full texts, data extraction and 'Risk of bias' assessment; all authors carried out data extraction and assessed risk of bias. LH, KHOD and JSB designed 'Risk of bias' assessment; JSB, KHOD, SMAA, SH, TJB, ASA and LH wrote to trial authors; LH, KHOD, JSB, TJB and ASA carried out data checks; JSB, TJB, SMAA, XW, LH and ASA tabulated intake and status data. NM, CB, FS, KHOD, JSB and LH provided methodological support. ASA and LH entered data into Review Manager 5 and ran meta-analyses, carried out sensitivity analyses and subgrouping. LH carried out the meta-regression, wrote the first draft of the review, and wrote the World Health Organization report. LH and ASA carried out GRADE assessment and interpretation. All review authors critically read and commented on the final draft, and agreed it for submission. LH is the guarantor.

#### DECLARATIONS OF INTEREST

ASA: This review was funded by a grant from the World Health Organization.

NM: None known

CB: None known

XW: This review was funded by a grant from the World Health Organization.

JSB: This review was funded by a grant from the World Health Organization.

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LH: This review was funded by a grant from the World Health Organization.

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#### Internal sources

- University of East Anglia, UK.
- Cochrane Heart Group, UK.

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#### **External sources**

• World Health Organization nutrition guidance expert advisory group (NUGAG), Switzerland. WHO NUGAG Subgroup on Diet and Health requested and funded this systematic review

#### DIFFERENCES BETWEEN PROTOCOL AND REVIEW

In the protocol we planned to omit small trials (that randomised fewer than 100 participants) due to concerns over small study bias and the consequent potential for random error to result in false positive conclusions (Roberts 2015).

To ensure that the largest body of RCT evidence was considered in the formulation of recommendations, the WHO NUGAG Subgroup on Diet and Health requested that trials of all sizes be included as long as they fit the other inclusion criteria.

To do this we re-assessed all titles and abstracts in duplicate to ensure that we collected all smaller as well as larger trials, and carried out a sensitivity analysis omitting trials that had randomised fewer than 100 participants, as well as omitting trials that randomised fewer than 250 participants (this sensitivity analysis was already agreed).

We were also requested by WHO NUGAG Subgroup on Diet and Health to add the following sensitivity analyses:

1. only including trials with a low risk of bias from compliance, and

2. only including trials at low summary risk of bias.

We intended to assess causality (another aspect of performance bias, where a trial intervention included changes other than the change in PUFA intake, when there would be high risk of bias) but as we limited inclusion to trials where the dietary changes were limited to dietary fats this was not needed and so omitted. We also planned to assess whether a trial was pre-registered on a trials register (registration date is before outcome data collection begins; Roberts 2015) but we incorporated the issue of pre-registration into selective outcome reporting and did not use a separate form of assessment. We recorded funding data in the Characteristics of included studies and did not use them as a separate issue for assessing risk of bias, as recommended (Higgins 2011a).

## INDEX TERMS

#### Medical Subject Headings (MeSH)

\*Primary Prevention; \*Secondary Prevention; Adiposity; Cardiovascular Diseases [mortality; \*prevention & control]; Cause of Death; Cholesterol [blood]; Fatty Acids, Unsaturated [\*administration & dosage; adverse effects]; Lipoproteins, HDL [blood]; Lipoproteins, LDL [blood]; Randomized Controlled Trials as Topic; Triglycerides [blood]; Weight Gain

#### MeSH check words

Adult; Humans