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A systematic review and meta-analysis of prospective cohort studies

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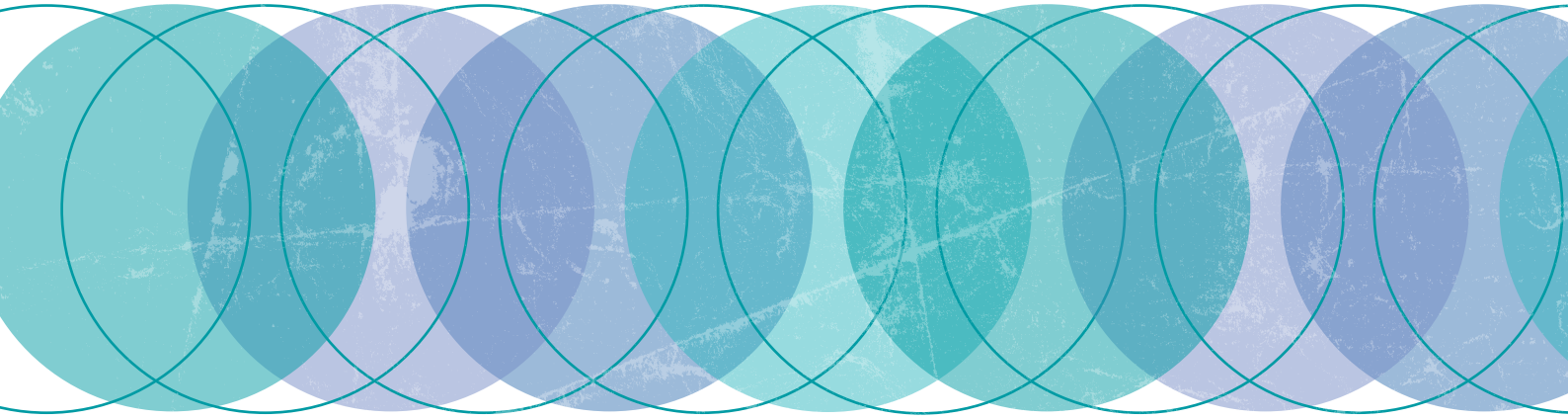

World Health Organization

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Contents

Abbreviations and acronyms

%E	per cent of energy from a nutrient
ACM	all-cause mortality
ALA	alpha-linolenic acid
ARA	arachidonic acid
CAD	coronary artery disease
CHD	coronary heart disease
CI	confidence interval
CVD	cardiovascular disease
d	day (in g/day)
DHA	docosahexaenoic acid
DNA	deoxyribonucleic acid
DPA	docosapentaenoic acid
EPA	eicosapentaenoic acid
FFQ	food frequency questionnaire
IHD	ischaemic heart disease
IL	interleukin
IQR	interquartile range
LA	linoleic acid
LDL	low density lipoprotein
mRNA	messenger ribonucleic acid
MUFA	monounsaturated fatty acids
mvRR	multivariable risk ratio
NFκB	nuclear factor κB
NOS	Newcastle-Ottawa Scale
PPARγ	peroxisome proliferator-activated receptor gamma
PUFA	polyunsaturated fatty acids
RR	risk ratio
SFA	saturated fatty acids
TFA	*trans*-fatty acids
TNF	tumour necrosis factor

Abstract

Objective: To systematically review prospective cohort studies and quantify associations between polyunsaturated fatty acids (PUFA) and all-cause mortality, cardiovascular disease (CVD), breast cancer, mental health, inflammatory bowel disease and type 2 diabetes.

Design: Systematic review and meta-analysis of prospective cohort studies.

Data Sources: MEDLINE (from 1946), EMBASE (from 1974), Cochrane Central Registry of Controlled Trials (from 1996), Evidence Based Medicine Reviews (from 1996) and CINAHL (from 1983) were searched through 19 December 2019. Reference lists of retrieved articles and previous systematic and narrative reviews were hand searched.

Eligibility criteria for selecting studies: Prospective cohort studies reporting associations between PUFA and all-cause mortality, CVD, breast cancer, mental health or type 2 diabetes were eligible.

Data extraction and synthesis: Two reviewers independently abstracted design features, participant characteristics, exposures and outcomes, and assessed risk of bias. Multivariable risk ratios were pooled using inverse-variance random-effects models. Heterogeneity was assessed (Q statistic) and quantified (I^2). Potential publication bias was assessed (funnel plots) and subgroup analyses were undertaken (meta-regression).

Results: A total of 4015 potentially eligible articles were identified; after full-text review, 170 primary reports of associations between PUFA and the health outcomes in prospective cohort studies (published between 1981 and 2020) provided 719 comparisons. In prospective cohort studies (considered the highest quality observational evidence available), higher intake of total and various subtypes of PUFA, compared with lower intake varied in terms of associations with chronic diseases. Higher intakes of **total PUFA** were associated with a 14% reduced risk of all-cause mortality (16 studies with 960 538 participants), 9% reduced risk of fatal CVD (13 studies with 907 721 participants) and 27% reduced risk of sudden cardiac death (1 study with 91 981 participants). **Total omega-3 fatty acids** were associated with a 6% reduced risk of fatal CVD (10 studies with 872 029 participants), 17% reduced risk of fatal coronary heart disease (CHD) (4 studies with 238 990 participants), 35% reduced risk of sudden cardiac death (2 studies with 149 953 participants), 57% reduced risk of myocardial infarction (1 study with 41 578 participants), 15% reduced risk of fatal stroke (2 studies with 82 122 participants), and 21% reduced risk of cognitive decline in older age (1 study with 4809 participants). Higher intakes of **long-chain omega-3 fatty acids** were associated with a 9% reduced risk of all-cause mortality (15 studies with 1 033 235 participants), 12% reduced risk of fatal CVD (18 studies with 1 070 906 participants), 20% reduced risk of fatal CHD (16 studies with 461 060 participants), 59% reduced risk of fatal myocardial infarction (2 studies with 39 586 participants), 45% reduced risk of haemorrhagic stroke (4 studies with 94 687 participants) and 28% reduced risk of ulcerative colitis (1 study with 170 805 participants). Higher intakes of total n-6 fatty acids were associated with a 9% reduced all-cause mortality (9 studies with 768 475 participants) but a 31% increased risk of postmenopausal breast cancer (6 studies with 174 816 participants). Higher intakes of **arachidonic acid** were associated with a 5% increased risk of breast cancer (3 studies with 180 342 participants). Higher intakes of linoleic acid were associated with a 16% reduced risk of all-cause mortality (9 studies with 706 400 participants), 17% reduced risk of fatal CVD (7 studies with 692 243 participants), 21% reduced risk of fatal CHD (13 studies with 306 050 participants), 32% reduced risk of sudden cardiac death (1 study with 91 181 participants) and 14% reduced risk of total CHD (14 studies with 267 201 participants), but a

26% increased risk of depression (3 studies with 57 538 participants). Higher intakes of **alpha-linolenic acid** were associated with a 7% reduced all-cause mortality (10 studies with 714 634 participants), 9% reduced risk of fatal CVD (11 studies with 800 724 participants), 18% reduced risk of fatal CHD (9 studies with 252 010 participants), 46% reduced risk of sudden cardiac death (2 studies with 99 183 participants) and 15% reduced risk of fatal stroke (3 studies with 103 532 participants). A higher polyunsaturated:saturated fat ratio was associated with an 18% increased risk of fatal CVD (3 studies with 65 598 participants) and 86% increased risk of postmenopausal breast cancer (1 study with 910 participants). A high omega-6:omega-3 ratio was associated with a 25% increased risk of cognitive decline and 45% increased risk of ulcerative colitis (1 study with 170 805 participants). A high omega-3:omega-6 ratio was associated with a 26% reduced risk of depression (3 studies with 57 538 participants), The confidence in the estimates for the association between PUFA and all outcomes using the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) approach ranged from very low to moderate.

Conclusions: On balance, higher intakes of PUFA are associated with reduced risks of all-cause and cardiovascular mortality, but the quality of the evidence is mostly very low. The benefits of n-3 fatty acids appear to be specific for CVDs, but few observational studies have directly observed or otherwise modelled the effects of replacing saturated or *trans*-unsaturated fats with PUFA on health outcomes. The interaction between different types of PUFA requires further research.

1. Introduction

Bang *(1, 2)* first ascribed the low risk of coronary heart disease (CHD) in Greenland Inuit to the high omega-3 fatty acid content of their diets. This observation has spawned decades of scientific interest in the protective role and possible mechanism of action of fish fat, specifically polyunsaturated fatty acids (PUFA). This interest has spread to encompass plant sources of PUFA, including plant oils rich in omega-3 fatty acids, including flax (linseed) and rapeseed (canola) oils *(3)*, and foods made from these oils (e.g. margarines) *(4)*.

The predominant omega-3 fats (also called Ω-3 or n-3 fats) from fish include eicosapentaenoic acid (EPA or 20:5), docosahexaenoic acid (DHA, 22:6) and docosapentaenoic acid (DPA, 22:5); these are the longer chain omega-3 fats. Alpha-linolenic acid (ALA or α-linolenic acid, 18:3) is the shorter chain omega-3 fat from plants and, more recently, from grass-fed meats. ALA is incompletely converted to longer chain omega-3 fatty acids in the human body. However, the efficiency of this conversion is still a matter of some debate; for example, the conversion may be affected by the time-course of studies or interactions with other dietary components (5, 6). Hence, the effectiveness of ALA conversion may differ from that of the longer chain omega-3 fats.

Proposed mechanisms for a protective role of omega-3 fats against cardiovascular diseases (CVDs) include lowering of blood pressure, altered lipid profile (notably, reduced serum triglyceride concentration), reduced thrombotic tendency, anti-inflammatory effects, antiarrhythmic effects (including reduction in heart rate), improved vascular endothelial function, increased plaque stability, increased paraoxonase levels and improved insulin sensitivity *(7–10)*. Some observational studies and many controlled feeding studies reported that linoleic acid (LA), the predominant n-6 PUFA in the western diet – found primarily in vegetable oils (e.g. sunflower, safflower, soya and corn) and nuts (walnuts) – reduces established risk factors for CHD. Higher LA intake reduces low density lipoprotein (LDL) cholesterol *(11, 12)*, promotes insulin sensitivity *(11, 12)* and reduces risk of hypertension *(13, 14)*. Substitution of dietary n-6 PUFA for saturated fatty acids (SFAs) has long been recommended to prevent CHD *(15)*, but there have been concerns about higher LA consumption being harmful to heart health because of its potential proinflammatory and thrombogenic properties *(16–18)*. In addition to their influence on heart health, PUFA may affect other health outcomes that have inflammatory components.

Studies have suggested that the consumption of specific dietary fats – particularly those low in omega-6 and high in *trans*-unsaturated fatty acids – increases the risk of type 2 diabetes, but the role of omega-3 fats remains unclear *(19)*. Omega-3 fats (particularly long-chain omega-3 fats from seafood sources) alter the expression of peroxisome proliferator–activator receptor genes, which are involved in signaling nutrition status *(20)*; they also affect the production of inflammatory cytokines, which are associated with type 2 diabetes *(21)*. These findings suggest that omega-3 fatty acids could lower the risk of type 2 diabetes.

The possible role of PUFA in protection from mental illness and depression has developed from the physiological role of PUFA and their presence in neuronal membrane dynamic structure and fluidity. Higher omega-3 PUFA concentrations lead to increased membrane fluidity, which increases serotonin transport *(11)*. These fatty acids are involved in receptor function, neurotransmitter reuptake and signal transmission. Depression has been associated with over-activity of the inflammatory response of the immune system, which increases the production of proinflammatory cytokines *(22)*. Omega-3 fatty acids have been suggested as inhibitors of some of these cytokines, especially of tumour necrosis factor α (TNF-α) and interleukin-1-beta (IL-1β). Both IL-1β and TNF-α may reduce the availability of neurotransmitter precursors such as

tryptophan, or may alter the metabolism of neurotransmitters and neurotransmitter transporter mRNA, thus influencing hypothalamic–pituitary adrenocortical axis activity.

Dietary fats influence intestinal inflammation and regulate mucosal immunity, and thus may be involved in the development of inflammatory bowel diseases such as Crohn's disease and ulcerative colitis. Dietary n-3 PUFA competitively inhibit formation of proinflammatory prostaglandins and leukotrienes through the arachidonic acid (ARA) pathway *(12)*; they also inhibit vascular adhesion and migration, angiogenesis and adaptive immune responses through pathways mediated by peroxisome proliferator-activated receptor gamma (PPARγ) and nuclear factor κB (NFκB) *(23)*.

The hypothesis that a high-fat diet promotes the development of postmenopausal breast cancer was supported by international data that showed a strong correlation between fat intake and breast cancer rates *(24)* and a modest positive association with high-fat diet in case–control studies *(25)*. However, total dietary fat intake is unrelated to the risk of breast cancer in cohort studies *(26)*. Animal models *(27)* and recent observations in humans have provided evidence that a high intake of PUFA stimulates several stages in the development of mammary and colon cancer, from an increase in oxidative DNA damage, to effects on cell proliferation and free estrogen levels, to hormonal catabolism. In contrast, omega-3 fatty acids derived from fish oil seem to prevent cancer by influencing the activity of enzymes and proteins related to intracellular signaling and, ultimately, cell proliferation.

Dietary guidelines from various bodies generally recommend that 20–35% of energy should come from fat, with most coming from PUFA and monounsaturated fats (MUFA) *(28–31)*. This review synthesizes prospective associations between PUFA and all-cause mortality, breast cancer, cognition and depression, type 2 diabetes, and cardiovascular morbidity and mortality risk; the review will inform the process of updating World Health Organization (WHO) guidance on PUFA intake. We assessed the confidence in the body of observational evidence using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach *(32, 33)*.

2. Methods

This review was conducted in accordance with WHO's guideline development process *(34)*, which is based on the Cochrane Collaboration approach *(35)*. Ethical approval was not required for this research.

2.1 Data sources

Independent searches were conducted for relevant observational studies assessing the association between PUFA and health outcomes through 19 December 2019. This included searching MEDLINE (from 1946), EMBASE (from 1974), Cochrane Central Registry of Controlled Trials (from 1996), Evidence Based Medicine Reviews (from 1996) and CINAHL (from 1983). Reference lists of retrieved articles and previous systematic and narrative reviews *(14, 15, 36–39)* were hand searched. No language restrictions were imposed.

2.2 Study selection

Studies were eligible if they were prospective cohort studies in humans that reported a measure of association (i.e. hazard ratios or incident rate ratios) between intakes of PUFA (total, n-3, long chain n-3, n-6, EPA, DHA, DPA, ARA, LA and aLA) or the polyunsaturated:saturated fat ratio (P:S), measured by self-report and all-cause mortality, CVD (including fatal and nonfatal composite cardiovascular events; fatal and nonfatal coronary events including myocardial infarction, ischaemic heart disease, atrial fibrillation and sudden cardiac death; and ischaemic or haemorrhagic strokes), breast cancer (premenopausal and postmenopausal), type 2 diabetes, depression, cognitive decline or inflammatory bowel disease (Crohn's disease or ulcerative colitis), measured by self-report and/or confirmed by medical records or registry linkage. Studies were excluded if they were of cohorts in which more than 20% of the sample was aged under 18 years, had a non-cardiometabolic disease (e.g. cancer) or were pregnant at baseline. We also excluded studies in which diet was assessed before adulthood, participants were asked to recall their diet before adulthood or dietary assessments were completed by proxies. One reviewer assessed titles and abstracts of all studies identified through electronic searches. Potentially eligible studies were reviewed independently by a second reviewer, with discrepancies resolved by discussion; where necessary, a senior author was consulted to reach consensus.

2.3 Data extraction

Pairs of authors independently extracted details of the study design, country of conduct, exposure and outcome assessment, participant characteristics and statistical analyses (including adjustment for confounders) from included studies using pretested instruments, with discrepancies resolved by discussion. Authors were contacted for additional data, where necessary. *Plot Digitizer*[1] was used to extract numerical estimates from graphs.

2.4 Study risk of bias

The Newcastle-Ottawa Scale (NOS) *(40)* was used to assess the risk of bias of the included studies on the basis of selection of study groups, comparability of groups and ascertainment of exposure(s) or outcome(s).

[1] http://plotdigitizer.sourceforge.net

2.5 GRADE approach

The GRADE approach was used to assess the confidence in the effect estimates derived from the body of evidence (quality of evidence) by outcome and to produce evidence profiles *(32, 33)*. We have limited the presentations of results in the main text to the synthesis of prospective cohort studies because these are considered the highest level of evidence for observational studies, and thus were used for the GRADE assessments of confidence. Evidence summaries and GRADE assessments were discussed and reviewed by all investigators and reviewed with the WHO Nutrition Guidance Expert Advisory Group (NUGAG) Subgroup on Diet and Health as part of WHO's guideline development process. Confidence in the estimate of each association was categorized into four levels, from very low (⊕◯◯◯) to high (⊕ ⊕ ⊕ ⊕).

2.6 Outcome definitions

The included studies provided different degrees of granularity with respect to outcomes assessment. Given the different mechanisms by which PUFA are likely to operate, especially for CVD, we have provided estimates for the finest possible degree of outcome specificity. The outcome definitions used were as listed here. *All-cause mortality*: deaths from any cause during the follow-up period. *Total CVD*: fatal and non-fatal CVD or events that occur during the follow-up period are grouped as a single outcome by the study authors; they include acute rheumatic fever, chronic rheumatic heart disease, hypertensive disease, **ischaemic heart disease**,[1] diseases of pulmonary circulation, **cerebrovascular disease (subarachnoid haemorrhage and intracerebral haemorrhage)**, diseases of arteries, arterioles and capillaries and other diseases of the circulatory system. *Fatal CVD*: death from CVD during the follow-up period, including acute rheumatic fever, chronic rheumatic heart disease, hypertensive disease, **ischaemic heart disease**, diseases of pulmonary circulation, **cerebrovascular disease (subarachnoid haemorrhage, intracerebral haemorrhage)**, diseases of arteries, arterioles and capillaries, and other diseases of the circulatory system. *Fatal CHD*: death from ischaemic heart disease, including myocardial infarction, angina pectoris or other forms of chronic ischaemic heart disease. *Sudden cardiac death*: sudden, unexpected death caused by loss of heart function (sudden cardiac arrest). *Nonfatal myocardial infarction*: a sudden and sometimes fatal occurrence of coronary thrombosis, typically resulting in the death of part of a heart muscle, but that does not result in death. *Total CHD*: nonfatal myocardial infarction, angina pectoris and fatal CHD. *Total stroke*: includes subarachnoid haemorrhage and intracerebral haemorrhage. *Fatal stroke*: includes death from any stroke. *Ischemic stroke*: thrombotic and embolic strokes. *Atrial fibrillation*: an abnormal heart rhythm characterized by rapid and irregular beating. *Dementia*: a set of symptoms that are caused by disorders affecting the brain, including memory loss and difficulties with thinking, problem solving or language, severe enough to reduce a person's ability to perform everyday activities (also includes Alzheimer's disease). *Cognitive decline*: operationalized as a change in cognitive status, or mild cognitive impairment, which is a slight but noticeable and measurable decline in cognitive abilities, including memory and thinking skills. *Depression*: major depressive disorder, characterized by a lengthy time (at least 2 weeks) during which a person feels sad or hopeless or lacks focus in life, on a daily or almost daily basis, for the most part of each day. *Inflammatory bowel disease*: ulcerative colitis or Crohn's disease. Breast cancer: premenopausal or postmenopausal, or total (unspecified).

2.7 Data synthesis and analysis

2.7.1 Statistical synthesis of effect estimates

The principal effect measures were the risk ratio (RR) between extreme levels of intake (highest vs lowest quantile). For each study, the following were calculated for each outcome: most-adjusted (i.e. the multivariable association measure with the highest number of covariates) estimates

[1] Bold indicates the most common outcomes.

and corresponding 95% confidence intervals (CIs). Where at least two studies provided data, a DerSimonian and Laird random-effects meta-analysis was performed, which yields conservative CIs around RRs in the presence of heterogeneity *(41)*. When three or fewer studies were combined, fixed-effect estimates were also considered.

2.7.2 Heterogeneity

Heterogeneity was detected using Cochran's Q test (significant at $P<0.10$), and quantified using the I2 statistic (ranging from 0% to 100%) *(42)*, and used to assess inconsistency as part of the GRADE assessment of evidence quality. If at least 10 studies were available *(43, 44)* and heterogeneity was substantial ($I^2>60\%$ or $P_Q<0.10$) *(42)*, meta-regression was used to explore heterogeneity.

2.7.3 Dose–response

The dose–response relation was estimated by using generalized least squares trend estimation, according to the methods developed by Greenland and Longnecker *(45)*, implemented in STATA (v. 13, College Station, TX) using the "glst" package written by Orsini *(46, 47)*. These methods require knowledge of the distribution of events and number of participants or person-years and mean or median quantity of intake across categories of exposure. If the number of individuals in each category of intake was not provided, we estimated this by:

$$\frac{\textit{Person–time (quintile x)}}{\textit{Total person–time}} \; \textit{x total participants}$$

If total energy was not reported (necessary for % energy dose–response), it was assumed to be 2200 kcal for studies that enrolled men only, 1800 kcal for studies that enrolled women only and 2000 kcal for a mixed-sex population. If total energy or PUFA intake was not reported for each quantile, we assumed equal space between reported quantiles, and took the median of these values as the imputed energy for non-reported quantiles. If only mean and standard deviation of intake for the cohort was provided, we assumed that the log-transformed distribution of dose was normal and assumed cutpoints corresponding to the quantiles (e.g. 25, 50 and 75 for quartiles; and 20, 40, 60 and 80 for quintiles).

The goodness-of-fit test was used to assess whether the linearity assumption was tenable. For this test, for $P<0.05$, the interpretation was that a straight line was not a good fit to the data and for $P>0.05$ the interpretation was that a straight line was an adequate fit. If the straight line was not a good fit (i.e. goodness-of-fit test $P<0.05$), we used a piecewise-polynomial approach, which assumes linear associations across certain ranges of doses ("segments"), the boundaries of which are called knots. To model the association between knots we applied restricted cubic splines to create three equally spaced knots across the distribution. Finally, we used the procedure described by Orsini et al. *(46)* to estimate the pooled RRs for increments of specific exposure values, scaled to desired units using the "*lincom*" command in STATA. Where these dose–response analyses yielded important findings, those findings are discussed in the relevant sections of the manuscript, and in the GRADE table footnote corresponding to the "Overall quality of evidence" (column 9) for each relevant analysis.

2.7.4 Sensitivity

Three a priori sensitivity analyses were conducted: 1) removing each single study from the meta-analyses, and recalculating the summary effect (the "leave-one-out" approach *(48)*); 2) removing studies with NOS scores of less than 7 and recalculating the pooled effect; and 3) removing risk estimates imputed due to incomplete reporting. A study was considered an influential outlier if its removal either pushed the significance level of the overall effect from less than 0.05 to 0.05 or more (or vice versa) or altered the nominal effect size by at least 10%. Where these sensitivity analyses yielded important findings, the findings are discussed in the GRADE table footnotes

corresponding to the relevant analysis. If the findings are not mentioned, the sensitivity analyses did not influence the association measure.

2.7.5 Publication bias

Where at least 10 studies were available *(49)*, the possibility of publication bias was explored by inspecting funnel plots and conducting Egger's and Begg's tests (each significant at $P<0.10$). If publication bias was suspected, results are shown without imputation and with "missing" studies imputed using Duval and Tweedie's *trim-and-fill* method *(50)*.

2.7.6 Software

Primary summary analyses were carried out separately for each outcome using RevMan (version 5.2; The Nordic Cochrane Center, the Cochrane Collaboration, and Copenhagen, Denmark). Meta-regression and sensitivity analyses were undertaken using STATA, version 12.1 (StataCorp, College Station, Texas, USA).

2.7.7 Role of the funding source

This review was commissioned and partially funded by WHO as an independent review conducted by researchers from McMaster University (Hamilton, Ontario, Canada).

3. Results

3.1 Literature flow

Our literature search identified 4015 potentially eligible articles. After duplicates were removed, 3859 records remained for title and abstract screening. After this process, 576 full-text papers were considered for inclusion in this synthesis. A total of 421 papers were excluded: 155 because they did not measure an outcome of interest, 138 because they did not measure a dietary exposure of interest, 52 because of an inappropriate study design (e.g. case study or case–control) or report format (i.e. abstract), 27 because the authors only reported blood measures of fatty acids, 14 because they were editorials or commentaries, nine because they were duplicate citations not initially caught by the de-duplication filter in *EndNote*, eight because we were unable to obtain the full text of the article (but 5 of these we are confident were abstracts that were later published as full-text articles and 3 were deemed "highly unlikely" to be eligible by duplicate reviewers), five because they were conducted in seriously ill populations (e.g. with cancer or chronic kidney disease), five because they were narrative or systematic reviews, four because they were duplicate publications from the same cohort study, three because they did not present a measure of association and one because it was an animal study (see Annex 1 for a full list of excluded studies). Hand-searching of a recent meta-analysis of LA and CHD *(37)* identified updated or previously unpublished data from five studies (Atherosclerosis Risk in Communities Study, Health Professionals' Follow-up study, Finnish Mobile Health Clinics, Israeli Ischaemic Heart Disease Study and Nurses' Health Study I; n=12 comparisons). Thus, in total, 170 primary studies were included in the synthesis (**Fig. 1a**).

As shown in **Table 1**, 170 reports of prospective cohort studies of PUFA and health outcomes in the main analysis of primary prevention studies (published between 1981 and 2020) provided 719 distinct associations between PUFA and at least one of the health outcomes of interest, with cohorts enrolled from:

- North America (n=60 studies, 248 data points: 1 study providing 2 data points from Canada; 59 studies providing 246 data points from the United States of America [USA]);
- Europe (69 studies providing 245 data points: 16 studies providing 37 data points from the Netherlands; 13 studies providing 62 data points from Sweden; 8 studies providing 38 data points from Finland; 10 studies providing 41 data points from Denmark; 5 studies providing 13 data points from the United Kingdom of Great Britain and Northern Ireland [United Kingdom]; 3 studies providing 10 data points from various pooled European analyses; 6 studies providing 27 data points from Spain; 3 studies providing 15 data points from France; 4 studies providing 11 data points from Italy; and 1 study providing 1 data point from Germany);
- Asia (25 studies providing 171 data points: 12 studies providing 79 data points from Japan; 3 studies providing 22 data points from Shanghai; 4 studies providing 18 data points from Singapore; and 7 studies providing 68 data points from the People's Republic of China; 4 studies providing 18 data points from Singapore; 1 study providing 5 data points from Iran; 1 study providing 1 data point from Israel); and
- Australia (3 studies providing 24 data points).

There was one global study providing five data points.

The distribution of background (i.e. average) PUFA intakes varied across studies and across types of PUFA. The background total PUFA intake ranged from 2.3% to 8.9% energy (median=5.9; mean=5.9) or 6.0 g to 18.3 g (median=12.6; mean=12.3). Long-chain n-3 PUFA intake ranged from

0.04% to 0.43% energy (median=0.17; mean=0.19) or 0 g to 1.02 g (median=0.286; mean=0.316). ALA intake ranged from 0.06% to 1.14% energy (median=0.5; mean=0.6) or 0.5 g/day to 2.0 g/day (median=1.2; mean=1.3). LA intake ranged from 1.5% to 7.8% energy (median=5.1; mean=45.1) or 1.3 g/day to 23.5 g/day (median=10.7; mean=11.2) (**Table 15**).

The focus of this review was on associations of dietary intakes of PUFA with the health outcomes of interest; thus, supplements were generally not included in the estimates of intake. Of the 25 studies that reported the association between long-chain n-3 fatty acids and mortality or cardiovascular outcomes, 24 (96.0%) reported associations for total dietary long-chain n-3 PUFA only, 14 (56.0%) also provided associations for fish and at least one outcome (data not extracted), one (4.0%) looked at supplemental long-chain n-3 PUFA separately from diet, one (4.0%) presented both dietary and supplemental long-chain n-3 PUFA and one (4.0%) measured serum long-chain n-3 PUFA.

All 14 studies that reported the association between total n-3 fatty acids and mortality or cardiovascular outcomes reported associations for total dietary n-3 PUFA only. Among these studies, four (28.6%) also provided associations for fish and at least one outcome (data not extracted). None of these 14 studies looked at supplemental n-3 PUFA separately from diet, and none presented both dietary and supplemental total n-3 PUFA.

An additional four studies of fish or PUFA in secondary prevention were also identified and summarized, as were four recent systematic reviews and meta-analyses of fish and CVD and type 2 diabetes, and one of walnut consumption and type 2 diabetes.

3.2 Study quality

Of the 170 publications assessed and included in the quantitative synthesis, the median NOS rating was 8 (range: 5–9; interquartile range [IQR]: 2). A total of 147 studies (86.5%) were rated 7 or higher; 19 studies (11.2%) were rated 6 and four studies (2.4%) were rated 5. Overall, 89% of publications scored 4 out of a possible 4 points for unbiased selection of participants (i.e. they ensured that the outcome of interest was not present at baseline and used a validated measure of dietary exposure); 47% scored 2 out of a possible 2 points for ensuring comparability of exposed and unexposed groups with respect to important confounders; and 58% scored 3 out a possible 3 points for rigorous outcome confirmation and adequate follow-up (>80%). Fifty-eight studies (34%) documented a measurement of trans-fatty acid (TFA) intake in the cohort (**Fig. 1b**, **Table 2**).

3.3 Total PUFA and health outcomes

3.3.1 All-cause mortality

Eleven prospective cohort studies (providing 16 comparisons, n=193 582 deaths) examined the association between total PUFA intake and all-cause mortality *(51–60)*. For PUFA and all-cause mortality, the summary most-adjusted multivariable risk ratio (mvRR) comparing the highest intake of dietary PUFA with the lowest intake was 0.86 (95% CI: 0.81 to 0.92; *P*<0.00001; I^2=82%; P_{het}<0.00001) (**Fig. 2**). There was no evidence of publication bias (**Fig. 84a**).

There was no evidence of effect modification by NOS score (*P*=0.36), the number of cases (*P*=0.63), measurement of TFA (*P*=0.90), follow-up time (*P*=0.53), sex distribution of the population (*P*=0.76), energy adjustment (*P*=0.95), blood pressure adjustment (*P*=0.39), age distribution of the population (*P*=0.15), smoking exposure history of the population (*P*=0.80) or method of diet assessment (*P*=0.15). There was evidence that the association was weaker in studies that did not adjust for dyslipidaemia than in those that did (mvRR=0.91 vs mvRR=0.79; *P*=0.047), and that the association differed by country of study (*P*=0.001) (**Fig. 85x**).

Assuming linearity, a 10 g increase in PUFA was associated with a 13% reduced risk of all-cause mortality (mvRR: 0.87; 95% CI: 0.79 to 0.95; *P*=0.003). Assuming linearity, a 5% increase in PUFA was associated with a 15% reduction in mortality (mvRR: 0.85; 95% CI: 0.79 to 0.91). There was

evidence of non-linearity, with a stabilizing of the risk reduction at about 5% beyond 6 g/day and a flattening of the slope from 2% to 6% (**Fig. 95** and **Fig. 96**).

3.3.2 Cardiovascular diseases

Total CVD

Four prospective cohort studies (5 comparisons; n=6270 events) provided estimates of the association between total PUFA and total CVD *(57, 61–63)*. For total CVD, the summary most-adjusted mvRR comparing the highest intake of dietary PUFA with the lowest was 1.02 (95% CI: 0.88 to 1.18; *P*=0.81; I^2=45%, P_{het}=0.12) (**Section 1.4.1** in **Fig. 2**).

Fatal CVD

Nine studies (13 comparisons; n=53 728 events) provided estimates of the association between total PUFA and fatal CVD *(51–54, 56, 57, 60, 62, 64)*. The summary most-adjusted mvRR comparing the highest intake of dietary PUFA with the lowest was 0.91 (95% CI: 0.83 to 1.01; *P*=0.06; I^2=64%, P_{het}=0.0009) (**Section 1.4.2** in **Fig. 2**). There was no evidence of publication bias (**Fig. 84b**). Assuming linearity, a 10 g increase in total PUFA was associated with a 9% reduced risk of CVD mortality (mvRR: 0.91; 95% CI: 0.88 to 0.95). The dose–response effect seemed to stabilize beyond 8 g/day. Assuming linearity, a 5% increase in energy from total PUFA was associated with a 14% reduced risk of CVD mortality (mvRR: 0.86; 95% CI: 0.77 to 0.96) (**Fig. 97** and **Fig. 98**).

There was no evidence of effect modification by NOS score (*P*=0.52), the number of cases (*P*=0.88), measurement of TFA (*P*=0.33), follow-up time (*P*=0.78), sex distribution of the population (*P*=0.99), energy adjustment (*P*=0.79), blood pressure adjustment (*P*=0.39), age distribution of the population (*P*=0.91), smoking exposure history of the population (*P*=0.80) or method of diet assessment (*P*=0.11). There was evidence that the association was weaker in studies that did not adjust for dyslipidaemia than in those that did (mvRR=0.99 vs mvRR=0.75; *P*=0.019) (**Figures 86m and 86n**), and that the association differed by country of study (*P*=0.008) (Fig. 86x).

Fatal CHD

Five studies (8 comparisons; n=1365 events) provided estimates of the association between total PUFA and fatal CHD *(65–70)*. The summary most-adjusted mvRR comparing the highest intake of dietary PUFA with the lowest was 0.95 (95% CI: 0.84 to 1.07; *P*=0.39; I^2=60%, P_{het}=0.02) (**Section 1.4.3** in **Fig. 2**). Assuming linearity, a 10 g increase in energy from total PUFA was associated with a 7% increased risk of CHD mortality (mvRR: 1.07; 95% CI: 0.95 to 1.21). Assuming linearity, a 5% increase in energy from total PUFA was associated with a 10% increased risk of CHD mortality (mvRR: 1.10; 95% CI: 0.96 to 1.26) (**Fig. 102** and **Fig. 103**).

Sudden cardiac death

One study (1 comparison; n=385 events) provided an estimate of the association between total PUFA and sudden cardiac death *(71)*. The summary most-adjusted mvRR comparing the highest intake of dietary PUFA with the lowest was 0.73 (95% CI: 0.53 to 1.01; *P*=0.06) (**Section 1.4.4** in **Fig. 3**).

Fatal myocardial infarction

No prospective cohort studies were identified that provided an estimate of the association between total PUFA and fatal myocardial infarction.

Nonfatal myocardial infarction

Two studies (2 comparisons; n=680 events) provided estimates of the association between total PUFA and nonfatal myocardial infarction *(69, 70)*. The summary most-adjusted mvRR comparing

the highest intake of dietary PUFA with the lowest was 1.10 (95% CI: 0.83 to 1.47; *P*=0.51; I^2=0%, P_{het}=0.58) (**Section 1.4.5** in **Fig. 3**).

Total CHD

Ten studies (17 comparisons; n=16 114 events) provided estimates of the association between total PUFA and total CHD *(61, 67, 69, 72–78)*. The summary most-adjusted mvRR comparing the highest intake of dietary PUFA with the lowest was 0.99 (95% CI: 0.89 to 1.10; *P*=0.84; I^2=67%, P_{het}<0.0001) (**Section 1.4.6** in **Fig. 3**). The fixed-effect estimate was 0.95 (95% CI: 0.90 to 1.00; *P*=0.05). There was no evidence of a dose–response association between total PUFA and total CHD (mvRR: 0.98 95% CI: 0.81 to 1.19 per 10 g; or 0.98; 95% CI: 0.83 to 1.15 per 5% energy (**Fig. 104** and **Fig. 105**). Egger's and Begg's tests suggested no publication bias (*P*>0.22) (**Fig. 84c**).

There was no evidence of effect modification by NOS score (*P*=0.19), sex distribution of the population (*P*=0.88), energy adjustment (*P*=0.21), blood pressure adjustment (*P*=0.21), dyslipidaemia adjustment (*P*=0.10) or the age distribution of the population (*P*=0.37). There was evidence that the association was associated with number of cases. Each 500-case increase in study size was associated with a 4% decrease in the estimate (mvRR: 0.96; 95% CI: 0.93, 0.98; *P*=0.003). These was also evidence that study effect size is associated with follow-up duration (*P*=0.002); studies of 20 or more years duration showed protection (mvRR=0.80; 95% CI: 0.73 to 0.87), whereas shorter studies showed a possible increased risk (15 to <20 years=1.11 [1.00, 1.25]; 10 to <15 years=1.06 [0.95, 1.19]; 5 to <10 years=1.14 [0.96, 1.36]). The effect was also stronger in studies that measured TFA (mvRR: 1.09 in studies that did not measure TFA; 0.84 in studies that did; *P*<0.0001), and in studies with a higher proportion of smokers (1.09 vs 1.00; *P*=0.096). There was also evidence that studies that used a food frequency questionnaire (FFQ) to measure diet showed a greater reduction in risk (0.88; 95% CI: 0.82 to 0.95), than those that used 24-hour recalls, diet histories or 7-day food records. The association differed by country of study (*P*=0.008) (**Figs. 84a to 84n**).

Total stroke

Four studies (4 comparisons; n=4128 events) provided estimates of the association between total PUFA and total stroke *(57, 79–81)*. The summary most-adjusted mvRR comparing the highest intake of dietary PUFA with the lowest was 0.98 (95% CI: 0.86 to 1,13; *P*=0.83; I^2=17%, P_{het}=0.18) (**Section 1.4.7** in **Fig. 3**).

Fatal stroke

One study (1 comparison; n=60 events) provided an estimate of the association between total PUFA and fatal stroke *(82)*. The summary most-adjusted mvRR comparing the highest intake of dietary PUFA with the lowest was 0.68 (95% CI: 0.34 to 1.36; *P*=0.28) (**Section 1.4.8** in **Fig. 3**)

Ischaemic stroke

Six studies (8 comparisons; n=3347 events) provided estimates of the association between total PUFA and ischaemic stroke *(61, 75, 78, 80, 83, 84)*. The summary most-adjusted mvRR comparing the highest intake of dietary PUFA with the lowest was 0.97 (95% CI: 0.86 to 1.09; *P*=0.62; I^2=0%, P_{het}=0.74) (**Section 1.4.9** in **Fig. 3**).

Haemorrhagic stroke

Three studies (3 comparisons; n=1819 events) provided estimates of the association between total PUFA and haemorrhagic stroke *(80, 81, 83)*. The summary most-adjusted mvRR comparing the highest intake of dietary PUFA with the lowest was 1.03 (95% CI: 0.89 to 1.20; *P*=0.69; I^2=0%, P_{het}=0.60) (**Section 1.4.10** in **Fig. 3**).

Atrial fibrillation

Two studies (3 comparisons; n=6521 events) provided an estimate of the association between total PUFA and atrial fibrillation *(85, 86)*. The summary most-adjusted mvRR comparing the highest intake of dietary PUFA with the lowest was 0.97 (95% CI: 0.84 to 1.11; *P*=0.64) (**Section 1.4.11** in **Fig. 3**). The fixed-effect estimate was 0.96 (95% CI: 0.87 to 1.06; *P*=0.43).

Myocardial infarction

One study (1 comparison; n=2143 events) provided an estimate of the association between total PUFA and myocardial infarction *(57)*. The summary most-adjusted mvRR comparing the highest intake of dietary PUFA with the lowest was 1.12 (95% CI: 0.93 to 1.34; *P*=0.22) (**Section 1.4.12** in **Fig. 3**).

3.3.3 Type 2 diabetes

Nine studies (10 comparisons; n=9868 cases) provided estimates of the association between total PUFA and type 2 diabetes *(87–95)*. The summary most-adjusted mvRR comparing the highest intake of dietary PUFA with the lowest was 0.91 (95% CI: 0.79 to 1.05; *P*=0.20; I^2=73%, P_{het}= 0.0001) (**Fig. 4**). There was no evidence of publication bias (**Fig. 84d**). There was no evidence of a linear dose–response association between total PUFA and type 2 diabetes (mvRR: 1.00; 95% CI: 0.94 to 1.07 per 10 g), but there was a suggestion that about 0–4 g/day (≈0–2%E) were associated with decreased risk; but doses of more than 4 g/day to 12 g/day (about 2% to 7%E) were associated with increased risk (**Fig. 107** and **Fig. 108**). There was no evidence that the association was modified by any of study size (i.e., number of cases), study risk of bias (i.e. NOS), measurement of TFA, sex distribution of participants and whether the study adjusted for energy, a measure of dyslipidaemia or hypertension, the age distribution of participants, smoking or country. All studies used an FFQ for diet assessment (**Fig. 88**).

3.3.4 Dementia

One study (1 comparison; n=197 cases) provided an estimate of the association between total PUFA and dementia *(96)*. The summary most-adjusted mvRR comparing the highest intake of dietary PUFA with the lowest was 1.05 (95% CI: 0.80 to 1.38; *P*=0.73) (**Fig. 5**).

3.3.5 Cognitive decline

Two studies (2 comparisons; n=616 cases) provided an estimate of the association between total PUFA and cognitive decline *(97, 98)*. The summary most-adjusted mvRR comparing the highest intake of dietary PUFA with the lowest was 0.87 (95% CI: 0.54 to 1.41; *P*=0.57; I^2=60%, P_{het}<0.001) (**Fig. 6a** and **Fig. 6b**).

3.3.6 Depression

Two studies (2 comparisons; n=1172 cases) provided an estimate of the association between total PUFA and depression *(99, 100)*. The summary most-adjusted mvRR comparing the highest intake of dietary PUFA with the lowest was 0.93 (95% CI: 0.63 to 1.38; *P*=0.72; I^2=79%; P_{het}=0.03) (**Fig. 7a** and **Fig. 7b**).

3.3.7 Inflammatory bowel disease

Crohn's disease

One study (1 comparison; n=269 cases) provided an estimate of the association between total PUFA and Crohn's disease *(101)*. The summary most-adjusted mvRR comparing the highest intake of dietary PUFA with the lowest was 0.95 (95% CI: 0.63 to 1.43; *P*=0.80) (**Section 1.9.1** in **Fig. 8**).

Ulcerative colitis

Two studies (2 comparisons; n=477 cases) provided an estimate of the association between total PUFA and ulcerative colitis *(101, 102)*. The summary most-adjusted mvRR comparing the highest intake of dietary PUFA with the lowest was 1.18 (95% CI: 080 to 1.76; *P*=0.41; I^2=33%, P_{het}=0.22) (**Section 1.9.2** in **Fig. 8**).

3.3.8 Breast cancer

Total breast cancer

Eight studies (8 comparisons; n=6418 cases) provided an estimate of the association between total PUFA and breast cancer, without distinguishing premenopausal from postmenopausal cases (103-110). The summary most-adjusted mvRR comparing the highest intake of dietary PUFA with the lowest was 0.96 (95% CI: 0.86 to 1.07; *P*=0.47; I^2=11%, P_{het}=0.35) (**Section 1.11.1** in **Fig. 9**).

Premenopausal breast cancer

Three studies (3 comparisons; n=1671 cases) provided an estimate of the association between total PUFA and premenopausal breast cancer *(105, 108, 109)*. The summary most-adjusted mvRR comparing the highest intake of dietary PUFA with the lowest was 1.10 (95% CI: 0.92 to 1.32; *P*=0.29; I^2=0%, P_{het}=0.40) (**Section 1.11.2** in **Fig. 9**).

Postmenopausal breast cancer

Nine studies (9 comparisons; n=11 986 cases) provided an estimate of the association between total PUFA and postmenopausal breast cancer *(108, 111–117)*. The summary mvRR comparing the highest intake of dietary PUFA with the lowest was 1.06 (95% CI: 0.89 to 1.26; *P*=0.53; I^2=79%; P_{het}<0.00001) (**Section 1.11.3** in **Fig. 9**).

3.3.9 GRADE assessment of quality of evidence

For the 22 outcomes assessed, the GRADE assessment of the confidence in the estimates of association between total PUFA and health outcomes was moderate for one outcome (4.5%) (mortality), and very low for 21 outcomes (95.5%). Two estimates (9.1%) are at serious risk of bias, five (22.7%) have serious inconsistency and 21 (95.5%) have serious imprecision (**Table 3**).

3.4 Omega-3 PUFA and health outcomes

3.4.1 All-cause mortality

Ten prospective cohort studies (11 comparisons; n=190 293 deaths) examined the association between total omega-3 PUFA intake and all-cause mortality *(53, 54, 58–60, 118–120)*. The summary most-adjusted mvRR comparing the highest intake of dietary omega-3 PUFA with the lowest was 0.98 (95% CI: 0.93 to 1.03; *P*=0.36; I^2=75%; P_{het}<0.0001) (**Fig. 10**). No publication bias was suspected (**Fig. 84e**). In meta-regression, there was no association between effect size estimate and study size (*P*=0.80), TFA measurement (*P*=0.90), duration of follow-up (*P*=0.84), sex distribution (*P*=0.60), adjustment for dyslipidaemia (0.64) or hypertension (*P*=0.52), age of participants (*P*=0.41), proportion of current or former smokers (*P*=0.83), or method of diet assessment (*P*=0.38). There was evidence of an association between effect size and study risk of bias (*P*=0.02), with lower quality studies showing more protective effects. Country of conduct also explained some heterogeneity (*P*=0.03 for difference in association by country), with studies in Australia and China showing harmful associations, and studies in Japan and the USA showing no association. We could not investigate the impact of adjustment for total energy because all studies adjusted for this factor (**Fig. 89**) (i.e. it is not appropriate to undertake meta-regression by this source of heterogeneity).

3.4.2 Cardiovascular diseases

Total CVD

One prospective cohort study (1 comparison; n=194 events) provided estimates of the association between total dietary omega-3 PUFA and total CVD. For total CVD, the summary most-adjusted mvRR comparing the highest intake of dietary PUFA with the lowest was 1.10 (95% CI: 0.83 to 1.45; *P*=0.50) (**Section 2.2.1** in **Fig. 11**).

Fatal CVD

Eight studies (10 comparisons; n=59 999 events) provided estimates of the association between total dietary omega-3 PUFA and fatal CVD *(53, 54, 59, 60, 118, 119, 121, 122)*. The summary most-adjusted mvRR comparing the highest total dietary omega-3 PUFA intake with the lowest was 0.94 (95% CI: 0.88 to 1.01; *P*=0.09; I^2=55%, P_{het}=0.09) (**Section 2.2.2** in **Fig. 11**). No publication bias was suspected (**Fig. 84f**).

Meta-regression found no association between effect size and study size (number of cases; *P*=0.59), study risk of bias (*P*=0.65), measurement of TFA (*P*=0.13), follow-up time (*P*=0.50), sex distribution (*P*=0.48), adjustment for dyslipidaemia (*P*=0.51), adjustment for blood pressure (*P*=0.66), age distribution of the population (*P*=0.86), proportion of smokers in the study (*P*=0.94), method of dietary assessment (*P*=0.94) or country of conduct (*P*=0.58). We could not investigate the impact of adjustment for total energy because all studies adjusted for this factor (**Fig. 92**) (i.e. it is not appropriate to undertake meta-regression by this source of heterogeneity).

Fatal CHD

Four studies (4 comparisons; n=4578 events) provided estimates of the association between total dietary omega-3 PUFA and fatal CHD *(59, 118, 122, 123)*. The summary most-adjusted mvRR comparing the highest intake of dietary PUFA with the lowest was 0.83 (95% CI: 0.71 to 0.97; *P*=0.02; I^2=20%, P_{het}=0.20) (**Section 2.2.3** in **Fig. 11**). Assuming linearity, a 1 g increase in n-3 PUFA was associated with a 23% reduced risk of CHD mortality (mvRR: 0.77, 95% CI: 0.67 to 0.88). Assuming linearity, a 0.5% increase in n-3 PUFA was associated with a 21% reduced risk of CHD mortality (mvRR: 0.79, 95% CI: 0.71 to 0.89) (**Fig. 109** and **Fig. 110**)

Sudden cardiac death

Two studies (2 comparisons; n=492 events) provided estimates of the association between total dietary omega-3 PUFA and sudden cardiac death *(71, 118)*. The summary most-adjusted mvRR comparing the highest intake of total dietary omega-3 PUFA with the lowest was 0.65 (95% CI: 0.47 to 0.90; *P*=0.009; I^2=0%; P_{het}=0.97) (**Section 2.2.4** in **Fig. 11**).

Fatal myocardial infarction

One study (1 comparison; n=329 events) provided an estimate of the association between total dietary omega-3 PUFA and fatal myocardial infarction *(118)*. In this study, the summary most-adjusted mvRR comparing the highest intake of total dietary omega-3 PUFA with the lowest was 0.75 (95% CI: 0.47 to 1.19; *P*=0.22) (**Section 2.2.5** in **Fig. 11**).

Nonfatal myocardial infarction

One study (1 comparison; n=1029 events) provided an estimate of the association between total dietary omega-3 PUFA and nonfatal myocardial infarction *(123)*. The summary most-adjusted mvRR comparing the highest intake of dietary PUFA with the lowest was 0.73 (95% CI: 0.57 to 0.93; *P*=0.01) (**Section 2.2.6** in **Fig. 11**). Assuming linearity, a 1 g increase in n-3 PUFA was associated with an 52% decrease in nonfatal myocardial infarction (mvRR: 0.48; 95% CI: 0.28 to 0.81) (**Fig. 111** and **Fig. 112**).

Total CHD

Four studies (7 comparisons; n=4 257 events) provided estimates of the association between total dietary omega-3 PUFA and total CHD *(75, 123–125)*. The summary most-adjusted mvRR comparing the highest intake of total dietary omega-3 PUFA with the lowest was 0.93 (95% CI: 0.77 to 1.12; *P*=0.44; I^2=65%, P_{het}=0.009) (**Section 2.2.7** in **Fig. 11**).

Total myocardial infarction

No studies were identified that provided an estimate of the association between total dietary omega-3 PUFA and total myocardial infarction.

Total stroke

Two studies (2 comparisons; n=815 events) provided estimates of the association between total dietary omega-3 PUFA and total stroke *(79, 126)*. The summary most-adjusted mvRR comparing the highest intake of dietary PUFA with the lowest was 0.85 (95% CI: 0.49 to 1.46; *P*=0.55; I^2=38%, P_{het}=0.20) (**Section 2.2.9** in **Fig. 11**).

Fatal stroke

Two studies (2 comparisons; n=1619 events) provided an estimate of the association between total dietary omega-3 PUFA and fatal stroke *(72)*. In this study, the summary most-adjusted mvRR comparing the highest intake of total dietary omega-3 PUFA with the lowest was 0.80 (95% CI: 0.66 to 0.98; *P*=0.03; I^2=0%, P_{het}=0.58) (**Section 2.2.10** in **Fig. 11**). Assuming linearity, a 1 g increase in n-3 PUFA was associated with an 25% decrease in risk of fatal stroke (mvRR: 0.75; 95% CI: 0.55 to 1.01). Assuming linearity, a 0.5% increase in n-3 PUFA was associated with a 24% decrease in risk of fatal stroke (mvRR: 0.76; 95% CI: 0.59 to 0.97) (**Fig. 113** and **Fig. 114**).

Fatal ischaemic stroke

One study (1 comparison; n=319 events) provided an estimate of the association between total dietary omega-3 PUFA and fatal ischaemic stroke *(72)*. In this study, the summary most-adjusted mvRR comparing the highest intake of total dietary omega-3 PUFA with the lowest was 1.17 (95% CI: 0.71 to 1.92; *P*=0.54) (**Section 2.2.11** in **Fig. 11**).

Ischaemic stroke

Two studies (3 comparisons; n=1 058 events) provided estimates of the association between total dietary omega-3 PUFA and ischaemic stroke *(75, 126)*. The summary most-adjusted mvRR comparing the highest intake of dietary PUFA with the lowest was 0.92 (95% CI: 0.73 to 1.15; *P*=0.45; I^2=19%, P_{het}=0.29) (**Section 2.2.12** in **Fig. 11**).

Haemorrhagic stroke

One study (1 comparison; n=181 events) provided an estimate of the association between total dietary omega-3 PUFA and haemorrhagic stroke *(127)*. In this study, the summary most-adjusted mvRR comparing the highest intake of total dietary omega-3 PUFA with the lowest was 0.76 (95% CI: 0.43 to 1.36; *P*=0.35) (**Section 2.2.13** in **Fig. 11**).

Thrombotic infarction

One study (1 comparison; n=264 events) provided an estimate of the association between total dietary omega-3 PUFA and thrombotic infarction *(127)*. In this study, the summary most-adjusted mvRR comparing the highest intake of total dietary omega-3 PUFA with the lowest was 0.67 (95% CI: 0.42 to 1.07; *P*=0.09) (**Section 2.2.14** in **Fig. 11**).

Atrial fibrillation

Two studies (3 comparisons; n=6 521 events) provided an estimate of the association between total dietary omega-3 PUFA and atrial fibrillation *(85, 86)*. The summary most-adjusted mvRR comparing the highest intake of total dietary omega-3 PUFA with the lowest was 0.98 (95% CI: 0.90 to 1.06; *P*=0.58; I^2=44%; P_{het}=0.17) (**Section 2.2.15** in **Fig. 11**).

3.4.3 Type 2 diabetes

Six studies (6 comparisons; n=7 073 events) provided estimates of the association between total dietary omega-3 PUFA and type 2 diabetes *(87, 89, 93, 95, 128, 129)*. The summary most-adjusted mvRR comparing the highest intake of dietary PUFA with the lowest was 0.99 (95% CI: 0.78 to 1.26; *P*=0.95; I^2=83%, P_{het}<0.0001) (**Fig. 12**).

3.4.4 Dementia

Three studies (3 comparisons; n=379 events) provided estimates of the association between total dietary omega-3 PUFA and new-onset dementia *(96, 130, 131)*. The summary most-adjusted random-effects mvRR comparing the highest intake of dietary omega-3 PUFA with the lowest was 0.86 (95% CI: 0.54 to 1.39; *P*=0.54; I^2=44%, P_{het}=0.17) (**Fig. 13a for random-effects**; **13b for fixed-effect**).

3.4.5 Cognitive decline

One study (1 comparison; n=598 events) provided estimates of the association between total dietary omega-3 PUFA and cognitive decline *(98)*. The summary most-adjusted mvRR comparing the highest intake of dietary omega-3 PUFA with the lowest was 0.79 (95% CI: 0.63 to 0.99; *P*=0.04) (**Fig. 14**) Assuming linearity, a 1 g increase in n-3 PUFA was associated with a 28% decrease in risk of cognitive decline (mvRR: 0.72; 95% CI: 0.53 to 0.98). Assuming linearity, a 0.5% increase in energy from n-3 PUFA was associated with a 29% decrease in risk of cognitive decline (mvRR: 0.71; 95% CI: 0.51 to 0.98) (**Fig. 115** and **Fig. 116**).

3.4.6 Depression

Three studies (3 comparisons; n=1016 events) provided estimates of the association between total dietary omega-3 PUFA and "mental disorders" (defined as physician-diagnosed depression, anxiety or stress), or use of antidepressant medications or tranquillizers – this was similar to the way in which other studies defined depression. The summary most-adjusted mvRR comparing the highest intake of dietary omega-3 PUFA with the lowest was 0.87 (95% CI: 0.71 to 1.06; *P*=0.17; I^2=16%; P_{het}=0.31) (**Fig. 15a**). The fixed-effect estimate was 0.87 (95% CI: 0.73 to 1.04; *P*=0.12; I^2=16%; P_{het}=0.31) (**Fig. 15b**). Assuming linearity, a 1 g increase in n-3 PUFA was associated with an 28% decrease in risk of depression (mvRR: 0.72; 95% CI: 0.53 to 0.98). Assuming linearity, a 0.5% increase in energy from n-3 PUFA was associated with an 29% decrease in risk of depression (mvRR: 0.71; 95% CI: 0.52 to 0.98) (**Fig. 117** and **Fig. 118**).

3.4.7 Inflammatory bowel disease

Crohn's disease

No prospective cohort studies were identified that provided an estimate of the association between dietary omega-3 PUFA and Crohn's disease.

Ulcerative colitis

Two studies (2 comparisons; n=360 cases) provided an estimate of the association between dietary omega-3 PUFA and ulcerative colitis *(101, 132)*. The summary most-adjusted mvRR comparing the highest intake of dietary omega-3 PUFA with the lowest was 0.67 (95% CI: 0.27 to 1.65; *P*=0.38; I^2=47%, P_{het}=0.17) (**Fig. 16**).

3.4.8 Breast cancer

Total breast cancer

Three studies (3 comparisons; n=988 cases) provided an estimate of the association between dietary omega-3 PUFA and breast cancer, without distinguishing premenopausal from postmenopausal cases *(106, 107, 110)*. The summary most-adjusted mvRR comparing the highest intake of dietary PUFA with the lowest was 0.88 (95% CI: 0.72 to 1.08; *P*=0.22; I^2=0%, P_{het}=0.58) (**Section 2.8.1** in **Fig. 17a**; **fixed-effect models** presented in **Fig. 17b**).

Premenopausal breast cancer

No prospective cohort studies were identified that reported the association between total dietary omega-3 PUFA and premenopausal breast cancer.

Postmenopausal breast cancer

Three studies (3 comparisons; n=783 cases) provided an estimate of the association between total dietary omega-3 PUFA and postmenopausal breast cancer *(107, 113, 117)*. The summary mvRR comparing the highest intake of dietary PUFA with the lowest was 1.13 (95% CI: 0.69 to 1.86; *P*=0.63; I^2=65%; P_{het}=0.06) (**Section 2.8.3** in **Fig. 17a**; **fixed-effect models** presented in **Fig. 17b**)).

3.4.9 GRADE assessment of quality of evidence

For the 22 outcomes assessed, the GRADE assessment of the confidence in the estimates of association between total omega-3 PUFA and health outcomes were moderate for three outcomes (4.5%) (fatal CHD, fatal stroke and cognitive decline); low for two outcomes (9.1%) (sudden cardiac death and nonfatal myocardial infarction) and very low for 17 outcomes (77.3%). Four estimates (18.2%) were at serious risk of bias, six (27.3%) had serious inconsistency and 16 (72.7%) had serious imprecision (**Table 4**).

3.5 Long-chain omega-3 PUFA and health outcomes

3.5.1 All-cause mortality

Eleven prospective cohort studies (15 comparisons; n=155 616 deaths) examined the association between long-chain omega-3 PUFA intake and all-cause mortality *(52, 54, 133–137)*. The summary most-adjusted mvRR comparing the highest intake of dietary long-chain omega-3 PUFA with the lowest was 0.91 (95% CI: 0.87 to 0.95; *P*<0.00001; I^2=62%; P_{het}=0.0008) (**Fig. 18**). No subgroup analyses or publication bias tests were performed (<10 studies). No study was an influential outlier.

Assuming linearity, a 0.5 g increase in long-chain n-3 PUFA was associated with an 9% reduced risk of all-cause mortality (mvRR: 0.91, 95% CI: 0.88 to 0.93). Assuming linearity, a 0.1% increase in long-chain n-3 PUFA was associated with an 4% reduced risk of all-cause mortality (mvRR: 0.96, 95% CI: 0.95 to 0.97). The goodness-of-fit test revealed departure from linearity, with a decrease in risk from 0 g/day to 0.25 g/day (≈0.1% energy) then no further benefit through a range of 0.25 to 1.25 g/day (~0.1% to 0.42% energy) (**Fig. 119** and **Fig. 120**). There was no evidence of publication bias (**Fig. 84g**).

Meta-regression found no association between effect size and study size (number of cases; *P*=0.86), study risk of bias (*P*=0.26), measurement of trans-fats (*P*=0.34), follow-up time (*P*=0.23), sex distribution (*P*=0.93), adjustment for total energy (*P*=0.46), adjustment for dyslipidaemia (*P*=0.49), adjustment for blood pressure (*P*=0.43), the age distribution of the population (*P*=0.96) or the distribution of smokers (*P*=0.68). There was evidence of heterogeneity by method of dietary assessment (*P*=0.02), with the one study that measured diet with 7-day food records showing a lower mvRR (0.74) than those who used FFQ (0.91) or 24-hour recalls (0.93), and country

(*P*<0.0001), with the studies in China showing lower estimates (0.78) than other countries (0.84–1.03) (**Fig. 91**).

3.5.2 Cardiovascular diseases

Total CVD

Four prospective cohort studies (4 comparisons; n=6682 events) provided estimates of the association between long-chain omega-3 PUFA intake and total CVD events *(138–140)*. The summary most-adjusted mvRR comparing the highest intake of dietary long-chain omega-3 PUFA with the lowest was 0.94 (95% CI: 0.75 to 1.18; *P*=0.60; I^2=73%; P_{het}=0.01; random-effects) (**Section 3.2.1** in **Fig. 19**). The fixed-effect estimate is 0.99 (0.89, 1.10).

Fatal CVD

Fourteen studies (18 comparisons; n=49 704 events) provided estimates of the association between long-chain omega-3 PUFA intake and fatal CVD *(52, 54, 59, 60, 122, 133, 134, 136–138, 141–144)*. The summary most-adjusted mvRR comparing the highest intake of total long-chain dietary omega-3 PUFA with the lowest was 0.88 (95% CI: 0.82 to 0.95; *P*=0.001; I^2=67%, P_{het}<0.0001) (**Section 3.2.2** in **Fig. 19**). Assuming linearity, a 0.5 g increase in long-chain n-3 PUFA was associated with a 10% reduced risk of CVD mortality (mvRR: 0.90; 95% CI: 0.86 to 0.94). Assuming linearity, a 0.1% increase in long-chain n-3 PUFA was associated with a 4% reduced risk of CVD mortality (mvRR: 0.96; 95% CI: 0.94 to 0.97). However, both associations were non-linear, and there appeared to be a decrease in risk from 0 g/day to 0.25 g/day (0–0.11% E) but a gradual increase in risk from this point through 1.4 g/day (0.5%E) (**Fig. 121** and **Fig. 122**). No publication bias was suspected (**Fig. 84h**).

Meta-regression found no association between effect size and study size (number of cases; *P*=0.71), study risk of bias (*P*=0.43), follow-up time (*P*=0.12), sex distribution (*P*=0.96), adjustment for total energy (*P*=0.95), adjustment for dyslipidaemia (*P*=0.75), adjustment for blood pressure (*P*=0.62), the age distribution of the population (*P*=0.94), the distribution of smokers (*P*=0.96), the method of dietary assessment (*P*=0.22) or country (*P*=0.60). There was evidence of heterogeneity by whether a study measured TFA (*P*=0.004), with studies that did not measure TFA finding an mvRR=0.84 and those that did measure TFA an mvRR=1.04 (**Fig. 92**).

Fatal CHD

Fourteen studies (16 comparisons; n=7525 events) provided estimates of the association between total long-chain dietary omega-3 PUFA and fatal CHD *(59, 67, 122, 127, 133, 134, 136, 137, 141, 144–148)*. The summary most-adjusted mvRR comparing the highest intake of total long-chain dietary omega-3 PUFA with the lowest was 0.80 (95% CI: 0.69 to 0.92; *P*=0.002; I^2=53%, P_{het}=0.006) (**Section 3.2.2** in **Fig. 19**). Assuming linearity, a 0.5 g increase in long-chain n-3 PUFA was associated with a 14% reduced risk of CHD mortality (mvRR: 0.86; 95% CI: 0.78 to 0.95). Assuming linearity, a 0.5% increase in long-chain n-3 PUFA was associated with a 26% reduced risk of CHD mortality (mvRR: 0.74; 95% CI: 0.60 to 0.90). Although the goodness-of-fit test was consistent with departure from linearity, there was no clear threshold of benefit (**Fig. 122** and **Fig. 123**). No publication bias was suspected (**Fig. 84i**).

Meta-regression found no association between effect size and study size (number of cases; *P*=0.38), study risk of bias (*P*=0.57), measurement of TFA (*P*=0.63), follow-up time (*P*=0.55), sex distribution (*P*=0.80), adjustment for total energy (*P*=0.18), adjustment for dyslipidaemia (*P*=0.55), adjustment for blood pressure (*P*=0.41), age distribution of the population (*P*=0.91), distribution of smokers (*P*=0.77) or country of conduct (*P*=0.60). There was evidence of heterogeneity by the method of dietary assessment (*P*=0.04), with studies that used 24-hour recalls finding lower estimates (0.64) than those that used FFQ (0.77) and those that used diet histories (0.92); and by country of conduct (*P*=0.009), with the one study conducted in Finland finding an mvRR of 1.30, whereas all others were less than 0.96 (**Fig. 92**).

Sudden cardiac death

Five studies (5 comparisons; n=614 events) provided estimates of the association between total long-chain dietary omega-3 PUFA and sudden cardiac death *(71, 127, 144, 145, 149)*. The summary most-adjusted mvRR comparing the highest intake of total dietary long-chain omega-3 PUFA with the lowest was 0.57 (95% CI: 0.34 to 0.93; *P*=0.02; I^2=41%; P_{het}=0.15) (**Section 3.2.4** in **Fig. 19**). The fixed-effect estimate was 0.61 (0.45, 0.83). Assuming linearity, a 0.5 g increase in energy from long-chain n-3 PUFA was associated with an 18% decrease in risk of sudden cardiac death (mvRR: 0.82; 95% CI: 0.64 to 1.05). Assuming linearity, a 0.1% increase in energy from long-chain n-3 PUFA was associated with a 13% decrease in risk of sudden cardiac death (mvRR: 0.87; 95% CI: 0.77 to 0.99) (**Fig. 124** and **Fig. 125**).

Fatal myocardial infarction

Two studies (2 comparisons; n=177 events) provided an estimate of the association between total long-chain dietary omega-3 PUFA and fatal myocardial infarction *(150)*. The summary most-adjusted mvRR comparing the highest intake of total dietary long-chain omega-3 PUFA with the lowest was 0.41 (95% CI: 0.25 to 0.65; *P*=0.0002; I^2=0%; P_{het}=0.80) (**Section 3.2.5** in **Fig. 19**). Assuming linearity, a 0.5 g increase in energy from long-chain n-3 PUFA was associated with an 85% decrease in risk of fatal myocardial infarction (mvRR: 0.15; 95% CI: 0.05 to 0.41). Assuming linearity, a 0.1% increase in energy from long-chain n-3 PUFA was associated with a 61% decrease in risk of fatal myocardial infarction (mvRR: 0.39; 95% CI: 0.24 to 0.64) (**Fig. 126** and **Fig. 127**).

Fatal arrhythmia

One study (1 comparison, 148 events) provided an estimate of the association between total long-chain dietary omega-3 PUFA and fatal arrhythmia. In this study, the most-adjusted mvRR comparing the highest intake of total dietary long-chain omega-3 PUFA with the lowest was 0.45 (95% CI: 0.25 to 0.81; *P*=0.008) (**Section 3.2.6** in **Fig. 19**). Assuming linearity, a 0.5 g increase in energy from long-chain n-3 PUFA was associated with an 85% decrease in risk of fatal arrythmia (mvRR: 0.15; 95% CI: 0.06 to 0.41). Assuming linearity, a 0.1% increase in energy from long-chain n-3 PUFA was associated with a 61% decrease in risk of fatal arrythmia (mvRR: 0.39; 95% CI: 0.24 to 0.64) (**Fig. 128** and **Fig. 129**).

Total haemorrhagic stroke

Three studies (4 comparisons; n=754 events) provided an estimate of the association between total dietary long-chain omega-3 PUFA and total haemorrhagic stroke *(81, 151, 152)*. In this study, the summary most-adjusted mvRR comparing the highest intake of total dietary long-chain omega-3 PUFA with the lowest was 0.55 (95% CI: 0.39 to 0.77; *P*=0.0007; I^2=0%, P_{het}=0.52) (**Section 3.2.7** in **Fig. 19**).

Total CHD

Four studies (6 comparisons; n=3149 events) provided estimates of the association between total dietary long-chain omega-3 PUFA and total CHD (67, 75, 127, 153). The summary most-adjusted mvRR comparing the highest intake of total dietary long-chain omega-3 PUFA with the lowest was 0.88 (95% CI: 0.71 to 1.10; *P*=0.26; I^2=65%, P_{het}=0.01; random-effects) (**Section 3.2.8** in **Fig. 19**). The fixed-effect estimate was 0.98 (0.88, 1.10).

Total myocardial infarction

Four studies (5 comparisons; n=4275 events) provided an estimate of the association between total dietary long-chain omega-3 PUFA and total myocardial infarction *(127, 138, 143, 154)*. The summary most-adjusted mvRR comparing the highest intake of total dietary long-chain omega-3 PUFA with the lowest was 0.91 (95% CI: 0.76 to 1.08; *P*=0.28; I^2=53%, P_{het}=0.07; random-effects) (**Section 3.2.9** in **Fig. 19**). The fixed-effect estimate was 0.92 (0.83, 1.02).

Total stroke

Four studies (5 comparisons; n=2963 events) provided estimates of the association between total dietary long-chain omega-3 PUFA and total stroke *(81, 138, 143, 151)*. The summary most-adjusted mvRR comparing the highest intake of total dietary long-chain ω-3 PUFA with the lowest was 0.92 (95% CI: 0.79 to 1.08; *P*=0.31; I^2=30%, P_{het}=0.22) (**Section 3.2.10** in **Fig. 19**).

Fatal stroke

Six studies (7 comparisons; n=2760 events) provided an estimate of the association between total dietary long-chain omega-3 PUFA and fatal stroke *(59, 122, 137, 141, 144, 150)*. In this study, the summary most-adjusted mvRR comparing the highest intake of total dietary long-chain omega-3 PUFA with the lowest was 0.90 (95% CI: 0.79 to 1.03; *P*=0.12; I^2=0%, P_{het}=0.75) (**Section 3.2.11** in **Fig. 19**).

Fatal ischaemic stroke

One study (1 comparison; n=404 events) provided an estimate of the association between total dietary long-chain omega-3 PUFA and fatal ischaemic stroke *(134)*. In this study, the summary most-adjusted mvRR comparing the highest intake of total dietary long-chain omega-3 PUFA with the lowest was 0.53 (95% CI: 0.34 to 0.82; *P*=0.005) (**Section 3.2.12** in **Fig. 19**). Assuming linearity, a 0.5 g increase in energy from long-chain n-3 PUFA was associated with a 63% decrease in risk of fatal ischaemic stroke (mvRR: 0.37; 95% CI: 0.14 to 0.99) (**Fig. 130**).

Ischaemic stroke

Four studies (6 comparisons; n=3992 events) provided estimates of the association between total dietary long-chain omega-3 PUFA and ischaemic stroke *(75, 143, 151, 152)*. The summary most-adjusted mvRR comparing the highest intake of total dietary long-chain omega-3 PUFA with the lowest was 1.06 (95% CI: 0.92 to 1.22; *P*=0.40; I^2=0%, P_{het}=0.66) (**Section 3.2.13** in **Fig. 19**).

Fatal haemorrhagic stroke

One study (1 comparison; n=460 events) provided an estimate of the association between total dietary long-chain omega-3 PUFA and fatal haemorrhagic stroke *(134)*. In this study, the summary most-adjusted mvRR comparing the highest intake of total dietary long-chain omega-3 PUFA with the lowest was 0.88 (95% CI: 0.63 to 1.22; *P*=0.44) (**Section 3.2.14** in **Fig. 19**).

Nonfatal myocardial infarction

Three studies (3 comparisons; n=694 events) provided an estimate of the association between total dietary long-chain omega-3 PUFA and nonfatal myocardial infarction *(138, 146, 148)*. The summary most-adjusted mvRR comparing the highest intake of total dietary long-chain omega-3 PUFA with the lowest was 0.99 (95% CI: 0.80 to 1.23; *P*=0.96; I^2=0%; P_{het}=0.67) (**Section 3.2.15** in **Fig. 19**).

Atrial fibrillation

Six studies (6 comparisons; n=9073 events) provided an estimate of the association between total dietary long-chain omega-3 PUFA and atrial fibrillation *(155–160)*. The summary most-adjusted mvRR comparing the highest intake of total dietary long-chain omega-3 PUFA with the lowest was 1.03 (95% CI: 0.89 to 1.19; *P*=0.68; I^2=64%, P_{het}=0.02; random-effects) (**Section 3.2.16** in **Fig. 19**). The fixed-effect estimate was 1.03 (0.96, 1.10).

Heart failure

Two studies (3 comparisons; n=3669 events) provided an estimate of the association between total dietary long-chain omega-3 PUFA and incident heart failure *(161, 162)*. In these studies, the summary most-adjusted mvRR comparing the highest intake of total dietary long-chain omega-3 PUFA with the lowest was 0.81 (95% CI: 0.69 to 0.94; *P*=0.005; I^2=0%; P_{het}=0.48) (**Section 3.2.17** in **Fig. 19**). Assuming linearity, a 0.5 g increase in long-chain n-3 PUFA was associated with an 18% decrease in risk of heart failure (mvRR: 0.82; 95% CI: 0.72 to 0.93). Assuming linearity, a 0.1% increase in energy from long-chain n-3 PUFA was associated with a 10% decrease in risk of heart failure (mvRR: 0.90; 95% CI: 0.85 to 0.96) (**Fig. 131** and **Fig. 132**).

3.5.3 Type 2 diabetes

Eleven studies (16 comparisons; n=22 451 events) provided estimates of the association between total dietary long-chain omega-3 PUFA and type 2 diabetes *(87, 88, 128, 129, 163–169)*. The summary most-adjusted mvRR comparing the highest intake of total dietary long-chain omega-3 PUFA with the lowest was 1.10 (95% CI: 0.99 to 1.23; *P*=0.07; I^2=77%, P_{het}=0.00001) (**Fig. 20**) Assuming linearity, a 0.5 g increase in long-chain n-3 PUFA was associated with a 17% increased risk of type 2 diabetes (mvRR: 1.17, 95% CI: 1.10 to 1.24). Assuming linearity, a 0.1% increase in energy from long-chain n-3 PUFA was associated with a 7% increased risk of type 2 diabetes (mvRR: 1.07, 95% CI: 1.05 to 1.10) (**Fig. 133** and **Fig. 134**). No publication bias was suspected (**Fig. 84j**).

Meta-regression found no association between effect size and study size (number of cases; *P*=0.66), study risk of bias (*P*=0.78), measurement of TFA (*P*=0.18), follow-up time (*P*=0.16), sex distribution (*P*=0.76), adjustment for total energy (*P*=0.26), adjustment for dyslipidaemia (*P*=0.67), adjustment for blood pressure (*P*=0.35), age distribution of the population (*P*=0.17), distribution of smokers (*P*=0.65) or country (*P*=0.60). There was evidence of heterogeneity by the method of dietary assessment (*P*=0.04), with studies that used 24-hour recalls finding higher estimates (pooled mvRR: 1.65) than those that used FFQ (1.08) and those that used 4-day food records (0.85); and by country of conduct (*P*=0.001), with the studies conducted in the USA finding an mvRR of 1.24, while all others found an mvRR of 0.9–1.1 (**Fig. 94**).

3.5.4 Dementia

No prospective cohort studies were identified that assessed the association between total dietary long-chain omega-3 PUFA and dementia.

3.5.5 Cognitive decline

Three studies (3 comparisons; n=979 events) provided estimates of the association between total dietary long-chain omega-3 PUFA and cognitive decline *(98, 170, 171)*. The summary most-adjusted mvRR comparing the highest intake of total dietary long-chain omega-3 PUFA with the lowest was 0.83 (95% CI: 0.65 to 1.05; *P*=0.12; I^2=52%, P_{het}=0.13; random-effects) (**Fig. 21**) The fixed-effect estimate was 0.86 (95% CI: 0.74 to 0.99; *P*=0.04; Fig. 21b). Assuming linearity, a 0.5 g increase in long-chain n-3 PUFA was associated with a 23% decrease in risk of cognitive decline (mvRR: 0.77; 95% CI: 0.61 to 0.97). Assuming linearity, a 0.1% increase in energy from long-chain n-3 PUFA was associated with an 11% decrease in risk of cognitive decline (mvRR: 0.89; 95% CI: 0.81 to 0.99) (**Fig. 135** and **Fig. 136**).

3.5.6 Depression

Three studies (4 comparisons; n=3662 events) provided estimates of the association between total dietary long-chain omega-3 PUFA and depression *(172–174)*. The summary most-adjusted mvRR comparing the highest intake of total dietary long-chain omega-3 PUFA with the lowest was 0.92 (95% CI: 0.82 to 1.04; *P*=0.19; I^2=0%, P_{het}=0.62) (**Fig. 22**).

3.5.7 Suicide

One study (2 comparisons; n=298 events) provided an estimate of the association between total dietary long-chain omega-3 PUFA and suicide *(175)*. The summary most-adjusted mvRR comparing the highest intake of total dietary long-chain omega-3 PUFA with the lowest was 1.02 (95% CI: 0.69 to 1.50; *P*=0.94; I^2=0%, P_{het}=0.69) (**Fig. 23**).

3.5.8 Inflammatory bowel disease

Crohn's disease

Two prospective cohort studies (2 comparisons; n=342 events) were identified that provided an estimate of the association between total dietary long-chain omega-3 PUFA and Crohn's disease *(101, 176)*. The summary most-adjusted mvRR comparing the highest intake of total dietary long-chain omega-3 PUFA with the lowest was 0.85 (95% CI: 0.59 to 1.23; *P*=0.38; I^2=0%, P_{het}=0.71) (**Section 3.7.1** in **Fig. 24**).

Ulcerative colitis

One study (1 comparison; n=338 cases) provided an estimate of the association between total dietary long-chain omega-3 PUFA and ulcerative colitis *(101)*. In this study, the most-adjusted mvRR comparing the highest intake of dietary long-chain omega-3 PUFA with the lowest was 0.72 (95% CI: 0.52 to 1.00; *P*=0.05) (**Section 3.7.2** in **Fig. 24a** and **fixed-effect estimate** in **Fig 24b**). Assuming linearity, a 0.5 g increase in long-chain n-3 PUFA was associated with a 29% decrease in risk of ulcerative colitis (mvRR: 0.71; 95% CI: 0.48 to 1.07). Assuming linearity, a 0.1% increase in long-chain n-3 PUFA was associated with a 13% decrease in risk of ulcerative colitis (mvRR: 0.87; 95% CI: 0.72 to 1.03) (**Fig. 137** and **Fig. 138**).

3.5.9 Breast cancer

Total breast cancer

Six studies (6 comparisons; n=5158 cases) provided an estimate of the association between total dietary long-chain omega-3 PUFA and breast cancer, without distinguishing premenopausal from postmenopausal cases *(105–107, 136, 137, 177)*. The summary most-adjusted mvRR comparing the highest intake of total dietary long-chain omega-3 PUFA with the lowest was 0.82 (95% CI: 0.66 to 1.02; *P*=0.08; I^2=77%, P_{het}=0.0005; random-effects) (**Section 3.8.1** in **Fig. 25**). The fixed-effect estimate was 1.05 (95% CI: 1.00 to 1.09; *P*=0.04), with the study by Holmes et al. *(105)* increasing in weight from 28.7% to 89.0%. Assuming linearity, a 0.5 g increase in long-chain n-3 PUFA was associated with a 6% decrease in risk of breast cancer (mvRR: 0.94; 95% CI: 0.86 to 1.04). Assuming linearity, a 0.1% increase in energy from long-chain n-3 PUFA was associated with a 2% decrease in risk of breast cancer (mvRR: 0.98; 95% CI: 0.95 to 1.01). However, there appeared to be an inflection point, whereby the risk increased (from about 0 through 0.20 g/day, or about 0.12% energy), then began to fall (**Fig. 139** and **Fig. 140**).

Premenopausal breast cancer

Two prospective cohort studies (2 comparisons; n=1498 events) were identified that reported the association between total dietary long-chain omega-3 PUFA and premenopausal breast cancer *(105, 178)*. The summary most-adjusted mvRR comparing the highest intake of total dietary long-chain omega-3 PUFA with the lowest was 1.09 (95% CI: 0.96 to 1.23; *P*=0.17; I^2=0%, P_{het}=0.76) (**Section 3.8.2** in **Fig. 25**).

Postmenopausal breast cancer

Two studies (2 comparisons; n=1989 cases) provided an estimate of the association between total dietary long-chain omega-3 PUFA and postmenopausal breast cancer *(105, 107)*. The summary mvRR comparing the highest intake of dietary PUFA with the lowest was 0.82 (95% CI: 0.40 to

1.66; *P*=0.58; I^2=77%; P_{het}=0.04) (**Section 3.8.3** in **Fig. 25**). The fixed-effect estimate was 1.08 (95% CI: 1.01 to 1.16; *P*=0.02), with the study by Holmes et al. *(105)* showing an increase in weight from 61.5% to 99.0%.

3.5.10 GRADE assessment of quality of evidence

For the 24 outcomes assessed, the GRADE assessment of the confidence in the estimates of association between total dietary long-chain omega-3 PUFA and health outcomes was moderate for five outcomes (20.8%) (mortality, fatal CHD, sudden cardiac death, fatal myocardial infarction and heart failure), low for two outcomes (8.3%) (haemorrhagic stroke and fatal arrythmia) and very low for 17 outcomes (70.8%). One estimate (4.2%) is at serious risk of bias, six have serious inconsistency (20.8%) and 18 have serious imprecision (75.0%) (**Table 5**).

3.6 EPA (20:5 omega-3) and health outcomes

3.6.1 All-cause mortality

Two studies (2 comparison; n=6258 deaths) examined the association between EPA intake and all-cause mortality *(120, 134)*. The summary most-adjusted mvRR comparing the highest intake of EPA with the lowest was 0.82 (95% CI: 0.70 to 0.96; *P*=0.02; I^2=31%; P_{het}=0.23) (**Fig. 26**). Assuming linearity, a 0.5 g increase in EPA was associated with a 27% decrease in risk of mortality (mvRR: 0.73; 95% CI: 0.53 to 1.01). Assuming linearity, a 0.1% increase in energy from EPA was associated with a 12% decrease in risk of mortality (mvRR: 0.88; 95% CI: 0.77, 1.01) (**Fig. 141** and **Fig. 142**).

3.6.2 Cardiovascular diseases

Total CVD

No prospective cohort studies were identified that assessed the association between EPA and total CVD.

Fatal CVD

One study (1 comparison; n=1789 events) examined the association between EPA intake and fatal CVD *(134)*. The summary most-adjusted mvRR comparing the highest intake of EPA with the lowest was 0.75 (95% CI: 0.63 to 0.90; *P*=0.002) (**Section 4.2.1** in **Fig. 27**). Assuming linearity, a 0.5 g increase in EPA was associated with a 27% decrease in risk of CVD mortality (mvRR: 0.73; 95% CI: 0.53 to 1.01). Assuming linearity, a 0.1% increase in energy from EPA was associated with a 12% decrease in risk of CVD mortality (mvRR: 0.88; 95% CI: 0.77, 1.01) .

Fatal CHD

One study (1 comparison; n=476 events) examined the association between EPA intake and CHD mortality *(134)*. The summary most-adjusted mvRR comparing the highest intake of EPA with the lowest was 0.84 (95% CI: 0.60 to 1.17; *P*=0.30) (**Section 4.2.2** in **Fig. 27**).

Fatal myocardial infarction

No prospective cohort studies were identified that assessed the association between EPA and fatal myocardial infarction.

Total CHD

Two studies (4 comparisons; n=1733 events) examined the association between EPA intake and total CHD *(124, 125)*. The summary most-adjusted mvRR comparing the highest intake of EPA with the lowest was 0.94 (95% CI: 0.78 to 1.14; *P*=0.56; I^2=26%; P_{het}=0.26) (**Section 4.2.4** in **Fig. 27**). The summary fixed-effect estimate was 0.94 (95% CI: 0.81 to 1.11; *P*=0.48).

Fatal stroke

No prospective cohort studies were identified that assessed the association between EPA and fatal stroke (without distinguishing type of stroke).

Fatal haemorrhagic stroke

One study (1 comparison; n=460 events) examined the association between EPA intake and fatal haemorrhagic stroke *(134)*. The summary most-adjusted mvRR comparing the highest intake of EPA with the lowest was 0.81 (95% CI: 0.58 to 1.13; *P*=0.21) (**Section 4.2.6** in **Fig. 27**).

Fatal ischaemic stroke

One study (1 comparison; n=404 events) examined the association between EPA intake and fatal ischaemic stroke *(134)*. The summary most-adjusted mvRR comparing the highest intake of EPA with the lowest was 0.56 (95% CI: 0.36 to 0.87; *P*=0.009) (**Section 4.2.7** in **Fig. 27**). Assuming linearity, a 0.5 g increase in EPA was associated with a 98% decrease in risk of mortality (mvRR: 0.02; 95% CI: 0.0006 to 0.46). Assuming linearity, a 0.1% increase in energy from EPA was associated with an 83% decrease in risk of fatal ischaemic stroke (mvRR: 0.17; 95% CI: 0.04 to 0.74) (**Fig. 143** and **Fig. 144**).

Total myocardial infarction

One study (2 comparisons; n=3028 events) examined the association between EPA intake and total myocardial infarction *(154)*. The summary most-adjusted mvRR comparing the highest intake of EPA with the lowest was 0.91 (95% CI: 0.80 to 1.02; *P*=0.12; I^2=0%; P_{het}=0.69) (**Section 4.2.8** in **Fig. 27**). Assuming linearity, a 0.5 g increase in EPA was associated with a 98% decrease in risk of mortality (mvRR: 0.02; 95% CI: 0.0006, 0.46). Assuming linearity, a 0.1% increase in energy from EPA was associated with an 83% decrease in risk of mortality (mvRR: 0.17; 95% CI: 0.04, 0.74) (**Fig. 145** and **Fig. 146**).

Total stroke

No prospective cohort studies were identified that assessed the association between EPA and total stroke.

Sudden cardiac death

No prospective cohort studies were identified that assessed the association between EPA and sudden cardiac death.

Atrial fibrillation

Three studies (3 comparisons; n=3285 events) examined the association between EPA intake and atrial fibrillation *(85, 157, 159)*. The summary most-adjusted mvRR comparing the highest intake of EPA with the lowest was 0.94 (95% CI: 0.82 to 1.07; *P*=0.33; I^2=0%; P_{het}=0.72) (**Section 4.2.11** in **Fig. 27**).

3.6.3 Type 2 diabetes

Four studies (4 comparisons; n=3093 events) examined the association between EPA intake and development of type 2 diabetes *(87, 89, 165, 169)*. The summary most-adjusted mvRR comparing the highest intake of EPA with the lowest was 1.02 (95% CI: 0.72 to 1.45; *P*=0.90; I^2=75%; P_{het}=0.007; random-effects) (**Fig. 28**). The fixed-effect estimate was 1.26 (1.12, 1.42).

3.6.4 Dementia

One study (1 comparison; n=131 events) examined the association between EPA intake and dementia *(134)*. The summary most-adjusted mvRR comparing the highest intake of EPA with the lowest was 0.90 (95% CI: 0.38 to 2.16; *P*=0.82) (**Fig. 29**).

3.6.5 Cognitive decline

One study (1 comparison; n=152 events) examined the association between EPA intake and risk of cognitive decline *(171)*. The summary most-adjusted mvRR comparing the highest intake of EPA with the lowest was 0.92 (95% CI: 0.77 to 1.10; *P*=0.36) (**Fig. 34**).

3.6.6 Suicide

One study (2 comparisons; n=298 events) provided an estimate of the association between EPA and suicide *(175)*. The summary most-adjusted mvRR comparing the highest intake of EPA with the lowest was 1.11 (95% CI: 0.74 to 1.65; *P*=0.62; I^2=0%, P_{het}=0.43) (**random effects**, **Fig. 30a** and **fixed-effect**, **Fig. 30b**).

3.6.7 Depression

Three studies (4 comparisons; n=1354 events) provided an estimate of the association between EPA and depression *(100, 172, 174)*. The summary most-adjusted mvRR comparing the highest intake of EPA with the lowest was 0.77 (95% CI: 0.66 to 0.91; *P*=0.002; I^2=0%, P_{het}=0.87) (**Fig. 31**). Assuming linearity, a 0.5 g increase in EPA was associated with a 30% decrease in risk of depression (mvRR: 0.70; 95% CI: 0.56, 0.88). The median EPA in the studied population was 0.15 g/day. Assuming linearity, a 0.1% increase in energy EPA was associated with a 16% decrease in risk of depression (mvRR: 0.84; 95% CI: 0.75, 0.94). The median EPA in the studied population was 0.04% energy (**Fig. 147** and **Fig. 148**).

3.6.8 Inflammatory bowel disease

Crohn's disease

One study (1 comparison; n=73 cases) assessed the association between EPA and Crohn's disease *(176)*. This study reported a multivariable RR of 8.56 (95% CI: 0.88 to 83.07; *P*=0.06) (**Section 4.7.1** in **Fig. 32**).

Ulcerative colitis

One study (1 comparison; n=126 cases) assessed the association between EPA and ulcerative colitis *(179)*. This study reported a multivariable RR of 2.58 (95% CI: 0.66 to 10.07; *P*=0.17) (**Section 4.7.2** in **Fig. 32**).

3.6.9 Breast cancer

Total breast cancer

Three studies (3 comparisons; n=3414 events) assessed the association between EPA and breast cancer (without specifying premenopausal or postmenopausal) *(105, 110, 180)*. The summary most-adjusted mvRR comparing the highest intake of EPA with the lowest was 0.89 (95% CI: 0.69 to 1.15; *P*=0.38; I^2=83%, P_{het}=0.003) (**Section 4.8.1** in **Fig. 33**). The fixed-effect estimate was 1.05 (95% CI: 1.01 to 1.09; *P*=0.01) with Holmes et al. *(105)* accounting for 97.9% of the weight (from 41.1% in the RE-model). Assuming linearity, a 0.5 g increase in energy EPA was associated with a 25% increase in risk of breast cancer (mvRR: 1.25; 95% CI: 0.95, 1.66). Assuming linearity, a 0.1% increase in energy from EPA was associated with a 9% increase in risk of breast cancer (mvRR: 1.09; 95% CI: 0.98, 1,20) (**Fig. 149** and **Fig. 150**).

Premenopausal breast cancer

No prospective cohort studies were identified that assessed the association between EPA and premenopausal breast cancer.

Postmenopausal breast cancer

One nested case–control study (1 comparison; n=941 events) and one prospective cohort study (1 comparison; n=470 events), with a total of 1411 events, assessed the association between EPA and postmenopausal breast cancer *(114, 117)*. The summary most-adjusted mvRR comparing the highest intake of EPA with the lowest was 0.74 (95% CI: 0.42 to 1.30; *P*=0.30; I^2=82%; P_{het}=0.02) (**Section 4.8.3** in **Fig. 33**). The summary most-adjusted fixed-effect mvRR was 0.76 (0.60, 0.97). Using the fixed-effect model and assuming linearity, a 0.5 g increase in EPA was associated with a 61% decrease in risk of postmenopausal breast cancer (mvRR: 0.39; 95% CI: 0.21, 0.74). Assuming linearity, a 0.1% increase in EPA was associated with a 32% decrease in risk of postmenopausal breast cancer (mvRR: 0.68; 95% CI: 0.52, 0.89). The horizontal line represents an RR of 1.0. The median EPA in the studied population was 0.025% energy (**Fig. 151** and **Fig. 152**).

3.6.10 GRADE assessment of quality of evidence

For the 16 outcomes assessed, the GRADE assessment of the confidence in the estimates of association between total dietary EPA and health outcomes was moderate for five outcomes (31.3%) (mortality, depression, heart failure, fatal ischaemic stroke and postmenopausal breast cancer), low for one outcome (6.3%) (fatal CVD) and very low for 10 outcomes (62.5%). One estimate is at serious risk of bias, two have serious inconsistency and 11 have serious imprecision (**Table 6**).

3.7 DHA (22–6 omega-3) and health outcomes

3.7.1 All-cause mortality

Two studies (2 comparisons; n=6258 deaths) assessed the association between DHA and all-cause mortality *(120, 134)*. The most-adjusted mvRR comparing the highest intake of DHA with the lowest was 0.82 (95% CI: 0.69 to 0.96; *P*=0.01; I^2=33%; P_{het}=0.22) (**Fig. 35a**). The fixed-effect estimate was 0.79 (0.72 to 0.87; *P*<0.00001) (**Fig. 35b**). Assuming linearity, a 0.5 g increase in DHA was associated with a 21% decrease in risk of all-cause mortality (mvRR: 0.79; 95% CI: 0.65, 0.96). Assuming linearity, a 0.1% increase in DHA was associated with a 10% decrease in risk of all-cause mortality (mvRR: 0.90; 95% CI: 0.83, 0.98) (**Fig. 153** and **Fig. 154**).

3.7.2 Cardiovascular diseases

Total CVD

No prospective cohort studies were identified that assessed the association between DHA and total CVD.

Fatal CVD

One study (1 comparison; n=1789 deaths) assessed the association between DHA and fatal CVD *(134)*. In this study, the most-adjusted mvRR comparing the highest intake of DHA with the lowest was 0.76 (95% CI: 0.64 to 0.91; *P*=0.003) (**Section 5.2.1** in **Fig. 36**). Assuming linearity, a 0.5 g/day increase in DHA was associated with a 39% decrease in risk of fatal CVD (mvRR: 0.61; 95% CI: 0.34, 1.07). Assuming linearity, a 0.1% increase in energy from DHA was associated with a 21% decrease in risk of fatal CVD (mvRR: 0.79; 95% CI: 0.61, 1.02) (**Fig. 155** and **Fig. 156**).

Fatal CHD

One study (1 comparison; n=476 deaths) assessed the association between DHA and fatal CHD *(134)*. In this study, the most-adjusted mvRR comparing the highest intake of DHA with the lowest was 0.79 (95% CI: 0.57 to 1.09; *P*=0.15) (**Section 5.2.2** in **Fig. 36**).

Fatal myocardial infarction

No prospective cohort studies were identified that assessed the association between DHA and fatal myocardial infarction.

Sudden cardiac death

No prospective cohort studies were identified that assessed the association between DHA and sudden cardiac death.

Total CHD

Two studies (4 comparison; n=1733 events) assessed the association between DHA and total CHD *(124, 125)*. The summary most-adjusted mvRR comparing the highest intake of DHA with the lowest was 0.93 (95% CI: 0.79 to 1.10; *P*=0.38; I^2=0%; P_{het}=0.45) (**Section 5.2.5** in **Fig. 36**).

Total myocardial infarction

One study (2 comparisons, 3028 events) assessed the association between DHA and total myocardial infarction. The summary most-adjusted mvRR comparing the highest intake of DHA with the lowest was 0.88 (95% CI: 0.78 to 1.01; *P*=0.06; I^2=0%; P_{het}=0.69) *(154)*. Assuming linearity, a 0.5 g/day increase in DHA was associated with a 5% decrease in risk of total myocardial infarction (mvRR: 0.95; 95% CI: 0.86, 1.04). Assuming linearity, a 0.1% increase in energy from DHA was associated with a 3% decrease in risk of total myocardial infarction (mvRR: 0.97; 95% CI: 0.91, 1.02) (**Fig. 157** and **Fig. 158**).

Atrial fibrillation

Three studies (3 comparisons, n=3285 events) assessed the association between DHA and atrial fibrillation *(85, 157, 159)*. The summary most-adjusted mvRR comparing the highest intake of DHA with the lowest was 0.84 (95% CI: 0.63 to 1.13; *P*=0.25; I^2=62%; P_{het}=0.07) (**Section 5.2.7** in **Fig. 36**). The summary fixed-effect estimate was 0.89 (95% CI: 0.79 to 1.02; *P*=0.09).

Fatal stroke

No prospective cohort studies were identified that assessed the association between DHA and fatal stroke (total).

Fatal haemorrhagic stroke

One study (1 comparison; n=460 events) assessed the association between DHA and fatal haemorrhagic stroke *(134)*. In this study, the most-adjusted mvRR comparing the highest intake of DHA with the lowest was 0.95 (95% CI: 0.50 to 1.81; *P*=0.88) (**Section 5.2.9** in **Fig. 35**).

Fatal ischaemic stroke

One study (1 comparison; n=404 events) assessed the association between DHA and fatal ischaemic stroke *(134)*. In this study, the most-adjusted mvRR comparing the highest intake of DHA with the lowest was 0.55 (95% CI: 0.36 to 0.84; *P*=0.005) (**Section 5.2.10** in **Fig. 35**). Assuming linearity, a 0.5 g increase in energy from DHA was associated with a 74% decrease in risk of fatal ischaemic stroke (mvRR: 0.26; 95% CI: 0.07, 0.98). Assuming linearity, a 0.1% increase in energy from DHA was associated with a 44% decrease in risk of fatal ischaemic stroke (mvRR: 0.56; 95% CI: 0.31, 1.007) (**Fig. 159** and **Fig. 160**).

Total stroke

No prospective cohort studies were identified that assessed the association between DHA and total stroke.

3.7.3 Type 2 diabetes

Four studies (4 comparisons; n=3093 events) examined the association between DHA intake and development of type 2 diabetes *(87, 89, 165, 169)*. The summary most-adjusted mvRR comparing the highest intake of DHA with the lowest was 1.01 (95% CI: 0.66 to 1.54; *P*=0.97; I^2=83%; P_{het}=0.0005; random-effects) (**Fig. 37**).

3.7.4 Dementia

Three studies (3 comparisons; n=272 events) examined the association between DHA and dementia *(131, 181, 182)*, two of which measured serum *(182)* or plasma *(181)* DHA. The summary most-adjusted mvRR comparing the highest level of DHA with the lowest was 0.42 (95% CI: 0.25 to 0.70; *P*=0.0009; I^2=0%; P_{het}=0.46) (**random-effects** in **Fig. 38a** and **fixed effect** in **Fig 38b**). Assuming linearity, a 0.5 g increase in energy from DHA was associated with a 99% decrease in risk of dementia (mvRR: 0.00003; 95% CI: 1.5 x 10–7 to 0.07). Assuming linearity, a 0.5 g increase in energy from DHA was associated with a 99% decrease in risk of dementia (mvRR: 0.012; 95% CI: 0.0014 to 0.12) (**Fig. 161** and **Fig. 162**).

3.7.5 Suicide

One study (2 comparisons; n=298 events) provided an estimate of the association between DHA and suicide *(175)*. The summary most-adjusted mvRR comparing the highest intake of DHA with the lowest was 1.09 (95% CI: 0.74 to 1.60; *P*=0.67; I^2=0%, P_{het}=0.67) (**Fig. 39**).

3.7.6 Depression

Three studies (4 comparisons; n=1354 events) provided an estimate of the association between DHA and depression *(172)*. The summary most-adjusted mvRR comparing the highest intake of DHA with the lowest was 0.79 (95% CI: 0.67 to 0.94; *P*=0.006; I^2=0%, P_{het}=0.88) (**Fig. 40**). Assuming linearity, a 0.5 g increase in DHA was associated with a 17% decrease in risk of depression (mvRR: 0.83; 95% CI: 0.71, 0.96). Assuming linearity, a 0.1% increase in energy from DHA was associated with a 9% decrease in risk of depression (mvRR: 0.91; 95% CI: 0.85 to 0.98) (**Fig. 163** and **Fig. 164**).

3.7.7 Inflammatory bowel disease

Crohn's disease

One study (1 comparison; n=73 cases) assessed the association between DHA and Crohn's disease *(176)*. This study reported a multivariable RR of 0.06 (95% CI: 0.01 to 0.51; *P*=0.01) (**Section 5.7.1** in **Fig. 41**).

Ulcerative colitis

One study (1 comparison; n=126 cases) assessed the association between DHA and ulcerative colitis *(179)*. This study reported a multivariable RR of 0.23 (95% CI: 0.06 to 0.92; *P*=0.04) (**Section 5.7.2** in **Fig. 41**).

3.7.8 Breast cancer

Total breast cancer

Three studies (3 comparisons; n=3414 events) assessed the association between DHA and breast cancer (without specifying premenopausal or postmenopausal cases) *(105, 110, 180)*. The

summary most-adjusted mvRR comparing the highest intake of DHA with the lowest was 0.93 (95% CI: 0.72 to 1.20; *P*=0.56; I^2=82%, P_{het}=0.004; random-effects) (**Section 5.8.1** in **Fig. 42**). The fixed-effect estimate was 1.04 (95% CI: 1.01 to 1.06; *P*=0.004) with Holmes et al. *(105)* accounting for 98.3% of the weight (from 41.5% in the RE-model). Assuming linearity, a 0.5 g increase in energy from DHA was associated with a 14% increase in risk of breast cancer (mvRR: 1.14; 95% CI: 0.93 to 1.40). However, the result for the goodness-of-fit test was a *P* value of 0.0075. Using a spline approach, it appears that the risk increases from 0 g/day to 0.05 g/day, then decreases from 0.05 g/day through 0.25 g/day (0.05–0.15% energy) (**Fig. 165** and **Fig. 166**).

Premenopausal breast cancer

No prospective cohort studies were identified that assessed the association between DHA and premenopausal breast cancer.

Postmenopausal breast cancer

One nested case–control study (1 comparison; n=941 events) and one prospective cohort study (1 comparison; n=470 events) assessed the association between DHA and postmenopausal breast cancer *(114, 117)*. The summary most-adjusted random-effects mvRR comparing the highest intake of DHA with the lowest was 0.73 (95% CI: 0.39 to 1.36; *P*=0.32; I^2=86%; P_{het}=0.008) (**Section 5.8.3** in **Fig. 42**). The summary most-adjusted fixed-effect mvRR was 0.74 (0.59, 0.94). Using the fixed-effect model, assuming linearity, a 0.5 g increase in energy from DHA was associated with a 50% reduced risk of postmenopausal breast cancer (mvRR: 0.50; 95% CI: 0.31 to 0.81). Assuming linearity, a 0.1% increase in energy from DHA was associated with a 24% reduced risk of postmenopausal breast cancer (mvRR: 0.76; 95% CI: 0.62 to 0.92) (**Fig. 167** and **Fig. 168**).

3.7.9 GRADE assessment of quality of evidence

For the 16 outcomes assessed, the GRADE assessment of the confidence in the estimates of association between DHA and health outcomes was moderate for four outcomes (all-cause mortality, dementia, depression, and fatal ischaemic stroke) (20.0%), low for two outcomes (fatal CVD and postmenopausal breast cancer) (12.5%) and very low for 10 outcomes (62.5%). One estimate is at serious risk of bias, four have serious inconsistency and 11 have serious imprecision (**Table 7**).

3.8 DPA (22:5 omega-3) and health outcomes

3.8.1 All-cause mortality

No prospective cohort studies were identified that assessed the association between DPA and all-cause mortality.

3.8.2 Cardiovascular diseases

Total CVD

No prospective cohort studies were identified that assessed the association between DPA and total CVD.

Fatal CVD

No prospective cohort studies were identified that assessed the association between DPA and fatal CVD.

Fatal CHD

No prospective cohort studies were identified that assessed the association between DPA and fatal CHD.

Sudden cardiac death

No prospective cohort studies were identified that assessed the association between DPA and sudden cardiac death.

Fatal myocardial infarction

No prospective cohort studies were identified that assessed the association between DPA and fatal myocardial infarction.

Nonfatal myocardial infarction

No prospective cohort studies were identified that assessed the association between DPA and nonfatal myocardial infarction.

Fatal arrhythmia

No prospective cohort studies were identified that assessed the association between DPA and fatal arrythmia.

Total CHD

Two studies (2 comparisons; n=1 124 events) provided estimates of the association between DPA and total CHD *(124)*. The summary most-adjusted mvRR comparing the highest intake of dietary DPA with the lowest was 0.91 (95% CI: 0.72 to 1.15; *P*=0.43; I^2=0%, P_{het}=0.74) (**Section 6.1.4** in **Fig. 42c**).

Total myocardial infarction

One study (2 comparisons; n=3028 events) provided estimates of the association between DPA and total myocardial infarction *(154)*. The summary most-adjusted mvRR comparing the highest intake of dietary DPA with the lowest was 0.89 (95% CI: 0.78 to 1.03; *P*=0.11; I^2=0%, P_{het}=0.55) (**Section 6.1.5** in **Fig. 42c**).

Atrial fibrillation

One study (1 comparison; n=240 events) provided estimates of the association between DPA and atrial fibrillation *(157)*. In this study, the most-adjusted mvRR comparing the highest intake of dietary DPA with the lowest was 0.95 (95% CI: 0.65 to 1.39; *P*=0.79).

3.8.3 Type 2 diabetes

One study (1 comparison; n=213 events) provided estimates of the association between DPA and type 2 diabetes *(169)*. In this study, the most-adjusted mvRR comparing the highest intake of dietary DPA with the lowest was 1.08 (95% CI: 0.74 to 1.57; *P*=0.69) (**Fig. 42d**).

3.8.4 Depression

One study (1 comparison; n=95 events) provided estimates of the association between DPA and depression *(174)*. In this study, the most-adjusted mvRR comparing the highest intake of dietary DPA with the lowest was 0.85 (95% CI: 0.49 to 1.47; *P*=0.96) (**Fig. 42e**).

3.8.5 Cognitive decline

One study (1 comparison; n=154 events) provided estimates of the association between DPA and cognitive decline *(174)*. In this study, the most-adjusted mvRR comparing the highest intake of dietary DPA with the lowest was 0.94 (95% CI: 0.77 to 1.15; *P*=0.55) (**Fig. 42f**).

3.8.6 Breast cancer

All breast cancer

One study (1 comparison; n=545 events) provided estimates of the association between DPA and all breast cancer (without specifying premenopausal or postmenopausal) *(110)*. In this study, the most-adjusted mvRR comparing the highest intake of dietary DPA with the lowest was 1.01 (95% CI: 0.77 to 1.33; *P*=0.94) (**Section 6.8.1** in **Fig. 42g**).

Premenopausal breast cancer

No prospective cohort studies were identified that assessed the association between DPA and premenopausal breast cancer.

Postmenopausal breast cancer

One study (1 comparison; n=470 events) provided estimates of the association between DPA and postmenopausal breast cancer *(117)*. In this study, the most-adjusted mvRR comparing the highest intake of dietary DPA with the lowest was 0.57 (95% CI: 0.40 to 0.82; *P*=0.002) (**Section 6.8.3** in **Fig. 42g**). Assuming linearity, a 0.05 g increase in DPA was associated with a 36% reduced risk of postmenopausal breast cancer (mvRR: 0.64; 95% CI: 0.49 to 0.85). The horizontal line represents a RR of 1.0. The median intake of DPA in the studied population was 0.025 g/day. Assuming linearity, a 0.02% increase in energy from DPA was associated with a 31% reduced risk of postmenopausal breast cancer (mvRR: 0.69; 95% CI: 0.55 to 0.87) (**Fig. 169** and **Fig. 170**).

3.8.7 GRADE assessment of quality of evidence

For the eight outcomes assessed (100.0%), the GRADE assessment of the confidence in the estimates of association between DPA and health outcomes was moderate for one outcome (12.5%) (postmenopausal breast cancer), and very low for seven outcomes (87.5%). Seven estimates have serious imprecision (**Table 8**).

3.9 ALA (18:3 omega-3) and health outcomes

3.9.1 All-cause mortality

Eight studies (10 comparisons; n=171 232 deaths) examined the association between ALA intake and all-cause mortality *(54, 56, 59, 60, 133, 144, 183, 184)*. The summary most-adjusted mvRR comparing the highest intake of ALA with the lowest was 0.93 (95% CI: 0.86 to 1.01; *P*=0.10; I^2=80%; P_{het}<0.00001) (**Fig. 43**). No publication bias is suspected (**Fig. 84k**) and the linear dose–response does not support the extreme-ends comparison. Assuming linearity, a 0.5 g/day increase in ALA was associated with a 1% increased risk of all-cause mortality (mvRR: 1.01; 95% CI: 0.99 to 1.03). Assuming linearity, a 0.2% increase in energy from ALA was associated with a 2% increased risk of all-cause mortality (mvRR: 1.02; 95% CI: 1.00 to 1.03). The non-linear spline model yielded estimates that were visually similar to those from the linear model (**Fig. 171** and **Fig. 172**).

Meta-regression indicated that the estimate was not associated with study size (number of cases) (*P*=0.27), measurement of TFA (*P*=0.12), sex distribution of participants (*P*=0.88), adjustment for energy (*P*=0.11), adjustment for dyslipidaemia (*P*=0.61), adjustment for blood pressure (*P*=0.14), or smoking history (*P*=0.80). There was an association between-study risk of bias and effect size (*P*=0.069); lower quality studies showed larger associations (mvRR=0.68 for NOS=6 and 0.66 for NOS=7) than the highest quality studies (0.94 for NOS=8 and 0.93 for NOS=9). There was an association (*P*=0.098) between length of follow-up and effect size. Shorter studies (<5 years) showed larger effects (mvRR=0.77) then studies of 10 to less than 15 years (0.96), 15–20 years (1.06) or more than 20 years (0.99). There was an association (*P*=0.072) between age of people in the sample and effect size. The effect estimates were larger in samples of people

aged over 65 years (mvRR=0.73) than in those aged under 65 years (mvRR=1.01). There was an association between dietary assessment method and effect size (*P*=0.006), with the study that used 7-day food records showing a positive association with mortality (mvRR=1.23), the studies that used 24-hour recalls a protective association (mvRR=0.82), and those that used FFQs had an mvRR=0.93. There was significant between-country heterogeneity in effect size (*P*-het=0.003). The one study conducted in China found an increased risk (mvRR=1.23), whereas studies in all other countries showed decreased risk (**Fig. 95**).

3.9.2 Cardiovascular diseases

Total CVD

One prospective cohort study (n=1941 events) assessed the association between ALA and total CVD *(143)*. The most-adjusted mvRR comparing the highest intake of dietary ALA with the lowest was 0.95 (95% CI: 0.82 to 1.11; *P*=0.51).

Fatal CVD start here for meta-reg, dose-response

Ten studies (11 comparisons; n=54 162 events) provided estimates of the association between ALA and fatal CVD *(54, 56, 59, 60, 133, 144, 155, 183)*. The summary most-adjusted mvRR comparing the highest intake of dietary ALA with the lowest was 0.91 (95% CI: 0.83 to 0.99; *P*=0.04; I^2=58%; P_{het}=0.008) (**Section 7.2.2** in **Fig. 44**). No publication bias is suspected (**Fig. 8kl**). Assuming linearity, a 0.5 g/day increase in ALA was associated with a 4% decreased risk of fatal CVD (mvRR: 0.96, 95% CI: 0.94 to 0.98). Assuming linearity, a 0.5% increase in energy from ALA was associated with an 8% decreased risk of fatal CVD (mvRR: 0.92, 95% CI: 0.89 to 0.96) (**Fig. 173** and **Fig. 174**).

In meta-regression, there was no association between effect size and study quality (*P*=0.79), follow-up time (*P*=0.81), sex distribution (*P*=0.98), energy adjustment (*P*=0.38), dyslipidaemia adjustment (*P*=0.11), blood pressure adjustment (*P*=0.11), age distribution of the sample (*P*=0.36), distribution of smokers (*P*=0.12), or country of conduct (*P*=0.35).

The effect size was associated with study size (number of cases; *P*=0.053), with smaller studies (<500 cases) showing slightly stronger effects (mvRR=0.84) than larger studies (mvRR=0.92) (**Fig. 96**). The effect size differed (*P*=0.028) between studies that measured TFA (mvRR=0.98) and those that did not (mvRR=0.82) (**Fig. 96**). The effect size differed (*P*=0.003) by method of diet assessment, with nominally larger risk redcutions in those studies measuring diet by 24-hour recalls (mvRR = 0.80) or 4-day diet record (mvRR = 0.63) than in those studies measuring diet by FFQ (mvRR = 0.93).

Fatal CHD

Nine studies (9 comparisons; n=5276 events) provided estimates of the association between ALA and fatal CHD *(60, 67, 122, 133, 144, 183, 185–187)*. The summary most-adjusted mvRR comparing the highest intake of ALA with the lowest was 0.82 (95% CI: 0.74 to 0.91; *P*=0.0002; I^2=0%; P_{het}=0.44) (**Section 7.2.3** in **Fig. 44**). Assuming linearity, a 0.5 g/day increase in ALA was associated with an 8% decreased risk of CHD mortality (mvRR: 0.92, 95% CI: 0.87 to 0.97). Assuming linearity, a 0.5% increase in ALA was associated with a 17% decreased risk of fatal CHD (mvRR: 0.83, 95% CI: 0.73 to 0.93) (**Fig. 175** and **Fig. 176**)

Fatal myocardial infarction

One prospective cohort study (n=417 events) assessed the association between ALA and fatal myocardial infarction *(188)*. The most-adjusted mvRR comparing the highest intake of dietary ALA with the lowest was 0.71 (95% CI: 0.47 to 1.08; *P*=0.11).

Sudden cardiac death

Two studies (2 comparisons; n=417 events) provided an estimate of the association between ALA and sudden cardiac death *(71, 144)*. The summary most-adjusted mvRR comparing the highest intake of dietary ALA with the lowest was 0.54 (95% CI: 0.37 to 0.81; *P*=0.003; I2=0%; P_{het}=0.45) (**Section 7.2.5** and **Fig. 44**). Assuming linearity, a 0.5 g increase in ALA was associated with a 27% reduced risk of sudden cardiac death (mvRR: 0.73; 95% CI: 0.61 to 0.88). Assuming linearity, a 0.2% increase in energy from ALA was associated with a 20% reduced risk of sudden cardiac death (mvRR: 0.80; 95% CI: 0.70 to 0.91) (**Fig. 177** and **Fig. 178**).

Total CHD

Six studies (7 comparisons; n=3360 events) provided estimates of the association between ALA and total CHD *(67, 153, 183, 185, 187, 189)*. The summary most-adjusted mvRR comparing the highest intake of dietary ALA with the lowest was 0.93 (95% CI: 0.83 to 1.04; *P*=0.21; I^2=0%, P_{het}=0.52) (**Section 7.2.6** in **Fig. 44**). There was no evidence of a dose–response association between ALA and risk of CHD (mvRR: 0.99, 95% CI: 0.96 to 1.03 per 0.5 g and mvRR: 0.99, 95% CI: 0.95 to 1.03 per 0.2%) (**Fig. 179** and **Fig. 180**).

Nonfatal myocardial infarction

One study (1 comparison; n=597 events) assessed the association between ALA and nonfatal myocardial infarction *(186)*. The mvRR comparing the highest intake of dietary ALA with the lowest was 0.85 (95% CI: 0.61 to 1.19; *P*=0.34) (**Section 7.2.7** in **Fig. 44**).

Fatal stroke

Three studies (3 comparisons; n=1644 events) assessed the association between dietary ALA and fatal stroke *(59, 122, 144)*. The summary most-adjusted mvRR comparing the highest intake of dietary ALA with the lowest was 0.85 (95% CI: 0.72 to 1.01; *P*=0.07; I^2=0%, P_{het}=0.49) (**Section 7.2.8** in **Fig. 44**).

Total stroke

Four studies (4 comparisons; n=3246 events) provided estimates of the association between ALA and total stroke *(81, 143, 183, 189)*. The summary most-adjusted mvRR comparing the highest category of dietary ALA with the lowest was 0.97 (95% CI: 0.79 to 1.18; *P*=0.74; I^2=56%; P_{het}=0.08) (**Section 7.2.9** in **Fig. 44**).

Ischaemic stroke

Four studies (4 comparisons; n=3088 events) provided estimates of the association between ALA and ischaemic stroke *(143, 183, 189, 190)*. The summary most-adjusted mvRR comparing the highest intake of ALA with the lowest was 0.88 (95% CI: 0.77 to 1.02; *P*=0.09; I^2=0%; P_{het}=0.49) (**Section 7.2.10** in **Fig. 44**).

Haemorrhagic stroke

Two studies (2 comparisons; n=289 cases) assessed the association between ALA and haemorrhagic stroke *(183)*. The summary most-adjusted mvRR comparing the highest intake of ALA with the lowest was 1.10 (95% CI: 0.45 to 2.67; *P*=0.84; I^2=66%; P_{het}=0.09) (**Section 7.2.11** in **Fig. 44**).

Atrial fibrillation

One study (1 comparison; n=1441 events) assessed the association between dietary ALA and atrial fibrillation *(85)*. In this study, the most-adjusted multivariable RR was 0.77 (95% CI: 0.67 to 1.04; *P*=0.09) (**Section 7.2.12** in **Fig. 44**).

Fatal arrhythmia

One study (1 comparison; n=135 cases) assessed the association between serum ALA and fatal arrhythmia *(183)*. In this study, the most-adjusted multivariable RR was 0.68 (95% CI: 0.38 to 1.22; *P*=0.20) (**Section 7.2.13** in **Fig. 44**).

Total myocardial infarction

Two studies (3 comparisons; n=3723 events) provided estimates of the association between ALA and total myocardial infarction *(143, 188)*. The summary most-adjusted mvRR comparing the highest intake of dietary ALA with the lowest was 0.96 (95% CI: 0.84 to 1.09; *P*=0.50; I^2=0%, P_{het}=0.48) (**Section 7.2.14** in **Fig. 44**).

3.9.3 Type 2 diabetes

Four studies (4 comparisons; n=2919 events) assessed the association between ALA and type 2 diabetes *(87, 95, 128, 169)*. In these studies, the summary multivariable RR comparing the highest ALA consumers with the lowest was 1.13 (95% CI: 0.69 to 1.86; *P*=0.62; I^2=86%; P_{het}<0.0001) (**Fig. 45**).

3.9.4 Dementia

One study (1 comparison; n=131 cases) assessed the association between ALA and dementia *(131)*. In this study, the multivariable RR comparing the highest ALA consumers with the lowest was 0.70 (95% CI: 0.30 to 1.62; *P*=0.40) (**Fig. 46**).

3.9.5 Cognitive decline

Two studies (2 comparisons; n=749 cases) assessed the association between ALA and cognitive decline *(98, 171)*. In these studies, the summary multivariable RR comparing the highest ALA consumers with the lowest was 0.91 (95% CI: 0.78 to 1.05; *P*=0.18; I^2=0%; P_{het}=0.94) (**random effects** in **Fig. 47a** and **fixed effect** in **Fig. 47b**).

3.9.6 Depression

Three studies (3 comparison; n=3433 cases) assessed the association between ALA and depression *(100, 173, 174)*. In this study, the multivariable RR comparing the highest ALA consumers with the lowest was 0.97 (95% CI: 0.74 to 1.29; *P*=0.85; I^2=80%; P_{het}=0.006) (**Fig. 48a**). The fixed-effect estimate was 0.99 (0.90 to 1.10; *P*=0.88) (**Fig. 48b**).

3.9.7Inflammatory bowel disease

Crohn's disease

One prospective study (1 comparison; n=73 cases) assessed the association between ALA and the development of Crohn's disease *(176)*. In this study, the multivariable RR comparing the highest ALA consumers with the lowest was 0.40 (95% CI: 0.07 to 2.19; *P*=0.29) (**Section 7.7.1** in **Fig. 49**).

Ulcerative colitis

One prospective study (1 comparison; n=126 cases) assessed the association between ALA and the development of ulcerative colitis *(179)*. In this study, the multivariable RR comparing the highest ALA consumers with the lowest was 1.28 (95% CI: 0.46 to 3.57; *P*=0.64) (**Section 7.7.2** in **Fig. 49**).

3.9.8 Breast cancer

Total breast cancer

Three studies (3 comparisons; n=3581 events) assessed the association between ALA and breast cancer (without specifying premenopausal or postmenopausal cases) *(105, 177, 180)*. The summary most-adjusted mvRR comparing the highest intake of ALA with the lowest was 0.91 (95% CI: 0.74 to 1.13; *P*=0.40; I^2=16%, P_{het}=0.30) (**Section 7.8.1** in **Fig. 50**).

Premenopausal breast cancer

No prospective cohort studies were identified that assessed the association between ALA and premenopausal breast cancer.

Postmenopausal breast cancer

One prospective cohort study (3 estimates; n=470 cases) *(117)*. The summary most-adjusted mvRR comparing the highest intake of ALA with the lowest was 1.07 (95% CI: 0.74 to 1.55; *P*=0.71; I2=59%, P_{het}=0.09) (**Section 7.8.3** in **Fig. 50**).

3.9.9 GRADE assessment of quality of evidence

For the 23 outcomes assessed, the GRADE assessment of the confidence in the estimates of association between ALA and health outcomes was moderate for three outcomes (fatal CVD, fatal CHD and sudden cardiac death) (13.0%), low for no outcomes (0.0%) and very low for 20 outcomes (87.0%). Four estimates are at serious risk of bias, six have serious inconsistency and 20 have serious imprecision (**Table 9**).

3.10 Omega-6 PUFA and health outcomes

3.10.1 All-cause mortality

Six studies (9 comparisons; n=182 318 deaths) examined the association between dietary total omega-6 PUFA and all-cause mortality. In these studies, the summary most-adjusted mvRR comparing the highest intake of total omega-6 PUFA with the lowest was 0.91 (95% CI: 0.85 to 0.97; *P*=0.003; I^2=72%, P_{het}=0.0003) (**Fig. 51**). Assuming linearity, a 5 g/day increase in total n-6 was associated with a 5% decreased risk of all-cause mortality (mvRR: 0.95, 95% CI: 0.90 to 1.001). Assuming linearity, a 5% increase in energy from total n-6 was associated with a 12% decreased risk of all-cause mortality (mvRR: 0.88, 95% CI: 0.81 to 0.96). (**Fig. 181** and **Fig. 182**). Wang et al. *(54)*, using direct modelling, reported that a 2% increase in energy from total n-6 was associated with a 10% decreased risk of all-cause mortality (mvRR: 0.90; 95% CI: 0.88 to 0.93)

3.10.2 Cardiovascular diseases

Total CVD

No prospective cohort studies were identified that assessed the association between total n-6 and total CVD.

Fatal CVD

Five studies (7 comparisons; n=53 082 events) assessed the association between dietary total omega-6 PUFA and fatal CVD *(53, 54, 59, 119)*. In these studies, the summary most-adjusted mvRR comparing the highest intake of total omega-6 PUFA with the lowest was 0.91 (95% CI: 0.83 to 1.00; *P*=0.06; I^2=60%, P_{het}=0.02) (**Section 9.2.1** in **Fig. 52**). Assuming linearity, a 5 g increase in n-6 fatty acids was associated with a 6% reduced risk of cardiovascular mortality (mvRR: 0.94; 95% CI: 0.92 to 0.97). Assuming linearity, a 2% increase in energy from n-6 fatty acids was associated with a 6% reduced risk of cardiovascular mortality (mvRR: 0.94; 95% CI: 0.89 to 0.99) (**Fig. 183** and **Fig. 184**).

Fatal CHD

One prospective study (1 comparison; n=978 cases) assessed the association between total omega-6 PUFA and fatal CHD *(59)*. In this study, the multivariable RR comparing the highest ALA consumers with the lowest was 0.93 (95% CI: 0.56 to 1.55; *P*=0.78) (**Section 9.2.2** in **Fig. 52**).

Total CHD

One study (2 comparisons; n=1021 events) provided an estimate of the association between total dietary omega-6 and total CHD *(75)*. The summary most-adjusted mvRR comparing the highest intake of dietary total omega-6 with the lowest was 1.10 (95% CI: 0.91 to 1.33; *P*=0.34; I^2=0%, P_{het}=0.59) (**Section 9.2.3** in **Fig. 52**).

Fatal stroke

One prospective study (1 comparison; n=321 cases) assessed the association between total omega-6 PUFA and fatal stroke *(59)*. In this study, the multivariable RR comparing the highest ALA consumers with the lowest was 0.71 (95% CI: 0.33 to 1.54; *P*=0.39) (**Section 9.2.4** in **Fig. 52**).

Total stroke

Two studies (2 comparisons; n=1821 events) provided an estimate of the association between total dietary omega-6 and total stroke *(79, 81)*. The summary most-adjusted mvRR comparing the highest category of total dietary omega-6 with the lowest was 1.05 (95% CI: 0.90 to 1.22; *P*=0.55; I^2=0%; P_{het}=0.48) (**Section 9.2.5** in **Fig. 52**).

Fatal myocardial infarction

No prospective cohort studies were identified that assessed the association between total dietary omega-6 and fatal myocardial infarction.

Ischaemic stroke

One study (2 comparisons; n=755 events) provided estimates of the association between total dietary omega-6 and ischaemic stroke *(75)*. The summary most-adjusted mvRR comparing the highest intake of total dietary omega-6 with the lowest was 0.98 (95% CI: 0.69 to 1.39; *P*=0.89; I^2=56%; P_{het}=0.13) (**Section 9.2.6** in **Fig. 52**). The fixed-effect estimate was 0.99 (95% CI: 0.78 to 1.24; *P*=0.90).

Haemorrhagic stroke

One prospective study (1 comparison; n=233 cases) assessed the association between total omega-6 PUFA and haemorrhagic stroke *(81)*. In this study, the multivariable RR comparing the highest ALA consumers with the lowest was 0.88 (95% CI: 0.58 to 1.34; *P*=0.55) (**Section 9.2.7** in **Fig. 52**).

Atrial fibrillation

Two studies (3 comparisons; n=6521 events) assessed the association between total dietary omega-6 and atrial fibrillation *(85, 86)*. In this study, the most-adjusted multivariable RR comparing the highest intake of total dietary omega-6 with the lowest was 0.98 (95% CI: 0.83 to 1.17; *P*=0.85; I^2=53%; P_{het}=0.12) (**Section 9.2.8** in **Fig. 52**).

Sudden cardiac death

One study (1 comparison; n=385 events) provided an estimate of the association between total dietary omega-6 and sudden cardiac death *(71)*. The summary most-adjusted mvRR comparing the highest intake of dietary total omega-6 with the lowest was 0.79 (95% CI: 0.57 to 1.10; *P*=0.17) (**Section 9.2.9** in **Fig. 52**).

Nonfatal myocardial infarction

No prospective cohort studies were identified that provided an estimate of the association between total dietary omega-6 and nonfatal myocardial infarction.

Fatal arrhythmia

No prospective cohort studies were identified that provided an estimate of the association between total dietary omega-6 and fatal arrhythmia.

3.10.3 Type 2 diabetes

Six studies (8 comparisons; n=25 372 cases) assessed the association between total dietary omega-6 and type 2 diabetes *(87, 93, 128, 129, 191, 192)*. The pooled most-adjusted multivariable RR was 0.93 (95% CI: 0.85 to 1.02; *P*=0.12; I^2=66%; P_{het}=0.004) (**Fig. 53a**).

3.10.4 Dementia

One study (1 comparison; n=197 cases) assessed the association between total dietary omega-6 and dementia *(96)*. In this study, the most-adjusted multivariable RR comparing the highest intake of total dietary omega-6 with the lowest was 1.03 (95% CI: 0.78 to 1.37; *P*=0.84) (**Fig 53b**).

3.10.5 Depression

Three studies (4 comparisons; n=1350 cases) assessed the association between total dietary omega-6 and depression *(100, 174, 193)*. The pooled most-adjusted multivariable RR was 1.28 (95% CI: 0.93 to 1.75; *P*=0.13; I^2=63%; P_{het}=0.05) (**Fig. 54a**).

3.10.6 Cognitive decline

One study (1 comparison; n=598 cases) assessed the association between total dietary omega-6 and cognitive decline *(98)*. The multivariable RR in this study was 1.03 (95% CI: 0.83 to 1.28; *P*=0.79) (**Fig. 54b**).

3.10.7 Inflammatory bowel disease

Crohn's disease

No prospective cohort studies were identified that provided an estimate of the association between total dietary omega-6 and Crohn's disease.

Ulcerative colitis

One study (1 comparison; n=338 cases) assessed the association between total dietary omega-6 and ulcerative colitis *(101)*. In this study, the most-adjusted RR comparing the highest intakes of total dietary omega-6 with the lowest was 1.08 (95% CI: 0.77 to 1.52; *P*=0.66) (**Section 9.7.2** in **Fig. 55**).

3.10.8 Breast cancer

Total breast cancer

Three studies (3 comparisons; n=988 cases) assessed the association between total dietary omega-6 and breast cancer (without delineating premenopausal from postmenopausal) *(106, 107, 110)*. In these studies, the pooled multivariable RR for higher intakes of total dietary omega-6 compared with lower intakes was 1.04 (95% CI: 0.83 to 1.30; *P*=0.74; I^2=6%; P_{het}=0.35) (**Section 9.8.1** in **Fig. 56**). Assuming linearity, a 5 g/day increase in total n-6 was not associated with risk of breast cancer (mvRR: 1.00; 95% CI: 0.90 to 1.11). Assuming linearity, a 2% increase in energy from total n-6 was not associated with risk of breast cancer (mvRR: 1.00, 95% CI: 0.92 to 1.09) (**Fig. 185** and **Fig. 186**).

Premenopausal breast cancer

No prospective cohort studies were identified that provided an estimate of the association between total dietary omega-6 and premenopausal breast cancer.

Postmenopausal breast cancer

Six studies (6 comparisons; n=6746 cases) assessed the association between total dietary omega-6 and postmenopausal breast cancer *(107, 113, 116, 194, 195)*. In these studies, the pooled multivariable RR for higher intakes of total dietary omega-6 compared with lower intakes was 1.31 (95% CI: 1.03 to 1.68; *P*=0.03; I^2=82%; P_{het}<0.0001) (**Section 9.8.3** in **Fig. 56**). Assuming linearity, a 5 g increase in energy from total n-6 was associated with a 2% increased risk of postmenopausal breast cancer (mvRR: 1.02; 95% CI: 0.99 to 1.05). Assuming linearity, a 2% increase in energy from total n-6 was associated with a 3% increased risk of postmenopausal breast cancer (mvRR: 1.03; 95% CI: 1.00 to 1.05). However, the lack of fit test was significant (*P*=0.0067). Visual inspection of the spline curve suggested an increased risk from 0 g/day to 6 g/day (0–3% energy), then a fall from 6 g/day to 16 g/day (»3–6% energy). All points on the curve were consistent with increased risk (**Fig. 186** and **Fig. 187**).

3.10.9 GRADE assessment of quality of evidence

For the 18 outcomes assessed, the GRADE assessment of the confidence in the estimates of association between total dietary omega-6 and health outcomes was moderate for one outcome (5.6%) (all-cause mortality), low for one outcome (5.6%) (fatal CVD) and very low for 16 outcomes (88.9%). One estimate is at serious risk of bias, none have serious inconsistency and 14 have serious imprecision (**Table 10**).

3.11 LA (18:2 omega-6) and health outcomes

3.11.1 All-cause mortality

Seven studies (9 comparisons; n=169 509 total deaths) assessed the association between LA and all-cause mortality *(54, 56, 59, 64, 133, 184, 196)* In these studies, the pooled multivariable RR for higher intakes of LA compared with lower intakes was 0.84 (95% CI: 0.79 to 0.90; *P*<0.00001; I^2=58%; P_{het}=0.02) (**Fig. 57**). Assuming linearity, a 5 g increase in LA was associated with an 8% decreased risk of all-cause mortality (mvRR: 0.92; 95% CI: 0.56 to 1.50). Assuming linearity, a 2% increase in LA was associated with a 6% decreased risk of all-cause mortality (mvRR: 0.94; 95% CI: 0.77 to 1.14). The association was non-linear, with an apparent plateau after 2% energy, after which the mvRR was about 0.90. (**Fig. 189** and **Fig. 190**). Wang et al. *(54)*, using direct modelling, reported that a 2% increase in energy from LA was associated with a 12% decreased risk of all-cause mortality (mvRR: 0.88; 95% CI: 0.86 to 0.91)

3.11.2 Cardiovascular diseases

Total CVDs

No prospective cohort studies were identified that provided an estimate of the association between dietary LA and total CVD.

Fatal CVD

Six studies (7 comparisons; n=48 348 events) assessed the association between dietary LA and fatal CVD. In these studies, the summary mvRR for higher intakes of LA compared with lower intakes was 0.83 (95% CI: 0.73 to 0.93; *P*=0.002; I^2=55%; P_{het}=0.04) (**Section 8.2.1** in **Fig. 58**) *(54, 59, 64, 133, 196)*. Assuming linearity, a 5 g increase in LA was associated with a 7% decreased risk of CVD mortality (mvRR: 0.93; 95% CI: 0.90 to 0.95). Assuming linearity, a 2% increase in LA was associated with a 6% decreased risk of CVD mortality (mvRR: 0.94; 95% CI: 0.93 to 0.94). The association departed from linearity, and it appeared that the maximal reduction was at 4 g/day

(or 2% of energy) and that the risk reduction was stable (**Fig. 191** and **Fig. 192**) Wang et al. *(54)*, using direct modelling, reported that a 2% increase in energy from LA was associated with a 15% decreased risk of all-cause mortality (mvRR: 0.85; 95% CI: 0.80 to 0.90)

Fatal CHD

Twelve studies (13 comparisons; n=7125 events) assessed the association between LA and fatal CHD. Of the 13 reported estimates of association, all but two *(59, 133)* were obtained from a recent meta-analysis by Farvid et al. *(37)*, which included longer follow-up of each of the cohorts: five primary publications were updated (67, 75, 133, 185, 197) and six estimates were published as part of the Pooling Project of Cohort Studies on Diet and Coronary Disease (the projects pooled were the Israeli Ischaemic Heart Disease, Finnish Mobile Health Clinic, Västerbotten Intervention Program, Iowa Women's Health Study, Women's Health Study and Atherosclerosis Risk in Communities) *(198)*. In the present update, the summary mvRR for higher intakes of LA compared with lower intakes was 0.80 (95% CI: 0.72 to 0.90; *P*<0.0001; I^2=0%; P_{het}=0.47) (**Section 8.2.2** in **Fig. 58**).

Although no publication bias was suspected (Egger's test: *P*=0.302; Begg's test: *P*=0.583; **Fig. 84m**), these tests can be underpowered. The trim-and-fill identified two "missed" studies. The "filled" RR was 0.79 (95% CI: 0.70 to 0.88).

Using published data from Farvid et al. *(37)* with the additional studies in the present update, assuming linearity, a 5 g increase in LA was associated with an 8% reduced risk of ischaemic heart disease mortality (mvRR: 0.92; 95% CI: 0.86 to 0.98). Assuming linearity, a 2% increase in energy from LA was associated with an 8% reduced risk of ischaemic heart disease mortality (mvRR: 0.92; 95% CI: 0.86 to 0.98). There was no evidence of a departure from linearity in either model (**Fig. 193** and **Fig. 194**).

The meta-regression found that the estimate was not associated with study size (number of cases; *P*=0.53), study risk of bias (*P*=0.14), TFA measurement (*P*=0.31), duration of follow-up (*P*=0.59), sex distribution (*P*=0.99), adjustment for total energy (*P*=0.21), adjustment for dyslipidaemia (*P*=0.19), adjustment for blood pressure (*P*=0.50), the age distribution of participants (*P*=0.86), smoking history of participants (*P*=0.33), method of diet assessment (*P*=0.49) or country of conduct (*P*=0.50) (**Fig. 97**).

Sudden cardiac death

One study (1 comparison; n=385 events) provided an estimate of the association between LA and sudden cardiac death *(71)*. In this study, the most-adjusted mvRR comparing the highest intake of dietary total LA with the lowest was 0.68 (95% CI: 0.49 to 0.95; *P*=0.02) (**Section 8.2.3** in **Fig. 58**). Assuming linearity, a 5 g/day increase in LA was associated with a 17% reduced risk of sudden cardiac death (mvRR: 0.83; 95% CI: 0.71 to 0.97). Assuming linearity, a 2% increase in energy from LA was associated with a 12% reduced risk of sudden cardiac death (mvRR: 0.88; 95% CI: 0.78 to 0.98) (**Fig. 195** and **Fig. 196**).

Fatal myocardial infarction

No prospective cohort studies were identified that provided an estimate of the association between dietary LA and fatal myocardial infarction.

Total CHD

Ten studies (14 comparisons; n=12 501 events) assessed the association between LA and total CHD. Of the 14 reported estimates of association, three were obtained from primary publications *(153, 189)*, and 11 were obtained from a recent meta-analysis by Farvid et al. *(37)*, which included longer follow-up of each of the cohorts: five primary publications were updated *(67, 75, 133, 185, 197)* and six estimates were published as part of the Pooling Project of Cohort Studies on Diet and

Coronary Disease (the pooled projects were the Israeli Ischaemic Heart Disease, Finnish Mobile Health Clinic, Västerbotten Intervention Program, Iowa Womens' Health Study, Women's' Health Study and Atherosclerosis Risk in Communities) *(198)*. In these studies, the summary mvRR for higher intakes of LA compared with lower intakes was 0.86 (95% CI: 0.76 to 0.97; *P*=0.02; I^2=35%; P_{het}=0.09) (**Section 8.2.5** in **Fig. 58**). No publication bias was suspected (**Fig. 84n**).

Using published data from Farvid et al. *(37)* with the additional studies in the present update, assuming linearity, a 5 g increase in LA was associated with a 7% reduced risk of CHD (mvRR: 0.93; 95% CI: 0.89 to 0.97). Assuming linearity, a 2% increase in energy from LA was associated with an 4% reduced risk of total CHD (mvRR: 0.96; 95% CI: 0.94 to 0.98). There was no evidence of a departure from linearity in either model (**Fig. 197** and **Fig. 198**).

Meta-regression (**Fig. 98**) found that the association estimate was not associated with study size (number of cases; *P*=0.71), study risk of bias (*P*=0.42), follow-up time (*P*=0.87), sex distribution (*P*=0.66), adjustment for blood pressure (*P*=0.39), age distribution (*P*=0.75), smoking status distribution (*P*=0.75), method of diet assessment (*P*=0.91) or country of conduct (*P*=0.16).

Whether or not a study measured TFA impacted the estimates (*P*=0.055) – studies that did adjust for TFA found a 20% reduced risk (mvRR=0.80) of fatal CHD with high consumption of LA, whereas those that did not adjust found a 3% reduced risk (mvRR=0.97). There was evidence of modification by adjustment for dyslipidemia (*P*=0.066). Studies that did adjust for dyslipidaemia found a greater risk reduction (mvRR=0.78) than those that did not (mvRR=0.96). All studies adjusted for total energy; thus, it is not appropriate to undertake meta-regression by this source of heterogeneity.

Fatal stroke

One prospective cohort study (1 comparison; n=321 cases) assessed the association between LA and fatal stroke *(59)*. In this study, the most-adjusted RR comparing highest intakes of LA with the lowest was 0.74 (95% CI: 0.35 to 1.58; *P*=0.44) (**Section 8.2.6** in **Fig. 55**).

Total stroke

No prospective cohort studies were identified that provided an estimate of the association between dietary LA and total stroke.

Atrial fibrillation

One study (2 estimates; n=7041 cases) assessed the association between LA and atrial fibrillation. In this study, the most-adjusted RR comparing highest intakes of LA with the lowest was 0.88 (95% CI: 0.78 to 1.00; *P*=0.05; I^2=0%; P_{het}=0.50) (**Section 8.2.8** in **Fig. 58**).

Nonfatal myocardial infarction

No prospective cohort studies were identified that provided an estimate of the association between dietary LA and nonfatal myocardial infarction.

3.11.3 Type 2 diabetes

Four studies (7 comparisons; n=19 050 cases) provided an estimate of the association between dietary LA and type 2 diabetes *(94, 95, 191, 192)*. The pooled most-adjusted mvRR comparing the highest intake of total dietary LA with the lowest was 0.90 (95% CI: 0.80 to 1.00; *P*=0.05; I^2=44%; P_{het}=0.10) (**Fig. 59a**). Assuming linearity, a 5 g increase in LA was associated with a 5% reduced risk of type 2 diabetes (mvRR: 0.95; 95% CI: 0.91 to 0.99). Assuming linearity, a 2% increase in energy from LA was associated with a 3% reduced risk of type 2 diabetes (mvRR: 0.97; 95% CI: 0.94 to 0.99) (**Fig. 199** and **Fig. 200**).

3.11.4 Depression

Three studies (3 comparisons; n=3433 cases) assessed the association between dietary LA and depression *(100, 173, 174)*. The pooled mvRR comparing the highest intake of total dietary LA with the lowest was 1.26 (95% CI: 1.09 to 1.46; *P*=0.002; I^2=0%; P_{het}=0.69) (**Fig. 59b** and fixed effect model in **Fig. 59c**). Assuming linearity, a 5 g increase in energy from LA was associated with a 14% higher risk of depression (mvRR: 1.14; 95% CI: 0.94 to 1.38). Assuming linearity, a 2% increase in energy from LA was associated with a 19% higher risk of depression (mvRR: 1.19; 95% CI: 0.79 to 1.80) (**Fig. 201** and **Fig. 202**).

3.11.5 Dementia

One study (2 comparisons; n=109 cases) assessed the association between dietary LA and dementia *(130, 199)*. The pooled most-adjusted mvRR comparing the highest intake of total dietary LA with the lowest was 0.77 (95% CI: 0.45 to 1.34; *P*=0.36; I^2=11%; P_{het}=0.29) (**Fig. 60**).

3.11.6 Inflammatory bowel disease

Crohn's disease

Two studies (2 comparisons; n=342 cases) assessed the association between dietary LA and Crohn's disease *(101, 176)*. The pooled most-adjusted mvRR comparing the highest intake of total dietary LA with the lowest was 1.23 (95% CI: 0.66 to 2.29; *P*=0.52; I^2=26%; P_{het}=0.25) (**Section 8.6.1** in **Fig. 61a**). The fixed-effect estimate was 1.13 (95% CI: 0.77 to 1.65).

Ulcerative colitis

Two studies (2 comparisons; n=464 cases) assessed the association between dietary LA and ulcerative colitis *(101, 179)*. The pooled most-adjusted mvRR comparing the highest intake of total dietary LA with the lowest was 1.41 (95% CI: 0.66 to 3.01; *P*=0.38; I^2=66%; P_{het}=0.09) (**Section 8.6.2** in **Fig. 61a**). The fixed-effect estimate was 1.17 (95% CI: 0.85 to 1.62; **Fig. 61b**).

3.11.7 Breast cancer

Total breast cancer

Five studies (5 comparisons; n=6227 cases) assessed the association between total dietary LA and breast cancer (without clearly distinguishing premenopausal from postmenopausal) *(105, 116, 177, 180, 200)*. In these studies, the pooled mvRR for higher intakes of total dietary LA compared with lower intakes was 0.95 (95% CI: 0.92 to 0.98; *P*=0.002; I^2=0%; P_{het}=0.48) (**Section 8.7.1** in **Fig. 62**). Assuming linearity, a 5 g increase in LA was associated with a 3% lower risk of breast cancer (mvRR: 0.97; 95% CI: 0.93 to 1.02). Assuming linearity, a 2% increase in LA was associated with a 2% lower risk of breast cancer (mvRR: 0.98; 95% CI: 0.96 to 1.01) (**Fig. 203** and **Fig. 204**).

Premenopausal breast cancer

No prospective cohort studies were identified that assessed the association between dietary LA and premenopausal breast cancer.

Postmenopausal breast cancer

Four studies (4 comparisons; n=6367 cases) assessed the association between LA and postmenopausal breast cancer (114, 117, 195, 201). In these studies, the pooled multivariable RR for higher intakes of total dietary LA compared with lower intakes was 1.02 (95% CI: 0.93 to 1.11; *P*=0.69; I^2=0%; P_{het}=0.43) (**Section 8.7.3** in **Fig. 62**).

3.11.8 GRADE assessment of quality of evidence

For the 15 outcomes assessed, the GRADE assessment of the confidence in the estimates of association between LA and health outcomes was moderate for seven outcomes (all-cause mortality, fatal CVD, fatal CHD, total CHD, type 2 diabetes, depression and all breast cancer) (46.7%), low for two outcomes (sudden cardiac death and total stroke) (13.3%) and very low for six outcomes (40.0%). One estimate is at serious risk of bias, one has serious inconsistency and six have serious imprecision (**Table 11**).

3.12 ARA (20:4 omega-6) and health outcomes

3.12.1 All-cause mortality

Four studies (6 comparisons; n=168 896 total deaths) assessed the association between ARA and all-cause mortality *(54, 59, 60, 120)*. In these studies, the pooled mvRR for higher lower intakes of ARA compared with lower intakes was 0.93 (95% CI: 0.82 to 1.05; *P*=0.26; I^2=93%; P_{het}<0.00001) (**Fig. 62**). Removal of Zhuang's NIH-AARP Diet and Health study *(59)* – a collaboration between the National Institutes of Health (NIH) and the AARP (formerly known as the American Association of Retired Persons) – yielded an mvRR of 0.90 (0.86, 0.94), with no heterogeneity.

Assuming linearity, a 0.1 g increase in ARA was not associated with risk of all-cause mortality (mvRR: 1.002; 95% CI: 0.98 to 1.03). Assuming linearity, a 0.3% increase in energy from ARA was not associated with increased risk of all-cause mortality (mvRR: 1.01; 95% CI: 0.87 to 1.18). However, excluding the Zhuang study (leaving 2 estimates), assuming linearity, a 0.1 g increase in ARA was associated with a 9% decreased risk of all-cause mortality (mvRR: 0.91; 95% CI: 0.88 to 0.95). Assuming linearity, a 0.3% increase in energy from ARA was associated with a 40% decreased risk of all-cause mortality (mvRR: 0.60; 95% CI: 0.48 to 0.74). Wang et al. *(54)*, using direct modelling, reported that a 0.3% increase in energy from LA was associated with a 42% decreased risk of all-cause mortality (mvRR: 0.58; 95% CI: 0.47 to 0.73) (**Fig. 205** and **Fig. 206**).

3.12.2 Cardiovascular diseases

Total CVD

No prospective cohort studies were identified that assessed the association between dietary total ARA and total CVD.

Fatal CVD

Three studies (4 comparisons; n=47 924 cases) assessed the association between dietary total ARA and fatal CVD (54, 59, 60). In these studies, the summary most-adjusted mvRR was 1.01 (95% CI: 0.91 to 1.13; *P*=0.83; I^2=67%; P_{het}=0.03) (**Section 10.2.1** in **Fig. 64**).

Fatal CHD

One study (1 comparison; n=978 events) provided an estimate of the association between ARA and fatal CHD *(60)*. The summary most-adjusted mvRR comparing the highest intake of dietary ARA with the lowest was 0.80 (95% CI: 0.58 to 1.11; *P*=0.18) (**Section 10.2.2** in **Fig. 64**).

Fatal myocardial infarction

No prospective cohort studies were identified that assessed the association between ARA and fatal myocardial infarction.

Fatal stroke

One study (1 comparison; n=321 events) provided an estimate of the association between ARA and fatal stroke *(60)*. The summary most-adjusted mvRR comparing the highest intake of dietary ARA with the lowest was 0.87 (95% CI: 0.47 to 1.61; *P*=0.66) (**Section 10.2.4** in **Fig. 64**).

Sudden cardiac death

One study (1 comparison; n=385 events) provided an estimate of the association between ARA and sudden cardiac death *(71)*. The summary most-adjusted mvRR comparing the highest intake of dietary ARA with the lowest was 0.88 (95% CI: 0.63 to 1.23; *P*=0.45) (**Section 10.2.5** in **Fig. 64**).

Total CHD

No prospective cohort studies were identified that provided an estimate of the association between dietary ARA and total CHD.

Total stroke

No prospective cohort studies were identified that provided an estimate of the association between dietary ARA and total stroke.

Atrial fibrillation

No prospective cohort studies were identified that provided an estimate of the association between dietary ARA and atrial fibrillation.

3.12.3 Type 2 diabetes

One study (1 comparison; n=199 cases) assessed the association between dietary ARA and type 2 diabetes *(89)*. In this one study, the most-adjusted RR, comparing the highest ARA consumers with the lowest was 0.87 (95% CI: 0.49 to 1.54; *P*=0.63) (**Fig. 65**).

3.12.4 Depression

Three studies (3 comparisons; n=3433 cases) assessed the association between dietary ARA and depression *(100, 173, 174)*. In these studies, the summary most-adjusted mvRR was 1.03 (95% CI: 0.90 to 1.18; *P*=0.64; I^2=0%; P_{het}=0.48) (**Fig. 66**).

3.12.5 Inflammatory bowel disease

Crohn's disease

One study (1 comparison; n=269 cases) assessed the association between dietary ARA and Crohn's disease *(101)*. The pooled most-adjusted mvRR comparing the highest intake of total dietary ARA with the lowest was 0.80 (95% CI: 0.55 to 1.17; *P*=0.25) (**Section 10.5.1** in **Fig. 67**).

Ulcerative colitis

One study (1 comparison; n=338 cases) assessed the association between dietary ARA and ulcerative colitis *(101)*. The pooled most-adjusted mvRR comparing the highest intake of total dietary LA with the lowest was 0.90 (95% CI: 0.64 to 1.26; *P*=0.54) (**Section 10.5.2** in **Fig. 67**).

3.12.6 Breast cancer

Total breast cancer

Three studies (3 comparisons; n=3581 cases) assessed the association between total dietary ARA and breast cancer (without clearly distinguishing premenopausal from postmenopausal) *(105, 177, 180)*. In these studies, the pooled mvRR for higher intakes of total dietary ARA compared with lower intakes was 1.05 (95% CI: 1.00 to 1.10; *P*=0.05; I^2=0%; P_{het}=0.86) (**Section 10.7.1** in **Fig. 68**).

Premenopausal breast cancer

No prospective cohort studies were identified that assessed the association between dietary ARA and premenopausal breast cancer.

Postmenopausal breast cancer

Two studies (2 comparisons; n=1411 cases) assessed the association between dietary ARA and postmenopausal breast cancer *(114, 117)*. In these studies, the pooled mvRR for higher intakes of total dietary ARA compared with lower intakes was 0.87 (95% CI: 0.65 to 1.15; *P*=0.32; I^2=36%; P_{het}=0.21) (**Section 10.7.3** in **Fig. 68**).

3.12.7 GRADE assessment of quality of evidence

For the 11 outcomes assessed, the GRADE assessment of the confidence in the estimates of association between ARA and health outcomes was moderate for one outcome (depression) (9.1%) and very low for the remaining 10 outcomes (90.9%). One estimate has serious inconsistency and 10 have serious imprecision (**Table 12**).

3.13 P:S and health outcomes

3.13.1 All-cause mortality

Four studies (5 comparisons; n=12 468 deaths) assessed the association between the P:S and all-cause mortality *(53, 64, 184, 202)*. In these studies, the summary mvRR for higher P:S compared with lower P:S was 1.02 (95% CI: 0.94 to 1.11; *P*=0.64; I^2=46%; P_{het}=0.12) (**Fig. 69**).

3.13.2 Cardiovascular diseases

Total CVD

One study (2 comparisons; n=908 events) assessed the association between P:S and total cardiovascular disease, which combined acute coronary events and stroke *(61)*. The summary most-adjusted mvRR comparing the highest P:S with the lowest was 0.88 (95% CI: 0.72 to 1.06; *P*=0.18) (**Section 11.2.1** in **Fig. 70**).

Fatal CVD

Two studies (3 comparisons; n=3533 cases) assessed the association between dietary P:S and fatal CVD *(53, 202)*. In these studies, the summary most-adjusted mvRR was 1.19 (95% CI: 0.99 to 1.42; *P*=0.06; I^2=66%; P_{het}=0.05; random-effects) (**Section 11.2.2** in **Fig. 70**). The fixed-effect estimate was 1.18 (95% CI: 1.07 to 1.31; *P*=0.001; forest plot not shown). Assuming linearity, a 0.25 increase in P:S ratio was associated with a 5% increased risk of CVD mortality (mvRR: 1.05; 95% CI: 1.02to 1.07) (**Fig. 207**).

Fatal myocardial infarction

No prospective cohort studies were identified that assessed the association between dietary P:S and fatal myocardial infarction.

Total CHD

One study (1 comparison; n=1766 events) provided an estimate of the association between P:S and total CHD *(197)*. The summary most-adjusted mvRR comparing the highest P:S with the lowest was 0.87 (95% CI: 0.72 to 1.05; *P*=0.15) (**Section 11.2.3** in **Fig. 70**).

Fatal myocardial infarction

No prospective cohort studies were identified that provided an estimate of the association between P:S and fatal myocardial infarction.

Total stroke

One study (1 comparison; n=141 cases) assessed the association between dietary P:S and total stroke *(79)*. In this study, the RR of higher P:S compared with lower P:S was 1.36 (95% CI: 0.70 to 2.66) (**Section 11.2.4** in **Fig. 70**).

Haemorrhagic stroke

No prospective cohort studies were identified that provided an estimate of the association between P:S and haemorrhagic stroke.

Ischaemic stroke

One study (2 comparisons; n=648 events) assessed the association between dietary P:S and ischaemic stroke *(61)*. The summary most-adjusted mvRR comparing the highest P:S with the lowest was 1.06 (95% CI: 0.85 to 1.32; *P*=0.62; I^2=0%; P_{het}=0.48) (**Section 11.2.6** in **Fig. 70**).

3.13.3 Type 2 diabetes

One study (1 comparison; n=414 cases) assessed the association between dietary P:S and type 2 diabetes *(203)*. In this one study, the most-adjusted RR, comparing the highest P:S with the lowest was 0.91 (95% CI: 0.81 to 1.03; *P*=0.12) (**Fig. 71**).

3.13.4 Breast cancer

Total breast cancer

One study (1 comparison; n=54 cases) assessed the association between dietary P:S and breast cancer (without delineating premenopausal from postmenopausal) *(103)*. In this study, the pooled mvRR for higher P:S compared with lower was 1.50 (95% CI: 0.77 to 2.93; *P*=0.23) (**Section 11.4.1** in **Fig. 72**).

Premenopausal breast cancer

No prospective cohort studies were identified that assessed the association between P:S and premenopausal breast cancer.

Postmenopausal breast cancer

One study (1 comparison; n=237 cases) assessed the association between P:S and postmenopausal breast cancer *(114)*. In this study, the mvRR for higher P:S compared with lower was 1.86 (95% CI: 1.13 to 3.07; *P*=0.01) (**Section 11.4.3** in **Fig. 72**). Assuming linearity, a 0.25-unit increase in P:S was associated with a 71% increased risk of breast cancer (mvRR: 1.71; 95% CI: 1.23 to 2.37) (**Fig. 208**).

3.13.5 GRADE assessment of quality of evidence

For the nine outcomes assessed, the GRADE assessment of the confidence in the estimates of association between the P:S ratio and health outcomes was very low for all associations (100%). Two estimates are at serious risk of bias, two have serious inconsistency and nine have serious imprecision (**Table 13**).

3.14 Omega-6:omega-3 ratio and health outcomes

3.14.1 All-cause mortality

Four studies (6 comparisons; n=78 332 deaths) assessed the association of the omega-6:omega-3 ratio with all-cause mortality *(54, 59, 60, 133)*. In these studies, the pooled mvRR comparing the highest omega-6:omega-3 ratio with the lowest was 0.99 (95% CI: 0.96 to 1.01; *P*=0.41; I2=0%; P_{het}=0.46) (**Fig. 73**).

3.14.2 Cardiovascular diseases

Total CVD

No prospective cohort studies were identified that assessed the association of the omega-6:omega-3 ratio with total CVD.

Fatal CVD

Three studies (4 comparisons; n=9449 events) assessed the association of the omega-6:omega-3 ratio with fatal CVD *(54, 59, 133)*. In these studies, the pooled mvRR was 0.94 (95% CI: 0.87 to 1.02; *P*=0.15; I^2=12%; P_{het}=0.33; random-effects). The fixed-effect estimate was 0.94 (95% CI: 0.86 to 1.01; *P*=0.10) (**Section 12.2.1** in **Fig. 74**).

Fatal CHD

Two studies (2 comparisons; n=1153 events) assessed the association of the omega-6:omega-3 ratio with fatal CHD *(59, 133)*. In this study, the mvRR was 1.02 (95% CI: 0.80 to 1.29; *P*=0.89; I^2=0%; P_{het}=0.69) (**Section 12.2.2** in **Fig. 74**).

Fatal stroke

One study (1 comparison; n=321 events) assessed the association of the omega-6:omega-3 ratio with fatal stroke. In this study, the mvRR was 0.90 (95% CI: 0.63 to 1.28; *P*=0.56) (**Section 12.2.3** in **Fig. 74**).

3.14.3 Type 2 diabetes

Six studies (6 comparisons; n=4766 events) assessed the association of the omega-6:omega-3 ratio with type 2 diabetes *(87, 89, 95, 165, 167, 204)*. In these studies, the pooled mvRR was 1.02 (95% CI: 0.90 to 1.16; *P*=0.74; I^2=24%; P_{het}=0.26) (**Fig. 75**).

3.14.4 Depression (omega-3:omega-6)

For this exposure, we report the ratio of n-3 to n-6 fatty acids, because this was the measure reported in the studies. Three studies (3 comparisons; n=3433 cases) assessed the association of the omega-3:omega-6 ratio with depression *(100, 173, 174)*. In this study, the mvRR was 0.74 (95% CI: 0.65 to 0.86; *P*<0.00001; I^2=0%; P_{het}=0.88) (Fig. 76). Assuming linearity, a 0.1-unit increase in the omega-3:omega-6 ratio was associated with a 21% lower risk of depression (mvRR: 0.79; 95% CI: 0.71 to 0.89) (**Fig. 209**).

3.14.5 Cognitive decline

One study (1 comparison; n=598 events) assessed the association of the omega-6:omega-3 ratio with cognitive decline *(98)*. In this study, the mvRR was 1.25 (95% CI: 1.01 to 1.55; *P*=0.04) (**Fig. 77**).

3.14.6 Suicide

One study (2 comparisons; n=298 events) assessed the association of the omega-6:omega-3 ratio with suicide *(175)*. In this study, the mvRR was 1.05 (95% CI: 0.63 to 1.74; *P* = 0.86; I^2=27%; P_{het} = 0.24) (**Fig. 78a**). The fixed-effect estimate was 1.01 (95% CI: 0.67 to 1.62; *P* = 0.96; I^2=27%; P_{het} = 0.24) (**Fig. 78b**).

3.14.7 Inflammatory bowel disease

Crohn's disease

One study (1 comparison; n=269 cases) assessed the association between the omega-6:omega-3 ratio and Crohn's disease *(101)*. The pooled most-adjusted mvRR comparing the highest omega-6:omega-3 ratio with the lowest was 1.18 (95% CI: 0.76 to 1.81; *P*=0.46) (**Section 12.7.1** in **Fig. 79**).

Ulcerative colitis

One study (1 comparison; n=338 cases) assessed the association between the omega-6:omega-3 ratio and ulcerative colitis *(101)*. The most-adjusted mvRR comparing the highest omega-6:omega-3 ratio with the lowest was 1.45 (95% CI: 1.02 to 2.05; *P*=0.04) (**Section 12.7.2** in **Fig. 79**).

3.14.8 Breast cancer

Total breast cancer

Three studies (3 comparisons; n=1613 events) assessed the association of the omega-6:omgea-3 ratio with breast cancer (without differentiating premenopausal from postmenopausal onset) *(107, 177, 180)*. The pooled mvRR was 1.13 (95% CI: 0.95 to 1.35; *P*=0.18; I^2=0%; P_{het}=0.61).

Premenopausal breast cancer

No prospective cohort studies were identified that assessed the association of the omega-6:omega-3 ratio with premenopausal breast cancer.

Postmenopausal breast cancer

Two studies (2 comparisons; n=707 events) assessed the association of the omega-6:omega-3 ratio with postmenopausal breast cancer *(113, 117)*. The pooled mvRR was 1.48 (95% CI: 1.13 to 1.94; *P*=0.004; I^2=0%; P_{het}=0.92).

3.14.9 GRADE assessment of quality of evidence

For the 12 outcomes assessed, the GRADE assessment of the confidence in the estimates of association between the omega-6:omega-3 ratio and health outcomes was moderate for one outcome (depression) (8.3%), low for three outcomes (all-cause mortality, cognitive decline and ulcerative colitis) (25.0%) and very low for eight outcomes (66.7%). One estimate is at serious risk of bias, none have serious inconsistency and seven have serious imprecision (**Table 14**).

3.15 Replacement of SFA by PUFA

We identified five cohort studies or pooling studies of cohort studies *(23, 37, 54, 90, 198)* that directly modelled the effect on health outcomes of replacing SFA with PUFA. Only one of these studies (other than the Farvid meta-analysis) *(54)* distinguished between omega-3 and omega-6 fatty acids as the replacement choice.

3.15.1 Pooling Project

The Pooling Project of Cohort Studies on Diet and Coronary Disease *(198)* had 4–10 years of follow-up, with 5249 coronary events and 2155 coronary deaths among 344 696 persons. In this project, replacement of 5% of energy intake from SFAs with PUFA was inversely associated with risk of coronary events (hazard ratio: 0.87; 95% CI: 0.77, 0.97) and coronary deaths (hazard ratio: 0.74; 95% CI: 0.61, 0.89).

3.15.2 Farvid et al. (2014)

In a large, high-quality systematic review and dose–response meta-analysis of 13 published and unpublished cohort studies with 310 602 participants *(37)*, replacement of 5% of energy from SFA with LA (an omega-6 PUFA) was associated with a 9% lower risk of CHD events (RR: 0.91; 95% CI: 0.87 to 0.96) and a 13% lower risk of CHD deaths (RR: 0.87; 95% CI: 0.82 to 0.94).

3.15.3 Wang et al. (2016)

In a 2016 pooled analysis of the NHS and HPFS cohorts (USA; n=126 233 men and women consuming about 12%E saturated fat and 6%E PUFA) that superseded the Pooling Project and the Farvid et al. *(37)* meta-analysis, Wang et al. *(54)* found that substitution of 5% of energy from SFA with PUFA was associated with a 27% reduced risk of all-cause mortality (mvRR: 0.73; 95% CI: 0.70 to 0.77), a 28% reduced risk of cardiovascular mortality (mvRR: 0.72; 95% CI: 0.65 to 0.80), a 14% reduced risk of cancer mortality (mvRR: 0.86; 95% CI: 0.79 to 0.84) and a 21% decreased risk of neurodegenerative disease mortality (mvRR: 0.79; 95% CI: 0.66 to 0.94).

Replacement of 2% of energy from SFA with omega-6 PUFA was associated with a 7% reduced risk of all-cause mortality (mvRR: 0.93; 95% CI: 0.91 to 0.96), an 11% decreased risk of cardiovascular mortality (mvRR: 0.89; 95% CI: 0.85 to 0.94), a 4% reduced risk of cancer mortality (mvRR: 0.96; 95% CI: 0.92 to 1.00) and a (nonsignificant) 7% increased risk of neurodegenerative disease mortality (mvRR: 1.07; 95% CI: 0.98 to 1.16).

Replacement of 0.3% of energy from SFA with omega-3 PUFA was associated with a 5% reduced risk of all-cause mortality (mvRR: 0.95; 95% CI: 0.93 to 0.96), a (nonsignificant) 1% increased risk of cardiovascular mortality (mvRR: 1.01; 95% CI: 0.97 to 1.05), a (nonsignificant) 2% reduced risk of cancer mortality (mvRR: 0.98; 95% CI: 0.95 to 1.01) and an 18% decreased risk of neurodegenerative disease mortality (mvRR: 0.82; 95% CI: 0.76 to 0.88).

3.15.4 Salmerón et al. (2001)

The Nurses' Health Study *(90)* enrolled 82 204 women aged 34–59 years free from diabetes in 1980. In that study, replacing 5% of energy from SFAs with PUFA was associated with a 35% lower risk (mvRR: 0.65; 95% CI: 0.54 to 0.78) of type 2 diabetes over 14 years of follow-up (2504 incident cases).

3.15.5 Praagman et al. (2016)

In the European Prospective Investigation into Cancer and Nutrition-Netherlands cohort (1587 cases in 35 193 participants over 12 years of follow-up), replacement of 5% of energy from saturated fat with polyunsaturated fat was associated with a 33% increased risk of ischaemic heart disease (mvRR: 1.33; 95% CI: 1.11 to 1.60) *(23, 77)*. The authors acknowledge the small range of SFA intake (IQR: 13.2–16.6% of energy) at a high mean intake level (15.0% of energy) and small range of PUFA intake (IQR: 5.6–7.9% of energy), may have limited the robustness of the substitution models. Furthermore, certain PUFA food sources consumed in this study population also contained TFA; for example, the most important PUFA source, margarines (17%), also provided 9% of the TFA intake.

3.15.6 Zhuang et al. (2019)

In the NIH-AARP study (129 328 deaths over 16 years) *(59)*, replacement of 5% of energy from saturated fat with total, omega-3 or omega-6 PUFA reduces mortality from several causes (adapted from **Fig. 2 of Zhuang et al 2019** *(60)*):

	Replace 5% of SFA with		
Outcome	**Total PUFA**	**Omega-3 PUFA**	**Omega-6 PUFA**
Total mortality	0.82 (0.81 to 0.84)	0.99 (0.98 to 1.01)	0.92 (0.91 to 0.93)
CVD mortality	0.85 (0.82 to 0.88)	0.98 (0.96 to 1.01)	0.94 (0.92 to 0.96)
Cancer mortality	0.82 (0.79 to 0.85)	1.00 (0.98 to 1.02)	0.92 (0.90 to 0.93)
Respiratory disease mortality	0.77 (0.72 to 0.82)	0.98 (0.94 to 1.02)	0.89 (0.86 to 0.92)
Alzheimer's disease mortality	0.91 (0.78 to 1.06)	0.88 (0.79 to 0.98)	0.99 (0.91 to 1.08)
Diabetes mortality	0.88 (0.78 to 0.98)	1.07 (1.00 to 1.15)	0.9 (0.86 to 0.97)

3.16 Meta-analyses of fish, walnuts and health outcomes

3.16.1 Fish and stroke

Xun et al. *(205)* meta-analysed 16 studies (19 cohorts), including 402 127 individuals (10 568 incident cases) with an average 12.8 years of follow-up. Compared with those who never consumed fish or ate fish less than once a month, the pooled adjusted hazard ratios of total stroke risk were 0.97 (95% CI: 0.87 to 1.08) for those who consumed fish one to three times a month, 0.86 (0.80 to 0.93) for those who consumed fish once a week, 0.91 (0.85 to 0.98) for those who consumed fish two to four times a week and 0.87 (0.79 to 0.96) for those who consumed fish about 5 times a week ($P_{linear\ trend}$)=0.09; $P_{non\text{-}linear\ trend}$=0.02). Study location was a modifier. An inverse association between fish intake and stroke incidence was found only in studies conducted in North America. The modest inverse associations were more pronounced with ischaemic stroke; they were attenuated with haemorrhagic stroke.

3.16.2 Fish and type 2 diabetes

Xun et al. *(205)* meta-analysed nine eligible studies (12 independent cohorts), including 438 214 individuals, with an average 11.4-year follow-up. Compared with those who never consumed fish or ate fish less than once per month, the pooled RR of incident diabetes was 0.99 (95% CI 0.85 to 1.16) for individuals who ate fish five or more times per week (P_{trend}=0.80). Similar results were found for long-chain omega-3 PUFA intake. Study location was an effect modifier. An inverse association between fish intake and diabetes incidence was found by combining studies conducted in eastern but not western countries.

3.16.3 Walnuts and type 2 diabetes

Pan et al. *(206)* prospectively followed 58 063 women aged 52–77 years in NHS (1998–2008) and 79 893 women aged 35–52 years in NHS II (1999–2009) without diabetes, CVD or cancer at baseline. The authors measured dietary intakes every 4 years using a validated FFQ; they documented 5930 incidents of type 2 diabetes cases during 10 years of follow-up. In the multivariable-adjusted Cox proportional hazards model without body mass index (BMI), consumption of walnuts (a source of ALA and LA) (was associated with a lower risk of type 2 diabetes, and the hazard ratios (95% CIs) for participants consuming one to three servings per month (where 1 serving=28 g) were 0.93 (0.88 to 0.99), for those consuming one serving per week, 0.81 (0.70 to 0.94) for those consuming two or more servings per week and 0.67 (0.54 to 0.82) for those who never or rarely consumed walnuts (P_{trend}<0.001).

3.16.4 Fish and CHD mortality

He at al. *(18)* meta-analysed 11 studies (13 cohorts), including 222 364 individuals with an average 11.8 years of follow-up. Compared with those who never consumed fish or ate fish less than once per month, individuals with a higher intake of fish had lower CHD mortality. The pooled

multivariate RRs for CHD mortality were 0.89 (95% CI: 0.79 to 1.01) for fish intake one to three times per month, 0.85 (95% CI: 0.76 to 0.96) for fish intake once per week, 0.77 (95% CI: 0.66 to 0.89) for fish intake two to four times per week and 0.62 (95% CI: 0.46 to 0.82) for fish intake five or more times per week. Each 20 g/day increase in fish intake was related to a 7% lower risk of CHD mortality (P_{trend}=0.03).

3.16.5 Prospective cohort studies of PUFA and fish in secondary prevention

Total PUFA

In the EUROASPIRE (European Action on Secondary Prevention through Intervention to Reduce Events) prospective cohort study *(207)*, Erkkilä et al. measured dietary intakes via food records and the fatty acid composition of serum cholesteryl esters (CEs) in 285 men and 130 women with coronary artery disease (CAD) (mean age: 61 years; range: 33–74 years). Participants were followed up for 5 years. During the follow-up, 36 patients died, 21 had myocardial infarctions and 12 had strokes. The RR of death (n=34) for a 1 standard deviation (SD) (1.7%) increase in PUFA was 0.92 (95% CI: 0.64 to 1.31), for CAD death (n=16) it was 0.92 (95% CI: 0.55 to 1.54), for CAD death or myocardial infarction (n=34) it was 1.08 (95% CI: 0.78 to 1.51) and for CVD death, acute myocardial infarction or stroke it was 1.08 (95% CI: 0.82 to 1.42). Consumption of fish was protective against all-cause mortality (mvRR: 0.37; 95% CI: 0.14 to 0.99) and CVD death (mvRR: 0.45; 95% CI: 0.19 to 1.08), but not for CAD death (mvRR: 0.49; 95% CI: 0.17 to 1.41) (**Fig. 78**).

Fish

Two prospective cohort studies (3 comparisons; **Fig. 81**) *(207, 208)* assessed the association between high intakes of fish in secondary prevention of CHD death in patients with established CHD. The pooled estimate from these three studies (92 events) was 0.49 (95% CI: 0.29 to 0.81; *P*=0.005; I^2=0%; P_{het}=0.76).

Long-chain omega-3 fatty acids

Two prospective cohort studies *(209, 210)* assessed the impact of long-chain omega-3 fatty acids in secondary prevention. In the first study, Benedetto et al. followed 2100 patients undergoing coronary artery bypass grafting in a tertiary care hospital *(209)*. At discharge, the decision to prescribe n-3 PUFA therapy (900 mg EPA+DHA) was at the discretion of the referring cardiologist. The treatment reduced all-cause mortality by 44% (mvRR: 0.56; 95% CI: 0.31 to 1.00). Greene et al. performed a retrospective observational cohort study including patients from five Italian local health units who were discharged from the hospital with a primary diagnosis of acute myocardial infarction *(210)*. Of the 11 269 patients enrolled, 2425 patients (21.5%) were prescribed omega-3 PUFA during follow-up. After adjusting for patient characteristics and concurrent therapies, omega-3 PUFA treatment was associated with reduced all-cause mortality (mvHR: 0.75, 95% CI 0.59 to 0.97) and recurrent acute myocardial infarction (mvHR: 0.65; 95% CI: 0.49 to 0.87) through 12-month follow-up. The pooled estimate of these two studies for all-cause mortality (n=1339 events) was 0.72 (95% CI: 0.57 to 0.91; I^2=0%, *P*=0.005).

4. Discussion

This systematic review and meta-analysis of prospective cohort studies of PUFA and health outcome in adults found that data for health outcomes other than CVD and diabetes have not been well studied. The confidence rating for all the reviewed associations ranged from very low (77.0%; n=151 assessments) to low (6.1%; n=12 assessments) to moderate (16.8%; n=33 assessments) (**Fig. 82**). The methodological quality of the included cohort studies was generally high, with more than 85% of included studies rating 7 out of 9 or higher on the NOS (**Fig. 1b**).

The most common reason for downgrading the confidence in the body of evidence for associations was imprecision, because the CIs for most summary estimates were wide and could not exclude a null association. This was not always simply attributable to low sample size, because many associations with more than 500 events were imprecise and included an RR of 1.0. It is likely that differences in results across studies are due in no small part to differences in comprehensiveness of dietary assessment methods, although our meta-regression was probably underpowered to detect this. For example, some studies measured diet with a single 24-hour recall, whereas others used multiple, updated semiquantitative food frequency questionnaires validated against biomarkers and other dietary instruments. When assumed effect sizes are small, as they typically are for dietary associations (RR usually from 0.7 to 1.3), power to detect these in the presence of measurement error is typically low.

Inconsistency across studies was present in most analyses. Explanations of inconsistency were not easy to find, but univariate meta-regression approaches identified study size, study quality (for total PUFA and all-cause mortality; and LA and total and fatal CHD), duration of follow-up (for total PUFA and all-cause mortality), measurement and appropriate adjustment of TFA (total PUFA and all-cause mortality; and long-chain omega-3 and fatal CVD and type 2 diabetes), measurement for causal intermediates (e.g. dyslipidaemia for long-chain PUFA and fatal CVD; and hypertension for long-chain omega-3 PUFA and type 2 diabetes), and method of dietary assessment (for total PUFA and all-cause mortality), dose range (for long-chain omega-3 PUFA and fatal CVD and type 2 diabetes), per cent of smokers in the study (for long-chain omega-3 and fatal CVD), and country of conduct (for long-chain omega-3 and type 2 diabetes) were common predictors that could explain 38–91% of the between-study variance across outcomes. Heterogeneity across studies for long-chain omega-3 PUFA and fatal CHD was not explained by any study-level attributes.

In cohort studies that have directly modelled substitution effects, replacement of SFA by PUFA (with a corresponding increase in P:S ratio) conferred the greatest reduction in CVD risk *(198, 211)*; although these studies did not distinguish between omega-3 and omega-6 fatty acids as the replacement choice. Several intervention studies that have replaced SFA with PUFA achieved relatively high P:S ratios (>1.0 to about 2.5) through replacement of SFA with predominantly soybean (omega-6 LA) and marine oils (n-3 EPA and DHA from sardines) *(212–214)*. At these levels, significant CHD benefits were seen, consistent with the finding that favourable effects of diets with reduced SFA on cardiovascular risk may depend on a significant reciprocal increase in PFA *(215)*. In a meta-analysis of cohort studies, replacement of 5% of energy from SFA with LA (omega-6 PUFA), was associated with a 9% lower risk of CHD events (RR: 0.91; 95% CI: 0.87 to 0.96 in 13 studies with 310 602 participants) and a 13% lower risk of CHD deaths (RR: 0.87; 95% CI: 0.82 to 0.94) *(37)*. A re-analysis of the Sydney Diet Heart Study and updated meta-analysis found no benefit, and possible harm, associated with replacement of SFA by LA (HR for CHD death: 1.33; 95% CI: 0.99 to 1.79 and HR for CVD: 1.27; 95% CI: 0.98 to 1.65) in secondary prevention trials *(18)*. However, the re-analysis could not remove intractable methodological problems with this study, particularly the non-continuous stay of participants in hospital, which may bias the

effect estimate towards the null, and the delay in blood sampling of readmitted participants, which may exaggerate the extent of cholesterol-lowering in the intervention group.

On balance, we found that higher intakes of PUFA are either protective or neutral, with respect to all-cause mortality and CVDs, consistent with previous meta-analyses. We note some trends for higher omega-3 PUFA to be associated with increased risk of type 2 diabetes, and for higher omega-6 PUFA to be associated with depression and some types of breast cancer. The reasons for these findings are unclear. ARA, a derivative of the omega-6 LA, may induce proinflammatory and prothrombotic effects when present in excess, which may promote adverse physiologic changes *(216, 217)*. However, in our meta-analysis we found no adverse association of ARA with breast cancers.

The influence of omega-6 fatty acids on depressive symptoms is poorly understood. However, studies examining tissue fatty acid composition have demonstrated that dietary omega-6 PUFA affect brain lipid content. Dietary omega-6 deficiency decreased omega-6 PUFA levels in the brain membranes of piglets, and this decrease was associated with reduced concentrations of both dopamine and serotonin *(218)*. Excessive serum levels of ARA and its cascade were first implicated in the pathogenesis of affective disorders in 1989 *(219)*, and the net overlapping effects of at least three mood stabilizers are decreased turnover of ARA, and decreased brain cyclo-oxygenase-2 and prostaglandin E(2) *(220)*.

LA may interact with ALA to produce effects on mood. For example, in a more detailed analysis of LA and depression in the Lucas study *(173)*, the impact of high LA was seen only in those women who also consumed high levels of ALA. Therefore, LA might not have a direct detrimental effect on depression, but rather through a potential biological interaction with ALA. However, an adverse effect of LA intake on risk of depression in susceptible individuals cannot be excluded. A high dietary omega-6:omega-3 ratio associated with increased risk of depression has been often reported *(221)*, but most reports only reflect the results derived from the inverse associations of long-chain omega-3 PUFA with the risk of depression. Wolfe and colleagues observed a positive association between dietary omega-6 PUFA intake (and corresponding blood levels) and risk of severe depression *(193)*. Furthermore, data from a cross-sectional study in pregnant Brazilian women found that high serum levels of omega-6 PUFA were associated with a greater likelihood of depression *(222)*.

This review has several strengths. First, the confidence in the estimates was assessed using GRADE, to facilitate guideline development. Second, studies were identified via a systematic search of the literature, augmented with manual searches of reference lists of published papers and systematic reviews. Third, the quantitative synthesis was focused on studies measuring comparable outcomes using similar designs, reducing methodological heterogeneity. Fourth, our data are largely consistent with randomized trials of duration 6 months to 5 years, which, under more tightly controlled conditions, show about a 20% reduced risk of CHD in those assigned to diets high in fish or supplemented with fish oil or PUFA *(38)*.

This review has important limitations related to evidence synthesis and quality. First, meta-analytic techniques depend on the availability of effect estimates that are conceptually similar and can be combined across studies. If such estimates are not available, the ability to pool all available and relevant data in a meaningful way is compromised, and the pooled estimate of effect may be suboptimal. Second, observational studies cannot provide causal evidence of an effect of PUFA on the development of health outcomes addressed, they can only describe associations. Third, measurement error is often serious in epidemiologic studies of diet and disease, which may bias such associations towards the null. Fourth, methodological limitations of original studies cannot be overcome with meta-analytic techniques. The risk-of-bias assessments (Newcastle-Ottawa Scale evaluations) of the included studies appear in Table 2 and in the footnotes to the GRADE tables. These include unrepresentative cohorts or a vaguely defined cohort sampling frame; misclassification of exposure due to inaccurate measurement tools (selection and exposure measurement biases); failure to account for major confounders such as

age, socioeconomic status, smoking, total energy, or family history (non-comparability biases); lack of validated outcome measures; or insufficient study duration to observe a high number of events (outcome assessment biases). Finally, random error or the inability to distinguish PUFA from TFA may attenuate the observed associations with health outcomes, suggesting that the true effect of consuming these nutrients may be larger than reported. This error may arise from several sources, including residual confounding, recall bias and exposure misclassification. The reviewed studies typically relied on FFQs, 24-hour recalls or 7-day food records, each of which have serious limitations in their ability to accurately capture long-term dietary fat intake.

On balance, higher intakes of PUFA are associated with reduced risks of all-cause and cardiovascular mortality, but the quality of the evidence is mostly very low. The benefits of dietary omega-3 fatty acids, largely from fish and seafood in these cohorts, appear to be specific for CVDs, but few observational studies have directly observed or otherwise modeled the effects on health outcomes of replacing SFA or TFA with PUFA. The interactions between different types of PUFA require further research.

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Annex 1. Tables

Table 1. Characteristics of included prospective cohort studies

SOURCE (COUNTRY)	AGE (YEARS)	SEX (% MEN)	NUMBER OF PARTICIPANTS	NUMBER OF EVENTS	FOLLOW-UP (YEARS)	EXPOSURES ASSESSED	EXPOSURE VS CONTRAST	OUTCOME VALIDATION	ADJUSTMENT FOR CONFOUNDERS	NOS SCORE	FUNDING
Albert et al. 2002 *(1)*, USA, Physicians' Health Study	49–68	100	278	201 sudden death from cardiac causes	17	Long-chain n-3, n-6 polyunsaturated, short-chain n-3, ALA (*serum sample*)	Q4 vs Q1 (6.87 vs 3.58 %E)	Events reported by postal authorities or next of kin, validated by review of medical records by blinded physicians.	Age, assignment to aspirin and beta-carotene treatment or placebo, BMI, history of diabetes, history of hypertension, history of hypercholesterolaemia, alcohol consumption, frequency of vigorous exercise, parental history of MI before the age of 60 years, *trans*-unsaturated fatty acid levels and monounsaturated fatty acid levels.	–	National Institutes of Health (USA); National Heart, Lung, and Blood Institute
Alhazmi et al. 2014 *(2)*, Australia, Australian Longitudinal Study on Women's Health	45–50	100	8370	311 incident T2DM	6	Total PUFA, n-3 PUFA, ALA, EPA, DHA, EPA+DHA, n-6 PUFA, n-6:n-3 (*validated FFQ*)	Q5 vs Q1 (g/day)	Events were self-reported and validated by random sample whose medical and pharmaceutical records were reviewed.	Area of residence, education, current smoker status, physical activity, self-rated health as good, menopausal status, BMI, alcohol consumption, total energy intake, fibre and specific types of fat.	–	Australian Government Department of Health and Ageing
Bassett et al. 2016 *(3)*, Australia, Melbourne Collaborative Cohort Study	54.8	0	2491	470 breast cancer	12	Total PUFA, n-3 PUFA, n-6 PUFA, n-6:n-3 PUFA (*FFQ+ blood*)	Q5 vs Q1 (% phospholipids, diet)	Cases were identified from notifications of first diagnoses of breast cancer to the Victorian Cancer Registry.	Country of birth, menopausal status, age at menarche, parity and lactation, oral contraceptive use, hormone therapy use, physical activity, alcohol consumption, smoking status, education, family history of cancer, total energy intake from food and BMI.	–	–

SOURCE (COUNTRY)	AGE (YEARS)	SEX (% MEN)	NUMBER OF PARTICIPANTS	NUMBER OF EVENTS	FOLLOW-UP (YEARS)	EXPOSURES ASSESSED	EXPOSURE VS CONTRAST	OUTCOME VALIDATION	ADJUSTMENT FOR CONFOUNDERS	NOS SCORE	FUNDING
Bork et al. 2016 *(4)*, Denmark, Danish Cohort Study Diet, Cancer and Health	50–64	48	57 053	3089 MI	17	ALA (*validated SQFFQ + adipose tissue analysis*)	Continuous (g/day and % content in adipose tissue)	Events were reported using Danish nationwide registers.	BMI, waist circumference, smoking, physical activity, alcohol consumption, length of education, menopausal status, use of hormone replacement therapy, self-reported history of hypercholesterolaemia or use of lipid-lowering medication, self-reported history of hypertension or use of antihypertensive medication, and self-reported history of diabetes mellitus.	–	None
Brostow et al. 2011 *(5)*, Singapore, The Singapore Chinese Health Study	45–74	»42	43 176	2252 incident T2DM	11	Total n-3, n-6, n6:n3, EPA+DHA (marine), nonmarine (ALA n-3) (*validated FFQ*)	Q5 vs Q1 (g/day)	Events were self-reported and were validated by reviewing hospital records and by participant completion of a supplementary questionnaire. A random sample who did not report diabetes were tested for blood sugar levels to ensure accurate self-report of no event.	Age, sex, dialect, year of interview, educational level, BMI, physical activity, smoking status, alcohol use, hypertension, intakes of n-6 or n-3, monounsaturated fat, saturated fat, dietary fibre, protein and total energy.	–	NIH
Brouwer et al. 2006 *(6)*, Netherlands, Rotterdam Study	59–76	41	5184	312 AF	8	EPA and DHA intake (*self-report and dietitian interview with validated FFQ*)	Q3 vs Q1 (≥144 vs ≤43 mg/day)	Events were reported by ECG readings by blinded physicians, GP reports and hospital discharge summaries.	Age, sex, energy intake, diabetes mellitus, alcohol intake, systolic BP, HDL and total cholesterol levels, intake of saturated fatty acids, smoking status and previous MI.	–	Dutch Government

SOURCE (COUNTRY)	AGE (YEARS)	SEX (% MEN)	NUMBER OF PARTICIPANTS	NUMBER OF EVENTS	FOLLOW-UP (YEARS)	EXPOSURES ASSESSED	EXPOSURE VS CONTRAST	OUTCOME VALIDATION	ADJUSTMENT FOR CONFOUNDERS	NOS SCORE	FUNDING
Byrne et al. 2002 *(7)*, USA, NHS	50	0	44 697	1071 breast cancer cases	14	LA intake (*FFQ*)	Q5 vs Q1	Events were self-reported, confirmed by review of medical records.	Age in months, height, age at menarche, combined age at menopause and use of postmenopausal hormones, combined parity and age at first birth, BMI at age 18, weight change since age 18, intake of total energy, alcohol intake, family history of breast cancer, vitamin A and other fat types.	–	NIH Grant "The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked *advertisement* in accordance with 18 USC Section 1734 solely to indicate this fact."
Chiuve et al. 2015 *(8)*, USA, Women's Health Study	≥45	0	33 665	1441 cases of incident AF (929 paroxysmal and 467 persistent/chronic)	20	Total PUFA intake (*validated FFQ*)	Q5 vs Q1 (7.6 vs 4.1 median%E)	Events were self-reported and confirmed by medical records.	Age, protein, total calories, smoking, BMI, height, alcohol, exercise, education, race, randomization group (beta-carotene, vitamin E and aspirin), systolic BP; diagnosis of hypertension, high cholesterol and diabetes, CVD, or congestive heart failure during follow-up; SFAs, MUFAs, total PUFA and TFA.	–	Watkins Discovery Award, National Heart Lung Blood Institute, National Institutes of Health (USA)
De Goede et al. 2013 *(9)*, Netherlands, Monitoring Project on Risk Factors for Chronic Diseases	20–65	53	358	179 incident cases of stroke (93 ischaemic strokes, 50 haemorrhagic strokes, and 36 unspecified strokes)	13	Plasma n-3 PUFA: LA, ARA, ALA EPA:DHA (*no fasting blood sample – mass percentages of total fatty acid methyl esters*)	Case vs controls	Events were ascertained using the national hospital discharge register and causes of death on Statistics Netherlands.	Age, gender, enrolment date, smoking, BMI, education level, alcohol intake, diabetes, hypertension and hypercholesterolaemia.	–	Alpro Foundation (Belgium), Ministry of Health, Welfare and Sport of the Netherlands, the National Institute for Public Health and the Environment, Bilthoven, The Netherlands, and the Europe Against Cancer Program of the European Union

SOURCE (COUNTRY)	AGE (YEARS)	SEX (% MEN)	NUMBER OF PARTICIPANTS	NUMBER OF EVENTS	FOLLOW-UP (YEARS)	EXPOSURES ASSESSED	EXPOSURE VS CONTRAST	OUTCOME VALIDATION	ADJUSTMENT FOR CONFOUNDERS	NOS SCORE	FUNDING
Djoussé et al. 2011 *(10)*, USA, Women's Health Study	54.6	0	36 328	2370 incident T2DM	16	EPA, DHA, ALA and fish intakes (*validated FFQ*)	Q5 vs Q1 (g/day)	Events were self-reported and validated primarily through the collection of supplementary information from participants.	Age, BMI, parental history of diabetes, smoking, exercise, alcohol intake, menopausal status, red meat intake, and quintiles of energy intake, LA, ALA, dietary magnesium, TFA, saturated fat, cereal fibre and glycaemic index.	–	National Cancer Institute, National Heart, Lung, and Blood Institute
Dominiguez et al. 2015 *(11)*, Spain, SUN Project	23–55	39–43	17 292	143 incident T2DM	15	Diabetes Dietary Score (*validated FFQ*)	Q5 vs Q1 (Diabetes Dietary Score high vs low)	Events were self-reported with data involving diagnoses and prescriptions. Reports from physicians with the detailed diagnosis were requested to supplement this information.	Age, year of recruitment, sex, total energy intake, following a special diet, snacking between meals, BMI, physical activity, hours of television watching, hours sitting down, smoking, marital status, personal history of hypertension and family history of diabetes.	–	Spanish Ministry of Health and European Regional Development Fund, Navarra Regional Government and Formación del Profesorado Universitario fellowship from the Spanish Government
Dow et al. 2016 *(12)*, France, E3N Cohort	52.9	0	71 334	2610 incident T2DM	18	Total PUFA, n-3 PUFA, n-6 PUFA (*validated dietary questionnaire*)	Q3 vs Q1 (g/day)	Events were self-reported using follow-up questionnaires or through diabetes drug reimbursement from health insurance records.	Daily energy intake, alcohol consumption, level of education, family history of diabetes, physical activity, hypertension, hypercholesterolaemia, smoking status and tertile groups of remaining fatty acid groups.	–	Cardiovasculaire, Obésité, Rein, Diabète Program

SOURCE (COUNTRY)	AGE (YEARS)	SEX (% MEN)	NUMBER OF PARTICIPANTS	NUMBER OF EVENTS	FOLLOW-UP (YEARS)	EXPOSURES ASSESSED	EXPOSURE VS CONTRAST	OUTCOME VALIDATION	ADJUSTMENT FOR CONFOUNDERS	NOS SCORE	FUNDING
Engeset et al. 2006 *(13)*, Europe, EPIC	25–70	0	310 671	4776 invasive incident breast cancers	12 max. (6.4 median)	Total fish intake (*FFQ and 24h food recall*)	Q5 vs Q1 (g/day)	Events were reported using country-specific population cancer registries and on a combination of methods including health insurance, cancer and pathology registries, and active follow-up through study subjects and their next of kin in three countries.	Centre location, adjusted for time of follow-up, energy intake from fat, alcohol intake, height, weight, age at menarche, number of full-term pregnancies and age at first full-term pregnancy, therapy, current use of oral contraceptives and menopausal status.	–	Europe Against Cancer Program of the European Commission, Deutsche Krebshilfe, Deutsches Krebsforschungszentrum, German Federal Ministry of Education and Research, Danish Cancer Society, Health Research Fund of the Spanish Ministry of Health, Spanish Regional Governments of Andalucia, Asturia, Basque Country, the Instituto de Salud Carlos III Network of Public Health Research Centres, Cancer Research UK, Medical Research Council, Stroke Association (UK), British Heart Foundation, Department of Health (UK), Food Standards Agency (UK), Wellcome Trust (UK), Italian Association for Research on Cancer, Compagnia di San Paolo (Italy), Dutch Ministry of Public Health, Welfare and Sports, World Cancer Research Fund, Norwegian Cancer Society, Research Council of Norway, French League against Cancer, National Institute for Health and Medical Research (France), Mutuelle Générale de l'Education Nationale (France), 3M Company, France, Greek Ministry of Health, Greek Ministry of Education, Swedish Cancer Society, Swedish Research Council, Regional Government of Skane

SOURCE (COUNTRY)	AGE (YEARS)	SEX (% MEN)	NUMBER OF PARTICIPANTS	NUMBER OF EVENTS	FOLLOW-UP (YEARS)	EXPOSURES ASSESSED	EXPOSURE VS CONTRAST	OUTCOME VALIDATION	ADJUSTMENT FOR CONFOUNDERS	NOS SCORE	FUNDING
Engeset et al. 2015 *(14)*, Europe, EPIC	35–70	28	509 308	32 587 deaths	18	Total fish consumption (*validated FFQ*), analysed by gender	Q5 vs Q1 (g/day) and continuous (10 g increment)	Events were recorded using cancer registries, boards of health and death indices.	Energy from fat, energy from carbohydrates and proteins, dietary fibres, red meat, processed meat, vegetables, fruit, alcohol intake, BMI, physical activity, smoking, education, lean and fatty fish.	–	European Commission and the International Agency for Research on Cancer, Danish Cancer Society (Denmark); Ligue Contre le Cancer, Institut Gustave Roussy, Mutuelle Générale de l'Education Nationale, Institut National de la Santé et de la Recherche Médicale (France); Deutsche Krebshilfe, Deutsches Krebsforschungszentrum and Federal Ministry of Education and Research (Germany); Ministry of Health and Social Solidarity, Stavros Niarchos Foundation and Hellenic Health Foundation (Greece); Italian Association for Research on Cancer, Compagnia di San Paolo, and National Research Council (Italy); Dutch Ministry of Public Health, Welfare and Sports, Netherlands Cancer Registry, LK Research Funds, Dutch Prevention Funds, Dutch Zorg Onderzoek Nederland, World Cancer Research Fund, Statistics Netherlands (The Netherlands); ERC-2009-AdG 232 997 and Nordforsk, Nordic Centre of Excellence programme on Food, Nutrition and Health (Norway); Health Research Fund, Regional Governments of Andalucìa, Asturias, Basque Country, Murcia and Navarra, ISCIII RETIC (Spain); *(continued)*

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											(Continued) Swedish Cancer Society, Swedish Scientific Council and Regional Government of Skåne and Västerbotten (Sweden); Cancer Research UK, Medical Research Council (UK)
Fehily et al. 1994 *(15)*, UK, Caerphilly IHD Study	45–59	100	665	21 new-onset IHD events	5	PUFA Intake (*blood sample after overnight fast and 7-day weighted food intake records*)	Q3 vs Q1 (%E), case vs control (g/100 g total fatty acids)	Events were retrieved in three ways: comparing baseline and follow-up ECGs, hospital records and deaths (not indicated how deaths were reported).	Age, BMI and smoking.	–	Not reported
Gammelmark et al. 2016 *(16)*, Denmark, Danish Cohort Study Diet, Cancer and Health	50–64	48	57 053	3089 incident MI	17	n-3 PUFA intake (*validated SQFFQ*)	Q5 vs Q1 (>28 g/day vs 0–8 g/day)	Events were retrieved using the Danish National Patient Registry and/or the Danish Causes of Death Registry.	Smoking, BMI, waist circumference, physical activity, alcohol intake, educational level, menopausal status, history of diabetes mellitus, hypertension and hypercholesterolaemia, total energy intake, intake of fruits and vegetables and intake of nuts.	–	The Danish Heart Association, Hertha Christensen Foundation, Danish Cancer Society
Gao et al. 2011 *(17)*, Singapore, Singapore Longitudinal Aging Studies	≥55	35/36 (from table)	1475	Cognitive decline	2	Daily long-chain n-3 PUFA supplement intake (*self-reported single question*)	Intake vs no intake of PUFA supplement	Events were recorded by comparing baseline MMSE scores to follow-up MMSE score. A drop of at least two MMSE points was defined as cognitive decline.	Age, gender, education, number of medical comorbidities, presence of vascular risk factors/diseases, smoking, alcohol drinking, depression, apolipoprotein E status (e4 allele carriers vs noncarriers), nutritional status, level of leisure activities, baseline MMSE and length of follow-up.	–	Biomedical Research Council, Agency for Science, Technology and Research in Singapore

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Gronroos et al. 2012 *(18)*, USA, Atherosclerosis Risk in Communities Cohort	45–64	48–55 (from table)	14 222 (fish analysis), 3817 (plasma DHA and EPA)	1604 AF events	17.6 (average)	Intake of fish and fish-derived EPA and DHA (*FFQ and plasma samples*)	Q4 vs Q1 (>2 vs 0 servings of fish per week), Q4 vs Q1 (% total fatty acid DHA+EPA)	Events were reported using three sources: hospital discharge notes, ECGs performed during follow-up exams and death certificates.	Centre, age, race, sex, energy intake, BMI, education, exercise levels, smoking status and amount, alcohol intake, LDL cholesterol, HDL cholesterol, use of cholesterol-lowering medications, systolic BP, use of antihypertensive medications, diabetes, CHD, and ECG-defined left ventricular hypertrophy.	–	National Heart, Lung, and Blood Institute, American Heart Association
González et al. 2000*(19)*, Spain, EPIC – Spain	29–69	44	11 883	Association between BMI and fat intake accounted for <1% of variance	0	PUFA intake (*validated diet history questionnaire*)	Obese vs overweight vs normal vs underweight (%E – multi linear regression model)	Events were recorded at follow-up appointments (height and weight measurements).	Age, housework, sport, other leisure activities, work activity, smoking, education level, parity, menopause and diet adjusted.	–	Europe Against Cancer Programme of the European Union, Health Research Fund, Spanish Ministry of Health
Haraldsdottir et al. 2017 *(20)*, Iceland, Age, Gene/ Environment Susceptibility Reykjavik Cohort Study and Reykjavik Study	54	0	9340	744 incidence breast cancer	27.3	Fish consumption (*validated FFQ*)	Q3 vs Q1 (>4 vs <2 portions per week)	Events were ascertained using the Icelandic Cancer Registry and the Directorate of Health.	Age upon entry, education, family history of breast cancer, BMI in midlife, age at first child, age at menarche, intake of milk, rye, meat, fish liver oil, salted/smoked fish in adolescence and fish and alcohol in midlife.	–	National Institutes of Health (Iceland), Intramural Research Program of the National Institute on Aging, the Icelandic Heart Association, and the Icelandic Parliament, Icelandic Centre for Research, Public Health Fund of the Icelandic Directorate of Health

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Harding et al. 2004 *(21)*, UK, EPIC-Norfolk	40–78	45	21 472	414 incident cases of diabetes	7	Polyunsaturated fat:saturated fat ratio (*SQFFQ*)	Q5 vs Q1 (>0.666 vs. <0.326	Events were reported by self-report of diabetes from the first and second follow-up health and lifestyle questionnaires, self-report of diabetes-specific medication, diabetes medication brought to a follow-up visit and an HbA1c level >7% at either the baseline or follow-up health check; hospital admissions data for EPIC-Norfolk participants were screened to identify those who were admitted to a hospital for a diabetes-related condition. Office of National Statistics death certificate data with coding for diabetes was also used.	Total energy intake, age, sex, family history of diabetes, smoking, physical activity, total fat, total protein, alcohol consumption, BMI and waist:hip ratio.	–	Cancer Research Campaign, the Medical Research Council, the Stroke Association, the British Heart Foundation, the Department of Health, the Commission of the European Union's Europe against Cancer Programme, and the Department for Environment, Food, and Rural Affairs

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Hu et al. 2002 *(22)*, USA, Nurses' Health Study	30–55	0	5103	362 incident cases of CHD (141 CHD deaths and 221 nonfatal MIs), 468 deaths from all causes (161 from CHD or stroke, 172 from cancer and 135 from other causes)	16	Average n-3 fatty acids, average frequency of fish intake (*SQFFQ*)	Q5 vs Q1 (g/day) and (≥5/week vs <1/month)	Events were self-reported and confirmed by medical records. Deaths were identified from state vital records and the National Death Index or reported by next of kin and the postal system.	Age, smoking status, BMI, alcohol intake, parental history of MI, menopausal status and postmenopausal hormone use, moderate-to-vigorous activities, usual aspirin use, multivitamin supplement use, vitamin E supplement use, history of hypertension, hypercholesterolaemia, duration of diabetes, hypoglycaemic medication, TFA, the ratio of polyunsaturated fat to saturated fat, and dietary fibre.	–	National Institutes of Health, American Heart Association Established Investigator Award
Hu et al. 1998 *(23)*, USA, Nurses' Health Study	34–59	0	86 016	1255 major coronary disease events (861 cases of nonfatal MI and 394 cases of fatal CHD)	14	Frequency of nut consumption (*61-Item Dietary Questionnaire*)	Q3 vs Q1 (≥2–4 vs almost never, consumption of nuts)	Events were reported through review of medical records by physicians blinded to risk factors. Deaths were reported by families and postal officials and through the National Death Index.	Age, time period, BMI, cigarette smoking, history of hypertension, history of diabetes and hypercholesterolaemia, menopausal status, parental history of MI before 60 years of age, use of multivitamins, use of vitamin E supplements, alcohol consumption, aspirin use, vigorous exercise >1/week and total energy intake.	–	US National Institutes of Health

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Jakobsen et al. 2004 *(24)*, Denmark, Diet, Cancer and Health follow-up study	30–71	44	3,686	326	16	Intake of PUFA, intake at different levels of intake of carbohydrates (*validated SQFFQ*)	5% increase in PUFA replacing carbohydrate	Events were reported through a self-administered questionnaire. The method was verified within the cohort.	Sex, age, BMI at recruitment, waist circumference at recruitment, education, smoking status, leisure-time physical activity, alcohol consumption, and intakes of proteins, long-chain n-3 PUFA and energy.	–	Danish Council for Strategic Research, European Commission as an Integrated Project under the 6th Framework Programme
Jakobsen et al. 2009 *(25)*, 11 American and European cohort studies	37–76 (from table)	Not listed	344 696	5249 coronary events and 2155 coronary deaths	10	PUFA, n-3 and n-6 fatty acids substitution for SFAs (*validated FFQ or dietary history interview*)	5% increase in PUFA replacing carbohydrate	Events were ascertained using standardized criteria.	Intake of MUFA, PUFA, TFA, protein, and carbohydrates expressed as percentages of total energy intake, total energy intake, age at baseline, calendar year in which the baseline questionnaire was administered, smoking, BMI, physical activity, highest attained education level, alcohol intake, history of hypertension, energy-adjusted quintiles of fibre intake and cholesterol intake.	–	National Heart, Lung, and Blood Institute, National Institutes of Health, the Danish Heart Foundation, Female Researchers in Joint Action program from the Danish Medical Research Council
Kromhout et al. 1995 *(26)*, Netherlands, longitudinal health survey (by one of the authors)	64–87	50	272	58 CHD, 67 cancer and 187 all-cause mortality	17	Consumption of fish (*dietitian estimations based on self-report, postal area and groceries*)	Fish vs no fish	Events reported through review of death certificates.	Age and smoking.	–	Netherlands Nutrition Council, Netherlands Prevention Foundation
Kushi et al., 1985 *(27)*; USA–Ireland (Ireland–Boston Heart Study)	40–60	100	1001	110 CHD deaths	23	Total PUFA (*Burke diet history*)	Top 3rd vs bottom 3rd	Death certificates for all decedents reviewed and adjudicated according to International Classification of Diseases-9.	Age, cohort, systolic BP, serum cholesterol, left ventricular hypertrophy, smoking, alcohol and cohort.	6	NIH, Irish Heart Foundation, Harvard School of Public Health

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Kyrozis et al. 2009 *(28)*, Greece, EPIC-Greece cohort	≥60	38	610	All participant evaluat-ed using 15-point generalized depression scale;	13	PUFA intake (*validated SQFFQ*)	Per 1-SD increase in PUFA (≈6.9 g/d)	Events were retrieved using the Geriatric Depression Scale, as well as assessments of cognitive function (MMSE) and medical variables (diagnosed with cancer, MI or stroke).	Gender, age, marital status, years of education, height, BMI, physical activity, smoking, alcohol intake, coffee intake, energy daily intake, hypertension at baseline, diabetes at baseline, MMSE score follow-up, cancer at follow-up, cardiac disease at follow-up, cerebrovascular disease at follow-up, total lipids, PUFA, monounsaturated lipids, saturated lipids, fish and seafood, seed oils and olive oil.	–	Europe Against Cancer Program of the European Commission, the Greek Ministry of Health, the Greek Ministry of Education, an unrestricted grant to the University of Athens in honour of ''Vasilios and Nafsika Tricha,'' the Hellenic Health Foundation, European Social Fund and National Resources
Larsson et al. 2017 *(29)*, Sweden, Cohort of Swedish Men and the Swedish Mammography Cohort	45–83	53	72 984	6095 incident AF	12	Fish consumption, n-3 PUFA (*validated FFQ*)	Q5 vs Q1 (>0.567 g/day vs <0.243 g/day)	Events were identified using the Swedish National Patient Register.	Age, sex, education, smoking, history of hypertension, diabetes, BMI, walking/bicycling, family history of MI, alcohol consumption, and total energy intake.	–	Swedish Research Council, Karolinska Institutet's Strategic Research Program
Larsson et al. 2012 *(30)*, Sweden, Swedish Mammography Cohort	49–83	0	34 670	1680 stroke events (1310 cerebral infarctions, 233 haem-orrhagic strokes, and 137 unspecified strokes)	Mean: 10.4	Intake of PUFA, ALA, long-chain n-3 PUFA, n-6 PUFA (*validated FFQ*)	Q5 vs Q1 (g/day)	Events were retrieved using the Swedish Hospital Discharge Registry. Information on dates of death for deceased participants was obtained from the Swedish Death Registry.	Age, smoking status and pack-years of smoking, education, BMI, total physical activity, history of hypertension, history of diabetes, aspirin use, family history of MI, and intakes of alcohol, protein, and dietary fibre.	–	Swedish Council for Working Life and Social Research and Karolinska Institutet

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Li et al. 2011 *(31)*, USA, National Health and Nutrition Examination Survey	25–74	40	5068	237 women and 562 men, severely depressed mood	11	Frequency of fish consumption (*3 month FFQ*)	Q3 vs Q1 (>1 serving per week vs <1 serving per week)	Events were reported at follow-up using the Center for Epidemiologic Studies Depression Scale questionnaire. Severe depressed mood was defined as score ≥22 and/or taking antidepression medicine.	Race/ethnicity, education attainment, family income level, marital status, types of residence area, occupation, employment status, BMI, alcohol drinking, cigarette smoking, serum total cholesterol, total dietary energy intake, saturated fatty intake, frequency of eating fruit and vegetables assessed at the baseline survey, and self-evaluated health status and history of major physical diseases (cancer, diabetes, stroke and heart attack).	–	National Center for Health Statistics; National Institute on Aging; National Cancer Institute; National Center for Chronic Disease Prevention and Health Promotion; National Institute of Child Health and Human Development; National Heart, Lung, and Blood Institute; National Institute on Alcohol Abuse and Alcoholism; National Institute of Mental Health; National Institute of Diabetes and Digestive and Kidney Diseases; National Institute of Arthritis and Musculoskeletal and Skin Diseases; National Institute of Allergy and Infectious Diseases; National Institute of Neurological and Communicative Disorders and Stroke; and US Department of Agriculture

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Lopez et al. 2011 *(32)*, USA, Rancho Bernardo Cohort	67–100	44–57 (depending on tertile)	266	42 had dementia and 30 had possible or probable Alzheimer's Disease	5	Plasma DHA (*nonfasting blood sample*) and dietary DHA (*validated FFQ*)	Q3 vs Q1	Failure of three baseline assessments determined participants at risk of developing dementia. Tests included MMSE, Heaton Visual Reproduction Test, Category Fluency Assessment, Buschke–Fuld Selective Reminding Test. These participants underwent extensive neuropsychological testing, neurological and general medical examinations, laboratory tests and computed tomography evaluation of the brain. Results aided neurologist in categorizing participants in diagnostic groups.	Age, sex, apolipoprotein E status, education and history of stroke.	–	National Institute of Diabetes and Digestive and Kidney Diseases, National Institute on Aging, National Institutes of Health/National Institute of Aging
Meyer et al. 2001 *(33)*, USA, Iowa Women's Health Study	55–69	0	35 988	1890 incident diabetes	11	Polyunsaturated fats, long-chain n-3 fatty acids (*validated FFQ*)	Q5 vs Q1 (g/day)	Events were self-reported and validated by a physician.	Age, smoking, alcohol consumption, BMI, waist:hip ratio, physical activity, demographic factors and dietary magnesium and cereal fibre.	–	National Cancer Institute (USA)
Morris et al. 2003 *(34)*, USA, Chicago Health and Aging Project	65-94	»38	815	131 cases of Alzheimer's Disease	6	Weekly frequency of fish consumption, n-3 fatty acids, DHA, EPA, ALA (*Harvard FFQ*)	Q5 vs Q1 (g/day)	Events were reported by comparing baseline results to follow-up from the East Boston Tests of Immediate and Delayed Recall, MMSE and Symbol Digit Modalities Test.	Age, sex, race (black or white), education (years), APOE–ϵ4 status (any ϵ4 allele vs none), and the interaction between race and APOE-ϵ4	–	National Institute on Aging

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Mozaffarian et al. 2003 *(35)*, USA, Cardiovascular Health Study (CHS)	≥65	≈72.5	3910	247 IHD deaths (48 primary and 100 secondary arrhythmic deaths) and 363 incident nonfatal MIs	9.3 (mean)	Amount and type of fish consumed (*validated FFQ*)	Q4 vs Q1 (≥3 servings per week vs <1 servings per month)	Events identified by annual follow-up and telephone interviews validated by centralized committee using interviews, medical records, death certificates, medical examiner forms, hospitalization paperwork.	Age, gender, education, diabetes, current smoking, pack-years of smoking, tuna/other fish, fried fish/fish sandwich consumption, BMI, systolic BP, LDL cholesterol, HDL cholesterol, triglycerides, C-reactive protein, and intake of saturated fat, alcohol, beef/pork, fruits and vegetables.	–	National Heart, Lung, and Blood Institute PI Salary Support: VA Health Services Research and Development fellowship at the VA Puget Sound Health Care Center
Owen et al. 2016 *(36)*, Australia, Australian Diabetes, Obesity and Lifestyle Study	51	45	11 247	–	13	n-3 PUFA, n-6 PUFA, fish intake (*validated SQFFQ*)	Q5 vs Q1 (g)	Events were recorded using the Australian National Death Index.	Age, sex, previous CVD, education, exercise, diabetes, total dietary energy and smoking.	–	Australian National Health and Medical Research Council, Australian Government Department of Health and Ageing, Abbott Australasia Pty Ltd, Alphapharm Pty Ltd, Amgen Australia, AstraZeneca, Bristol-Myers Squibb, City Health Centre Diabetes Service Canberra, Department of Health and Community Services Northern Territory, Department of Health and Human Services Tasmania, Department of Health New South Wales, Department of Health Western Australia, Department of Health South Australia, Department of Human Services Victoria, Diabetes Australia, Diabetes Australia Northern Territory, Eli Lilly Australia, Estate of the Late Edward Wilson, GlaxoSmithKline, Jack

(continued)

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											(Continued) Brockhoff Foundation, Janssen-Cilag, Kidney Health Australia, Marian & FH Flack Trust, Menzies Research Institute, Merck Sharp & Dohme, Novartis Pharmaceuticals, Novo Nordisk Pharmaceuticals, Pfizer Pty Ltd, Pratt Foundation, Queensland Health, Roche Diagnostics Australia, Royal Prince Alfred Hospital, Sydney, Sanofi Aventis, Sanofi-Synthélabo, Victorian Government Operational Infrastructure Support Program, National Health and Medical Research Council Fellowship
Owen et al. 2016 *(36)*, Australia, Australian Diabetes, Obesity and Lifestyle Study	25–84	45	11 247	1265 deaths , 277 CVD deaths	12.6 median	n-3 and n-6 median PUFA intake (*SQFFQ*)	Q5 vs Q1 (g)	Vital status and causes of death were collected by death registry linkage.	Age, sex, previous CVD, education, exercise, diabetes, total dietary energy and smoking.	–	Australian National Health and Medical Research Council, Australian Government Department of Health and Ageing, Abbott Australasia Pty Ltd, Alphapharm Pty Ltd, Amgen Australia, AstraZeneca, Bristol-Myers Squibb, City Health Centre Diabetes Service Canberra, Department of Health and Community Services Northern Territory, Department of Health and Human Services Tasmania, Department of Health New South Wales, Department of Health Western Australia, Department of Health South Australia, Department of Human Services Victoria, *(continued)*

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											(Continued) Diabetes Australia, Diabetes Australia Northern Territory, Eli Lilly Australia, Estate of the Late Edward Wilson, GlaxoSmithKline, Jack Brockhoff Foundation, Janssen-Cilag, Kidney Health Australia, Marian & FH Flack Trust, Menzies Research Institute, Merck Sharp & Dohme, Novartis Pharmaceuticals, Novo Nordisk Pharmaceuticals, Pfizer Pty Ltd, Pratt Foundation, Queensland Health, Roche Diagnostics Australia, Royal Prince Alfred Hospital, Sydney, Sanofi Aventis, Sanofi-Synthélabo, Victorian Government Operational Infrastructure Support Program, National Health and Medical Research Council Fellowship
Patel et al. 2010 *(37)*, England, EPIC, Norfolk study	40–79	53	383	199 T2DM	≈8 to 12 y	PUFA n-3: ALA (18:3 n-3), EPA (20:5 n-3), DPA (22:5 n-3), DHA (22:6 n-3) PUFA n-6: LA (18:2 n-6), c-LA (18:3 n-6), eicosadienoic acid (20:2 n-6), dihomo-c-LA (20:3 n-6), ARA (20:4 n-6), adrenic acid (22:4 n-6) (*validated FFQ*)	Q3 vs Q1	Events were ascertained by using multiple sources: self-report of a physician's diagnosis of diabetes or diabetes medication on any of the follow-up health and lifestyle questionnaires, or diabetes medication brought to the follow-up health check visit, record linkage used to trace each participant for diabetes diagnosis. Diabetes-related deaths were flagged by linkage to the National Death Registry.	Age, sex, family history of diabetes, BMI, smoking status, physical activity and alcohol intake.	–	Medical Research Council UK and Cancer Research UK, European Union; Stroke Association; British Heart Foundation; Department of Health; Food Standards Agency; Ministry of Agriculture, Fisheries and Food; Wellcome Trust; InterAct project

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Pietinen et al. 1997 *(38)*, Finland, Finish α-Tocopherol, Beta-Carotene Cancer Prevention Study	50–69	100	21 930	1399 major coronary events (first nonfatal MI), 635 coronary deaths	6	PUFA, LA, linolenic acid, n-3 fish fatty acids (*validated FFQ*)	Q5 vs Q1 (g)	National hospital discharge, registered diagnosis and hospital and pathology reports; deaths confirmed through national population register.	Age, treatment group, smoking, BMI, BP, energy, alcohol, fibre, education and physical activity.	8	National Cancer Institute (USA), Academy of Finland
Rhee et al. 2017 *(39)*, USA, Women's Health Study	54	0	39 876	1941 CVD	11	Intakes of tuna and dark fish, ALA and EPA+DHA (*validated SQFFQ*)	Q5 vs Q1 (%E)	Events were self-reported on incident physician diagnoses of cardiovascular events. Medical records were obtained to verify all cardiovascular events. Deaths were confirmed by review of autopsy reports, death certificates, medical records, or information obtained from next of kin or family members.	Randomized treatment assignment, age, BMI, smoking, alcohol intake, physical activity, oral contraceptive use, HRT, multivitamin use, total energy intake, family history of MI, and baseline history of hypertension, high cholesterol, and diabetes; dietary fibre, fruits and vegetables, trans fat, sodium, and ratio of PUFA to saturated fat	–	NIH (USA)
Sala-Vila et al. 2016 *(40)*, Spain, PREDIMED trial	67	42.5	7202	431 deaths occurred (including 104 CVD, 55 CHD, 32 sudden cardiac death, 25 stroke)	5.9	Long-chain n-3 PUFA, ALA (*validated SQFFQ*)	Control vs MedDiet + nets vs MedDiet + extra virgin olive oil (assigned intervention)	Endpoints were ascertained using yearly questionnaires and examinations for all participants, contact with primary care physicians, yearly review of medical records, and linkage to the National Death Index. Medical records of deceased participants were requested.	Age, sex, BMI, current smoking status, physical activity, total energy intake; history of diabetes, hyperlipidaemia, hypertension; alcohol intake, fibre, vegetables, fruits, red meat, and meeting the International Society for the Study of Fatty Acids and Lipids recommendation of EPA and DHA consumption for primary cardiovascular prevention.	–	Instituto de Salud Carlos III (Spanish Ministry of Economy), Centro Nacional de Investigaciones Cardiovasculares, Spanish Ministry of Science and Innovation, California Walnut Commission

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Sanchez-Villegas et al. 2007 *(41)*, Spain, SUN Cohort	Not indicated	Not indicated	7903	173 cases of depression, 335 cases of anxiety, and 4 cases of stress	2	Mean consumption of n-3 fatty acids and fish consumption (*validated FFQ*)	Q5 vs Q1 (g/day)	Events were self-reported physician diagnosis and medication prescription.	Age, sex, incapacitating disease, energy intake, physical activity during leisure time, and change in physical activity since baseline.	–	Spanish Ministry of Health, Navarra Regional Government
Sanchez-Villegas et al. 2011 *(42)*, Spain, SUN Cohort	37.5 (SD: 11.5)	42	12 059	657 new cases of depression	10	Polyunsaturated fat intake (*validated FFQ*)	Q5 vs Q1 (19.0 vs 9.3 g/day)	Events were self-reported diagnosis by a doctor or use of antidepressant medication.	Sex, age, smoking, leisure-time physical activity, total energy intake, BMI and adherence to the Mediterranean Dietary Pattern.	–	Spanish Government Instituto de Salud Carlos III, Fondo de Investigaciones Sanitarias and the Navarra Regional Government
Shen et al. 2011 *(43)*, USA, Framingham Heart Study	62 ± 10	44	4526	296 incident AF (177 men, 119 women)	4	Mean n-3 PUFA intake and weekly total fish and dark fish intake (*validated FFQ*)	Q4 vs Q1 (460 vs 80 mg/day) and Q3 vs Q1 (>4 servings/week vs never or <1 serving/week)	Events were recorded during interim medical evaluations at hospitals and by external clinicians. All cases were reviewed by Framingham Health Study cardiologists. Review included ECGs and outside records.	Age, sex, BMI, systolic BP, hypertension treatment, ECG, PR interval, significant heart murmur, and heart failure.	–	National Heart, Lung, and Blood Institute, National Institute of Diabetes and Digestive and Kidney Diseases, US Department of Agriculture Research, American Heart Association and National Institutes of Health
Smith-Warner et al. 2001 *(44)*, USA, Pooling Project	28–90 (widest range), varied depending on study	0	351 821	7329 incident invasive breast cancer cases		PUFA intake (*validated FFQ*)	Q4 vs Q1 (pooled analysis), per 5% increases in energy from total fat and specific fat subtypes	Event reporting varied depending on the study included.	%E from protein, %E from alcohol, age at menarche, parity, age at birth of first child, menopausal status at diagnosis, postmenopausal hormone use, oral contraceptive use, history of benign breast disease, family history of breast cancer, smoking status, education, BMI, BMI–menopausal status at diagnosis interaction term, height, fibre intake and energy intake.	–	National Institutes of Health, Cancer Research Foundation of America/American Society of Preventive Oncology, American Cancer Society

SOURCE (COUNTRY)	AGE (YEARS)	SEX (% MEN)	NUMBER OF PARTICIPANTS	NUMBER OF EVENTS	FOLLOW-UP (YEARS)	EXPOSURES ASSESSED	EXPOSURE VS CONTRAST	OUTCOME VALIDATION	ADJUSTMENT FOR CONFOUNDERS	NOS SCORE	FUNDING
Solfrizzi et al. 2006 *(45)*, Italy, Italian Longitudinal Study on Aging	65–84	55	95 (completed final survey), 578 (met inclusion criteria)	Mini-Mental State Examination (MMSE) score decline, assessed between repeated examinations	8.5	PUFA intake (*validated FFQ*)	Change in cognitive function vs baseline	MMSE previously validated in each study center against DSM-III-R15 clinical diagnosis of dementia; cutoff point of 23/24 has a sensitivity of 95% and a specificity of 90% (referenced in Solfrizzi et al., 1999)	Sex, age, education, Charlson comorbidity index, BMI, MMSE baseline score, and total energy intake at baseline.	–	Italian Longitudinal Study on Aging, Associazione per la Formazione e la Ricerca in Geriatria
Sonestedt et al. 2007 *(46)*, Sweden, Malmö Diet and Cancer	50–73	0	12 781	428 postmenopausal incident breast cancer	9.5 (average)	n-6 fatty acids (*validated FFQ*)	Q5 vs Q1 14.1 vs 6.6 g/day)	Events retrieved from Swedish Cancer Registry and Southern Swedish Regional Cancer Registry.	Total energy, age, method version, diet interviewer and season.	–	Swedish Cancer Society, Swedish Medical Research Council, European Commission and City of Malmö
Strom et al. 2012 *(47)*, Denmark, Danish National Birth Cohort	15.7–46.9	100	48 627	577 total cardiovascular events (328 hypertensive disease, 146 cerebrovascular disease, 103 IHD)	12	Fish intake and long-chain n-3 fatty acids intake (*FFQ*)	>30 g/day vs 0–3 g/day Q5 vs Q1 (0.73 vs 0.06 median g/day)	Events retrieved through Danish National Patient Registry and Danish Register of Causes of Death.	Physical activity, prepregnant BMI, smoking, school, cohabitant status, parity, occupation, prepregnant alcohol intake, total energy intake, intake of saturated fat, dietary fibre, and TFA.	–	Faroese Research Council, Fisheries Research Fund of the Faroe Islands, European Union Sixth Framework SEAFOODplus Integrated Research Programme, European Union Sixth Framework Programme Education and Research Networking Evolution Study, and Nordic Working Group on Fishery Research
van Dam et al. 2002 *(48)*, USA, Health Professionals Follow-Up Study	40–75	100	42 504	1321 incident T2DM	12	LA, ALA, oleic acid, long-chain n-3 fat (*validated FFQ*)	Q5 vs Q1 (%E)	Events self-reported, validated with sample of medical records.	Age, total energy intake, time period, physical activity, cigarette smoking, alcohol consumption. Hypercholesterolaemia, hypertension, family history of T2DM, intake of cereal fibre, intake of magnesium and BMI.	–	National Institutes of Health (USA), American Diabetes Association

SOURCE (COUNTRY)	AGE (YEARS)	SEX (% MEN)	NUMBER OF PARTICIPANTS	NUMBER OF EVENTS	FOLLOW-UP (YEARS)	EXPOSURES ASSESSED	EXPOSURE VS CONTRAST	OUTCOME VALIDATION	ADJUSTMENT FOR CONFOUNDERS	NOS SCORE	FUNDING
van Gelder et al. 2007 *(49)* Netherlands, Zutphen Elderly Study	70–89	100	210	Men who did not consume fish had a cognitive decline of 1.2 points, four times the decline in men who consumed fish	5	Fish consumption, DHA+EPA intake (*validated cross-check)dietary history*)	Q3 vs Q1 (g/day)	MMSE was used to identify cognitive decline throughout follow-up period.	Age, education, alcohol consumption, smoking status, physical activity, energy intake and baseline cognitive functioning.	–	European Union (to one author) for the Healthy Ageing: Longitudinal study in Europe
Velie et al. 2000 *(50)*, United States, Breast Cancer Detection Demonstration Project	41–91	0	40 022	996 breast cancer	5.3 (average), 14 max.	Oleic acid, LA (*validated FFQ*)	Q5 vs Q1	Event status obtained from self-report, death certificates, pathology reports and relatives.	Total energy, BMI, height, family history of breast cancer, birth, educational level, alcohol use, age at menarche, and history of benign breast disease	–	National Cancer Institute (USA)
Vercambre et al. 2010 *(51)*	76–82	0	4809	518 DECO score <33; 716 4-IADL score 0; 268 both declines	16 check	PUFA n-6 fatty acids, n-3 fatty acids, ALA, long-chain n-3, n-6:n-3 fatty acids ratio (*validated FFQ*)	Q3 vs Q1 (g)	Events were self-reported and were confirmed using a 4-IADL score telephone interview.	Age, education level, BMI, physical activity, daily energy intake, smoking status, supplement of vitamin D, supplement of other vitamins, use of post-menopausal hormones, history of depression, history of cancer, history of CHD, history of stroke, history of diabetes mellitus, history of hypertension and history of hypercholesterolaemia.	–	French League against Cancer, the European Community, 3M Company, Mutuelle Générale de l'Éducation Nationale, French Institute of Health and Medical Research, Gustave Roussy Institute, several general councils in France, Statlife Company and Association Nationale de la Recherche Technique

SOURCE (COUNTRY)	AGE (YEARS)	SEX (% MEN)	NUMBER OF PARTICIPANTS	NUMBER OF EVENTS	FOLLOW-UP (YEARS)	EXPOSURES ASSESSED	EXPOSURE VS CONTRAST	OUTCOME VALIDATION	ADJUSTMENT FOR CONFOUNDERS	NOS SCORE	FUNDING
Virtanen et al. 2008 *(52)*, USA, Health Professionals Follow-Up Study	40–75	100	40 230	9715 major chronic disease events occurred, including 3639 CVD events, 4690 cancers, and 1386 deaths from non-traumatic causes.	18	EPA+DHA (*validated FFQ*)	Q5 vs Q1 (≥ 0.6 vs <.05 g/day)	Events were self-reported, confirmed with medical records by blinded physicians. Deaths were ascertained from relatives, postal authorities, or the National Death Index, and cause of death was classified according to medical records, death certificates, and autopsy findings.	Age, BMI, smoking, physical activity; history of diabetes, hypertension, or hypercholesterolaemia; first-degree family history of MI before age 60 y, or of colon cancer; use of aspirin or multivitamin supplements; glycaemic load; and intakes of protein, fibre, TFA, saturated fat, n-6 fatty acids, ALA, red meat, total calories and alcohol.	–	National Institutes of Health, Finnish Cultural Foundation, Helsingin Sanomat Centennial Foundation, Finnish Foundation for Cardiovascular Research, Yrjö Jahnsson Foundation, and University of Kuopio
Virtanen et al. 2014 *(53)*, USA, Kuopio IHD Risk Factor study	42–60	100	2212	422 incident T2DM	20	EPA, DPA, ALA, EPA+DHA+DPA (*serum PUFA*)	Q4 vs Q1 (%)	Events assessed by self-administered questionnaires, fasting and 2-hour oral glucose tolerance test blood glucose measurement at re-examination after the baseline, record linkage to hospital discharge registry, and reimbursement register on diabetes medication expenses.	Age, examination year, BMI, family history of T2DM, smoking, education years, leisure-time physical activity, intake of alcohol, and serum LA.	–	Not listed in this publication
Wiberg et al. 2006 *(54)*, Sweden, Uppsala Longitudinal Study of Adult Men	50–83	100	2313	421 stroke or transient ischaemic attack	32 (average 29.3)	LA, gamma-linolenic acid, ALA, ARA, DHA (*serum cholesterol ester levels*)	Stroke outcome vs baseline	Events identified via hospital discharge records and cause of death registries.	Antihypertensive, antidiabetic and lipid-lowering drugs, hypertension, diabetes, AF, CVD, metabolic syndrome, serum cholesterol, smoking and physical activity.	–	Medical Faculty at Uppsala University, Uppsala Geriatric Fund, and Swedish Heart Lung Foundation

SOURCE (COUNTRY)	AGE (YEARS)	SEX (% MEN)	NUMBER OF PARTICIPANTS	NUMBER OF EVENTS	FOLLOW-UP (YEARS)	EXPOSURES ASSESSED	EXPOSURE VS CONTRAST	OUTCOME VALIDATION	ADJUSTMENT FOR CONFOUNDERS	NOS SCORE	FUNDING
Yaemsiri et al., 2013 *(55)*, USA, Women's Health Initiative Observational Study	50–79	0	1928 (964 matched pairs)	964 cases of incident ischaemic stroke (96 athero-thrombotic strokes, 250 lacunar strokes, 209 cardi-oembolic strokes, 42 ischaemic strokes of other determined cause, 366 ischaemic strokes of undeter-mined cause, one was miss-ing subtype informa-tion)	10	18:3 n-3, 20:4 n-3, 20:5 n-3, 22:5 n-3, 22:6 n-3, 18:2 n-6, 18:3 n-6, 20:2 n-6, 20:3 n-6, 20:4 n-6, 22:4 n-6, 22:5 n-6 (*serum fatty acids*)	1 SD increment in serum fatty acids	Events were self-reported, confirmed by physician through medical charts, brain imaging or death certificates.	Age, race, time to follow-up, BMI, smoking, diabetes mellitus, aspirin use, total cholesterol:HDL-C ratio, normalized triglycerides, systolic BP and antihypertensive medication use.	–	National Heart, Lung, and Blood Institute, National Institutes of Health, US Department of Health and Human Services, National Institute of Neurological Disorders and Stroke, American Heart Association
Yary et al. 2017 *(56)*, Finland, Kuopio IHD Risk Factor Study	42–60	100	2179	58 hospital discharge diagnosis of depression	21.5	Dihomo-gamma-linolenic acid (serum fatty acids)	–	Events were identified at baseline using the 18-item Human Population Laboratory Depression Scale and were obtained during follow-up using linkage to the National Hospital Discharge Register.	Age, examination year, smoking status, marital status, education, alcohol intake, leisure-time physical activity, BMI, total energy intake; history of CVDs, diabetes, mental illness; percentages of linolenic acid, EPA, DHA, ALA, gamma-linolenic acid, ARA; C-reactive protein (mg/L); and depressive symptoms at baseline.	–	Not reported

AdG: advanced grant; AF: atrial fibrillation; ALA: alpha-linolenic acid; APOE: apolipoprotein E; ARA: arachidonic acid; BMI: body mass index; BP: blood pressure; CHD: coronary heart disease; CLA: conjugated linoleic acid; CVD: cardiovascular disease; DECO: Détérioration de Cognition Observée; DHA: docosahexaenoic acid; DPA: docosapentaenoic acid; E: energy; E3N: Etude Epidémiologique auprès de Femmes de la Mutuelle Générale de l'Éducation Nationale; ECG: electrocardiogram; EPA: eicosapentaenoic acid; EPIC: European Prospective Investigation into Cancer and Nutrition; ERC: European Research Council; FFQ: food frequency questionnaire; GP: general practitioner/physician; h: hour; HbA1c: haemoglobin A1C; HDL: high-density lipoprotein; HDL-C: high-density lipoprotein cholesterol; HRT: hormone replacement therapy; IADL: Instrumental Activities of Daily Living; IHD: ischaemic heart disease; ISCIII: Instituto de Salud Carlos III; LA: linoleic acid; LDL: low-density lipoprotein; max.: maximum; MedDiet: Mediterranean Dietary Pattern; MI: myocardial infarction; MMSE: Mini-Mental State Examination; MUFA: monounsaturated fatty acids; NHS: Nurses' Health Study; NIH: National Institutes of Health; NOS: Newcastle-Ottawa Scale; PI: principal investigator; PREDIMED: Prevención con Dieta Mediterránea; PUFA: polyunsaturated fatty acids; Q: question; RETICS: Las Redes Temáticas de Investigación Cooperativa en Salud; SD: standard deviation; SFA: saturated fatty acids; SQFFQ: semiquantitative food frequency questionnaire; SUN: Seguimiento Universidad de Navarra; T2DM: type 2 diabetes; TFA: trans-fatty acids; UK: United Kingdom; US: United States; USA: United States of America; USC: United States Code; VA: Department of Veterans Affairs; y: years.

Table 2. Summary of Newcastle-Ottawa Scale ratings of included prospective cohort studies

REFERENCE	ASSESSMENT ITEM GROUP				COMMENTS
	SELECTION OF STUDY GROUPS (MAX. SCORE 4)	COMPARABILITY OF STUDY GROUPS (MAX. SCORE 2)	OUTCOME OF INTEREST (MAX. SCORE 3)	TOTAL (MAX. SCORE 9)	
Akbaraly et al. 2011 *(57)*	4	2	2	8	Whitehall II Study; registry deaths only
Albert et al. 2002 *(1)*	4	1	3	8	Blood levels; Physicians' Health Study; no adjustment for total energy
Alhazmi et al. 2014 *(2)*	4	1	1	6	Did not control for family history; self-report of diabetes only with 70% confirmation in a subset; attrition rate unclear
Amiano et al. 2014 *(58)*	4	2	3	9	EPIC-Spain (55–60% participation); 10.4 years follow-up; cases validated by study team review
Ananthakrishnan et al. 2014 *(59)*	4	2	3	9	NHS I and II; adjusted for aspirin and NSAID use
Ascherio et al. 1996 *(60)*	4	1	2	7	HPFS; no adjustment for socioeconomic status
Bassett 2016 et al. *(3)*	4	2	3	9	Excluded women with any existing cancers, validated FFQ; no TFA; medical records review, 8.9 years follow-up
Bell 2014 et al. *(61)*	4	2	3	9	VITAL cohort; FFQ validated; excluded people with malabsorptive syndromes; registry cases adjudicated by study team; 4–6 years follow-up
Brostow et al. 2011 *(5)*	4	2	3	9	Singapore Chinese Health Study, population recruitment; validated FFQ; some had CHD at baseline (about 3–5%) but estimates for those without diagnosis at baseline; registry for deaths but "virtually complete"
Brouwer et al. 2006 *(6)*	4	1	3	8	Rotterdam Study; response rate 78% (from all 10 275 inhabitants of Omoord, suburb of Rotterdam); adjusted for age, sex, education, energy, vitamin E; mean age 68 years; 6 years follow-up
Byrne et al. 2002 *(7)*	4	2	3	9	NHS I
Chan et al. 2014 *(62)*	4	1	3	8	EPIC-Europe; 11 countries; all FFQ validation was country specific; did not adjust for NSAID use, ethnicity, aspirin use; 6–13 years follow-up
Chiuve et al. 2012 *(63)*	4	2	3	9	NHS; selecting one profession helps homogenize SES
Chiuve et al. 2015 *(8)*	4	2	3	9	NHS; selecting one profession helps homogenize SES
Cho et al. 2003 *(64)*	4	2	3	9	NHS II; 8 years follow-up; validated FFQ
Colangelo et al. 2009 *(65)*	4	1	2	7	Coronary Artery Risk Development in Young Adults study; validated and reliable FFQ; adjusted for some but not all important confounders; Center for Epidemiological Studies – Depression scale; large proportion excluded (1798/5500) because of no diet data at year 10; 20 years follow-up
De Goede et al. 2011 *(66)*	4	2	3	9	Monitoring Project on Risk Factors for Chronic Diseases Study; validated FFQ published; validated probabilistic determinant model for cause of death (+1); 8–13 years follow-up

REFERENCE	ASSESSMENT ITEM GROUP				COMMENTS
	SELECTION OF STUDY GROUPS (MAX. SCORE 4)	COMPARABILITY OF STUDY GROUPS (MAX. SCORE 2)	OUTCOME OF INTEREST (MAX. SCORE 3)	TOTAL (MAX. SCORE 9)	
De Goede et al. 2012 *(67)*	4	2	3	9	Monitoring Project on Risk Factors for Chronic Diseases Study; validated FFQ published; validated probabilistic determinant model for cause of death (+1); 8–13 years follow-up
Dijkstra et al. 2009 *(68)*	4	1	3	8	Rotterdam Study; response rate 78% (from all 10 275 inhabitants of Omoord, suburb of Rotterdam); adjusted for age, sex, education, energy, vitamin E; mean age 68 years; followed for 6 years
Djoussé et al. 2011 *(10)*	4	2	2	8	WHS; 12.4 years follow-up; good adjustment for covariates, validation of cases by interview; no reports on attrition
Dolocek et al. 1992 *(69)*	4	1	2	7	24-hour recall (x 4); 10.5 years follow-up; no description of dropouts; independent coding of deaths; no adjustment for total energy
Englehart et al. 2012 (Rotterdam) *(70)*	4	1	3	8	Rotterdam Study; response rate 78% (from all 10 275 inhabitants of Omoord, suburb of Rotterdam); adjusted for age, sex, education, energy, vitamin E; mean age 68 years; 6 year follow-up
Esrey et al. 1996 *(71)*	3	0	2	5	No adjustment for socioeconomic status; no family history; attrition
Fehily et al. 1994 *(15)*	4	0	3	7	Had ischaemic heart disease at baseline; no adjustment for socioeconomic status, family history or energy; 5.6% died before 5-year visit or were lost to attrition
Folsom et al. 2004 *(72)*	4	2	1	7	Confirmed cases with interview or survey; unclear dropout
Fretts et al. 2014 *(73)*	4	1	3	8	Did not adjust for total energy intake; 9.3 years follow-up
Gago-Dominguez et al. 2003 *(74)*	4	1	2	7	No adjustment for total energy; cases from registry only (no confirmation)
Gao et al. 2011 *(17)*	4	0	2	6	Singapore Longitudinal Aging Studies (78% response); supplement users (validated by producing supplements); little adjustment; cognitive decline over 1.5 years; high LTFU (n=889/1475)
Gillman et al. 1997 *(75)*	4	0	3	7	24-hour recall, but validated; no adjustment for family history; <2% attrition
Gronroos et al. 2012 *(18)*	4	2	3	9	Atherosclerosis Risk in Communities study; hospital discharge codes validated (positive predictive value = 89%); 17.6 years follow-up; validated FFQ
Harding et al. 2004 *(21)*	4	1	3	8	Did not adjust for socioeconomic status
Hart et al. 2008 *(76)*	4	0	2	6	Country-specific validated FFQ; doctor confirmed diagnosis of registry-identified cases; no description of follow-up; no matching for smoking or socioeconomic status; no adjustment for energy, or aspirin or NSAID use
He et al. 2003 *(77)*	4	1	2	7	HPFS cohort; no adjustment for family history
Holmes et al. 1999 *(78)*	4	2	3	9	NHS I; adjusted for postmenopausal hormone use, height, weight
Hu et al. 1999 *(79)*	4	1	2	7	NHS cohort; no adjustment for socioeconomic status

REFERENCE	ASSESSMENT ITEM GROUP				COMMENTS
	SELECTION OF STUDY GROUPS (MAX. SCORE 4)	COMPARABILITY OF STUDY GROUPS (MAX. SCORE 2)	OUTCOME OF INTEREST (MAX. SCORE 3)	TOTAL (MAX. SCORE 9)	
Hu et al. 2002 *(22)*	4	2	3	9	NHS cohort; no adjustment for socioeconomic status; 16 years follow-up
Inflammatory Bowel Disease in EPIC Study Investigators et al. 2009 *(80)*	4	1	3	8	Inflammatory Bowel Disease in EPIC study; validated FFQ; not fully adjusted
Iso et al. 2006 *(81)*	4	2	2	8	Japan Public Health Center-Based Study (population-based sample; 80% participation rate); FFQ validated and reproducible; 11 years follow-up; no details of LTFU
Jakobsen et al. 2004 *(24)*	4	2	2	8	Excluded people with diabetes; socioeconomic status data from record linkage only
Jarvinen et al. 2006 *(82)*	4	1	2	7	20 years follow-up; random sample of men and women; registry deaths and people who died abroad; validated diet interview with 26 questions about fish; no adjustment for family history; dropout rate unclear
John et al. 2010 *(83)*	4	1	2	7	7-day food diaries, validated with 16-day weighted food records, biomarkers; registry cases reviewed by study gastroenterologist; age-matched (prospective case–control); adjusted for energy, smoking, other fats; 4.2 years follow-up (short)
Joensen et al. 2010 *(84)*	4	1	3	8	Danish Diet, Cancer, and Health study; validated FFQ; no adjustment for total energy; 7.6 years follow-up
Kalmijn et al. (ZES]) 1997 *(85)*	3	2	1	6	ZES (74% response rate to initial invitation); detailed dietary interview; 32% cognitively impaired in 1990 but this study measured cognitive decline; cognitive status assessed by trained research assistants; 3 years follow-up in very old men; 342/476 (29%) had follow-up information
Kalmijn et al. (Rotterdam) 1997 *(86)*	4	1	3	8	Rotterdam Study; response rate 78% (from all 10 275 inhabitants of Omoord, suburb of Rotterdam); adjusted for age, sex, education, energy, vitamin E; mean age 68 years; 6 years follow-up
Kamphuis et al. 2006 *(87)*	4	2	3	9	10 years follow-up; ZES population-based prospective cohort study of healthy elderly men; no LTFU
Kaushik et al. 2009 *(88)*	4	2	3	9	NHS I, NHS II, HPFS
Kim et al. 2006 *(89)*	4	2	3	9	20 years follow-up
Koh et al. 2015 *(90)*	4	2	3	9	Singapore Chinese Health Study, population recruitment; validated FFQ; some had CHD at baseline (about 3–5%) but estimates were made for participants without diagnosis at baseline; registry for deaths "virtually complete"
Knekt et al. 1990 *(91)*	4	1	2	7	Enrolled women had no previous cancer; diet history method was good, with a reproducibility study; only adjusted for age; 20 years follow-up and histological confirmation of registry-identified cases; no dropout description

REFERENCE	ASSESSMENT ITEM GROUP				COMMENTS
	SELECTION OF STUDY GROUPS (MAX. SCORE 4)	COMPARABILITY OF STUDY GROUPS (MAX. SCORE 2)	OUTCOME OF INTEREST (MAX. SCORE 3)	TOTAL (MAX. SCORE 9)	
Kushi et al. 1985 *(27)*	2	0	3	5	Diet history; unclear if free from CHD at baseline; no adjustment for socioeconomic status or energy
Kushi et al. 1992 *(92)*	4	1	3	8	Iowa Womens' Health Study; detailed LTFU data
Laaksonen et al. 2005 *(93)*	4	2	3	9	Random, age-stratified sample from Eastern Finland; coefficient of variation 5%, 4-day diet records; validated deaths; no attrition
Leosdottir et al. 2005 *(94)*	4	1	2	7	No adjustment for family history
Leosdottir et al. 2007 *(95)*	4	1	2	7	No adjustment for family history
Li et al. 2015 *(96)*	4	2	3	9	NHS, HPFS
Linos et al. 2010 *(97)*	4	2	3	9	NHS
Lof et al. 2007 *(98)*	4	2	2	8	No description of LTFU
Lopez et al. 2011 *(32)*	4	1	3	8	Rancho Bernardo Study; adjusted for age, sex, history of stroke, and education
Lucas et al. 2011 *(99)*	4	2	3	9	NHS; 10 years follow-up
Meyer et al. 2001 *(33)*	4	1	1	6	Iowa Women's Health Study; self-reports of diabetes and validation substudy showed 36% over-reported diabetes (poor specificity a threat to validity); no adjustment for family history
Miyagawa et al. 2014 *(100)*	4	1	2	7	Japan, NIPPON DATA80 study; 24 years follow-up; 3-day weighted food records; did not adjust for total energy; record linkage only; LTFU described
Morris et al. 1995 *(101)*	4	1	2	7	Physicians' Health Study; validated and reproducible for fish specifically; did not adjust for total energy; all endpoints reviewed by study physician; 4 years follow-up (>99.7%)
Morris et al. 2003 *(34)*	4	1	3	8	Chicago Health and Aging Project; 74% participation; residents of south-side Chicago; no Alzheimer's disease at baseline; 3.9 years follow-up in participants aged 65–94; follow-up complete; adjusted for age and education but not baseline score or total energy
Mozaffarian et al. 2003 *(35)*	4	1	3	8	Did not adjust for total energy intake; 9.3 years follow-up
Murff et al. 2011 *(102)*	4	2	3	9	SWHS; 92% response; 8.9 years follow-up, high follow-up rate (>97%); cases found in registry verified by hospital chart review
Nagata et al. 2012 *(103)*	4	2	3	9	Takayama Study; validated semiquantitative FFQ (Standard Tables of Food Composition in Japan)
Oh et al. 2005 *(104)*	4	1	2	7	NHS cohort; no adjustment for socioeconomic status
Oomen et al. 2001 *(105)*	3	2	1	6	ZES population-based prospective cohort of healthy elderly men; 10 years follow-up; no LTFU
Owen et al. 2016 *(36)*	4	2	2	8	12.6 years follow-up; mortality data only, adjusted for age, sex and total energy; registry data only; validated FFQ

REFERENCE	ASSESSMENT ITEM GROUP				COMMENTS
	SELECTION OF STUDY GROUPS (MAX. SCORE 4)	COMPARABILITY OF STUDY GROUPS (MAX. SCORE 2)	OUTCOME OF INTEREST (MAX. SCORE 3)	TOTAL (MAX. SCORE 9)	
Park et al. 2012 *(106)*	4	2	2	9	Multiethnic cohort; 14 years follow-up; validated FFQ; cases from registry only, not reviewed
Patel et al. 2010 *(37)*	4	1	1	6	Adjusted for age, family history and smoking; data on participation rate and dropout not clear
Pietinen et al. 1997 *(38)*	4	1	3	8	Finnish Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study; no family history data collected, acknowledged as a limitation
Posner et al. 1991 *(107)*	4	1	3	8	24-hour recall but validated; no adjustment for family history; <2% attrition
Poudel-Tandukar et al. 2011 *(108)*	4	2	2	8	Japan Public Health Center-Based Study, population-based sample, 80% participation rate; FFQ validated and reproducible; 11 years follow-up; no details of LTFU
Salmeron et al. 2001 *(109)*	4	1	3	8	NHS cohort; no adjustment for socioeconomic status
Sanchez-Villegas et al. 2007 *(41)*	4	0	3	7	Excluded depression at baseline; self-reported depression but self-report validated against doctor diagnosis in subsample; university graduates; no adjustment for socioeconomic status or family history of depression
Sauvaget et al. 2004 *(110)*	1	2	2	5	Atomic bomb survivors; used only 1-day diary but well trained in its use; unclear if all participants free of cardiovascular disease at baseline; used death certificates only
Schaefer et al. 2006 *(111)*	4	1	2	7	Framingham Heart Study; dementia diagnosed according to Diagnostic and Statistical Manual IV; validated FFQ; 4 years follow-up; excluded dementia before 20th examination
Sczaniecka et al. 2012 *(112)*	4	2	3	9	Excluded breast cancer at baseline and in pre- or perimenopausal women; LTFU <1%
Sanchez-Villegas et al. 2011 *(42)*	4	0	3	7	Excluded depression at baseline; self-reported depression but self-report validated against doctor diagnosis in subsample; university graduates; no adjustment for socioeconomic status or family history of depression
Schulze et al. 2008 *(113)*	4	1	3	8	EPIC-Potsdam; validated FFQ; response >90%; self-report confirmed by family doctor; no adjustment for family history
Seino et al. 1997 *(114)*	4	0	3	7	Validated FFQ; all Japanese people >40 years eligible; no adjustment for smoking, socioeconomic status or family history
Shekelle et al. 1981 *(115)*	3	0	3	6	Dietary history not validated; did not control for family history, socioeconomic status or total energy intake
Shen et al. 2011 *(43)*	4	1	2	7	Framingham Heart Study; atrial fibrillation validated by study cardiologists who reviewed and classified all available electrocardiograms from study clinic and outside records; validated FFQ; 4 years follow-up
Simila et al. 2012 *(116)*	4	1	3	8	Finnish Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study; no family history data collected

REFERENCE	ASSESSMENT ITEM GROUP				COMMENTS
	SELECTION OF STUDY GROUPS (MAX. SCORE 4)	COMPARABILITY OF STUDY GROUPS (MAX. SCORE 2)	OUTCOME OF INTEREST (MAX. SCORE 3)	TOTAL (MAX. SCORE 9)	
Solfrizzi et al. 2005 *(117)*	4	0	3	7	Italian Longitudinal Study on Aging; elderly cohort; no adjustment for energy or TFA
Solfrizzi et al. 2006 *(45)*	4	0	3	7	Italian Longitudinal Study on Aging; elderly cohort; no adjustment for energy or TFA
Sonestedt et al. 2007 *(46)*	4	1	1	6	Malmö Diet and Cancer study; validated semiquantitative FFQ; adjustment for total energy and age only; 9.5 years follow-up; no description of attrition; registry link only
Song et al. 2004 *(118)*	4	2	3	9	Representative sample; long follow-up; validated exposures and outcomes
Streppel et al. 2008 *(119)*	4	2	2	8	Dietary cross-check; validated; 40 years follow-up; no details on follow-up
Strom et al. 2012 *(47)*	4	1	1	6	Danish National Birth Cohort; pregnant women only; registry deaths only; 8 years follow-up; no description of dropouts; did not control for family history
Takata et al. 2013 *(120)*	4	2	2	8	SMHS and SWHS; death certificates only; 92–94% follow-up and 12 years follow-up
Thiebaut et al. 2007 *(121)*	4	1	1	6	National Institutes of Health American Association of Retired Persons Diet and Health Study Diet and Health Study; 4.4 years follow-up; valid and reproducible FFQ; cases through registry linkage only; did not adjust for height or family history
Van Dam et al. 2002 *(48)*	4	1	2	7	HPFS cohort; no adjustment for family history
Van den Brandt et al. 1993 *(122)*	4	1	1	6	Case–cohort study (3500 of 120 700 men and women aged 55–69) in The Netherlands (population); registry cases only; did not adjust for postmenopausal hormone use; 3.3 years follow-up only
Van Woudenbergh et al. 2009 *(122)*	4	1	3	8	Rotterdam Study; response rate 78% (from all 10 275 inhabitants of Omoord, suburb of Rotterdam); adjusted for age, sex, education, energy, vitamin E; mean age 68 years; 6-year follow-up
Vedtofte et al. 2011 *(123)*	4	2	3	9	Glostrup Population Studies (1914, Monitoring of Trends and Determinants in Cardiovascular Disease I and III); those with previous CHD excluded; validation studies of events published and good; 23 years follow-up; no adjustment for TFA
Velie et al. 2000 *(50)*	4	2	3	9	Breast Cancer Detection Demonstration Project; validated block FFQ; 5.3 years follow-up
Vercambre et al. 2010 *(51)*	4	2	3	9	Etude Epidémiologique auprès de Femmes de la Mutuelle Générale de l'Éducation Nationale; no TFA
Virtanen et al. 2008 *(52)*	4	2	3	9	NHS I and II
Virtanen et al. 2009 *(124)*	3	1	3	7	Kuopio Ischemic Heart Disease Study; serum measures only; no adjustment for diet; linked data reviewed by study physician; 17.7 years; only 3 people LTFU
Virtanen et al. 2014 *(125)*	4	2	2	8	Kuopio Ischemic Heart Disease Study; serum and diet measures; no adjustment for total energy; linked data reviewed by study physician; 19.3 years; only 3 people LTFU

REFERENCE	ASSESSMENT ITEM GROUP				COMMENTS
	SELECTION OF STUDY GROUPS (MAX. SCORE 4)	COMPARABILITY OF STUDY GROUPS (MAX. SCORE 2)	OUTCOME OF INTEREST (MAX. SCORE 3)	TOTAL (MAX. SCORE 9)	
Villegas et al. 2011 *(126)*	4	2	2	8	SWHS, SMHS; response 92% from women, 75% from men; high follow-up (>97%); cases self-reported. "Confirmed" if case also met at least 1 of the American Diabetes Association criteria (i.e. 2-hour post-oral glucose tolerance test glucose >11.1 mmol/L; fasting glucose ≥7.0 mmol/L on 2 separate occasions; use of hypoglycemic medications or insulin). Limiting to only confirmed cases did not change the result; follow-up for SMHS 4.1 years, SWHS 8.9 years
Villegas et al. 2015 *(127)*	4	2	2	8	Southern Community Cohort Study; 5.5 years follow-up; lower socioeconomic status; validated for antioxidants; link to National Death Index only
Voorrips et al. 2002 *(128)*	4	2	2	8	Netherlands Cohort Study on Diet and Cancer; validated FFQ; excluded prevalent cancers; no adjustment for postmenopausal hormone use (but adjusted for age of menarche, menopause, etc.); registry cases only; no LTFU
Wakai et al. 2005 *(129)*	4	2	3	9	Documented follow-up; FFQ validated
Wakai et al. 2014 *(130)*	4	2	2	8	Response rate 83%
Wallstrom et al. 2012 *(131)*	4	2	2	8	Population-based, men and women living in Malmö born 1923–1950 and living there in 1991–1996; validated FFQ; <1% LTFU; medical record review for cases
Wang et al. 2016 *(132)*	4	2	3	9	NHS and HPFS; selecting one profession helps to homogenize socioeconomic status
Wiberg et al. 2006 *(54)*	3	0	2	5	All men residing in Uppsala County eligible (82% participation); no reliability measures for fatty acids; no adjustment for socioeconomic status, family history, energy; no independent adjudication
Wirfalt et al. 2002 *(133)*	4	1	1	6	Case–control study (but prospective exposure); did not control for family history; registry cases only; follow-up may be as low as 3 years for those recruited in 1996 (through 1999)
Wolfe et al. 2009 *(134)*	3	1	3	7	National Health and Nutrition Examination Survey I Epidemiologic Follow-up Study; 10 years follow-up; 1 single 24-hour recall; incomplete adjustment
Wolk et al. 1998 *(135)*	4	2	2	8	Validated FFQ; histologically confirmed cases; no description of dropouts
Xu et al. 2006 *(136)*	3	1	3	7	Strong Heart Study cohort; single 24-hour dietary recall; no socioeconomic status data
Yaemsiri et al. 2012 *(137)*	4	1	3	8	No adjustment for family history
Yamagishi et al. 2008 *(138)*	4	1	2	7	Japan Collaborative Cohort Study for Evaluation of Cancer Risk; 12.7 years follow-up; FFQ validated; all death certificates reviewed (mandatory report) but unclear how data collected if death occurred outside Japan

REFERENCE	ASSESSMENT ITEM GROUP				COMMENTS
	SELECTION OF STUDY GROUPS (MAX. SCORE 4)	COMPARABILITY OF STUDY GROUPS (MAX. SCORE 2)	OUTCOME OF INTEREST (MAX. SCORE 3)	TOTAL (MAX. SCORE 9)	
Yuan et al. 2001 *(139)*	4	2	3	9	Shanghai; FFQ validated well; no data collected on history of cancer; 99% complete follow-up, LTFU described; no adjustment for follow-up but did adjust for risk factors; 12 years follow-up
Zhang et al, 2019 (CHNS) *(140)*	4	1	2	7	Did not adjust for family history; no description of follow-up
Zhang et al, 2018 (NIH-AARP) *(141)*	4	2	2	8	validated 124-item semiquantitative FFQ; record linkage only- no clear adjudication
Zheng et al., 2019 *(142)*	4	2	2	8	Described loss-to-follow up; 85% follow-up rate
Zhuang et al., 2019 (CNHS/NHANES) *(143)*	4	2	2	8	CHNS: daily interview + weighed FR; NHANES: 24-h recall (1 day); only self-report in CHNS; record linkage in NHANES
Zhuang et al., 2019 (NIH-AARP)	4	2	2	8	validated 124-item SQFFQ; recond linkage only- no clear adjudication
Zong et al., 2019 *(144)*	4	2	2	8	NHS and HPFS; selecting one profession helps to homogenize SES; this publication did not report reasons for loss-to-follow up

A: atomic; BMI: body mass index; CHD: coronary heart disease; EPIC: European Prospective Investigation into Cancer and Nutrition; FFQ: food frequency questionnaire; HPFS: Health Professionals Follow-up Study; IWHS: Iowa Women's Health Study; LTFU: loss to-follow-up; max.: maximum; NHS: Nurses' Health Study; NIPPON DATA: The National Integrated Project for Prospective Observation of Non-communicable Disease and its Trends in the Aged; NSAID: nonsteroidal anti-inflammatory drug; SES: socioeconomic status; SMHS: Shanghai Men's Health Study; SWHS: Shanghai Women's Health Study; TFA: trans-fatty acids; VITAL: Vitamins and Lifestyle Study; WHS: Women's Health Study; ZES: Zutphen Elderly Study.

Table 3. GRADE evidence profile for prospective cohort studies of PUFA and health outcomes

QUALITY ASSESSMENT									SUMMARY OF FINDINGS			IMPORTANCE
EXPOSURE	OUTCOME	PARTICIPANTS (NO. STUDIES)	RISK OF BIAS	INCONSISTENCY	INDIRECTNESS	IMPRECISION	PUBLICATION BIAS	OVERALL QUALITY OF EVIDENCE	STUDY EVENT RATE (%)	ABSOLUTE RISK DIFFERENCE, ADJUSTED (PER 10 000)[1]	RELATIVE RISK, ADJUSTED	
Total PUFA	All-cause mortality	960 538 (16 studies)	No serious risk of bias[2]	No serious inconsistency[3]	No indirectness	No serious imprecision	No serious risk of bias[4]	⨁⨁⨁◯ MODERATE[5]	193 582/ 960 538 (20.2%)	160 fewer (from 217 fewer to 91 fewer)	0.86 (0.81, 0.92)	CRITICAL
	CVD, total	171 708 (5 studies)	No serious risk of bias[6]	No serious inconsistency (145)[7]	No indirectness	Serious imprecision[8]	Unreliable to assess[9]	⨁◯◯◯ VERY LOW[10]	6270/ 171 708 (3.7%)	91 more (from 547 fewer to 820 more)	1.02 (0.88, 1.18)	CRITICAL
	CVD, fatal	907 721 (13 studies)	No serious risk of bias[11]	Serious inconsistency[12]	No indirectness	Serious imprecision[13]	No serious risk of bias[14]	⨁◯◯◯ VERY LOW[15]	53 728/ 907 721 (5.9%)	52 fewer (from 99 fewer to 59 more)	0.91 (0.83 to 1.01)	–
	CHD, fatal	34 296 (8 studies)	No serious risk of bias[16]	Serious inconsistency[17]	No indirectness	Serious imprecision[18]	Unreliable to assess[19]	⨁◯◯◯ VERY LOW[20]	1365/34 296 (4.0%)	18 fewer (from 38 fewer to 6 more)	0.95 (0.84 to 1.07)	CRITICAL

1 See Annex 2 for sources of absolute event rates.

2 Median NOS=8 (range: 7–9). No evidence of bias due to any of the factors in the metaregression.

3 I^2=82%, 8 of 9 point estimates show benefit; 2 of 16 find nonsignificant increased risk.

4 Egger's test: *P*=0.173; Begg's test: *P*=0.843. Trim-and-fill identified no "missed" studies. No publication bias suspected.

5 Prospective cohort studies start with GRADE of LOW. Upgraded to MODERATE for dose–response association. Assuming linearity, a 10 g increase in PUFA was associated with a 13% reduced risk of all-cause mortality (mvRR=0.87; 95% CI: 0.79 to 0.95); a 5% increase in PUFA was associated with a 15% reduction in mortality (mvRR=0.85; 95% CI: 0.79 to 0.91).

6 Median NOS=7 (range: 6–8); difference in estimates by NOS score not assessed because there were too few studies, but unlikely.

7 I^2=45%; removal of Guasch-Ferre et al. (2015) *(145)*, the only study to find significant benefit, changes RR to 1.05 (95% CI: 0.96 to 1.06).

8 95% CI of pooled association consistent with a 12% decreased through 18% increased risk of events.

9 Due to small number of studies (*n*<10), risk of publication bias was not formally assessed.

10 Prospective cohort studies start with GRADE of LOW. Downgraded for risk of bias and imprecision.

11 Median NOS=8 (range: 6–9). Removal of the lowest quality study (Guasch-Ferre *(145)*) does not change the point estimate substantially (to 0.93; 95% CI: 0.85 to 1.01).

12 I^2=64%; 10 of 13 studies have point estimates consistent with protection; 3 that do not are all nonsignificant on their own (1.18; 95% CI: 1.02 to 1.35; all in Japanese populations).

13 95% CI of pooled association consistent with a 17% decreased through 1% increased risk of events.

14 Egger's test: *P*=0.529; Begg's test: *P*=0.428. Trim-and-fill identified no "missed" studies. No publication bias suspected.

15 Prospective cohort studies start with GRADE of LOW. Downgraded for risk of bias and imprecision. Assuming linearity, a 10 g increase in total PUFA was associated with a 9% reduced risk of CVD mortality (mvRR=0.91; 95% CI: 0.88 to 0.95) but nonlinearity suspected. Assuming linearity, a 5% increase in energy from total PUFA was associated with a 14% reduced risk of CVD mortality (mvRR=0.86; 95% CI: 0.77 to 0.96) but nonlinearity suspected.

16 Median NOS=7 (range: 5–9). Four estimates 1 from[Shekelle *(115)*, 2 from Kushi *(146)*and 1 from Esrey *(71)*] were at high risk of bias and also did not adjust for TFA. In these studies, mvRR=0.95 (95% CI: 0.86 to 1.04). In the remaining studies with lower risk of bias, estimated mvRR=0.85 (95% CI: 0.58 to 1.24).

17 I^2=69%; 5 point estimates <1.0; 2 point estimates >1.0; 2 point estimates very close to 1.0.

18 95% CI of pooled association consistent with a 19% decreased through 3% increased risk of events.

19 Due to small number of studies (*n*<10), risk of publication bias was not formally assessed.

20 Prospective cohort studies start with GRADE of LOW. Downgraded for inconsistency and imprecision. Linear dose–response associations suggest increasing risk with increasing PUFA, but not significant. Assuming linearity, a 10 g increase in energy from total PUFA was associated with a 7% increased risk of CHD mortality (mvRR=1.07; 95% CI: 0.95 to 1.21). Assuming linearity, a 5% increase in energy from total PUFA was associated with a 10% increased risk of CHD mortality (mvRR=1.10; 95% CI: 0.96 to 1.26).

QUALITY ASSESSMENT									SUMMARY OF FINDINGS			IMPORTANCE
EXPOSURE	OUTCOME	PARTICIPANTS (NO. STUDIES)	RISK OF BIAS	INCONSISTENCY	INDIRECTNESS	IMPRECISION	PUBLICATION BIAS	OVERALL QUALITY OF EVIDENCE	STUDY EVENT RATE (%)	ABSOLUTE RISK DIFFERENCE, ADJUSTED (PER 10 000)[1]	RELATIVE RISK, ADJUSTED	
Total PUFA	Sudden cardiac death	91 981 (1 study)	No serious risk of bias	Not assessed	No indirectness	Serious imprecision[21]	Not assessed	⊕◯◯◯ VERY LOW[22]	385/91 981 (0.4%)	2 fewer (from 4 fewer to 0 more)	0.73 (0.53 to 1.01)	IMPORTANT
	MI, nonfatal	4920 (2 studies)	No serious risk of bias[23]	Not assessed	No indirectness	Serious imprecision[24]	Not assessed	⊕◯◯◯ VERY LOW[25]	680/4920 (13.8%)	8 more (from 14 fewer to 38 more)	1.10 (0.83 to 1.47)	IMPORTANT
	CHD, total	277 734 (17 studies)	Serious risk of bias[26]	Serious inconsistency[27]	No indirectness	Serious imprecision[28]	No evidence of publication bias[29]	⊕◯◯◯ VERY LOW[30]	16 114/ 277 734 (5.8%)	4 fewer (from 46 fewer to 42 more)	0.99 (0.89, 1.10}	CRITICAL
	Stroke, total	173 121 (4 studies)	No serious risk of bias[31]	No serious inconsistency[32]	No indirectness	Serious imprecision[33]	Unreliable to assess[34]	⊕◯◯◯ VERY LOW[35]	4128/ 173 121 (2.4%)	1 fewer (from 7 fewer to 6 more)	0.98 (0.86, 1.13)	IMPORTANT
	Stroke, fatal	3 731 (1 study)	Serious risk of bias[36]	Not assessed	No indirectness	Serious imprecision[37]	Unreliable to assess[38]	⊕◯◯◯ VERY LOW[39]	60/3731 (1.6%)	8 fewer (from 16 fewer to 9 more)	0.68 (0.34 to 1.36)	IMPORTANT

[21] Fewer than 500 events.
[22] Prospective cohort studies start with GRADE of LOW. Downgraded for risk of bias, inconsistency and imprecision.
[23] NOS=of 2 studies are 7 and 8; both measured TFA.
[24] 95% CI consistent with a 17% reduced through 47% increased risk of nonfatal myocardial infarction.
[25] Prospective cohort studies start with GRADE of LOW. Downgraded for imprecision.
[26] Median NOS=8 (range: 7–9). For studies that assessed TFA intake [Pietinen *(38)*, Li (HPFS and NHS) *(96)* and Xu *(136)*] mvRR=0.87 (95% CI: 0.81 to 0.94); for studies that did not assess TFA intake, mvRR=1.09 (95% CI: 1.00 to 1.18).
[27] I^2=63%; 9 of 16 studies have point estimates consistent with harm (but none are statistically significant). Only the pooled studies by Li et al (NHS, HPFS) *(96)* show statistically significant benefit.
[28] 95% CI consistent with a 9% decreased through 14% increased risk.
[29] Egger's test: *P*=0.380; Begg's test: *P*=0.224. Trim-and-fill identified no "missed" studies. No publication bias suspected.
[30] Prospective cohort studies start with GRADE of LOW. Downgraded for imprecision and risk of bias. There was no evidence of a dose–response association between total PUFA and total CHD.
[31] Median NOS=7 (range: 7–8). No study reported measures of TFA.
[32] I^2=17%; considerable CI overlap.
[33] Pooled estimate 95% CI ranges from 14% reduced risk to 13% increased risk.
[34] Due to small number of studies (*n*<10), risk of publication bias was not formally assessed.
[35] Prospective cohort studies start with GRADE of LOW. Downgraded for serious imprecision.
[36] NOS=5; atomic bomb survivors and only 1-day food diary.
[37] 95% CI ranges from 66% reduced risk to 36% increased risk, with <500 events.
[38] Due to small number of studies (*n*<10), risk of publication bias was not formally assessed.
[39] Prospective cohort studies start with GRADE of LOW. Downgraded for serious risk of bias and imprecision.

QUALITY ASSESSMENT									SUMMARY OF FINDINGS			IMPORTANCE
EXPOSURE	OUTCOME	PARTICIPANTS (NO. STUDIES)	RISK OF BIAS	INCONSISTENCY	INDIRECTNESS	IMPRECISION	PUBLICATION BIAS	OVERALL QUALITY OF EVIDENCE	STUDY EVENT RATE (%)	ABSOLUTE RISK DIFFERENCE, ADJUSTED (PER 10 000)[1]	RELATIVE RISK, ADJUSTED	
Total PUFA	Stroke, ischaemic	216 177 (8 studies)	No serious risk of bias[40]	No serious inconsistency[41]	No indirectness	Serious imprecision[42]	Unreliable to assess[43]	⨁◯◯◯ VERY LOW[44]	3347/ 216 177 (1.5%)	1 fewer (from 7 fewer to 6 more)	0.97 (0.86 to 1.09)	IMPORTANT
	Stroke, haemorrhagic	79 234 (3 studies)	No serious risk of bias[45]	No serious inconsistency[46]	No indirectness	Serious imprecision[47]	Unreliable to assess[48]	⨁◯◯◯ VERY LOW[49]	1819/79 234 (2.3%)	1 more (from 3 fewer to 6 more)	1.03 (0.89 to 1.20)	IMPORTANT
	Atrial fibrillation	88 686 (3 studies)	No serious risk of bias[50]	Not assessed	No indirectness	Serious imprecision[51]	Unreliable to assess[52]	⨁◯◯◯ VERY LOW[53]	6521/88 686 (7.4%)	1 fewer (from 6 fewer to 4 more)	0.97 (0.84 to 1.11)	IMPORTANT
	MI, total	135 335 (1 study)	No serious risk of bias[54]	Not assessed	No indirectness	Serious imprecision[55]	Unreliable to assess[56]	⨁◯◯◯ VERY LOW[57]	2143/ 135 335 (1.6%)	10 more (from 6 fewer to 29 more)	1.12 (0.93 to 1.34)	IMPORTANT

[40] Median NOS=7 (range: 7–9); 2 studies [Yaemsiri *(137)* and He *(77)*] measured TFA separately; mvRR in these 2 studies is 0.99 (95% CI: 0.81 to 1.21). In remaining studies that did not measure TFA, mvRR=0.96 (95% CI: 0.83 to 1.11).
[41] I^2=0%; most CIs overlap.
[42] 95% CI ranges from 11% reduced risk to 9% increased risk, with >500 events.
[43] Due to small number of studies (n<10), risk of publication bias wasnot formally assessed.
[44] Prospective cohort studies start with GRADE of LOW. Downgraded for serious imprecision.
[45] Three studies, NOS=7 for all.
[46] I^2=0% (both studies with wide, overlapping CI).
[47] 95% CI ranges from 11% decreased risk through 20% increased risk, with >500 events.
[48] Due to small number of studies (n<10), risk of publication bias was not formally assessed.
[49] Prospective cohort studies start with GRADE of LOW. Downgraded for imprecision.
[50] Two studies, 1 with NOS=9 with adjustment for TFA, the other NOS=8 (2 arms), with no adjustment for TFA.
[51] 95% CI from this study ranges from 16% decreased risk to 11% increased risk, >6500 events.
[52] Due to small number of studies (n<10), risk of publication bias was not formally assessed.
[53] Prospective cohort studies start with GRADE of LOW. Downgraded for imprecision.
[54] One study, multicountry; NOS=8; did not measure TFA.
[55] 95% CI ranges from 7% decreased through 34% increased risk.
[56] Due to small number of studies (n<10), risk of publication bias was not formally assessed.
[57] Prospective cohort studies start with GRADE of LOW. Downgraded for imprecision.

QUALITY ASSESSMENT									SUMMARY OF FINDINGS			IMPORTANCE
EXPOSURE	OUTCOME	PARTICIPANTS (NO. STUDIES)	RISK OF BIAS	INCONSISTENCY	INDIRECTNESS	IMPRECISION	PUBLICATION BIAS	OVERALL QUALITY OF EVIDENCE	STUDY EVENT RATE (%)	ABSOLUTE RISK DIFFERENCE, ADJUSTED (PER 10 000)[1]	RELATIVE RISK, ADJUSTED	
Total PUFA	T2DM	258 937 (10 studies)	No serious risk of bias[58]	Serious inconsistency[59]	No indirectness	Serious imprecision[60]	No evidence of publication bias[61]	⊕◯◯◯ VERY LOW[62]	9868/ 258 937 (3.8%)	50 fewer (from 118 fewer to 45 more)	0.91 (0.79 to 1.05)	IMPORTANT
	Dementia	5 395 (1 study)	No serious risk of bias[63]	Not assessed	No indirectness	Serious imprecision[64]	Not assessed	⊕◯◯◯ VERY LOW[65]	197/5 395 (3.7%)	46 more (from 187 fewer to 358 more)	1.05 (0.80 to 1.38)	IMPORTANT
	Cognitive decline	5 087 (2 studies)	No serious risk of bias[66]	Serious inconsistency[67]	No indirectness	Serious imprecision[68]	Unreliable to assess[69]	⊕◯◯◯ VERY LOW[70]	616/5087 (12.1%)	172 fewer (from 611 fewer to 543 more)	0.87 (0.54 to 1.41)	–
	Depression	13 879 (2 studies)	No serious risk of bias[71]	No serious inconsistency[72]	No indirectness	Serious imprecision[73]	Not assessed	⊕◯◯◯ VERY LOW[74]	1172/13 879 (8.4%)	245 fewer (from 1295 fewer to 1330 more)	0.93 (0.63 to 1.38)	CRITICAL
	Crohn's disease	170 085 (1 study)	No serious risk of bias[75]	Not assessed	No indirectness	Serious imprecision[76]	Not assessed	⊕◯◯◯ VERY LOW[77]	269/170 085 (0.16%)	0 (from 2 fewer to 2 more)	0.95 (0.63 to 1.43)	IMPORTANT

[58] Median NOS=8 (range: 6–9). Five studies [Salmeron *(109)*, Meyer *(33)*, Schulze *(113)*, Simila *(116)*, and Dow *(12)*] adjusted for TFA: mvRR=0.93 (95% CI: 0 80 to 1.09). In those that did not [Patel *(37)*, Alhazmi *(2)*, Guasch-Ferre *(147)*, Mirmiran *(148)*], mvRR=0.83 (95% CI: 0.58 to 1.17).

[59] I^2=73%; 3 studies report point estimates consistent with 25% or greater reduced risk (1 at P<0.05). The remaining 7 show no association with diabetes mellitus.

[60] 95% CI for association ranges from 21% decreased risk through 5% increased risk.

[61] Egger's test: P=0.424; Begg's test: P=0.858. Trim-and-fill identified no "missed" studies. No publication bias suspected.

[62] Prospective cohort studies start with GRADE of LOW. Downgraded for inconsistency and imprecision. There was no evidence of a linear dose–response association between total PUFA and type 2 diabetes (mvRR=1.00; 95% CI: 0.94 to 1.07 per 10 g), but the association was nonlinear (P=0.0002 for GOF). There was a suggestion that approximately 0–5 g/day (approximately 0–2% energy) were associated with decreased risk, but doses >4–12 g/day (approximately >2–7% energy) were associated with increased risk.

[63] One study, NOS=9 with adjustment for TFA.

[64] 95% CI from this study ranges from 20% decreased risk to 38% increased risk, with <500 events.

[65] Prospective cohort studies start with GRADE of LOW. Downgraded for imprecision.

[66] Two studies with NOS of 7 and 9. No TFA assessment in either.

[67] I^2=60%; 1 study [Solfrizzi *(45)*] point estimate mvRR=0.63, the other [Vercambre *(51)*] point estimate mvRR=1.04.

[68] 95% CI consistent with 46% decreased risk through 41% increased risk, >500 events.

[69] Due to small number of studies (<10), risk of publication bias was not formally assessed.

[70] Prospective cohort studies start with GRADE of LOW. Downgraded for imprecision and inconsistency.

[71] Two studies, NOS=7 and 9; neither study measured TFA.

[72] I^2=79%; 95% CI of study estimates overlap. No serious inconsistency.

[73] 95% CI consistent with 37% decreased through 38% increased risk, 1172 cases. Downgraded.

[74] Prospective cohort studies start with GRADE of LOW. Downgraded for imprecision.

[75] NOS=9; measured TFA.

[76] 95% CI consistent with 37% reduced risk through 43% increased risk, <500 events.

[77] Prospective cohort studies start with GRADE of LOW. Downgraded for imprecision.

QUALITY ASSESSMENT									SUMMARY OF FINDINGS			IMPORTANCE
EXPOSURE	OUTCOME	PARTICIPANTS (NO. STUDIES)	RISK OF BIAS	INCONSISTENCY	INDIRECTNESS	IMPRECISION	PUBLICATION BIAS	OVERALL QUALITY OF EVIDENCE	STUDY EVENT RATE (%)	ABSOLUTE RISK DIFFERENCE, ADJUSTED (PER 10 000)[1]	RELATIVE RISK, ADJUSTED	
Total PUFA	Ulcerative colitis	431 391 (2 studies)	Serious risk of bias[78]	No serious inconsistency[79]	No indirectness	Serious imprecision[80]	Not assessed	⨁◯◯◯ VERY LOW[81]	477/431 491 (0.11%)	1 more (from 2 fewer to 8 more)	1.18 (0.80 to 1.76)	IMPORTANT
	All breast cancer	322 415 (8 studies)	No serious risk of bias[82]	No serious inconsistency[83]	No indirectness	Serious imprecision[84]	Not assessed[85]	⨁◯◯◯ VERY LOW[86]	6418/322 415 (2.0%)	83 fewer (from 292 fewer to 146 more)	0.96 (0.86 to 1.07)	IMPORTANT
	Premenopausal breast cancer	172 632 (3 studies)	No serious risk of bias[87]	No serious inconsistency[88]	No indirectness	Serious imprecision[89]	Not assesssed[90]	⨁◯◯◯ VERY LOW[91]	1671/ 172 632 (1.0%)	4 more (from 3 fewer to 13 more)	1.10 (0.92 to 1.32)	–
	Postmenopausal breast cancer	429 023 (9 studies)	No serious risk of bias[92]	Serious inconsistency[93]	No serious indirectness	Serious imprecision[94]	Not assessed[95]	⨁◯◯◯ VERY LOW[96]	11 986/ 429 023 (2.8%)	102 more (from 187 fewer to 444 more)	1.06 (0.89 to 1.26)	–

CHD: coronary heart disease; CI: confidence interval; CVD: cardiovascular disease; GOF: goodness of fit; GRADE: Grading of Recommendations Assessment, Development, and Evaluation; HPFS: Health Professionals Follow-up Study; MI: myocardial infarction; mvRR: multivariable risk ratio; NHS: Nurses' Health Study; no.: number; NOS: Newcastle-Ottawa Scale; NSAID: nonsteroidal anti-inflammatory drugPUFA: polyunsaturated fatty acids; RR: risk ratio; SES: socioeconomic status; T2DM: type 2 diabetes mellitus; TFA: *trans*-fatty acids.

[78] Two studies (NOS=6 and 9). The larger study [Hart *(76)*] did not adjust for several relevant confounders (smoking, SES, energy, aspirin/NSAID use).
[79] I^2=33%; both point estimates >1.0
[80] 95% CI consistent with 20% decreased risk through 76% increased risk.
[81] Prospective cohort studies start with GRADE of LOW. Downgraded for imprecision and risk of bias.
[82] Median NOS=8 (range: 7–9). Only 1 study [Holmes *(78)*] adjusted for TFA; in this study, mvRR=0.91 (95% CI: 0.79 to 1.04); in the other 7 studies, mvRR=1.00 (95% CI: 0.86 to 1.15).
[83] I^2=11%; no studies showed statistically significant association.
[84] 95% CI of pooled estimates consistent with 14% decreased risk through 7% increased risk.
[85] Due to small number of studies (<10), risk of publication bias was not formally assessed.
[86] Prospective cohort studies start with GRADE of LOW. Downgraded for imprecision.
[87] Median NOS=9 (range: 8–9); 1 study did not assess TFA; in this study, mvRR=1.29 (95% CI: 0.96 to 1.73); in other 2 studies, mvRR=1.12 (95% CI: 0.86 to 1.45).
[88] I^2=0%.
[89] 95% CI of pooled estimates consistent with 8% decreased through 32% increased risk, >500 events.
[90] Due to small number of studies (<10), risk of publication bias was not formally assessed.
[91] Prospective cohort studies start with GRADE of LOW. Downgraded for imprecision.
[92] Median NOS=8 (range: 6–9). Only 1 study [Kim *(89)*] adjusted for TFA; in this study, mvRR=0.94 (95% CI: 0.82 to 1.09); in remaining 8 studies, mvRR=1.09 (95% CI: 0.88 to 1.35).
[93] I^2=79%; 1 of 7 studies [Wirfalt *(133)*; 6.6% weight] estimates 3-fold increased risk; 1 study (Lof *(98)*; 8.0% weight) estimates 46% reduced risk. Four point estimates consistent with harm, 4 with benefit.
[94] 95% CI crosses 1; consistent with 11% decreased risk through 26% increased risk, >500 events.
[95] Due to small number of studies (<10), risk of publication bias was not formally assessed.
[96] Prospective cohort studies start with GRADE of LOW. Downgraded for inconsistency and imprecision.

Table 4. GRADE evidence profile for prospective cohort studies of omega-3 PUFA and health outcomes

QUALITY ASSESSMENT									SUMMARY OF FINDINGS			IMPORTANCE
EXPOSURE	OUTCOME	PARTICIPANTS (NO. STUDIES)	RISK OF BIAS	INCONSISTENCY	INDIRECTNESS	IMPRECISION	PUBLICATION BIAS	OVERALL QUALITY OF EVIDENCE	STUDY EVENT RATE (%)	ABSOLUTE RISK DIFFERENCE, ADJUSTED (PER 10 000)[1]	RELATIVE RISK, ADJUSTED	
n-3 PUFA	All-cause mortality	830 509 (11 studies)	No serious risk of bias[2]	Serious inconsistency[3]	No serious indirectness	Serious imprecision[4]	No evidence of publication bias[5]	⨁◯◯◯ VERY LOW[6]	190 293/ 830 509 (22.9%)	23 fewer (from 80 fewer to 34 more)	0.98 (0.93 to 1.03)	CRITICAL
	CVD, total	17 810 (1 study)	Serious risk of bias[7]	Not assessed	No serious indirectness	Serious imprecision[8]	Not assessed	⨁◯◯◯ VERY LOW[9]	194/17 810 (1.1%)	517 more (from 879 fewer to 2330 more)	1.10 (0.83 to 1.45)	CRITICAL
	CVD, fatal	872 029 (10 studies)	No serious risk of bias[10]	Serious inconsistency[11]	No serious indirectness	Serious imprecision[12]	No serious publication bias[13]	⨁◯◯◯ VERY LOW[14]	59 999/ 872 028 (6.9%)	35 fewer (from 71 fewer to 6 more)	0.94 (0.88 to 1.01)	CRITICAL
	CHD, fatal	238 990 (4 studies)	No serious risk of bias[15]	No serious inconsistency[16]	No serious indirectness	No serious imprecision[17]	Unable to reliably assess[18]	⨁⨁⨁◯ MODERATE[19]	4578/238 990 (1.9%)	71 fewer (from 122 fewer to 13 fewer)	0.83 (0.71 to 0.97)	CRITICAL

[1] See Annex 2 for sources of absolute event rates.

[2] Median NOS=8 (range: 7–9). For 2 studies that adjusted for TFA intake, mvRR=0.95 (95% CI: 0.92 to 0.99). For studies that did not, mvRR=0.99 (95% CI: 0.93 to 1.05).

[3] I^2=75%; 7 of 11 estimates consistent with protection; 2 studies [Owen *(36)* and Zhuang, NIH-AARP 2019 (143)] show statistically significant risk of harm (FE mvRR=1.02; 95% CI: 1.00 to 1.05).

[4] 95% CI crosses 1. Pooled estimate consistent with 7% decreased risk through 3% increased risk; 190 293 cases.

[5] Egger's test: *P*=0.760; Begg's test: *P*=0.640. Trim-and-fill identified no "missed" studies. No publication bias suspected.

[6] Prospective cohort studies start with GRADE of LOW. Downgraded for risk of bias, inconsistency and imprecision.

[7] NOS=7 for this study. Did not adjust for total energy, and only 4 years of follow-up (but >99% complete).

[8] 95% CI consistent with 17% decreased risk through 45% increased risk, <500 events.

[9] Prospective cohort studies start with GRADE of LOW. Downgraded for risk of bias and imprecision.

[10] Median NOS=8 (range: 7–9). Two studies measured TFA. In these studies, mvRR=1.00 (95% CI: 0.81 to 1.24); in remaining 6 studies, mvRR=0.92 (95% CI: 0.85 to 0.99).

[11] I^2=55%; removal of Harvard HPFS cohort (Wang 2016 (132); 27.8% of total weight) results in significant mvRR estimate (mvRR=0.92; 95% CI: 0.85 to 0.99). Six of 8 remaining comparisons have point estimates <1.0.

[12] 95% CI of random-effects estimate crosses 1 (consistent with 12% reduced risk through 1% increased risk). Removal of Wang (HPFS) (132) or use of FE model results in narrow CI (consistent with between 15% and 1% reduced risk without Wang HPFS (132) or between 7% and 0% reduced risk using all studies, FE).

[13] Egger's test *P*=0.392; Begg's test *P*=0.858. Trim-and-fill identified no "missed" studies. No publication bias suspected.

[14] Prospective cohort studies start with GRADE of LOW. Downgraded for risk of bias and imprecision.

[15] Median NOS=8.5 (range: 7–9). One study measured TFA [Hu 2002 *(22)*]. Its removal does not drastically alter the pooled estimate (from 0.84 to 0.87).

[16] I^2=13%. All point estimates consistent with protection.

[17] 95% CI consistent with between 29% and 3% reduced risk of fatal CVD; >4500 events.

[18] Due to small number of studies (*n*<10), risk of publication bias was not formally assessed.

[19] Prospective cohort studies start with GRADE of LOW. Not downgraded. Upgraded to MODERATE for dose–response association. Assuming linearity, a 0.5% increase in n-3 PUFA was associated with an 21% reduced risk of CHD mortality (mvRR=0.79, 95% CI: 0.71 to 0.89). Assuming linearity, a 1 g increase in n-3 PUFA was associated with a 23% reduced risk of CHD mortality (mvRR=0.77, 95% CI: 0.67 to 0.88).

QUALITY ASSESSMENT									SUMMARY OF FINDINGS			IMPORTANCE
EXPOSURE	OUTCOME	PARTICIPANTS (NO. STUDIES)	RISK OF BIAS	INCONSISTENCY	INDIRECTNESS	IMPRECISION	PUBLICATION BIAS	OVERALL QUALITY OF EVIDENCE	STUDY EVENT RATE (%)	ABSOLUTE RISK DIFFERENCE, ADJUSTED (PER 10 000)[1]	RELATIVE RISK, ADJUSTED	
n-3 PUFA	Sudden cardiac death	149 953 (2 studies)	No serious risk of bias[20]	No serious inconsistency[21]	No serious indirectness	No serious imprecision[22]	Unable to reliably assess[23]	⨁⨁◯◯ LOW[24]	492/149 953 (0.3%)	26 fewer (between 42 fewer and 7 fewer)	0.65 (0.47 to 0.90)	IMPORTANT
	MI, total	0 (0 studies)	–	–	–	–	–	–	–	–	–	IMPORTANT
	MI, fatal	57 972 (1 study)	No serious risk of bias[25]	Not assessed	No serious indirectness	Serious imprecision[26]	Unable to reliably assess[27]	⨁◯◯◯ VERY LOW[28]	329/57 972 (0.6%)	1 fewer (from 4 fewer to 0)	0.75 (0.47 to 1.19)	IMPORTANT
	MI, nonfatal	84 688 (1 study)	No serious risk of bias[29]	Not assessed	No serious indirectness	No serious imprecision[30]	Not assessed	⨁⨁◯◯ LOW[31]	1029/84 688 (1.2%)	14 fewer (from 25 fewer to 4 fewer)	0.73 (0.57 to 0.93)	IMPORTANT
	CHD, total	200 256 (7 studies)	No serious risk of bias[32]	Serious inconsistency[33]	No serious indirectness	Serious imprecision[34]	Unable to reliably assess[35]	⨁◯◯◯ VERY LOW[36]	4257/200 256 (2.1%)	29 fewer (from 97 fewer to 50 more)	0.93 (0.77 to 1.12	CRITICAL
	Stroke, total	82 122 (2 studies)	Serious risk of bias[37]	Serious inconsistency[38]	No serious indirectness	Serious imprecision[39]	Unable to reliably assess	⨁◯◯◯ VERY LOW[40]	815/81 307 (0.99%)	7 fewer (from 24 fewer to 22 more)	0.85 (0.49 to 1.46)	IMPORTANT

[20] Median NOS=8 (range: 7–9). Similar results in the study that did measure TFA [Chiuve] to the study that did not [Yamagishi 2008 (138)].
[21] I^2=0%. Chiuve *(63)* and Yamagishi (138) show significant protection (mvRR=0.65).
[22] 95% CI consistent with between 53% and 10% reduced risk of sudden cardiac death; 492 events.
[23] Due to small number of studies (*n*<10), risk of publication bias was not formally assessed.
[24] Prospective cohort studies start with GRADE of LOW. Not downgraded.
[25] NOS=7; study failed to adjust for family history of CVD.
[26] 95% CI of estimate from this study consistent with 53% decreased risk through 19% increased risk; <500 cases.
[27] Not likely to be operating; several other major cohorts have published this finding, but typically as part of a composite endpoint (CVD, IHD or CHD) such that it cannot be assessed on its own.
[28] Prospective cohort studies start with GRADE of LOW. Downgraded for risk of imprecision.
[29] NOS=9; 1 study in women (NHS) [Hu *(22)*].
[30] 95% CI ranges from 53% decreased risk to 7% decreased risk; >500 events.
[31] Prospective cohort studies start with GRADE of LOW. Not downgraded.
[32] Median NOS=9 (range: 8–9); 1 study that measured TFA [Hu *(22)*] shows statistically significant mvRR=0.69 (95% CI: 0.57 to 0.84); others do not: pooled mvRR=1.00 (95% CI: 0.88 to 1.13).
[33] I^2=65%; 4 studies (58% weight) point estimates are protective; 3 are harmful (42% weight).
[34] 95% CI ranges from 23% decreased risk through 12% increased risk; >4500 events. FE estimate ranges from 19% decreased risk through 1% decreased risk.
[35] Due to small number of studies (*n*<10), risk of publication bias was not formally assessed.
[36] Prospective cohort studies start with GRADE of LOW. Downgraded for serious imprecision and inconsistency.
[37] Two studies (Seino (114); NOS=7 and Iso [2001] (149); NOS=8). Neither study reported or adjusted for TFA.
[38] I^2=38%; 1 study [Iso, 2001 (149)] shows statistically significant RR=0.72 and the other [Seino, 1997 (114)] shows nonsignificant RR 1.37.
[39] 95% CI of pooled estimate consistent with 51% decrease through 46% increased risk; >500 events.
[40] Prospective cohort studies start with GRADE of LOW. Downgraded for imprecision and inconsistency.

QUALITY ASSESSMENT									SUMMARY OF FINDINGS			IMPORTANCE
EXPOSURE	OUTCOME	PARTICIPANTS (NO. STUDIES)	RISK OF BIAS	INCONSISTENCY	INDIRECTNESS	IMPRECISION	PUBLICATION BIAS	OVERALL QUALITY OF EVIDENCE	STUDY EVENT RATE (%)	ABSOLUTE RISK DIFFERENCE, ADJUSTED (PER 10 000)[1]	RELATIVE RISK, ADJUSTED	
n-3 PUFA	Stroke, fatal	96 330 (2 studies)	No serious risk of bias[41]	No serious inconsistency[42]	No serious indirectness	No serious imprecision[43]	Unable to reliably assess	⊕⊕⊕◯ MODERATE[44]	1619/96 330 (1.7%)	10 fewer (from 19 fewer to 1 fewer)	0.80 (0.66 to 0.98)	IMPORTANT
	Stroke, ischaemic	100 513 (3 studies)	No serious risk of bias[45]	No serious inconsistency[46]	No serious indirectness	Serious imprecision[47]	Unable to reliably assess	⊕◯◯◯ VERY LOW[48]	1058/100 513 (1.1%)	22 fewer (from 73 fewer to 41 more)	0.92 (0.73 to 1.15)	IMPORTANT
	Stroke, haemorrhagic	79 839 (1 study)	No serious risk of bias[49]	Not assessed	No serious indirectness	Serious imprecision[50]	Unable to reliably assess	⊕◯◯◯ VERY LOW[51]	181/79 839 (0.23%)	8 fewer (from 19 fewer to 15 more)	0.76 (0.43 to 1.36)	IMPORTANT
	Stroke, thrombotic	79 839 (1 study)	No serious risk of bias[52]	Not assessed	No serious indirectness	Serious imprecision[53]	Unable to reliably assess	⊕◯◯◯ VERY LOW[54]	264/79 839 (0.33%)	10 fewer (from 20 fewer to 2 more)	0.67 (0.42 to 1.07)	IMPORTANT
	Atrial fibrillation	88 686 (3 studies)	No serious risk of bias[55]	Not assessed	No serious indirectness	Serious imprecision[56]	Unreliable to assess[57]	⊕◯◯◯ VERY LOW[58]	6521/88 686 (7.4%)	1 fewer (from 4 fewer to 2 more)	0.98 (0.90 to 1.06)	IMPORTANT

[41] Two studies; NOS=8 and 9; no TFA reporting.
[42] I^2=0%; both point estimates consistent.
[43] 95% CI consistent with a 34% decrease through 2% decreased risk; >1600 events; not downgraded.
[44] Prospective cohort studies start with GRADE of LOW. Upgraded because dose–response association suggests a 1 g increase in n-3 PUFA is associated with a 25% decrease in fatal stroke (1 study); or a 0.5% increase in energy (%) from n-3 PUFA is associated with a 24% decrease in risk (1 study).
[45] Median NOS=9 (range: 8–9). No studies quantified TFA.
[46] I^2=19%.
[47] 95% CI crosses 1, consistent with a 27% decreased through 15% increased risk; no study CI excluded 1.
[48] Prospective cohort studies start with GRADE of LOW. Downgraded for imprecision.
[49] One study, NOS=9. TFA measured.
[50] 95% CI crosses 1; consistent with a 57% decreased risk through 36% increased risk; <500 events.
[51] Prospective cohort studies start with GRADE of LOW. Downgraded for imprecision.
[52] One study, NOS=9. TFA measured.
[53] 95% CI crosses 1; consistent with a 56% decreased risk through 7% increased risk; <500 events.
[54] Prospective cohort studies start with GRADE of LOW. Downgraded for imprecision.
[55] Both studies with NOS=9 but only 1 [Chiuve, 2015 *(8)*] adjusted for TFA.
[56] 95% CI ranges from 10% decreased risk to 6% increased risk.
[57] Due to small number of studies (*n*<10), risk of publication bias was not formally assessed.
[58] Prospective cohort studies start with GRADE of LOW. Downgraded for imprecision.

QUALITY ASSESSMENT									SUMMARY OF FINDINGS			IMPORTANCE
EXPOSURE	OUTCOME	PARTICIPANTS (NO. STUDIES)	RISK OF BIAS	INCONSISTENCY	INDIRECTNESS	IMPRECISION	PUBLICATION BIAS	OVERALL QUALITY OF EVIDENCE	STUDY EVENT RATE (%)	ABSOLUTE RISK DIFFERENCE, ADJUSTED (PER 10 000)[1]	RELATIVE RISK, ADJUSTED	
n-3 PUFA	T2DM	164 870 (6 studies)	No serious risk of bias[59]	Serious inconsistency[60]	No serious indirectness	Serious imprecision[61]	Unable to reliably assess[62]	⨁◯◯◯ VERY LOW[63]	7073/164 870 (4.3%)	6 fewer (from 123 fewer to 124 more)	0.99 (0.78 to 1.26)	CRITICAL
	Dementia	6 522 (3 studies)	No serious risk of bias[64]	No serious inconsistency[65]	No serious indirectness	Serious imprecision[66]	Unable to assess reliably[67]	⨁◯◯◯ VERY LOW[68]	379/6522 (5.8%)	88 fewer (from 307 fewer to 253 more)	0.86 (0.54 to 1.39)	IMPORTANT
	Cognitive decline	4 809 (1 study)	No serious risk of bias[69]	Not assessed	No serious indirectness	No serious imprecision[70]	Unable to assess reliably[71]	⨁⨁⨁◯ MODERATE[72]	598/4809 (12.4%)	277 fewer (from 494 fewer to 13 fewer)	0.79 (0.63 to 0.99)	IMPORTANT
	Depression	10 809 (3 studies)	Serious risk of bias73	No serious inconsistency[74]	No serious indirectness	Serious imprecision[75]	Not assessed	⨁◯◯◯ VERY LOW[76]	1016/10 809 (9.4%)	455 fewer (from 1,015 fewer to 210 more)	0.87 (0.71 to 1.06)	IMPORTANT
	Crohn's disease	0 (0 studies)	–	–	–	–	–	–	–	–	–	IMPORTANT

[59] Median NOS=8 (6 to 9); only Dow [2016 *(12)*] adjusted for TFA; removal moves mvRR to 0.92 (95% CI: 0.70 to 1.23).

[60] I2=63%; 1 study [Brostow *(5)*] finds significant protection (mvRR=0.78); 2 studies [Alhazmi *(2)*, Dow *(12)*] find significant harm.

[61] 95% CI consistent with 22% decreased risk through 27% increased risk; >7000 cases.

[62] Due to small number of studies (n<10), risk of publication bias was not formally assessed.

[63] Prospective cohort studies start with GRADE of LOW. Downgraded for imprecision, inconsistency.

[64] Median NOS=8 (range: 6–8).

[65] I^2=44%.

[66] 95% CI includes 54% decreased risk through 39% increased risk; <500 studies.

[67] Due to small number of studies (n<10), risk of publication bias was not formally assessed.

[68] Prospective cohort studies start with GRADE of LOW. Downgraded for imprecision.

[69] One study; NOS=9.

[70] 95% CI consistent with from 37% to 1% decrease; >500 events.

[71] Due to small number of studies (n<10), risk of publication bias was not formally assessed.

[72] Prospective cohort studies start with GRADE of LOW. Upgraded because dose–response association suggests a 1 g increase in n-3 PUFA is associated with a 28% decreased risk of cognitive decline (mvRR=0.72; 95% CI: 0.53 to 0.98); and a 0.5% increase in energy from n-3 PUFA is associated with a 29% decreased risk of cognitive decline (mvRR=0.71; 95% CI: 0.51 to 0.98).

[73] Median NOS=7 (7-9); 1 study measured TFA and its mvRR=1.04 (95% CI: 0.78, 1.39). In 2 studies that did not, mvRR=0.78 (95% CI: 0.62 to 0.97).

[74] I^2=0%.

[75] 95% CI consistent with 29% decreased risk through 6% increased risk; >1000 cases.

[76] Prospective cohort studies start with GRADE of LOW. Downgraded for risk of bias. One study found a 1 g increase in n-3 PUFA was associated with a 28% decreased risk of depression (mvRR=0.72; 95% CI: 0.53 to 0.98); or a 0.5% increase in energy was associated with 29% decreased risk (mvRR=0.71; 95% CI: 0.52 to 0.98).

QUALITY ASSESSMENT									SUMMARY OF FINDINGS			IMPORTANCE
EXPOSURE	OUTCOME	PARTICIPANTS (NO. STUDIES)	RISK OF BIAS	INCONSISTENCY	INDIRECTNESS	IMPRECISION	PUBLICATION BIAS	OVERALL QUALITY OF EVIDENCE	STUDY EVENT RATE (%)	ABSOLUTE RISK DIFFERENCE, ADJUSTED (PER 10 000)[1]	RELATIVE RISK, ADJUSTED	
n-3 PUFA	Ulcerative colitis	170 918 (2 studies)	No serious risk of bias[77]	No serious inconsistency[78]	No serious indirectness	Serious imprecision[79]	Unable to assess reliably[80]	⊕◯◯◯ VERY LOW[81]	360/170 918 (0.21%)	2 fewer (from 8 fewer to 6 more)	0.67 (0.27 to 1.65)	IMPORTANT
	All breast cancer	93 340 (3 studies)	No serious risk of bias[82]	No serious inconsistency[83]	No serious indirectness	Serious imprecision[84]	Unable to assess reliably[85]	⊕◯◯◯ VERY LOW[86]	988/93 340 (1.1%)	208 fewer (from 585 fewer to 167 more)	0.88 (0.72 to 1.08)	CRITICAL
	Premenopausal breast cancer	0 (0 studies)	–	–	–	–	–	–	–	–	–	CRITICAL
	Postmenopausal breast cancer	21 015 (3 studies)	Serious risk of bias[87]	Serious inconsistency[88]	No serious indirectness	Serious imprecision[89]	Unable to assess reliably[90]	⊕◯◯◯ VERY LOW[91]	783/21 015 (3.7%)	221 more (from 187 fewer to 1467 more)	1.13 (0.89 to 1.86)	CRITICAL

CHD: coronary heart disease; CI: confidence interval; CVD: cardiovascular disease; FE: fixed effects; GRADE: Grading of Recommendations Assessment, Development, and Evaluation; HPFS: Health Professionals Follow-up Study; IHD: ischaemic heart disease; JPHC: Japan Public Health Center; MI: myocardial infarction; mvRR: multivariable risk ratio; NHS: Nurses' Health Study; NIH-AARP: National Institutes of Health American Association of Retired Persons Diet and Health Study; no.: number; NOS: Newcastle-Ottawa Scale; PUFA: polyunsaturated fatty acids; RE: random effects; RR: risk ratio; T2DM: type 2 diabetes mellitus; TFA: *trans*-fatty acids.

[77] Two studies; NOS=9 (Ananthakrishnahan *(59)*; adjusted for TFA) and 7 (John *(83)*; no adjustment for TFA).
[78] I^2=47%; both point estimates < 1.0.
[79] 95% CI crosses 1; consistent with 73% reduced risk through 65% increased risk. FE estimate: 0.83 (95% CI: 0.60 to 1.16).
[80] Due to small number of studies (*n*<10), risk of publication bias was not formally assessed.
[81] Prospective cohort studies start with GRADE of LOW. Downgraded for imprecision.
[82] Three studies; median NOS=7 (range: 7–9); Gago-Dominguez *(74)* and Sellem *(150)* did not adjust for TFA. No impact on estimates.
[83] I^2=0%; all 3 point estimates consistent with protection.
[84] 95% CI consistent with 28% decreased risk through 8% increased risk; N=988 events.
[85] Due to small number of studies (*n*<10), risk of publication bias was not formally assessed.
[86] Prospective cohort studies start with GRADE of LOW. Downgraded for imprecision.
[87] Three studies; NOS=9 for Wakai (2005) *(129)* and Bassett (2016) *(3)*, but 6 for Wirfalt (2002) *(133)*; Wirfalt did not adjust for some key covariates, and cases were identified through registry link only (no review by study team).
[88] I^2=65%; 1 study consistent with 81% increased risk (95% CI: 9 to 300%); the others find nonsignificant protection (12% decreased risk; from 36% reduced risk through 20% increased risk).
[89] 95% CI consistent with 18% decreased risk through 40% increased risk.
[90] Due to small number of studies (*n*<10), risk of publication bias was not formally assessed.
[91] Prospective cohort studies start with GRADE of LOW. Downgraded for imprecision, inconsistency.

Table 5. GRADE evidence profile for prospective cohort studies of long-chain omega-3 PUFA and health outcomes.

QUALITY ASSESSMENT									SUMMARY OF FINDINGS			IMPORTANCE
EXPOSURE	OUTCOME	PARTICIPANTS (NO. STUDIES)	RISK OF BIAS	INCONSISTENCY	INDIRECTNESS	IMPRECISION	PUBLICATION BIAS	OVERALL QUALITY OF EVIDENCE	STUDY EVENT RATE (%)	ABSOLUTE RISK DIFFERENCE, ADJUSTED (PER 10 000)[1]	RELATIVE RISK, ADJUSTED	
Long-chain n-3 PUFA	All-cause mortality	1 033 235 (15 studies)	No serious risk of bias[2]	No serious inconsistency[3]	No serious indirectness	No serious imprecision[4]	Not detected[5]	⨁⨁⨁◯ MODERATE[6]	155 616/ 1 033 235 (15.1%)	103 fewer (from 148 fewer to 57 fewer)	0.91 (0.87 to 0.95)	CRITICAL
	CVD, total	148 640 (4 studies)	Serious risk of bias[7]	No serious inconsistency[8]	No serious indirectness	Serious imprecision[9]	Unable to assess reliably[10]	⨁◯◯◯ VERY LOW[11]	6682/ 148 640 (4.5%)	273 fewer (from 1139 fewer to 820 more)	0.94 (0.75 to 1.18)	CRITICAL
	CVD, fatal	1 070 906 (18 studies)	No serious risk of bias[12]	No serious inconsistency[13]	No serious indirectness	Serious imprecision[14]	No evidence of publication bias[15]	⨁◯◯◯ VERY LOW[16]	49 704/ 1 070 906 (3.8%)	70 fewer (from 104 fewer t 29 fewer)	0.88 (0.82 to 0.95)	CRITICAL

[1] See Annex 2 for sources of absolute event rates.

[2] Median NOS=8 (range: 6–9). Metaregression found no association (*P*=0.26) between NOS and study association estimate; all but 1 study [Dolocek (69)] clearly adjusted for energy intake but study does not contribute much weight to final analysis (<1%); studies in a Japanese population [Nagata 2012 *(103)*] may show slightly higher risk (mvRR=1.03; 95% CI: 0.91 to 1.18) than China (0.78; 95% CI: 0.72 to 0.84), but otherwise most countries' estimates overlap. Not downgraded.

[3] I^2=62%; 13 of 15 estimates consistent with protection; 2 studies (2 arms from Nagata, 2012 *(103)*; 6.9% weight) shows small, nonsignificant risk of harm (mvRR=1.04; *P*=0.62).

[4] Pooled estimate consistent with 13% decreased risk through 5% decreased risk.

[5] Egger's test: *P*=0.801; Begg's test: *P*=0.767. Trim-and-fill identified no "missed" studies. No publication bias suspected.

[6] Prospective cohort studies start with GRADE of LOW. Not downgraded. Upgraded to MODERATE for dose–response association. Assuming linearity, a 0.5 g increase in long-chain n-3 PUFA was associated with a 9% reduced risk of all-cause mortality (mvRR=0.91, 95% CI: 0.88 to 0.93). Assuming linearity, a 0.1% increase in long-chain n-3 PUFA was associated with a 4% reduced risk of all-cause mortality (mvRR=0.96, 95% CI: 0.95 to 0.97).

[7] Median NOS=7 (range: 6–9). One study [Strom (47)] which showed significant protection (mvRR=0.52) was at risk of bias due to failure to adjust for family history, and for a poor description of follow-up.

[8] I^2=73%. Removal of Strom (47) reduces heterogeneity to 0%.

[9] 95% CI of pooled estimate consistent with 25% reduced risk through 18% increased risk; *n*>6600 cases.

[10] Due to small number of studies (*n*<10), publication bias was not formally assessed.

[11] Prospective cohort studies begin with GRADE of LOW. Downgraded for imprecision, risk of bias.

[12] Median NOS=8 (range: 6–9); 4 studies (Rhee (39), Bell (61), Wang HPFS and NHS *(132)*)) adjusted for TFA. In these studies, mvRR=1.04 (95% CI: 0.91 to 1.20); in remaining: 0.84 (95% CI: 0.79 to 0.89)—overall pooled association still protective. No strong trend for any subgroup difference otherwise.

[13] I^2=67%; 13 of 18 studies point estimates protective (7 significant).

[14] 95% CI of pooled estimate consistent with 12% decreased through 5% decreased risk of fatal CVD.

[15] Begg's test *P*=0.841; Egger's test *P*=0.762. Trim-and-fill identified no "missed" studies. No publication bias suspected.

[16] Prospective cohort studies begin with GRADE of LOW. Downgraded because assuming linearity, a 0.1% increase in long-chain n-3 PUFA was associated with a 4% reduced risk of CVD mortality (mvRR=0.96, 95% CI: 0.94 to 0.97). However, *P*<0.0001 for GOF; dose–response association suggests decreased risk from 0% to 0.12% energy, then an increased risk from 0.2% to 0.5% energy. Assuming linearity, a 0.5 g increase in long-chain n-3 PUFA was associated with an 10% reduced risk of CVD mortality (mvRR=0.90, 95% CI: 0.86 to 0.94). However, *P*<0.0001 for GOF; suggests decreased risk through 0.4 g/day; then increased risk from 0.4 through 1.4 g/day.

QUALITY ASSESSMENT									SUMMARY OF FINDINGS			IMPORTANCE
EXPOSURE	OUTCOME	PARTICIPANTS (NO. STUDIES)	RISK OF BIAS	INCONSISTENCY	INDIRECTNESS	IMPRECISION	PUBLICATION BIAS	OVERALL QUALITY OF EVIDENCE	STUDY EVENT RATE (%)	ABSOLUTE RISK DIFFERENCE, ADJUSTED (PER 10 000)[1]	RELATIVE RISK, ADJUSTED	
Long-chain n-3 PUFA	CHD, fatal	460 960 (16 studies)	No serious risk of bias[17]	No serious inconsistency[18]	No serious indirectness	No serious imprecision[19]	No evidence of publication bias[20]	⨁⨁⨁◯ MODERATE[21]	7525/460960 (1.6%)	40 fewer (from 63 fewer to 16 fewer)	0.80 (0.69 to 0.92)	CRITICAL
	Sudden cardiac death	142 412 (5 studies)	No serious risk of bias[22]	No serious inconsistency[23]	No serious indirectness	No serious imprecision[24]	Unable to assess reliably[25]	⨁⨁⨁◯ MODERATE[26]	614/ 142 412 (0.43%)	32 fewer (from 52 fewer to 5 fewer)	0.57 (0.34, 0.93)	IMPORTANT
	MI, total	156 265 (5 studies)	No serious risk of bias[27]	No serious inconsistency[28]	No serious indirectness	Serious imprecision[29]	Unable to assess reliably[30]	⨁◯◯◯ VERY LOW[31]	4275/ 156 265 (2.7%)	8 fewer from 20 fewer to 7 more)	0.91 (0.76, 1.08)	IMPORTANT
	MI, fatal	39 586 (2 studies)	No serious risk of bias[32]	Not assessed	No serious indirectness	No serious imprecision[33]	Unable to assess reliably[34]	⨁⨁⨁◯ MODERATE[35]	177/39 409 (0.4%)	2 fewer (from 9 fewer to 1 fewer)	0.41 (0.25, 0.65)	IMPORTANT

[17] Median NOS=7 (range: 6–9); 3 studies measured TFA [de Goede (66), Pietinen (38), Bell (61)]. In these studies, mvRR=0.78 (95% CI: 0.41 to 1.46); in the remaining 13, mvRR=0.80 (95% CI: 0.70 to 0.90).

[18] I^2=53%; 13 of 16 studies have point estimates consistent with benefit (6 significant). Studies with shorter follow-up (5 to <10 years: 0.68; 95% CI: 0.57 to 0.82), which is lower than the overall pooled estimate (0.80); studies using 24-hour recalls for diet assessment (*n*=2; Doleczek (69) and Zhuang *(143)*, NHANES) showed greater mvRR reduction (0.64) vs the group (0.80).

[19] 95% CI consistent with 31 to 8% decreased risk; >7500 events.

[20] Begg's test *P*=0.112; Egger's test *P*=0.260. Trim-and-fill identified no "missed" studies. No publication bias suspected.

[21] Prospective cohort studies begin with GRADE of LOW. Not downgraded. Upgraded to MODERATE for dose–response association. Assuming linearity, a 0.5 g increase in long-chain n-3 PUFA was associated with a 14% reduced risk of CHD mortality (mvRR=0.86, 95% CI: 0.78 to 0.95). Assuming linearity, a 0.5% increase in long-chain n-3 PUFA was associated with a 26% reduced risk of CHD mortality (mvRR=0.74, 95% CI: 0.60 to 0.90).

[22] Median NOS=8 (range: 8–9); study that did not adjust for TFA also had the fewest events. Its point estimate in the same direction as the other 3 studies.

[23] I^2=0%; Iso (2006) (81) finds nonsignificant increase in risk (1.24), but removal does not change point estimate substantially (0.61).

[24] 95% CI of pooled estimate consistent with 66% through 7% reduced risk (RE).

[25] Due to small number of studies (*n*<10), publication bias was not formally assessed.

[26] Prospective cohort studies begin with GRADE of LOW. Upgraded for dose–response association. Assuming linearity, a 0.1% increase in energy from long-chain n-3 PUFA is associated with an 13% decrease in risk of sudden cardiac death (mvRR=0.87; 95% CI: 0.77 to 0.99). Assuming linearity, a 0.5 g increase in energy from long-chain n-3 PUFA is associated with an 18% decrease in risk of sudden cardiac death (mvRR=0.82; 95% CI: 0.64 to 1.05).

[27] Median NOS=7 (range: 6–8); removal of highest risk-of-bias study [Rhee (39)] yields mvRR=0.87 (95% CI: 0.68 to 1.11).

[28] I^2=53%. Removal of study with significant point estimate of reduction (Iso (81), 7.5% weight) yields estimate of mvRR=0.94 (95% CI: 0.85 to 1.05).

[29] 95% CI consistent with a 24% reduced through an 8% increased risk.

[30] Due to small number of studies (*n*<10), publication bias was not formally assessed.

[31] Prospective cohort studies begin with GRADE of LOW. Downgraded for imprecision.

[32] NOS=9 for both studies, Yuan *(139)* did not adjust for TFA (mvRR=0.43), de Goede (66) did adjust (mvRR=0.38).

[33] 95% CI consistent with 75% through 35% decreased risk; *n*=177 events. Not downgraded because 35% decreased risk still important.

[34] Due to small number of studies (*n*<10), publication bias was not formally assessed.

[35] Prospective cohort studies begin with GRADE of LOW. Not downgraded.

QUALITY ASSESSMENT									SUMMARY OF FINDINGS			
EXPOSURE	OUTCOME	PARTICIPANTS (NO. STUDIES)	RISK OF BIAS	INCONSISTENCY	INDIRECTNESS	IMPRECISION	PUBLICATION BIAS	OVERALL QUALITY OF EVIDENCE	STUDY EVENT RATE (%)	ABSOLUTE RISK DIFFERENCE, ADJUSTED (PER 10 000)[1]	RELATIVE RISK, ADJUSTED	IMPORTANCE
Long-chain n-3 PUFA	Arrythmia, fatal	3 910 (1 study)	No serious risk of bias[36]	Not assessed	No serious indirectness	No serious imprecision[37]	Unable to assess reliably[38]	⨁◯◯◯ LOW[39]	148/3910 (3.8%)	41 fewer (from 60 to 14 fewer)	0.45 (0.25 to 0.81)	IMPORTANT
	MI, nonfatal	33 5367 (3 studies)	No serious risk of bias[40]	No serious inconsistency[41]	No serious indirectness	Serious imprecision[42]	Unable to assess reliably	⨁◯◯◯ VERY LOW[43]	694/ 33 537 (2.1%)	1 fewer (from 16 fewer to 19 more)	0.99 (0.80, 1.23)	IMPORTANT
	CHD, total	87 459 (6 studies)	No serious risk of bias[44]	No serious inconsistency[45]	No serious indirectness	Serious imprecision[46]	Unable to assess reliably[47]	⨁◯◯◯ VERY LOW[48]	3 149/ 87 459 (3.6%)	50 fewer (from 122 fewer to 42 more)	0.88 (0.71, 1.10)	CRITICAL
	Stroke, total	101 497 (5 studies)	No serious risk of bias[49]	Serious inconsistency[50]	No serious indirectness	Serious imprecision[51]	Unable to assess reliably[52]	⨁◯◯◯ VERY LOW[53]	2963/ 101 497 (2.9%)	4 fewer (from 10 fewer to 4 more)	0.92 (0.79, 1.08)	IMPORTANT
	Stroke, fatal	172 802 (7 studies)	No serious risk of bias[54]	No serious inconsistency[55]	No serious indirectness	Serious imprecision[56]	Unable to assess reliably[57]	⨁◯◯◯ VERY LOW[58]	2760/ 172 082 (1.6%)	5 fewer (from 11 fewer to 2 more)	0.90 (0.79, 1.03)	IMPORTANT

[36] NOS=8.
[37] 95% CI consistent with a 75% through 19% risk reduction; all these values are clinically meaningful reductions.
[38] Due to small number of studies (n<10), publication bias was not formally assessed.
[39] Cohort studies begin with a GRADE of low. Not downgraded.
[40] Three studies; median NOS=8 (range: 7–9) and 8.
[41] I^2=0% all CIs overlap.
[42] 95% CI consistent with 20% decreased risk through 23% increased risk; 694 events.
[43] Prospective cohort studies begin with GRADE of LOW. Downgraded for imprecision.
[44] Median NOS=9 (range: 8–9). All studies NOS=9; Iso *(81)* did not measure TFA. Removal of this study yields mvRR=0.94 (95% CI: 0.76 to 1.16).
[45] I2=65%. Four point estimates below 1.0 (1 significant); 2 above. Not downgraded.
[46] 95% CI consistent with 29% reduced risk through 10% increased risk; 3149 cases.
[47] Due to small number of studies (n<10), publication bias was not formally assessed.
[48] Prospective cohort studies begin with GRADE of LOW. Downgraded for imprecision.
[49] Median NOS=9 (range: 7–9). Two studies (1 publication, 2 arms) that measured TFA showed nonsignificant benefit of PUFA (mvRR=0.67; 95% CI: 0.38 to 1.17); the study that did not showed no effect (mvRR=1.01; 95% CI: 0.65 to 1.59).
[50] I^2=45%. Two studies (1 publication, 2 arms) that measured TFA showed nonsignificant benefit of PUFA (mvRR=0.67; 95% CI: 0.38 to 1.17); 3 which did not showed no effect (mvRR=0.96; 95% CI: 0.85 to 1.07).
[51] 95% CI consistent with 21% reduced risk through 8% increased risk; >2900 events.
[52] Due to small number of studies (n<10), publication bias was not formally assessed.
[53] Prospective cohort studies begin with GRADE of LOW. Downgraded for inconsistency and imprecision.
[54] Median NOS=7 (range: 7–9).
[55] I^2=0; 5/7 point estimates <1.0.
[56] 95% CI consistent with a 21% decreased risk through 4% increased risk; n>2700 events.
[57] Due to small number of studies (n<10), publication bias was not formally assessed.
[58] Prospective cohort studies begin with GRADE of LOW. Downgraded for imprecision.

QUALITY ASSESSMENT									SUMMARY OF FINDINGS			IMPORTANCE
EXPOSURE	OUTCOME	PARTICIPANTS (NO. STUDIES)	RISK OF BIAS	INCONSISTENCY	INDIRECTNESS	IMPRECISION	PUBLICATION BIAS	OVERALL QUALITY OF EVIDENCE	STUDY EVENT RATE (%)	ABSOLUTE RISK DIFFERENCE, ADJUSTED (PER 10 000)[1]	RELATIVE RISK, ADJUSTED	
Long-chain n-3 PUFA	Stroke, ischaemic	119 089 (6 studies)	No serious risk of bias[59]	No serious inconsistency[60]	No serious indirectness	Serious imprecision[61]	Unable to reliably assess[62]	⨁◯◯◯ VERY LOW[63]	3992/ 119 089 (3.4%)	98 more (from 132 fewer to 366 more)	1.06 (0.92, 1.22)	IMPORTANT
	Stroke, haemorrhagic	94 687 (4 studies)	No serious risk of bias[64]	No serious inconsistency[65]	No serious indirectness	No serious imprecision66	Unable to reliably assess[67]	⨁◯◯◯ LOW[68]	754/ 94 687 (0.8%)	14 fewer (from 21 fewer to 1 fewer)	0.55 (0.39 to 0.77)	IMPORTANT
	Stroke, thrombotic	0 (0 studies)	–	–	–	–	–	–	–	–	–	IMPORTANT
	Atrial fibrillation	152 153 (6 studies)	No serious risk of bias[69]	Serious inconsistency[70]	No serious indirectness	Serious imprecision[71]	Unable to reliably assess[72]	⨁◯◯◯ VERY LOW[73]	9073/ 152 153 (6.0%)	1 more (from 5 fewer to 10 more)	1.03 (0.89, 1.19)	IMPORTANT
	Heart failure	74 708 (3 studies)	No serious risk of bias[74]	Not assessed	No serious indirectness	No serious imprecision[75]	Unable to reliably assess[76]	⨁⨁◯◯ MODERATE[77]	3669/ 74 708 (4.9%)	384 fewer (from 651 to 119 fewer)	0.81 (0.69 to 0.94)	IMPORTANT

[59] Median NOS=9 (range: 6–9); Wallstrom *(131)* did not adjust for trans-fat; de Goede *(67)* did; pooled results in opposite directions (Wallstrom: mvRR=1.08; 95% CI: 0.85 to 1.38 and de Goede: mvRR=0.75; 95% CI: 0.46 to 1.22). Removal of highest risk-of-bias study yields mvRR=1.07 (95% CI: 0.90 to 1.28). Not downgraded.

[60] I^2=0%.

[61] 95% CI consistent with 8% decreased risk through 22% increased risk.

[62] Due to small number of studies (n<10), publication bias was not formally assessed.

[63] Prospective cohort studies begin with GRADE of LOW. Downgraded for imprecision.

[64] Median NOS=9 (range: 7–9).

[65] I^2=0%.

[66] 95% CI consistent with 61% through 23% reduced risk; n=754 events. Range of meaningful benefit.

[67] Due to small number of studies (n<10), publication bias was not formally assessed.

[68] Prospective cohort studies begin with GRADE of LOW. Not downgraded.

[69] Median NOS=7.5 (range: 7–9); 1 study that measured TFA [Brouwer *(6)*] showed results compatible with other studies.

[70] I^2=64%; 2 studies [Virtanen *(124)*, Gronroos *(18)*] show possible benefit (pooled mvRR=0.78, 95% CI: 0.53 to 1.16); 4 show possible harm (pooled mvRR=1.11; 95% CI: 0.99 to 1.24).

[71] 95% CI of pooled estimate consistent with 11% lower through 19% higher risk.

[72] Due to small number of studies (n<10), publication bias was not formally assessed.

[73] Prospective cohort studies begin with GRADE of LOW. Downgraded for inconsistency and imprecision.

[74] Two studies, both with NOS=8; 1 adjusted for TFA; the other did not. Results consistent.

[75] Two studies (3 estimates), 95% CI consistent with 31% through 6% reduced risk; n=3669 events.

[76] Due to small number of studies (n<10), publication bias was not formally assessed.

[77] Prospective cohort studies begin with GRADE of LOW. Assuming linearity, a 0.5 g increase in long-chain n-3 PUFA is associated with an 18% decrease in risk of heart failure (mvRR=0.82; 95% CI: 0.72 to 0.93). Assuming linearity, a 0.1% increase in energy from long-chain n-3 PUFA is associated with an 10% decrease in risk of heart failure (mvRR=0.90; 95% CI: 0.85 to 0.96).

QUALITY ASSESSMENT									SUMMARY OF FINDINGS			
EXPOSURE	OUTCOME	PARTICIPANTS (NO. STUDIES)	RISK OF BIAS	INCONSISTENCY	INDIRECTNESS	IMPRECISION	PUBLICATION BIAS	OVERALL QUALITY OF EVIDENCE	STUDY EVENT RATE (%)	ABSOLUTE RISK DIFFERENCE, ADJUSTED (PER 10 000)[1]	RELATIVE RISK, ADJUSTED	IMPORTANCE
Long-chain n-3 PUFA	T2DM	463 462 (16 studies)	No serious risk of bias[78]	Serious inconsistency[79]	No serious indirectness	Serious imprecision[80]	No evidence of publication bias[81]	⨁◯◯◯ VERY LOW[82]	22 451/ 463 462 (4.8%)	56 more (from 6 fewer to 129 more)	1.10 (0.99, 1.23)	IMPORTANT
	Dementia	0 (0 studies)	–	–	–	–	–	–	–	–	–	–
	Cognitive decline	6 976 (3 studies)	No serious risk of bias[83]	No serious inconsistancy[84]	No serious indirectness	Serious imprecision85	Unable to reliably assess[86]	⨁◯◯◯ VERY LOW[87]	979/6976 (14.0%)	224 fewer (from 467 fewer to 66 more)	0.83 (0.65 to 1.05)	IMPORTANT
	Depression	59 035 (4 studies)	No serious risk of bias[88]	No serious inconsistency[89]	No serious indirectness	Serious imprecision[90]	Unable to reliably assess[91]	⨁◯◯◯ VERY LOW[92]	3662/ 59 035 (6.2%)	280 fewer (from 630 fewer to 140 more)	0.92 (0.82 to 1.04)	IMPORTANT

[78] Median NOS=8 (range: 6–9); the 2 low-quality studies (NOS=6) reported significantly increased risk of long-chain n-3 PUFA (mvRR=1.20; 95% CI: 1.04 to 1.39) but weight in overall analysis <15%; in remaining studies, mvRR=1.07 (95% CI: 0.95 to 1.20).

[79] I^2=77%; 9 of 16 studies have point estimates >1.0; 6 statistically significant [Kaushik (NHS I and II) *(88)*, Djoussé *(10)*, Meyer *(33)*, Zhang *(140)* (males and females)]; 1 of 6 showing protection was statistically significant [Villegas *(126)*].

[80] 95% CI consistent with 1% decreased risk through 23% increased risk.

[81] Egger's test: *P*=0.604; Begg's test: *P*=0.753. Trim-and-fill identified no "missed" studies. No publication bias suspected.

[82] Prospective cohort studies begin with GRADE of LOW. Downgraded for inconsistency and imprecision. Assuming linearity, a 0.5 g increase in long-chain n-3 PUFA was associated with a 17% increased risk of type 2 diabetes (mvRR=1.17, 95% CI: 1.10 to 1.24). Assuming linearity, a 0.1% increase in energy from long-chain n-3 PUFA was associated with a 7% increased risk of type 2 diabetes (mvRR=1.07, 95% CI: 1.05 to 1.10).

[83] Three studies; median NOS=8 (6-9); in Vercambre *(51)*, NOS= 9; in Gao *(17)*, NOS=6 (failure to adjust sufficiently for covariates, very high LTFU). Removal of Gao (that looked at supplements only) does not alter estimate substantially, to mvRR=0.88 (95% CI: 0.76 to 1.02).

[84] I^2=52%; largest effect in poorest quality study (that looked at supplements only). Removal of Gao *(17)* reduces heterogeneity to 0%.

[85] 95% CI consistent with 35% decreased risk through 5% increased risk. FE model mvRR=0.86 (95% CI: 0.74, 0.99); >900 events.

[86] Due to small number of studies (*n*<10), publication bias was not formally assessed.

[87] Prospective cohort studies begin with GRADE of LOW. Downgraded for risk of bias and imprecision. Assuming linearity, a 0.5 g increase in long-chain n-3 PUFA is associated with a 23% decrease in risk of cognitive decline (mvRR=0.77; 95% CI: 0.61 to 0.97). Assuming linearity, a 0.1% increase in energy from long-chain n-3 PUFA is associated with an 11% decrease in risk of cognitive decline (mvRR=0.89; 95% CI: 0.81 to 0.99).

[88] Median NOS=7 (range: 7–9).

[89] I^2=0%; all point estimates protective.

[90] 95% CI crosses 1; pooled estimate consistent with 18% decreased though 4% increased risk; >3600 events.

[91] Due to small number of studies (*n*<10), publication bias was not formally assessed.

[92] Prospective cohort studies begin with GRADE of LOW. Downgraded for imprecision.

QUALITY ASSESSMENT									SUMMARY OF FINDINGS			IMPORTANCE
EXPOSURE	OUTCOME	PARTICIPANTS (NO. STUDIES)	RISK OF BIAS	INCONSISTENCY	INDIRECTNESS	IMPRECISION	PUBLICATION BIAS	OVERALL QUALITY OF EVIDENCE	STUDY EVENT RATE (%)	ABSOLUTE RISK DIFFERENCE, ADJUSTED (PER 10 000)[1]	RELATIVE RISK, ADJUSTED	
Long-chain n-3 PUFA	Suicide	101 507 (2 studies)	No serious risk of bias[93]	No serious inconsistency[94]	No serious indirectness	Serious imprecision[95]	Unable to reliably assess[96]	⊕◯◯◯ VERY LOW[97]	298/101 507 (0.29%)	0 (from 0 to 1 more)	1.02 (0.69 to 1.50)	IMPORTANT
	Crohn's disease	171 168 (2 studies)	No serious risk of bias[98]	No serious inconsistency[99]	No serious indirectness	Serious imprecision[100]	Unable to reliably assess[101]	⊕◯◯◯ VERY LOW[102]	342/171 168 (0.20%)	0 (from 3 fewer to 1 more)	0.85 (0.59 to 1.23)	IMPORTANT
	Ulcerative colitis	170 805 (1 study)	No serious risk of bias[103]	Not assessed	No serious indirectness	Serious imprecision[104]	Not assessed	⊕◯◯◯ VERY LOW[105]	338/170 805 (0.20%)	1 fewer (from 4 fewer to 0)	0.72 (0.52 to 1.00)	IMPORTANT
	All breast cancer	266 408 (6 studies)	No serious risk of bias[106]	Serious inconsistency[107]	No serious indirectness	Serious imprecision[108]	Unable to reliably assess[109]	⊕◯◯◯ VERY LOW[110]	5158/266408 (1.9%)	7 fewer (from 13 fewer to 1 more)	0.82 (0.66 to 1.02)	CRITICAL

[93] NOS=8 for both studies; no measure of TFA.
[94] I^2=0%; both studies show no association.
[95] 95% CI crosses 1; pooled estimate consistent with 31% decreased though 50% increased risk; <500 events.
[96] Due to small number of studies (*n*<10), publication bias was not formally assessed.
[97] Prospective cohort studies begin with GRADE of LOW. Downgraded for risk of imprecision.
[98] Median NOS=8.5 (range: 8–9); 1 study measured TFA, the other did not.
[99] I^2=0%; both 95% CI overlap.
[100] 95% CI of pooled estimate consistent with 41% decreased through 23% increased risk; <500 events.
[101] Due to small number of studies (*n*<10), publication bias was not formally assessed.
[102] Prospective cohort studies begin with GRADE of LOW. Downgraded for risk of imprecision.
[103] NOS=9; TFA measured.
[104] 95% CI of estimate includes 1; consistent with 48% reduced risk through 0 change); <500 events.
[105] Prospective cohort studies begin with GRADE of LOW. Downgraded for risk of imprecision.
[106] Median NOS=9 (range: 7–9); 2 studies adjusted for TFA [Holmes *(78)*, Bell *(61)*].
[107] I^2=77%. Two studies adjusted for TFA [Holmes *(78)*, Bell *(61)*] and in these studies, mvRR=1.08 (95% CI: 1.03 to 1.13); in remaining 4 studies, mvRR=0.76 (95% CI: 0.61 to 0.94). Further, RE estimate: 0.82 (95% CI: 0.66 to 1.02) with 29% of weight carried by Holmes (1999) *(78)*, but FE estimate: 1.05 (95% CI: 1.00 to 1.09) with 89% of weight carried by Holmes (1999) *(78)*.
[108] 95% CI (of RE model) consistent with 34% reduced through 2% increased risk; 95% CI (of FE model) consistent with 0% through 9% increased risk; >5000 cases.
[109] Due to small number of studies (*n*<10), publication bias was not formally assessed.
[110] Prospective cohort studies begin with GRADE of LOW. Downgraded for risk of imprecision and inconsistency.

QUALITY ASSESSMENT									SUMMARY OF FINDINGS			IMPORTANCE
EXPOSURE	OUTCOME	PARTICIPANTS (NO. STUDIES)	RISK OF BIAS	INCONSISTENCY	INDIRECTNESS	IMPRECISION	PUBLICATION BIAS	OVERALL QUALITY OF EVIDENCE	STUDY EVENT RATE (%)	ABSOLUTE RISK DIFFERENCE, ADJUSTED (PER 10 000)[1]	RELATIVE RISK, ADJUSTED	
Long-chain n-3 PUFA	Premenopausal breast cancer	179 450 (2 studies)	No serious risk of bias[111]	No serious inconsistency[112]	No serious indirectness	Serious imprecision[113]	Unable to reliably assess[114]	⨁◯◯◯ VERY LOW[115]	1498/179 450 (0.83%)	3 more (from 2 fewer to 9 more)	1.09 (0.96 to 1.23)	CRITICAL
	Postmenopausal breast cancer	106 333 (2 studies)	No serious risk of bias[116]	Serious inconsistency[117]	No serious indirectness	Serious imprecision[118]	Unable to reliably assess[119]	⨁◯◯◯ VERY LOW[120]	1989/106 333 (1.9%)	31 fewer (from 102 fewer to 112 more	0.82 (0.40 to 1.66)	CRITICAL

CHD: coronary heart disease; CI: confidence interval; CVD: cardiovascular disease; FE: fixed effects; GOF: goodness of fit; GRADE: Grading of Recommendations Assessment, Development, and Evaluation; HPFS: Health Professionals Follow-up Study; LTFU: loss to-follow-u; MI: myocardial infarction; mvRR: multivariable risk ratio; NHANES: National Health and Nutrition Examination Survey; NHS: Nurses' Health Study; no.: number; NOS: Newcastle-Ottawa Scale; PUFA: polyunsaturated fatty acids; RE: random effects; T2DM: type 2 diabetes mellitus; TFA: *trans*-fatty acids.

[111] Both studies had NOS=9 and measured TFA.
[112] I^2=0%; both studies' point estimates >1.0.
[113] 95% CI of summary estimate consistent with 4% decreased through 23% increased risk; >1400 events.
[114] Due to small number of studies (*n*<10), publication bias was not formally assessed.
[115] Prospective cohort studies begin with GRADE of LOW. Downgraded for risk of imprecision and inconsistency.
[116] Both studies had NOS=9; Holmes *(78)* reported TFA but Wakai *(129)* did not.
[117] I^2=77%; Holmes *(78)* finds 9% increased risk (P<0.05) but Wakai *(129)* finds 48% decreased risk (from 74% decreased through 4% increased); >1900 events.
[118] RE estimate: 0.82 (95% CI: 0.40 to 1.66) [weight: 61.5% Holmes *(78)*; 38.5% Wakai *(129)*]; FE estimate: 1.08 (95% CI: 1.01 to 1.16) [weight: 99% Holmes; 1% Wakai]
[119] Due to small number of studies (*n*<10), publication bias was not formally assessed.
[120] Prospective cohort studies begin with GRADE of LOW. Downgraded for risk of imprecision, inconsistency.

Table 6. GRADE evidence profile for prospective cohort studies of EPA and health outcomes.

QUALITY ASSESSMENT									SUMMARY OF FINDINGS			IMPORTANCE
EXPOSURE	OUTCOME	PARTICIPANTS (NO. STUDIES)	RISK OF BIAS	INCONSISTENCY	INDIRECTNESS	IMPRECISION	PUBLICATION BIAS	OVERALL QUALITY OF EVIDENCE	STUDY EVENT RATE (%)	ABSOLUTE RISK DIFFERENCE, ADJUSTED (PER 10 000)[1]	RELATIVE RISK, ADJUSTED	
EPA	All-cause mortality	135 350 (2 studies)	No serious risk of bias[2]	No serious inconsistency[3]	No serious indirectness	No serious imprecision[4]	Not assessed	⨁⨁⨁◯ MODERATE[5]	6258/135 530 (4.6%)	205 fewer (from 342 fewer to 46 fewer)	0.82 (0.70, 0.96)	CRITICAL
	CVD, total	0 (0 studies)	–	–	–	–	–	–	–	–		CRITICAL
	CVD, fatal	134 296 (1 study)	No serious risk of bias[6]	Not assessed	No serious indirectness	No serious imprecision[7]	Not assessed	⨁⨁◯◯ LOW[8]	1789/134 296 (1.3%)	99 fewer (from 148 fewer to 40 fewer)	0.75 (0.63, 0.90)	CRITICAL
	CHD, fatal	134 296 (1 study)	No serious risk of bias[9]	Not assessed	No serious indirectness	Serious imprecision[10]	Unable to assess reliably[11]	⨁◯◯◯ VERY LOW[12]	476/134 296 (0.35%)	34 fewer (from 81 fewer to 34 more)	0.83 (0.60, 1.17)	CRITICAL
	Sudden cardiac death	0 (0 studies)	–	–	–	–	–	–	–	–	–	IMPORTANT
	MI, total	54 904 (2 studies)	No serious risk of bias[13]	No serious inconsistency[14]	No serious indirectness	Serious imprecision[15]	Unable to assess reliably[16]	⨁◯◯◯ VERY LOW[17]	3028/54 904 (5.5%)	8 fewer (from 17 fewer to 2 more)	0.91 (0.80 to 1.02)	IMPORTANT
	MI, fatal	0 (0 studies)	–	–	–	–	–	–	–	–	–	IMPORTANT
	MI, nonfatal	0 (0 studies)	–	–	–	–	–	–	–	–	–	IMPORTANT

[1] See Annex 2 for sources of absolute event rates.
[2] NOS=7 and 8; no adjustment for TFA.
[3] I^2=31%; both point estimates protective.
[4] 95% CI of estimate consistent with 30% through 2% reduced risk; *n*>6200 deaths.
[5] Prospective cohort studies begin with GRADE of LOW. Upgraded for dose–response association. Assuming linearity, a 0.5 g increase in EPA is associated with an 27% decrease in risk of mortality (mvRR=0.73; 95% CI: 0.53 to 1.01). Assuming linearity, a 0.1% increase in energy from EPA is associated with an 12% decrease in risk of mortality (mvRR=0.88; 95% CI: 0.77 to 1.01).
[6] NOS=8; no adjustment for TFA.
[7] 95% CI of estimate consistent with 37% through 10% reduced risk; *n*>1700 events.
[8] Prospective cohort studies begin with GRADE of LOW. Not downgraded.
[9] NOS=8; study did not report TFA.
[10] 95% CI of summary estimate consistent with 40% decreased through 17% increased risk; *n*>800 events.
[11] Due to small number of studies (*n*<10), publication bias was not formally assessed.
[12] Prospective cohort studies begin with GRADE of LOW. Downgraded for imprecision.
[13] NOS=7.
[14] I^2=0%.
[15] 95% CI crosses 1; estimates consistent with a 20% reduction through 2% increased risk.
[16] Due to small number of studies (*n*<10), publication bias was not formally assessed.
[17] Prospective cohort studies begin with GRADE of LOW. Downgraded for imprecision.

QUALITY ASSESSMENT									SUMMARY OF FINDINGS			IMPORTANCE
EXPOSURE	OUTCOME	PARTICIPANTS (NO. STUDIES)	RISK OF BIAS	INCONSISTENCY	INDIRECTNESS	IMPRECISION	PUBLICATION BIAS	OVERALL QUALITY OF EVIDENCE	STUDY EVENT RATE (%)	ABSOLUTE RISK DIFFERENCE, ADJUSTED (PER 10 000)[1]	RELATIVE RISK, ADJUSTED	
EPA	Fatal arrhythmia	0 (0 studies)	–	–	–	–	–	–	–	–	–	IMPORTANT
	CHD, total	94 894 (4 studies)	No serious risk of bias[18]	No serious inconsistency[19]	No serious indirectness	Serious imprecision[20]	Unable to assess reliably[21]	⨁◯◯◯ VERY LOW[22]	1733/94 894 (1.8%)	36 fewer (from 132 fewer to 84 more)	0.94 (0.78, 1.14)	CRITICAL
	Stroke, total	0 (0 studies)	–	–	–	–	–	–	–	–	–	IMPORTANT
	Stroke, fatal	0 (0 studies)	–	–	–	–	–	–	–	–	–	IMPORTANT
	Stroke, ischaemic (fatal)	134 296 (1 study)	No serious risk of bias[23]	Not assessed	No serious indirectness	No serious imprecision[24]	Not assessed	⨁⨁⨁◯ MODERATE[25]	404/134 296 (0.3%)	22 fewer (from 37 fewer to 6 fewer)	0.56 (0.36, 0.87)	IMPORTANT
	Stroke, haemorrhagic (fatal)	134 296 (1 study)	No serious risk of bias[26]	Not assessed	No serious indirectness	Serious imprecision[27]	Not assessed	⨁◯◯◯ VERY LOW[28]	460/134 296 (0.34%)	6 fewer (from 13 fewer to 4 more)	0.81 (0.58, 1.13)	IMPORTANT
	Stroke, thrombotic	0 (0 studies)	–	–	–	–	–	–	–	–	–	IMPORTANT
	Atrial fibrillation	50 051 (3 studies)	No serious risk of bias[29]	No serious inconsistency[30]	No serious indirectness	Serious imprecision[31]	Unable to assess reliably[32]	⨁◯◯◯ VERY LOW[33]	3285/50 051 (6.6%)	2 fewer (from 7 fewer to 3 more)	0.94 (0.82, 1.07)	IMPORTANT
	Heart failure	0 (0 studies)	–	–	–	–	–	–	–	–	–	IMPORTANT

[18] Median NOS=8.5 (range: 8–9); no study adjusted for TFA.
[19] I^2=26%; 3 of 4 point estimates <1.0 but none exclude small benefit or harm.
[20] 95% CI of summary estimate consistent with 22% decreased through 14% increased risk; *n*>1700 cases.
[21] Due to small number of studies (*n*<10), publication bias was not formally assessed.
[22] Prospective cohort studies begin with GRADE of LOW. Downgraded for imprecision.
[23] NOS=8; no adjustment for TFA.
[24] 95% CI of estimate consistent with 64% through 13% reduced risk; <500 events.
[25] Prospective cohort studies begin with GRADE of LOW. Downgraded for imprecision. Assuming linearity, a 0.5 g increase in EPA is associated with an 99% decrease in risk of mortality (mvRR=0.02; 95% CI: 0.0006 to 0.4568). Assuming linearity, a 0.1% increase in energy from EPA is associated with an 83% decrease in risk of fatal ischaemic stroke (mvRR=0.17; 95% CI: 0.04 to 0.74).
[26] NOS=8; no adjustment for TFA.
[27] 95% CI of estimate consistent with 42% decreased through 13% increased risk; <500 events.
[28] Prospective cohort studies begin with GRADE of LOW. Downgraded due to imprecision.
[29] Median NOS=9 (range: 7–9). Only Chiuve *(8)* adjusted for TFA.
[30] I^2=0%; all CIs overlap.
[31] 95% CI of summary estimate consistent with 18% reduced through 7% increased risk.
[32] Due to small number of studies (*n*<10), publication bias was not formally assessed.
[33] Prospective cohort studies begin with GRADE of LOW. Downgraded due to imprecision.

QUALITY ASSESSMENT									SUMMARY OF FINDINGS			IMPORTANCE
EXPOSURE	OUTCOME	PARTICIPANTS (NO. STUDIES)	RISK OF BIAS	INCONSISTENCY	INDIRECTNESS	IMPRECISION	PUBLICATION BIAS	OVERALL QUALITY OF EVIDENCE	STUDY EVENT RATE (%)	ABSOLUTE RISK DIFFERENCE, ADJUSTED (PER 10 000)[1]	RELATIVE RISK, ADJUSTED	
EPA	T2DM	48 151 (4 studies)	Serious risk of bias[34]	Serious inconsistency[35]	No serious indirectness	Serious imprecision[36]	Unable to assess reliably[37]	⊕◯◯◯ VERY LOW[38]	3093/48 151 (6.4%)	11 more (from 157 fewer to 252 more)	1.02 (0.72, 1.45)	IMPORTANT
	Dementia	815 (1 study)	No serious risk of bias[39]	Not assessed	No serious indirectness	Serious imprecision[40]	Not assessed	⊕◯◯◯ VERY LOW[41]	131/815 (16.1%)	92 fewer (from 585 fewer to 1086 more)	0.90 (0.38, 2.16)	IMPORTANT
	Cognitive decline	689 (1 study)	–	Not assessed	No serious indirectness	Serious imprecision[42]	Not assessed	⊕◯◯◯ VERY LOW[43]	152/689 (22.1%)	106 fewer (from 306 fewer to 132 more)	0.92 (0.77, 1.10)	IMPORTANT
	Depression	6 223 (4 studies)	No serious risk of bias[44]	No serious inconsistency[45]	No serious indirectness	No serious imprecision[46]	Unable to assess reliably[47]	⊕⊕⊕◯ MODERATE[48]	1354/6223 (21.8%)	805 fewer (from 1191 to 315 fewer)	0.77 (0.66, 0.91)	IMPORTANT
	Suicide	101 507 (2 studies)	No serious risk of bias[49]	No serious inconsistency[50]	No serious indirectness	Serious imprecision[51]	Unable to assess reliably[52]	⊕◯◯◯ VERY LOW[53]	298/101 507 (0.29%)	0 (from 0 to 2 more)	1.11 (0.74, 1.65)	IMPORTANT

[34] Median NOS=7 (range: 6–8). Two studies [Patel *(37)*, Alhazmi *(2)*] have NOS=6. Two studies that show harm have NOS=6 and NOS=8; 2 that show protection have NOS=7 and NOS=9.

[35] I^2=67%; Djoussé adjusted for TFA, and found significant increased risk (mvRR=1.38; 95% CI: 1.20 to 1.58); Alhazmi and Patel (NOS=6) find opposite associations (mvRR=0.66; 95% CI: 0.37 to 1.18; Patel) and (mvRR=1.24; 95% CI: 0.85 to 1.81; Alhazmi), neither statistically significant. Zhang *(140)* shows no effect; did not adjust for TFA.

[36] 95% CI consistent with 28% reduced through 45% increased risk; *n*>3000 cases. FE model yields mvRR=1.26 (95% CI: 1.12 to 1.42).

[37] Due to small number of studies (*n*<10), publication bias was not formally assessed.

[38] Prospective cohort studies begin with GRADE of LOW. Downgraded due to imprecision, risk of bias, and inconsistency.

[39] NOS=8 with measurement of TFA.

[40] 95% CI of estimate consistent with 62% reduced through 116% increased risk; <200 events.

[41] Prospective cohort studies begin with GRADE of LOW. Downgraded due to imprecision.

[42] 95% CI consistent with a 23% reduced through 10% increased risk; <200 cases.

[43] Prospective cohort studies begin with GRADE of LOW. Downgraded due to imprecision.

[44] Median NOS=7 (range: 7–9).

[45] I^2=0%.

[46] 95% CI of summary estimate consistent with 34% decreased through 9% decreased risk; *n*>1300 events.

[47] Due to small number of studies (*n*<10), publication bias was not formally assessed.

[48] Prospective cohort studies begin with GRADE of LOW. Upgraded for dose–response association. Assuming linearity, a 0.5 g increase in EPA is associated with a 30% decrease in risk of depression (mvRR=0.70; 95% CI: 0.56 to 0.88). The median EPA in the studied population was 0.15 g/day. Assuming linearity, a 0.1% increase in energy from EPA is associated with a 16% decrease in risk of depression (mvRR=0.84; 95% CI: 0.75 to 0.94). The median EPA in the studied population was 0.04% energy.

[49] NOS=9; adjustment for TFA.

[50] One study presents estimates separately for men and women; both effects suggest no association.

[51] 95% CI of pooled estimate consistent with 26% reduced through 65% increased risk; *n*<300 cases.

[52] Due to small number of studies (*n*<10), publication bias was not formally assessed.

[53] Prospective cohort studies begin with GRADE of LOW. Downgraded due to imprecision.

QUALITY ASSESSMENT									SUMMARY OF FINDINGS			IMPORTANCE
EXPOSURE	OUTCOME	PARTICIPANTS (NO. STUDIES)	RISK OF BIAS	INCONSISTENCY	INDIRECTNESS	IMPRECISION	PUBLICATION BIAS	OVERALL QUALITY OF EVIDENCE	STUDY EVENT RATE (%)	ABSOLUTE RISK DIFFERENCE, ADJUSTED (PER 10 000)[1]	RELATIVE RISK, ADJUSTED	
EPA	Crohn's disease	362 (1 study)	No serious risk of bias[54]	Not assessed	No serious indirectness	Serious imprecision[55]	Unable to assess reliably[56]	⊕◯◯◯ VERY LOW[57]	73/362 (20.2%)[58]	24 more (from 0 to 436 more)	8.56 (0.88, 83.07)	IMPORTANT
	Ulcerative colitis	203 193 (1 study)	No serious risk of bias[59]	Not assessed	No serious indirectness	Serious imprecision[60]	Unable to assess reliably[61]	⊕◯◯◯ VERY LOW[62]	126/203 193 (0.06%)	12 more (from 3 fewer to 90 more)	2.58 (0.66, 10.07)	IMPORTANT
	All breast cancer	139 208 (3 studies)	No serious risk of bias[63]	Serious inconsistency[64]	No serious indirectness	Serious imprecision[65]	Unable to assess reliably[66]	⊕◯◯◯ VERY LOW[67]	3414/139 208 (2.5%)	229 fewer (from 647 fewer to 312 more)	0.89 (0.69, 1.15)	IMPORTANT
	Premenopausal breast cancer	0 (0 studies)	–	–	–	–	–	–	–	–		IMPORTANT

[54] NOS=8; no adjustment for TFA.
[55] 95% CI of study estimate consistent with 12% decreased through 8207% increased risk; *n*<100 cases.
[56] Due to small number of studies (*n*<10), publication bias was not formally assessed.
[57] Prospective cohort studies begin with GRADE of LOW. Downgraded due to imprecision.
[58] Prospective case–control study.
[59] NOS=8; no adjustment for TFA.
[60] 95% CI of study estimate consistent with 34% decreased through 907% increased risk; *n*<200 cases.
[61] Due to small number of studies (*n*<10), publication bias was not formally assessed.
[62] Prospective cohort studies begin with GRADE of LOW. Downgraded due to imprecision.
[63] Three studies, NOS=7-9; Holmes *(78)* adjusted for TFA, Sczaniecka *(112)* and Sellem *(150)* did not.
[64] I^2=83%. Holmes (1999) finds significantly increased risk (mvRR=1.06; 95% CI: 1.02 to 1.10); Sczaniecka *(112)* and Sellem *(150)*pooled do not (mvRR=0.79 [95% CI: 0.66 to 0.95]). FE model mvRR=1.05 (95% CI: 1.01 to 1.09); 98% of weight taken by Holmes.
[65] 95% CI of summary estimate consistent with 31% decreased through 15% increased risk; *n*>3400 cases.
[66] Due to small number of studies (*n*<10), publication bias was not formally assessed.
[67] Prospective cohort studies begin with GRADE of LOW. Downgraded due to imprecision and inconsistency. Dose–response association conducted. Assuming linearity, a 0.5 g increase in energy from EPA is associated with a 25% increase in risk of breast cancer (mvRR=1.25; 95% CI: 0.95 to 1.66). Assuming linearity, a 0.1% increase in energy from EPA is associated with a 9% increase in risk of breast cancer (mvRR=1.09; 95% CI: 0.98 to 1.20). However, a nonlinear model is a better fit. Dose–response association appears to increase from 0.0 to 0.05 g/day (0 to 0.02% energy), then decrease from 0.05 through 0.25 g/day (0.02% through 0.12%).

QUALITY ASSESSMENT									SUMMARY OF FINDINGS			IMPORTANCE
EXPOSURE	OUTCOME	PARTICIPANTS (NO. STUDIES)	RISK OF BIAS	INCONSISTENCY	INDIRECTNESS	IMPRECISION	PUBLICATION BIAS	OVERALL QUALITY OF EVIDENCE	STUDY EVENT RATE (%)	ABSOLUTE RISK DIFFERENCE, ADJUSTED (PER 10 000)[1]	RELATIVE RISK, ADJUSTED	
EPA	Postmenopausal breast cancer	4 089 (2 studies)[68]	No serious risk of bias[69]	Not assessed	No serious indirectness	Serious imprecision[70]	Unable to assess reliably[71]	⨁⨁⨁◯ MODERATE[72]	1411/4089 (34.5%)	442 fewer (from 991 fewer to 511 more)	0.74 (0.42, 1.30)	IMPORTANT

CHD: coronary heart disease; CI: confidence interval; CVD: cardiovascular disease; EPA: eicosapentaenoic acid; FE: fixed effects; GRADE: Grading of Recommendations Assessment, Development, and Evaluation; MI: myocardial infarction; mvRR: multivariable risk ratio; no.: number; NOS: Newcastle-Ottawa Scale; RR: risk ratio; T2DM: type 2 diabetes mellitus; TFA: *trans*-fatty acids.

[68] One study was a prospective case–control study [Voorrips *(128)*].

[69] NOS=8 and 9; with adjustment for TFA in 1 study [Voorrips *(128)*].

[70] 95% CI of FE estimate consistent with 40% through 3% decreased risk; *n*>1400 cases.

[71] Due to small number of studies (*n*<10), publication bias was not formally assessed.

[72] Prospective cohort studies begin with GRADE of LOW. Not downgraded. Dose–response association meta-analysis conducted. Assuming linearity, a 0.5 g increase in EPA is associated with a 61% decrease in risk of postmenopausal breast cancer (mvRR=0.39; 95% CI: 0.21 to 0.74). Assuming linearity, a 0.1% increase in EPA is associated with a 32% decrease in risk of postmenopausal breast cancer (mvRR=0.68; 95% CI: 0.52 to 0.89).

Table 7. GRADE evidence profile for prospective cohort studies of DHA and health outcomes

QUALITY ASSESSMENT									SUMMARY OF FINDINGS			IMPORTANCE
EXPOSURE	OUTCOME	PARTICIPANTS (NO. STUDIES)	RISK OF BIAS	INCONSISTENCY	INDIRECTNESS	IMPRECISION	PUBLICATION BIAS	OVERALL QUALITY OF EVIDENCE	STUDY EVENT RATE (%)	ABSOLUTE RISK DIFFERENCE, ADJUSTED (PER 10 000)[1]	RELATIVE RISK, ADJUSTED	
DHA	All-cause mortality	135 350 (2 studies)	No serious risk of bias[2]	Not assessed	No serious indirectness	No serious imprecision[3]	Not assessed	⨁⨁⨁◯ MODERATE[4]	6258/135 350 (4.6%)	205 fewer (354 fewer to 46 fewer)	0.82 (0.69, 0.96)	CRITICAL
	CVD, total	0 (0 studies)	–	–	–	–	–	–	–	–		CRITICAL
	CVD, fatal	134 296 (1 study)	No serious risk of bias[5]	Not assessed	No serious indirectness	No serious imprecision[6]	Not assessed	⨁⨁◯◯ LOW[7]	1789/134 296 (1.33%)	95 fewer (from 144 fewer to 36 fewer)	0.76 (0.64, 0.91)	CRITICAL
	CHD, fatal	134 296 (1 study)	No serious risk of bias[8]	Not assessed	No serious indirectness	Serious imprecision[9]	Not assessed	⨁◯◯◯ VERY LOW[10]	476/134 296 (0.35%)	59 fewer (from 121 fewer to 25 more)	0.79 (0.57, 1.09)	CRITICAL
	Sudden cardiac death	0 (0 studies)	–	–	–	–	–	–	–	–	–	IMPORTANT
	MI, total	54 904 (2 studies)	No serious risk of bias[11]	No serious inconsistency[12]	No serious indirectness	Serious imprecision[13]	Unable to assess reliably[14]	⨁◯◯◯ VERY LOW[15]	3028/54 904 (5.5%)	8 fewer (from 17 fewer to 2 more)	0.88 (0.78, 1.01)	IMPORTANT
	MI, fatal	0 (0 studies)	–	–	–	–	–	–	–	–	–	IMPORTANT

1 See Annex 2 for sources of absolute event rates.
2 NOS=7–8; no adjustment for TFA.
3 95% CI of estimate consistent with 31% through 4% decreased risk; >6000 events.
4 Prospective cohort studies begin with GRADE of LOW. Upgraded for dose–response association. Assuming linearity, a 0.5 g increase in DHA is associated with a 21% decrease in risk of all-cause mortality (mvRR=0.79; 95% CI: 0.65 to 0.96). Assuming linearity, a 0.1% increase in DHA is associated with a 10% decrease in risk of all-cause mortality (mvRR=0.90; 95% CI: 0.83 to 0.98).
5 NOS=8; no adjustment for TFA.
6 95% CI of estimate consistent with 36% through 9% decreased risk; >1700 events.
7 Prospective cohort studies begin with GRADE of LOW. Not downgraded. Assuming linearity, a 0.5 g/day increase in DHA is associated with a 39% decrease in risk of fatal CVD (mvRR=0.61; 95% CI: 0.34 to 1.07). Assuming linearity, a 0.1% increase in energy from DHA is associated with a 21% decrease in risk of fatal CVD (mvRR=0.79; 95% CI: 0.61 to 1.02).
8 NOS=8; no adjustment for TFA.
9 95% CI of estimate consistent with 43% decreased through 9% increased risk; <500 events.
10 Prospective cohort studies begin with GRADE of LOW. Downgraded for imprecision.
11 NOS=7.
12 I2=0%.
13 95% CI crosses 1; estimates consistent with a 22% reduction through 1% increased risk.
14 Due to small number of studies (n<10), publication bias was not formally assessed.
15 Prospective cohort studies begin with GRADE of LOW. Downgraded for imprecision; dose–response association not significant, so not upgraded. Assuming linearity, a 0.5 g/day increase in DHA is associated with a 5% decrease in risk of total myocardial infarction (mvRR=0.95; 95% CI: 0.86 to 1.04). Assuming linearity, a 0.1% increase in energy from DHA is associated with a 3% decrease in risk of total myocardial infarction (mvRR=0.97; 95% CI: 0.91 to 1.02).

QUALITY ASSESSMENT									SUMMARY OF FINDINGS			IMPORTANCE
EXPOSURE	OUTCOME	PARTICIPANTS (NO. STUDIES)	RISK OF BIAS	INCONSISTENCY	INDIRECTNESS	IMPRECISION	PUBLICATION BIAS	OVERALL QUALITY OF EVIDENCE	STUDY EVENT RATE (%)	ABSOLUTE RISK DIFFERENCE, ADJUSTED (PER 10 000)[1]	RELATIVE RISK, ADJUSTED	
DHA	MI, non-fatal	0 (0 studies)	–	–	–	–	–	–	–	–	–	IMPORTANT
	Fatal arrhythmia	0 (0 studies)	–	–	–	–	–	–	–	–	–	IMPORTANT
	CHD, total	94 894 (4 studies)	No serious risk of bias[16]	No serious inconsistency[17]	No serious indirectness	Serious imprecision[18]	Unreliable to assess[19]	⨁◯◯◯ VERY LOW[20]	1733/94 894 (1.83%)	42 fewer (from 126 fewer to 60 more)	0.93 (0.79, 1.10)	CRITICAL
	Stroke, total	0 (0 studies)	–	–	–	–	–	–	–	–	–	IMPORTANT
	Stroke, fatal	0 (0 studies)	–	–	–	–	–	–	–	–	–	IMPORTANT
	Stroke, ischaemic (fatal)	134 296 (1 study)	No serious risk of bias[21]	Not assessed	No serious indirectness	No serious imprecision[22]	Not assessed	⨁⨁⨁◯ MODERATE[23]	404/134 296 (0.3%)	122 fewer (from 174 to 43 fewer)	0.55 (0.36, 0.84)	IMPORTANT
	Stroke, haemorrhagic (fatal)	134 296 (1 study)	No serious risk of bias[24]	Not assessed	No serious indirectness	Serious imprecision[25]	Not assessed	⨁◯◯◯ VERY LOW[26]	460/134 296 (0.34%)	2 fewer (from 16 fewer to 25 more)	0.95 (0.50, 1.81)	IMPORTANT
	Stroke, thrombotic	0 (0 studies)	–	–	–	–	–	–	–	–	–	IMPORTANT
	Atrial fibrillation	50 051 (3 studies)	No serious risk of bias[27]	Serious inconsistency[28]	No serious indirectness	Serious imprecision[29]	Unreliable to assess[30]	⨁◯◯◯ VERY LOW[31]	3285/50 051 (6.56%)	8 fewer (from 19 fewer to 6 more)	0.84 (0.63, 1.13)	IMPORTANT

[16] NOS=8 and 9; neither study assessed TFA.

[17] I^2=0%; ¾ point estimates <1.0; all 95% CI overlap.

[18] 95% CI consistent with 21% decreased through 10% increased risk; *n*>1700 events.

[19] Due to small number of studies (*n*<10), risk of publication bias was not formally assessed.

[20] Prospective cohort studies begin with GRADE of LOW. Downgraded for imprecision.

[21] NOS=8; no adjustment for TFA.

[22] 95% CI of estimate consistent with 64% through 16% decreased risk; <500 events.

[23] Prospective cohort studies begin with GRADE of LOW. Not downgraded. Assuming linearity, a 0.5 g increase in energy from DHA is associated with a 74% decrease in risk of fatal ischaemic stroke (mvRR=0.26; 95% CI: 0.07 to 0.98). Assuming linearity, a 0.1% increase in energy from DHA is associated with a 44% decrease in risk of fatal ischaemic stroke (mvRR=0.56; 95% CI: 0.31 to 1.007).

[24] NOS=8; no adjustment for TFA.

[25] 95% CI of estimate consistent with 50% decreased through 81% increased risk; <500 events.

[26] Prospective cohort studies begin with GRADE of LOW. Downgraded for imprecision.

[27] Median NOS=9 (range: 7–9); 1 study [Chiuve *(8)*] adjusted for TFA.

[28] I^2=62%; 1 study [Virtanen *(124)*] found significant protection (mvRR=0.58, 95% CI: 0.39 to 0.87); the other 2 [Gronroos *(18)*, *(8)*] find no association (mvRR=0.94, 95% CI: 0.82 to 1.08).

[29] 95% CI of summary estimate consistent with 37% decreased through 13% increased risk (RE); FE estimate: mvRR=0.89 (95% CI: 0.79 to 1.02).

[30] Due to small number of studies (*n*<10), risk of publication bias was not formally assessed.

[31] Prospective cohort studies begin with GRADE of LOW. Downgraded for imprecision and inconsistency.

QUALITY ASSESSMENT									SUMMARY OF FINDINGS			IMPORTANCE
EXPOSURE	OUTCOME	PARTICIPANTS (NO. STUDIES)	RISK OF BIAS	INCONSISTENCY	INDIRECTNESS	IMPRECISION	PUBLICATION BIAS	OVERALL QUALITY OF EVIDENCE	STUDY EVENT RATE (%)	ABSOLUTE RISK DIFFERENCE, ADJUSTED (PER 10 000)[1]	RELATIVE RISK, ADJUSTED	
DHA	Heart failure	0 (0 studies)	–	–	–	–	–	–	–	–	–	IMPORTANT
	T2DM	48 151 (4 studies)	Serious risk of bias[32]	Serious inconsistency[33]	No serious indirectness	Serious imprecision[34]	Unable to assess reliably[35]	⨁◯◯◯ VERY LOW[36]	3093/48 151 (6.42%)	6 more (from 191 fewer to 303 more)	1.01 (0.66, 1.54)	IMPORTANT
	Dementia	1980 (3 studies)	No serious risk of bias[37]	No serious inconsistency38	No serious indirectness	No serious imprecision[39]	Unable to assess reliably[40]	⨁⨁⨁◯ MODERATE41	272/1980 (13.74%)	696 fewer (from 970 fewer to 344 fewer)	0.42 (0.25, 0.70)	IMPORTANT
	Cognitive decline	0 (0 studies)	–	–	–	–	–	–	–	–	–	IMPORTANT
	Depression	6 223 (4 studies)	No serious risk of bias[42]	No serious inconsistency[43]	No serious indirectness	No serious imprecision[44]	Unable to assess reliably[45]	⨁⨁⨁◯ MODERATE[46]	1354/6223 (21.8%)	805 fewer (from 1191 to 315 fewer)	0.79 (0.67, 0.94)	IMPORTANT

[32] Median NOS=6 (range: 6–8). Two studies [Patel *(37)*, Alhazmi *(2)*] have NOS=6.

[33] I^2=78%; Djoussé *(10)* adjusted for TFA, and found significant increased risk (mvRR=1.52; 95% CI: 1.33 to 1.74); Alhazmi *(2)* and Patel *(37)* (NOS=6) find opposite associations (mvRR=0.63; 95% CI: 0.35 to 1.13;Patel) and (mvRR=1.19; 95% CI: 0.81 to 1.74; Alhazmi), neither statistically significant.

[34] 95% CI consistent with 26% reduced through 74% increased risk; *n*>2800 cases. FE model yields mvRR=1.42 (95% CI: 1.25 to 1.61; 85% of weight is from the Djoussé study).

[35] Due to small number of studies (*n*<10), publication bias was not formally assessed.

[36] Prospective cohort studies begin with GRADE of LOW. Downgraded due to imprecision, risk of bias, and inconsistency.

[37] Median NOS=8 (range: 7–8); Morris *(151)* adjusted for TFA.

[38] I^2=0%; all studies' point estimates contained by each other's 95% CI. The study that adjusted for TFA (Morris) observed similar associations to other 2 studies.

[39] 95% CI of summary estimate consistent with 30% through 58% reduced risk; *n*=272 events.

[40] Due to small number of studies (*n*<10), publication bias was not formally assessed.

[41] Prospective cohort studies begin with GRADE of LOW. Not downgraded. Assuming linearity, a 0.5 g increase in energy from DHA is associated with a 99% decrease in risk of dementia (mvRR=0.012; 95% CI: 0.0014 to 0.12). The median DHA in the studied population was 0.0425 g/day. Assuming linearity, a 0.1% increase in energy from DHA is associated with a 99% decrease in risk of dementia (mvRR=0.012; 95% CI: 0.0014 to 0.12).

[42] Median NOS=7 (range: 7–9).

[43] I^2=0%.

[44] 95% CI of summary estimate consistent with 34% decreased through 9% decreased risk; *n*>1300 events.

[45] Due to small number of studies (*n*<10), publication bias was not formally assessed.

[46] Prospective cohort studies begin with GRADE of LOW. Upgraded for dose–response association. Assuming linearity, a 0.5 g increase in DHA is associated with a 30% decrease in risk of depression (mvRR=0.70; 95% CI: 0.56 to, 0.88). Assuming linearity, a 0.1% increase in energy from DHA is associated with a 9% decrease in risk of depression (mvRR=0.91; 95% CI: 0.85 to 0.98).

QUALITY ASSESSMENT									SUMMARY OF FINDINGS			
EXPOSURE	OUTCOME	PARTICIPANTS (NO. STUDIES)	RISK OF BIAS	INCONSISTENCY	INDIRECTNESS	IMPRECISION	PUBLICATION BIAS	OVERALL QUALITY OF EVIDENCE	STUDY EVENT RATE (%)	ABSOLUTE RISK DIFFERENCE, ADJUSTED (PER 10 000)[1]	RELATIVE RISK, ADJUSTED	IMPORTANCE
DHA	Suicide	101 507 (2 studies)	No serious risk of bias[47]	No serious inconsistency[48]	No serious indirectness	Serious imprecision[49]	Unable to assess reliably[50]	⊕◯◯◯ VERY LOW[51]	298/101 507 (0.29%)	0 (from 0 to 2 more)	1.09 (0.74, 1.60)	IMPORTANT
	Crohn's disease	362 (1 study)	No serious risk of bias[52]	Not assessed	No serious indirectness	Serious imprecision[53]	Unable to assess reliably[54]	⊕◯◯◯ VERY LOW[55]	73/362 (20.17%)	3 fewer (from 13 fewer to 1 fewer)	0.06 (0.01, 0.51)	IMPORTANT
	Ulcerative colitis	203 193 (1 study)	No serious risk of bias[56]	Not assessed	No serious indirectness	Serious imprecision[57]	Unable to assess reliably58	⊕◯◯◯ VERY LOW[59]	126/203 193 (0.06%)	6 fewer (from 15 fewer to 0)	0.23 (0.06, 0.92)	IMPORTANT
	All breast cancer	139 228 (3 studies)	No serious risk of bias[60]	Serious inconsistency[61]	No serious indirectness	Serious imprecision[62]	Unable to assess reliably[63]	⊕◯◯◯ VERY LOW[64]	3414/139 228 (2.5%)	146 fewer (from 584 fewer to 417 more)	0.93 (0.72, 1.20)	IMPORTANT

[47] NOS=9; adjustment for TFA.

[48] One study presents estimates separately for men and women; both effects suggest no association.

[49] 95% CI of pooled estimate consistent with 26% reduced through 60% increased risk; *n*<300 cases.

[50] Due to small number of studies (*n*<10), publication bias was not formally assessed.

[51] Prospective cohort studies begin with GRADE of LOW. Downgraded due to imprecision.

[52] NOS=8; no adjustment for TFA.

[53] 95% CI of study estimate consistent with 49% decreased through 99% increased risk; *n*<100 cases.

[54] Due to small number of studies (*n*<10), publication bias was not formally assessed.

[55] Prospective cohort studies begin with GRADE of LOW. Downgraded due to imprecision.

[56] NOS=8; no adjustment for TFA.

[57] 95% CI of study estimate consistent with 8% through 94% decreased risk; *n*<200 cases.

[58] Due to small number of studies (*n*<10), publication bias was not formally assessed.

[59] Prospective cohort studies begin with GRADE of LOW. Downgraded due to imprecision.

[60] Three studies, NOS=7–9 for both; Holmes *(78)* adjusted for TFA, Sczaniecka *(112)* and Sellem *(150)* did not adjust for TFA.

[61] I^2=82%; Holmes (1999) *(78)* finds significantly increased risk (mvRR=1.04; 95% CI: 1.02 to 1.07); Sczaniecka and Sellem pooled (mvRR=0.85; 95% CI: 0.71 to 1.02). FE model mvRR=1.04; 95% CI: 1.01 to 1.06; 98% of weight from Holmes.

[62] 95% CI of summary estimate consistent with 28% decreased through 20% increased risk; *n*>3400 cases.

[63] Due to small number of studies (*n*<10), publication bias was not formally assessed.

[64] Prospective cohort studies begin with GRADE of LOW. FE meta-analysis consistent with mvRR=1.04 (95% CI: 1.01 to 1.06). Dose–response association meta-analysis done. Assuming linearity, a 0.5 g increase in energy from DHA is associated with a 14% increase in risk of breast cancer (mvRR=1.14; 95% CI: 0.93 to 1.40). However, GOF test *P*=0.0075. Using spline approach, appears as if risk increases from 0 g/day to 0.05 g/day; then decreases from 0.05 g/day through 0.25 g/day (0.05% energy through 0.15% energy).

QUALITY ASSESSMENT									SUMMARY OF FINDINGS			IMPORTANCE
EXPOSURE	OUTCOME	PARTICIPANTS (NO. STUDIES)	RISK OF BIAS	INCONSISTENCY	INDIRECTNESS	IMPRECISION	PUBLICATION BIAS	OVERALL QUALITY OF EVIDENCE	STUDY EVENT RATE (%)	ABSOLUTE RISK DIFFERENCE, ADJUSTED (PER 10 000)[1]	RELATIVE RISK, ADJUSTED	
DHA	Premenopausal breast cancer	0 (0 studies)	–	–	–	–	–	–	–	–		IMPORTANT
	Postmenopausal breast cancer	4 089 (2 studies)	No serious risk of bias[65]	Serious inconsistency[66]	No serious indirectness	Serious imprecision[67]	Unable to assess reliably[68]	⨁⨁◯◯ LOW[69]	1411/4089 (34.5%)[70]	442 fewer (from 991 fewer to 511 more)	0.74 (0.59, 0.94)	IMPORTANT

CHD: coronary heart disease; CI: confidence interval; CVD: cardiovascular disease; DHA: docosahexaenoic acid; FE: fixed effects; GOF: goodness of fit; GRADE: Grading of Recommendations Assessment, Development, and Evaluation; MI: myocardial infarction; mvRR: multivariable risk ratio; no.: number; NOS: Newcastle-Ottawa Scale; RE: random effects; RR: risk ratio; T2DM: type 2 diabetes mellitus; TFA: *trans*-fatty acids.

[65] NOS=8 and 9; with adjustment for TFA in 1 study [Voorrips *(128)*].

[66] I-squared = 86%; Bassett (2016) finds significantly reduced risk (mvRR=0.53; 95% CI: 0.38 to 0.74); Vooripps (2012) finds no association (mvRR = 1.00; 95% CI: 0.72 to 1.38).

[67] 95% CI of fixed estimate consistent with 41% through 6% decreased risk; *n*>1400 cases.

[68] Due to small number of studies (*n*<10), publication bias was not formally assessed.

[69] Prospective cohort studies begin with GRADE of LOW. Assuming linearity, a 0.5 g increase in energy from DHA is associated with a 50% reduced risk of postmenopausal breast cancer (mvRR=0.50; 95% CI: 0.31 to 0.81). Assuming linearity, a 0.1% increase in energy from DHA is associated with a 24% reduced risk of postmenopausal breast cancer (mvRR=0.76; 95% CI: 0.62 to 0.92). Concerns around inconsistency, imprecision in highest vs. lowest comparisons. Kept as LOW.

[70] Prospective case–control study [Voorrips *(128)*].

Table 8. GRADE evidence profile for prospective cohort studies of DPA and health outcomes

QUALITY ASSESSMENT									SUMMARY OF FINDINGS			IMPORTANCE
EXPOSURE	OUTCOME	PARTICIPANTS (NO. STUDIES)	RISK OF BIAS	INCONSISTENCY	INDIRECTNESS	IMPRECISION	PUBLICATION BIAS	OVERALL QUALITY OF EVIDENCE	STUDY EVENT RATE (%)	ABSOLUTE RISK DIFFERENCE, ADJUSTED (PER 10 000)[1]	RELATIVE RISK, ADJUSTED	
DPA	All-cause mortality	0 (0 studies)	–	–	–	–	–	–	–	–	–	CRITICAL
	CVD, total	0 (0 studies)	–	–	–	–	–	–	–	–	–	CRITICAL
	CVD, fatal	0 (0 studies)	–	–	–	–	–	–	–	–	–	CRITICAL
	CHD, fatal	0 (0 studies)	–	–	–	–	–	–	–	–	–	CRITICAL
	Sudden cardiac death	0 (0 studies)	–	–	–	–	–	–	–	–	–	IMPORTANT
	MI, total	54 904 (2 studies)[2]	No serious risk of bias[3]	No serious inconsistency[4]	No serious indirectness	Serious imprecision[5]	Unable to assess reliably[6]	⨁◯◯◯ VERY LOW[7]	3028/54 904 (5.5%)	9 fewer (from 19 fewer to 3 more)	0.89 (0.78, 1.03)	IMPORTANT
	MI, fatal	0 (0 studies)	–	–	–	–	–	–	–	–	–	IMPORTANT
	MI, nonfatal	0 (0 studies)	–	–	–	–	–	–	–	–	–	IMPORTANT
	Fatal arrhythmia	0 (0 studies)	–	–	–	–	–	–	–	–	–	IMPORTANT
	CHD, total	53 803 (2 studies)	No serious risk of bias[8]	No serious inconsistency[9]	No serious indirectness	Serious imprecision[10]	Not assessed	⨁◯◯◯ VERY LOW[11]	1124/53 803 (2.1%)	54 fewer (from 168 fewer to 90 more)	0.91 (0.72 to 1.15)	CRITICAL
	Stroke, total	0 (0 studies)	–	–	–	–	–	–	–	–	–	IMPORTANT
	Stroke, fatal	0 (0 studies)	–	–	–	–	–	–	–	–	–	IMPORTANT
	Stroke, ischaemic (fatal)	0 (0 studies)	–	–	–	–	–	–	–	–	–	IMPORTANT

[1] See Annex 2 for sources of absolute event rates.
[2] Two estimates from same publication.
[3] One study, NOS=7; did not adjust for TFA.
[4] I^2=0%.
[5] 95% CI includes 1.0. Consistent with 22% decreased through 3% increased risk.
[6] Due to small number of studies (n<10), publication bias was not formally assessed.
[7] Prospective cohort studies begin with GRADE of LOW. Downgraded for imprecision.
[8] NOS=8; no adjustment for TFA.
[9] Study presented associations for men and women separately; I2=0%.
[10] 95% CI of study estimate consistent with 26% reduced through 57% increased risk; n<500 events.
[11] Prospective cohort studies begin with GRADE of LOW. Downgraded for imprecision.

QUALITY ASSESSMENT									SUMMARY OF FINDINGS			IMPORTANCE
EXPOSURE	OUTCOME	PARTICIPANTS (NO. STUDIES)	RISK OF BIAS	INCONSISTENCY	INDIRECTNESS	IMPRECISION	PUBLICATION BIAS	OVERALL QUALITY OF EVIDENCE	STUDY EVENT RATE (%)	ABSOLUTE RISK DIFFERENCE, ADJUSTED (PER 10 000)[1]	RELATIVE RISK, ADJUSTED	
DPA	Stroke, haemorrhagic (fatal)	0 (0 studies)	–	–	–	–	–	–	–	–	–	IMPORTANT
	Stroke, thrombotic	0 (0 studies)	–	–	–	–	–	–	–	–	–	IMPORTANT
	Atrial fibrillation	2 174 (1 study)	No serious risk of bias[12]	Not assessed	No serious indirectness	Serious imprecision[13]	Not assessed	⨁◯◯◯ VERY LOW[14]	1124/53 803 (2.1%)	2 fewer (from 13 fewer to 15 more)	0.95 (0.65 to 1.39)	IMPORTANT
	Heart failure	0 (0 studies)	–	–	–	–	–	–	–	–	–	IMPORTANT
	T2DM	2 174 (1 study)	No serious risk of bias[15]	Not assessed	No serious indirectness	Serious imprecision[16]	Not assessed	⨁◯◯◯ VERY LOW[17]	213/2671 (8.0%)	45 more (from 146 fewer to 319 more)	1.08 (0.74 to 1.57)	IMPORTANT
	Dementia	0 (0 studies)	–	–	–	–	–	–	–	–	–	IMPORTANT
	Cognitive decline	691 (1 study)	No serious risk of bias[18]	Not assessed	No serious indirectness	Serious imprecision[19]	Not assessed	⨁◯◯◯ VERY LOW[20]	154/691 (22.3%)	79 fewer (from 306 fewer to 199 more)	0.94 (0.77 to 1.15)	IMPORTANT
	Depression	1 086 (1 study)	No serious risk of bias[21]	Not assessed	No serious indirectness	Serious imprecision22	Not assessed	⨁◯◯◯ VERY LOW[23]	95/1086 (8.7%)	525 fewer (from 1786 to 1645 more)	0.85 (0.49 to 1.47)	IMPORTANT
	Suicide	0 (0 studies)	–	–	–	–	–	–	–	–	–	IMPORTANT
	Crohn's disease	0 (0 studies)	–	–	–	–	–	–	–	–	–	IMPORTANT
	Ulcerative colitis	0 (0 studies)	–	–	–	–	–	–	–	–	–	IMPORTANT

[12] NOS=7; no adjustment for TFA.
[13] 95% CI of study estimate consistent with 35% reduced through 39% increased risk; *n*<300 events.
[14] Prospective cohort studies begin with GRADE of LOW. Downgraded for imprecision.
[15] One study, NOS=8; no measure of TFA.
[16] 95% CI of study estimate consistent with 35% reduced through 39% increased risk; *n*<300 events.
[17] Prospective cohort studies begin with GRADE of LOW. Downgraded for imprecision.
[18] One study, NOS=8; no measure of TFA.
[19] 95% CI of study estimate consistent with 23% reduced through 15% increased risk; *n*<200 events.
[20] Prospective cohort studies begin with GRADE of LOW. Downgraded for imprecision.
[21] One study, NOS=8; no measure of TFA.
[22] 95% CI of study estimate consistent with 51% reduced through 47% increased risk; *n*>500 events.
[23] Prospective cohort studies begin with GRADE of LOW. Downgraded for imprecision.

QUALITY ASSESSMENT									SUMMARY OF FINDINGS			IMPORTANCE
EXPOSURE	OUTCOME	PARTICIPANTS (NO. STUDIES)	RISK OF BIAS	INCONSISTENCY	INDIRECTNESS	IMPRECISION	PUBLICATION BIAS	OVERALL QUALITY OF EVIDENCE	STUDY EVENT RATE (%)	ABSOLUTE RISK DIFFERENCE, ADJUSTED (PER 10 000)[1]	RELATIVE RISK, ADJUSTED	
DPA	All breast cancer	31 437 (1 study)	No serious risk of bias[24]	Not assessed	No serious indirectness	Serious imprecision[25]	Not assessed	⨁◯◯◯ VERY LOW[26]	545/31 437 (1.7%)	21 more (from 479 more to 688 more)	1.01 (0.77 to 1.33)	IMPORTANT
	Premenopausal breast cancer	0 (0 studies)	–	–	–	–	–	–	–	–	–	IMPORTANT
	Postmenopausal breast cancer	2 491 (1 study)	No serious risk of bias[27]	Not assessed	No serious indirectness	No serious imprecision[28]	Not assessed	⨁⨁⨁◯ MODERATE[29]	470/2491 (18.9%)	731 fewer (from 1030 to 305 fewer)	0.57 (0.40 to 0.82)	IMPORTANT

CHD: coronary heart disease; CI: confidence interval; CVD: cardiovascular disease; DPA: docosapentaenoic acid; GRADE: Grading of Recommendations Assessment, Development, and EvaluationMI: myocardial infarction; mvRR: multivariable risk ratio; no.: number; NOS: Newcastle-Ottawa Scale; RR: risk ratio; T2DM: type 2 diabetes mellitus; TFA: trans-fatty acids.

[24] One study, NOS=7; no measure of TFA.
[25] 95% CI of study estimate consistent with 23% reduced through 33% increased risk; *n*<100 events.
[26] Prospective cohort studies begin with GRADE of LOW. Downgraded for imprecision.
[27] NOS=9; no measurement of TFA.
[28] 95% CI of study estimate consistent with 60% through 18% reduced risk; *n*<500 events.
[29] Prospective cohort studies begin with GRADE of LOW. Upgraded for dose–response association. Assuming linearity, a 0.05 g increase in DPA is associated with a 36% reduced risk of postmenopausal breast cancer (mvRR=0.64; 95% CI: 0.49 to 0.85). Assuming linearity, a 0.02% increase in energy from DPA is associated with a 31% reduced risk of postmenopausal breast cancer (mvRR=0.69; 95% CI: 0.55 to 0.87).

Table 9. GRADE evidence profile for prospective cohort studies of ALA and health outcomes

QUALITY ASSESSMENT									SUMMARY OF FINDINGS			IMPORTANCE
EXPOSURE	OUTCOME	PARTICIPANTS (NO. STUDIES)	RISK OF BIAS	INCONSISTENCY	INDIRECTNESS	IMPRECISION	PUBLICATION BIAS	OVERALL QUALITY OF EVIDENCE	STUDY EVENT RATE (%)	ABSOLUTE RISK DIFFERENCE, ADJUSTED (PER 10 000)[1]	RELATIVE RISK, ADJUSTED	
ALA	All-cause mortality	714 634 (10 studies)	Serious risk of bias[2]	Serious inconsistency[3]	No serious indirectness	Serious imprecision[4]	No suspected publication bias[5]	⨁◯◯◯ VERY LOW[6]	171 232/714 634 [24.0%]	80 fewer (160 fewer to 11 more)	0.93 (0.86, 1.01]	CRITICAL
	CVD, total	38 398 (1 study)	No serious risk of bias[7]	Unable to assess	No serious indirectness	Serious imprecision[8]	Unable to assess reliably[9]	⨁◯◯◯ VERY LOW[10]	1941/38 398 (5.1%)	228 fewer (from 820 fewer to 501 more)	0.95 (0.82, 1.11)	CRITICAL
	CVD, fatal	800 724 (11 studies)	No serious risk of bias[11]	No serious inconsistency[12]	No serious indirectness	No serious imprecision[13]	No publication bias detected[14]	⨁⨁⨁◯ MODERATE15	54 162/ 800 724 (6.8%)	5 fewer (from 10 fewer to 0 fewer)	0.91 (0.83 to 0.99)	CRITICAL
	CHD, fatal	2521 010 (9 studies)	No serious risk of bias[16]	No serious inconsistency[17]	No serious indirectness	No serious imprecision[18]	Unable to assess reliably[19]	⨁⨁⨁◯ MODERATE[20]	5276/ 251 010 (2.1%)	36 fewer (from 53 fewer to 18 fewer)	0.82 (0.74 to 0.91)	CRITICAL

[1] See Annex 2 for sources of absolute event rates.

[2] Median NOS=8 (range: 6–9); 1 Harvard study (containing data for 2 cohorts) [Wang *(132)*] adjusted for TFA; 2 other USA cohorts [Dolocek *(69)* and Fretts *(73)*] did not. Results differ by this stratification. Two lowest quality studies [Sala-Villa *(40)* and Fortes *(152)*] find pooled mvRR=0.66 (95% CI: 0.47 to 0.94).

[3] I^2=80%. Two studies [USA cohorts, NHS and HPFS, Wang *(132)*] mvRR=0.99 (95% CI: 0.95 to 1.04 with 33 304 deaths [95%]); additional 2 studies (also USA) mvRR=0.72 (95% CI: 0.61 to 0.86; with 1956 deaths).

[4] 95% CI of summary estimate consistent with 14% decreased through 1% increased risk (RE). Using FE model, estimate consistent with 0 to 5% increased risk and 94% of weight to the 2 Harvard cohorts + the NIH-AARP study.

[5] Egger's test: *P*=0.014; Begg's test: *P*=0.371. Trim-and-fill identified no "missed" studies. No publication bias suspected.

[6] Prospective cohort studies begin with GRADE of LOW. Downgraded for imprecision, inconsistency.

[7] NOS=6; adjusted for TFA.

[8] 95% CI consistent with 18% reduced through 11% increased risk.

[9] Due to small number of studies (*n*<10), publication bias was not formally assessed.

[10] Prospective cohort studies begin with GRADE of LOW. Downgraded for imprecision.

[11] Median NOS=8 (6 to 9 range). Two studies adjusted for TFA [NHS and HPFS, Wang, 2016 *(132)*].

[12] I^2=58%. Ten of 11 point estimates consistent with protection. Studies that adjusted for TFA yield similar estimates to those that did not.

[13] 95% CI of summary estimate consistent with 17% through 1% decreased risk.

[14] Egger's test: *P*=0.055; Begg's test: *P*=0.436. Trim-and-fill identified no "missed" studies. No publication bias suspected.

[15] Prospective cohort studies begin with GRADE of LOW. Upgraded to MODERATE for dose–response association. Assuming linearity, a 0.5% increase in energy from ALA was associated with an 8% decreased risk of CVD mortality (mvRR=0.92, 95% CI: 0.89 to 0.96).

[16] Median NOS=7 (range: 6–9). Four studies adjusted for TFA.

[17] I^2=0%.

[18] 95% CI of summary estimate consistent with 26% through 9% reduced risk.

[19] Due to small number of studies (*n*<10), publication bias was not formally assessed.

[20] Prospective cohort studies begin with GRADE of LOW. Upgraded for dose–response association. Assuming linearity, a 0.5 g/day increase in ALA was associated with an 8% decreased risk of CHD mortality (mvRR=0.92, 95% CI: 0.87 to 0.97). Assuming linearity, a 0.2% increase in energy from ALA is associated with a 20% reduced risk of sudden cardiac death (mvRR=0.80; 95% CI: 0.70 to 0.91).

QUALITY ASSESSMENT									SUMMARY OF FINDINGS			IMPORTANCE
EXPOSURE	OUTCOME	PARTICIPANTS (NO. STUDIES)	RISK OF BIAS	INCONSISTENCY	INDIRECTNESS	IMPRECISION	PUBLICATION BIAS	OVERALL QUALITY OF EVIDENCE	STUDY EVENT RATE (%)	ABSOLUTE RISK DIFFERENCE, ADJUSTED (PER 10 000)[1]	RELATIVE RISK, ADJUSTED	
ALA	Sudden cardiac death	99 183 (2 studies)	No serious risk of bias[21]	No serious inconsistency[22]	No serious indirectness	No serious imprecision[23]	Unable to assess reliably[24]	⨁⨁⨁◯ MODERATE[25]	417/99 183 (0.42%)	35 fewer (from 50 fewer to 14 fewer)	0.54 (0.37, 0.81)	IMPORTANT
	MI, total	92 299 (3 studies)	No serious risk of bias[26]	No serious inconsistency[27]	No serious indirectness	Serious imprecision[28]	Unable to assess reliably[29]	⨁◯◯◯ VERY LOW[30]	3723/92 299 (4.0%)	3 fewer (from 14 fewer to 8 more)	0.96 (0.84, 1.09)	IMPORTANT
	MI, fatal	2 978 (1 study)	No serious risk of bias[31]	Not assessed	No serious indirectness	Serious imprecision[32]	Unable to assess reliably[33]	⨁◯◯◯ VERY LOW[34]	417/2978 (14.0%)	1 fewer (from 5 fewer to 0 more)	0.71 (0.47 to 1.08)	IMPORTANT
	MI, nonfatal	72 283 (1 study)	No serious risk of bias[35]	Not assessed	No serious indirectness	Serious imprecision[36]	Unable to assess reliably[37]	⨁◯◯◯ VERY LOW[38]	597/72 283 (0.83%)	8 fewer (from 22 fewer to 11 more)	0.85 (0.61 to 1.19)	IMPORTANT
	Fatal arrhythmia	2 583 (1 study)	No serious risk of bias[39]	Not assessed	No serious indirectness	Serious imprecision[40]	Unable to assess reliably[41]	⨁◯◯◯ VERY LOW[42]	135/2583 (5.2%)	24 fewer (from 48 fewer to 17 more)	0.68 (0.38 to 1.22)	IMPORTANT

[21] NOS=5 and 9; both studies consistent.
[22] I^2=0%.
[23] 95% CI of estimate consistent with 63% through 19% decreased risk; *n*=417 cases.
[24] Due to small number of studies (*n*<10), publication bias was not formally assessed.
[25] Prospective cohort studies begin with GRADE of LOW. Not downgraded. Assuming linearity, a 0.5 g increase in ALA is associated with a 27% reduced risk of sudden cardiac death (mvRR=0.73; 95% CI: 0.61 to 0.88).
[26] NOS 6 and 9; no obvious biases.
[27] I^2=0%.
[28] 95% CI of estimate consistent with 26% reduced through 9% increased risk; *n*=3723 cases.
[29] Due to small number of studies (*n*<10), publication bias was not formally assessed.
[30] Prospective cohort studies begin with GRADE of LOW. Downgraded for imprecision.
[31] NOS=9.
[32] 95% CI of estimate consistent with 53% reduced through 8% increased risk; *n*=417 cases.
[33] Due to small number of studies (*n*<10), publication bias was not formally assessed.
[34] Prospective cohort studies begin with GRADE of LOW. Downgraded for imprecision.
[35] NOS=7 with adjustment for TFA.
[36] 95% CI of estimate consistent with 39% decreased through 19% increased risk.
[37] Due to small number of studies (*n*<10), publication bias was not formally assessed.
[38] Prospective cohort studies begin with GRADE of LOW. Downgraded for imprecision.
[39] NOS=7; did not adjust for TFA or total energy.
[40] 95% CI of estimate consistent with 62% decreased through 22% increased risk.
[41] Due to small number of studies (*n*<10), publication bias was not formally assessed.

QUALITY ASSESSMENT									SUMMARY OF FINDINGS			IMPORTANCE
EXPOSURE	OUTCOME	PARTICIPANTS (NO. STUDIES)	RISK OF BIAS	INCONSISTENCY	INDIRECTNESS	IMPRECISION	PUBLICATION BIAS	OVERALL QUALITY OF EVIDENCE	STUDY EVENT RATE (%)	ABSOLUTE RISK DIFFERENCE, ADJUSTED (PER 10 000)[1]	RELATIVE RISK, ADJUSTED	
ALA	CHD, total	92 283 (7 studies)	No serious risk of bias[43]	No serious inconsistency[44]	No serious indirectness	Serious imprecision[45]	Unable to assess reliably[46]	⊕◯◯◯ VERY LOW[47]	3360/92 283 (3.6%)	42 fewer (from 102 fewer to 24 more)	0.93 (0.83 to 1.04)	CRITICAL
	Stroke, total	95 720 (4 studies)	Serious risk of bias[48]	Serious inconsistency[49]	No serious indirectness	Serious imprecision[50]	Unable to assess reliably[51]	⊕◯◯◯ VERY LOW[52]	3246/95 720 (3.4%)	1 fewer (from 10 fewer to 9 more)	0.97 (0.79 to 1.18)	IMPORTANT
	Stroke, fatal	103 532 (3 studies)	No serious risk of bias[53]	No serious inconsistency[54]	No serious indirectness	Serious imprecision[55]	Unable to assess reliably[56]	⊕◯◯◯ VERY LOW[57]	1644/103 532 (1.6%)	8 fewer (from 15 fewer to 1 more)	0.85 (0.72 to 1.01)	IMPORTANT
	Stroke, ischaemic	118 103 (4 studies)	No serious risk of bias[58]	No serious inconsistency[59]	No serious indirectness	Serious imprecision[60]	Unable to assess reliably[61]	⊕◯◯◯ VERY LOW[62]	3088/118 103 (2.6%)	196 fewer (from 387 fewer to 33 more)	0.88 (0.77, 1.02)	IMPORTANT

[42] Prospective cohort studies begin with GRADE of LOW. Downgraded for imprecision.
[43] Median NOS=8 (range: 6–9). Removal of higher risk study (Oomen *(105)*, NOS=6) does not alter summary association estimate.
[44] I^2=0%.
[45] 95% CI of summary estimate consistent with 17% decreased through 4% increased risk; removal of Oomen et al. *(105)* does not alter this estimate.
[46] Due to small number of studies (*n*<10), publication bias was not formally assessed.
[47] Prospective cohort studies begin with GRADE of LOW. Downgraded for imprecision. There was no evidence of a dose–response association between ALA and risk of CHD (per 0.5 g: mvRR=0.99, 95% CI: 0.96 to 1.03; or per 0.2%: mvRR=0.99, 95% CI: 0.95 to 1.03).
[48] Median NOS=7.5 (range: 6–9).
[49] I^2=56%; 2 studies with lowest risk of bias [Fretts *(73)*, de Goede *(66)*)] show protection (mvRR=0.78 [95% CI: 0.59 to 1.03]); 2 studies with highest risk of bias [Rhee *(39)*, Larsson *(30)*] show harm (mvRR=1.10 [95% CI: 0.96 to 1.25]).
[50] 95% CI consistent with 21% decreased risk through 18% increased risk; N=3200 events.
[51] Due to small number of studies (*n*<10), publication bias was not formally assessed.
[52] Prospective cohort studies begin with GRADE of LOW. Downgraded for risk of bias, inconsistency, and imprecision.
[53] Median NOS=8 (range: 6–9); no measure of TFA.
[54] I^2=0%.
[55] 95% CI consistent with 28% decreased through 1% increased risk; *n*>1600 cases.
[56] Due to small number of studies (*n*<10), publication bias was not formally assessed.
[57] Prospective cohort studies begin with GRADE of LOW. Downgraded for imprecision.
[58] Median NOS= 8.5 (range: 6–9) but not clearly due to different TFA-adjustment (Fretts *(73)*; no adjustment for TFA; and de Goede *(66)* has adjustment for TFA both have same point estimates).
[59] I^2=0%.
[60] 95% CI of summary estimate consistent with 23% decreased through 2% increased risk; >3000 cases.
[61] Due to small number of studies (*n*<10), publication bias was not formally assessed.
[62] Prospective cohort studies begin with GRADE of LOW. Downgraded for imprecision.

QUALITY ASSESSMENT									SUMMARY OF FINDINGS			IMPORTANCE
EXPOSURE	OUTCOME	PARTICIPANTS (NO. STUDIES)	RISK OF BIAS	INCONSISTENCY	INDIRECTNESS	IMPRECISION	PUBLICATION BIAS	OVERALL QUALITY OF EVIDENCE	STUDY EVENT RATE (%)	ABSOLUTE RISK DIFFERENCE, ADJUSTED (PER 10 000)[1]	RELATIVE RISK, ADJUSTED	
ALA	Stroke, haemorrhagic	37 253 (2 studies)	Serious risk of bias[63]	Serious inconsistency[64]	No serious indirectness	Serious imprecision[65]	Unable to assess reliably[66]	⊕◯◯◯ VERY LOW[67]	289/37 253 (0.8%)	3 more (from 17 fewer to 52 more)	1.10 (0.45, 2.67)	IMPORTANT
	Stroke, thrombotic	0 (0 studies)	–	–	–	–	–	–	–	–	–	IMPORTANT
	Atrial fibrillation	33 655 (1 study)	No serious risk of bias[68]	Not assessed	No serious indirectness	Serious imprecision[69]	Unable to assess reliably[70]	⊕◯◯◯ VERY LOW[71]	1441/33 655 (4.28%)	9 fewer (from 16 fewer to 1 more)	0.77 (0.57 to 1.04)	IMPORTANT
	Heart failure	0 (0 studies)	–	–	–	–	–	–	–	–	–	IMPORTANT
	T2DM	56 356 (4 studies)	Serious risk of bias[72]	Serious inconsistency[73]	No serious indirectness	Serious imprecision[74]	Unable to assess reliably[75]	⊕◯◯◯ VERY LOW[76]	2919/56 356 (5.2%)	73 fewer (from 174 fewer to 493 more)	1.13 (0.69, 1.86)	IMPORTANT
	Dementia	815 (1 study)	No serious risk of bias[77]	Not assessed	No serious indirectness	Serious imprecision[78]	Unable to assess reliably[79]	⊕◯◯◯ VERY LOW[80]	131/815 (16.1%)	275 fewer (from 669 fewer to 577 more)	0.70 (0.30 to 1.62)	IMPORTANT

[63] NOS=7 and 8; 1 of 2 did not adjust for total energy or TFA.
[64] I^2=66%; 1 study shows significant protection (0.77); the other nonsignificant harm (1.96).
[65] 95% CI consistent with 55% reduced risk through 167% increased risk; *n*<300 events.
[66] Due to small number of studies (*n*<10), publication bias was not formally assessed.
[67] Prospective cohort studies begin with GRADE of LOW. Downgraded for risk of bias, inconsistency, and imprecision.
[68] NOS=9 with adjustment for TFA.
[69] 95% CI consistent with 43% decreased through 4% increased risk.
[70] Due to small number of studies (*n*<10), publication bias was not formally assessed.
[71] Prospective cohort studies begin with GRADE of LOW. Downgraded for imprecision.
[72] Four studies, median NOS=7.5 (range: 6–9); 1 study with NOS=6 [Alhazmi *(2)*] had poor follow-up reporting and did not control for family history, with only 70% case confirmation.
[73] High- and low-quality studies show opposite associations; high-quality study shows protection (mvRR=0.79; 95% CI: 0.67 to 0.92; 2252 cases) and low-quality studies suggest increased risk (mvRR=1.35 [95% CI: 0.84 to 2.16]).
[74] 95% CI of summary estimate consistent with 31% reduced risk through 86% increased risk (RE); using FE model, which increases Brostow weight to 99% and CI consistent with 18% reduced risk through 8% increased risk (mvRR=0.94 [95% CI: 0.82 to 1.08]). N>2500 cases.
[75] Due to small number of studies (*n*<10), publication bias was not formally assessed.
[76] Prospective cohort studies begin with GRADE of LOW. Downgraded for imprecision and inconsistency.
[77] NOS=7.
[78] 95% CI of study estimate consistent with 70% reduced risk through 62% increased risk.
[79] Due to small number of studies (*n*<10), publication bias was not formally assessed.
[80] Prospective cohort studies begin with GRADE of LOW. Downgraded for imprecision, risk of bias, and inconsistency.

QUALITY ASSESSMENT									SUMMARY OF FINDINGS			IMPORTANCE
EXPOSURE	OUTCOME	PARTICIPANTS (NO. STUDIES)	RISK OF BIAS	INCONSISTENCY	INDIRECTNESS	IMPRECISION	PUBLICATION BIAS	OVERALL QUALITY OF EVIDENCE	STUDY EVENT RATE (%)	ABSOLUTE RISK DIFFERENCE, ADJUSTED (PER 10 000)[1]	RELATIVE RISK, ADJUSTED	
ALA	Cognitive decline	5 497 (2 studies)	No serious risk of bias[81]	No serious inconsistency[82]	No serious indirectness	Serious imprecision[83]	Unable to assess reliably[84]	⊕◯◯◯ VERY LOW[85]	749/5497 (13.6%)	119 fewer (from 293 fewer to 66 more)	0.91 (0.78 to 1.05)	IMPORTANT
	Depression	57 583 (3 studies)	No serious risk of bias[86]	Serious incon-sistency[87]	No serious indirectness	Serious imprecision[88]	Unable to assess reliably[89]	⊕◯◯◯ VERY LOW[90]	3 433/57 538 (6.0%)	105 fewer (from 910 fewer to 1015 more)	0.97 (0.74, 1.29)	IMPORTANT
	Suicide											IMPORTANT
	Crohn's disease	362 (1 study)	No serious risk of bias[91]	Not assessed	No serious indirectness	Serious imprecision[92]	Unable to assess reliably[93]	⊕◯◯◯ VERY LOW[94]	73/362 (20.2%)	2 fewer (from 9 fewer to 5 more)	0.40 (0.07 to 2.19)	IMPORTANT
	Ulcerative colitis	203 193 (1 study)	No serious risk of bias[95]	Not assessed	No serious indirectness	Serious imprecision[96]	Unable to assess reliably[97]	⊕◯◯◯ VERY LOW[98]	126/203 193 (0.06%)	2 more (from 5 fewer to 25 more)	1.28 (0.46 to 3.57)	IMPORTANT

[81] NOS=8-9; did not report TFA.
[82] I^2=0%.
[83] 95% CI of the estimate consistent with a 22% decreased through 5% increased risk; 749 cases.
[84] Due to small number of studies (*n*<10), publication bias was not formally assessed.
[85] Prospective cohort studies begin with GRADE of LOW. Downgraded for imprecision.
[86] Median NOS=9 (7-9); 1 study adjusts for TFA [Lucas *(99)*].
[87] Largest study (*n*=2823 cases) shows protection (mvRR=0.81; 95% CI: 0.69 to 0.95). For remaining 2 pooled studies (*n*=510 pooled cases), mvRR=1.13 (95% CI: 0.99 to 1.28). FE meta-analysis gives 60% weight to Horikawa *(153)*; mvRR=0.99; 95% CI: 0.90 to 1.10.
[88] 95% CI consistent with 26% decreased through 29% decreased risk; *n*>3400 cases.
[89] Due to small number of studies (*n*<10), publication bias was not formally assessed.
[90] Prospective cohort studies begin with GRADE of LOW. Downgraded for inconsistency and imprecision.
[91] NOS=8; no adjustment for TFA.
[92] 95% CI consistent with 93% decreased risk through 119% increased risk; *n*<100 cases.
[93] Due to small number of studies (*n*<10), publication bias was not formally assessed.
[94] Prospective cohort studies begin with GRADE of LOW. Downgraded for imprecision.
[95] NOS=8; IBD in EPIC did not adjust for TFA.
[96] 95% CI consistent with 54% decreased risk through 257% increased risk; *n*<200 cases.
[97] Due to small number of studies (*n*<10), publication bias was not formally assessed.
[98] Prospective cohort studies begin with GRADE of LOW. Downgraded for imprecision.

QUALITY ASSESSMENT									SUMMARY OF FINDINGS			IMPORTANCE
EXPOSURE	OUTCOME	PARTICIPANTS (NO. STUDIES)	RISK OF BIAS	INCONSISTENCY	INDIRECTNESS	IMPRECISION	PUBLICATION BIAS	OVERALL QUALITY OF EVIDENCE	STUDY EVENT RATE (%)	ABSOLUTE RISK DIFFERENCE, ADJUSTED (PER 10 000)[1]	RELATIVE RISK, ADJUSTED	
ALA	All breast cancer	180 342 (3 studies)	No serious risk of bias[99]	No serious inconsistency[100]	No serious indirectness	Serious imprecision[101]	Unable to assess reliably[102]	⨁◯◯◯ VERY LOW[103]	3581/ 180 342 (1.99%)	19 fewer (from 54 fewer to 27 more)	0.91 (0.74 to 1.13)	IMPORTANT
	Premeno-pausal breast cancer	0 (0 studies)	–	–	–	–	–	–	–	–	–	IMPORTANT
	Postmeno-pausal breast cancer	2 490 (3 studies)[104]	No serious risk of bias[105]	Serious incon-sistency[106]	No serious indirectness	Serious imprecision[107]	Unable to assess reliably[108]	⨁◯◯◯ VERY LOW[109]	471/2490 (18.9%)	119 more (from 443 fewer to 938 more)	1.07 (0.74 to 1.55)	IMPORTANT

ALA: alpha-linolenic acid; CHD: coronary heart disease; CI: confidence interval; CVD: cardiovascular disease; EPIC: European Prospective Investigation into Cancer and Nutrition; FE: fixed effects; GRADE: Grading of Recommendations Assessment, Development, and Evaluation; HPFS: Health Professionals Follow-up Study; IBD: inflammatory bowel disease; MI: myocardial infarction; mvRR: multivariable risk ratio; NHS: Nurses' Health Study; NIH-AARP: National Institutes of Health American Association of Retired Persons Diet and Health Study; no.: number; NOS: Newcastle-Ottawa Scale; RE: random effects; RR: risk ratio; T2DM: type 2 diabetes mellitus; TFA: trans-fatty acids; USA: United States of America.

[99] NOS=9 for all 3 studies; only Holmes (1999) *(78)* adjusted for TFA.
[100] I^2=16%.
[101] 95% CI consistent with a 26% decreased through 13% increased risk; *n*>3500 events.
[102] Due to small number of studies (*n*<10), publication bias was not formally assessed.
[103] Prospective cohort studies begin with GRADE of LOW. Downgraded for imprecision.
[104] One study with 3 arms.
[105] One study with 3 arms; NOS=9.
[106] I^2=59%; trend towards increased risk in lowest age group (54 years) mvRR=1.56; 95% CI: 0.99 to 2.45; and decreased risk in highest age group (68 years) mvRR=0.77; 95% CI: 0.49 to 1.20.
[107] 95% CI consistent with a 26% decreased through 55% increased risk; *n*<500 events.
[108] Due to small number of studies (*n*<10), publication bias was not formally assessed.
[109] Prospective cohort studies begin with GRADE of LOW. Downgraded for inconsistency and imprecision.

Table 10. GRADE evidence profile for prospective cohort studies of total omega-6 PUFA and health outcomes

QUALITY ASSESSMENT									SUMMARY OF FINDINGS			IMPORTANCE
EXPOSURE	OUTCOME	PARTICIPANTS (NO. STUDIES)	RISK OF BIAS	INCONSISTENCY	INDIRECTNESS	IMPRECISION	PUBLICATION BIAS	OVERALL QUALITY OF EVIDENCE	STUDY EVENT RATE (%)	ABSOLUTE RISK DIFFERENCE, ADJUSTED (PER 10 000)[1]	RELATIVE RISK, ADJUSTED	
Total n-6 PUFA	All-cause mortality	768 475 (9 studies)	No serious risk of bias[2]	No serious inconsistency[3]	No serious indirectness	No serious imprecision[4]	Unable to assess reliably[5]	⨁⨁⨁◯ MODERATE[6]	182 318/ 768 475 (23.7%)	103 fewer (from 171 fewer to 34 fewer)	0.91 (0.85 to 0.97)	CRITICAL
	CVD, total	0 (0 studies)	–	–	–	–	–	–	–	–	–	CRITICAL
	CVD, fatal	753 426 (7 studies)	No serious risk of bias[7]	No serious inconsistency[8]	No serious indirectness	No serious imprecision[9]	Unable to assess reliably[10]	⨁◯◯◯ LOW[11]	53 082/ 753 426 (7.0%)	5 fewer (from 10 fewer to 0)	0.91 (0.83 to 1.00)	CRITICAL
	CHD, fatal	37 032 (1 study)	No serious risk of bias[12]	Not assessed	No serious indirectness	Serious imprecision[13]	Not assessed	⨁◯◯◯ VERY LOW[14]	978/37 032 (2.6%)	14 fewer (from 88 fewer to 110 more)	0.93 (0.56, 1.55)	CRITICAL
	Sudden cardiac death	91 981 (1 study)	No serious risk of bias[15]	Not assessed	No serious indirectness	Serious imprecision[16]	Not assessed	⨁◯◯◯ VERY LOW[17]	385/91 981 (0.42%)	16 fewer (from 33 fewer to 8 more)	0.79 (from 0.57 to 1.10)	IMPORTANT
	MI, total	0 (0 studies)	–	–	–	–	–	–	–	–	–	IMPORTANT
	MI, fatal	0 (0 studies)	–	–	–	–	–	–	–	–	–	IMPORTANT

[1] See Annex 2 for sources of absolute event rates.

[2] Median NOS=8 (range: 7–9).

[3] I^2=72%; 6 of 9 studies show significant reduced risk, mvRR=0.87 (95% CI: 0.85 to 0.90); 3 studies show nonsignificant increased risk [Zhuang *(143)*, Owen *(36)*, Wakai *(130)* (men)], mvRR=1.09 (95% CI: 1.00 to 1.18).

[4] 95% CI consistent with 15% reduced through 3% reduced risk; *n*>180 000 deaths.

[5] Due to small number of studies (*n*<10), publication bias was not formally assessed.

[6] Prospective cohort studies begin with GRADE of LOW. Upgraded for dose–response association. Assuming linearity, a 5 g/day increase in total n-6 PUFA was associated with a 5% decreased risk of all-cause mortality (mvRR=0.95, 95% CI: 0.90 to 1.001). Assuming linearity, a 5% increase in energy from total n-6 PUFA was associated with a 12% decreased risk of all-cause mortality (mvRR=0.88, 95% CI: 0.81 to 0.96). Wang *(132)*, using direct modelling, reported that a 2% increase in energy from total n-6 PUFA was associated with a 10% decreased risk of all-cause mortality (mvRR=0.90; 95% CI: 0.88 to 0.93).

[7] Median NOS=8.5 (range: 8–9).

[8] I^2=60%. Four studies show significant reduced risk; 46 625 cases: mvRR=0.86 (95% CI: 0.77 to 0.96). One study shows nonsignificant risk; 1665 cases: mvRR=1.18 (95% CI: 0.98 to 1.42). Six of 7 studies' point estimates are protective.

[9] 95% CI includes 1.0; pooled RE estimate consistent with 17% reduced risk through 0%; pooled FE estimate consistent with 12% reduced through 4% reduced risk (mvRR=0.92; 95% CI: 0.88 to 0.96.

[10] Due to small number of studies (*n*<10), publication bias was not formally assessed.

[11] Prospective cohort studies begin with GRADE of LOW. Not downgraded.

[12] NOS=8; did not adjust for TFA.

[13] 95% CI includes 1.0; consistent with 44% reduced risk through 55% increased risk.

[14] Prospective cohort studies begin with GRADE of LOW. Downgraded for imprecision.

[15] NOS=9; adjusted for TFA.

[16] 95% CI of estimate consistent with 43% reduced through 10% increased risk.

[17] Prospective cohort studies begin with GRADE of LOW. Downgraded for imprecision.

QUALITY ASSESSMENT									SUMMARY OF FINDINGS			IMPORTANCE
EXPOSURE	OUTCOME	PARTICIPANTS (NO. STUDIES)	RISK OF BIAS	INCONSISTENCY	INDIRECTNESS	IMPRECISION	PUBLICATION BIAS	OVERALL QUALITY OF EVIDENCE	STUDY EVENT RATE (%)	ABSOLUTE RISK DIFFERENCE, ADJUSTED (PER 10 000)[1]	RELATIVE RISK, ADJUSTED	
Total n-6 PUFA	MI, nonfatal	0 (0 studies)	–	–	–	–	–	–	–	–	–	IMPORTANT
	CHD, total	20 647 (2 studies)	No serious risk of bias[18]	Not assessed	No serious indirectness	Serious imprecision[19]	Unable to assess reliably[20]	⨁◯◯◯ VERY LOW[21]	1021/20 674 (4.9%)	60 more (from 54 fewer to 198 more)	1.10 (0.91 to 1.33)	CRITICAL
	Stroke, total	36 953 (2 studies)	No serious risk of bias[22]	No serious inconsistency[23]	No serious indirectness	Serious imprecision[24]	Not assessed	⨁◯◯◯ VERY LOW[25]	1821/36 953 (4.9%)	2 more (from 5 fewer to 11 more)	1.05 (0.90 to 1.22)	IMPORTANT
	Stroke, fatal	36 032 (1 study)	No serious risk of bias[26]	Not assessed	No serious indirectness	Serious imprecision[27]	Not assessed	⨁◯◯◯ VERY LOW[28]	321/36 032 (0.9%)	15 fewer (from 36 fewer to 28 more)	0.71 (0.33, 1.54)	IMPORTANT
	Stroke, ischaemic	20 674 (2 studies)	No serious risk of bias[29]	Not assessed	No serious indirectness	Serious imprecision[30]	Unable to assess reliably[31]	⨁◯◯◯ VERY LOW[32]	755/20 674 (3.7%)	5 fewer (from 84 fewer to 106 more)	0.98 (0.69 to 1.39)	IMPORTANT
	Stroke, haemor-rhagic	34 670 (1 study)	No serious risk of bias[33]	Not assessed	No serious indirectness	Serious imprecision[34]	Unable to assess reliably[35]	⨁◯◯◯ VERY LOW[36]	233/34 437 (0.7%)	4 fewer (13 fewer to 10 more)	0.88 (0.58 to 1.34)	IMPORTANT

[18] NOS=9; no reported TFA intake.
[19] 95% CI consistent with 9% reduced through 33% increased risk; *n*>1000 events.
[20] Due to small number of studies (*n*<10), publication bias was not formally assessed.
[21] Prospective cohort studies begin with GRADE of LOW. Downgraded for imprecision.
[22] NOS=7 for both studies; no measure of TFA reported.
[23] I^2=0%.
[24] 95% CI of study estimate consistent with 10% reduced risk through 22% increased risk; >1800 events.
[25] Prospective cohort studies begin with GRADE of LOW. Downgraded for imprecision.
[26] NOS=8; no measure of TFA reported.
[27] 95% CI of study estimate consistent with 67% reduced risk through 54% increased risk; <500 events.
[28] Prospective cohort studies begin with GRADE of LOW. Downgraded for imprecision.
[29] NOS=9; no adjustment for TFA.
[30] 95% CI of pooled estimate consistent with 48% through 39% increased risk; *n*>700 events.
[31] Due to small number of studies (*n*<10), publication bias was not formally assessed.
[32] Prospective cohort studies begin with GRADE of LOW. Downgraded for imprecision.
[33] NOS=7; did not adjust for TFA.
[34] 95% CI includes 1; consistent with 42% reduced through 34% increased risk.
[35] Due to small number of studies (*n*<10), publication bias was not formally assessed.
[36] Prospective cohort studies begin with GRADE of LOW. Downgraded for imprecision.

QUALITY ASSESSMENT									SUMMARY OF FINDINGS			IMPORTANCE
EXPOSURE	OUTCOME	PARTICIPANTS (NO. STUDIES)	RISK OF BIAS	INCONSISTENCY	INDIRECTNESS	IMPRECISION	PUBLICATION BIAS	OVERALL QUALITY OF EVIDENCE	STUDY EVENT RATE (%)	ABSOLUTE RISK DIFFERENCE, ADJUSTED (PER 10 000)[1]	RELATIVE RISK, ADJUSTED	
Total n-6 PUFA	Stroke, thrombotic	0 (0 studies)	–	–	–	–	–	–	–	–	–	IMPORTANT
	Atrial fibrillation	88 686 (3 studies)	No serious risk of bias[37]	No serious inconsistency[38]	No serious indirectness	Serious imprecision[39]	Not assessed	⨁◯◯◯ VERY LOW[40]	6521/88 686 (7.4%)	1 fewer (from 9 fewer to 8 more)	0.98 (0.83, 1.17)	IMPORTANT
	Heart failure	0 (0 studies)	–	–	–	–	–	–	–	–	–	IMPORTANT
	T2DM	376 759 (8 studies)	No serious risk of bias[41]	No serious inconsistency[42]	No serious indirectness	Serious imprecision[43]	Unable to assess reliably[44]	⨁◯◯◯ VERY LOW[45]	25 372/ 376 759 (6.7%)	39 fewer (from 84 fewer to 11 more)	0.93 (0.85, 1.02)	IMPORTANT
	Dementia	5 395 (1 study)	No serious risk of bias[46]	Not assessed	No serious indirectness	Serious imprecision[47]	Not assessed	⨁◯◯◯ VERY LOW[48]	197/5395 (3.7%)	27 more (from 206 fewer to 348 more)	1.03 (0.78 to 1.37)	IMPORTANT
	Cognitive decline	4 809 (1 study)	No serious risk of bias[49]	Not assessed	No serious indirectness	Serious imprecision[50]	Unable to assess reliably[51]	⨁◯◯◯ VERY LOW[52]	598/4809 (12.4%)	40 more (from 225 fewer to 372 more)	1.03 (0.83 to 1.28)	IMPORTANT

[37] Two studies; NOS=8-9; only Chiuve (8)adjusted for TFA.

[38] I^2=53%. Chiuve *(8)* finds trend for increased risk (mvRR=1.20; 95% CI: 0.95 to 1.52); Dinesen *(154)* does not find trend for increased risk; finds trend for decreased risk (mvRR=0.91; 95% CI: 0.80 to 1.03).

[39] 95% CI of the estimate consistent with 17% reduced through 17% increased risk; *n*>6500 events.

[40] Prospective cohort studies begin with GRADE of LOW. Downgraded for imprecision.

[41] Median NOS=8 (range: 6–9); 1 study with NOS=6. Alhazmi *(2)*] was the only one to show increased risk (mvRR=1.60; 95% CI: 1.03 to 2.48); for 6 other studies, pooled mvRR=0.91 (95% CI: 0.84 to 0.99). Impact of Alhazmi study on overall summary risk is small (weight is 4%).

[42] I^2=66%; Alhazmi *(2)* was the only study to show increased risk (mvRR=1.60; 95% CI: 1.03 to 2.48); for 6 other studies, pooled mvRR=0.91 (95% CI: 0.84 to 0.99). Impact of Alhazmi on overall summary risk is small (weight is 4%). Impact of Alhazmi on overall summary risk is small (weight=4%). Removal of 2 "extreme" studies (Alhazmi and Zong *(144)*, HPFS) reduced heterogeneity to 0%, with mvRR=0.96 (95% CI: 0.91 to 1.01).

[43] 95% CI of pooled estimate consistent with 15% lower through 2% higher risk of type 2 diabetes mellitus; *n*>25 000 events.

[44] Due to small number of studies (*n*<10), publication bias was not formally assessed.

[45] Prospective cohort studies begin with GRADE of LOW. Downgraded for imprecision.

[46] NOS=9 with adjustment for TFA.

[47] 95% CI of the estimate consistent with 22% decreased through 37% increased risk; *n*<200 events.

[48] Prospective cohort studies begin with GRADE of LOW. Downgraded for imprecision.

[49] NOS=9.

[50] 95% CI of the estimate consistent with 17% decreased through 28% increased risk; *n*>500 events.

[51] Due to small number of studies (*n*<10), publication bias was not formally assessed.

[52] Prospective cohort studies begin with GRADE of LOW. Downgraded for imprecision.

QUALITY ASSESSMENT									SUMMARY OF FINDINGS			IMPORTANCE
EXPOSURE	OUTCOME	PARTICIPANTS (NO. STUDIES)	RISK OF BIAS	INCONSISTENCY	INDIRECTNESS	IMPRECISION	PUBLICATION BIAS	OVERALL QUALITY OF EVIDENCE	STUDY EVENT RATE (%)	ABSOLUTE RISK DIFFERENCE, ADJUSTED (PER 10 000)[1]	RELATIVE RISK, ADJUSTED	
Total n-6 PUFA	Depression	9 762 (4 studies)	No serious risk of bias[53]	No serious inconsistency[54]	No serious indirectness	Serious imprecision[55]	Unable to assess reliably[56]	⨁◯◯◯ VERY LOW[57]	1360/9762 (13.9%)	980 more (from 245 fewer to 2626 more)	1.28 (0.93 to 1.75)	IMPORTANT
	Suicide	0 (0 studies)	–	–	–	–	–	–	–	–	–	IMPORTANT
	Crohn's disease	0 (0 studies)	–	–	–	–	–	–	–	–	–	IMPORTANT
	Ulcerative colitis	170 805 (1 study)	No serious risk of bias[58]	Not assessed	No serious indirectness	Serious imprecision[59]	Not assessed	⨁◯◯◯ VERY LOW[60]	338/170 805 (0.20%)	1 more (from 2 fewer to 5 more)	1.08 (0.77 to 1.52)	IMPORTANT
	All breast cancer	93 340 (3 studies)	No serious risk of bias[61]	No serious inconsistency[62]	No serious indirectness	Serious imprecision[63]	Unable to assess reliably[64]	⨁◯◯◯ VERY LOW[65]	988/93 340 (1.1%)	83 more (from 354 fewer to 626 more)	1.04 (0.83, 1.30)	IMPORTANT
	Premeno-pausal breast cancer	0 (0 studies)	–	–	–	–	–	–	–	–	–	IMPORTANT

[53] Median NOS=7 (range: 7–9). Diet assessment with 1 x 24 hour recall in the Wolfe study *(134)* and incomplete adjustment for confounders; but results consistent.

[54] In Wolfe *(134)*, association was different in men (mvRR=2.34; 95% CI: 1.41 to 3.68) and women (mvRR=1.01; 95% CI: 0.74 to 1.37); removing the 'men' arm brings RR to mvRR=1.15 (95% CI: 0.91 to 1.46), so no serious impact on overall result.

[55] 95% CI of summary estimate consistent with 7% decreased risk through 78% increased risk.

[56] Due to small number of studies (n<10), publication bias was not formally assessed.

[57] Prospective cohort studies begin with GRADE of LOW. Downgraded for imprecision.

[58] NOS=7; adjustment for TFA.

[59] 95% CI of estimate consistent with 23% reduced through 52% increased risk.

[60] Prospective cohort studies begin with GRADE of LOW. Downgraded for imprecision.

[61] NOS=7 (range:7–9). Gago-Dominguez *(74)* did not adjust for total energy and did not confirm registry-located cases. Pooled estimate not affected when Gago-Dominguez study removed (mvRR=0.90; 95% CI: 0.67, 1.21).

[62] I^2=6%.

[63] 95% CI consistent with 17% decreased through 30% increased risk; n=988 events.

[64] Due to small number of studies (n<10), publication bias was not formally assessed.

[65] Prospective cohort studies begin with GRADE of LOW. Downgraded for imprecision. Assuming linearity, a 5 g/day increase in total n-6 PUFA was associated with a 0% increased risk of breast cancer (mvRR=1.00, 95% CI: 0.90 to 1.11). Assuming linearity, a 2% increase in energy from total n-6 PUFA was associated with a 0% increased risk of breast cancer (mvRR=1.00, 95% CI: 0.92 to 1.09). No evidence of dose–response association, no upgrade.

QUALITY ASSESSMENT									SUMMARY OF FINDINGS			IMPORTANCE
EXPOSURE	OUTCOME	PARTICIPANTS (NO. STUDIES)	RISK OF BIAS	INCONSISTENCY	INDIRECTNESS	IMPRECISION	PUBLICATION BIAS	OVERALL QUALITY OF EVIDENCE	STUDY EVENT RATE (%)	ABSOLUTE RISK DIFFERENCE, ADJUSTED (PER 10 000)[1]	RELATIVE RISK, ADJUSTED	
Total n-6 PUFA	Postmeno-pausal breast cancer	174 816 (6 studies)	Serious risk of bias[66]	No serious inconsistency[67]	No serious indirectness	No serious imprecision[68]	Unable to assess reliably[69]	⨁◯◯◯ VERY LOW[70]	6746/174 816 (3.9%)	527 more (from 51 to 1162 more)	1.31 (1.03 to 1.68)	IMPORTANT

CHD: coronary heart disease; CI: confidence interval; CVD: cardiovascular disease; FE: fixed effects; GRADE: Grading of Recommendations Assessment, Development, and Evaluation; HPFS: Health Professionals Follow-up Study; MI: myocardial infarction; mvRR: multivariable risk ratio; no.: number; NOS: Newcastle-Ottawa Scale; PUFA: polyunsaturated fatty acids; T2DM: type 2 diabetes mellitus; RE: random effects; RR: risk ratio; TFA: *trans*-fatty acids.

[66] Median NOS=6 (range 6–9); Wirfalt *(133)* did not control for family history and had low rates of follow-up for those recruited in 1996 (through 1999). Incomplete covariate adjustment in Sonesadt *(46)* (incomplete confounder adjustment, did not describe attrition, and did not verify cases from registry). Estimated risk in these 2 studies higher than in Wakai (NOS=9). Pooled estimate in studies with NOS=9: mvRR=1.15 (95% CI: 0.72 to 1.84). Pooled estimate in studies with NOS=6: mvRR=1.56 (95% CI: 0.86 to 2.53).

[67] I^2=85%; 4 estimates consistent with harm (pooled mvRR=1.70; 95% CI: 1.22 to 2.38), 2 with small protective effect (pooled mvRR=0.97; 95% CI: 0.89 to 1.06).

[68] 95% CI of summary estimate consistent with 3% increase through 68% increased risk; N>6500 events. Not downgraded.

[69] Due to small number of studies (n<10), publication bias was not formally assessed.

[70] Prospective cohort studies begin with GRADE of LOW. Downgraded for risk of bias. Not upgraded for dose–response association. Assuming linearity, a 5 g increase in energy from total n-6 PUFA was associated with a 2% increased risk of postmenopausal breast cancer (mvRR=1.02, 95% CI: 0.99 to 1.05). Assuming linearity, a 2% increase in energy from total n-6 PUFA was associated with a 3% increased risk of postmenopausal breast cancer (mvRR=1.03, 95% CI: 1.00 to 1.05). However, neither association was linear. Risk appears to increase from 0% to 3% energy, then decrease from 3% to 6% (increases from 0 to 6 g; decreases from 6 to 16 g/day).

Table 11. GRADE evidence profile for prospective cohort studies of LA and health outcomes

QUALITY ASSESSMENT									SUMMARY OF FINDINGS			IMPORTANCE
EXPOSURE	OUTCOME	PARTICIPANTS (NO. STUDIES)	RISK OF BIAS	INCONSISTENCY	INDIRECTNESS	IMPRECISION	PUBLICATION BIAS	OVERALL QUALITY OF EVIDENCE	STUDY EVENT RATE (%)	ABSOLUTE RISK DIFFERENCE, ADJUSTED (PER 10 000)[1]	RELATIVE RISK, ADJUSTED	
LA	All-cause mortality	706 400 (9 studies)	No serious risk of bias[2]	No serious inconsistency[3]	No serious indirectness	No serious imprecision[4]	Unable to assess reliably[5]	⨁⨁⨁◯ MODERATE[6]	169 509/ 706 400 (24.0%)	182 fewer (from 240 fewer to 159 fewer)	0.84 (0.79 to 0.86)	CRITICAL
	CVD, total	0 (0 studies)	–	–	–	–	–	–	–	–	–	CRITICAL
	CVD, fatal	692 243 (7 studies)	No serious risk of bias[7]	No serious inconsistency[8]	No serious indirectness	No serious imprecision[9]	Unable to assess reliably[10]	⨁⨁⨁◯ MODERATE[11]	48 348/ 692 243 (7.0%)	99 fewer (from 157 fewer to 41 fewer)	0.83 (0.73 to 0.93)	CRITICAL
	CHD, fatal	306 050 (13 studies)	No serious risk of bias[12]	No serious inconsistency[13]	No serious indirectness	No serious imprecision[14]	No evidence of publication bias[15]	⨁⨁⨁◯ MODERATE[16]	7125/ 306 050 (2.3%)	40 fewer (from 57 to 20 fewer)	0.80 (0.72 to 0.90)	CRITICAL

[1] See Annex 2 for sources of absolute event rates.

[2] Median NOS=8 (range: 6–9); removing study with high risk of bias (Fortes; weight=0.9%) does not alter pooled estimate.

[3] I^2=58%. Removal of Zhuang (143) studies in CHNS, NHANES reduces heterogeneity to 0% with no important estimate change (mvRR=0.81; 95% CI: 0.78 to 0.85).

[4] 95% CI consistent with 10% through 21% decreased risk.

[5] Due to small number of studies (*n*<10), publication bias was not formally assessed.

[6] Prospective cohort studies begin with GRADE of LOW. Upgraded to MODERATE for dose–response association. Assuming linearity, a 5 g increase in LA was associated with a 16% decreased risk of all-cause mortality (mvRR=0.84; 95% CI: 0.82 to 0.88). Assuming linearity, a 5 g increase in LA was associated with an 8% decreased risk of all-cause mortality (mvRR=0.92; 95% CI: 0.56 to 1.50). Assuming linearity, a 2% increase in LA was associated with a 6% decreased risk of all-cause mortality (mvRR=0.94; 95% CI: 0.77 to 1.14). Wang et al. (2016) (132), using direct modeling, reported that a 2% increase in energy from LA was associated with a 12% decreased risk of all-cause mortality (mvRR=0.88; 95% CI: 0.86 to 0.91). Upgraded for dose–response association.

[7] Median NOS=8 (range: 7–9); lowest quality study [Dolocek (69)] carried only 2.4% weight. Removal results in identical point estimate: mvRR=0.83 (95% CI: 0.73 to 0.94).

[8] I^2=58%; 8 of 9 studies show benefit. Removal of largest study (38 000 cases) reduces I^2 to 0%; new estimate: mvRR=0.78 (95% CI: 0.71 to 0.85).

[9] 95% CI of summary estimate consistent with 7% through 27% reduced risk; *n*>48 000 events.

[10] Due to small number of studies (*n*<10), publication bias was not formally assessed.

[11] Prospective cohort studies begin with GRADE of LOW. Upgraded to MODERATE for dose–response association. Assuming linearity, a 5 g increase in LA was associated with a 7% decreased risk of CVD mortality (mvRR=0.93; 95% CI: 0.90 to 0.95). Assuming linearity, a 2% increase in LA was associated with a 6% decreased risk of CVD mortality (mvRR=0.94; 95% CI: 0.93 to 0.94). Nonlinearity suspected; suggests dose is steepest for (0–4 g/day increase) or 0–2% energy. Continues to decrease after this, but slope is more gradual. Wang et al. (2016) (132), using direct modeling, reported that a 2% increase in energy from LA was associated with a 15% decreased risk of all-cause mortality (mvRR=0.85; 95% CI: 0.80 to 0.90).

[12] Median NOS=8 (range: 7–9; 8 comparisons). Twelve of the 13 comparisons in this analysis were estimates obtained from Farvid et al. (2014) (155), who updated several previously published publications. NOS ratings applied to these studies are for the original publications, where possible, but include a full 2/2 on the domain of comparability because the Farvid et al. study reanalysed the data using a consistent confounder-adjustment strategy. Insufficient information to assess study risk of bias for FMC and VIP.

[13] I^2=0%; 3 studies [Ascherio (60), Oh (104), Wallstrom (131)] provided 73.5% of the weight (summary mvRR=0.77; 95% CI: 0.68 to 0.88; *n*=4420 events). The remaining 9 studies have summary mvRR=0.89 (95% CI: 0.72 to 1.10); *n*=2705 events.

[14] 95% CI of pooled estimate consistent with 12% through 29% decreased risk.

[15] Egger's test *P*=0.302; Begg's test *P*=0.583; Trim and fill identified 2 "trimmed" studies, corrected association: 0.79 (95% CI: 0.70 to 0.88; *P*<0.001).

[16] Prospective cohort studies begin with GRADE of LOW. Upgraded for dose–response association. We updated Farvid's dose–response association meta-analysis with 1 additional study. Our analysis finds that, assuming linearity, a 5 g increase of n-6 PUFA is associated with an 8% reduced risk of ischaemic heart disease mortality (mvRR=0.92; 95% CI: 0.86 to 0.98). Assuming linearity, a 2% increase in energy from LA is associated with an 8% reduced risk of ischaemic heart disease mortality (mvRR=0.92; 95% CI: 0.86 to 0.98). No evidence of departure from linearity.

QUALITY ASSESSMENT									SUMMARY OF FINDINGS			IMPORTANCE
EXPOSURE	OUTCOME	PARTICIPANTS (NO. STUDIES)	RISK OF BIAS	INCONSISTENCY	INDIRECTNESS	IMPRECISION	PUBLICATION BIAS	OVERALL QUALITY OF EVIDENCE	STUDY EVENT RATE (%)	ABSOLUTE RISK DIFFERENCE, ADJUSTED (PER 10 000)[1]	RELATIVE RISK, ADJUSTED	
LA	Sudden cardiac death	91 981 (1 study)	No serious risk of bias[17]	Not assessed	No serious indirectness	No serious imprecision[18]	Unable to assess reliably[19]	⨁◯◯◯ LOW[20]	385/91 981 (0.42%)	24 fewer (from 40 fewer to 4 fewer)	0.68 (0.49 to 0.95)	IMPORTANT
	MI, total	0 (0 studies)	–	–	–	–	–	–	–	–	–	IMPORTANT
	MI, fatal	0 (0 studies)	–	–	–	–	–	–	–	–	–	IMPORTANT
	MI, nonfatal	0 (0 studies)	–	–	–	–	–	–	–	–	–	IMPORTANT
	CHD, total	267 201 (14 studies)	No serious risk of bias[21]	No serious inconsistency[22]	No serious indirectness	No serious imprecision[23]	No evidence of publication bias[24]	⨁⨁⨁◯ MODERATE[25]	12 501/ 267 201 (4.7%)	84 fewer (from 144 to 18 fewer)	0.86 (0.76 to 0.97)	CRITICAL
	Stroke, total	0 (0 studies)	–	–	–	–	–	–	–	–	–	IMPORTANT
	Stroke, fatal	36 032 (1 study)	No serious risk of bias26	Not assessed	No serious indirectness	Serious imprecision[27]	Unable to assess reliably[28]	⨁◯◯◯ VERY LOW[29]	321/36 032 (0.9%)	13 fewer (35 fewer to 30 more)	0.74 (0.35, 1.58)	IMPORTANT
	Stroke, ischaemic	57 053 (1 study)	No serious risk of bias[30]	Not assessed	No serious indirectness	No serious imprecision[31]	Unable to assess reliably[32]	⨁◯◯◯ LOW[33]	1879/57 053 (3.3%)	277 fewer (from 506 to 32 fewer)	0.83 (0.70, 0.98)	IMPORTANT

[17] NOS=9; adjusted for TFA.

[18] 95% CI of estimate consistent with 51% reduced through 5% reduced risk.

[19] Due to small number of studies (n<10), publication bias was not formally assessed.

[20] Prospective cohort studies begin with GRADE of LOW. Not downgraded.

[21] Median NOS=9 (range: 8–9; 9 comparisons). Eleven of the 14 comparisons in this analysis were estimates obtained from Farvid et al. (2014), who updated several previous publications. NOS ratings applied to these studies are for the original publications, where possible, but include a full 2/2 on the domain of comparability because the Farvid et al. study reanalyzed the data using a consistent confounder-adjustment strategy. Insufficient information to assess study risk of bias for FMC, WHS, and VIP studies.

[22] I^2=35%; 3 studies [Ascherio (60), Oh (104), and Wallstrom (131)] contributed 55.9% of the weight (summary mvRR=0.87; 95% CI: 0.73 to 1.04; n=9204 events). Remaining 9 studies have summary mvRR=0.84 (95% CI: 0.69 to 1.03; n=3297 events).

[23] 95% CI of pooled estimate (RE) consistent with 24% through 3% reduced risk; pooled FE estimate=0.85, consistent with 22% through 8% reduced risk.

[24] Egger's test: P=0.901; Begg's test: P=0.669. Trim-and-fill identified no "missed" studies. No publication bias suspected.

[25] Prospective cohort studies begin with GRADE of LOW. Upgraded for dose–response association. Assuming linearity, a 5 g increase in LA is associated with a 7% reduced risk of total ischaemic heart disease (mvRR=0.93; 95% CI: 0.89 to 0.97). Assuming linearity, a 2% increase in energy from LA is associated with a 4% reduced risk of total ischaemic heart disease (mvRR=0.96; 95% CI: 0.94 to 0.98).

[26] NOS=8; no adjustment for TFA.

[27] 95% CI includes 1.0; consistent with 65% lower through 55% higher reduced risk.

[28] Due to small number of studies (n<10), publication bias was not formally assessed.

[29] Prospective cohort studies begin with GRADE of LOW. Downgraded for imprecision.

[30] NOS=7.

[31] 95% CI consistent with 30% through 2% reduced risk.

[32] Due to small number of studies (n<10), publication bias was not formally assessed.

[33] Prospective cohort studies begin with GRADE of LOW. Not downgraded.

QUALITY ASSESSMENT									SUMMARY OF FINDINGS			IMPORTANCE
EXPOSURE	OUTCOME	PARTICIPANTS (NO. STUDIES)	RISK OF BIAS	INCONSISTENCY	INDIRECTNESS	IMPRECISION	PUBLICATION BIAS	OVERALL QUALITY OF EVIDENCE	STUDY EVENT RATE (%)	ABSOLUTE RISK DIFFERENCE, ADJUSTED (PER 10 000)[1]	RELATIVE RISK, ADJUSTED	
LA	Stroke, haemorrhagic	0 (0 studies)	–	–	–	–	–	–	–	–	–	IMPORTANT
	Stroke, thrombotic	0 (0 studies)	–	–	–	–	–	–	–	–	–	IMPORTANT
	Atrial fibrillation	80 688 (2 studies)[34]	No serious risk of bias[35]	No serious inconsistency[36]	No serious indirectness	Serious imprecision[37]	Unable to assess reliably[38]	⨁◯◯◯ VERY LOW[39]	7041/80 688 (8.7%)	6 fewer (from 11 fewer to 0)	0.88 (0.78, 1.00)	IMPORTANT
	Heart failure	0 (0 studies)	–	–	–	–	–	–	–	–	–	IMPORTANT
	T2DM	219 898 (7 studies)	No serious risk of bias[40]	No serious inconsistency[41]	No serious indirectness	No serious imprecision[42]	Unable to assess reliably[43]	⨁⨁⨁◯ MODERATE[44]	19 050/ 219 898 (8.7%)	56 fewer (from 112 fewer to 0)	0.90 (0.80, 1.00)	IMPORTANT
	Dementia	5 728 (2 studies)	Serious risk of bias[45]	No serious inconsistency[46]	No serious indirectness	Serious imprecision[47]	Unable to assess reliably[48]	⨁◯◯◯ VERY LOW[49]	109/5728 (1.9%)	210 fewer (from 525 fewer to 316 more)	0.77 (0.45 to 1.34)	IMPORTANT
	Cognitive decline	0 (0 studies)	–	–	–	–	–	–	–	–	–	IMPORTANT

[34] Two arms from 1 study (men/women).
[35] NOS=8; no serious risk of bias.
[36] I^2=0%.
[37] 95% CI consistent with 22% through 0% reduced risk.
[38] Due to small number of studies (n<10), publication bias was not formally assessed.
[39] Prospective cohort studies begin with GRADE of LOW. Downgraded for risk of bias.
[40] Median NOS=7.5 (range: 5–8). Removing studies at high risk of bias (Patel (37), Guash-Ferre (147)) yields mvRR=0.89 (95% CI: 0.78 to 1.01); not substantially different from full model.
[41] I^2=44%; substantial overlap with all studies' 95% CI.
[42] 95% CI of summary estimate consistent with 20% decreased through 0% increased risk.
[43] Due to small number of studies (n<10), publication bias was not formally assessed.
[44] Prospective cohort studies begin with GRADE of LOW. Upgraded for dose–response association. Assuming linearity, a 5 g increase in LA is associated with a 5% reduced risk of type 2 diabetes (mvRR=0.95; 95% CI: 0.91 to 0.99). Assuming linearity, a 2% increase in energy from LA is associated with a 3% reduced risk of type 2 diabetes (mvRR=0.97; 95% CI: 0.94 to 0.99).
[45] Two studies by Kalmijn (85, 86), NOS=6 (ZES) and 8 (Rotterdam Study). 29% LTFU in ZES and short follow-up in these studies (possible bias).
[46] I^2=11%.
[47] 95% CI of summary estimate consistent with 55% decreased through 34% increased risk; n<150 events.
[48] Due to small number of studies (n<10), publication bias was not formally assessed.
[49] Prospective cohort studies begin with GRADE of LOW. Downgraded for risk of bias.

QUALITY ASSESSMENT									SUMMARY OF FINDINGS			IMPORTANCE
EXPOSURE	OUTCOME	PARTICIPANTS (NO. STUDIES)	RISK OF BIAS	INCONSISTENCY	INDIRECTNESS	IMPRECISION	PUBLICATION BIAS	OVERALL QUALITY OF EVIDENCE	STUDY EVENT RATE (%)	ABSOLUTE RISK DIFFERENCE, ADJUSTED (PER 10 000)[1]	RELATIVE RISK, ADJUSTED	
LA	Depression	57 538 (3 studies)	No serious risk of bias[50]	No serious inconsistency[51]	No serious indirectness	No serious imprecision[52]	Unable to assess reliably[53]	⊕⊕⊕◯ MODERATE[54]	3433/57 538 (6.0%)	910 more (from 315 to 1611 more)	1.26 (1.09, 1.46)	IMPORTANT
	Suicide	0 (0 studies)	–	–	–	–	–	–	–	–	–	IMPORTANT
	Crohn's disease	171 163 (2 studies)	No serious risk of bias[55]	No serious inconsistency[56]	No serious indirectness	Serious imprecision[57]	Unable to reliably assess[58]	⊕◯◯◯ VERY LOW[59]	342/171 163 (0.20%)	1 more (from 1 fewer to 7 more)	1.23 (0.66 to 2.29)	IMPORTANT
	Ulcerative colitis	373 998 (2 studies)	No serious risk of bias[60]	Serious incon-sistency[61]	No serious indirectness	Serious imprecision[62]	Not assessed	⊕◯◯◯ VERY LOW[63]	464/373 998 (0.12%)	3 more (from 3 fewer to 20 more)	1.41 (0.66 to 3.01)	IMPORTANT
	All breast cancer	270 144 (5 studies)	No serious risk of bias[64]	No serious inconsistency[65]	No serious indirectness	No serious imprecision[66]	Unable to reliably assess[67]	⊕⊕⊕◯ MODERATE[68]	4577/ 220 364 (2.1%)	104 fewer (from 167 fewer to 42 fewer)	0.95 (0.92, 0.98)	IMPORTANT
	Premeno-pausal breast cancer	0 (0 studies)	–	–	–	–	–	–	–	–	–	IMPORTANT

[50] Median NOS=8 (range: 7–9).

[51] I^2=0%.

[52] 95% CI consistent with 9% through 46% increased risk.

[53] Due to small number of studies (*n*<10), publication bias was not formally assessed.

[54] Prospective cohort studies begin with GRADE of LOW. Upgraded for dose–response association. Assuming linearity, a 5 g increase in energy from LA is associated with a 14% higher risk of depression (mvRR=1.14; 95% CI: 0.94 to 1.38). Assuming linearity, a 2% increase in energy from LA is associated with a 19% higher risk of depression (mvRR=1.19; 95% CI: 0.79 to 1.80).

[55] Median NOS: 8.5 (range: 8–9); 1 study measured TFA, the other did not.

[56] I^2=26%; both 95% CI overlap.

[57] 95% CI of pooled estimate consistent with 34% decreased through 129% increased risk; <500 events.

[58] Due to small number of studies (*n*<10), publication bias was not formally assessed.

[59] Prospective cohort studies begin with GRADE of LOW. Downgraded for risk of imprecision.

[60] NOS=8 and 9, for 2 studies; IBD in EPIC (80) did not adjust for TFA; Ananthakrishnan 2014 (59) did adjust for TFA.

[61] Ananthakrishnan 2014 (59) adjusted for TFA (mvRR=1.04; 95% CI: 0.73 to 1.48); IBD in EPIC (80) did not adjust for TFA (mvRR=2.31; 95% CI: 0.99 to 5.37).

[62] 95% CI of summary estimate consistent with 34% decreased risk through 201% increased risk); *n*<500 events.

[63] Prospective cohort studies begin with GRADE of LOW. Downgraded for inconsistency and imprecision.

[64] Median NOS=9 (6 to 9); removing highest risk-of-bias study (Thiebaut; 4.0% wt) yields mvRR=0.97 [95% CI: 0.91 to 1.03]. One study [Holmes, 1999 (78)] adjusted for TFA

[65] I^2=0%; all 95% CI overlap.

[66] 95% CI consistent with 2% through 8% decreased risk.

[67] Due to small number of studies (*n*<10), publication bias was not formally assessed.

[68] Prospective cohort studies begin with GRADE of LOW. Upgraded for dose–response association. Assuming linearity, a 5 g increase in LA is associated with a 3% lower risk of breast cancer (mvRR=0.97; 95% CI: 0.93 to 1.02). Assuming linearity, a 2% increase in LA is associated with a 2% lower risk of breast cancer (mvRR=0.98; 95% CI: 0.96 to 1.01).

QUALITY ASSESSMENT									SUMMARY OF FINDINGS			IMPORTANCE
EXPOSURE	OUTCOME	PARTICIPANTS (NO. STUDIES)	RISK OF BIAS	INCONSISTENCY	INDIRECTNESS	IMPRECISION	PUBLICATION BIAS	OVERALL QUALITY OF EVIDENCE	STUDY EVENT RATE (%)	ABSOLUTE RISK DIFFERENCE, ADJUSTED (PER 10 000)[1]	RELATIVE RISK, ADJUSTED	
	Postmeno-pausal breast cancer	133 875 (4 studies)	No serious risk of bias[69]	No serious inconsistency[70]	No serious indirectness	Serious imprecision[71]	Unable to reliably assess[72]	⨁◯◯◯ VERY LOW[73]	6367/ 133 875 (4.8%)	34 more (from 119 fewer to 188 more)	1.02 (0.93 to 1.11)	IMPORTANT

CHD: coronary heart disease; CHNS: China Health and Nutrition Survey; CI: confidence interval; CVD: cardiovascular disease; EPIC: European Prospective Investigation into Cancer and Nutrition; FE: fixed effects; FMC: Finnish Mobile Health Clinic; GRADE: Grading of Recommendations Assessment, Development, and Evaluation; IBD: inflammatory bowel disease; LA: linoleic acid; LTFU: loss to-follow-up; MI: myocardial infarction; mvRR: multivariable risk ratio; NHANES: National Health and Nutrition Examination Survey; no.: number; NOS: Newcastle-Ottawa Scale; RE: random effects; RR: risk ratio; T2DM: type 2 diabetes mellitus; TFA: *trans*-fatty acids; VIP: Västerbotten Intervention Program; WHS: Women's Health Study; ZES: Zutphen Elderly Study.

[69] Four studies, median NOS=8.5 (range: 8–9).
[70] I^2=0%.
[71] Summary estimate consistent with 7% decreased through 11% increased risk; n>6000 cases.
[72] Due to small number of studies (n<10), publication bias was not formally assessed.
[73] Prospective cohort studies begin with GRADE of LOW. Downgraded for imprecision.

Table 12. GRADE evidence profile for prospective cohort studies of ARA and health outcomes

QUALITY ASSESSMENT									SUMMARY OF FINDINGS			IMPORTANCE
EXPOSURE	OUTCOME	PARTICIPANTS (NO. STUDIES)	RISK OF BIAS	INCONSISTENCY	INDIRECTNESS	IMPRECISION	PUBLICATION BIAS	OVERALL QUALITY OF EVIDENCE	STUDY EVENT RATE (%)	ABSOLUTE RISK DIFFERENCE, ADJUSTED (PER 10 000)[1]	RELATIVE RISK, ADJUSTED	
ARA	All-cause mortality	698 556 (6 studies)	No serious risk of bias[2]	Serious inconsistency[3]	No serious indirectness	Serious imprecision[4]	Unreliable to assess[5]	⨁◯◯◯ VERY LOW6	168 896/ 698 556 (24.2%)	80 fewer (from 205 fewer to 57 more)	0.93 (0.82, 1.05)	CRITICAL
	CVD, total	0 (0 studies)	–	–	–	–	–	–	–	–	–	CRITICAL
	CVD, fatal	684 507 (4 studies)	No serious risk of bias[7]	No serious inconsistency[8]	No serious indirectness	Serious imprecision[9]	Unreliable to assess[10]	⨁◯◯◯ VERY LOW[11]	47 924/ 684 507 (7.0%)	1 more (from 5 fewer to 7 more)	1.01 (0.91, 1.13)	CRITICAL
	CHD, fatal	37 032 (1 study)	No serious risk of bias[12]	Not assessed	No serious indirectness	Serious imprecision[13]	Unreliable to assess[14]	⨁◯◯◯ VERY LOW[15]	978/37 032 (2.6%)	40 fewer (from 85 fewer to 22 more)	0.80 (0.58, 1.11)	CRITICAL
	Sudden cardiac death	91 981 (1 study)	No serious risk of bias[16]	Not assessed	No serious indirectness	Serious imprecision[17]	Not assessed	⨁◯◯◯ VERY LOW[18]	385/91 981 (0.42%)	9 fewer (from 28 fewer to 17 more)	0.88 (0.63, 1.23)	IMPORTANT
	MI, total	0 (0 studies)	–	–	–	–	–	–	–	–	–	IMPORTANT

[1] See Annex 2 for sources of absolute event rates.

[2] NOS=8 (range: 7–9). Nothing to suspect any study is seriously biased.

[3] I^2=93%. Two Harvard cohorts [Wang *(132)*] adjusted for TFA. NIH-AARP study shows significantly increased risk. Removal of two Harvard cohorts [Wang *(132)*] does not change estimate substantively (mvRR=0.96; 95% CI: 0.81 to 1.12; I-squared = 78%). Removal of NIH-AARP data drops I^2 to 0%, estimate changed (mvRR=0.90 [95% CI: 0.86 to 0.94]).

[4] 95% CI of summary estimate consistent with 18% reduced through 5% increased risk; >165 000 deaths.

[5] Due to small number of studies (*n*<10), risk of publication bias was not formally assessed.

[6] Prospective cohort studies begin with GRADE of LOW. Downgraded for inconsistency. Assuming linearity, a 0.1 g increase in ARA was associated with a 0.2% increased risk of all-cause mortality (mvRR=1.002; 95% CI: 0.98 to 1.03). Assuming linearity, a 0.3% increase in energy from ARA was associated with a 1% increased risk of all-cause mortality (mvRR=1.01; 95% CI: 0.87 to 1.18). Wang (132), using direct modelling, reported that a 0.3% increase in energy from ARA was associated with a 42% decreased risk of all-cause mortality (mvRR=0.58; 95% CI: 0.47 to 0.73).

[7] Median NOS=8 (8 to 9).

[8] I^2=67%. Two Harvard cohorts adjusted for TFA. NIH-AARP study shows significantly increased risk. Removal of two Harvard cohorts (Wang) does not change estimate substantively (mvRR=0.97; 95% CI: 0.72 to 1.32; I-squared = 82%). Removal of NIH-AARP data drops I^2 to 22%, estimate changed (mvRR=0.97 [95% CI: 0.87 to 1.08]).

[9] 95% CI of summary estimate consistent with 42% decreased through 11% increased risk; >47 000 events.

[10] Due to small number of studies (*n*<10), risk of publication bias was not formally assessed.

[11] Prospective cohort studies begin with GRADE of LOW. Downgraded for imprecision.

[12] NOS=8; no measurement of TFA.

[13] 95% CI of summary estimate consistent with 9% decreased through 13% increased risk; >47 000 events.

[14] Due to small number of studies (*n*<10), risk of publication bias was not formally assessed.

[15] Prospective cohort studies begin with GRADE of LOW. Downgraded for imprecision.

[16] NOS=9; measured TFA.

[17] 95% CI of study estimate consistent with 37% decreased through 23% increased risk; N<400 events.

[18] Prospective cohort studies begin with GRADE of LOW. Downgraded for imprecision.

QUALITY ASSESSMENT									SUMMARY OF FINDINGS			IMPORTANCE
EXPOSURE	OUTCOME	PARTICIPANTS (NO. STUDIES)	RISK OF BIAS	INCONSISTENCY	INDIRECTNESS	IMPRECISION	PUBLICATION BIAS	OVERALL QUALITY OF EVIDENCE	STUDY EVENT RATE (%)	ABSOLUTE RISK DIFFERENCE, ADJUSTED (PER 10 000)[1]	RELATIVE RISK, ADJUSTED	
ARA	MI, fatal	0 (0 studies)	–	–	–	–	–	–	–	–	–	IMPORTANT
	MI, nonfatal	0 (0 studies)	–	–	–	–	–	–	–	–	–	IMPORTANT
	Fatal arrhythmia	0 (0 studies)	–	–	–	–	–	–	–	–	–	IMPORTANT
	CHD, total	0 (0 studies)	–	–	–	–	–	–	–	–	–	CRITICAL
	Stroke, total	0 (0 studies)	–	–	–	–	–	–	–	–	–	CRITICAL
	Stroke, fatal	36 032 (1 study)	No serious risk of bias[19]	Not assessed	No serious indirectness	Serious imprecision[20]	Not assessed	⨁◯◯◯ VERY LOW[21]	321/36 032 (0.9%)	7 fewer (from 28 fewer to 32 more)	0.87 (0.47 to 1.61)	IMPORTANT
	Stroke, ischaemic (fatal)	0 (0 studies)	–	–	–	–	–	–	–	–	–	IMPORTANT
	Stroke, haemor-rhagic (fatal)	0 (0 studies)	–	–	–	–	–	–	–	–	–	IMPORTANT
	Stroke, thrombotic	0 (0 studies)	–	–	–	–	–	–	–	–	–	IMPORTANT
	Atrial fibrillation	0 (0 studies)	–	–	–	–	–	–	–	–	–	IMPORTANT
	Heart failure	0 (0 studies)	–	–	–	–	–	–	–	–	–	IMPORTANT
	T2DM	382 (1 study)	No serious risk of bias[22]	Not assessed	No serious indirectness	Serious imprecision[23]	Not assessed	⨁◯◯◯ VERY LOW[24]	199/382 (52.1%)[25]	73 fewer (from 286 fewer to 303 more)	0.87 (0.49, 1.54)	IMPORTANT
	Dementia	0 (0 studies)	–	–	–	–	–	–	–	–	–	IMPORTANT
	Cognitive decline	0 (0 studies)	–	–	–	–	–	–	–	–	–	IMPORTANT

[19] Zhuang *(140)* NOS = 8.
[20] 95% CI of study estimate consistent with 53% decreased through 61% increased risk; N<400 events.
[21] Prospective cohort studies begin with GRADE of LOW. Downgraded for imprecision.
[22] NOS=6; Study authors [Patel *(37)*] adjusted for age, family history, and smoking; data on participation rate/dropout not clear.
[23] 95% CI of study estimate consistent with 51% reduced risk through 54% increased risk.
[24] Prospective cohort studies begin with GRADE of LOW. Downgraded for imprecision.
[25] Case–control study with prospective exposure measurement.

QUALITY ASSESSMENT									SUMMARY OF FINDINGS			IMPORTANCE
EXPOSURE	OUTCOME	PARTICIPANTS (NO. STUDIES)	RISK OF BIAS	INCONSISTENCY	INDIRECTNESS	IMPRECISION	PUBLICATION BIAS	OVERALL QUALITY OF EVIDENCE	STUDY EVENT RATE (%)	ABSOLUTE RISK DIFFERENCE, ADJUSTED (PER 10 000)[1]	RELATIVE RISK, ADJUSTED	
ARA	Depression	57 538 (3 studies)	No serious risk of bias[26]	No serious inconsistency[27]	No serious indirectness	No serious imprecision[28]	Unable to assess reliably[29]	⊕⊕⊕◯ MODERATE[30]	3433/57 538 (6.0%)	105 more (from 350 fewer to 630 more)	1.03 (0.90 to 1.18)	IMPORTANT
	Suicide	0 (0 studies)	–	–	–	–	–	–	–	–	–	IMPORTANT
	Crohn's disease	170 805 (1 study)	No serious risk of bias[31]	Not assessed	No serious indirectness	Serious imprecision[32]	Unable to assess reliably[33]	⊕◯◯◯ VERY LOW[34]	269/170 805 (0.16%)	1 fewer (from 3 fewer to 1 more)	0.80 (0.55, 1.17)	IMPORTANT
	Ulcerative colitis	170 805 (1 study)	No serious risk of bias[35]	Not assessed	No serious indirectness	Serious imprecision[36]	Unable to assess reliably[37]	⊕◯◯◯ VERY LOW[38]	338/170 805 (0.2%)	1 fewer (from 4 fewer to 2 more)	0.90 (0.64, 1.26)	IMPORTANT
	All breast cancer	180 342 (3 studies)	No serious risk of bias[39]	No serious inconsistency[40]	No serious indirectness	Serious imprecision[41]	Unable to assess reliably[42]	⊕◯◯◯ VERY LOW[43]	3581/ 180 342 (2.0%)	10 more (from 0 to 21 more)	1.05 (1.00, 1.10)	IMPORTANT
	Premeno-pausal breast cancer	0 (0 studies)	–	–	–	–	–	–	–	–	–	IMPORTANT

[26] Median NOS=8 (range: 7–9).
[27] I^2=0%.
[28] 95% CI consistent with 10% reduced% through 18% increased risk.
[29] Due to small number of studies (*n*<10), publication bias was not formally assessed.
[30] Prospective cohort studies begin with GRADE of LOW.
[31] Three studies, all NOS=9; Holmes (1999) (78) adjusted for TFA.
[32] 95% CI of estimate consistent with 45% decreased through 17% increased risk; *n*<300 events.
[33] Due to small number of studies (*n*<10), publication bias was not formally assessed.
[34] Prospective cohort studies begin with GRADE of LOW. Downgraded for imprecision.
[35] NOS=9; adjusted for TFA.
[36] 95% CI of estimate consistent with 36% decreased through 26% increased risk; *n*<400 events.
[37] Due to small number of studies (*n*<10), publication bias was not formally assessed.
[38] Prospective cohort studies begin with GRADE of LOW. Downgraded for imprecision.
[39] NOS=9; adjusted for TFA.
[40] I^2=0%.
[41] 95% CI of summary estimate consistent with 0% to 10% increased risk; *n*>3000 events.
[42] Due to small number of studies (*n*<10), publication bias was not formally assessed.
[43] Prospective cohort studies begin with GRADE of LOW. Downgraded for imprecision.

QUALITY ASSESSMENT									SUMMARY OF FINDINGS			IMPORTANCE
EXPOSURE	OUTCOME	PARTICIPANTS (NO. STUDIES)	RISK OF BIAS	INCONSISTENCY	INDIRECTNESS	IMPRECISION	PUBLICATION BIAS	OVERALL QUALITY OF EVIDENCE	STUDY EVENT RATE (%)	ABSOLUTE RISK DIFFERENCE, ADJUSTED (PER 10 000)[1]	RELATIVE RISK, ADJUSTED	
ARA	Postmeno-pausal breast cancer	4 089 (2 studies)	No serious risk of bias[44]	No serious inconsistency[45]	No serious indirectness	Serious imprecision[46]	Unable to assess reliably[47]	⨁◯◯◯ VERY LOW[48]	1411/4089 (34.5%)	221 fewer (from 598 fewer to 255 more)	0.87 (0.65 to 1.15)	IMPORTANT

ARA: arachidonic acid; CHD: coronary heart disease; CI: confidence interval; CVD: cardiovascular disease; GRADE: Grading of Recommendations Assessment, Development, and Evaluation; LA: linoleic acid; MI: myocardial infarction; mvRR: multivariable risk ratio; NIH-AARP: National Institutes of Health American Association of Retired Persons Diet and Health Study; no.: number; NOS: Newcastle-Ottawa Scale; RR: risk ratio; T2DM: type 2 diabetes mellitus; TFA: *trans*-fatty acids.

[44] Two studies; NOS=8-9; 1 measured TFA.
[45] I^2=36%.
[46] 95% CI of estimate consistent with 35% reduced risk through 15% increased risk; *N*>1400 cases.
[47] Due to small number of studies (*n*<10), publication bias was not formally assessed.
[48] Prospective cohort studies begin with GRADE of LOW. Downgraded for imprecision

Table 13. GRADE evidence profile for prospective cohort studies of polyunsaturated:saturated fat and health outcomes

QUALITY ASSESSMENT									SUMMARY OF FINDINGS			IMPORTANCE
EXPOSURE	OUTCOME	PARTICIPANTS (NO. STUDIES)	RISK OF BIAS	INCONSISTENCY	INDIRECTNESS	IMPRECISION	PUBLICATION BIAS	OVERALL QUALITY OF EVIDENCE	STUDY EVENT RATE (%)	ABSOLUTE RISK DIFFERENCE, ADJUSTED (PER 10 000)[1]	RELATIVE RISK, ADJUSTED	
P:S fat	All-cause mortality	68 238 (5 studies)	No serious risk of bias[2]	Serious inconsistency[3]	No serious indirectness	Serious imprecision[4]	Unreliable to assess[5]	⊕◯◯◯ VERY LOW[6]	12 468/ 68 238 (18.3%)	23 more (from 68 fewer to 125 more)	1.02 (0.94, 1.11)	CRITICAL
	Total CVD	27 394 (2 studies)	No serious risk of bias[7]	No serious inconsistency[8]	No serious indirectness	Serious imprecision[9]	Unreliable to assess[10]	⊕◯◯◯ VERY LOW[11]	908/27 394 (3.3%)	40 fewer (from 93 fewer to 20 more)	0.88 (0.72, 1.06)	–
	CVD, fatal	65 598 (3 studies)	No serious risk of bias[12]	Serious inconsistency[13]	No serious indirectness	No serious imprecision[14]	Unreliable to assess[15]	⊕◯◯◯ VERY LOW[16]	3533/65 598 (5.39%)	72 more (from 28 more to 124 more)	1.18 (1.07, 1.31)	CRITICAL
	CHD, fatal	0 (0 studies)	–	–	–	–	–	–	–	–		CRITICAL
	Sudden cardiac death	0 (0 studies)	–	–	–	–	–	–	–	–	–	IMPORTANT
	MI, total	0 (0 studies)	–	–	–	–	–	–	–	–	–	IMPORTANT
	MI, fatal	0 (0 studies)	–	–	–	–	–	–	–	–	–	IMPORTANT
	MI, nonfatal	0 (0 studies)	–	–	–	–	–	–	–	–	–	IMPORTANT
	Fatal arrhythmia	0 (0 studies)	–	–	–	–	–	–	–	–	–	IMPORTANT

[1] See Annex 2 for sources of absolute event rates.

[2] Four studies, all NOS=8–9; 1 study [Akbaraly *(57)*] adjusted for TFA.

[3] I^2=54%; ¾ point estimates >1.0, and CIs overlap. One study (Laaksonen *(93)*; 6% weight) finds significantly reduced risk of all-cause mortality (0.71; 95% CI: 0.51 to 0.98) and 1 estimate (Wakai (men) *(130)*; 32% weight) finds borderline increased risk (mvRR=1.09; 95% CI: 1.00 to 1.19).

[4] 95% CI of summary estimate consistent with 6% decreased through 11% increased risk; *n*>12 000 deaths.

[5] Due to small number of studies (*n*<10), risk of publication bias was not formally assessed.

[6] Prospective cohort studies begin with GRADE of LOW. Assuming linearity, a 0.25 increase in P:S ratio was associated with a 6% increased risk of CVD mortality (mvRR=1.06; 95% CI: 1.005 to 1.11).

[7] NOS=7; no adjustment for TFA.

[8] I^2=0%.

[9] 95% CI of summary estimate consistent with 28% lower through 6% increased risk; *n*>900 events.

[10] Due to small number of studies (*n*<10), risk of publication bias was not formally assessed.

[11] Prospective cohort studies begin with GRADE of LOW. Downgraded for imprecision.

[12] Three studies, all NOS=8; 1 study [Akbaraly *(57)*] adjusted for TFA.

[13] I^2=66%; Wakai (women) *(130)* showed significant increased risk, with high P:S (mvRR=1.39; 95% CI: 1.16 to 1.66). Pooled arms of Wakai (males and females, with >95% of cases) yield mvRR=1.28 (95% CI: 1.09 to 1.51).

[14] 95% CI of summary estimate consistent with 1% decreased through 42% increased risk; *n*>12 000 deaths. FE estimate: 1.18 (95% CI: 1.07 to 1.31).

[15] Due to small number of studies (*n*<10), risk of publication bias was not formally assessed.

[16] Prospective cohort studies begin with GRADE of LOW. Downgraded for inconsistency. Assuming linearity, a 0.25 increase in P:S ratio was associated with a 6% increased risk of CVD mortality (mvRR=1.06; 95% CI: 1.005 to 1.11).

QUALITY ASSESSMENT									SUMMARY OF FINDINGS			IMPORTANCE
EXPOSURE	OUTCOME	PARTICIPANTS (NO. STUDIES)	RISK OF BIAS	INCONSISTENCY	INDIRECTNESS	IMPRECISION	PUBLICATION BIAS	OVERALL QUALITY OF EVIDENCE	STUDY EVENT RATE (%)	ABSOLUTE RISK DIFFERENCE, ADJUSTED (PER 10 000)[1]	RELATIVE RISK, ADJUSTED	
P:S fat	CHD, total	78 778 (1 study)	No serious risk of bias[17]	Not assessed	No serious indirectness	Serious imprecision[18]	Unreliable to assess[19]	⊕◯◯◯ VERY LOW[20]	1766/78 778 (2.2%)	78 fewer (from 168 fewer to 30 more)	0.87 (0.72, 1.05)	CRITICAL
	Stroke, total	2283 (1 study)	No serious risk of bias[21]	Not assessed	No serious indirectness	Serious imprecision[22]	Unreliable to assess[23]	⊕◯◯◯ VERY LOW[24]	141/2283 (6.2%)	17 more (from 14 fewer to 80 more)	1.36 (0.70, 2.66)	IMPORTANT
	Stroke, fatal	0 (0 studies)	–	–	–	–	–	–	–	–	–	IMPORTANT
	Stroke, ischaemic	27 394 (2 studies)	No serious risk of bias[25]	No serious inconsistency[26]	No serious indirectness	Serious imprecision[27]	Unreliable to assess[28]	⊕◯◯◯ VERY LOW[29]	648/27 394 (2.4%)	16 more (from 41 fewer to 87 more)	1.06 (0.85, 1.32)	IMPORTANT
	Stroke, haemorrhagic (fatal)	0 (0 studies)	–	–	–	–	–	–	–	–	–	IMPORTANT
	Stroke, thrombotic	0 (0 studies)	–	–	–	–	–	–	–	–	–	IMPORTANT
	Atrial fibrillation	0 (0 studies)	–	–	–	–	–	–	–	–	–	IMPORTANT
	Heart failure	0 (0 studies)	–	–	–	–	–	–	–	–	–	IMPORTANT

[17] NOS=7; adjusted for TFA.
[18] 95% CI of estimate consistent with 28% decreased through 5% increased risk; *n*>1700 events.
[19] Due to small number of studies (*n*<10), risk of publication bias was not formally assessed.
[20] Prospective cohort studies begin with GRADE of LOW. Downgraded for inconsistency.
[21] NOS=7; no adjustment for TFA.
[22] 95% CI consistent with 30% decreased through 166% increased risk; *n*<200 cases.
[23] Due to small number of studies (*n*<10), risk of publication bias was not formally assessed.
[24] Prospective cohort studies begin with GRADE of LOW. Downgraded for imprecision.
[25] NOS=7; no adjustment for TFA.
[26] I^2=0%.
[27] 95% CI of summary estimate consistent with 15% lower through 32% increased risk; *n*>600 events.
[28] Due to small number of studies (*n*<10), risk of publication bias was not formally assessed.
[29] Prospective cohort studies begin with GRADE of LOW. Downgraded for imprecision.

QUALITY ASSESSMENT									SUMMARY OF FINDINGS			IMPORTANCE
EXPOSURE	OUTCOME	PARTICIPANTS (NO. STUDIES)	RISK OF BIAS	INCONSISTENCY	INDIRECTNESS	IMPRECISION	PUBLICATION BIAS	OVERALL QUALITY OF EVIDENCE	STUDY EVENT RATE (%)	ABSOLUTE RISK DIFFERENCE, ADJUSTED (PER 10 000)[1]	RELATIVE RISK, ADJUSTED	
P:S fat	T2DM	21 472 (1 study)	No serious risk of bias[30]	Not assessed	No serious indirectness	Serious imprecision[31]	Unreliable to assess[32]	⊕◯◯◯ VERY LOW[33]	414/21 472 (1.9%)	50 fewer (from 107 fewer to 17 more)	0.91 (0.81, 1.03)	IMPORTANT
	Dementia	0 (0 studies)	–	–	–	–	–	–	–	–	–	IMPORTANT
	Cognitive decline	0 (0 studies)	–	–	–	–	–	–	–	–	–	IMPORTANT
	Depression	0 (0 studies)	–	–	–	–	–	–	–	–	–	IMPORTANT
	Suicide	0 (0 studies)	–	–	–	–	–	–	–	–	–	IMPORTANT
	Crohn's disease	0 (0 studies)	–	–	–	–	–	–	–	–	–	IMPORTANT
	Ulcerative colitis	0 (0 studies)	–	–	–	–	–	–	–	–	–	IMPORTANT
	All breast cancer	3 988 (1 study)	No serious risk of bias	Not assessed	No serious indirectness	Serious imprecision[34]	Not assessed	⊕◯◯◯ VERY LOW[35]	54/3988 (1.4%)	104 more (from 48 fewer to 403 more)	1.50 (0.77, 2.93)	IMPORTANT
	Premeno-pausal breast cancer	0 (0 studies)	–	–	–	–	–	–	–	–	–	IMPORTANT
	Postmeno-pausal breast cancer	910 (1 study)	Serious risk of bias[36]	Not assessed	No serious indirectness	Serious imprecision[37]	Not assessed	⊕◯◯◯ VERY LOW[38]	237/910 (26.0%)	146 more (from 22 more to 353 more)	1.86 (1.13, 3.07)	IMPORTANT

CHD: coronary heart disease; CI: confidence interval; CVD: cardiovascular disease; FE: fixed effects; FFQ: food frequency questionnaire; GRADE: Grading of Recommendations Assessment, Development, and Evaluation; MI: myocardial infarction; mvRR: multivariable risk ratio; no.: number; NOS: Newcastle-Ottawa Scale; P:S: polyunsaturated:saturated; SES: socioeconomic status; T2DM: type 2 diabetes mellitus; TFA: *trans*-fatty acids.

[30] NOS=7; no adjustment for TFA.
[31] 95% CI of estimate consistent with 19% decreased through 3% increased risk; *n*<500 events.
[32] Due to small number of studies (*n*<10), risk of publication bias was not formally assessed.
[33] Prospective cohort studies begin with GRADE of LOW. Downgraded for imprecision.
[34] 95% CI of estimate consistent with 23% decreased through 193% increased risk.
[35] Prospective cohort studies begin with GRADE of LOW. Downgraded for imprecision.
[36] NOS=6; this study [Wirfalt *(133)*] was a case–control study (but prospective exposure); authors did not control for family history; and did not report a review of identified registry cases only; follow-up may be as low as 3 years for those recruited in 1996 (through 1999).
[37] 95% CI of this study consistent with 13% to 207% increased risk; *n*<300 cases.
[38] Prospective cohort studies begin with GRADE of LOW. Downgraded for risk of bias and imprecision.

Table 14. GRADE evidence profile for prospective cohort studies of omega-6:omega-3 PUFA and health outcomes

QUALITY ASSESSMENT									SUMMARY OF FINDINGS			IMPORTANCE
EXPOSURE	OUTCOME	PARTICIPANTS (NO. STUDIES)	RISK OF BIAS	INCONSISTENCY	INDIRECTNESS	IMPRECISION	PUBLICATION BIAS	OVERALL QUALITY OF EVIDENCE	STUDY EVENT RATE (%)	ABSOLUTE RISK DIFFERENCE, ADJUSTED (PER 10 000)[1]	RELATIVE RISK, ADJUSTED	
n-6:n-3 PUFA	All-cause mortality	625 428 (6 studies)	No serious risk of bias[2]	No serious inconsistency[3]	No serious indirectness	No serious imprecision[4]	Unable to assess reliably[5]	⨁⨁◯◯ LOW6	78 332/ 703 760 (11.1%)	11 fewer (from 46 fewer to 11 more)	0.99 (0.96 to 1.01)	CRITICAL
	CVD, total	0 (0 studies)	–	–	–	–	–	–	–	–	–	CRITICAL
	CVD, fatal	168 645 (4 studies)	No serious risk of bias[7]	No serious inconsistency[8]	No serious indirectness	Serious imprecision[9]	Unable to assess reliably[10]	⨁◯◯◯ VERY LOW[11]	9449/ 168 645 (5.6%)	3 fewer (from 7 fewer to 1 more)	0.94 (0.87 to 1.02)	CRITICAL
	CHD, fatal	42 290 (2 studies)	No serious risk of bias[12]	No serious inconsistency[13]	No serious indirectness	Serious imprecision[14]	Unable to assess reliably[15]	⨁◯◯◯ VERY LOW[16]	1153/42 290 (2.7%)	4 more (from 40 fewer to 58 more)	1.02 (0.80, 1.29)	CRITICAL
	Sudden cardiac death	0 (0 studies)	–	–	–	–	–	–	–	–	–	IMPORTANT
	MI, total	0 (0 studies)	–	–	–	–	–	–	–	–	–	IMPORTANT
	MI, fatal	0 (0 studies)	–	–	–	–	–	–	–	–	–	IMPORTANT
	MI, nonfatal	0 (0 studies)	–	–	–	–	–	–	–	–	–	IMPORTANT
	Fatal arrhythmia	0 (0 studies)	–	–	–	–	–	–	–	–	–	IMPORTANT

[1] See Annex 2 for sources of absolute event rates.
[2] Median NOS=9 (range: 7–9). Dolocek *(69)* did not adjust for TFA.
[3] I^2=0% ; all point estimates are close with overlapping 95% CI.
[4] 95% CI of summary estimate consistent with 4% decreased through 1% increased risk; *N*>78 000 events.
[5] Due to small number of studies (*n*<10), publication bias was not formally assessed.
[6] Prospective cohort studies begin with GRADE of LOW.
[7] Median NOS=9 (range: 7–9). Dolocek *(69)* did not adjust for TFA.
[8] I^2=12% ; all point estimates are close, with overlapping 95% CI.
[9] 95% CI included no effect; summary estimate consistent with 13% decreased through 2% increased risk; N>9000 events.
[10] Due to small number of studies (*n*<10), publication bias was not formally assessed.
[11] Prospective cohort studies begin with GRADE of LOW. Downgraded for imprecision.
[12] NOS=7 and 8. No adjustment in this study for TFA.
[13] I^2=0%.
[14] 95% CI of estimate consistent with 20% reduced risk through 29% increased risk; >1100 events.
[15] Due to small number of studies (*n*<10), publication bias was not formally assessed.
[16] Prospective cohort studies begin with GRADE of LOW. Downgraded for imprecision.

QUALITY ASSESSMENT									SUMMARY OF FINDINGS			IMPORTANCE
EXPOSURE	OUTCOME	PARTICIPANTS (NO. STUDIES)	RISK OF BIAS	INCONSISTENCY	INDIRECTNESS	IMPRECISION	PUBLICATION BIAS	OVERALL QUALITY OF EVIDENCE	STUDY EVENT RATE (%)	ABSOLUTE RISK DIFFERENCE, ADJUSTED (PER 10 000)[1]	RELATIVE RISK, ADJUSTED	
n-6:n-3 PUFA	CHD, total	0 (0 studies)	–	–	–	–	–	–	–	–	–	CRITICAL
	Stroke, total	0 (0 studies)	–	–	–	–	–	–	–	–	–	IMPORTANT
	Stroke, fatal	36 032 (1 study)	No serious risk of bias[17]	Not assessed	No serious indirectness	Serious imprecision[18]	Not assessed	⨁◯◯◯ VERY LOW[19]	321/36 032 (0.9%)	5 fewer (from 20 fewer to 14 more)	0.90 (0.63, 1.28)	IMPORTANT
	Stroke, ischaemic	0 (0 studies)	–	–	–	–	–	–	–	–	–	IMPORTANT
	Stroke, haemor-rhagic	0 (0 studies)	–	–	–	–	–	–	–	–	–	IMPORTANT
	Stroke, thrombotic	0 (0 studies)	–	–	–	–	–	–	–	–	–	IMPORTANT
	Atrial fibrillation	0 (0 studies)	–	–	–	–	–	–	–	–	–	IMPORTANT
	Heart failure	0 (0 studies)	–	–	–	–	–	–	–	–	–	IMPORTANT
	T2DM	92 425 (6 studies)	No serious risk of bias[20]	No serious inconsistency[21]	No serious indirectness	Serious imprecision[22]	Unable to assess reliably[23]	⨁◯◯◯ VERY LOW[24]	4766/92 425 (5.2%)	11 more (from 56 fewer to 90 more)	1.02 (0.90, 1.16)	IMPORTANT
	Dementia	0 (0 studies)	–	–	–	–	–	–	–	–	–	IMPORTANT
	Cognitive decline	4 809 (1 study)	No serious risk of bias[25]	Not assessed	No serious indirectness	No serious imprecision[26]	Unable to assess reliably[27]	⨁⨁◯◯ LOW[28]	598/4809 (12.4%)	330 more (from 13 more to 733 more)	1.25 (1.01 to 1.55)	IMPORTANT

[17] NOS=8.
[18] 95% CI of study estimate consistent with 37% decreased through 28% increased risk; N<400 events.
[19] Prospective cohort studies begin with GRADE of LOW. Downgraded for imprecision.
[20] Median NOS=7 (range: 6–8). Study with NOS=6 [Alhazmi *(2)*] with poor follow-up reporting, and did not control for family history, with only 70% case confirmation; the other study with NOS=6 [Patel *(37)*] failed to control for important confounders, and data on participation rate/dropout not clear. Removal of these studies does not alter the pooled estimate (without these studies, mvRR=1.03 [95% CI: 0.89 to 1.21]).
[21] I^2=24%; all CIs overlap.
[22] 95% CI consistent with a 10% decrease through 16% increased risk; *n*>4700 cases.
[23] Due to small number of studies (*n*<10), publication bias was not formally assessed.
[24] Prospective cohort studies begin with GRADE of LOW. Downgraded for imprecision.
[25] NOS=9; no TFA adjustment.
[26] 95% CI of summary estimate consistent with 1% to 55% increased risk; *N*>500 cases.
[27] Due to small number of studies (*n*<10), publication bias was not formally assessed.
[28] Prospective cohort studies begin with GRADE of LOW. Not downgraded.

QUALITY ASSESSMENT									SUMMARY OF FINDINGS			IMPORTANCE
EXPOSURE	OUTCOME	PARTICIPANTS (NO. STUDIES)	RISK OF BIAS	INCONSISTENCY	INDIRECTNESS	IMPRECISION	PUBLICATION BIAS	OVERALL QUALITY OF EVIDENCE	STUDY EVENT RATE (%)	ABSOLUTE RISK DIFFERENCE, ADJUSTED (PER 10 000)[1]	RELATIVE RISK, ADJUSTED	
n-6:n-3 PUFA	Depression (n-3:n-6)	57 538 (3 studies)	No serious risk of bias[29]	No serious inconsistency[30]	No serious indirectness	No serious imprecision[31]	Unable to assess reliably[32]	⨁⨁⨁◯ MODERATE[33]	3433/57 538 (6.0%)	910 fewer (from 1226 fewer to 490 fewer)	0.74 (0.65, 0.86)	IMPORTANT
	Suicide	101 507 (2 studies)	No serious risk of bias	No serious inconsistency[34]	No serious indirectness	Serious imprecision[35]	Not assessed	⨁◯◯◯ VERY LOW[36]	298/101 507 (0.29%)	0 (from 0 to 2 more)	1.05 (0.63 to 1.74)	IMPORTANT
	Crohn's disease	170 805 (1 study)	No serious risk of bias37	Not assessed	No serious indirectness	Serious imprecision38	Not assessed	⨁◯◯◯ VERY LOW39	269/170 805 (0.16%)	1 more (from 1 fewer to 5 more)	1.18 (0.76 to 1.81)	IMPORTANT
	Ulcerative colitis	170 805 (1 study)	No serious risk of bias[40]	Not assessed	No serious indirectness	No serious imprecision[41]	Not assessed	⨁⨁◯◯ LOW[42]	338/170 805 (0.2%)	3 more (from 0 more to 12 more)	1.45 (1.02 to 2.05)	IMPORTANT
	All breast cancer	129 114 (3 studies)	No serious risk of bias[43]	No serious inconsistency[44]	No serious indirectness	Serious imprecision[45]	Unable to assess reliably[46]	⨁◯◯◯ VERY LOW[47]	1613/129 114 (1.25%)	0 (from 0 to 2 more)	1.13 (0.95 to 1.35)	IMPORTANT

[29] NOS=9 with adjustment for TFA.
[30] I^2=0%.
[31] 95% CI consistent with 17% to 55% increased risk; >3400 events.
[32] Due to small number of studies (*n*<10), publication bias was not formally assessed.
[33] Prospective cohort studies begin with GRADE of LOW. Not downgraded. Assuming linearity, a 0.1 unit increase in n-3:n-6 is associated with a 21% lower risk of depression (mvRR=0.79; 95% CI: 0.71 to 0.89). Upgraded.
[34] I^2=27%; 95% CI of individual studies overlap.
[35] 95% CI of pooled estimate consistent with 37% reduced through 74% increased risk; N<300 cases.
[36] Prospective cohort studies begin with GRADE of LOW. Downgraded for imprecision.
[37] NOS=9 with adjustment for TFA.
[38] 95% CI of study estimate consistent with 24% reduced risk through 81% increased risk; *n*<300 cases.
[39] Prospective cohort studies begin with GRADE of LOW. Downgraded for imprecision.
[40] NOS=9 with adjustment for TFA.
[41] 95% CI of study estimate consistent with 2% through 105% increased risk; *n*<400 cases.
[42] Prospective cohort studies begin with GRADE of LOW. Not downgraded.
[43] Median NOS=8 (range: 8–9); no studies adjusted for TFA.
[44] I^2=0%.
[45] 95% CI of summary estimate consistent with 5% decreased through 35% increased risk.
[46] Due to small number of studies (*n*<10), publication bias was not formally assessed.
[47] Prospective cohort studies begin with GRADE of LOW. Downgraded for imprecision.

QUALITY ASSESSMENT									SUMMARY OF FINDINGS			IMPORTANCE
EXPOSURE	OUTCOME	PARTICIPANTS (NO. STUDIES)	RISK OF BIAS	INCONSISTENCY	INDIRECTNESS	IMPRECISION	PUBLICATION BIAS	OVERALL QUALITY OF EVIDENCE	STUDY EVENT RATE (%)	ABSOLUTE RISK DIFFERENCE, ADJUSTED (PER 10 000)[1]	RELATIVE RISK, ADJUSTED	
n-6:n-3 PUFA	Premenopausal breast cancer	0 (0 studies)	–	–	–	–	–	–	–	–	–	IMPORTANT
	Postmenopausal breast cancer	3 401 (2 studies)	Serious risk of bias[48]	Not assessed	No serious indirectness	No serious imprecision[49]	Not assessed	⨁◯◯◯ VERY LOW[50]	707/3401 (20.8%)	816 more (from 221 to 1608 more)	1.48 (1.13, 1.94)	IMPORTANT

CHD: coronary heart disease; CI: confidence interval; CVD: cardiovascular disease; GRADE: Grading of Recommendations Assessment, Development, and Evaluation; MI: myocardial infarction; mvRR: multivariable risk ratio; no.: number; NOS: Newcastle-Ottawa Scale; PUFA: polyunsaturated fatty acids; T2DM: type 2 diabetes mellitus; TFA: *trans*-fatty acids.

[48] Study with NOS=6 [Wirfalt *(133)*] did not control for family history and had low rates of follow-up for those recruited in 1996 (through 1999).
[49] 95% CI consistent with a 13% through 94% increased risk. All of this would be of interest.
[50] Prospective cohort studies begin with GRADE of LOW. Downgraded for imprecision and risk of bias.

Table 15. Distribution of directly reported background (average) PUFA intakes across studies

PUFA TYPE	STUDIES (N)	MEAN	SD	MEDIAN	25TH QUARTILE	75TH QUARTILE
Total PUFA						
% energy	68	5.7	1.0	5.9	5.4	6.4
g	52	12.3	3.1	12.6	10.6	14.5
Total n-3						
% energy						
g	36	1.3	0.7	1.3	1.0	1.6
Long-chain n-3						
% energy	14	0.2	0.1	0.2	0.1	0.3
g	61	0.316	0.234	0.286	0.140	0.425
EPA						
% energy	2	0.04	0.02	0.04	0.03	0.05
g	35	0.123	0.102	0.079	0.046	0.178
DHA						
% energy	2	0.09	0.04	0.09	0.06	0.12
g	37	0.216	0.188	0.132	0.086	0.300
ALA						
% energy	14	0.6	0.2	0.5	0.5	0.6
g	36	1.3	0.3	1.2	1.0	1.5
Total n-6						
% energy						
g	29	10.2	2.6	10.4	8.4	12.2
LA						
% energy	25	5.1	1.2	5.1	4.6	5.6
g	29	11.2	3.7	10.7	9.9	13.0
ARA						
% energy	19	0.13	0.05	0.12	0.09	0.17
g	8	0.07	0.01	0.08	0.07	0.08
n-6:n-3						
Ratio	19	10.0	12.3	7.6	5.9	9.0

ALA: alpha-linolenic acid; ARA: arachidonic acid; DHA: docosahexaenoic acid; EPA: eicosapentaenoic acid; LA: linoleic acid; PUFA: polyunsaturated fatty acids; SD: standard deviation.

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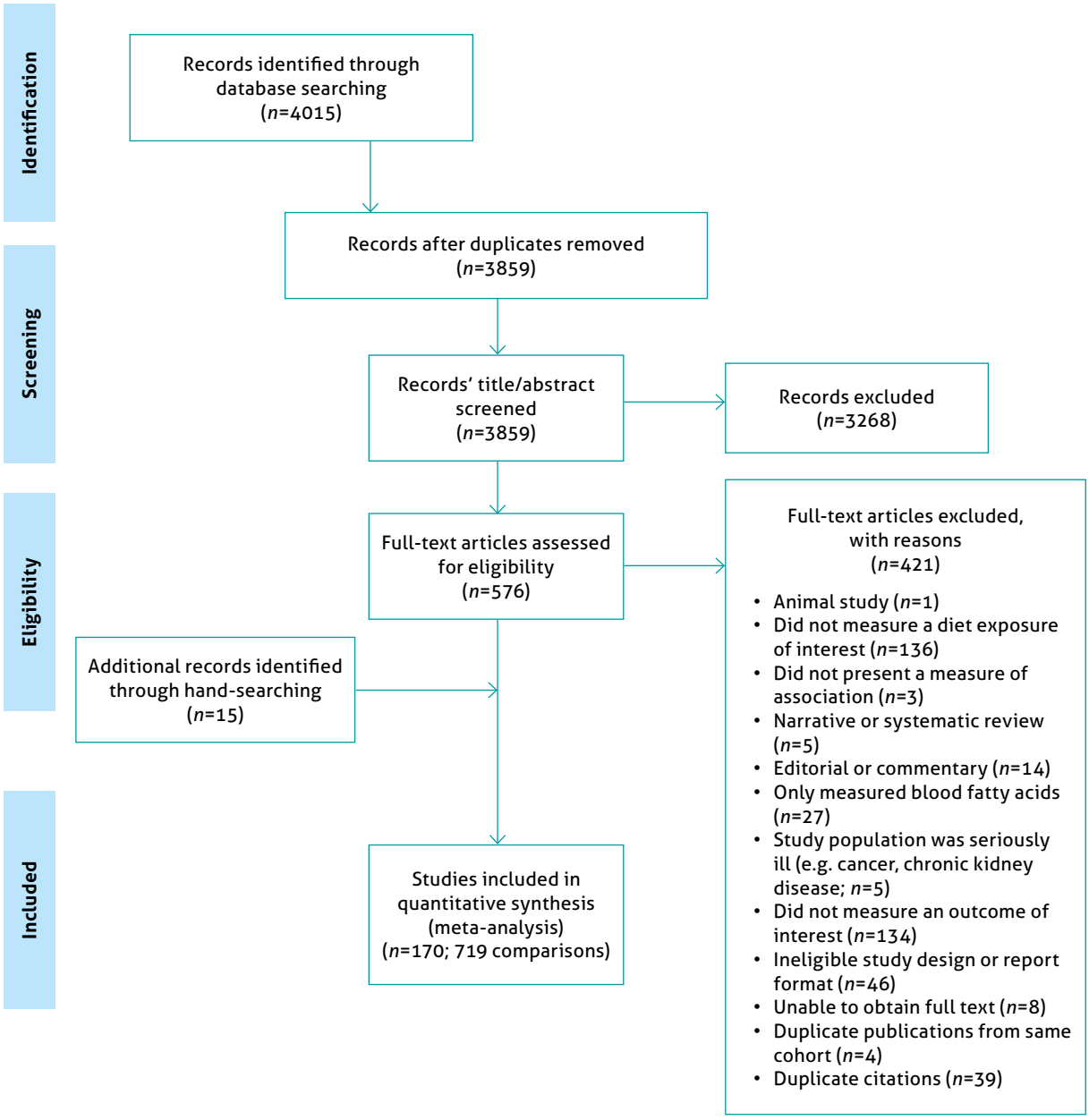
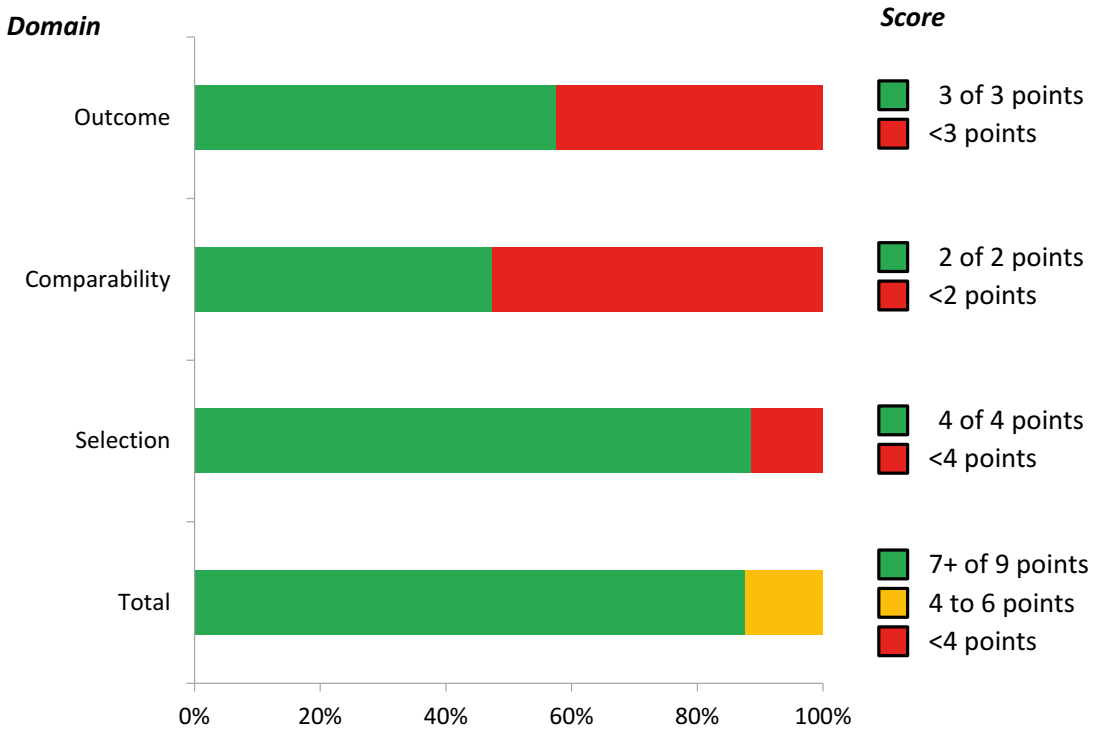
Annex 2. Figures

Fig. 1a. PRISMA 2009 flow diagram (Moher et al., 2009)



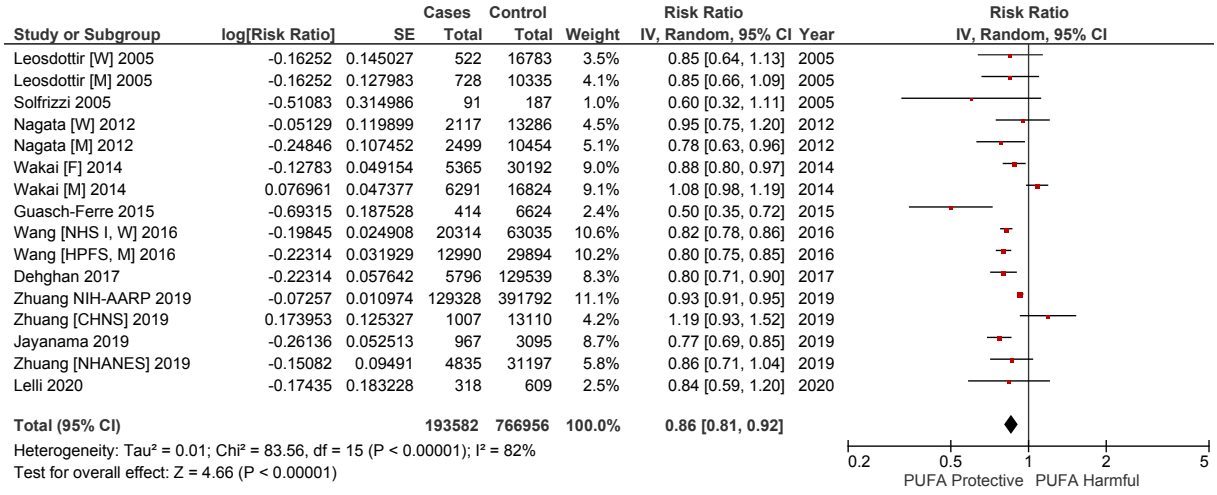
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Fig. 1b. Summary of NOS ratings on each domain and summary score



NOS: Newcastle-Ottawa Scale.

Fig. 2. Pooled most-adjusted (random-effects) RR of total PUFA and all-cause mortality in primary prevention (*n*=16 unique estimates)

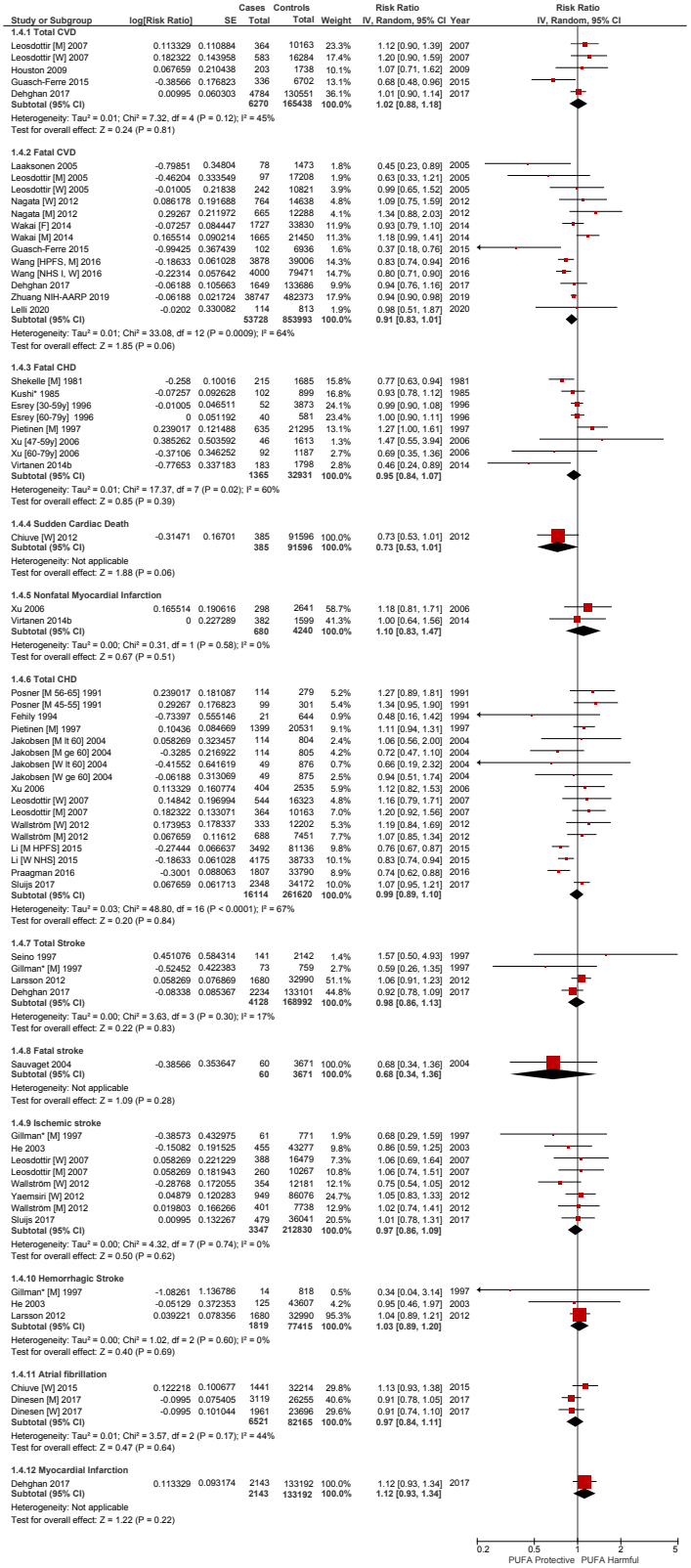


Study or Subgroup	log[Risk Ratio]	SE	Cases Total	Control Total	Weight	Risk Ratio IV, Random, 95% CI	Year
Leosdottir [W] 2005	-0.16252	0.145027	522	16783	3.5%	0.85 [0.64, 1.13]	2005
Leosdottir [M] 2005	-0.16252	0.127983	728	10335	4.1%	0.85 [0.66, 1.09]	2005
Solfrizzi 2005	-0.51083	0.314986	91	187	1.0%	0.60 [0.32, 1.11]	2005
Nagata [W] 2012	-0.05129	0.119899	2117	13286	4.5%	0.95 [0.75, 1.20]	2012
Nagata [M] 2012	-0.24846	0.107452	2499	10454	5.1%	0.78 [0.63, 0.96]	2012
Wakai [F] 2014	-0.12783	0.049154	5365	30192	9.0%	0.88 [0.80, 0.97]	2014
Wakai [M] 2014	0.076961	0.047377	6291	16824	9.1%	1.08 [0.98, 1.19]	2014
Guasch-Ferre 2015	-0.69315	0.187528	414	6624	2.4%	0.50 [0.35, 0.72]	2015
Wang [NHS I, W] 2016	-0.19845	0.024908	20314	63035	10.6%	0.82 [0.78, 0.86]	2016
Wang [HPFS, M] 2016	-0.22314	0.031929	12990	29894	10.2%	0.80 [0.75, 0.85]	2016
Dehghan 2017	-0.22314	0.057642	5796	129539	8.3%	0.80 [0.71, 0.90]	2017
Zhuang NIH-AARP 2019	-0.07257	0.010974	129328	391792	11.1%	0.93 [0.91, 0.95]	2019
Zhuang [CHNS] 2019	0.173953	0.125327	1007	13110	4.2%	1.19 [0.93, 1.52]	2019
Jayanama 2019	-0.26136	0.052513	967	3095	8.7%	0.77 [0.69, 0.85]	2019
Zhuang [NHANES] 2019	-0.15082	0.09491	4835	31197	5.8%	0.86 [0.71, 1.04]	2019
Lelli 2020	-0.17435	0.183228	318	609	2.5%	0.84 [0.59, 1.20]	2020
Total (95% CI)			**193582**	**766956**	**100.0%**	**0.86 [0.81, 0.92]**	

Heterogeneity: Tau² = 0.01; Chi² = 83.56, df = 15 (P < 0.00001); I² = 82%
Test for overall effect: Z = 4.66 (P < 0.00001)

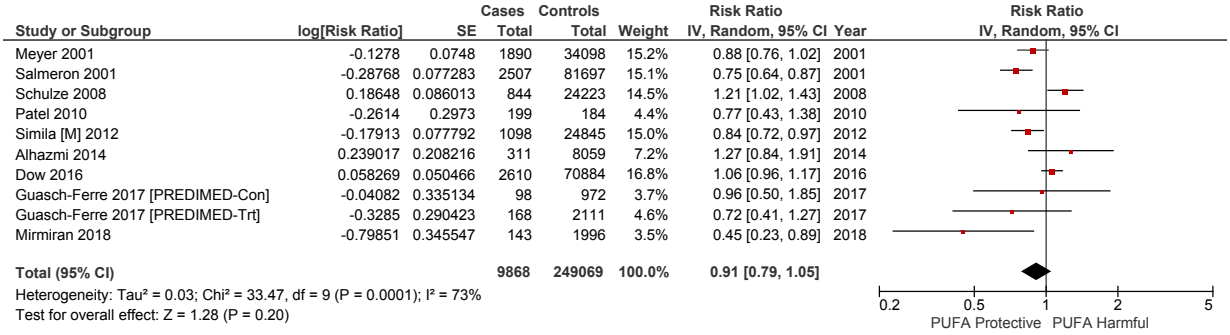
CHNS: China Health and Nutrition Survey; CI: confidence interval; df: degrees of freedom; F: female; HPFS: Health Professionals Follow-up Study; IV: inverse variance; M: male; NHANES: National Health and Nutrition Examination Survey; NHS I: Nurses' Health Study I; NIH-AARP: National Institutes of Health American Association of Retired Persons Diet and Health Study; PUFA: polyunsaturated fatty acids; RR: risk ratio; SE: standard error; W: women.

Fig. 3. **Pooled most-adjusted (random-effects) RR of total PUFA and CVD in primary prevention (*n*=48 unique estimates)**



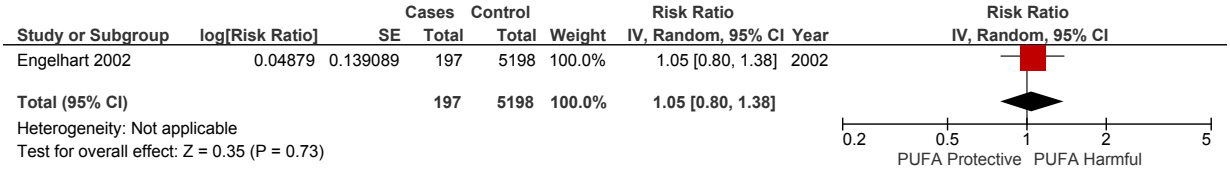
CHD: coronary heart disease; CI: confidence interval; CVD: cardiovascular disease; df: degrees of freedom; F: female; ge: greater than or equal to; HPFS: Health Professionals Follow-up Study; IV: inverse variance; lt: less than; M: male; NHS I: Nurses' Health Study I; NIH-AARP: National Institutes of Health American Association of Retired Persons Diet and Health Study; PUFA: polyunsaturated fatty acids; RR: risk ratio; SE: standard error; W: women; y: years.

Fig. 4. Pooled most-adjusted (random-effects) RR of total PUFA and type 2 diabetes (*n*=10 unique estimates)



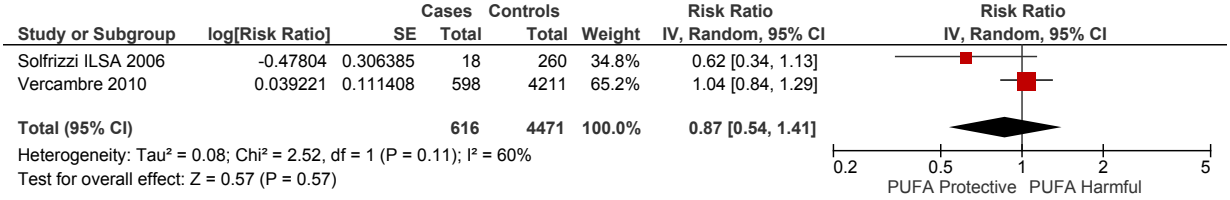
CI: confidence interval; df: degrees of freedom; IV: inverse variance; M: male; PREDIMED-Con: Prevención con Dieta Mediterránea (control); PREDIMED-Trt: Prevención con Dieta Mediterránea (treatment); PUFA: polyunsaturated fatty acids; RR: risk ratio; SE: standard error.

Fig. 5. Pooled most-adjusted RR of total PUFA and dementia (*n*=1 unique estimate)



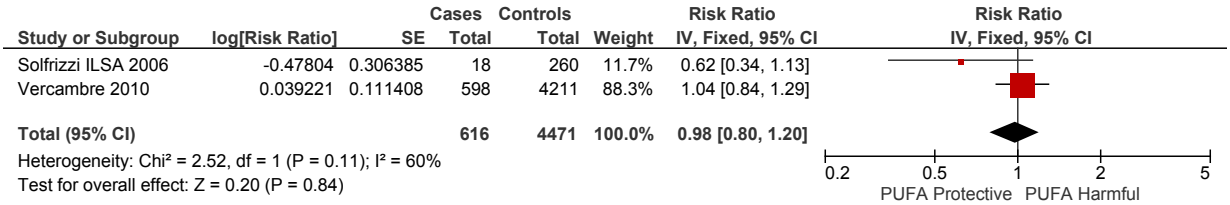
CI: confidence interval; IV: inverse variance; PUFA: polyunsaturated fatty acids; RR: risk ratio; SE: standard error.

Fig. 6a. Pooled most-adjusted (random-effects) RR of total PUFA and cognitive decline (*n*=2 unique estimates)



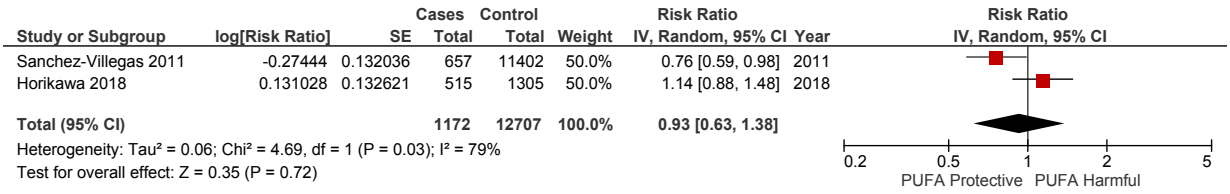
CI: confidence interval; df: degrees of freedom; ILSA: Italian Longitudinal Study on Aging; IV: inverse variance; PUFA: polyunsaturated fatty acids; RR: risk ratio; SE: standard error.

Fig. 6b. Pooled most-adjusted (fixed-effect) RR of total PUFA and cognitive decline (*n*=2 unique estimates)



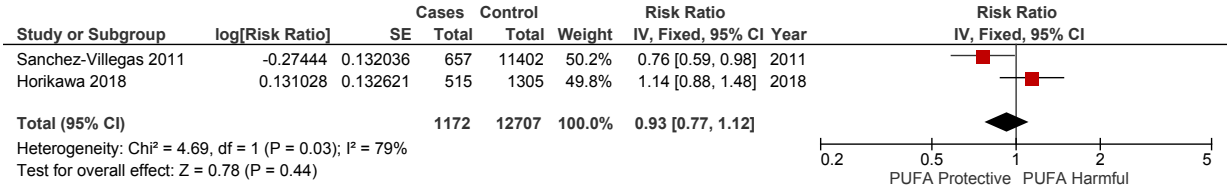
CI: confidence interval; df: degrees of freedom; ILSA: Italian Longitudinal Study on Aging; IV: inverse variance; PUFA: polyunsaturated fatty acids; RR: risk ratio; SE: standard error.

Fig. 7a. Pooled most-adjusted (random-effects) RR of total PUFA and depression (*n*=2 unique estimates)



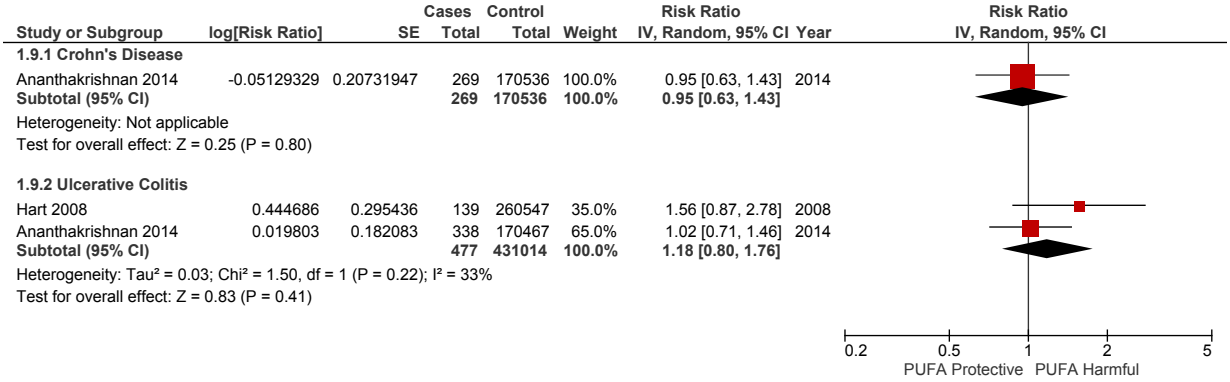
CI: confidence interval; df: degrees of freedom; IV: inverse variance; PUFA: polyunsaturated fatty acids; RR: risk ratio; SE: standard error.

Fig. 7b. Pooled most-adjusted (fixed-effect) RR of total PUFA and depression (*n*=2 unique estimates)



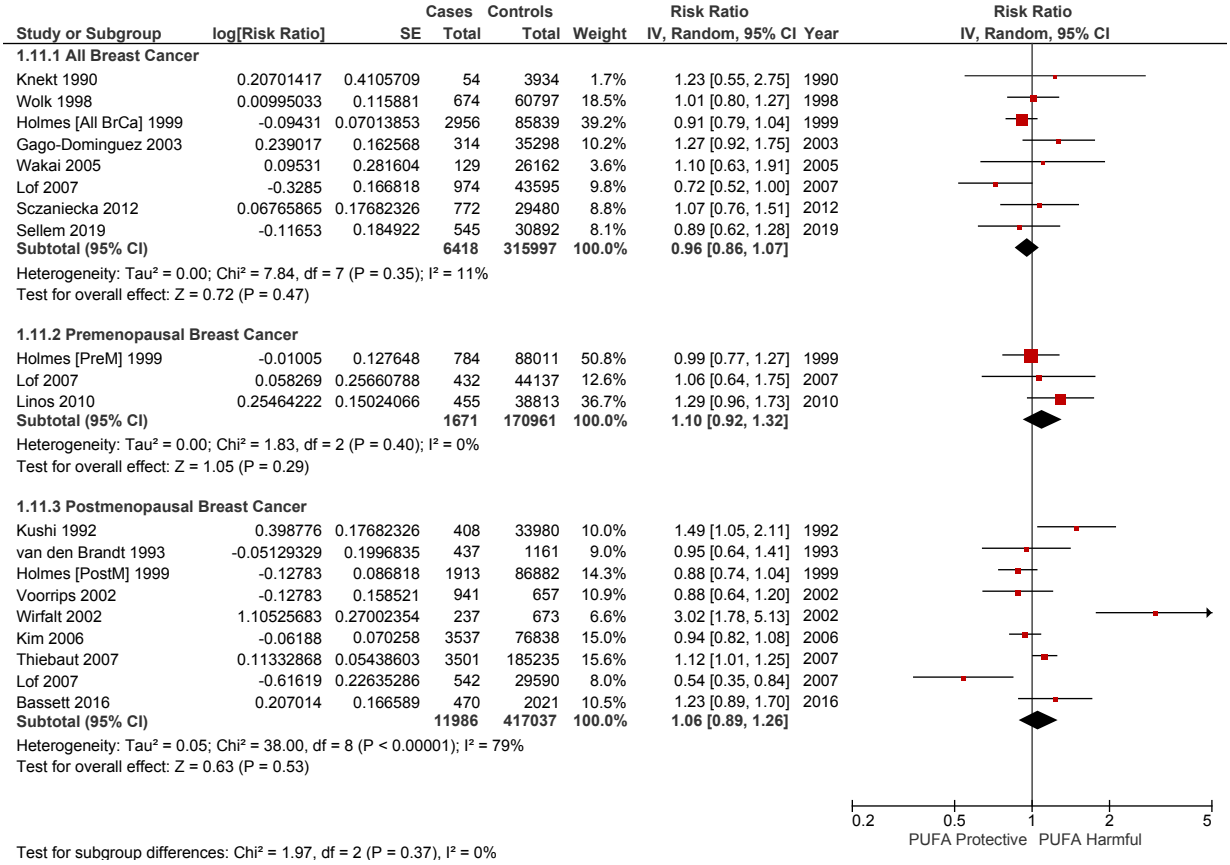
CI: confidence interval; df: degrees of freedom; IV: inverse variance; PUFA: polyunsaturated fatty acids; RR: risk ratio; SE: standard error.

Fig. 8. Pooled most-adjusted RR of total PUFA and inflammatory bowel disease (*n*=3 unique estimates)



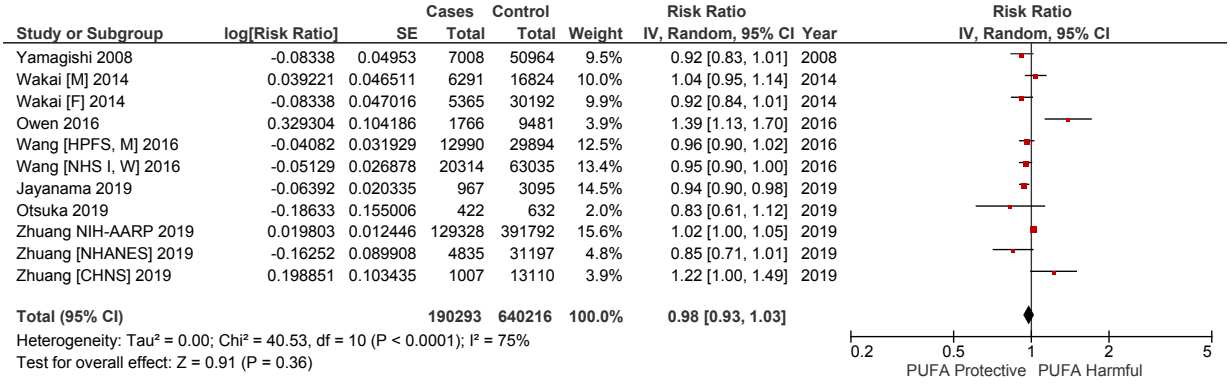
CI: confidence interval; df: degrees of freedom; IV: inverse variance; PUFA: polyunsaturated fatty acids; RR: risk ratio; SE: standard error.

Fig. 9. Pooled most-adjusted RR of total PUFA and breast cancer (*n*=18 unique estimates)



BrCa: breast cancer; CI: confidence interval; df: degrees of freedom; IV: inverse variance; PostM: postmenopausal; PreM: premenopausal; PUFA: polyunsaturated fatty acids; RR: risk ratio; SE: standard error.

Fig. 10. Pooled most-adjusted RR of omega-3 PUFA and all-cause mortality (*n*=11 unique estimates)



CHNS: China Health and Nutrition Survey; CI: confidence interval; df: degrees of freedom; F: female; HPFS: Health Professionals Follow-up Study; IV: inverse variance; M: male; NHANES: National Health and Nutrition Examination Survey; NHS I: Nurses' Health Study I; NIH-AARP: National Institutes of Health American Association of Retired Persons Diet and Health Study; PUFA: polyunsaturated fatty acids; RR: risk ratio; SE: standard error; W: women.

Fig. 11. Pooled most-adjusted RR of omega-3 PUFA and CVD (*n*=24 unique estimates)

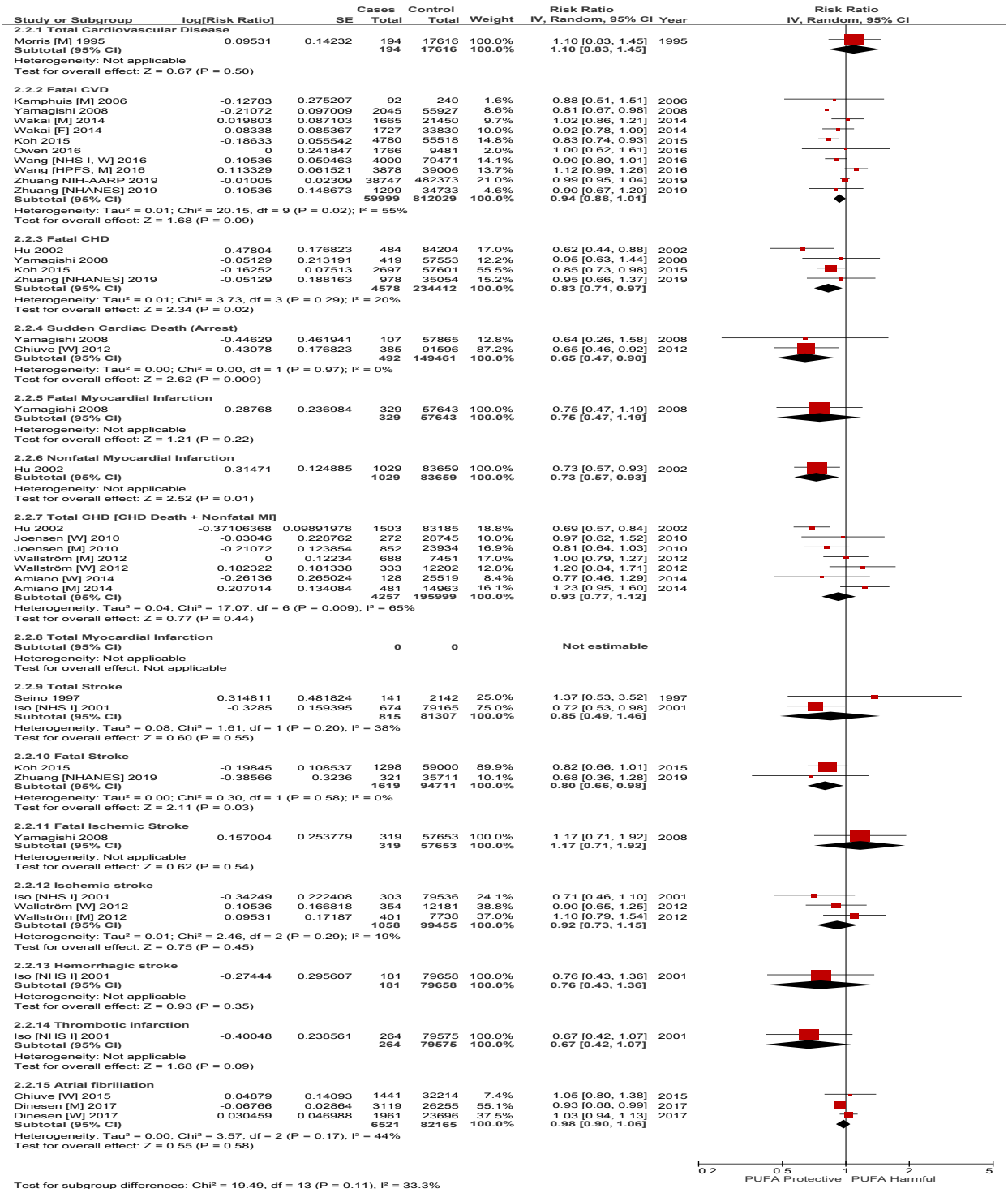
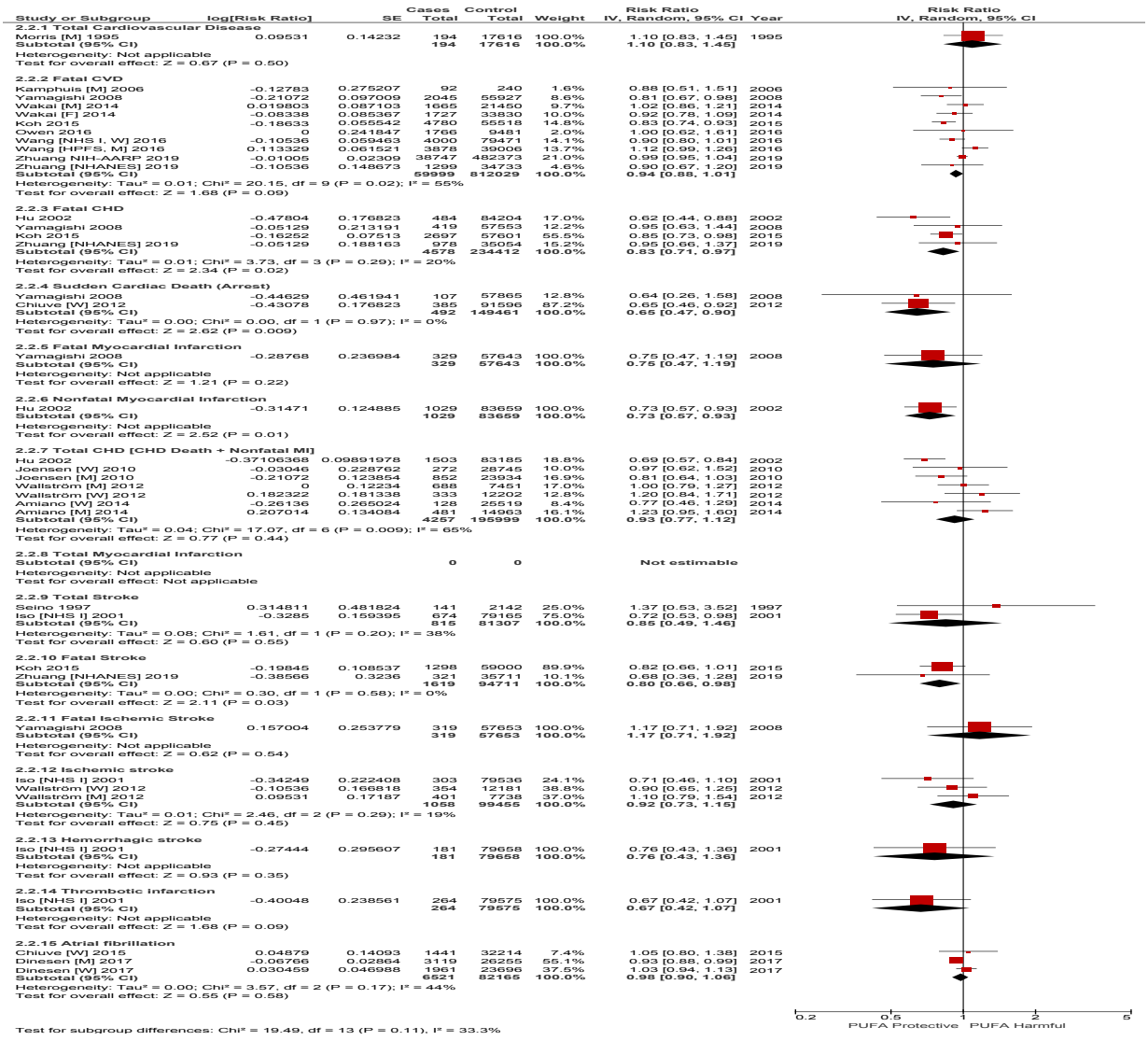
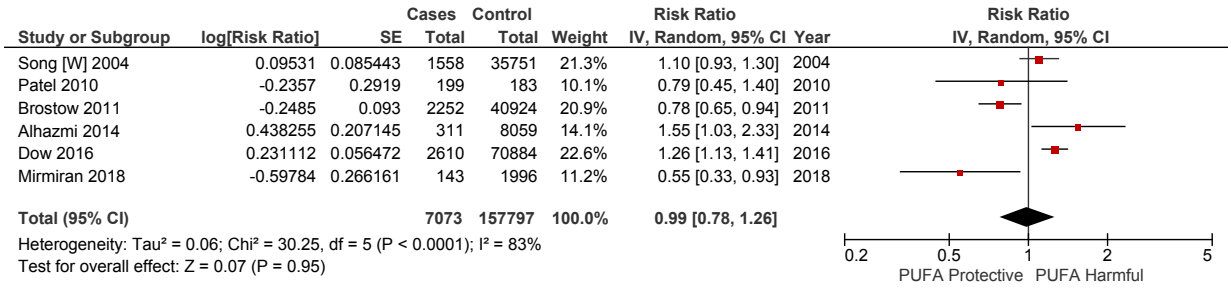


Fig. 11 (cont'd). Pooled most-adjusted RR of omega-3 PUFA and CVD (*n*=24 unique estimates)



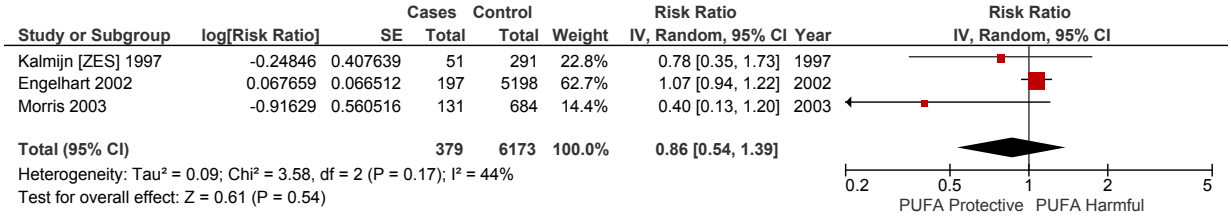
CHD: coronary heart disease; CI: confidence interval; CVD: cardiovascular disease; df: degrees of freedom; F: female; HPFS: Health Professionals Follow-up Study; IV: inverse variance; M: male; MI: myocardial infarction; NHANES: National Health and Nutrition Examination Survey; NHS I: Nurses' Health Study I; NIH-AARP: National Institutes of Health American Association of Retired Persons Diet and Health Study; PUFA: polyunsaturated fatty acids; RR: risk ratio; SE: standard error; W: women.

Fig. 12. Pooled most-adjusted RR of omega-3 PUFA and type 2 diabetes (*n*=6 unique estimates)



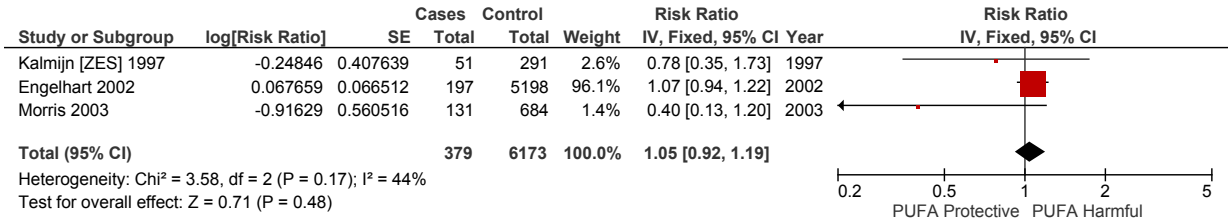
CI: confidence interval; df: degrees of freedom; IV: inverse variance; PUFA: polyunsaturated fatty acids; RR: risk ratio; SE: standard error; W: women.

Fig. 13a. Pooled most-adjusted (random-effects) RR of omega-3 PUFA and dementia (*n*=3 unique estimates)



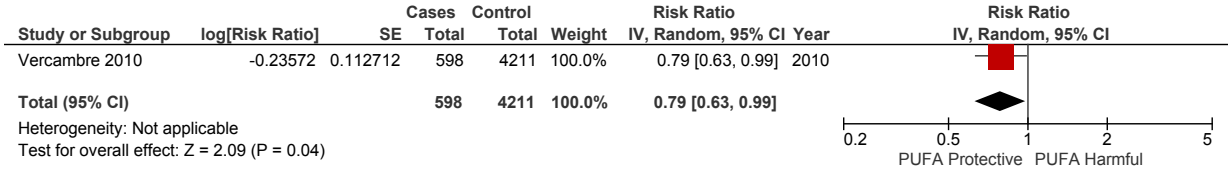
CI: confidence interval; df: degrees of freedom; IV: inverse variance; PUFA: polyunsaturated fatty acids; RR: risk ratio; SE: standard error; ZES: Zutphen Elderly Study.

Fig. 13b. Pooled most-adjusted (fixed-effect) RR of omega-3 PUFA and dementia (*n*=3 unique estimates)



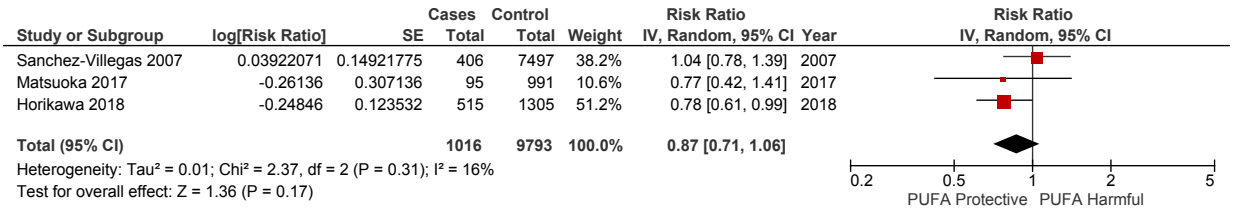
CI: confidence interval; df: degrees of freedom; IV: inverse variance; PUFA: polyunsaturated fatty acids; RR: risk ratio; SE: standard error; ZES: Zutphen Elderly Study.

Fig. 14. Pooled most-adjusted RR of omega-3 PUFA and cognitive decline (*n*=1 unique estimate)



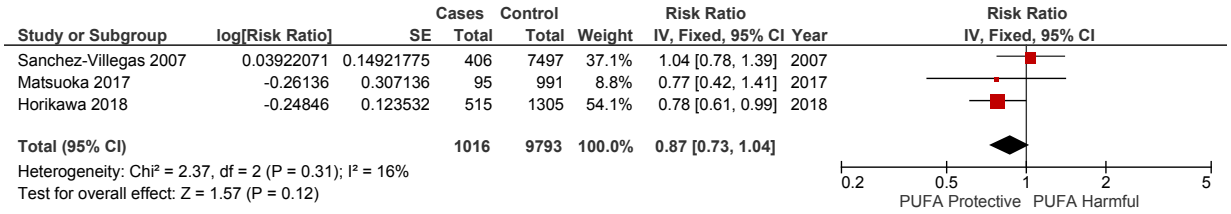
CI: confidence interval; IV: inverse variance; PUFA: polyunsaturated fatty acids; RR: risk ratio; SE: standard error.

Fig. 15a. Pooled most-adjusted (random-effects) RR of omega-3 PUFA and depression (*n*=3 unique estimates)



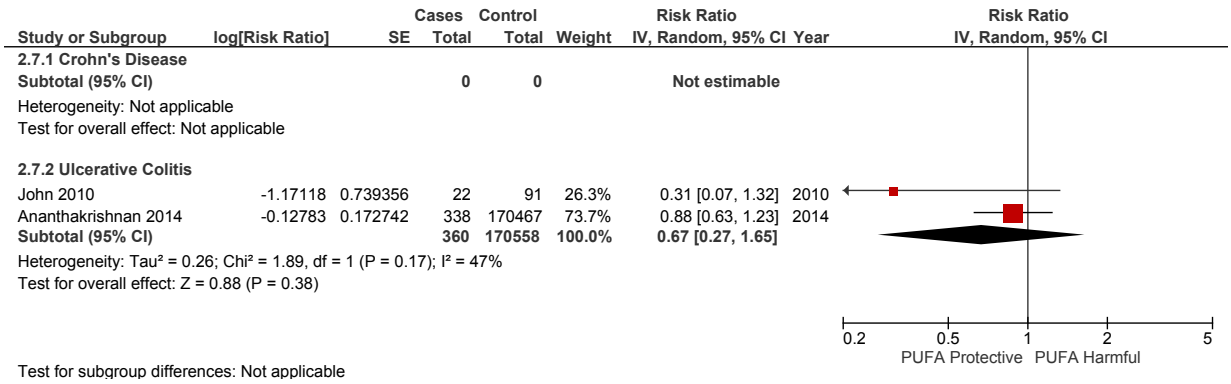
CI: confidence interval; df: degrees of freedom; IV: inverse variance; PUFA: polyunsaturated fatty acids; RR: risk ratio; SE: standard error.

Fig. 15b. Pooled most-adjusted (fixed-effect) RR of omega-3 PUFA and depression (*n*=3 unique estimates)



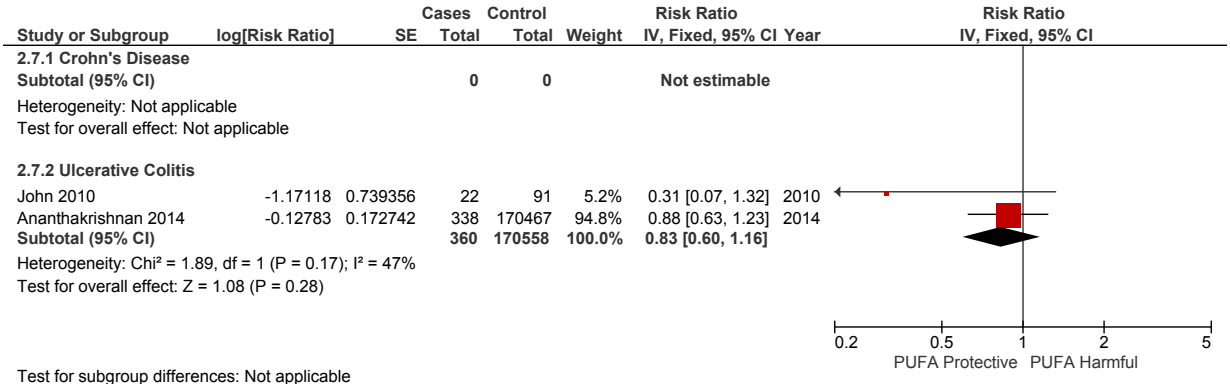
CI: confidence interval; df: degrees of freedom; IV: inverse variance; PUFA: polyunsaturated fatty acids; RR: risk ratio; SE: standard error.

Fig. 16a. Pooled most-adjusted (random-effects) RR of omega-3 PUFA and inflammatory bowel disease (*n*=2 unique estimates)



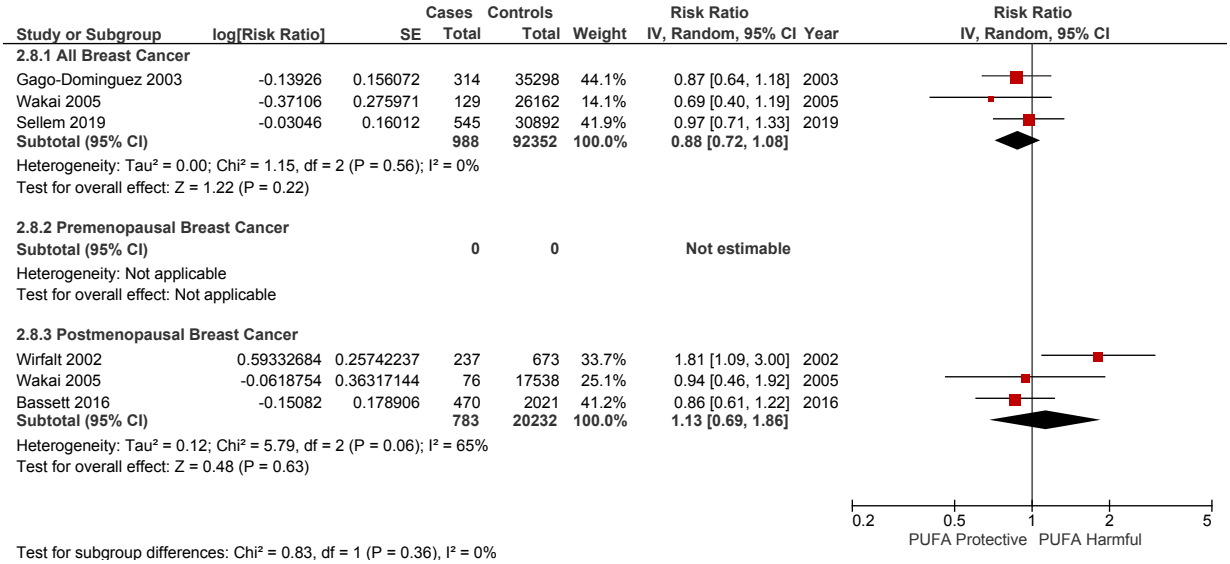
CI: confidence interval; df: degrees of freedom; IV: inverse variance; PUFA: polyunsaturated fatty acids; RR: risk ratio; SE: standard error.

Fig. 16b. Pooled most-adjusted (fixed-effect) RR of omega-3 PUFA and inflammatory bowel disease (*n*=2 unique estimates)



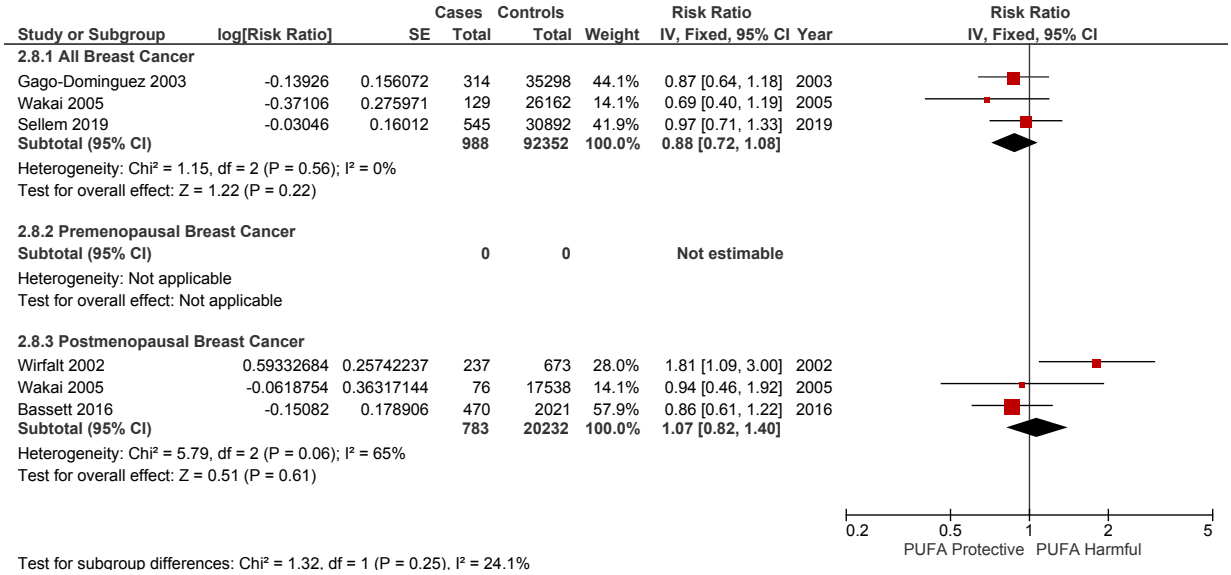
CI: confidence interval; df: degrees of freedom; IV: inverse variance; PUFA: polyunsaturated fatty acids; RR: risk ratio; SE: standard error.

Fig. 17a. Pooled most-adjusted (random-effects) RR of omega-3 PUFA and breast cancer (*n*=5 unique estimates)



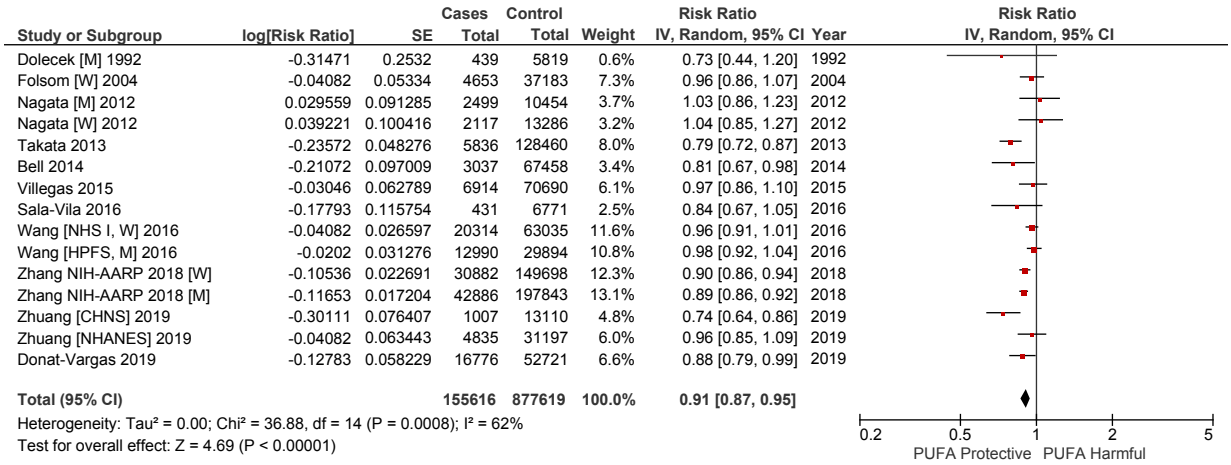
CI: confidence interval; df: degrees of freedom; IV: inverse variance; PUFA: polyunsaturated fatty acids; RR: risk ratio; SE: standard error.

Fig. 17b. Pooled most-adjusted (fixed-effect) RR of omega-3 PUFA and breast cancer (*n*=5 unique estimates)



CI: confidence interval; df: degrees of freedom; IV: inverse variance; PUFA: polyunsaturated fatty acids; RR: risk ratio; SE: standard error.

Fig. 18. Pooled most-adjusted RR of long-chain omega-3 PUFA and all-cause mortality (*n*=15 unique estimates)



CHNS: China Health and Nutrition Survey; CI: confidence interval; df: degrees of freedom; HPFS: Health Professionals Follow-up Study; IV: inverse variance; M: male; NHANES: National Health and Nutrition Examination Survey; NHS I: Nurses' Health Study I; NIH-AARP: National Institutes of Health American Association of Retired Persons Diet and Health Study; PUFA: polyunsaturated fatty acids; RR: risk ratio; SE: standard error; W: women.

Fig. 19. Pooled most-adjusted RR of long-chain omega-3 PUFA and CVD (*n*=49 studies)

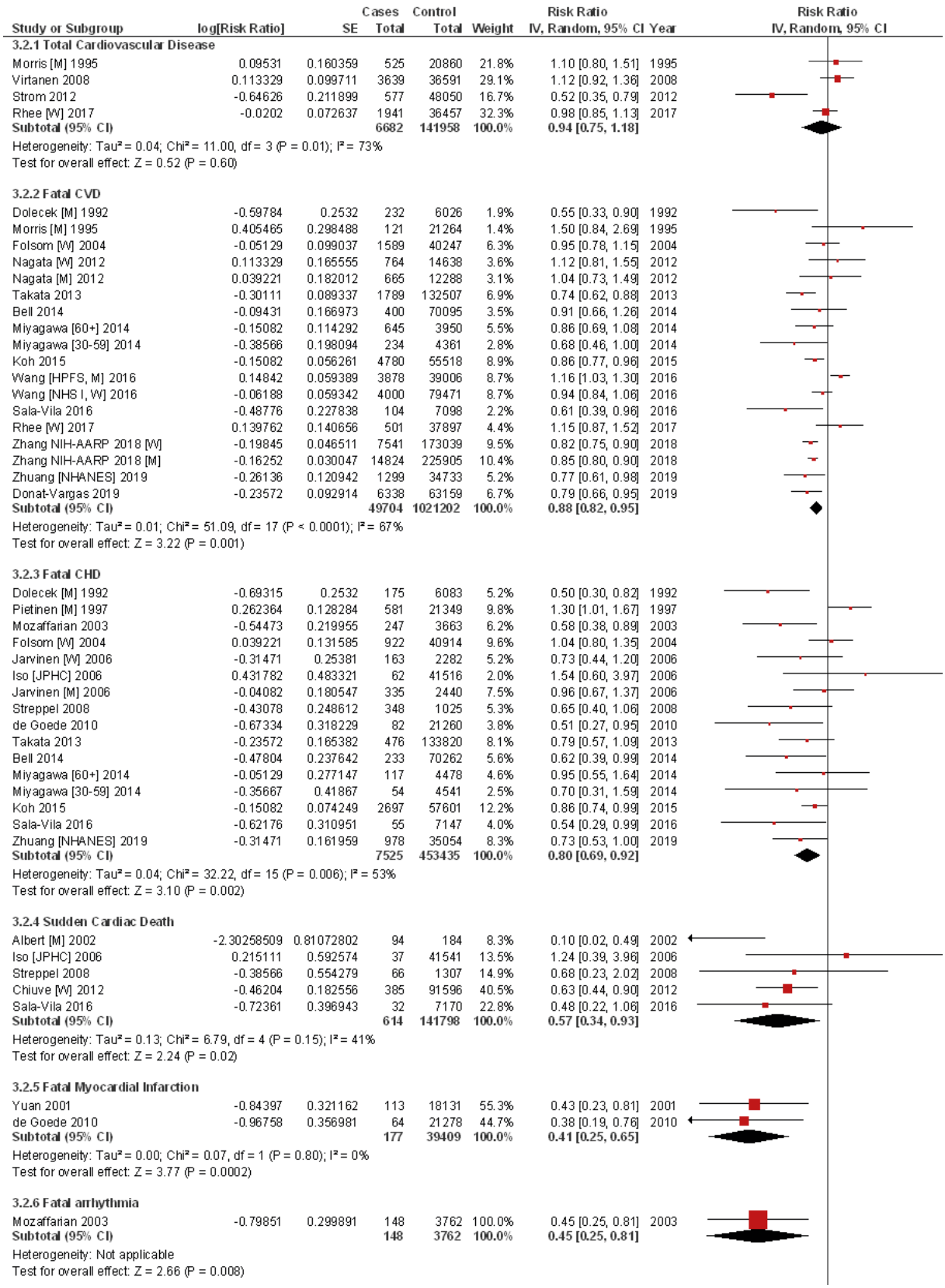


Fig. 19 (cont'd). Pooled most-adjusted RR of long-chain omega-3 PUFA and CVD (*n*=49 studies)

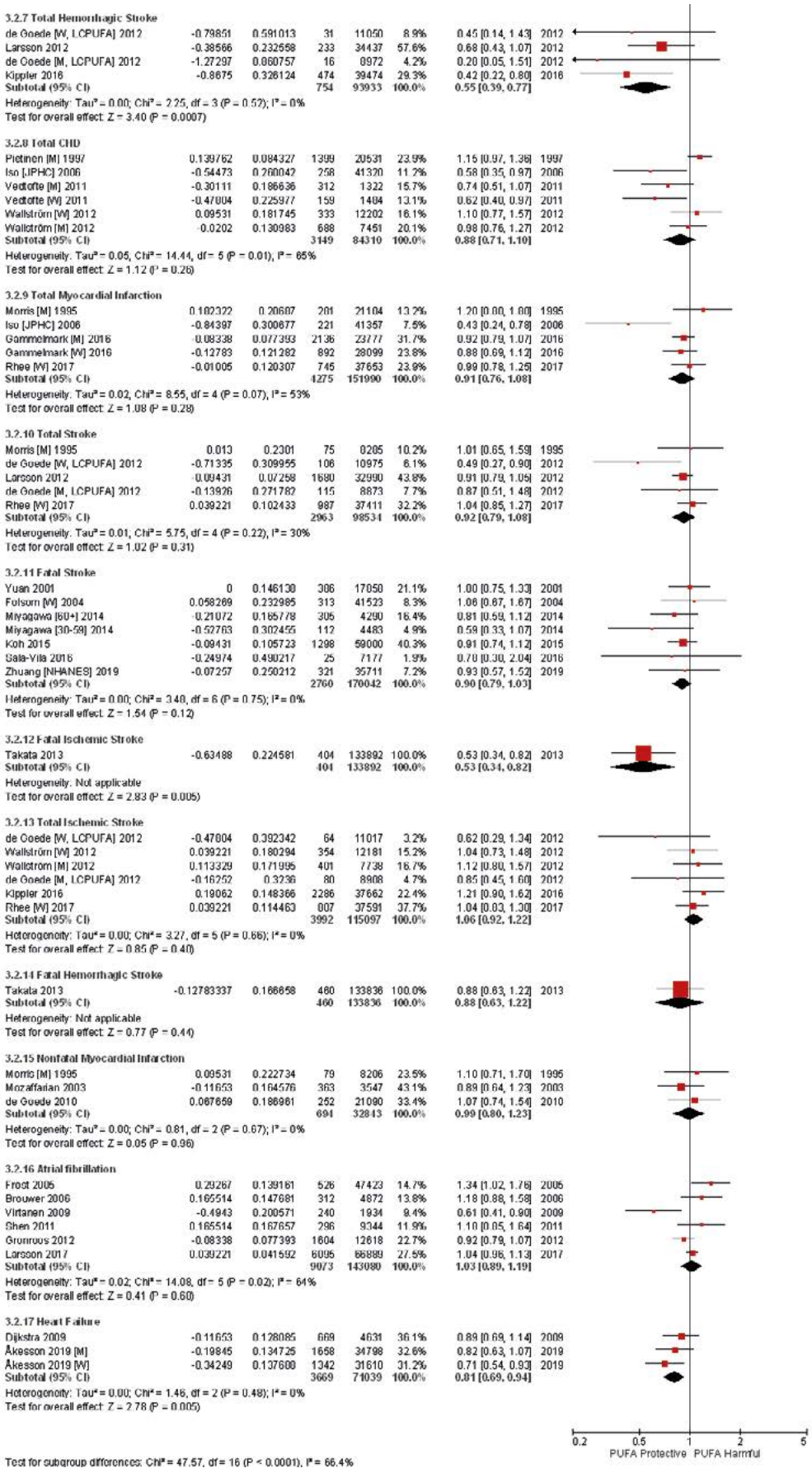
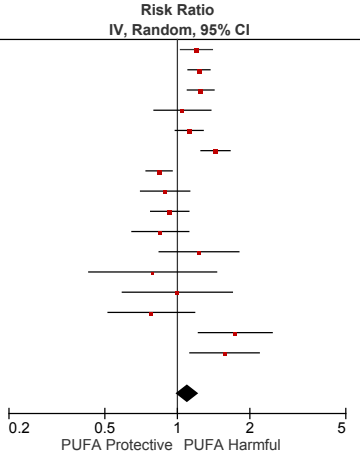


Fig. 20. Pooled most-adjusted RR of long-chain omega-3 PUFA and type 2 diabetes (*n*=16 studies)

Study or Subgroup	log[Risk Ratio]	SE	Cases Total	Control Total	Weight	Risk Ratio IV, Random, 95% CI	Year
Meyer 2001	0.1823	0.0779	1890	34098	8.1%	1.20 [1.03, 1.40]	2001
Kaushik [NHS I] 2009	0.207014	0.053686	4159	56872	8.8%	1.23 [1.11, 1.37]	2009
Kaushik [NHS II] 2009	0.223144	0.065139	2728	88941	8.5%	1.25 [1.10, 1.42]	2009
van Woudenbergh 2009	0.0488	0.1387	463	4009	6.0%	1.05 [0.80, 1.38]	2009
Kaushik [HPFS] 2009	0.113329	0.068128	2493	40011	8.4%	1.12 [0.98, 1.28]	2009
Djousse 2011	0.364643	0.070824	2370	34358	8.3%	1.44 [1.25, 1.65]	2011
Villegas [SWHS] 2011	-0.1743	0.0637	3034	61195	8.5%	0.84 [0.74, 0.95]	2011
Villegas [SMHS] 2011	-0.11653	0.119899	833	51130	6.6%	0.89 [0.70, 1.13]	2011
Brostow 2011	-0.07257	0.093297	2252	40924	7.5%	0.93 [0.77, 1.12]	2011
Virtanen 2014	-0.16252	0.138804	422	1790	6.0%	0.85 [0.65, 1.12]	2014
Alhazmi 2014	0.207014	0.194423	311	8059	4.4%	1.23 [0.84, 1.80]	2014
Guasch-Ferre 2017 [PREDIMED-Con]	-0.23572	0.311838	98	972	2.3%	0.79 [0.43, 1.46]	2017
Guasch-Ferre 2017 [PREDIMED-Trt]	0	0.26846	168	2111	2.9%	1.00 [0.59, 1.69]	2017
Zheng 2019	-0.24846	0.211194	213	2458	4.0%	0.78 [0.52, 1.18]	2019
Zhang CNHS 2019 [W]	0.553885	0.179941	492	6577	4.7%	1.74 [1.22, 2.48]	2019
Zhang CNHS 2019 [M]	0.451076	0.169076	525	7506	5.0%	1.57 [1.13, 2.19]	2019
Total (95% CI)			**22451**	**441011**	**100.0%**	**1.10 [0.99, 1.23]**	

Heterogeneity: Tau² = 0.03; Chi² = 66.01, df = 15 (P < 0.00001); I² = 77%
Test for overall effect: Z = 1.81 (P = 0.07)

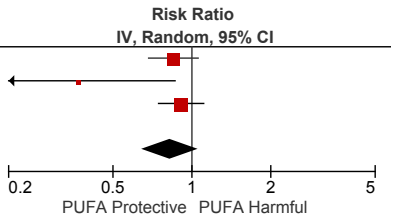


CHNS: China Health and Nutrition Survey; CI: confidence interval; df: degrees of freedom; HPFS: Health Professionals Follow-up Study; IV: inverse variance; M: male; NHS I: Nurses' Health Study I; NHS II: Nurses' Health Study II; PREDIMED-Con: Prevención con Dieta Mediterránea (control); PREDIMED-Trt: Prevención con Dieta Mediterránea (treatment); PUFA: polyunsaturated fatty acids; RR: risk ratio; SE: standard error; SMHS: Shanghai Men's Health Study; SWHS: Shanghai Women's Health Study; W: women.

Fig. 21a. Pooled most-adjusted (random-effects) RR of long-chain omega-3 PUFA and cognitive decline (*n*=3 studies)

Study or Subgroup	log[Risk Ratio]	SE	Cases Total	Control Total	Weight	Risk Ratio IV, Random, 95% CI	Year
Vercambre 2010	-0.16252	0.11083	598	4211	44.9%	0.85 [0.68, 1.06]	2010
Gao 2011	-0.99425	0.431969	226	1249	7.4%	0.37 [0.16, 0.86]	2011
Bigornia 2018	-0.09431	0.101126	155	537	47.7%	0.91 [0.75, 1.11]	2018
Total (95% CI)			**979**	**5997**	**100.0%**	**0.83 [0.65, 1.05]**	

Heterogeneity: Tau² = 0.02; Chi² = 4.14, df = 2 (P = 0.13); I² = 52%
Test for overall effect: Z = 1.54 (P = 0.12)

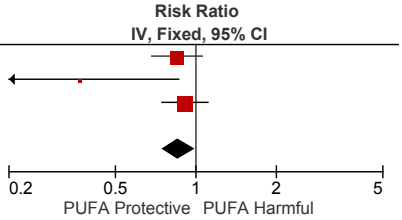


CI: confidence interval; df: degrees of freedom; IV: inverse variance; PUFA: polyunsaturated fatty acids; RR: risk ratio; SE: standard error.

Fig. 21b. Pooled most-adjusted (fixed-effect) RR of long-chain omega-3 PUFA and cognitive decline (*n*=3 studies)

Study or Subgroup	log[Risk Ratio]	SE	Cases Total	Control Total	Weight	Risk Ratio IV, Fixed, 95% CI	Year
Vercambre 2010	-0.16252	0.11083	598	4211	44.1%	0.85 [0.68, 1.06]	2010
Gao 2011	-0.99425	0.431969	226	1249	2.9%	0.37 [0.16, 0.86]	2011
Bigornia 2018	-0.09431	0.101126	155	537	53.0%	0.91 [0.75, 1.11]	2018
Total (95% CI)			**979**	**5997**	**100.0%**	**0.86 [0.74, 0.99]**	

Heterogeneity: Chi² = 4.14, df = 2 (P = 0.13); I² = 52%
Test for overall effect: Z = 2.04 (P = 0.04)

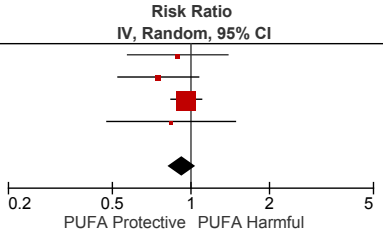


CI: confidence interval; df: degrees of freedom; IV: inverse variance; PUFA: polyunsaturated fatty acids; RR: risk ratio; SE: standard error.

Fig. 22. Pooled most-adjusted RR of long-chain omega-3 PUFA and depression (*n*=4 unique estimates)

Study or Subgroup	log[Risk Ratio]	SE	Cases Total	Control Total	Weight	Risk Ratio IV, Random, 95% CI	Year
Colangelo [M] 2009	-0.11653	0.225562	259	1222	7.2%	0.89 [0.57, 1.38]	2009
Colangelo [W] 2009	-0.28768	0.181592	485	1351	11.1%	0.75 [0.53, 1.07]	2009
Lucas 2011	-0.040822	0.06879173	2823	51809	77.3%	0.96 [0.84, 1.10]	2011
Matsuoka 2017	-0.17435	0.288966	95	991	4.4%	0.84 [0.48, 1.48]	2017
Total (95% CI)			**3662**	**55373**	**100.0%**	**0.92 [0.82, 1.04]**	

Heterogeneity: Tau² = 0.00; Chi² = 1.77, df = 3 (P = 0.62); I² = 0%
Test for overall effect: Z = 1.31 (P = 0.19)

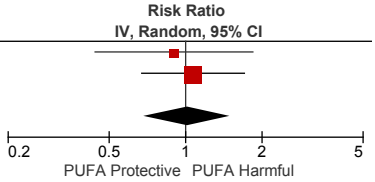


CI: confidence interval; df: degrees of freedom; IV: inverse variance; M: male; PUFA: polyunsaturated fatty acids; RR: risk ratio; SE: standard error; W: women.

Fig. 23a. Pooled most-adjusted (random-effects) RR of long-chain omega-3 PUFA and suicide (*n*=2 studies)

Study or Subgroup	log[Risk Ratio]	SE	Cases Total	Control Total	Weight	Risk Ratio IV, Random, 95% CI	Year
Poudel-Tandukar [W] 2011	-0.10536	0.364986	85	54071	29.8%	0.90 [0.44, 1.84]	2011
Poudel-Tandukar [M] 2011	0.06765865	0.23752699	213	47138	70.2%	1.07 [0.67, 1.70]	2011
Total (95% CI)			**298**	**101209**	**100.0%**	**1.02 [0.69, 1.50]**	

Heterogeneity: Tau² = 0.00; Chi² = 0.16, df = 1 (P = 0.69); I² = 0%
Test for overall effect: Z = 0.08 (P = 0.94)

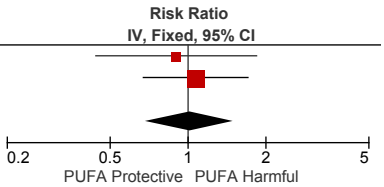


CI: confidence interval; df: degrees of freedom; IV: inverse variance; M: male; PUFA: polyunsaturated fatty acids; RR: risk ratio; SE: standard error; W: women.

Fig. 23b. Pooled most-adjusted (fixed-effect) RR of long-chain omega-3 PUFA and suicide (*n*=2 studies)

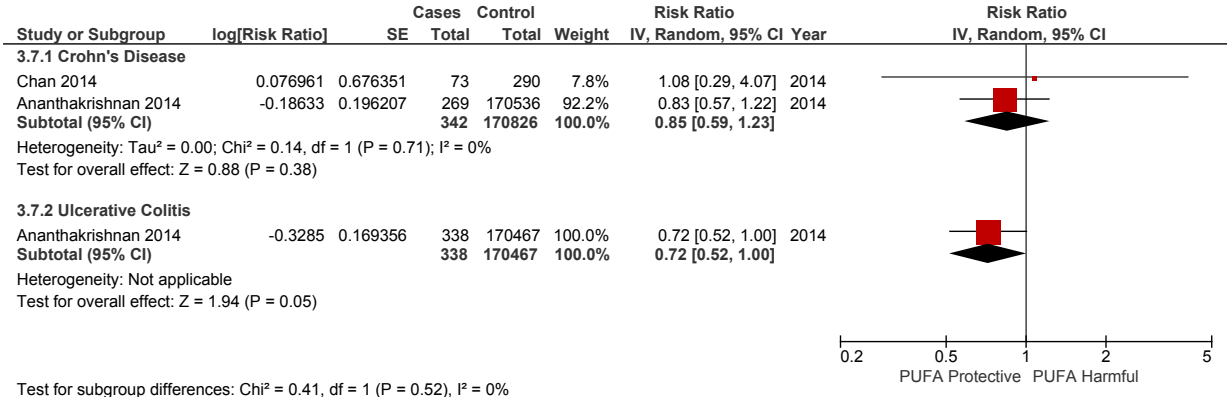
Study or Subgroup	log[Risk Ratio]	SE	Cases Total	Control Total	Weight	Risk Ratio IV, Fixed, 95% CI	Year
Poudel-Tandukar [W] 2011	-0.10536	0.364986	85	54071	29.8%	0.90 [0.44, 1.84]	2011
Poudel-Tandukar [M] 2011	0.06765865	0.23752699	213	47138	70.2%	1.07 [0.67, 1.70]	2011
Total (95% CI)			**298**	**101209**	**100.0%**	**1.02 [0.69, 1.50]**	

Heterogeneity: Chi² = 0.16, df = 1 (P = 0.69); I² = 0%
Test for overall effect: Z = 0.08 (P = 0.94)



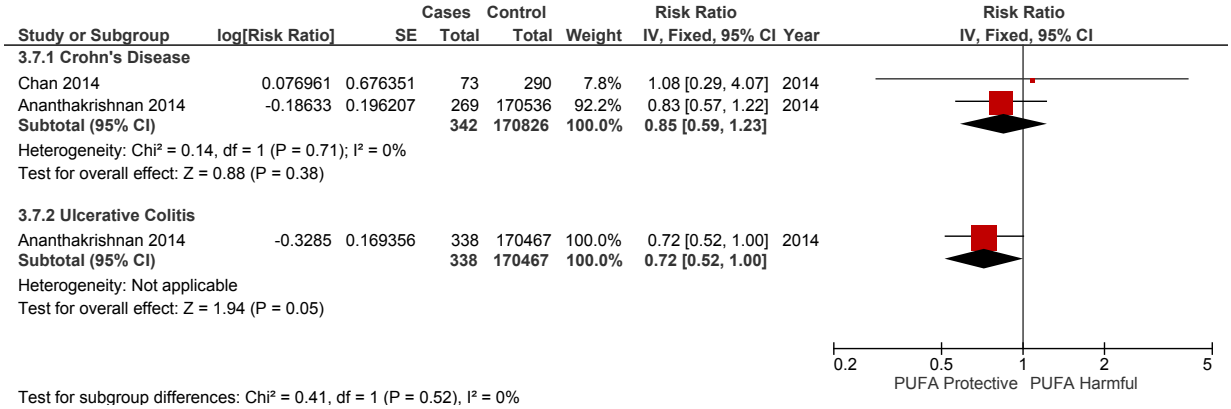
CI: confidence interval; df: degrees of freedom; IV: inverse variance; M: male; PUFA: polyunsaturated fatty acids; RR: risk ratio; SE: standard error; W: women.

Fig. 24a. Pooled most-adjusted (random-effects) RR of long-chain omega-3 PUFA and inflammatory bowel disease (*n*=3 studies)



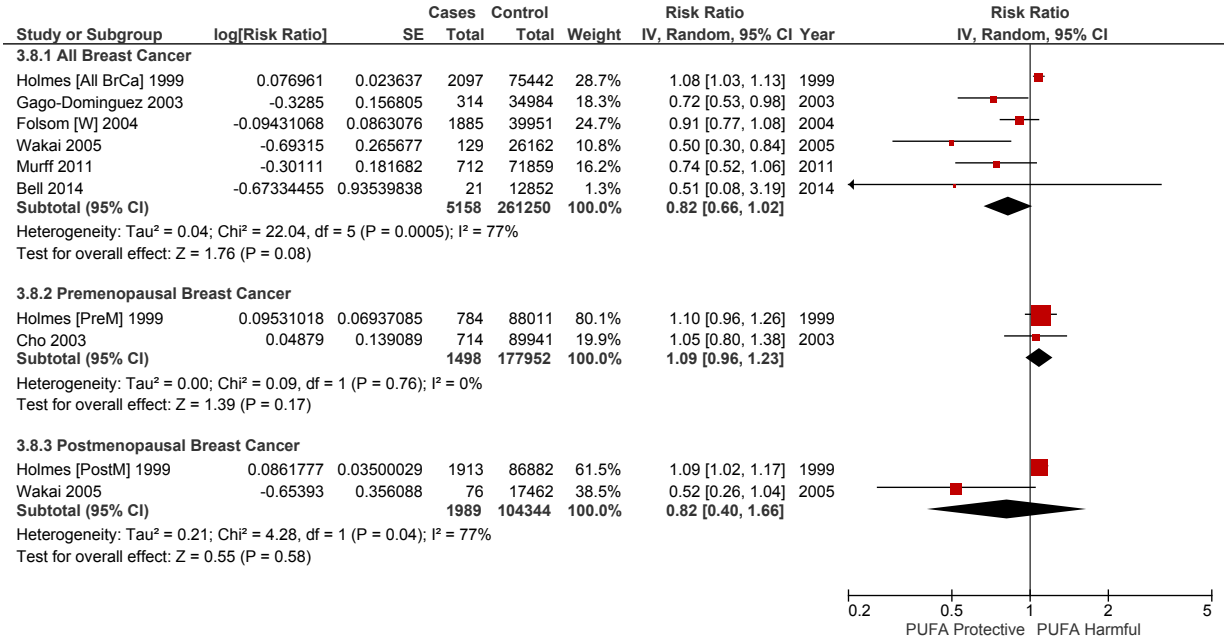
CI: confidence interval; df: degrees of freedom; IV: inverse variance; PUFA: polyunsaturated fatty acids; RR: risk ratio; SE: standard error.

Fig. 24b. Pooled most-adjusted (fixed-effect) RR of long-chain omega-3 PUFA and inflammatory bowel disease (*n*=3 studies)



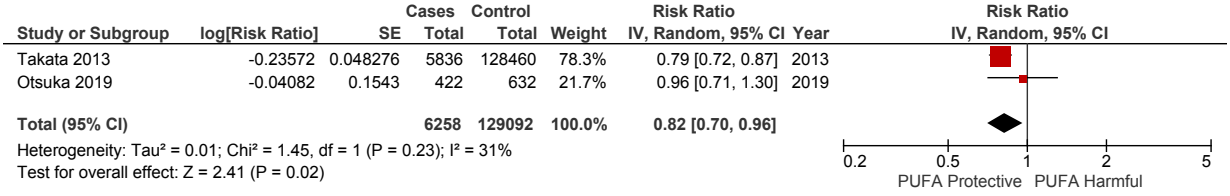
CI: confidence interval; df: degrees of freedom; IV: inverse variance; PUFA: polyunsaturated fatty acids; RR: risk ratio; SE: standard error.

Fig. 25. Pooled most-adjusted RR of long-chain omega-3 PUFA and breast cancer (*n*=9 studies)



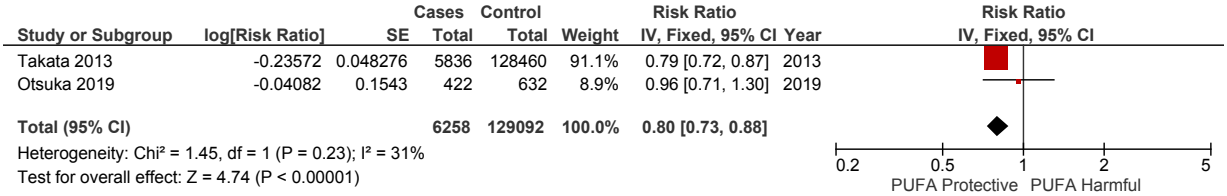
BrCa: breast cancer; CI: confidence interval; df: degrees of freedom; IV: inverse variance; PostM: postmenopausal; PreM: premenopausal; PUFA: polyunsaturated fatty acids; RR: risk ratio; SE: standard error; W: women.

Fig. 26a. Pooled most-adjusted (random-effects) RR of EPA and all-cause mortality (*n*=2 unique estimates)



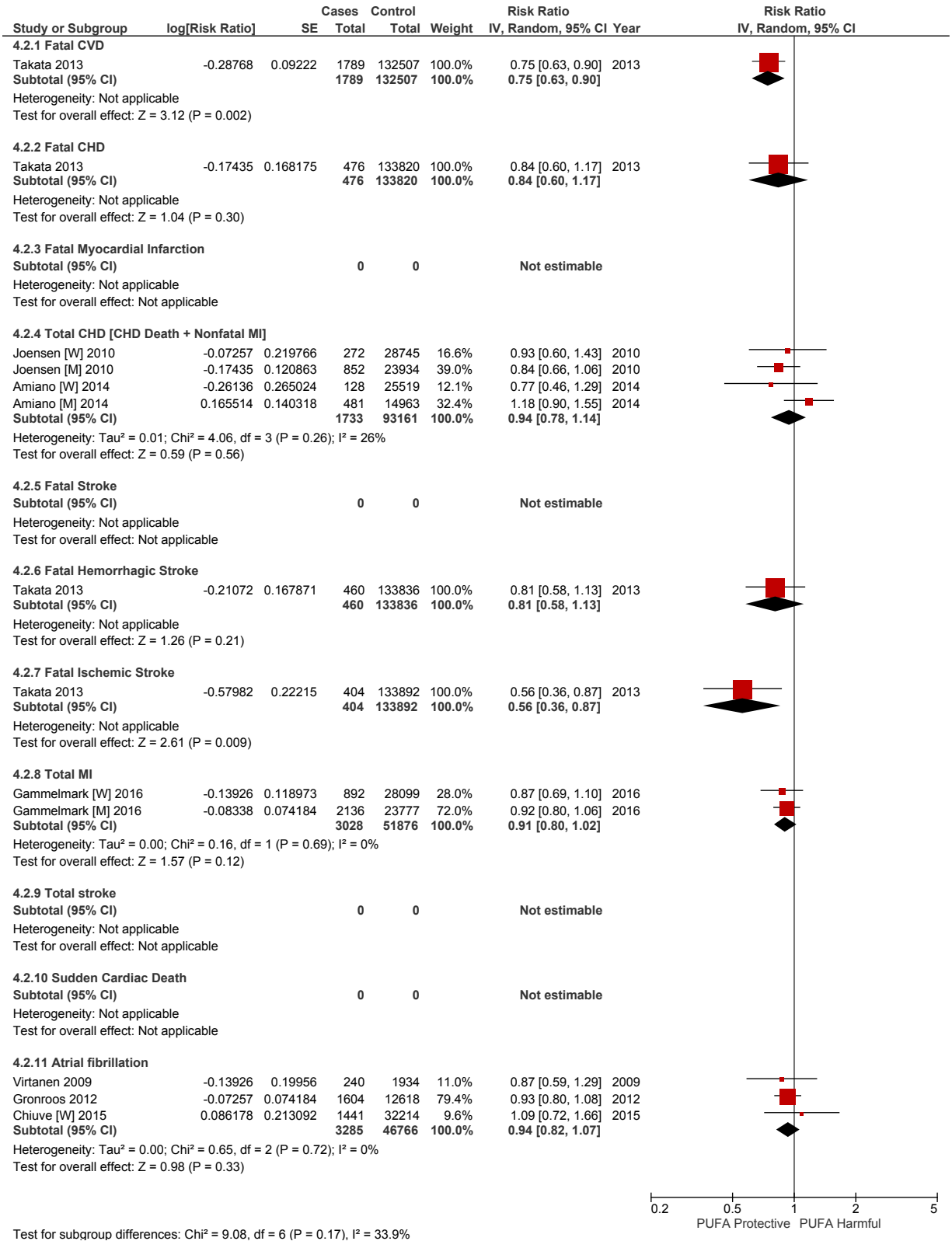
CI: confidence interval; df: degrees of freedom; EPA: eicosapentaenoic acid; IV: inverse variance; PUFA: polyunsaturated fatty acids; RR: risk ratio; SE: standard error.

Fig. 26b. Pooled most-adjusted (fixed-effect) RR of EPA and all-cause mortality (*n*=2 unique estimates)



CI: confidence interval; df: degrees of freedom; EPA: eicosapentaenoic acid; IV: inverse variance; PUFA: polyunsaturated fatty acids; RR: risk ratio; SE: standard error.

Fig. 27. Pooled most-adjusted RR of EPA and CVD (*n*=11 studies)

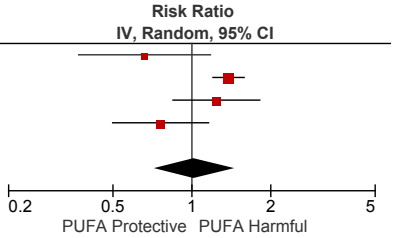


CHD: coronary heart disease; CI: confidence interval; CVD: cardiovascular disease; df: degrees of freedom; EPA: eicosapentaenoic acid; IV: inverse variance; M: male; MI: myocardial infarction; PUFA: polyunsaturated fatty acids; RR: risk ratio; SE: standard error; W: women.

Fig. 28. Pooled most-adjusted RR of EPA and type 2 diabetes (*n*=4 studies)

Study or Subgroup	log[Risk Ratio]	SE	Cases Total	Control Total	Weight	Risk Ratio IV, Random, 95% CI	Year
Patel 2010	-0.4155	0.2953	199	183	18.0%	0.66 [0.37, 1.18]	2010
Djousse 2011	0.322083	0.069672	2370	34358	33.6%	1.38 [1.20, 1.58]	2011
Alhazmi 2014	0.215111	0.194223	311	8059	25.0%	1.24 [0.85, 1.81]	2014
Zheng 2019	-0.27444	0.214686	213	2458	23.4%	0.76 [0.50, 1.16]	2019
Total (95% CI)			**3093**	**45058**	**100.0%**	**1.02 [0.72, 1.45]**	

Heterogeneity: Tau² = 0.09; Chi² = 12.05, df = 3 (P = 0.007); I² = 75%
Test for overall effect: Z = 0.13 (P = 0.90)

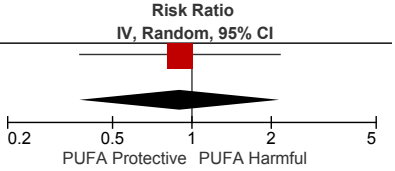


CI: confidence interval; df: degrees of freedom; EPA: eicosapentaenoic acid; IV: inverse variance; PUFA: polyunsaturated fatty acids; RR: risk ratio; SE: standard error.

Fig. 29. Pooled most-adjusted RR of EPA and dementia (*n*=1 study)

Study or Subgroup	log[Risk Ratio]	SE	Cases Total	Control Total	Weight	Risk Ratio IV, Random, 95% CI	Year
Morris 2003	-0.10436	0.446224	131	684	100.0%	0.90 [0.38, 2.16]	2003
Total (95% CI)			**131**	**684**	**100.0%**	**0.90 [0.38, 2.16]**	

Heterogeneity: Not applicable
Test for overall effect: Z = 0.23 (P = 0.82)

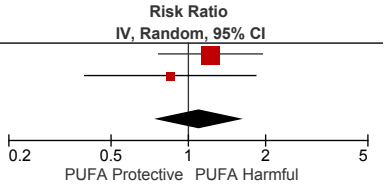


CI: confidence interval; EPA: eicosapentaenoic acid; IV: inverse variance; PUFA: polyunsaturated fatty acids; RR: risk ratio; SE: standard error.

Fig. 30a. Pooled most-adjusted (random-effects) RR of EPA and suicide (*n*=2 studies)

Study or Subgroup	log[Risk Ratio]	SE	Cases Total	Control Total	Weight	Risk Ratio IV, Random, 95% CI	Year
Poudel-Tandukar [M] 2011	0.198851	0.237039	213	47138	73.2%	1.22 [0.77, 1.94]	2011
Poudel-Tandukar [W] 2011	-0.16252	0.391565	85	54071	26.8%	0.85 [0.39, 1.83]	2011
Total (95% CI)			**298**	**101209**	**100.0%**	**1.11 [0.74, 1.65]**	

Heterogeneity: Tau² = 0.00; Chi² = 0.62, df = 1 (P = 0.43); I² = 0%
Test for overall effect: Z = 0.50 (P = 0.62)

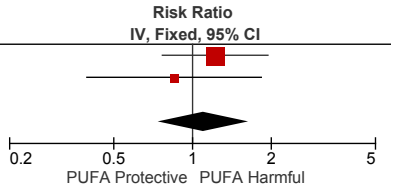


CI: confidence interval; df: degrees of freedom; EPA: eicosapentaenoic acid; IV: inverse variance; M: male; PUFA: polyunsaturated fatty acids; RR: risk ratio; SE: standard error; W: women.

Fig. 30b. Pooled most-adjusted (fixed-effect) RR of EPA and suicide (*n*=2 studies)

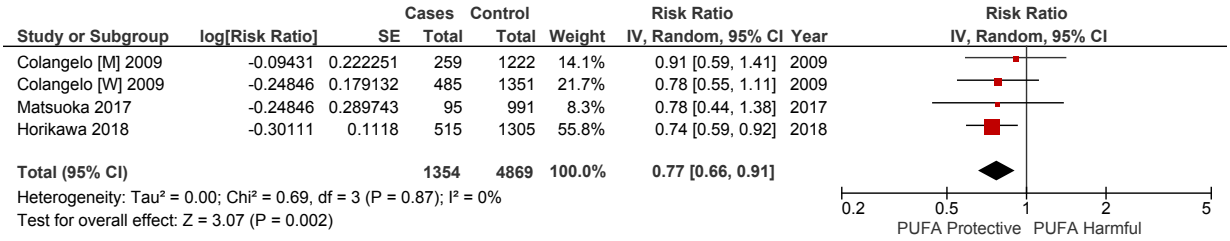
Study or Subgroup	log[Risk Ratio]	SE	Cases Total	Control Total	Weight	Risk Ratio IV, Fixed, 95% CI	Year
Poudel-Tandukar [M] 2011	0.198851	0.237039	213	47138	73.2%	1.22 [0.77, 1.94]	2011
Poudel-Tandukar [W] 2011	-0.16252	0.391565	85	54071	26.8%	0.85 [0.39, 1.83]	2011
Total (95% CI)			**298**	**101209**	**100.0%**	**1.11 [0.74, 1.65]**	

Heterogeneity: Chi² = 0.62, df = 1 (P = 0.43); I² = 0%
Test for overall effect: Z = 0.50 (P = 0.62)



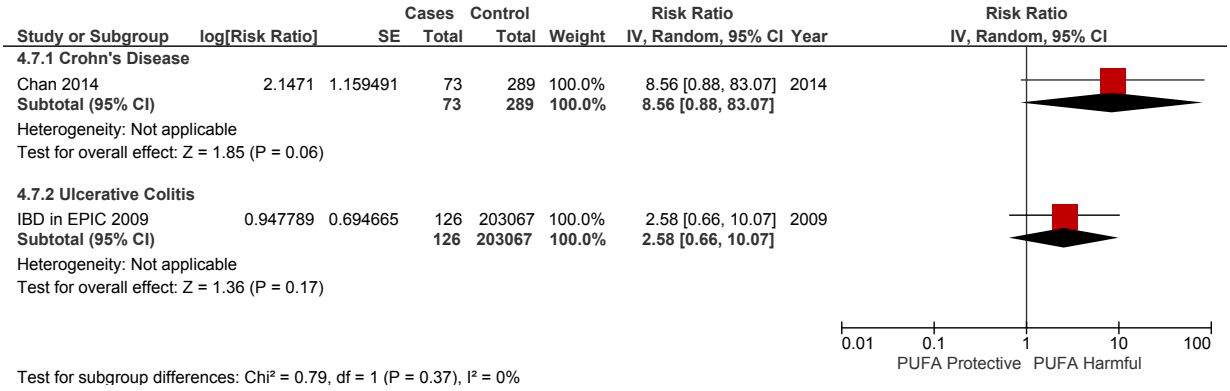
CI: confidence interval; df: degrees of freedom; EPA: eicosapentaenoic acid; IV: inverse variance; M: male; PUFA: polyunsaturated fatty acids; RR: risk ratio; SE: standard error; W: women.

Fig. 31. Pooled most-adjusted RR of EPA and depression (*n*=4 unique estimates)



CI: confidence interval; df: degrees of freedom; EPA: eicosapentaenoic acid; IV: inverse variance; M: male; PUFA: polyunsaturated fatty acids; RR: risk ratio; SE: standard error; W: women.

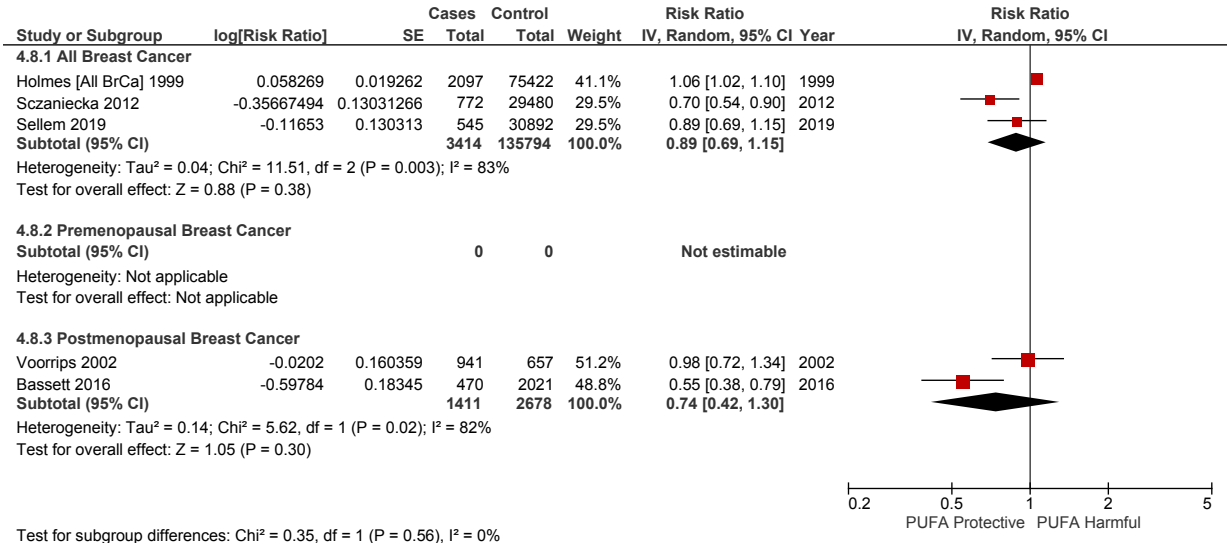
Fig. 32. Pooled most-adjusted RR of EPA and inflammatory bowel disease (*n*=2 studies)



NOTE: scale from 0.01 to 100

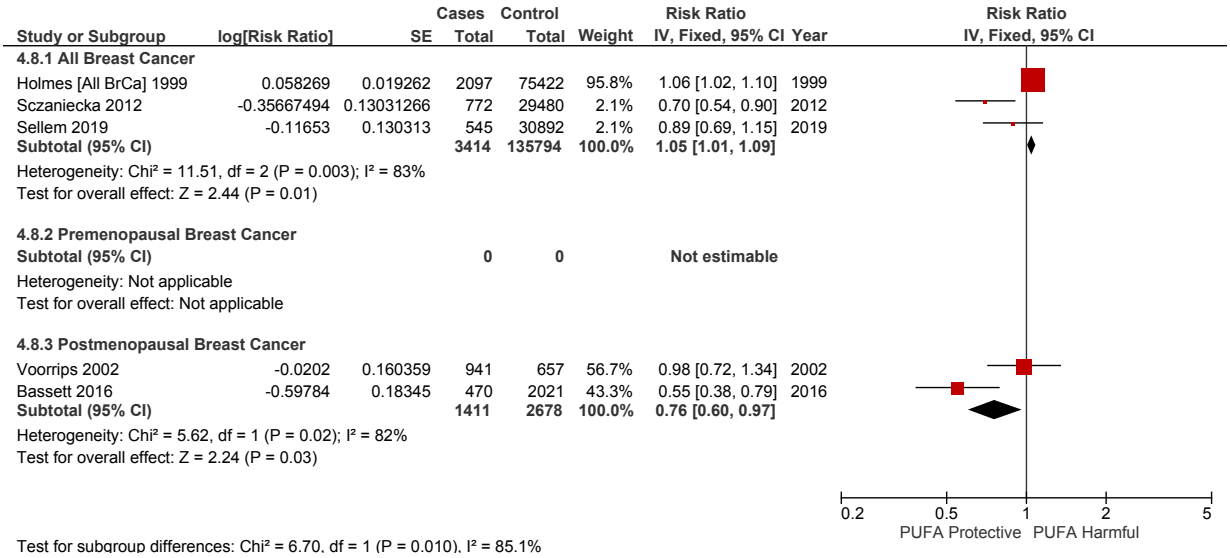
CI: confidence interval; df: degrees of freedom; EPA: eicosapentaenoic acid; EPIC: European Prospective Investigation into Cancer and Nutrition; IBD: inflammatory bowel disease; IV: inverse variance; PUFA: polyunsaturated fatty acids; RR: risk ratio; SE: standard error.

Fig. 33a. Pooled most-adjusted (random-effects) RR of EPA and breast cancer (*n*=3 studies)



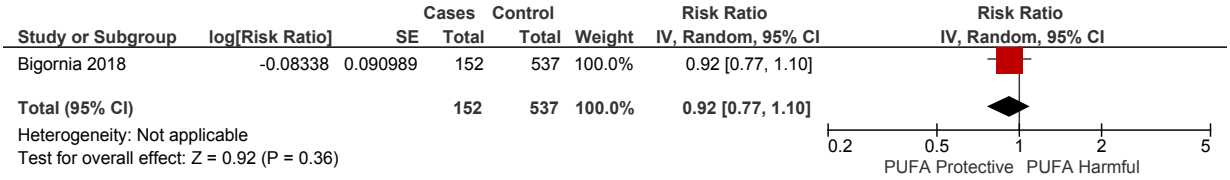
BrCa: breast cancer; CI: confidence interval; df: degrees of freedom; EPA: eicosapentaenoic acid; IV: inverse variance; PUFA: polyunsaturated fatty acids; RR: risk ratio; SE: standard error.

Fig. 33b. Pooled most-adjusted (fixed-effect) RR of EPA and breast cancer (*n*=3 studies)



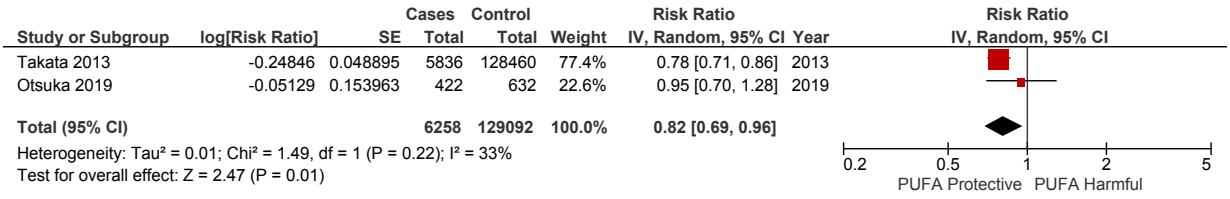
BrCa: breast cancer; CI: confidence interval; df: degrees of freedom; EPA: eicosapentaenoic acid; IV: inverse variance; PUFA: polyunsaturated fatty acids; RR: risk ratio; SE: standard error.

Fig. 34. Pooled most-adjusted RR of EPA and cognitive decline (*n*=1 study)



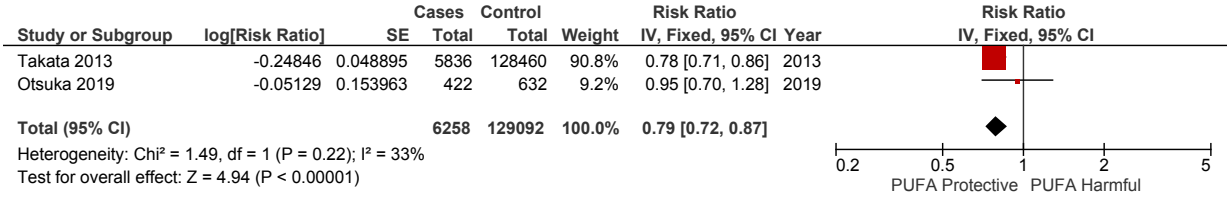
CI: confidence interval; EPA: eicosapentaenoic acid; IV: inverse variance; PUFA: polyunsaturated fatty acids; RR: risk ratio; SE: standard error.

Fig. 35a. Pooled most-adjusted (random-effects) RR of DHA and all-cause mortality (*n*=2 studies)



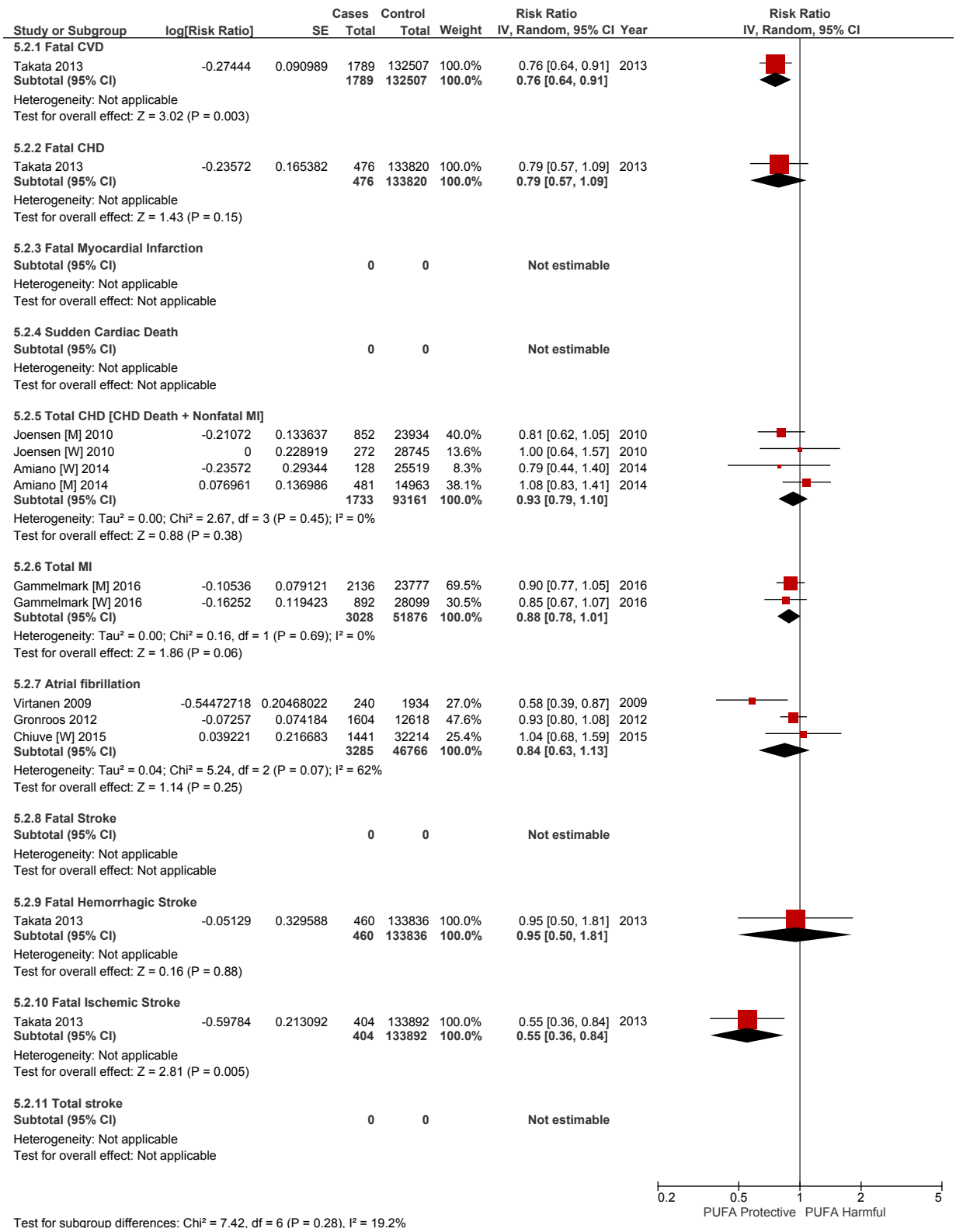
CI: confidence interval; df: degrees of freedom; DHA: docosahexaenoic acid; IV: inverse variance; PUFA: polyunsaturated fatty acids; RR: risk ratio; SE: standard error.

Fig. 35b. Most-adjusted (fixed effect) RR of DHA and all-cause mortality (*n*=2 studies)



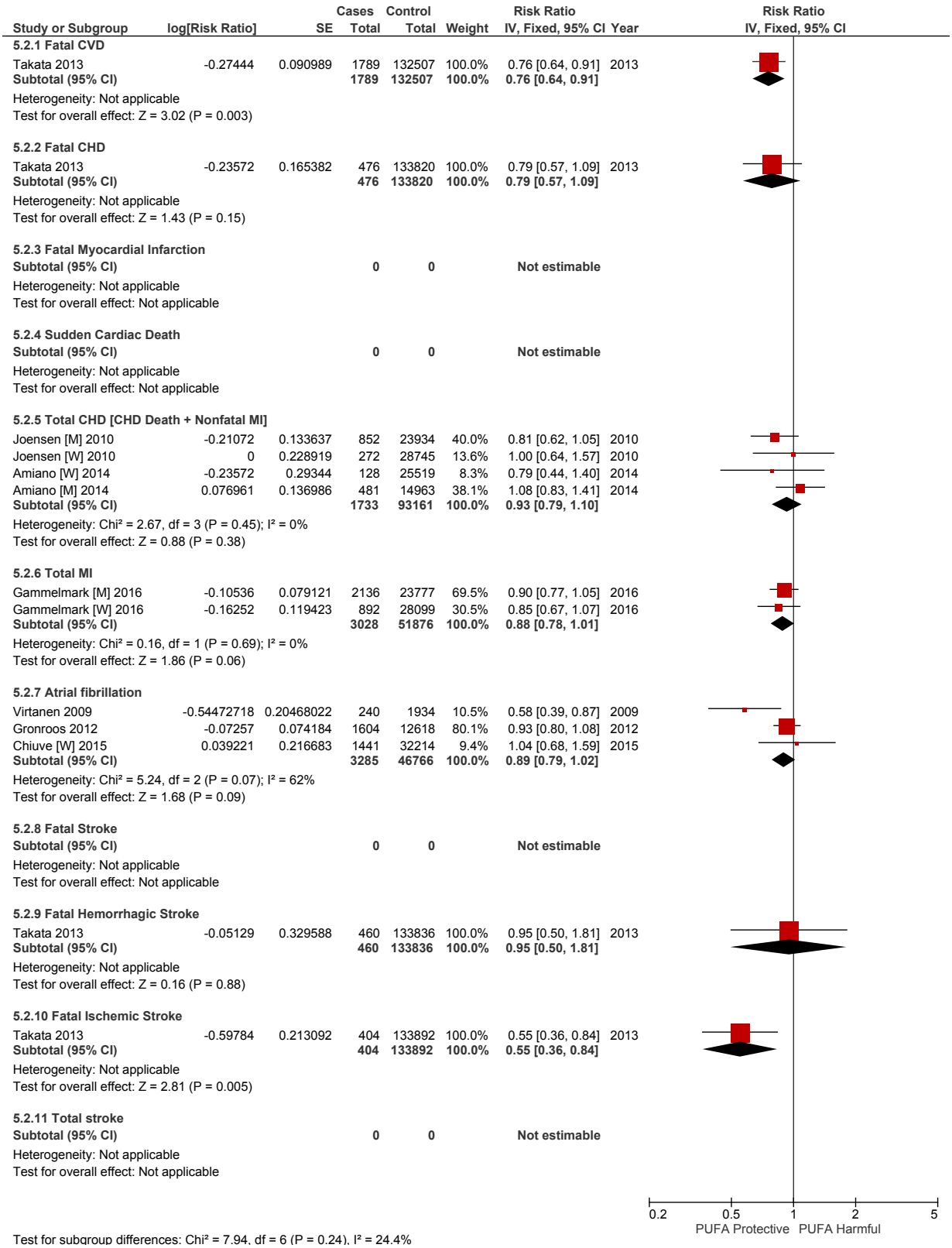
CI: confidence interval; df: degrees of freedom; DHA: docosahexaenoic acid; IV: inverse variance; PUFA: polyunsaturated fatty acids; RR: risk ratio; SE: standard error.

Fig. 36a. Pooled most-adjusted (random-effects) RR of DHA and CVD (*n*=10 studies)



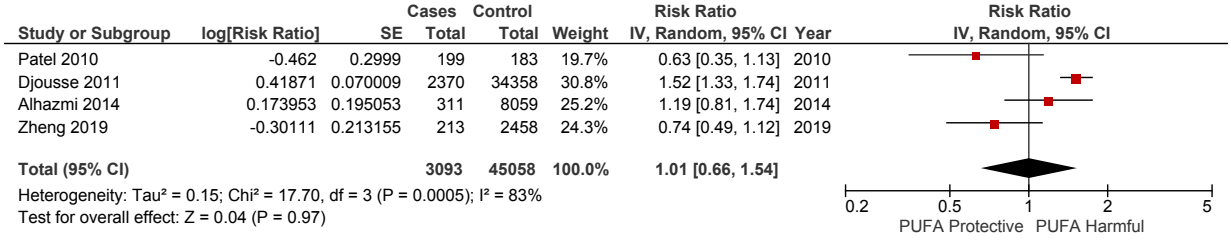
CHD: coronary heart disease; CI: confidence interval; CVD: cardiovascular disease; df: degrees of freedom; DHA: docosahexaenoic acid; IV: inverse variance; M: male; MI: myocardial infarction; PUFA: polyunsaturated fatty acids; RR: risk ratio; SE: standard error; W: women.

Fig. 36b. Pooled most-adjusted (fixed-effect) RR of DHA and CVD (*n*=10 studies)



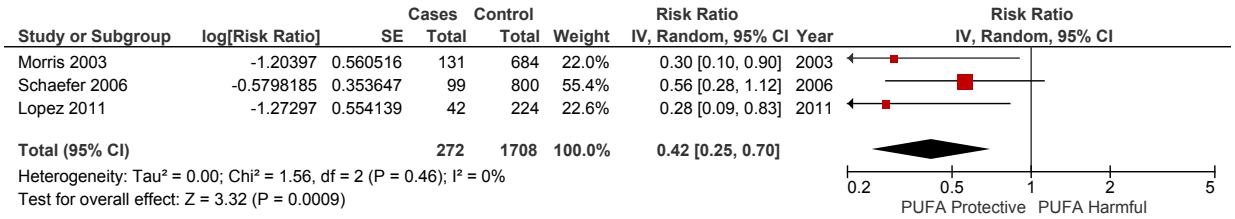
CHD: coronary heart disease; CI: confidence interval; CVD: cardiovascular disease; df: degrees of freedom; DHA: docosahexaenoic acid; IV: inverse variance; M: male; MI: myocardial infarction; PUFA: polyunsaturated fatty acids; RR: risk ratio; SE: standard error; W: women.

Fig. 37. Pooled most-adjusted RR of DHA and type 2 diabetes (*n*=4 studies)



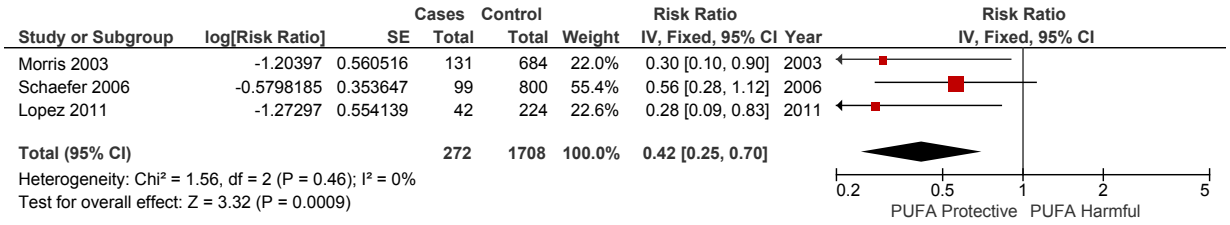
CI: confidence interval; df: degrees of freedom; DHA: docosahexaenoic acid; IV: inverse variance; PUFA: polyunsaturated fatty acids; RR: risk ratio; SE: standard error.

Fig. 38a. Pooled most-adjusted (random-effects) RR of DHA and dementia (*n*=3 studies)



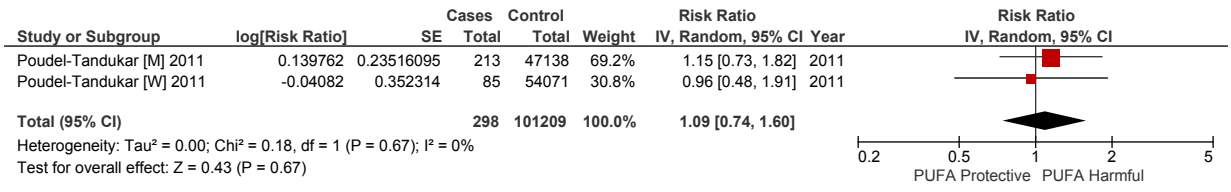
CI: confidence interval; df: degrees of freedom; DHA: docosahexaenoic acid; IV: inverse variance; PUFA: polyunsaturated fatty acids; RR: risk ratio; SE: standard error.

Fig. 38b. Pooled most-adjusted (fixed-effect) RR of DHA and dementia (*n*=3 studies)



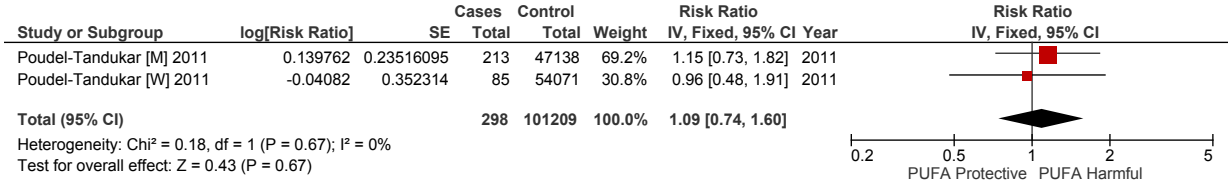
CI: confidence interval; df: degrees of freedom; DHA: docosahexaenoic acid; IV: inverse variance; PUFA: polyunsaturated fatty acids; RR: risk ratio; SE: standard error.

Fig. 39a. Pooled most-adjusted (random-effects) RR of DHA and suicide (*n*=2 studies)



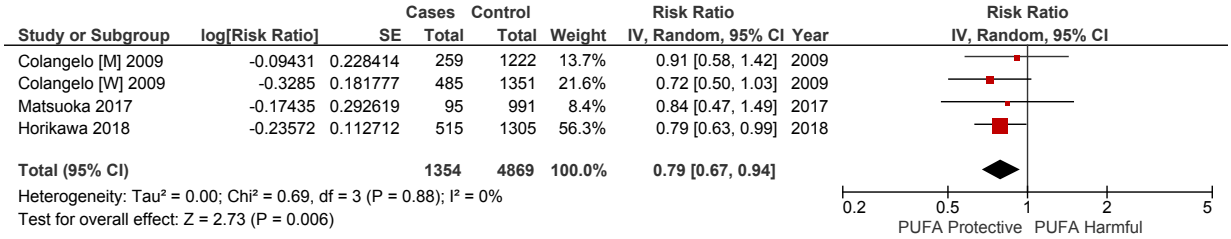
CI: confidence interval; df: degrees of freedom; DHA: docosahexaenoic acid; IV: inverse variance; M: male; PUFA: polyunsaturated fatty acids; RR: risk ratio; SE: standard error; W: women.

Fig. 39b. Pooled most-adjusted (fixed-effect) RR of DHA and suicide (*n*=2 studies)



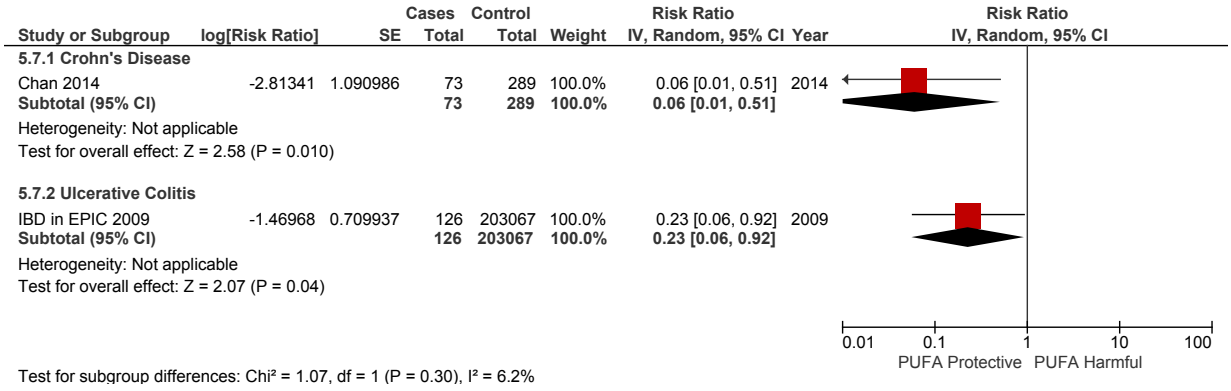
CI: confidence interval; df: degrees of freedom; DHA: docosahexaenoic acid; IV: inverse variance; M: male; PUFA: polyunsaturated fatty acids; RR: risk ratio; SE: standard error; W: women.

Fig. 40. Pooled most-adjusted RR of DHA and depression (*n*=4 studies)



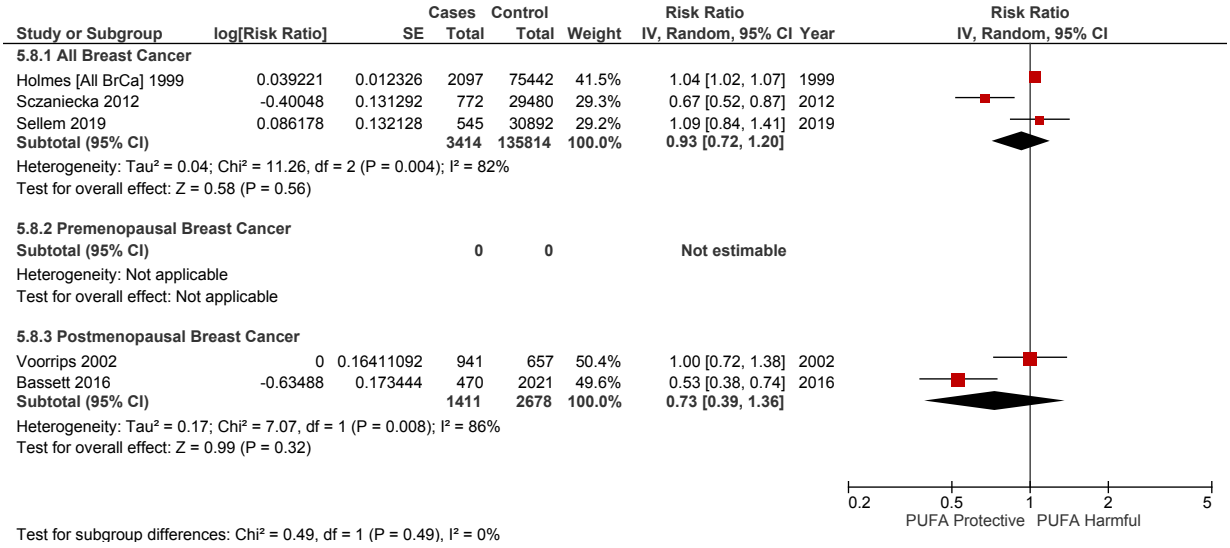
CI: confidence interval; df: degrees of freedom; DHA: docosahexaenoic acid; IV: inverse variance; M: male; PUFA: polyunsaturated fatty acids; RR: risk ratio; SE: standard error; W: women.

Fig. 41. Pooled most-adjusted RR of DHA and inflammatory bowel disease (*n*=2 studies)



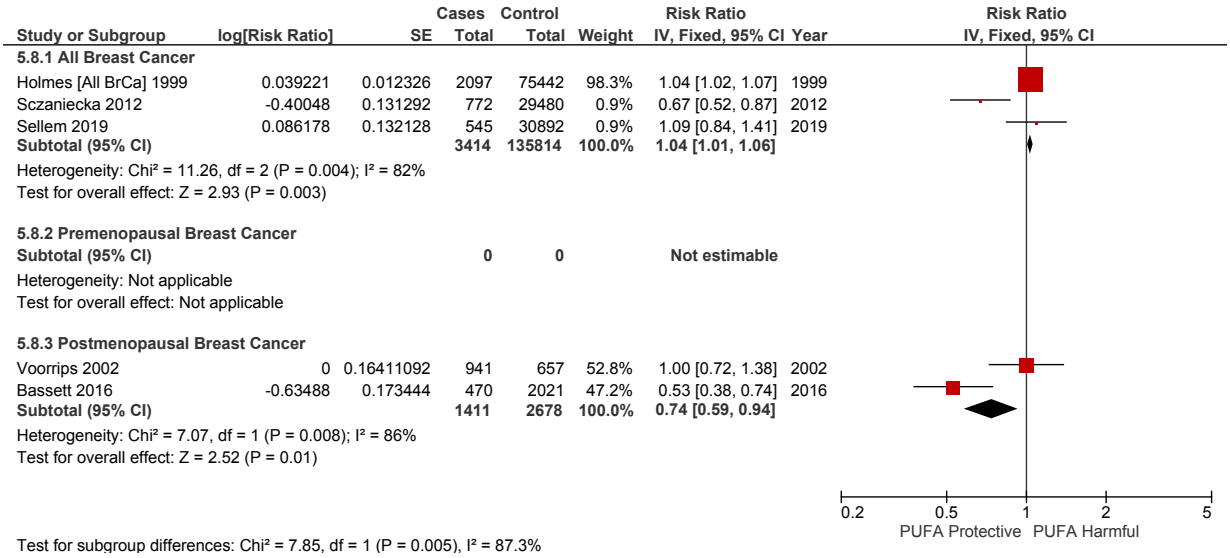
CI: confidence interval; df: degrees of freedom; DHA: docosahexaenoic acid; EPIC: European Prospective Investigation into Cancer and Nutrition; IBD: inflammatory bowel disease; IV: inverse variance; PUFA: polyunsaturated fatty acids; RR: risk ratio; SE: standard error.

Fig. 42a. Pooled most-adjusted (random-effects) RR of DHA and breast cancer (*n*=5 studies)



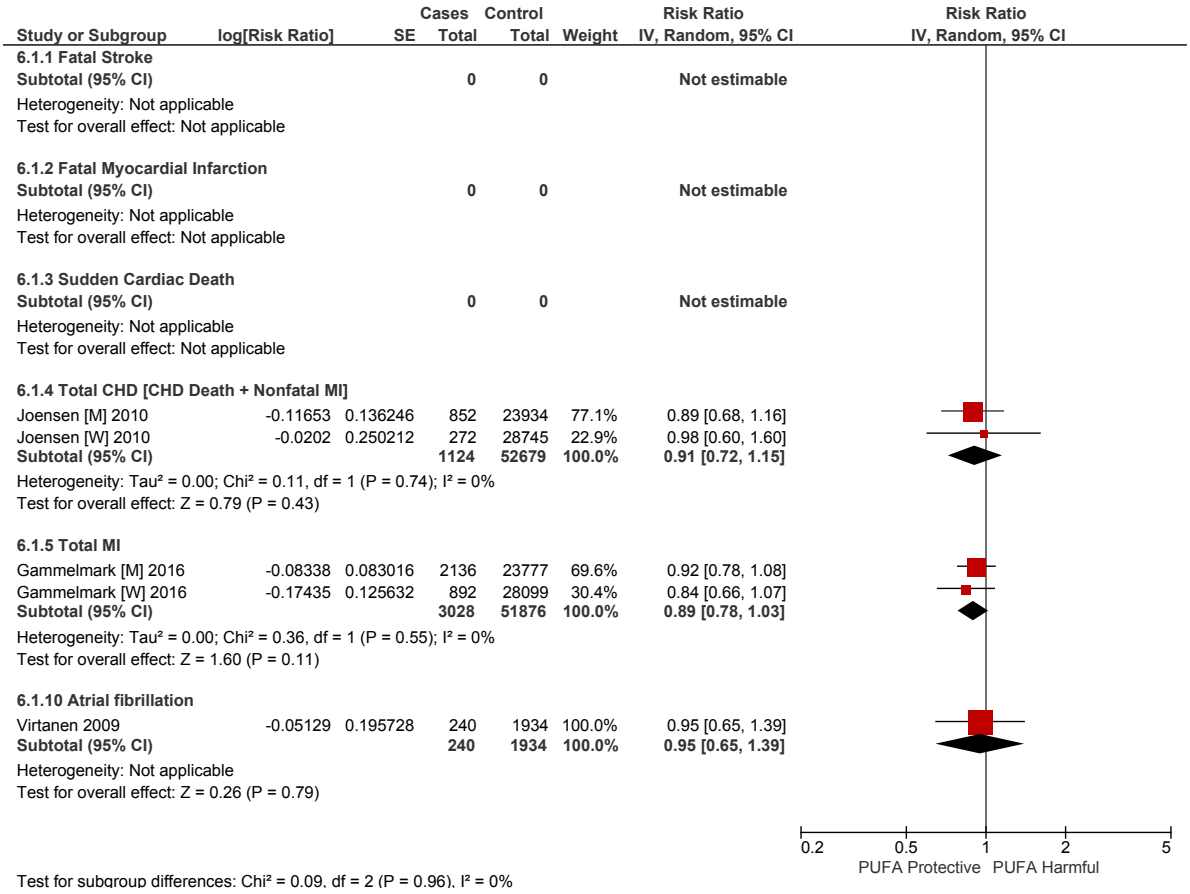
BrCa: breast cancer; CI: confidence interval; df: degrees of freedom; DHA: docosahexaenoic acid; IV: inverse variance; PUFA: polyunsaturated fatty acids; RR: risk ratio; SE: standard error.

Fig. 42b. Pooled most-adjusted (fixed-effect) RR of DHA and breast cancer (*n*=5 studies)



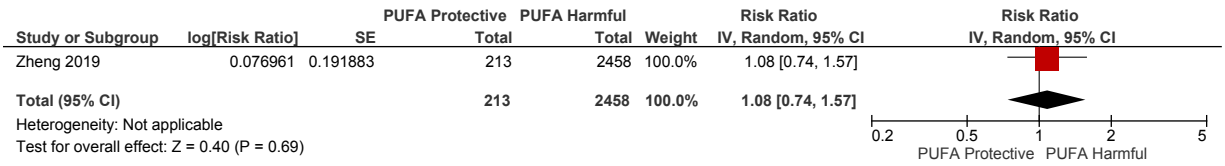
BrCa: breast cancer; CI: confidence interval; df: degrees of freedom; DHA: docosahexaenoic acid; IV: inverse variance; PUFA: polyunsaturated fatty acids; RR: risk ratio; SE: standard error.

Fig. 42c. Pooled most-adjusted (random-effects) RR of DPA and CVD (*n*=3 studies)



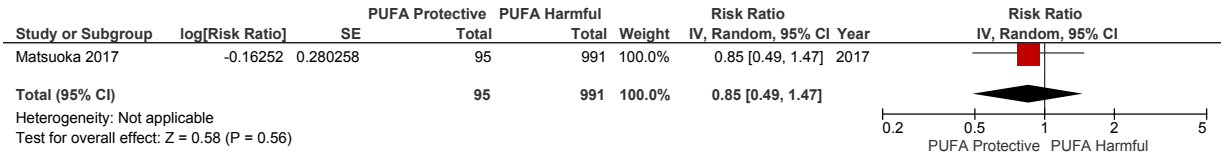
CHD: coronary heart disease; CI: confidence interval; CVD: cardiovascular disease; df: degrees of freedom; DPA: docosapentaenoic acid; IV: inverse variance; M: male; MI: myocardial infarction; PUFA: polyunsaturated fatty acids; RR: risk ratio; SE: standard error; W: women.

Fig. 42d. Pooled most-adjusted (random-effects) RR of DPA and type 2 diabetes (*n*=1 study)



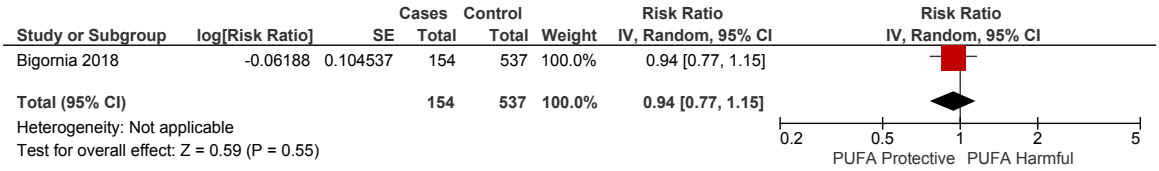
CI: confidence interval; DPA: docosapentaenoic acid; IV: inverse variance; PUFA: polyunsaturated fatty acids; RR: risk ratio; SE: standard error.

Fig. 42e. Pooled most-adjusted (random-effects) RR of DPA and depression (*n*=1 study)



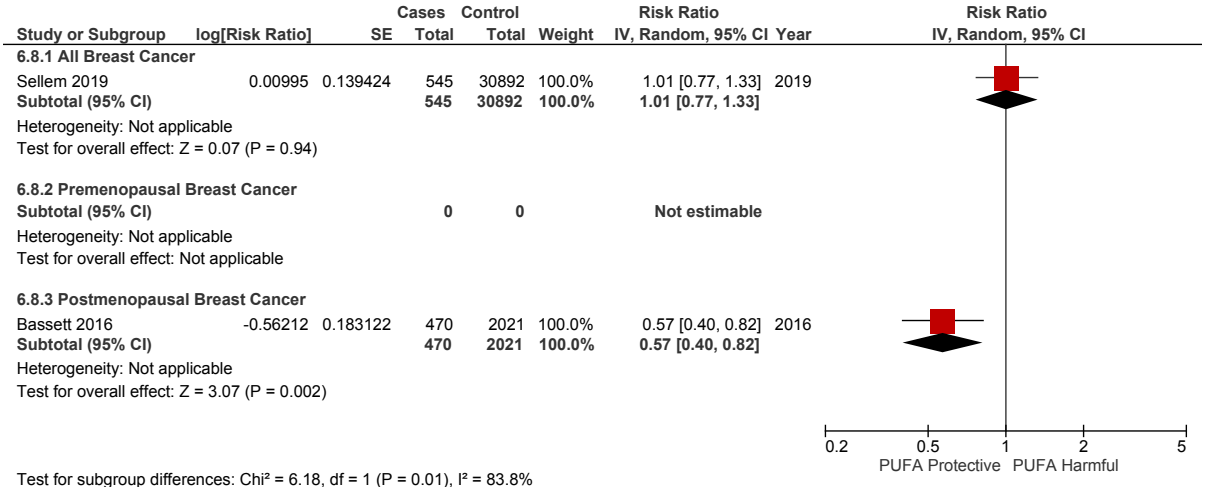
CI: confidence interval; DPA: docosapentaenoic acid; IV: inverse variance; PUFA: polyunsaturated fatty acids; RR: risk ratio; SE: standard error.

Fig. 42f. Pooled most-adjusted (random-effects) RR of DPA and cognitive decline (*n*=1 study)



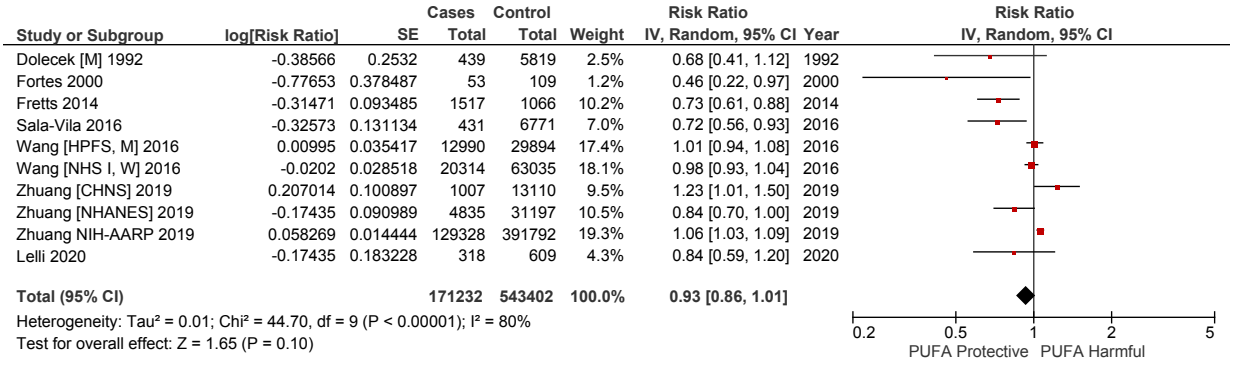
CI: confidence interval; DPA: docosapentaenoic acid; IV: inverse variance; PUFA: polyunsaturated fatty acids; RR: risk ratio; SE: standard error.

Fig. 42g. Pooled most-adjusted (random-effects) RR of DPA and breast cancer (*n*=1 study)



CI: confidence interval; df: degrees of freedom; DPA: docosapentaenoic acid; IV: inverse variance; PUFA: polyunsaturated fatty acids; RR: risk ratio; SE: standard error.

Fig. 43. Pooled most-adjusted RR of ALA and all-cause mortality (*n*=10 unique estimates)



ALA: alpha-linolenic acid; CHNS: China Health and Nutrition Survey; CI: confidence interval; df: degrees of freedom; HPFS: Health Professionals Follow-up Study; IV: inverse variance; M: male; NHANES: National Health and Nutrition Examination Survey; NHS I: Nurses' Health Study I; NIH-AARP: National Institutes of Health American Association of Retired Persons Diet and Health Study; PUFA: polyunsaturated fatty acids; RR: risk ratio; SE: standard error; W: women.

Fig. 44. Pooled most-adjusted RR of ALA and cardiovascular outcomes (*n*=25 studies)

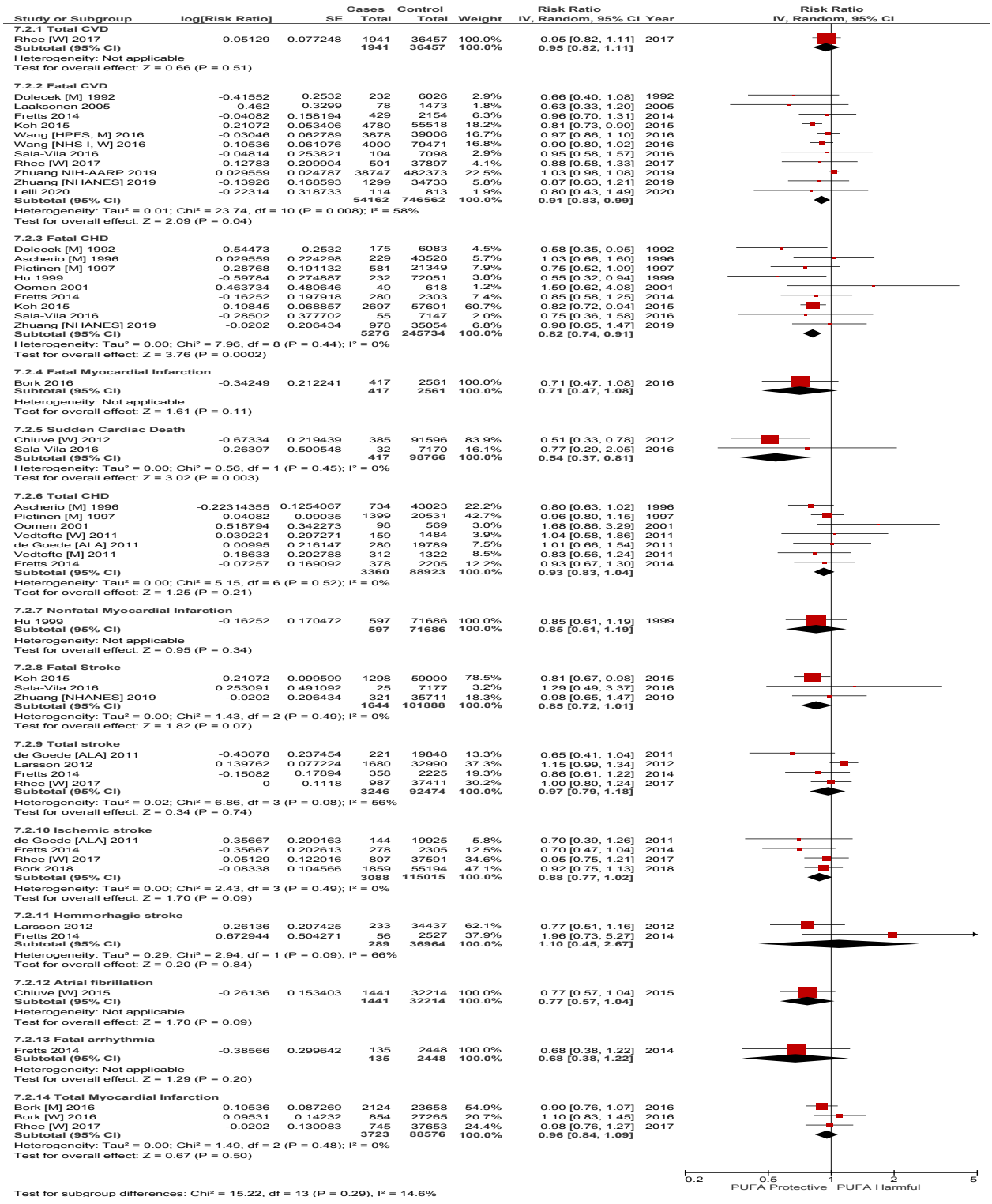
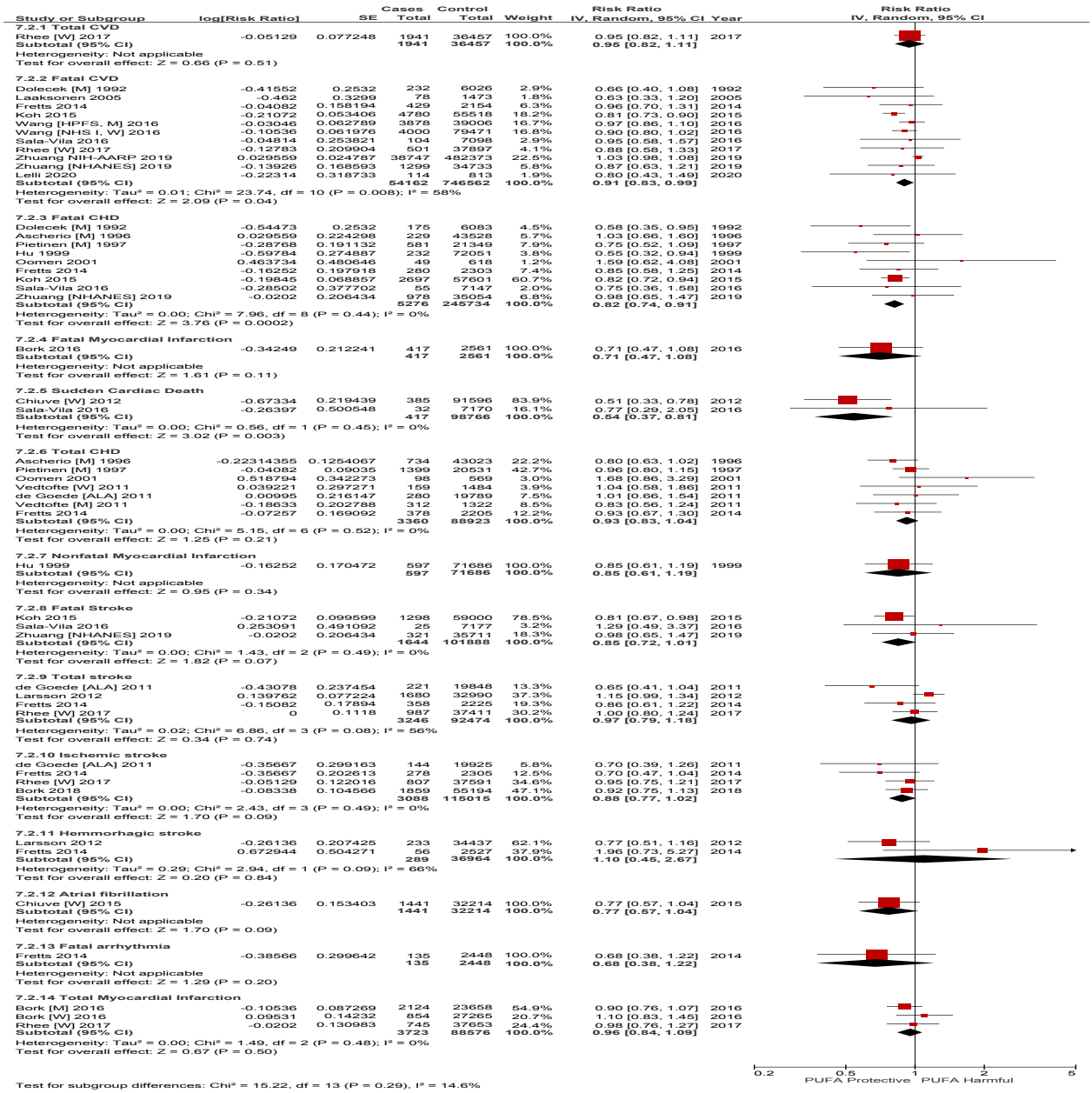


Fig. 44 (cont'd). Pooled most-adjusted RR of ALA and cardiovascular outcomes (*n*=25 studies)

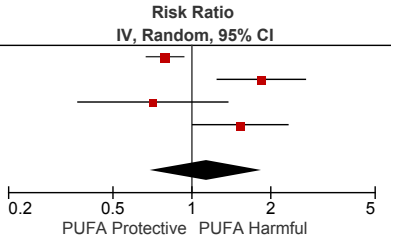


ALA: alpha-linolenic acid; CHD: coronary heart disease; CI: confidence interval; CVD: cardiovascular disease; df: degrees of freedom; HPFS: Health Professionals Follow-up Study; IV: inverse variance; M: male; NHANES: National Health and Nutrition Examination Survey; NHS I: Nurses' Health Study I; NIH-AARP: National Institutes of Health American Association of Retired Persons Diet and Health Study; PUFA: polyunsaturated fatty acids; RR: risk ratio; SE: standard error; W: women.

Fig. 45. Pooled most-adjusted RR of ALA and type 2 diabetes (*n*=4 studies)

Study or Subgroup	log[Risk Ratio]	SE	Cases Total	Control Total	Weight	Risk Ratio IV, Random, 95% CI	Year
Brostow 2011	-0.23572	0.08365	2252	40924	29.5%	0.79 [0.67, 0.93]	2011
Alhazmi 2014	0.609766	0.197399	311	8059	25.7%	1.84 [1.25, 2.71]	2014
Mirmiran 2018	-0.34249	0.3358	143	1996	19.8%	0.71 [0.37, 1.37]	2018
Zheng 2019	0.425268	0.213244	213	2458	25.0%	1.53 [1.01, 2.32]	2019
Total (95% CI)			**2919**	**53437**	**100.0%**	**1.13 [0.69, 1.86]**	

Heterogeneity: Tau² = 0.21; Chi² = 21.81, df = 3 (P < 0.0001); I² = 86%
Test for overall effect: Z = 0.50 (P = 0.62)

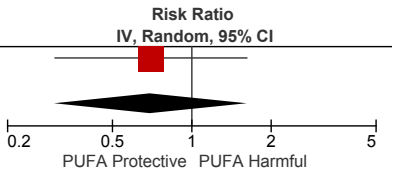


ALA: alpha-linolenic acid; CI: confidence interval; df: degrees of freedom; IV: inverse variance; PUFA: polyunsaturated fatty acids; RR: risk ratio; SE: standard error.

Fig. 46. Pooled most-adjusted RR of ALA and dementia (*n*=1 study)

Study or Subgroup	log[Risk Ratio]	SE	Cases Total	Control Total	Weight	Risk Ratio IV, Random, 95% CI	Year
Morris 2003	-0.35667	0.427035	131	684	100.0%	0.70 [0.30, 1.62]	2003
Total (95% CI)			**131**	**684**	**100.0%**	**0.70 [0.30, 1.62]**	

Heterogeneity: Not applicable
Test for overall effect: Z = 0.84 (P = 0.40)

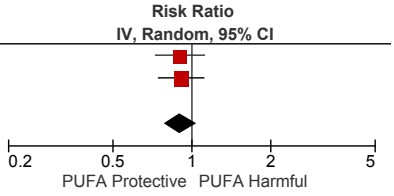


ALA: alpha-linolenic acid; CI: confidence interval; IV: inverse variance; PUFA: polyunsaturated fatty acids; RR: risk ratio; SE: standard error.

Fig. 47a. Pooled most-adjusted (random-effects) RR of ALA and cognitive decline (*n*=2 studies)

Study or Subgroup	log[Risk Ratio]	SE	Cases Total	Control Total	Weight	Risk Ratio IV, Random, 95% CI	Year
Vercambre 2010	-0.10536	0.109194	598	4211	46.2%	0.90 [0.73, 1.11]	2010
Bigornia 2018	-0.09431	0.101126	151	537	53.8%	0.91 [0.75, 1.11]	2018
Total (95% CI)			**749**	**4748**	**100.0%**	**0.91 [0.78, 1.05]**	

Heterogeneity: Tau² = 0.00; Chi² = 0.01, df = 1 (P = 0.94); I² = 0%
Test for overall effect: Z = 1.34 (P = 0.18)

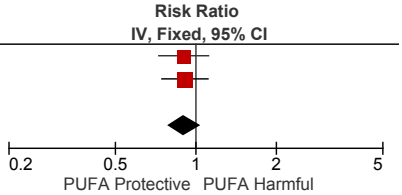


ALA: alpha-linolenic acid; CI: confidence interval; df: degrees of freedom; IV: inverse variance; PUFA: polyunsaturated fatty acids; RR: risk ratio; SE: standard error.

Fig. 47b. Pooled most-adjusted (fixed-effect) RR of ALA and cognitive decline (*n*=2 studies)

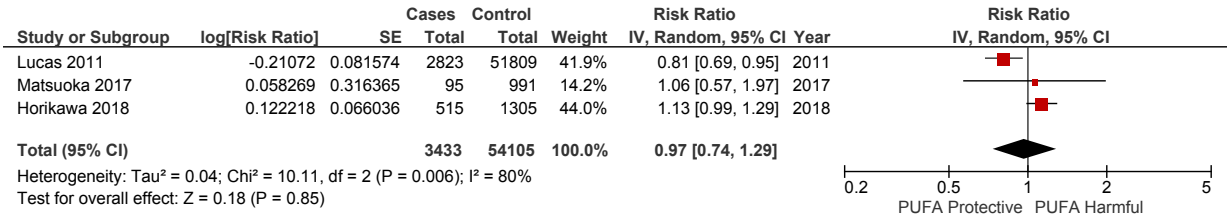
Study or Subgroup	log[Risk Ratio]	SE	Cases Total	Control Total	Weight	Risk Ratio IV, Fixed, 95% CI	Year
Vercambre 2010	-0.10536	0.109194	598	4211	46.2%	0.90 [0.73, 1.11]	2010
Bigornia 2018	-0.09431	0.101126	151	537	53.8%	0.91 [0.75, 1.11]	2018
Total (95% CI)			**749**	**4748**	**100.0%**	**0.91 [0.78, 1.05]**	

Heterogeneity: Chi² = 0.01, df = 1 (P = 0.94); I² = 0%
Test for overall effect: Z = 1.34 (P = 0.18)



ALA: alpha-linolenic acid; CI: confidence interval; df: degrees of freedom; IV: inverse variance; PUFA: polyunsaturated fatty acids; RR: risk ratio; SE: standard error.

Fig. 48a. Pooled most-adjusted (random-effects) RR of ALA and depression (*n*=3 studies)

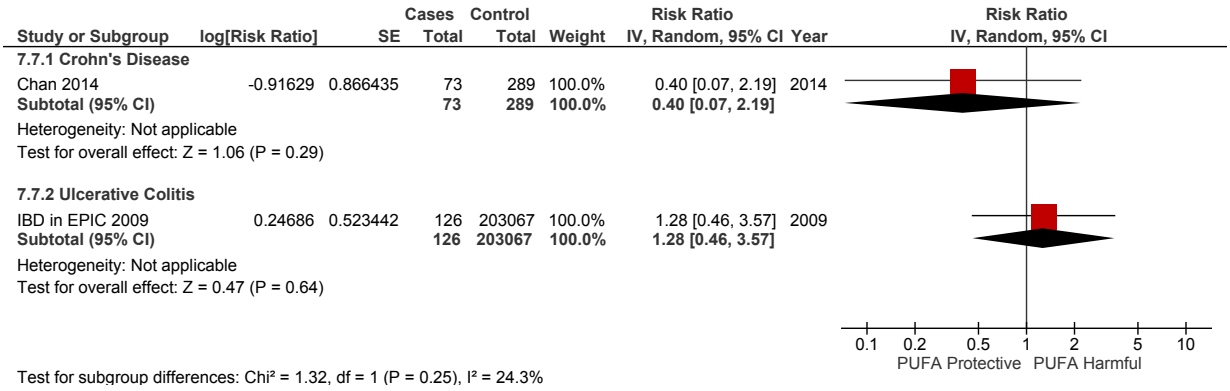


ALA: alpha-linolenic acid; CI: confidence interval; df: degrees of freedom; IV: inverse variance; PUFA: polyunsaturated fatty acids; RR: risk ratio; SE: standard error.

Fig. 48b. Pooled most-adjusted (fixed-effect) RR of ALA and depression (*n*=3 studies)

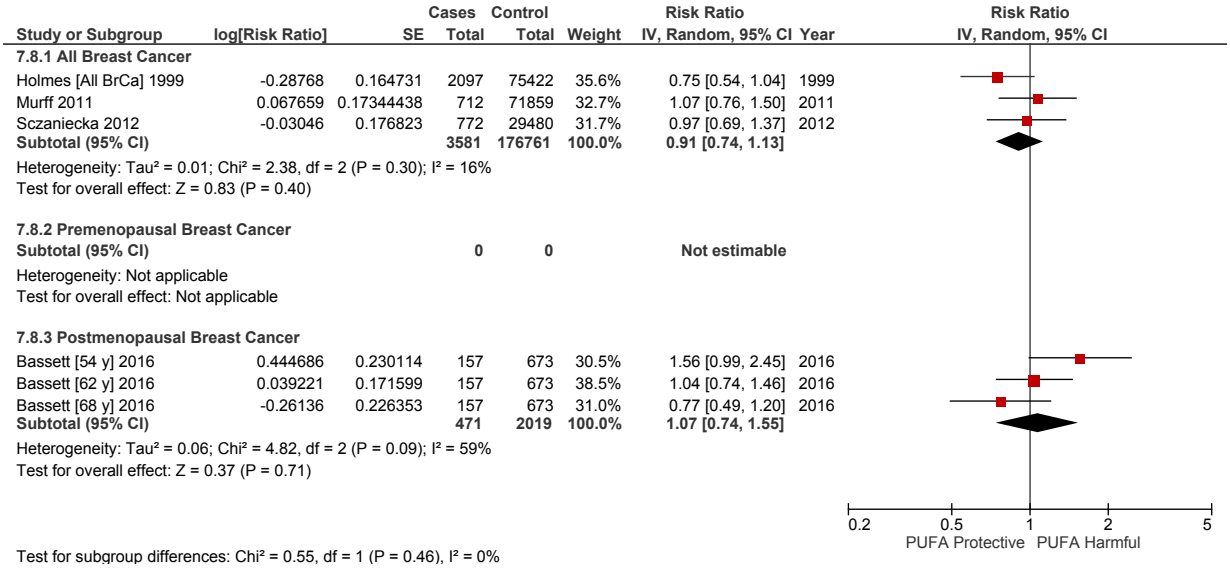
ALA: alpha-linolenic acid; CI: confidence interval; df: degrees of freedom; IV: inverse variance; PUFA: polyunsaturated fatty acids; RR: risk ratio; SE: standard error.

Fig. 49. Pooled most-adjusted RR of ALA and inflammatory bowel disease (*n*=2 studies)



ALA: alpha-linolenic acid; CI: confidence interval; df: degrees of freedom; EPIC: European Prospective Investigation into Cancer and Nutrition; IBD: inflammatory bowel disease; IV: inverse variance; PUFA: polyunsaturated fatty acids; RR: risk ratio; SE: standard error.

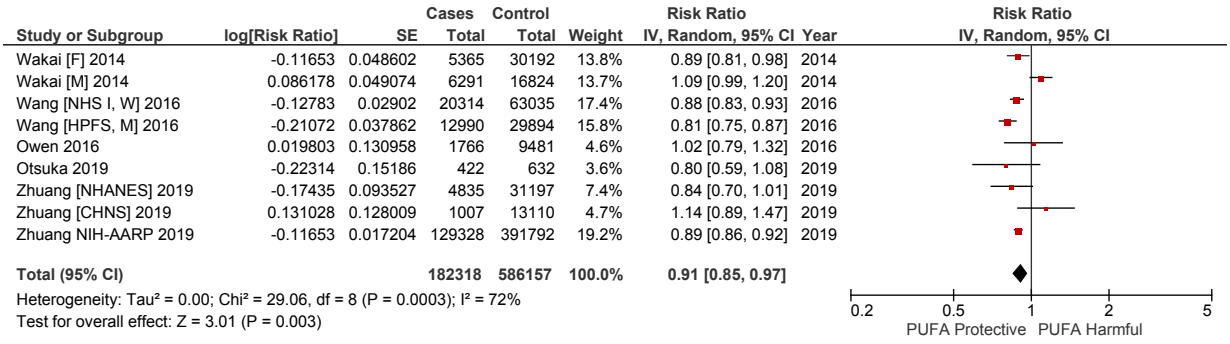
Fig. 50. Pooled most-adjusted RR of ALA and breast cancer (*n*=3 studies)



*Note that the total number of cases in this study is 470; estimates presented were stratified by age, so an equal distribution of cases was assumed for display purposes; this does not affect the presented point estimates or their confidence intervals.

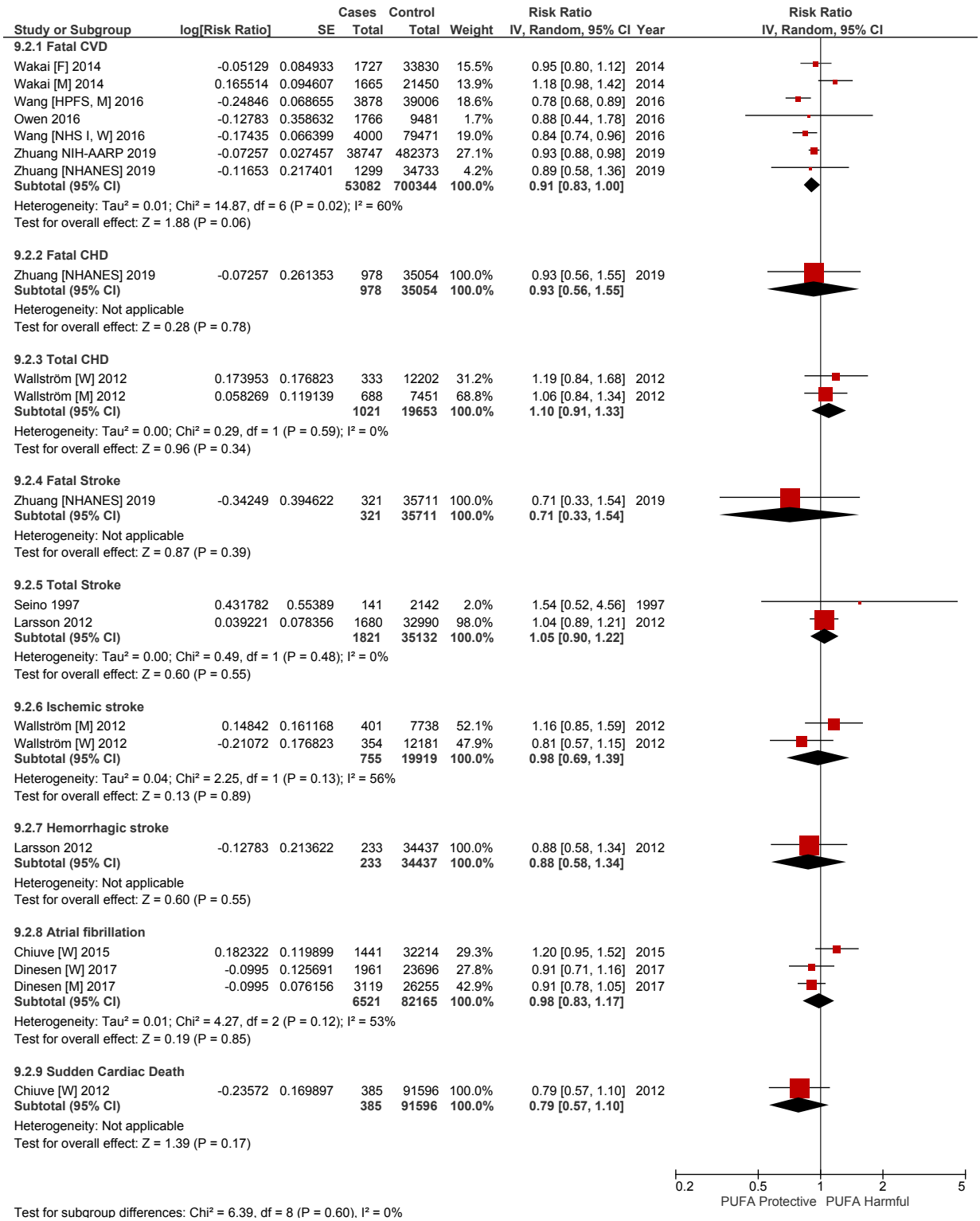
ALA: alpha-linolenic acid; BrCa: breast cancer; CI: confidence interval; df: degrees of freedom; IV: inverse variance; PUFA: polyunsaturated fatty acids; RR: risk ratio; SE: standard error; y: years.

Fig. 51. Pooled most-adjusted RR of omega-6 PUFA and all-cause mortality (*n*=9 studies)



CHNS: China Health and Nutrition Survey; CI: confidence interval; df: degrees of freedom; F: female; HPFS: Health Professionals Follow-up Study; IV: inverse variance; M: male; NHANES: National Health and Nutrition Examination Survey; NHS I: Nurses' Health Study I; NIH-AARP: National Institutes of Health American Association of Retired Persons Diet and Health Study; PUFA: polyunsaturated fatty acids; RR: risk ratio; SE: standard error; W: women.

Fig. 52. Pooled most-adjusted RR of omega-6 PUFA and CVD (*n*=15 studies)

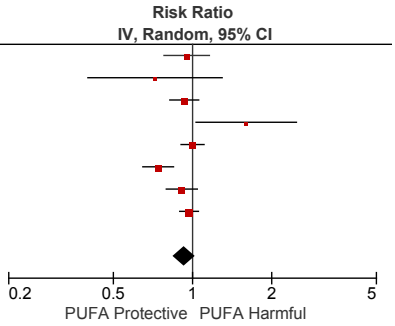


CHD: coronary heart disease; CI: confidence interval; CVD: cardiovascular disease; df: degrees of freedom; F: female; HPFS: Health Professionals Follow-up Study; IV: inverse variance; M: male; NHANES: National Health and Nutrition Examination Survey; NHS I: Nurses' Health Study I; NIH-AARP: National Institutes of Health American Association of Retired Persons Diet and Health Study; PUFA: polyunsaturated fatty acids; RR: risk ratio; SE: standard error; W: women.

Fig. 53a. Pooled most-adjusted RR of omega-6 PUFA and type 2 diabetes (*n*=8 studies)

Study or Subgroup	log[Risk Ratio]	SE	Cases Total	Control Total	Weight	Risk Ratio IV, Random, 95% CI	Year
Song [W] 2004	-0.05129	0.101245	1558	35751	11.1%	0.95 [0.78, 1.16]	2004
Patel 2010	-0.3285	0.2999	199	183	2.2%	0.72 [0.40, 1.30]	2010
Brostow 2011	-0.07257	0.064436	2252	40924	15.8%	0.93 [0.82, 1.06]	2011
Alhazmi 2014	0.470004	0.224158	311	8059	3.7%	1.60 [1.03, 2.48]	2014
Dow 2016	0	0.051192	2610	70884	17.7%	1.00 [0.90, 1.11]	2016
Zong [HPFS, M] 2019	-0.30111	0.06843	3607	38164	15.2%	0.74 [0.65, 0.85]	2019
Zong [NHS2, W] 2019	-0.09431	0.069198	5460	83150	15.1%	0.91 [0.79, 1.04]	2019
Zong [NHS, W] 2019	-0.03046	0.04174	9375	74272	19.1%	0.97 [0.89, 1.05]	2019
Total (95% CI)			**25372**	**351387**	**100.0%**	**0.93 [0.85, 1.02]**	

Heterogeneity: Tau² = 0.01; Chi² = 20.87, df = 7 (P = 0.004); I² = 66%
Test for overall effect: Z = 1.54 (P = 0.12)



CI: confidence interval; df: degrees of freedom; HPFS: Health Professionals Follow-up Study; IV: inverse variance; M: male; NHS: Nurses' Health Study; NHS2: Nurses' Health Study 2; PUFA: polyunsaturated fatty acids; RR: risk ratio; SE: standard error; W: women.

Fig. 53b. Pooled most-adjusted RR of omega-6 PUFA and dementia (*n*=1 study)

Study or Subgroup	log[Risk Ratio]	SE	Cases Total	Control Total	Weight	Risk Ratio IV, Random, 95% CI
Engelhart 2002	0.029559	0.145115	197	5198	100.0%	1.03 [0.78, 1.37]
Total (95% CI)			**197**	**5198**	**100.0%**	**1.03 [0.78, 1.37]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.20 (P = 0.84)

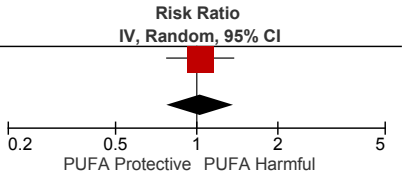
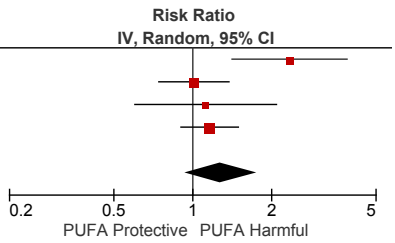


Fig. 54a. Pooled most-adjusted RR of omega-6 PUFA and depression (*n*=4 studies)

Study or Subgroup	log[Risk Ratio]	SE	Cases Total	Control Total	Weight	Risk Ratio IV, Random, 95% CI	Year
Wolfe [M] 2009	0.850151	0.257568	221	1726	20.4%	2.34 [1.41, 3.88]	2009
Wolfe [F] 2009	0.00995	0.157121	529	2380	30.2%	1.01 [0.74, 1.37]	2009
Matsuoka 2017	0.113329	0.317141	95	991	16.1%	1.12 [0.60, 2.09]	2017
Horikawa 2018	0.14842	0.128606	515	1305	33.3%	1.16 [0.90, 1.49]	2018
Total (95% CI)			**1360**	**6402**	**100.0%**	**1.28 [0.93, 1.75]**	

Heterogeneity: Tau² = 0.06; Chi² = 8.04, df = 3 (P = 0.05); I² = 63%
Test for overall effect: Z = 1.51 (P = 0.13)

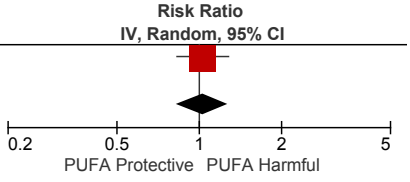


CI: confidence interval; df: degrees of freedom; F: female; IV: inverse variance; M: male; PUFA: polyunsaturated fatty acids; RR: risk ratio; SE: standard error.

Fig. 54b. Pooled most-adjusted RR of omega-6 PUFA and cognitive decline (*n*=1 study)

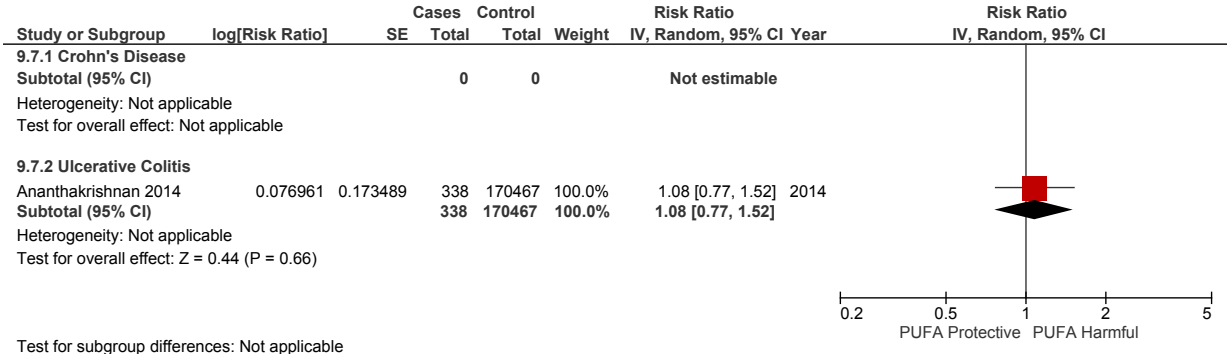
Study or Subgroup	log[Risk Ratio]	SE	Cases Total	Control Total	Weight	Risk Ratio IV, Random, 95% CI
Vercambre 2010	0.029559	0.110508	598	4211	100.0%	1.03 [0.83, 1.28]
Total (95% CI)			**598**	**4211**	**100.0%**	**1.03 [0.83, 1.28]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.27 (P = 0.79)



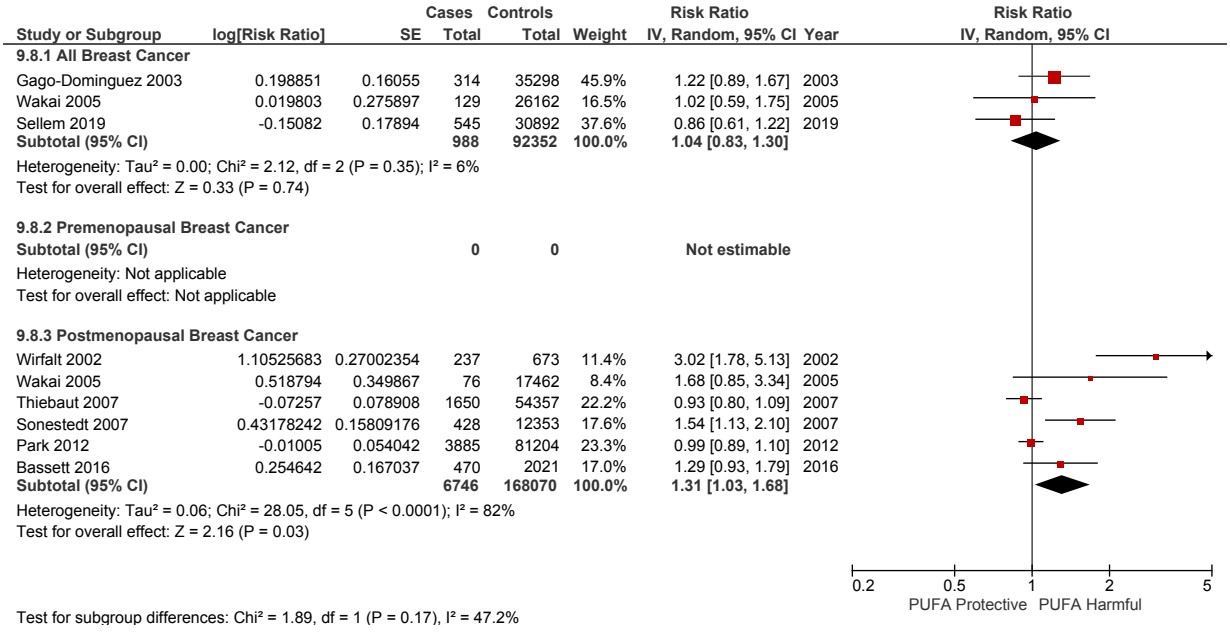
CI: confidence interval; IV: inverse variance; PUFA: polyunsaturated fatty acids; RR: risk ratio; SE: standard error.

Fig. 55. Pooled most-adjusted RR of omega-6 PUFA and inflammatory bowel disease (*n*=1 study)



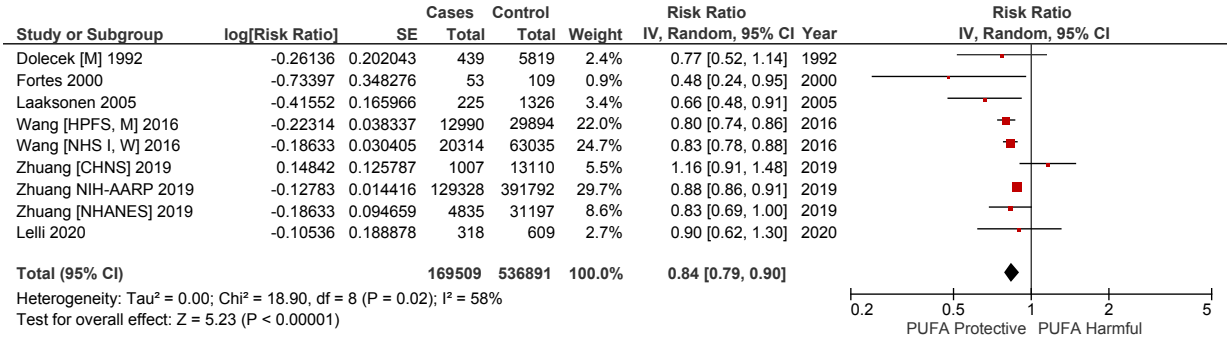
CI: confidence interval; IV: inverse variance; PUFA: polyunsaturated fatty acids; RR: risk ratio; SE: standard error.

Fig. 56. Pooled most-adjusted RR of omega-6 PUFA and breast cancer (*n*=8 studies)



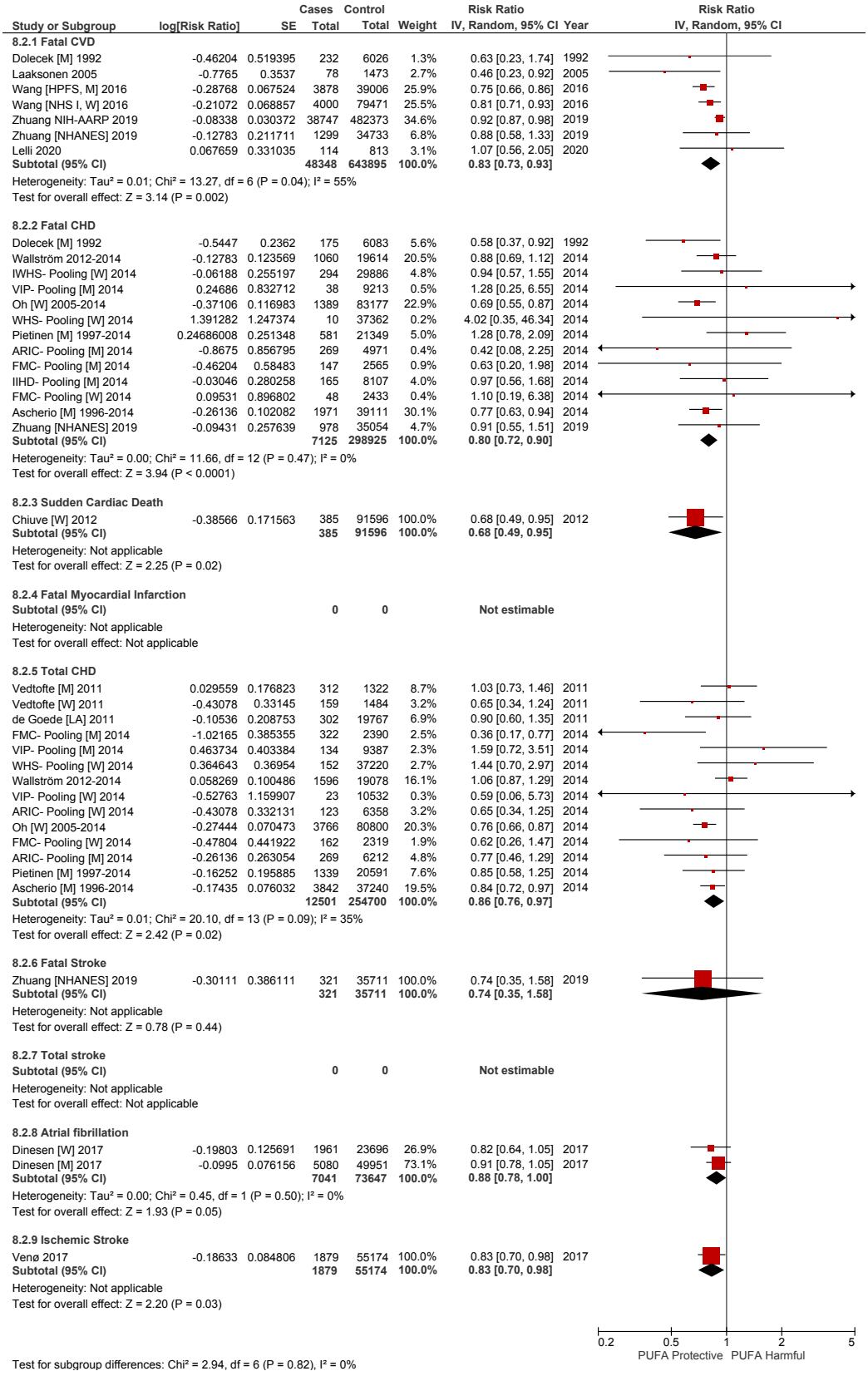
CI: confidence interval; df: degrees of freedom; IV: inverse variance; PUFA: polyunsaturated fatty acids; RR: risk ratio; SE: standard error.

Fig. 57. Pooled most-adjusted RR of LA and all-cause mortality (*n*=9 studies)



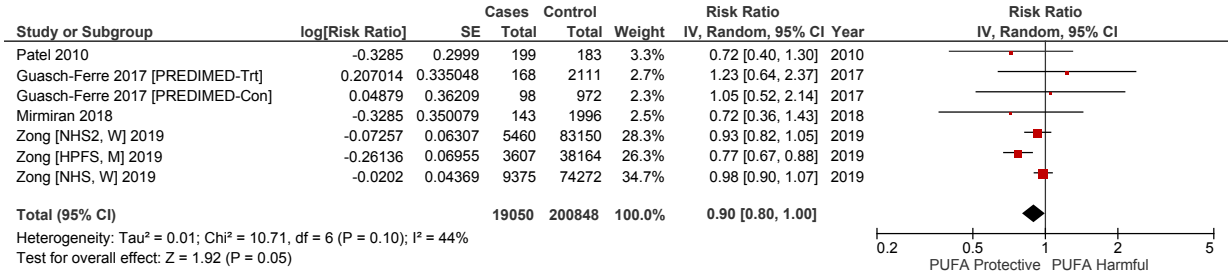
CHNS: China Health and Nutrition Survey; CI: confidence interval; df: degrees of freedom; HPFS: Health Professionals Follow-up Study; IV: inverse variance; LA: linoleic acid; M: male; NHANES: National Health and Nutrition Examination Survey; NHS I: Nurses' Health Study I; NIH-AARP: National Institutes of Health American Association of Retired Persons Diet and Health Study; PUFA: polyunsaturated fatty acids; RR: risk ratio; SE: standard error; W: women.

Fig. 58. Pooled most-adjusted RR of LA and CVD (*n*=27 studies)



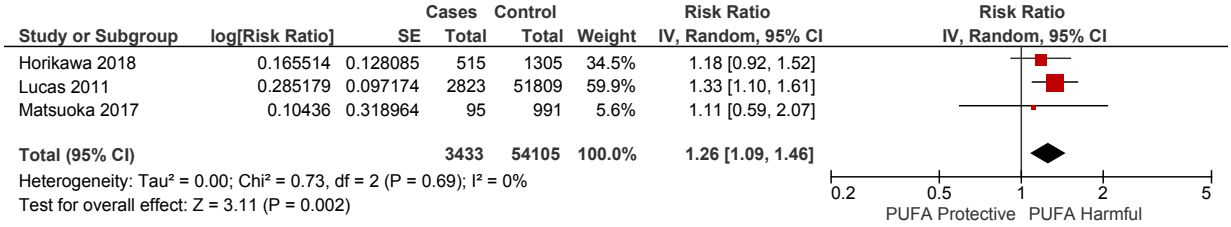
ARIC: Atherosclerosis Risk in Communities; CHD: coronary heart disease; CI: confidence interval; CVD: cardiovascular disease; df: degrees of freedom; FMC: Finnish Mobile Health Clinic; HPFS: Health Professionals Follow-up Study; IIHD: Israeli Ischemic Heart Disease; IV: inverse variance; IWHS: Iowa Women's Health Study; LA: linoleic acid; M: male; NHANES: National Health and Nutrition Examination Survey; NHS I: Nurses' Health Study I; NIH-AARP: National Institutes of Health American Association of Retired Persons Diet and Health Study; PUFA: polyunsaturated fatty acids; RR: risk ratio; SE: standard error; VIP: Västerbotten Intervention Program; W: women; WHS: Women's Health Study.

Fig. 59a. Pooled most-adjusted RR of LA and type 2 diabetes (*n*=7 unique comparisons)



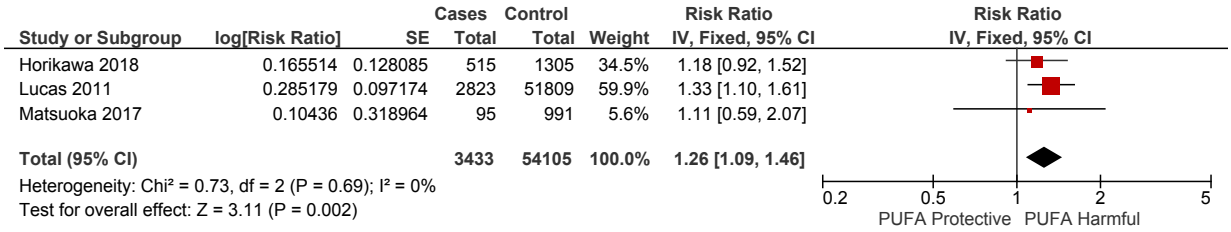
CI: confidence interval; df: degrees of freedom; HPFS: Health Professionals Follow-up Study; IV: inverse variance; LA: linoleic acid; M: male; NHS: Nurses' Health Study; NHS2: Nurses' Health Study 2; PREDIMED-Con: Prevención con Dieta Mediterránea (control); PREDIMED-Trt: Prevención con Dieta Mediterránea (treatment); PUFA: polyunsaturated fatty acids; RR: risk ratio; SE: standard error; W: women.

Fig. 59b. Pooled most-adjusted (random effects) risk ratio of LA and depression (*n*=3 studies)



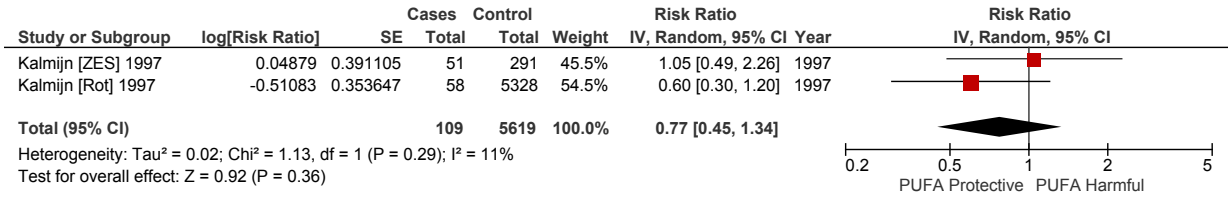
CI: confidence interval; df: degrees of freedom; IV: inverse variance; LA: linoleic acid; PUFA: polyunsaturated fatty acids; RR: risk ratio; SE: standard error.

Fig. 59c. Pooled most-adjusted (fixed effect) risk ratio of LA and depression (*n*=3 studies)



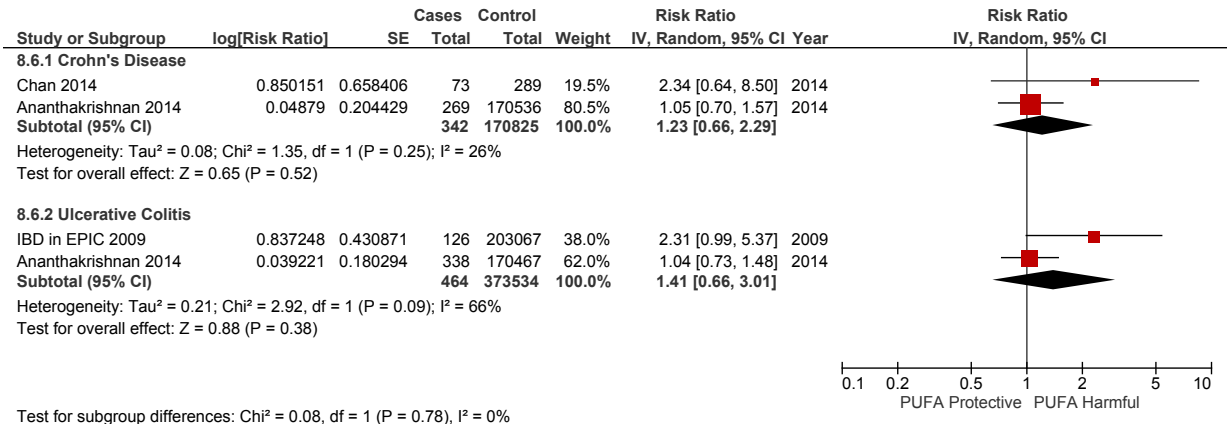
CI: confidence interval; df: degrees of freedom; IV: inverse variance; LA: linoleic acid; PUFA: polyunsaturated fatty acids; RR: risk ratio; SE: standard error.

Fig. 60. Pooled most-adjusted RR of LA and dementia (*n*=2 studies)



CI: confidence interval; df: degrees of freedom; IV: inverse variance; LA: linoleic acid; PUFA: polyunsaturated fatty acids; Rot: Rotterdam Study; RR: risk ratio; SE: standard error; ZES: Zutphen Elderly Study.

Fig. 61a. Pooled most-adjusted RR of LA and inflammatory bowel disease (*n*=3 studies)



CI: confidence interval; df: degrees of freedom; EPIC: European Prospective Investigation into Cancer and Nutrition; IBD: inflammatory bowel disease; IV: inverse variance; LA: linoleic acid; PUFA: polyunsaturated fatty acids; RR: risk ratio; SE: standard error.

Fig. 61b. Pooled most-adjusted RR of LA and inflammatory bowel disease (*n*=3 studies; fixed-effect)

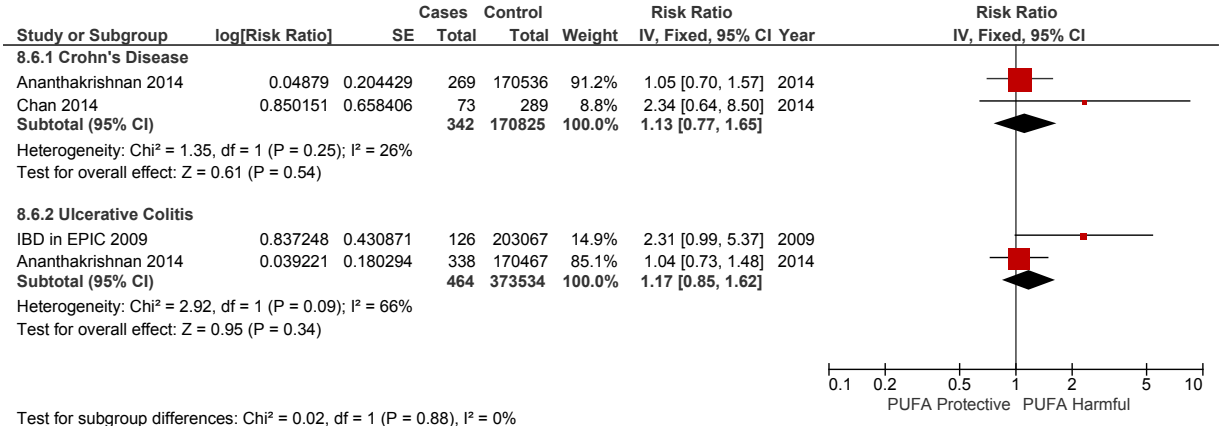
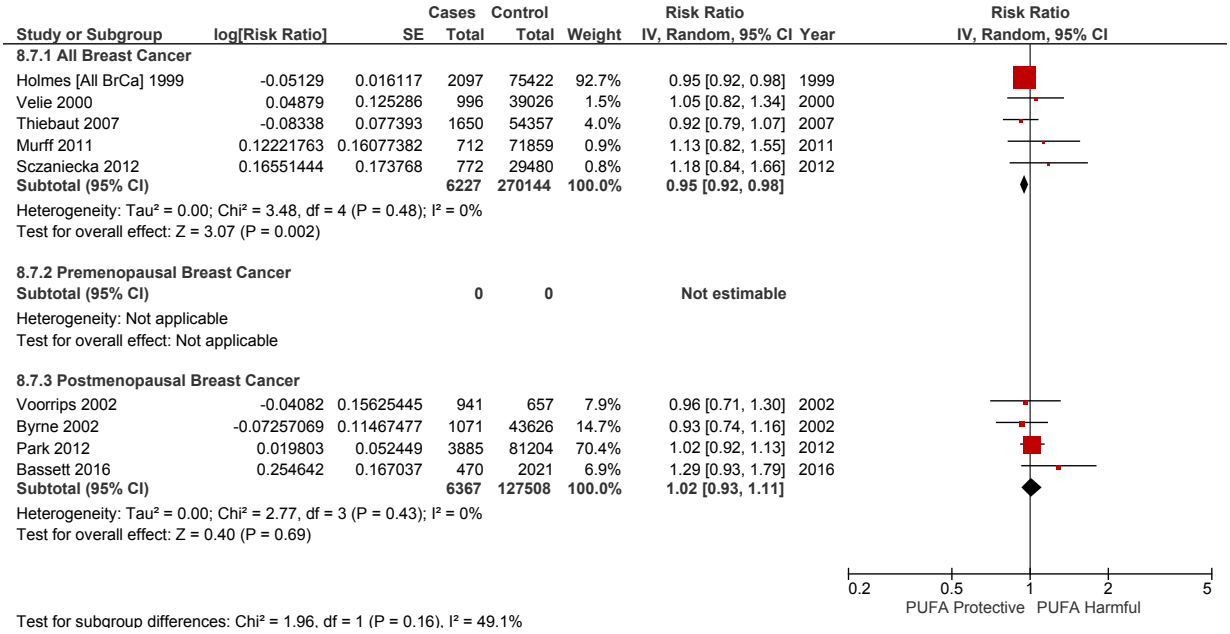
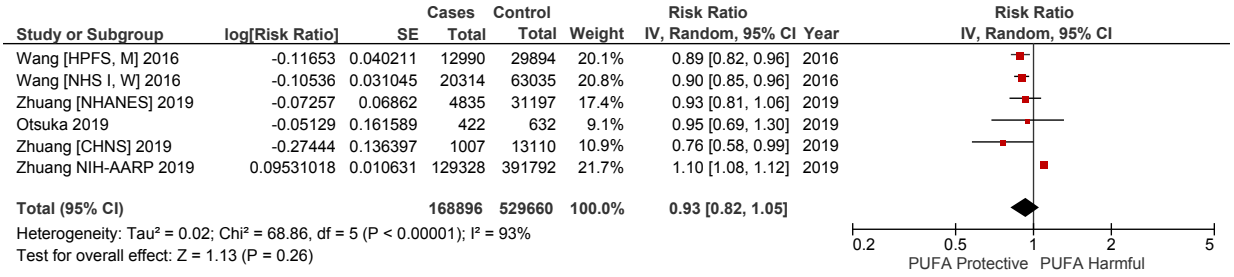


Fig. 62. Pooled most-adjusted RR of LA and breast cancer (*n*=5 studies)



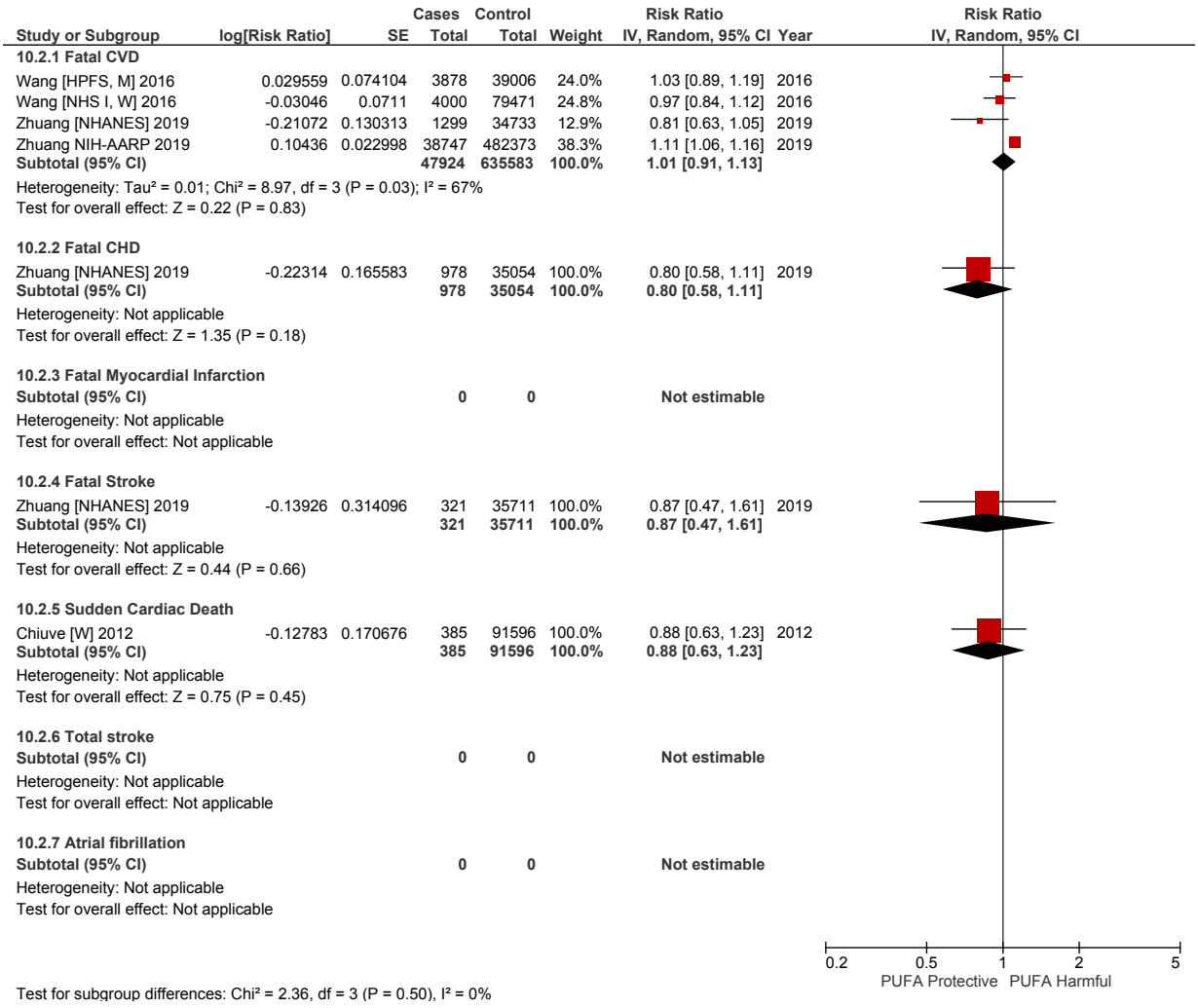
BrCa: breast cancer; CI: confidence interval; df: degrees of freedom; IV: inverse variance; LA: linoleic acid; PUFA: polyunsaturated fatty acids; RR: risk ratio; SE: standard error.

Fig. 63. Pooled most-adjusted RR of ARA and all-cause mortality (*n*=6 studies)



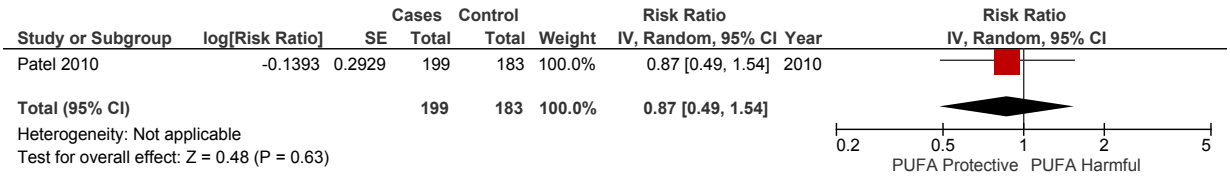
ARA: arachidonic acid; CHNS: China Health and Nutrition Survey; CI: confidence interval; df: degrees of freedom; HPFS: Health Professionals Follow-up Study; IV: inverse variance; M: male; NHANES: National Health and Nutrition Examination Survey; NHS I: Nurses' Health Study I; NIH-AARP: National Institutes of Health American Association of Retired Persons Diet and Health Study; PUFA: polyunsaturated fatty acids; RR: risk ratio; SE: standard error; W: women.

Fig. 64. Pooled most-adjusted RR of ARA and CVD (*n*=5 studies)



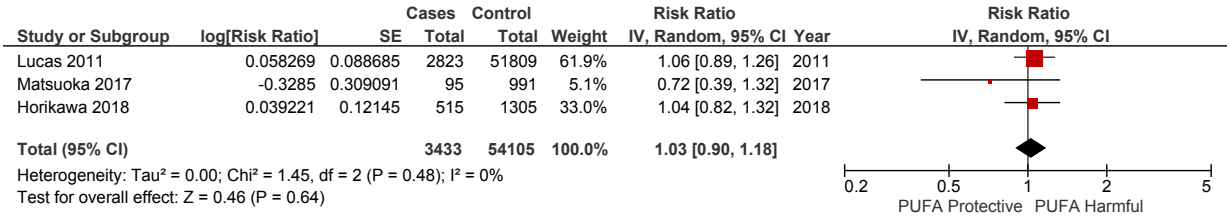
ARA: arachidonic acid; CHD: coronary heart disease; CI: confidence interval; CVD: cardiovascular disease; df: degrees of freedom; HPFS: Health Professionals Follow-up Study; IV: inverse variance; M: male; NHANES: National Health and Nutrition Examination Survey; NHS I: Nurses' Health Study I; NIH-AARP: National Institutes of Health American Association of Retired Persons Diet and Health Study; PUFA: polyunsaturated fatty acids; RR: risk ratio; SE: standard error; W: women.

Fig. 65. Pooled most-adjusted RR of ARA and type 2 diabetes (*n*=1 study)



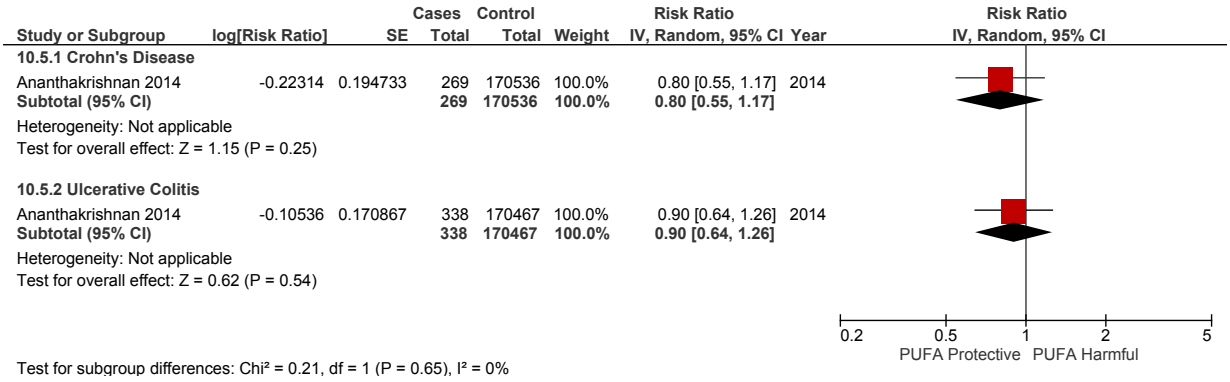
ARA: arachidonic acid; CI: confidence interval; IV: inverse variance; PUFA: polyunsaturated fatty acids; RR: risk ratio; SE: standard error.

Fig. 66. Pooled most-adjusted RR of ARA and depression (*n*=3 studies)



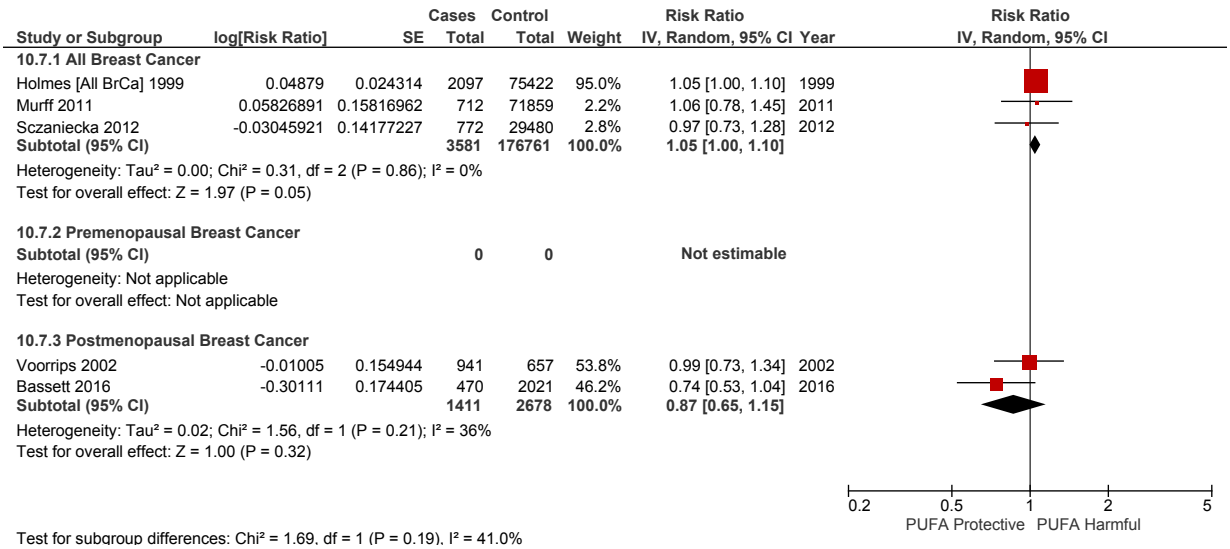
ARA: arachidonic acid; CI: confidence interval; df: degrees of freedom; IV: inverse variance; PUFA: polyunsaturated fatty acids; RR: risk ratio; SE: standard error.

Fig. 67. Pooled most-adjusted RR of ARA and inflammatory bowel disease (*n*=1 study)



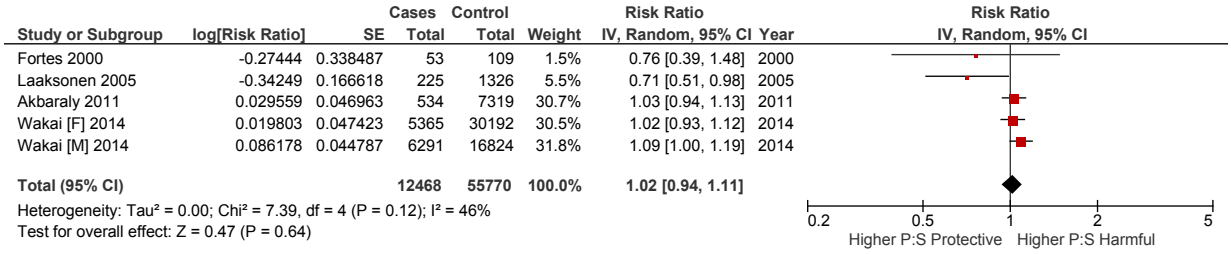
ARA: arachidonic acid; CI: confidence interval; df: degrees of freedom; IV: inverse variance; PUFA: polyunsaturated fatty acids; RR: risk ratio; SE: standard error.

Fig. 68. Pooled most-adjusted RR of ARA and breast cancer (*n*=5 studies)



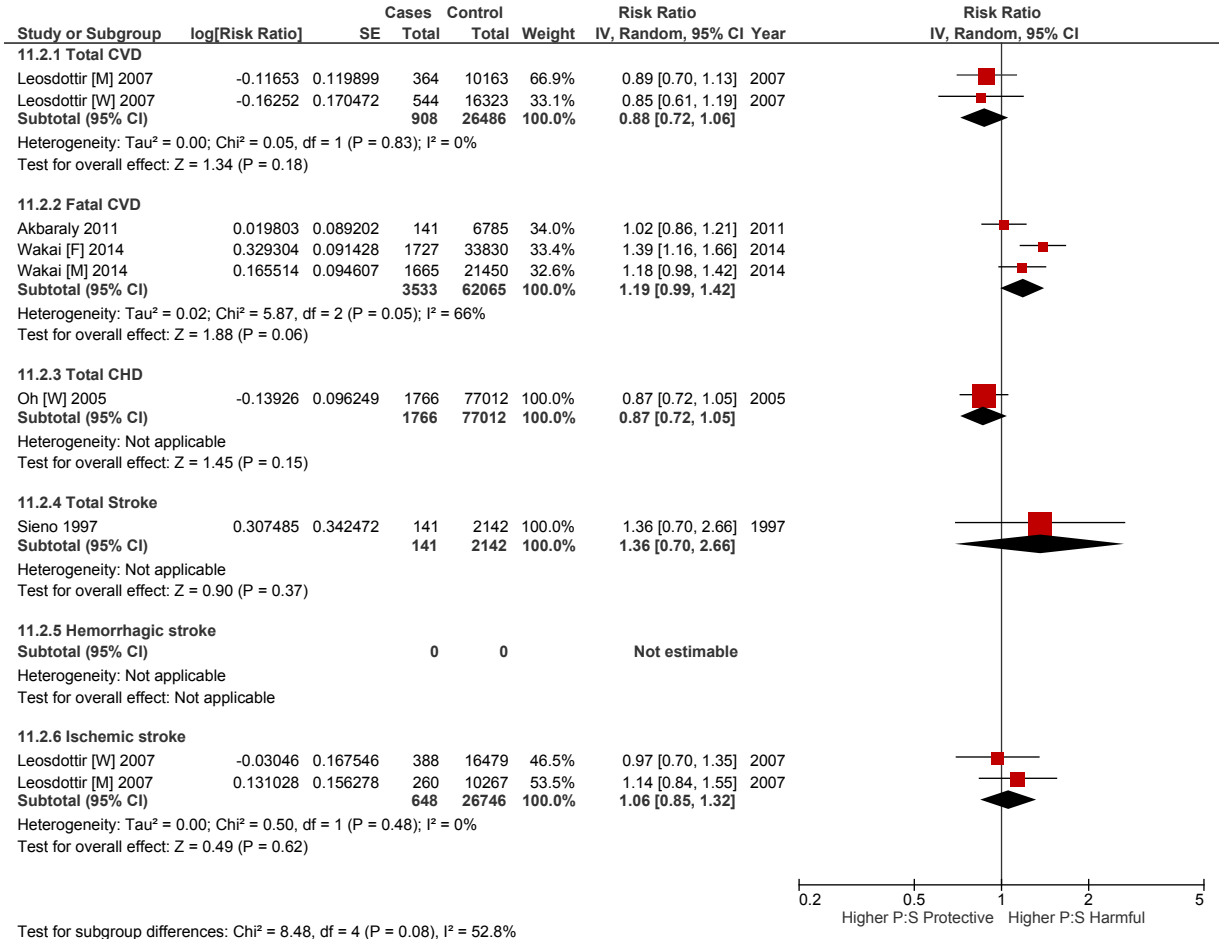
ARA: arachidonic acid; BrCa: breast cancer; CI: confidence interval; df: degrees of freedom; IV: inverse variance; PUFA: polyunsaturated fatty acids; RR: risk ratio; SE: standard error.

Fig. 69. Pooled most-adjusted RR of P:S and all-cause mortality (*n*=5 studies)



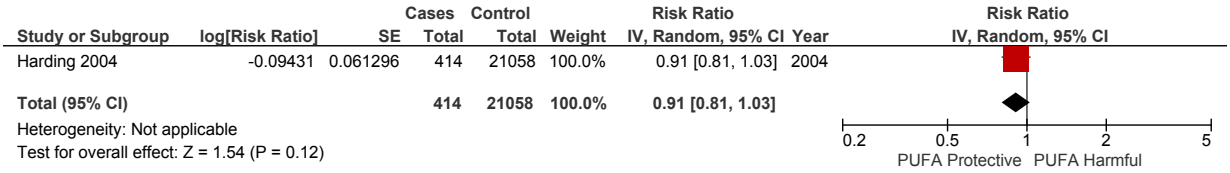
CI: confidence interval; df: degrees of freedom; F: female; IV: inverse variance; M: male; P:S: Polyunsaturated: Saturated Fat Ratio; RR: risk ratio; SE: standard error.

Fig. 70. Pooled most-adjusted RR of P:S and CVD (*n*=7 studies)



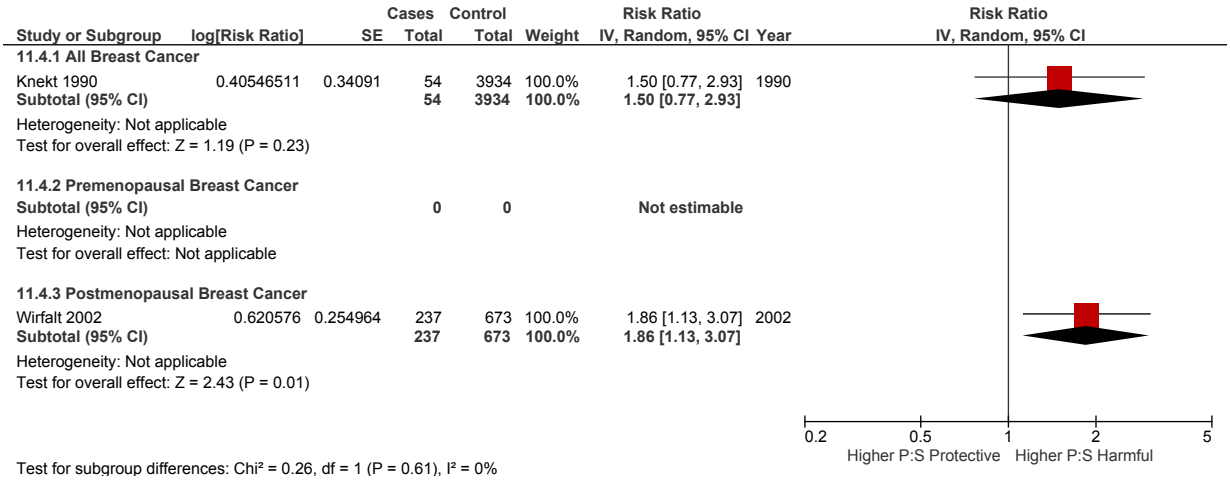
CHD: coronary heart disease; CI: confidence interval; CVD: cardiovascular disease; df: degrees of freedom; F: female; IV: inverse variance; M: male; P:S: Polyunsaturated: Saturated Fat Ratio; RR: risk ratio; SE: standard error; W: women.

Fig. 71. Most-adjusted RR of P:S and type 2 diabetes (*n*=1 study)



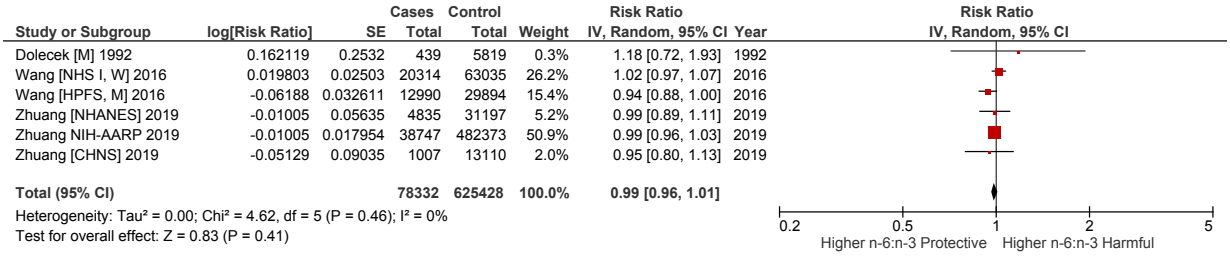
CI: confidence interval; IV: inverse variance; P:S: Polyunsaturated: Saturated Fat Ratio; PUFA: polyunsaturated fatty acids; RR: risk ratio; SE: standard error.

Fig. 72. Most-adjusted RR of P:S and breast cancer (*n*=2 studies)



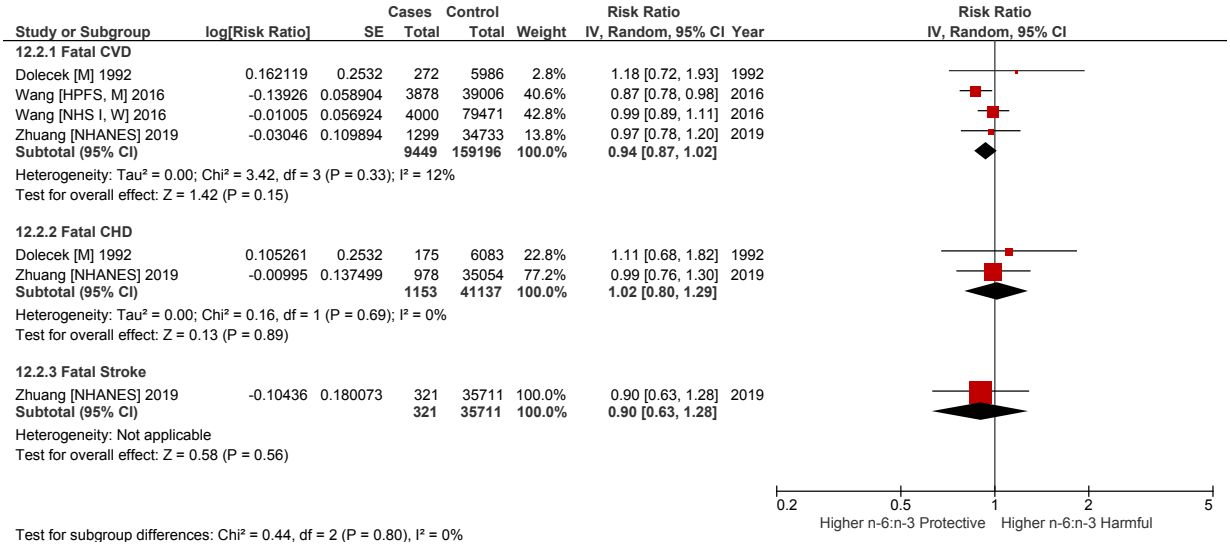
CI: confidence interval; df: degrees of freedom; IV: inverse variance; P:S: Polyunsaturated: Saturated Fat Ratio; RR: risk ratio; SE: standard error.

Fig. 73. Pooled most-adjusted RR of omega-6:omega-3 ratio and all-cause mortality (*n*=6 studies)



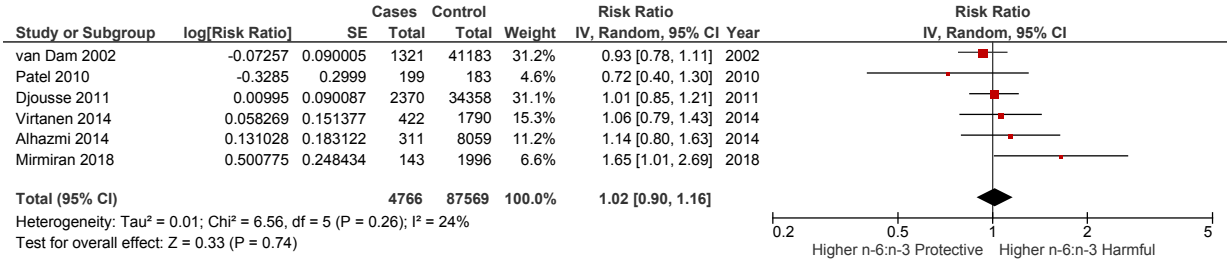
CHNS: China Health and Nutrition Survey; CI: confidence interval; df: degrees of freedom; HPFS: Health Professionals Follow-up Study; IV: inverse variance; M: male; NHANES: National Health and Nutrition Examination Survey; NHS I: Nurses' Health Study I; NIH-AARP: National Institutes of Health American Association of Retired Persons Diet and Health Study; RR: risk ratio; SE: standard error; W: women.

Fig. 74. Pooled most-adjusted RR of omega-6:omega-3 ratio and CVD (*n*=4 studies)



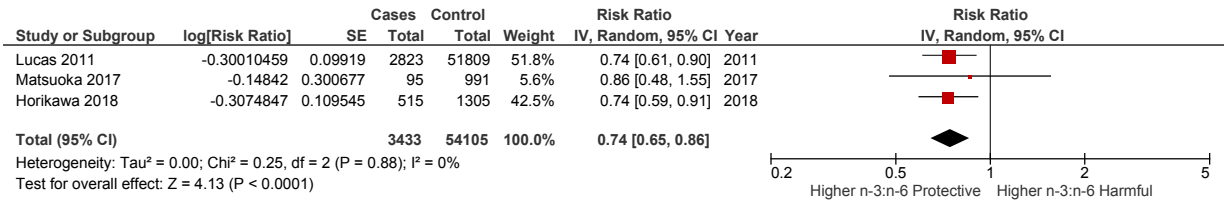
CHD: coronary heart disease; CI: confidence interval; CVD: cardiovascular disease; df: degrees of freedom; HPFS: Health Professionals Follow-up Study; IV: inverse variance; M: male; NHANES: National Health and Nutrition Examination Survey; NHS I: Nurses' Health Study I; RR: risk ratio; SE: standard error; W: women.

Fig. 75. Pooled most-adjusted RR of omega-6:omega-3 ratio and type 2 diabetes (*n*=6 studies)



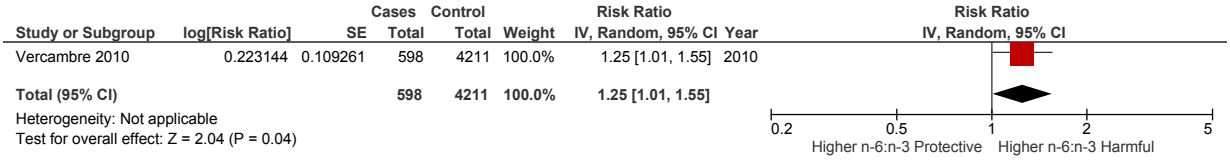
CI: confidence interval; df: degrees of freedom; IV: inverse variance; RR: risk ratio; SE: standard error.

Fig. 76. Pooled most-adjusted RR of omega-3:omega-6 ratio and depression (*n*=3 studies)



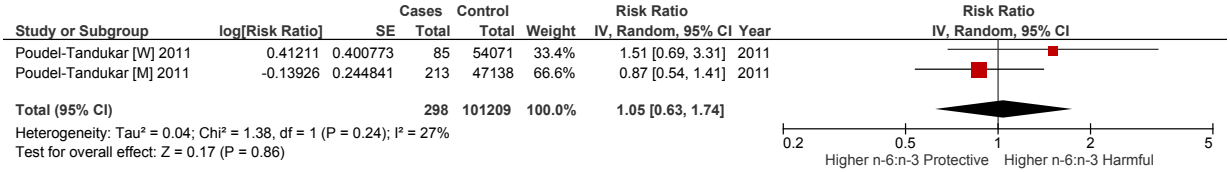
CI: confidence interval; df: degrees of freedom; IV: inverse variance; RR: risk ratio; SE: standard error.

Fig. 77. Most-adjusted RR of omega-6:omega-3 ratio and cognitive decline (*n*=1 study)



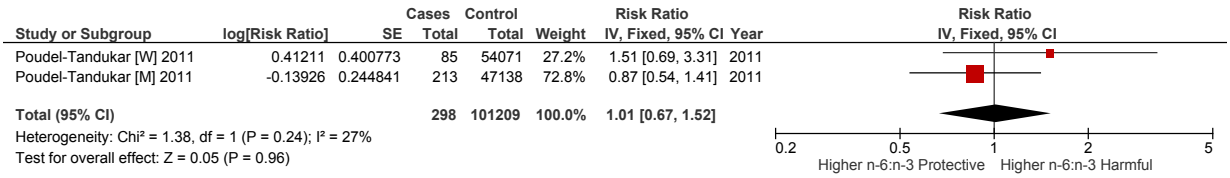
CI: confidence interval; IV: inverse variance; RR: risk ratio; SE: standard error.

Fig. 78a. Pooled most-adjusted (random-effects) RR of omega-6:omega-3 ratio and suicide (*n*=2 studies)



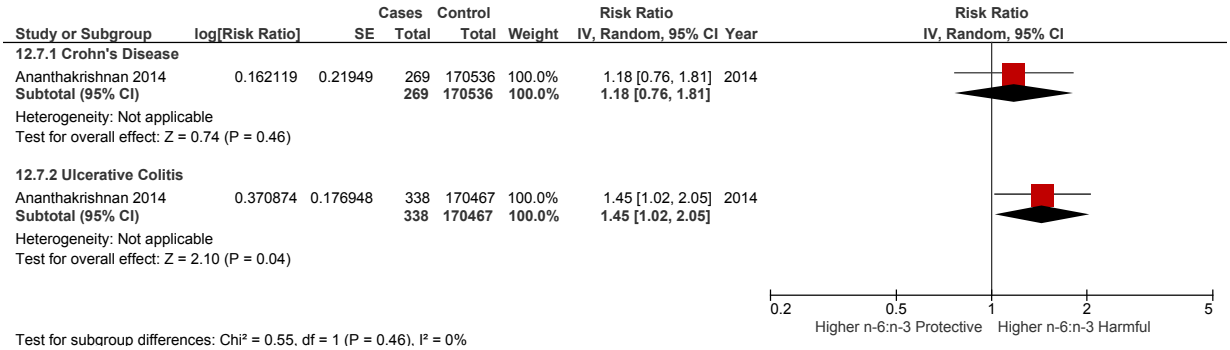
CI: confidence interval; df: degrees of freedom; IV: inverse variance; M: male; RR: risk ratio; SE: standard error; W: women.

Fig. 78b. Pooled most-adjusted (fixed-effect) RR of omega-6:omega-3 ratio and suicide (*n*=2 studies)



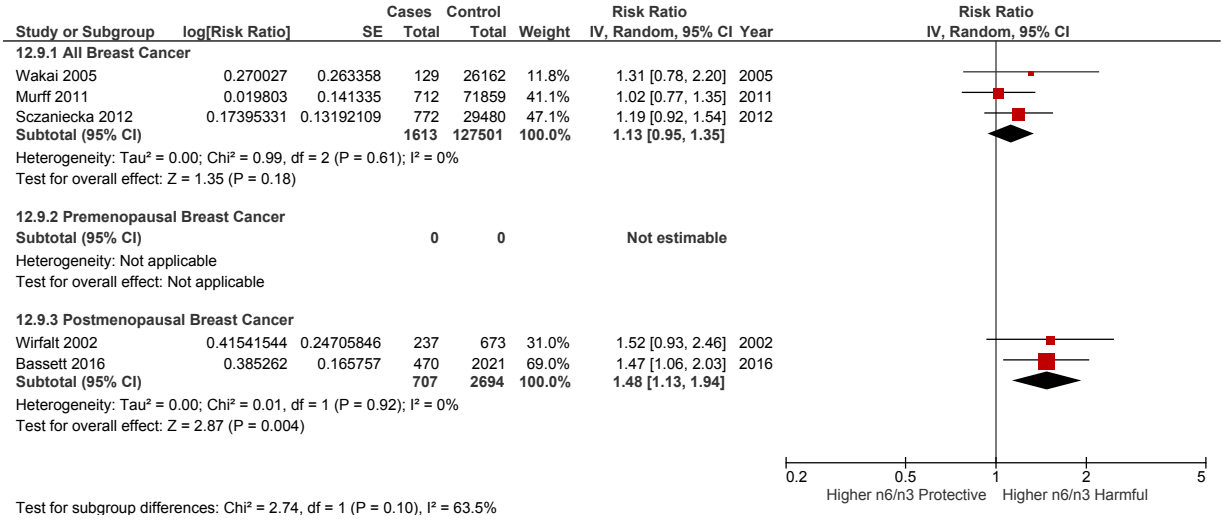
CI: confidence interval; df: degrees of freedom; IV: inverse variance; M: male; RR: risk ratio; SE: standard error; W: women.

Fig. 79. Most-adjusted RR of omega-6:omega-3 ratio and inflammatory bowel disease (*n*=1 study)



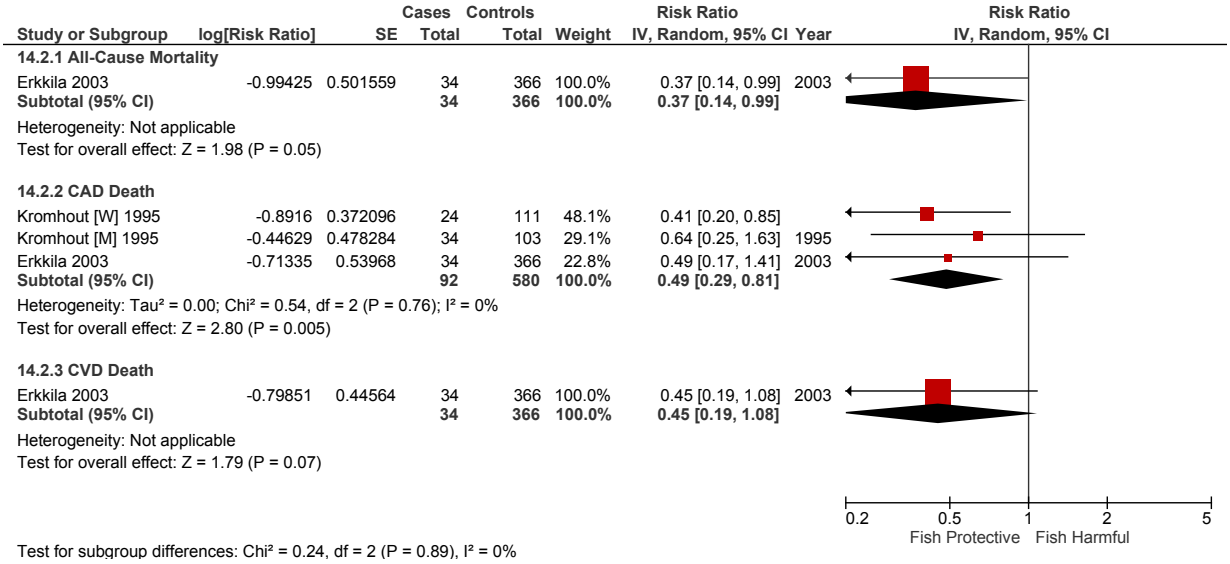
CI: confidence interval; df: degrees of freedom; IV: inverse variance; RR: risk ratio; SE: standard error.

Fig. 80. Pooled most-adjusted risk ratio of omega-6:omega-3 ratio and breast cancer (*n*=5 studies)



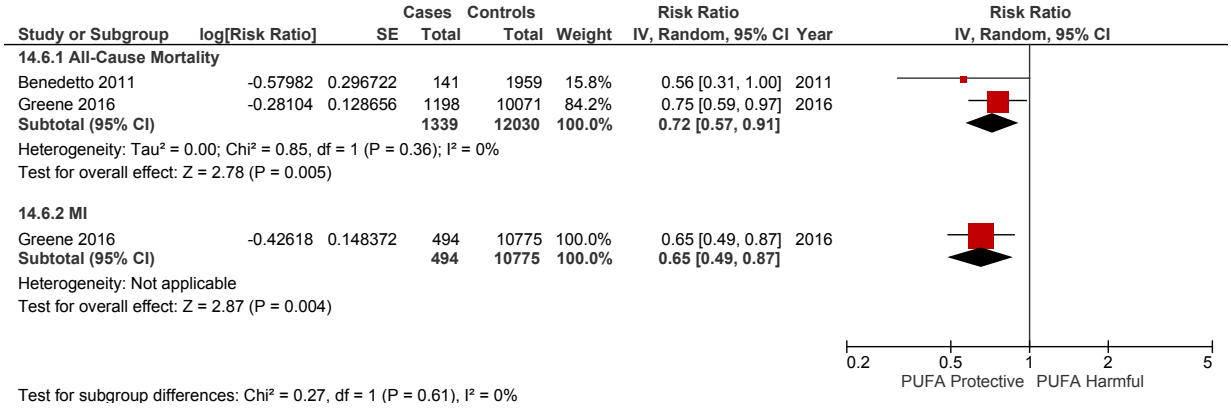
CI: confidence interval; df: degrees of freedom; IV: inverse variance; RR: risk ratio; SE: standard error.

Fig. 81. Pooled most-adjusted RR of fish in secondary prevention (*n*=2 studies)



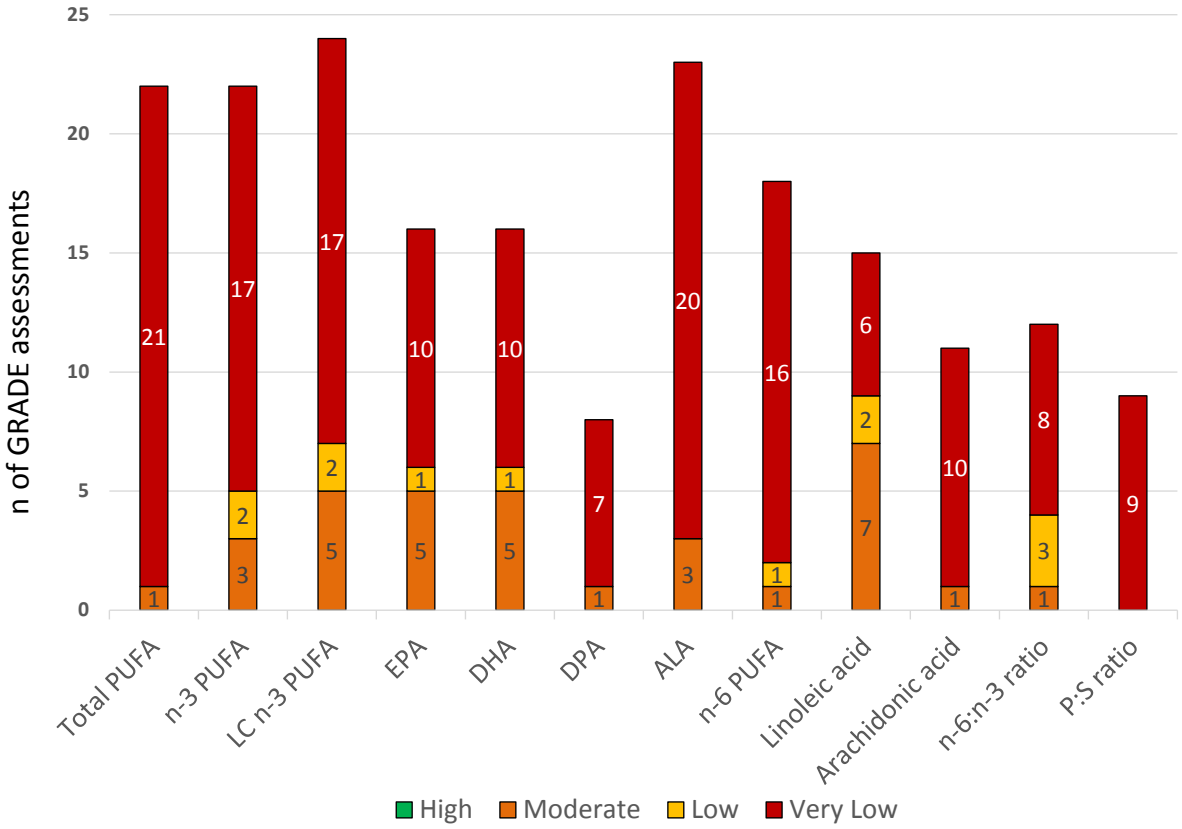
CAD: coronary artery disease; CI: confidence interval; CVD: cardiovascular disease; df: degrees of freedom; IV: inverse variance; M: male; RR: risk ratio; SE: standard error; W: women.

Fig. 82. Pooled most-adjusted RR of long-chain *n*-3 fatty acids in secondary prevention (*n*=2 studies)



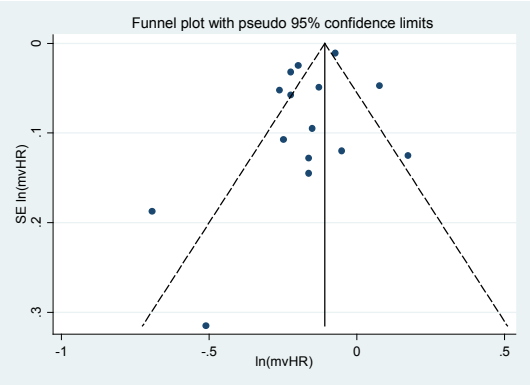
CI: confidence interval; df: degrees of freedom; IV: inverse variance; MI: myocardial infarction; PUFA: polyunsaturated fatty acids; RR: risk ratio; SE: standard error.

Fig. 83. Summary of GRADE assessments of confidence in the body of evidence for each fatty acid (or class of fatty acids) and health outcomes



ALA: alpha-linolenic acid; DHA: docosahexaenoic acid; DPA: docosapentaenoic acid; EPA: eicosapentaenoic acid; GRADE: Grading of Recommendations Assessment, Development, and Evaluation; LC: long-chain; n: number; P:S: Polyunsaturated: Saturated Fat Ratio; PUFA: polyunsaturated fatty acids.

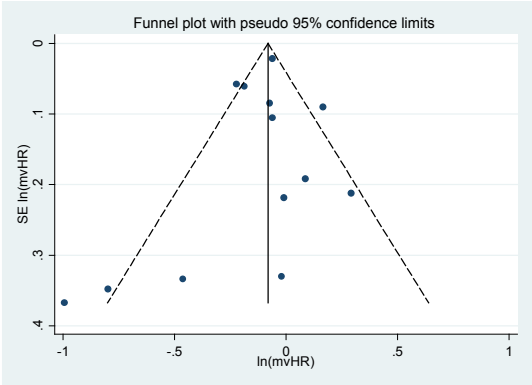
Fig. 84a. Publication bias plots for comparisons with 10 or more studies; Panel A – total PUFA and all-cause mortality



Egger's test: *P*=0.173; Begg's test: *P*=0.843. Trim-and-fill identified no "missed" studies. No publication bias suspected.

mvHR: multivariable hazard ratio; PUFA: polyunsaturated fatty acids; SE: standard error.

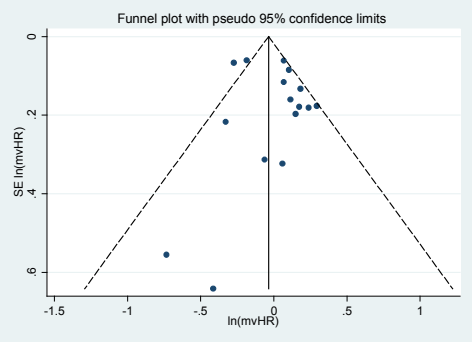
Fig. 84b. Publication bias plots for comparisons with 10 or more studies; Panel B – total PUFA and CVD mortality



Egger's test: *P*=0.529; Begg's test: *P*=0.428. Trim-and-fill identified no "missed" studies. No publication bias suspected.

CVD: cardiovascular disease; mvHR: multivariable hazard ratio; PUFA: polyunsaturated fatty acids; SE: standard error.

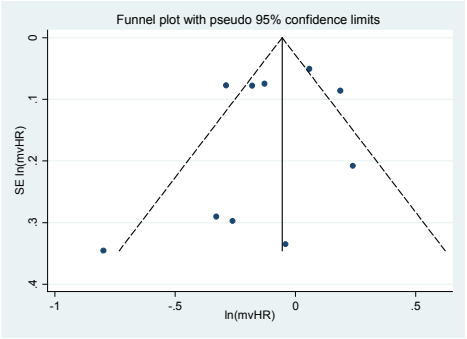
Fig. 84c. Publication bias plots for comparisons with 10 or more studies; Panel C – total PUFA and total CHD



Egger's test: *P*=0.380; Begg's test: *P*=0.224. Trim-and-fill identified no "missed" studies. No publication bias suspected.

CHD: coronary heart disease; mvHR: multivariable hazard ratio; PUFA: polyunsaturated fatty acids; SE: standard error.

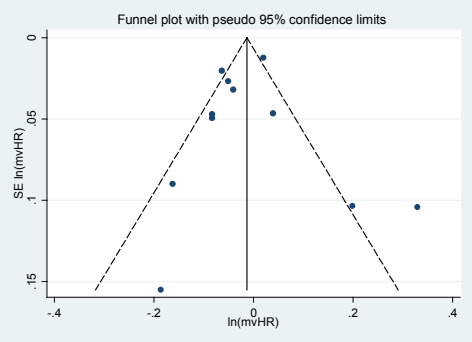
Fig. 84d. Publication bias plots for comparisons with 10 or more studies; Panel D – total PUFA and type 2 diabetes



Egger's test: *P*=0.424; Begg's test: *P*=0.858. Trim-and-fill identified no "missed" studies. No publication bias suspected.

mvHR: multivariable hazard ratio; PUFA: polyunsaturated fatty acids; SE: standard error.

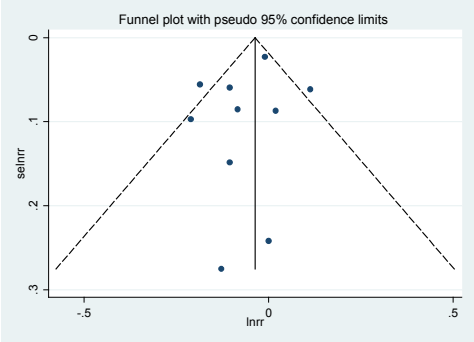
Fig. 84e. Publication bias plots for comparisons with 10 or more studies; Panel E – total n-3 PUFA and all-cause mortality



Egger's test: *P*=0.760; Begg's test: *P*=0.640. Trim-and-fill identified no "missed" studies. No publication bias suspected.

mvHR: multivariable hazard ratio; PUFA: polyunsaturated fatty acids; SE: standard error.

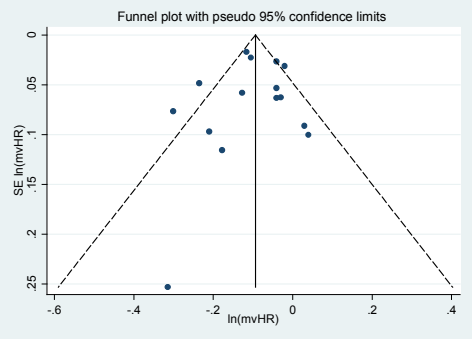
Fig. 84f. Publication bias plots for comparisons with 10 or more studies; Panel F – total n-3 PUFA and CVD mortality



Egger's test: *P*=0.392; Begg's test: *P*=0.858. Trim-and-fill identified no "missed" studies. No publication bias suspected.

CVD: cardiovascular disease; PUFA: polyunsaturated fatty acids; rr: risk ratio; se: standard error.

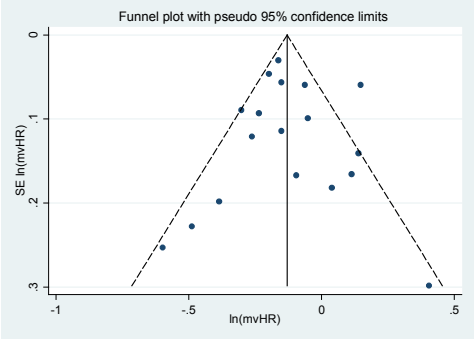
Fig. 84g. Publication bias plots for comparisons with 10 or more studies; Panel G – long-chain n-3 PUFA and all-cause mortality



Egger's test: *P*=0.801; Begg's test: *P*=0.767. Trim-and-fill identified no "missed" studies. No publication bias suspected.

mvHR: multivariable hazard ratio; PUFA: polyunsaturated fatty acids; SE: standard error.

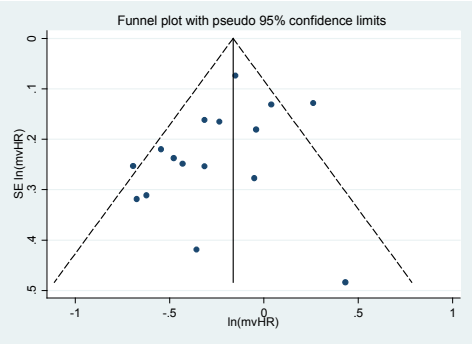
Fig. 84h. Publication bias plots for comparisons with 10 or more studies; Panel H – long-chain n-3 PUFA and CVD mortality



Egger's test: *P*=0.841; Begg's test: *P*=0.762. Trim-and-fill identified no "missed" studies. No publication bias suspected.

CVD: cardiovascular disease; mvHR: multivariable hazard ratio; PUFA: polyunsaturated fatty acids; SE: standard error.

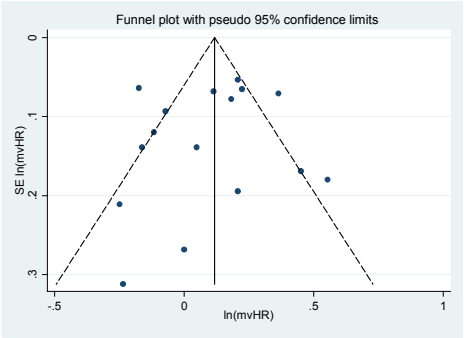
Fig. 84i. Publication bias plots for comparisons with 10 or more studies; Panel I – long-chain n-3 PUFA and CHD mortality



Egger's test: *P*=0.112; Begg's test: *P*=0.260. Trim-and-fill identified no "missed" studies. No publication bias suspected.

CHD: coronary heart disease; mvHR: multivariable hazard ratio; PUFA: polyunsaturated fatty acids; SE: standard error.

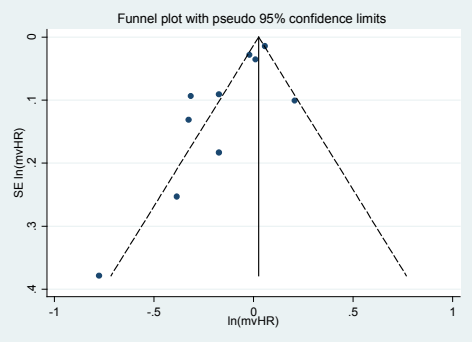
Fig. 84j. Publication bias plots for comparisons with 10 or more studies; Panel J – long-chain n-3 PUFA and type 2 diabetes



Egger's test: *P*=0.604; Begg's test: *P*=0.753. Trim-and-fill identified no "missed" studies. No publication bias suspected.

mvHR: multivariable hazard ratio; PUFA: polyunsaturated fatty acids; SE: standard error.

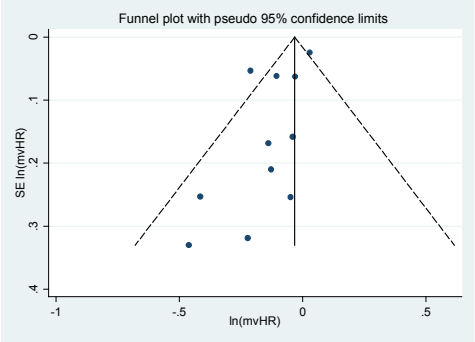
Fig. 84k. Publication bias plots for comparisons with 10 or more studies; Panel K – ALA and all-cause mortality



Egger's test: *P*=0.014; Begg's test: *P*=0.371. Trim-and-fill identified no "missed" studies. No publication bias suspected.

ALA: alpha-linolenic acid; mvHR: multivariable hazard ratio; SE: standard error.

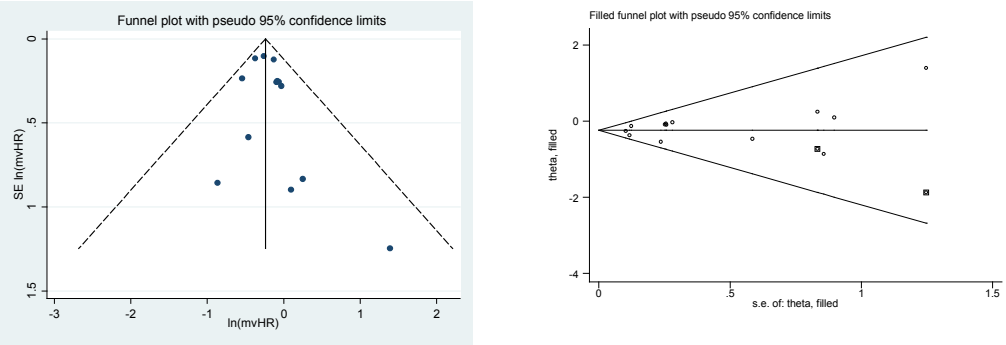
Fig. 84l. Publication bias plots for comparisons with 10 or more studies; Panel L – ALA and CVD mortality



Egger's test: *P*=0.055; Begg's test: *P*=0.436. Trim-and-fill identified no "missed" studies. No publication bias suspected.

ALA: alpha-linolenic acid; CVD: cardiovascular disease; mvHR: multivariable hazard ratio; SE: standard error.

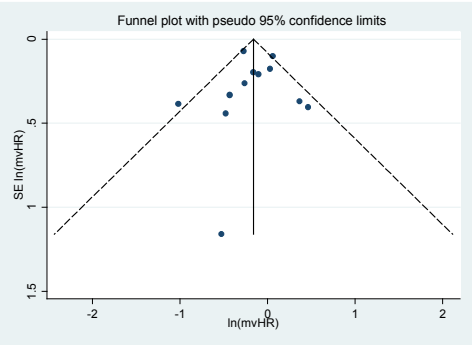
Fig. 84m. Publication bias plots for comparisons with 10 or more studies; Panel M – LA and CHD mortality



Egger's test: *P*=0.302; Begg's test: *P*=0.583. Trim-and-fill identified 2 "missed" studies. "Filled" RR=0.79 (95% CI: 0.70 to 0.88). =pseudostudy.

CHD: coronary heart disease; CI: confidence interval; LA: linoleic acid; mvHR: multivariable hazard ratio; RR: risk ratio; s.e.: standard error; SE: standard error.

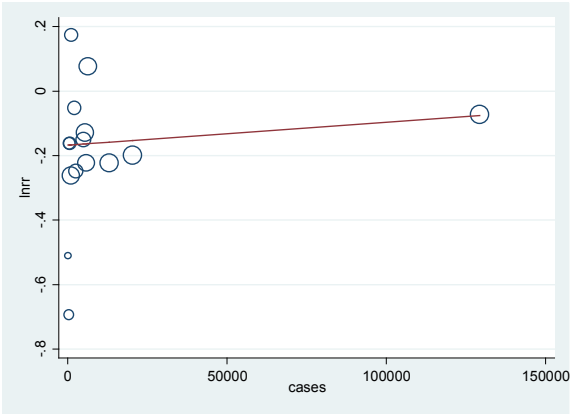
Fig. 84n. Publication bias plots for comparisons with 10 or more studies; Panel N – LA and total CHD



Egger's test: *P*=0.901; Begg's test: *P*=0.669. Trim-and-fill identified no "missed" studies. No publication bias suspected.

CHD: coronary heart disease; LA: linoleic acid; mvHR: multivariable hazard ratio; SE: standard error.

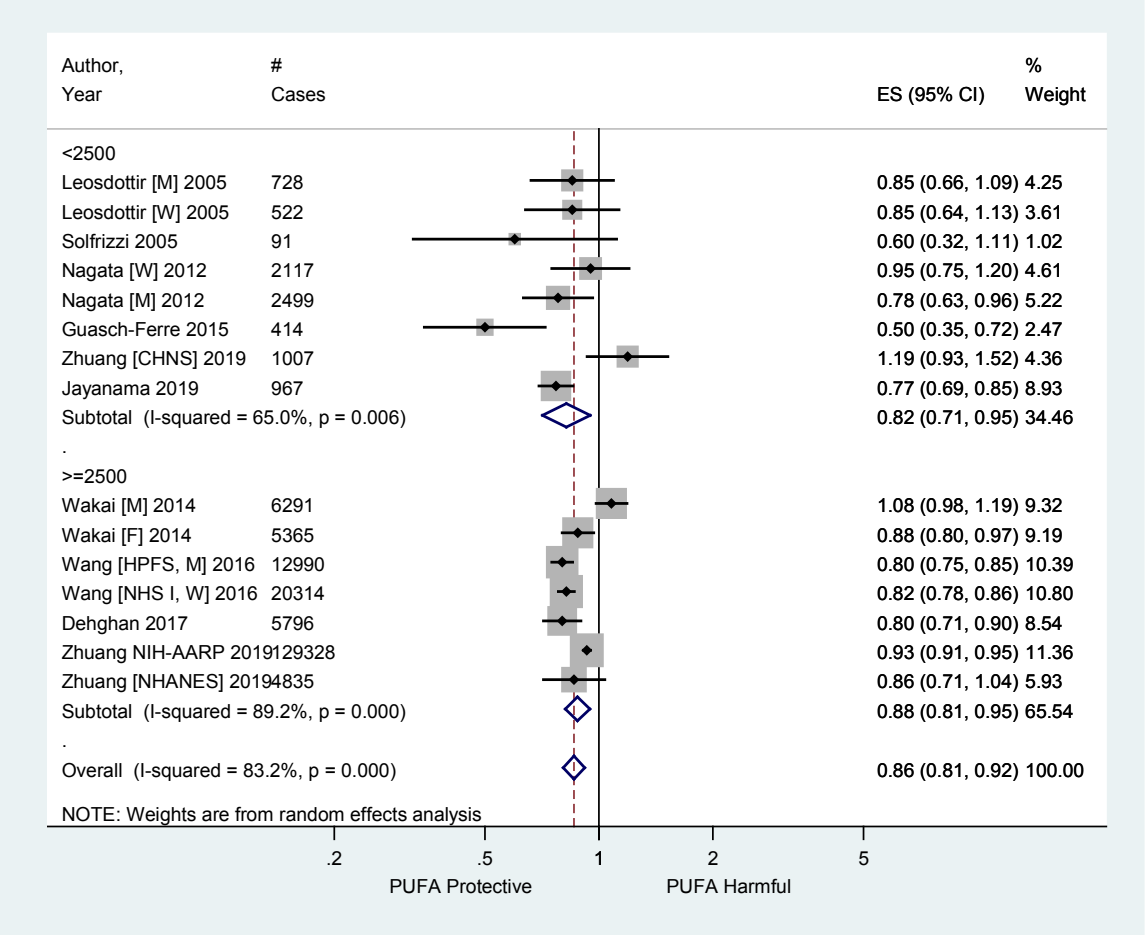
Fig. 85a. Metaregression of total PUFA and all-cause mortality; number of cases; Panel A – effect size



The number of cases in the study was not associated with the effect estimate (*P*=0.63).

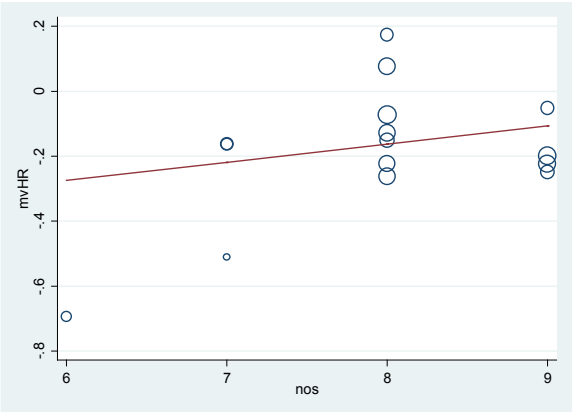
CI: confidence interval; mvRR: multivariable risk ratio; PUFA: polyunsaturated fatty acids; rr: risk ratio.

Fig. 85b. Metaregression of total PUFA and all-cause mortality; number of cases; Panel B – subgroup analysis by number of cases (median=2500)



#: number; CHNS: China Health and Nutrition Survey; CI: confidence interval; ES: effect size; F: female; HPFS: Health Professionals Follow-up Study; M: male; NHANES: National Health and Nutrition Examination Survey; NHS I: Nurses' Health Study I; NIH-AARP: National Institutes of Health American Association of Retired Persons Diet and Health Study; PUFA: polyunsaturated fatty acids; W: women.

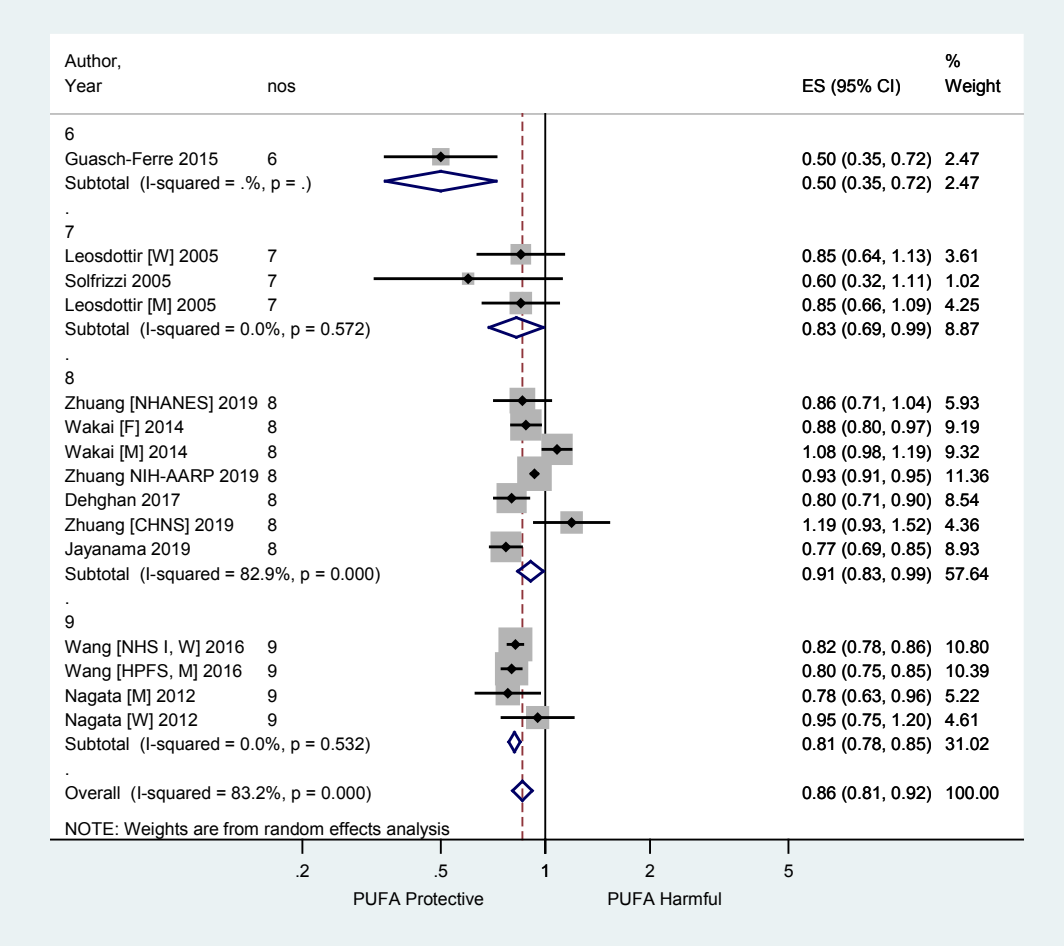
Fig. 85c. Meta-regression of total PUFA and all-cause mortality; NOS assessment; Panel A – effect size



The effect size was not associated with adjustment for NOS assessment in the final model (*P*=0.36).

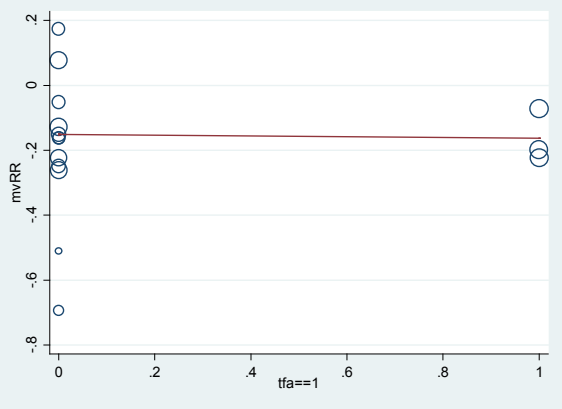
mvHR: multivariable hazard ratio; nos: Newcastle-Ottawa Scale; NOS: Newcastle-Ottawa Scale; PUFA: polyunsaturated fatty acids.

Fig. 85d. Meta-regression of total PUFA and all-cause mortality; NOS assessment; Panel B – subgroup analysis by NOS score



CHNS: China Health and Nutrition Survey; CI: confidence interval; ES: effect size; F: female; HPFS: Health Professionals Follow-up Study; M: male; NHANES: National Health and Nutrition Examination Survey; NHS I: Nurses' Health Study I; NIH-AARP: National Institutes of Health American Association of Retired Persons Diet and Health Study; nos: Newcastle-Ottawa Scale; NOS: Newcastle-Ottawa Scale; PUFA: polyunsaturated fatty acids; W: women.

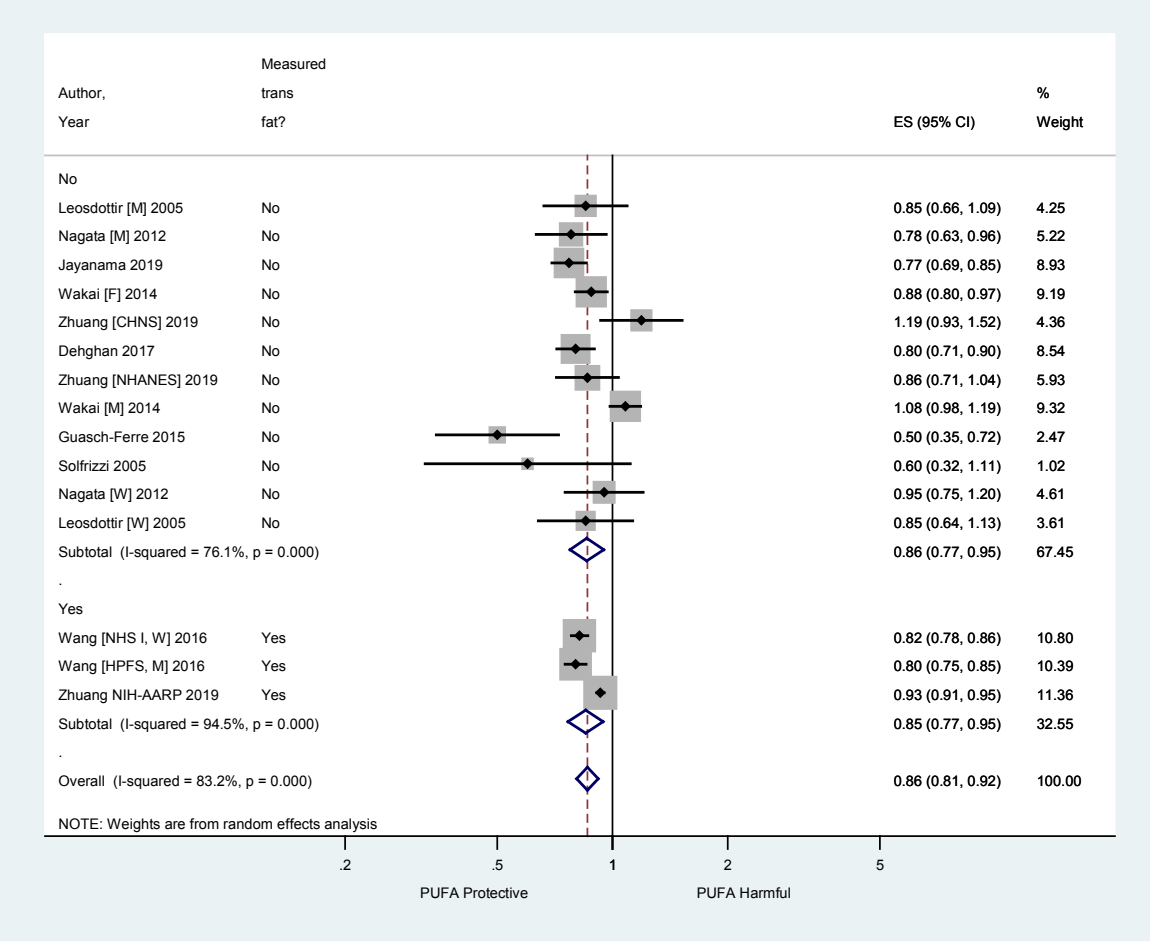
Fig. 85e. Meta-regression of total PUFA and all-cause mortality by measurement of TFA; Panel A – effect size



The effect size was not associated with adjustment for diet assessment method in the final model (*P*=0.90).

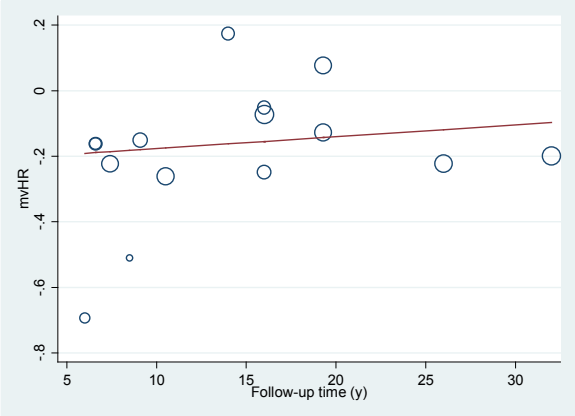
PUFA: polyunsaturated fatty acids; TFA: trans-fatty acids.

Fig. 85f. Meta-regression of total PUFA and all-cause mortality; TFA assessment; Panel B – subgroup analysis (yes/no)



CHNS: China Health and Nutrition Survey; CI: confidence interval; ES: effect size;F: female; HPFS: Health Professionals Follow-up Study; M: male; NHANES: National Health and Nutrition Examination Survey; NHS I: Nurses' Health Study I; NIH-AARP: National Institutes of Health American Association of Retired Persons Diet and Health Study; PUFA: polyunsaturated fatty acids; TFA: trans-fatty acids; W: women.

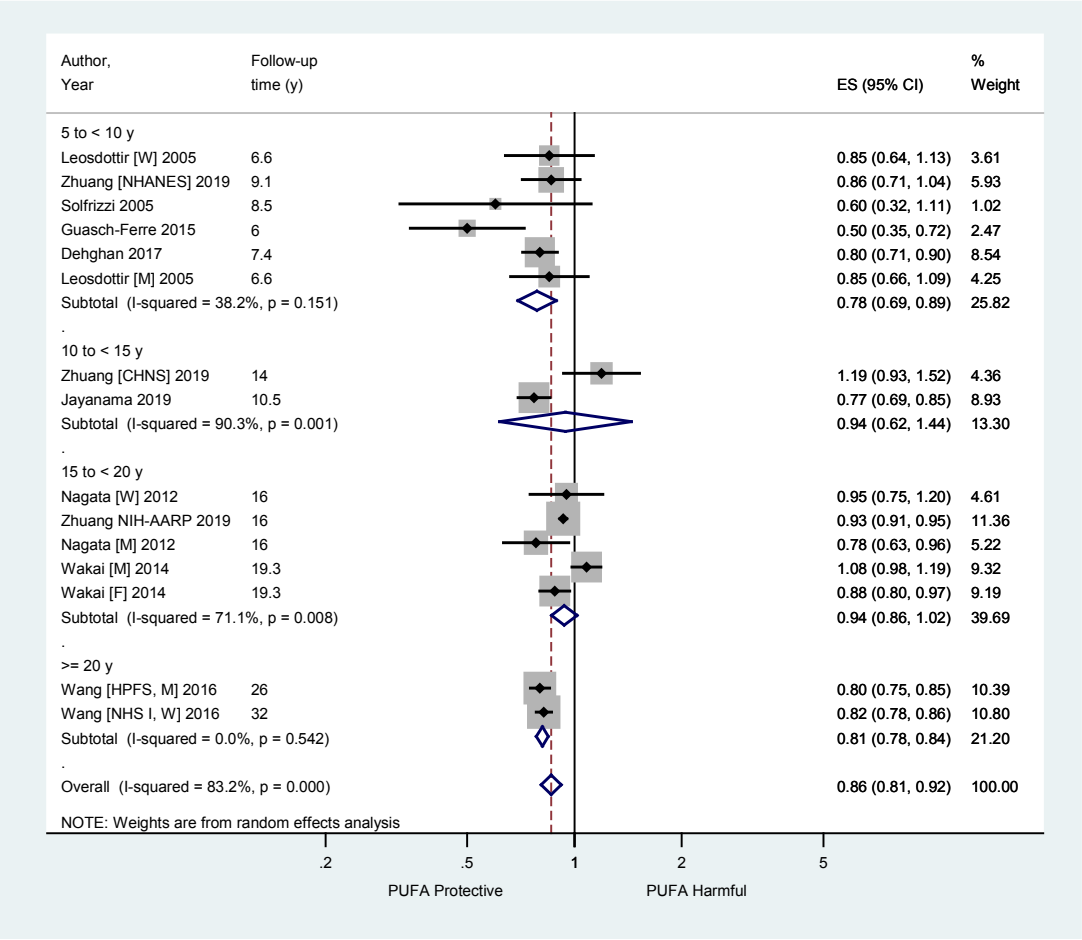
Fig. 85g. Meta-regression of total PUFA and all-cause mortality; follow-up time; Panel A – effect size



The effect size was not associated with adjustment for follow-up time in the final model (*P*=0.53).

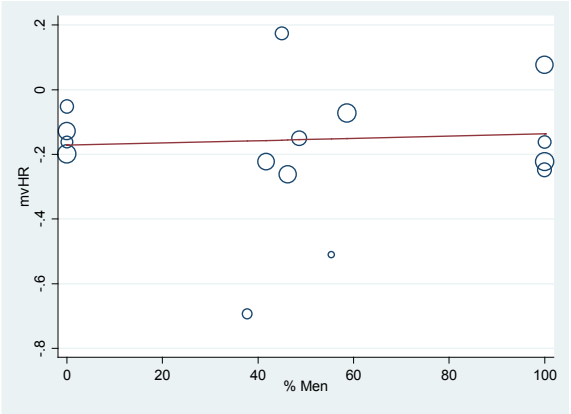
mvHR: multivariable hazard ratio; PUFA: polyunsaturated fatty acids; y: years.

Fig. 85h. Meta-regression of total PUFA and all-cause mortality; follow-up time; Panel B – subgroup analysis (yes/no)



CHNS: China Health and Nutrition Survey; CI: confidence interval; ES: effect size; F: female;HPFS: Health Professionals Follow-up Study; M: male; NHANES: National Health and Nutrition Examination Survey; NHS I: Nurses' Health Study I; NIH-AARP: National Institutes of Health American Association of Retired Persons Diet and Health Study; PUFA: polyunsaturated fatty acids; W: women; y: years.

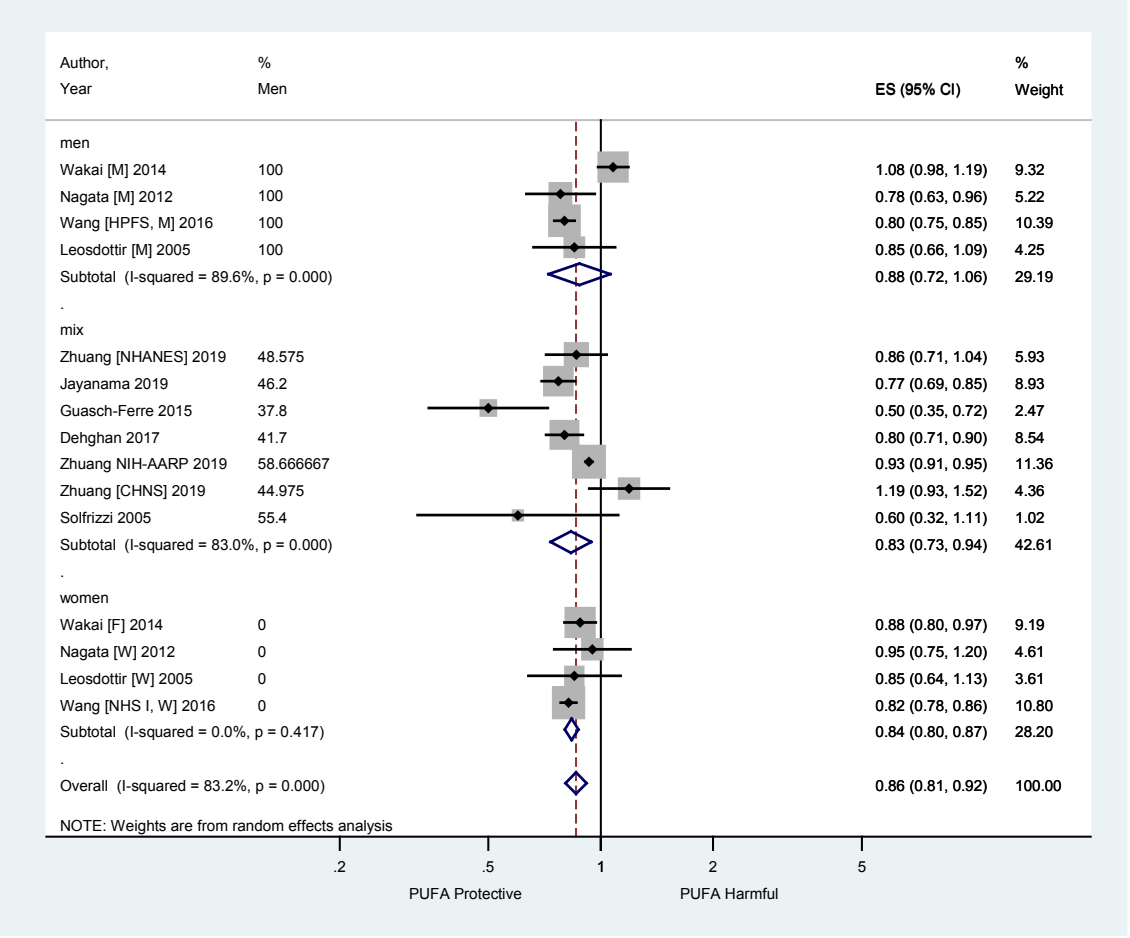
Fig. 85i. Meta-regression of total PUFA and all-cause mortality; sex; Panel A – effect size



The effect size was not associated with adjustment for the percentage of men in the study in the final model (*P*=0.76).

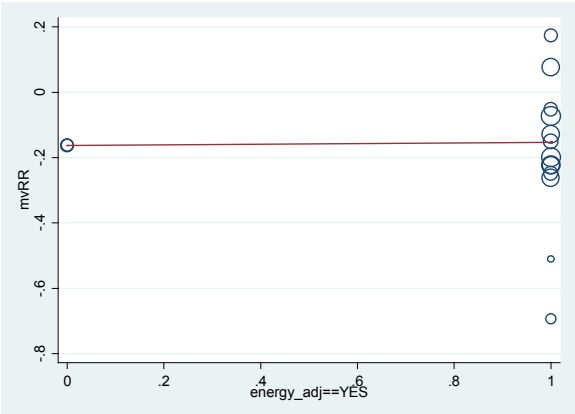
mvHR: multivariable hazard ratio; PUFA: polyunsaturated fatty acids.

Fig. 85j. Meta-regression of total PUFA and all-cause mortality; sex; Panel B – subgroup analysis (by sex of study participants)



CHNS: China Health and Nutrition Survey; CI: confidence interval; ES: effect size; F: female; HPFS: Health Professionals Follow-up Study; M: male; NHANES: National Health and Nutrition Examination Survey; NHS I: Nurses' Health Study I; NIH-AARP: National Institutes of Health American Association of Retired Persons Diet and Health Study; PUFA: polyunsaturated fatty acids; W: women.

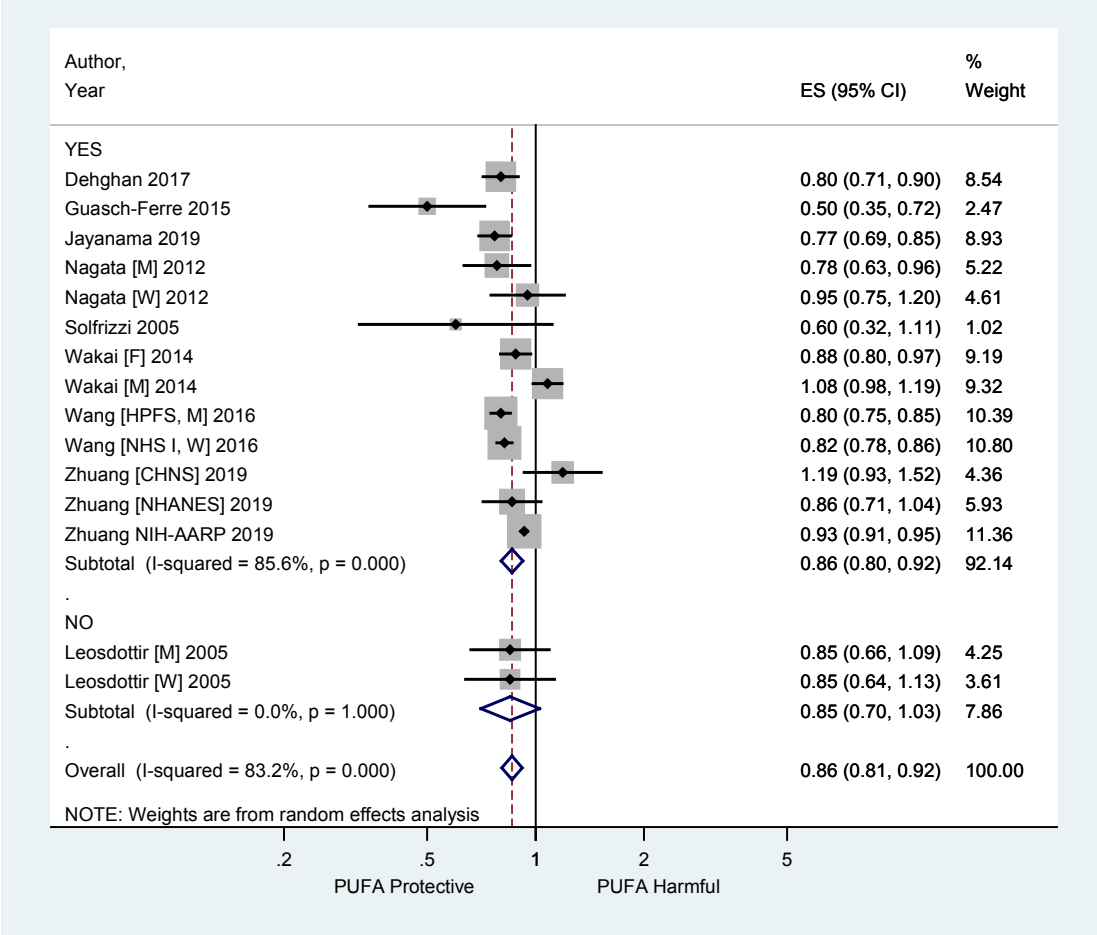
Fig. 85k. Meta-regression of total PUFA and all-cause mortality; energy adjustment; Panel A – effect size



The effect size was not associated with adjustment for energy in the final model (*P*=0.95).

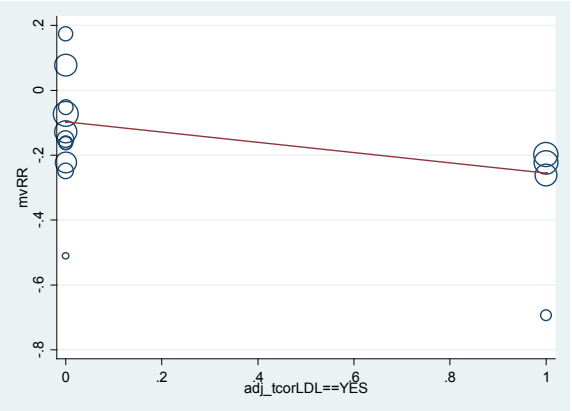
PUFA: polyunsaturated fatty acids.

Fig. 85l. Meta-regression of total PUFA and all-cause mortality; energy adjustment; Panel B – subgroup analysis (yes/no)



CHNS: China Health and Nutrition Survey; CI: confidence interval; ES: effect size; F: female; HPFS: Health Professionals Follow-up Study; M: male; NHANES: National Health and Nutrition Examination Survey; NHS I: Nurses' Health Study I; NIH-AARP: National Institutes of Health American Association of Retired Persons Diet and Health Study; PUFA: polyunsaturated fatty acids; W: women.

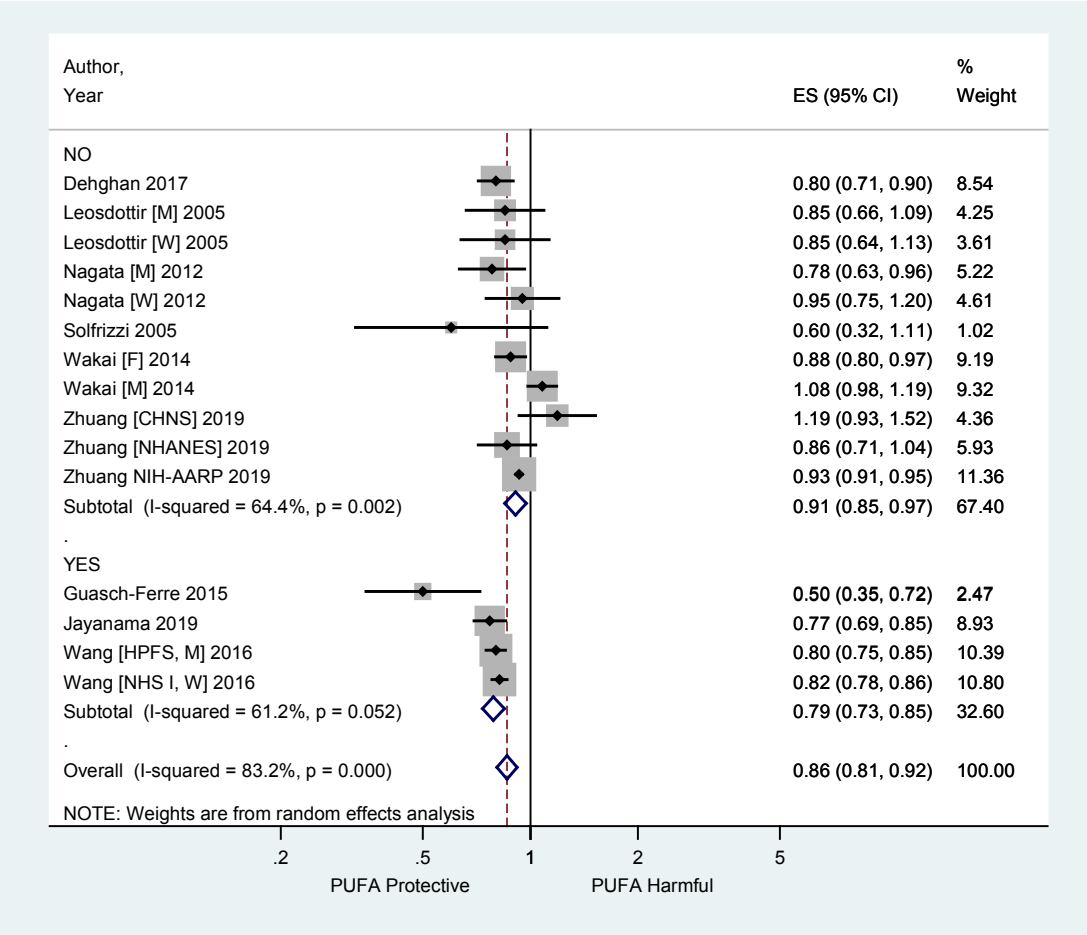
Fig. 85m. Meta-regression of total PUFA and all-cause mortality; dyslipidaemia adjustment; Panel A – effect size



The effect size was associated with adjustment for a measure of dyslipidaemia in the final model (*P*=0.047).

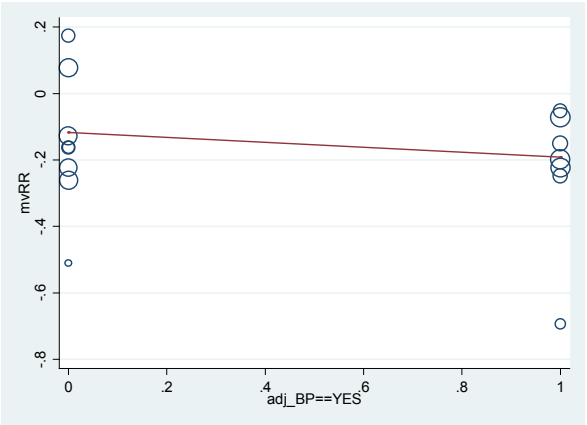
PUFA: polyunsaturated fatty acids.

Fig. 85n. Meta-regression of total PUFA and all-cause mortality; dyslipidaemia adjustment; Panel B – subgroup analysis (yes/no)



CHNS: China Health and Nutrition Survey; CI: confidence interval; ES: effect size; F: female; HPFS: Health Professionals Follow-up Study; M: male; NHANES: National Health and Nutrition Examination Survey; NHS I: Nurses' Health Study I; NIH-AARP: National Institutes of Health American Association of Retired Persons Diet and Health Study; PUFA: polyunsaturated fatty acids; W: women.

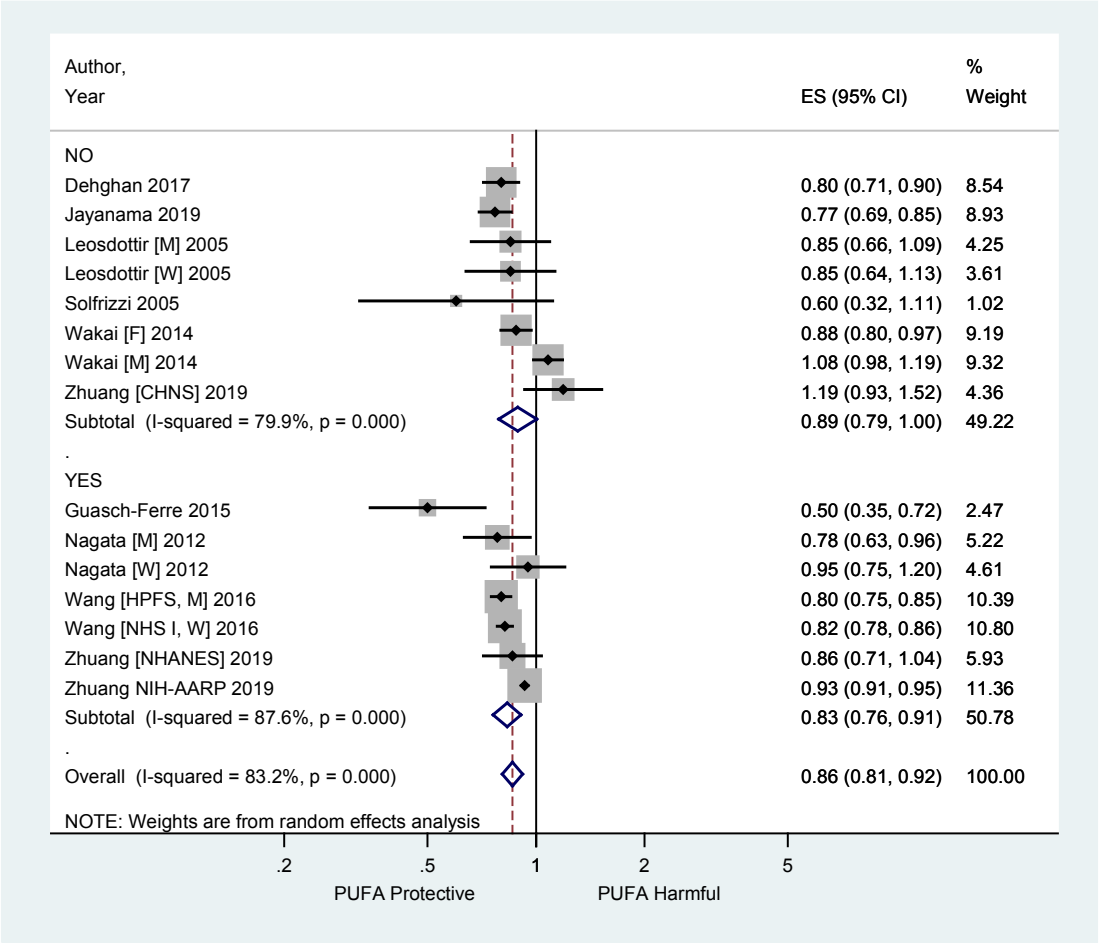
Fig. 85o. Meta-regression of total PUFA and all-cause mortality; blood pressure adjustment; Panel A – effect size



The effect size was not associated with adjustment for a measure of blood pressure in the final model (*P*=0.39).

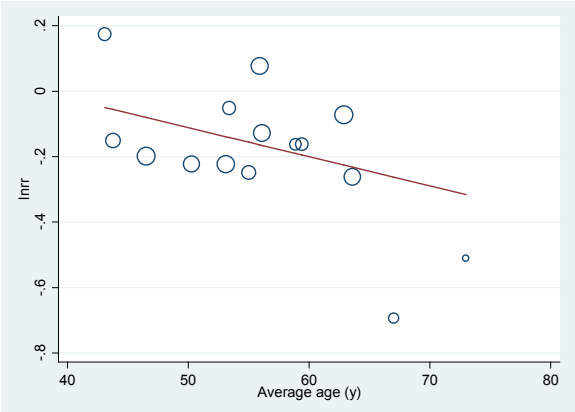
PUFA: polyunsaturated fatty acids.

Fig. 85p. Meta-regression of total PUFA and all-cause mortality; blood pressure adjustment; Panel B – subgroup analysis (yes/no)



CHNS: China Health and Nutrition Survey; CI: confidence interval; ES: effect size; F: female; HPFS: Health Professionals Follow-up Study; M: male; NHANES: National Health and Nutrition Examination Survey; NHS I: Nurses' Health Study I; NIH-AARP: National Institutes of Health American Association of Retired Persons Diet and Health Study; PUFA: polyunsaturated fatty acids; W: women.

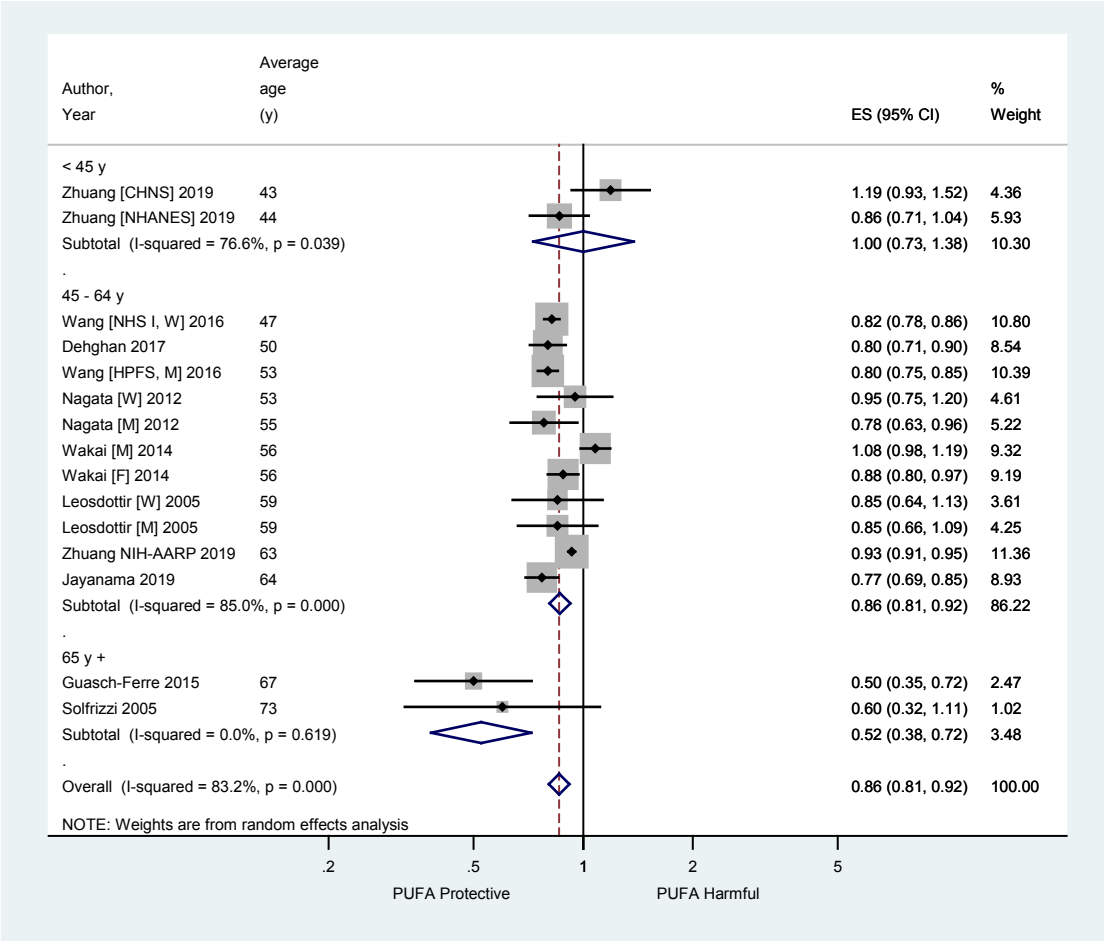
Fig. 85q. Meta-regression of total PUFA and all-cause mortality; age; Panel A – effect size



The effect size was not associated with adjustment for average age of the study sample in the final model (P=0.15).

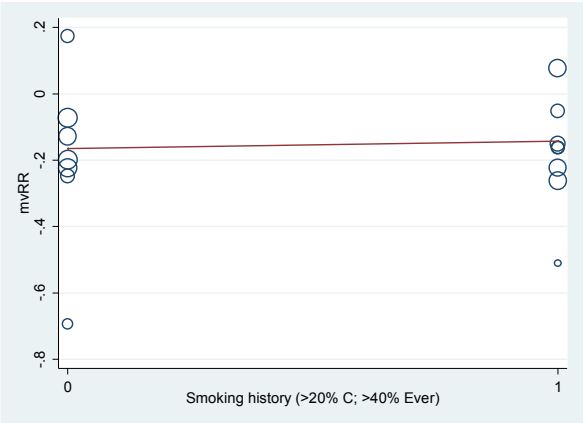
PUFA: polyunsaturated fatty acids; rr: risk ratio; y: years.

Fig. 85r. Meta-regression of total PUFA and all-cause mortality; age; Panel B – subgroup analysis (age group)



CHNS: China Health and Nutrition Survey; CI: confidence interval; ES: effect size; F: female; HPFS: Health Professionals Follow-up Study; M: male; NHANES: National Health and Nutrition Examination Survey; NHS I: Nurses' Health Study I; NIH-AARP: National Institutes of Health American Association of Retired Persons Diet and Health Study; PUFA: polyunsaturated fatty acids; W: women; y: years.

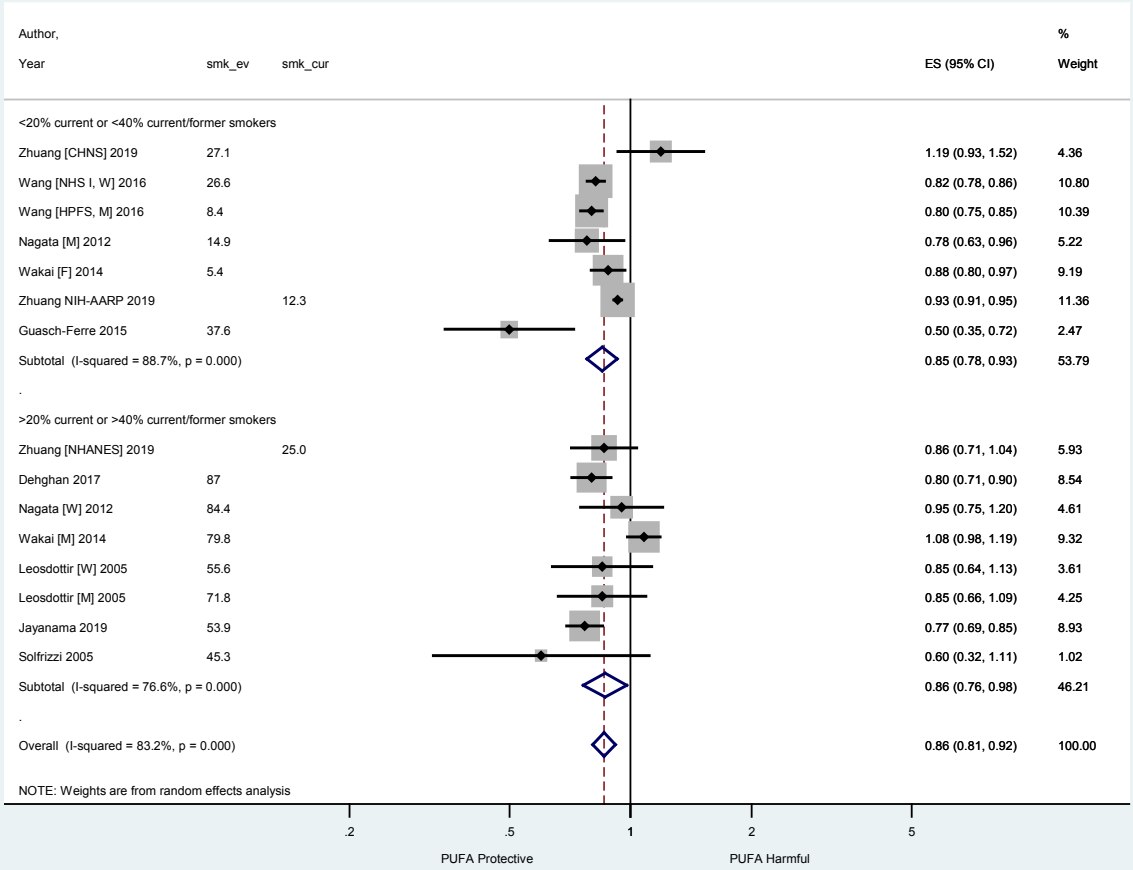
Fig. 85s. Meta-regression of total PUFA and all-cause mortality; smoking; Panel A – effect size



The effect size was not associated with adjustment for smoking history of the study sample in the final model (*P*=0.80). High smokers ≥40% current/former or >20% current.

PUFA: polyunsaturated fatty acids.

Fig. 85t. Meta-regression of total PUFA and all-cause mortality; smoking; Panel B – subgroup analysis (by smoking status)



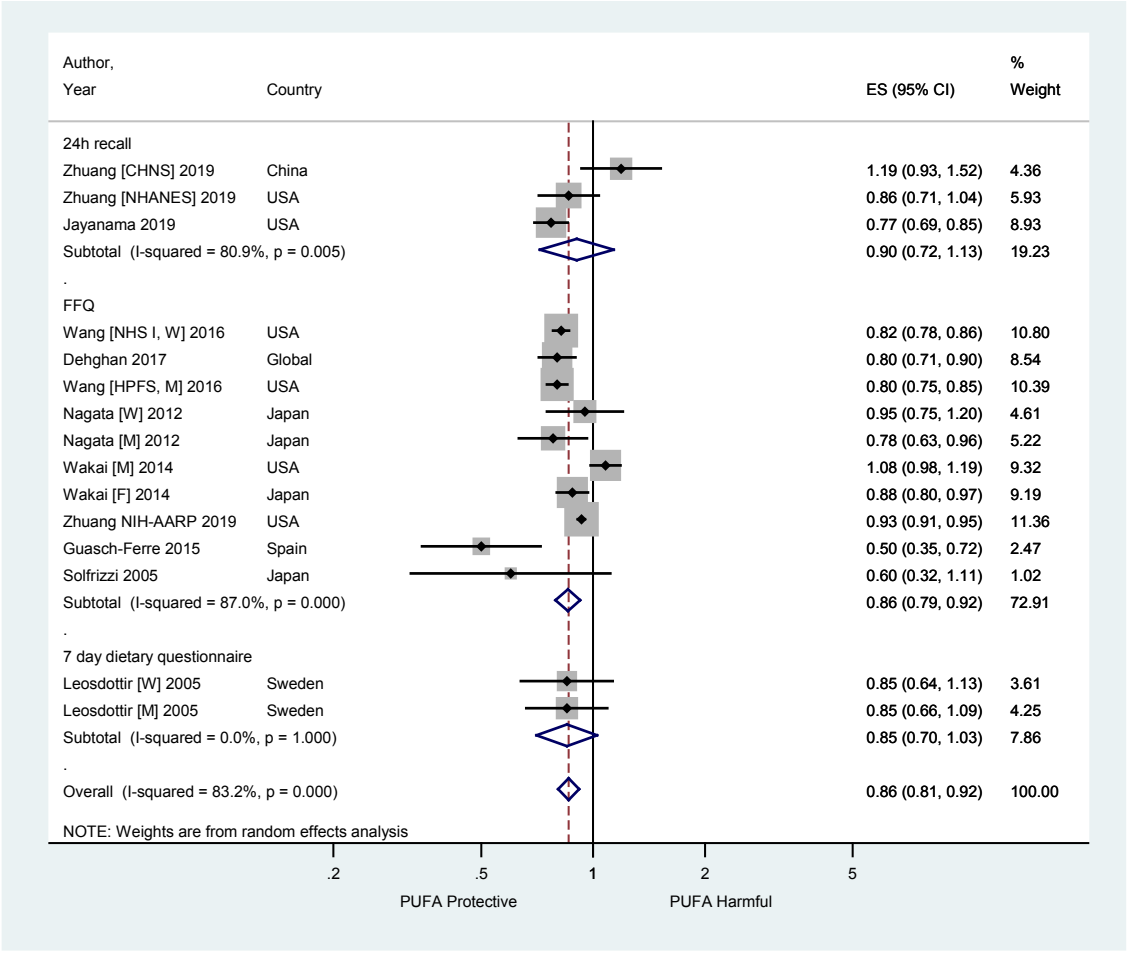
CHNS: China Health and Nutrition Survey; CI: confidence interval; ES: effect size; F: female; HPFS: Health Professionals Follow-up Study; M: male; NHANES: National Health and Nutrition Examination Survey; NHS I: Nurses' Health Study I; NIH-AARP: National Institutes of Health American Association of Retired Persons Diet and Health Study; PUFA: polyunsaturated fatty acids; smk_cur: current smokers; smk_ev: ever smoked; W: women.

Fig. 85u. Meta-regression of total PUFA and all-cause mortality; diet assessment method; Panel A – effect size

The effect size was not associated with adjustment for diet assessment method in the final model (Phet=0.15). Because the predictor variable had more than 2 levels, it is not appropriate to show the continuous meta-regression line; therefore, we present the "by method" estimates separately by method in Panel B **(Fig. 85v)**.

PUFA: polyunsaturated fatty acids.

Fig. 85v. Meta-regression of total PUFA and all-cause mortality; diet assessment method; Panel B – subgroup analysis (by diet assessment method)



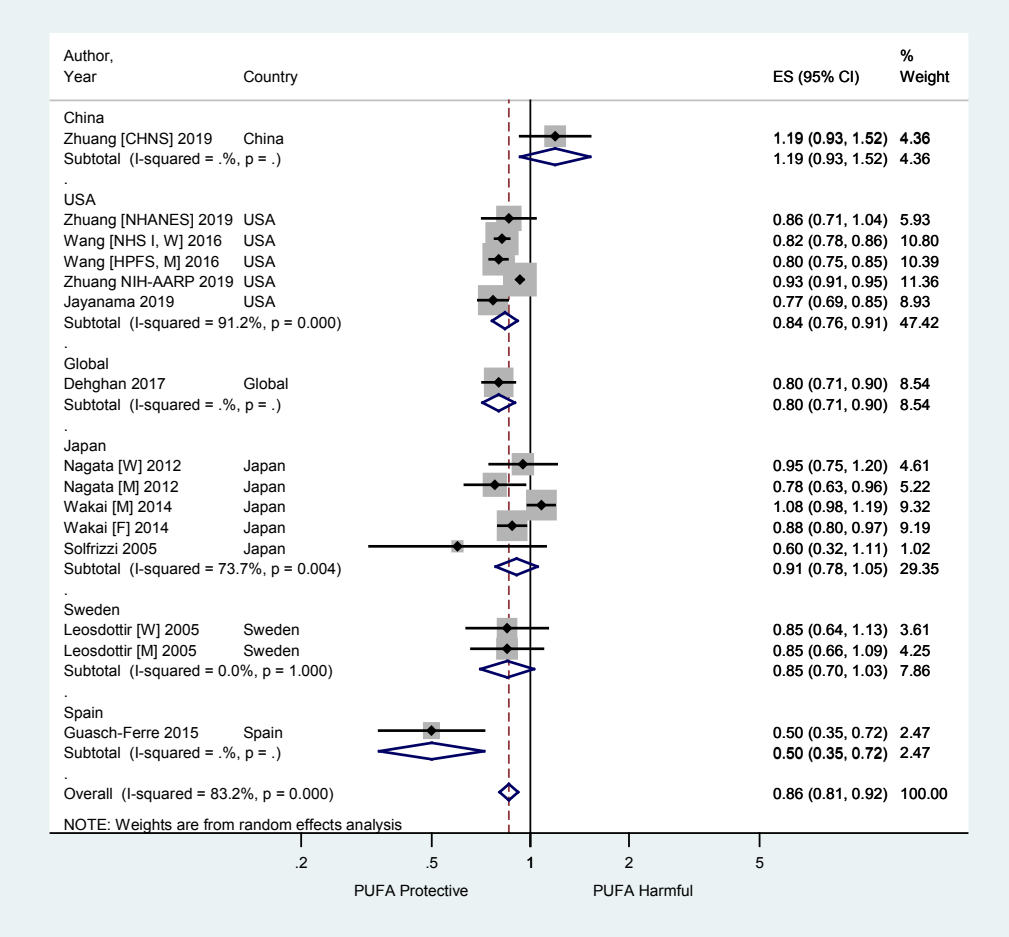
CHNS: China Health and Nutrition Survey; CI: confidence interval; ES: effect size; F: female; FFQ: food frequency questionnaire; h: hour; HPFS: Health Professionals Follow-up Study; M: male; NHANES: National Health and Nutrition Examination Survey; NHS I: Nurses' Health Study I; NIH-AARP: National Institutes of Health American Association of Retired Persons Diet and Health Study; PUFA: polyunsaturated fatty acids; USA: United States of America; W: women.

Fig. 85w. Meta-regression of total PUFA and all-cause mortality; country of conduct; Panel A – effect size

There was significant between-country heterogeneity in effect size (Phet=0.001). Because the predictor variable had more than 2 levels, it is not appropriate to show the continuous meta-regression line; therefore, we present the "by method" estimates separately by method in Panel B **(Fig. 85x)**.

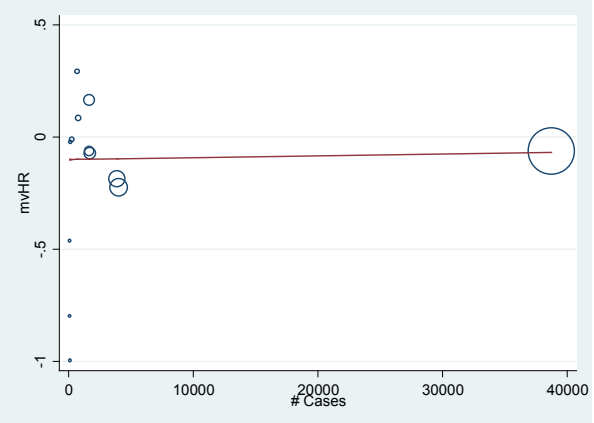
PUFA: polyunsaturated fatty acids.

Fig. 85x. Meta-regression of total PUFA and all-cause mortality; country of conduct; Panel B – subgroup analysis (by country)



CHNS: China Health and Nutrition Survey; CI: confidence interval; ES: effect size; F: female; HPFS: Health Professionals Follow-up Study; M: male; NHANES: National Health and Nutrition Examination Survey; NHS I: Nurses' Health Study I; NIH-AARP: National Institutes of Health American Association of Retired Persons Diet and Health Study; PUFA: polyunsaturated fatty acids; USA: United States of America; W: women.

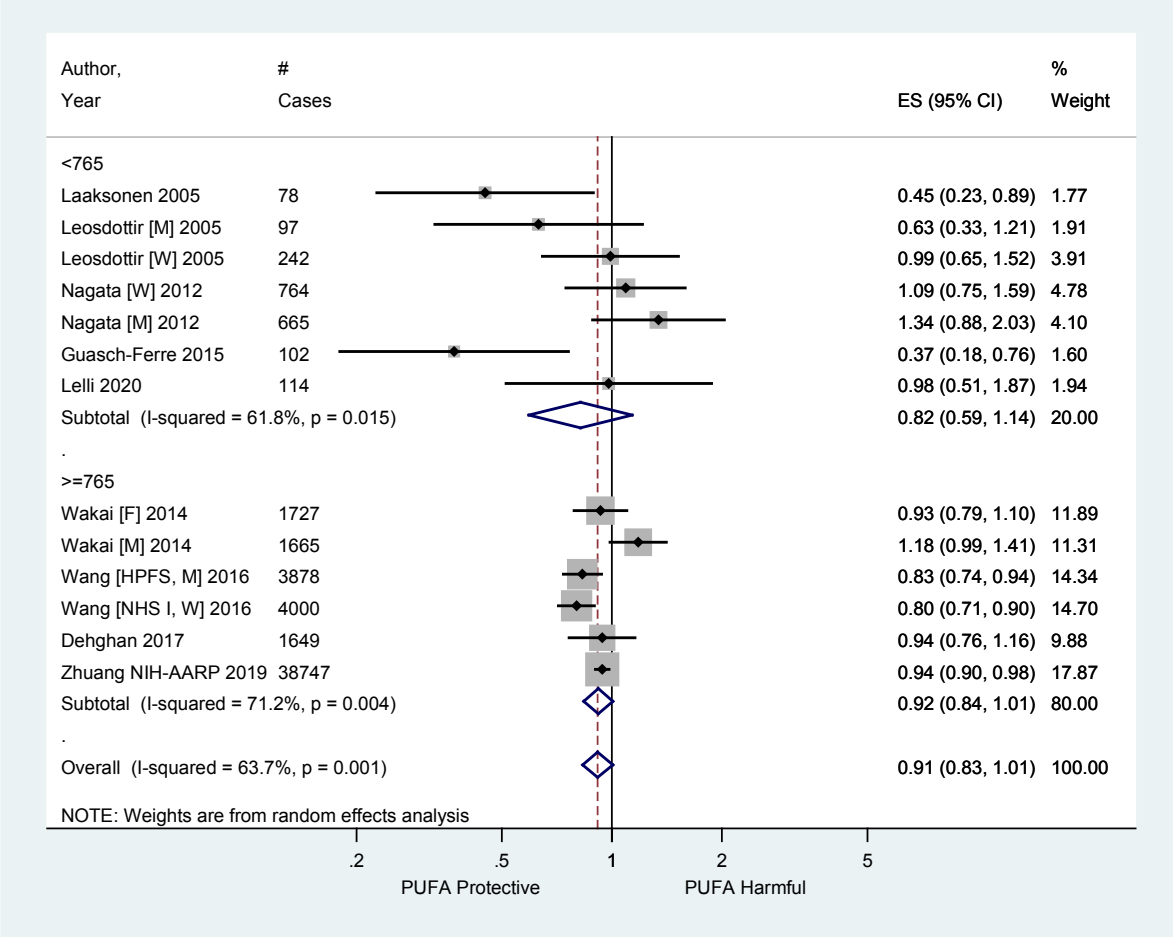
Fig. 86a. Meta-regression of total PUFA and CVD mortality; number of cases; Panel A – effect size



The number of cases in the study was not associated with the effect estimate (*P*=0.88).

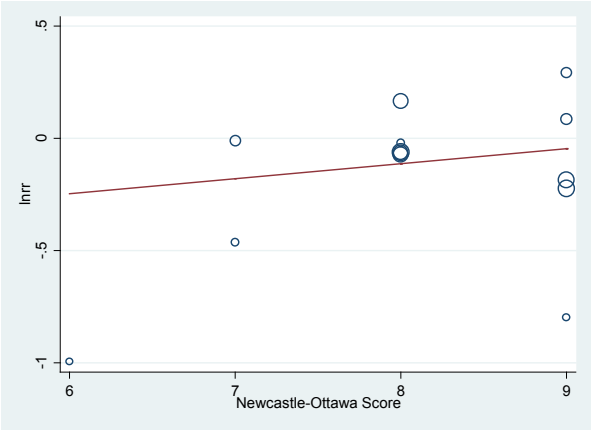
#: number; CVD: cardiovascular disease; mvHR: multivariable hazard ratio; PUFA: polyunsaturated fatty acids.

Fig. 86b. Meta-regression of total PUFA and CVD mortality; number of cases; Panel B – subgroup analysis by number of cases (median=765)



CVD: cardiovascular disease; NOS: Newcastle-Ottawa Scale; PUFA: polyunsaturated fatty acids; rr: risk ratio.

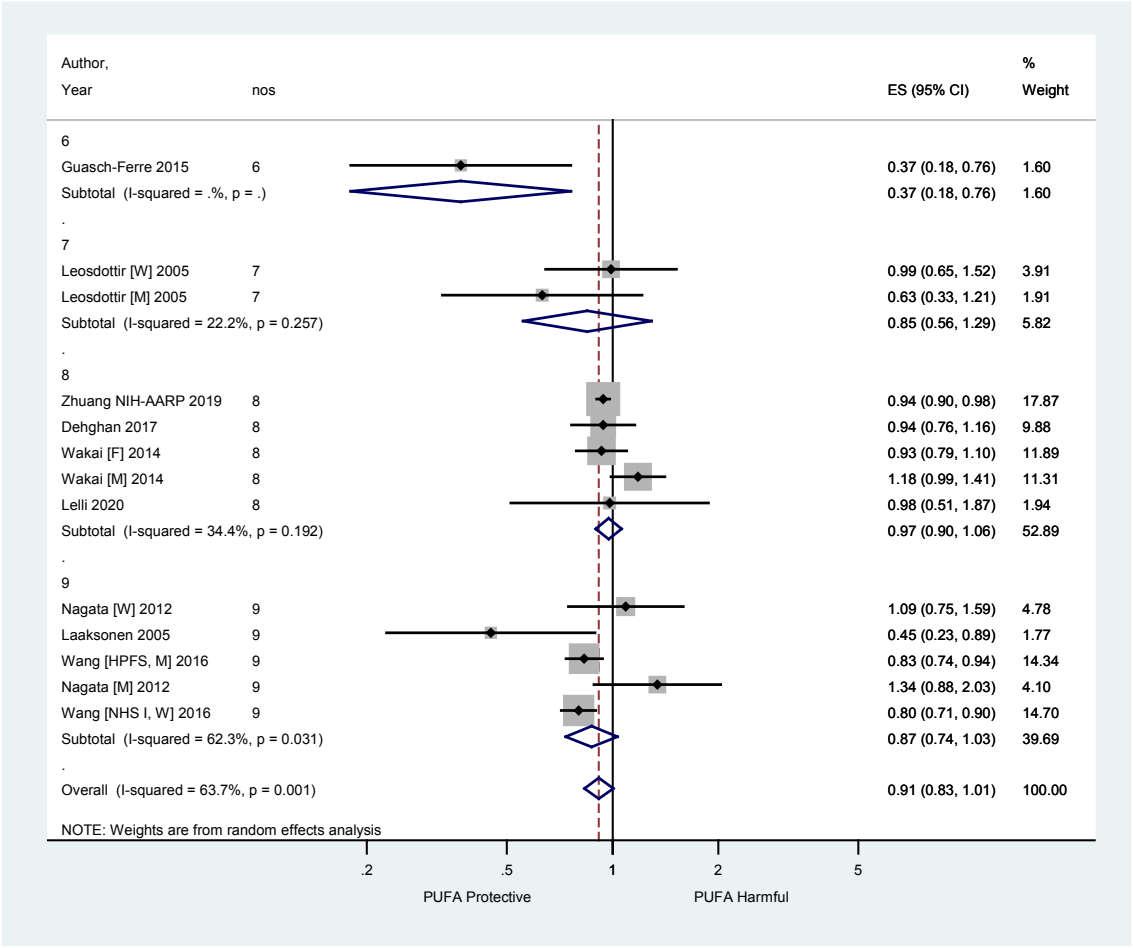
Fig. 86c. Meta-regression of total PUFA and CVD mortality; NOS assessment; Panel A – effect size



Study effect size was not associated with NOS score (P=0.52).

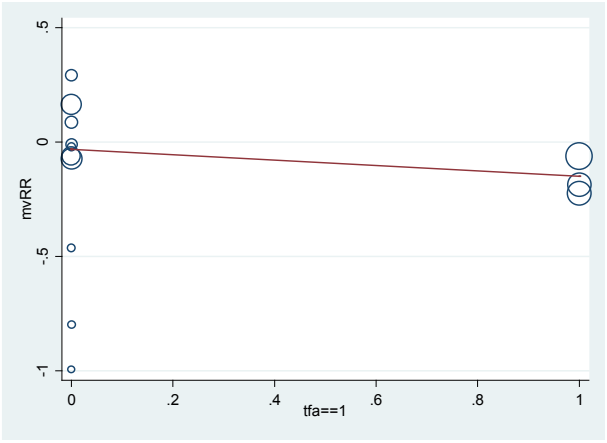
CVD: cardiovascular disease; NOS: Newcastle-Ottawa Scale; PUFA: polyunsaturated fatty acids; rr: risk ratio.

Fig. 86d. Meta-regression of total PUFA and CVD mortality; NOS assessment; Panel B – subgroup analysis by NOS score



CI: confidence interval; CVD: cardiovascular disease; ES: effect size; F: female; HPFS: Health Professionals Follow-up Study; M: male; NHS I: Nurses' Health Study I; NIH-AARP: National Institutes of Health American Association of Retired Persons Diet and Health Study; nos: Newcastle-Ottawa Scale; NOS: Newcastle-Ottawa Scale; PUFA: polyunsaturated fatty acids; W: women.

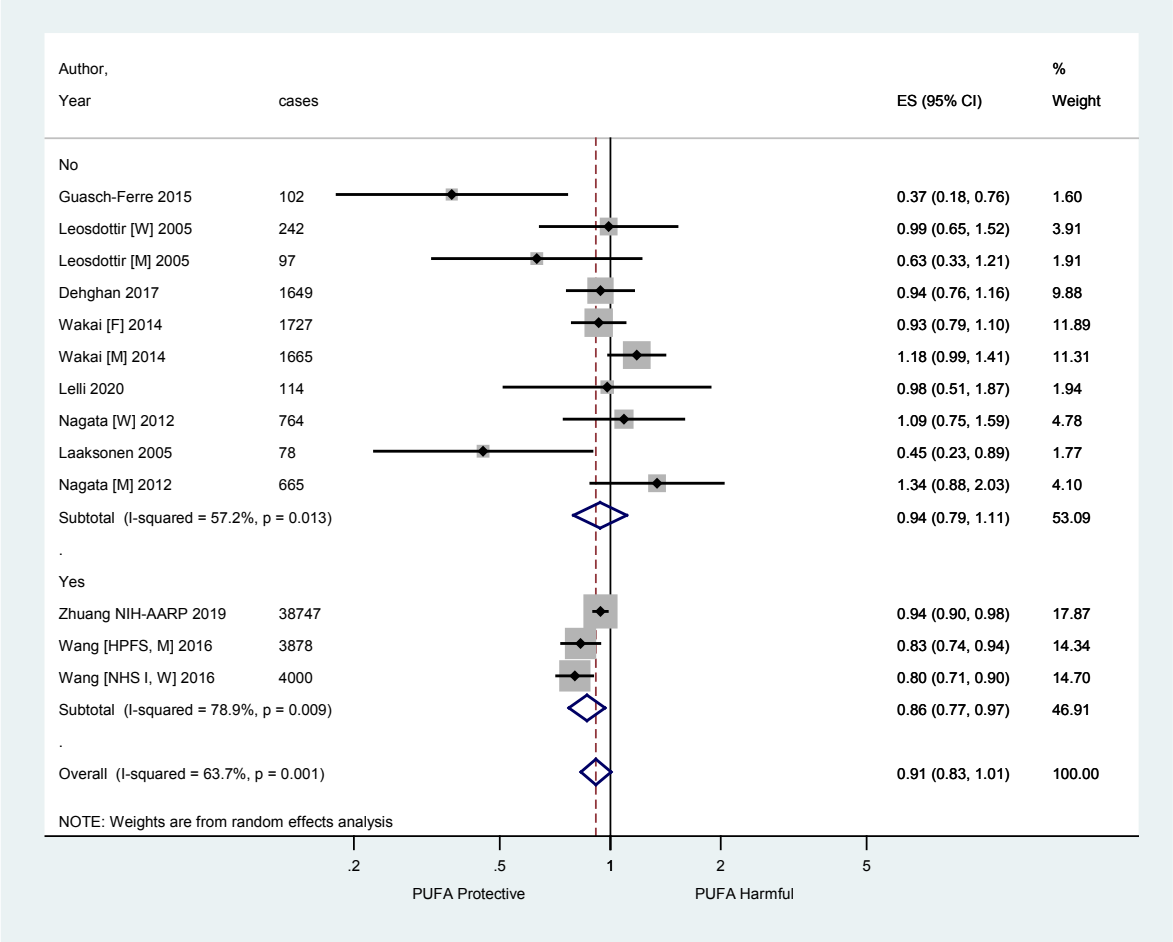
Fig. 86e. Meta-regression of total PUFA and CVD mortality; TFA assessment; Panel A – effect size



Study effect size was not associated with measurement of TFA (*P*=0.33).

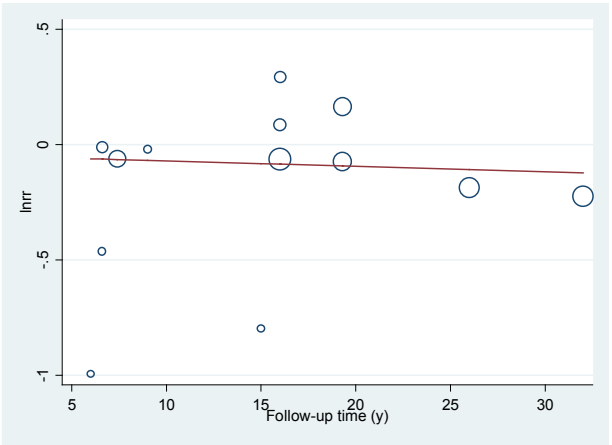
CVD: cardiovascular disease; PUFA: polyunsaturated fatty acids; TFA/tfa: trans-fatty acids.

Fig. 86f. Meta-regression of total PUFA and CVD mortality; TFA assessment; Panel B – subgroups (yes/no)



CI: confidence interval; CVD: cardiovascular disease; ES: effect size; F: female; HPFS: Health Professionals Follow-up Study; M: male; NHS I: Nurses' Health Study I; NIH-AARP: National Institutes of Health American Association of Retired Persons Diet and Health Study; PUFA: polyunsaturated fatty acids; TFA: trans-fatty acids; W: women.

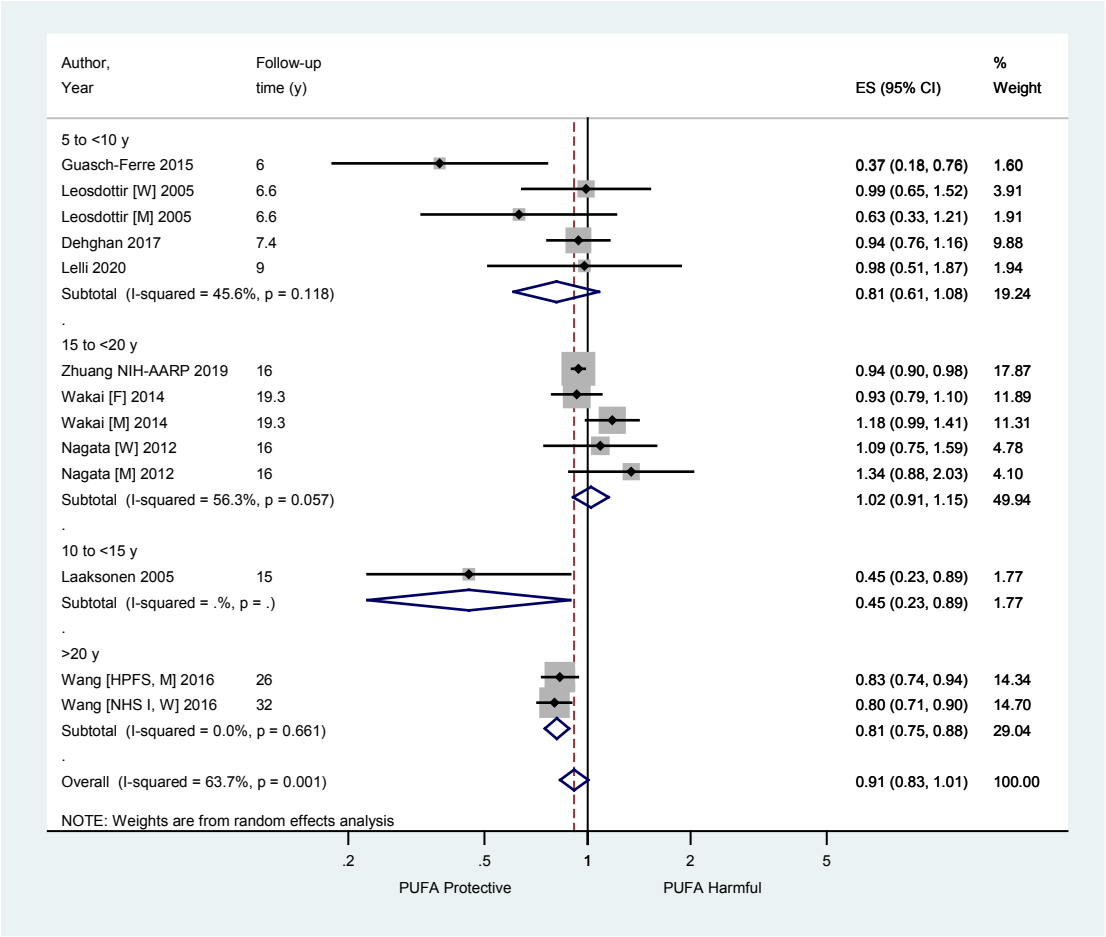
Fig. 86g. Meta-regression of total PUFA and CVD mortality; follow-up time; Panel A – effect size



The effect size was not associated with follow-time of the study (*P*=0.78).

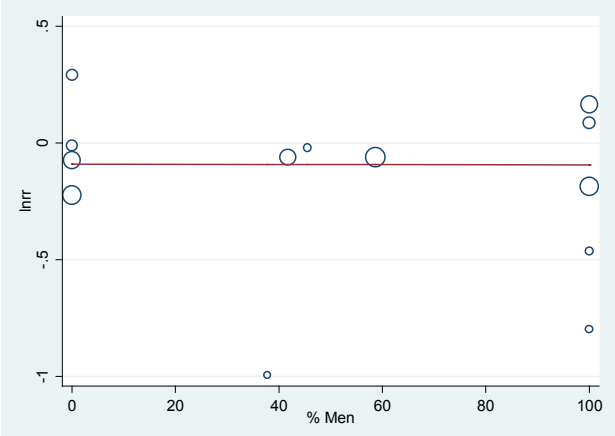
CVD: cardiovascular disease; PUFA: polyunsaturated fatty acids; rr: risk ratio; y: years.

Fig. 86h. Meta-regression of total PUFA and CVD mortality; follow-up time; Panel B – subgroup by study duration



CI: confidence interval; CVD: cardiovascular disease; ES: effect size; F: female; HPFS: Health Professionals Follow-up Study; M: male; NHS I: Nurses' Health Study I; NIH-AARP: National Institutes of Health American Association of Retired Persons Diet and Health Study; PUFA: polyunsaturated fatty acids; W: women; y: years.

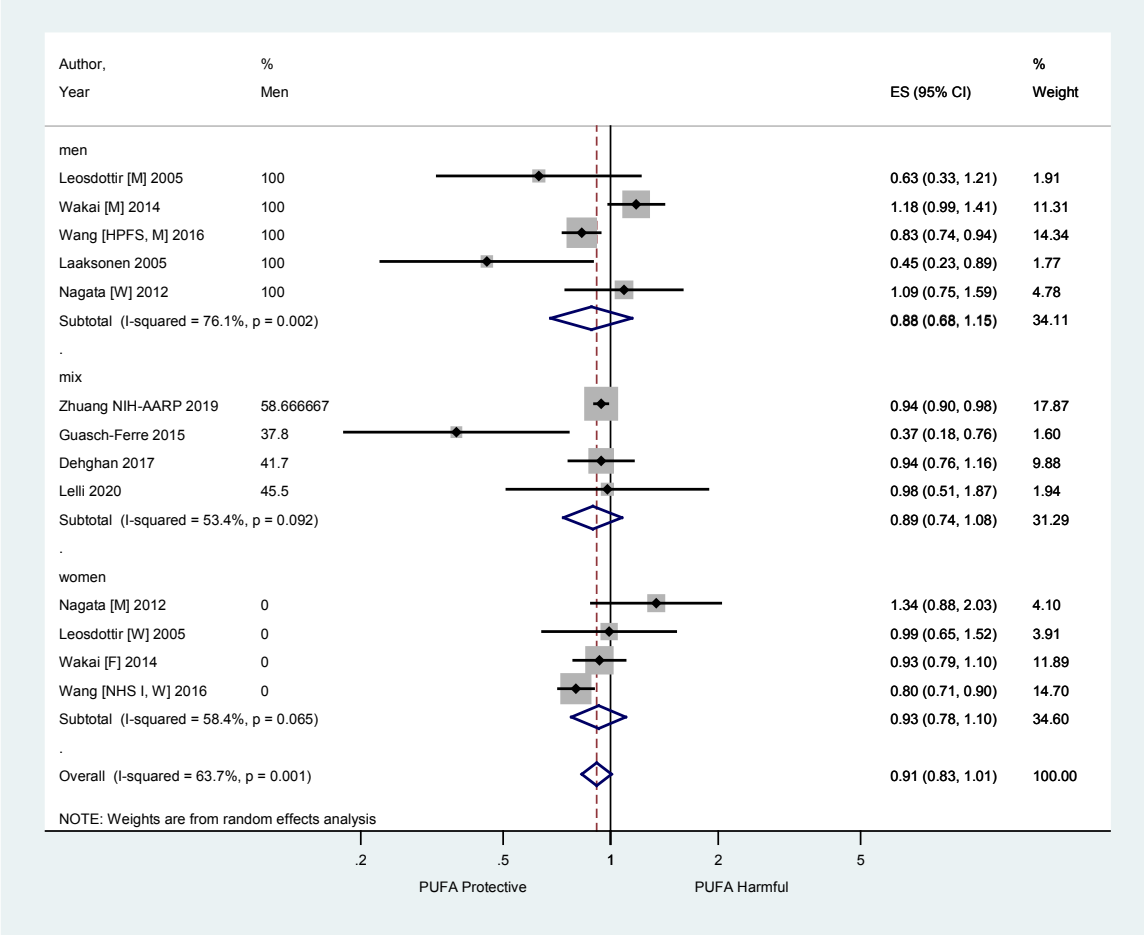
Fig. 86i. Meta-regression of total PUFA and CVD mortality; sex; Panel A – effect size



The effect size was not associated with the percentage of men in the study (P=0.99).

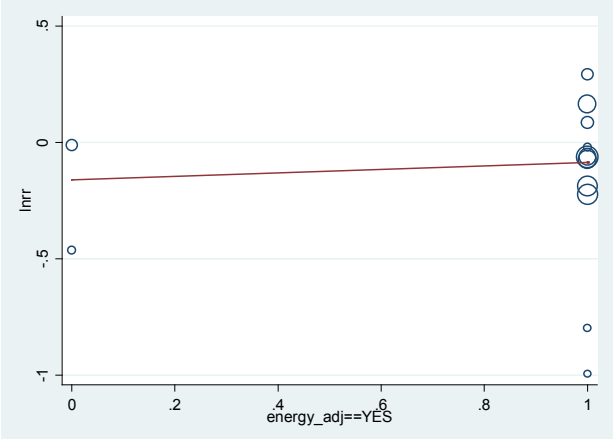
CVD: cardiovascular disease; PUFA: polyunsaturated fatty acids; rr: risk ratio.

Fig. 86j. Meta-regression of total PUFA and CVD mortality; sex; Panel B – subgroups analysis (sex)



CI: confidence interval; CVD: cardiovascular disease; ES: effect size; F: female; HPFS: Health Professionals Follow-up Study; M: male; NHS I: Nurses' Health Study I; NIH-AARP: National Institutes of Health American Association of Retired Persons Diet and Health Study; PUFA: polyunsaturated fatty acids; W: women.

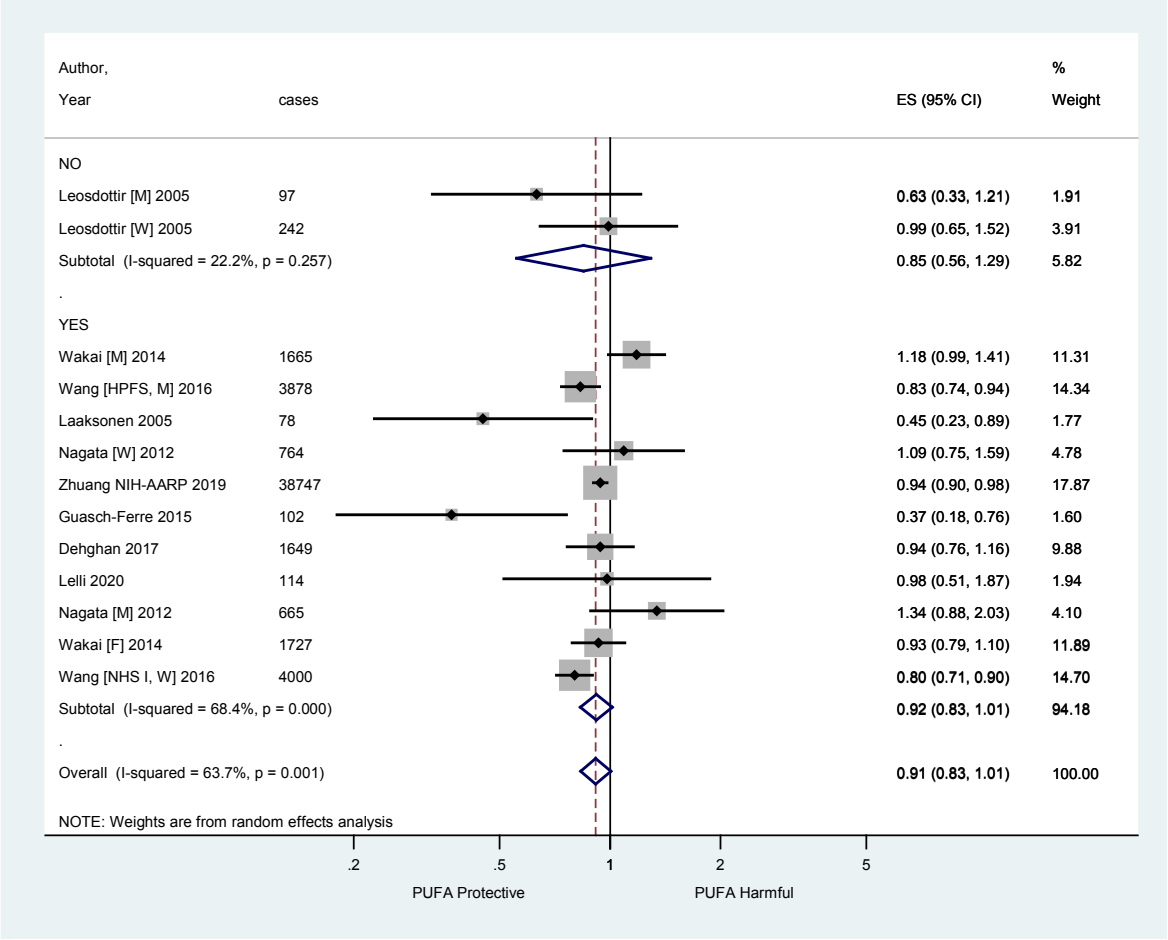
Fig. 86k. Meta-regression of total PUFA and CVD mortality; energy adjustment; Panel A – effect size



The effect size was not associated with energy adjustment (*P*=0.79).

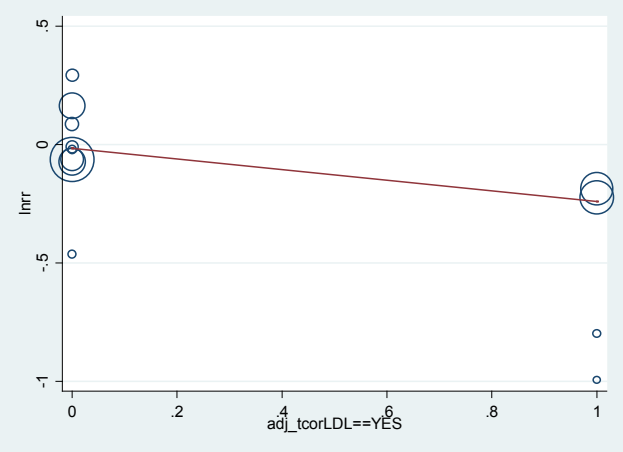
CVD: cardiovascular disease; energy_adj: adjusted for energy; PUFA: polyunsaturated fatty acids; rr: risk ratio.

Fig. 86l. Meta-regression of total PUFA and CVD mortality; energy adjustment; Panel B – subgroup analysis (adjustment for energy, yes/no)



CI: confidence interval; CVD: cardiovascular disease; ES: effect size; F: female; HPFS: Health Professionals Follow-up Study; M: male; NHS I: Nurses' Health Study I; NIH-AARP: National Institutes of Health American Association of Retired Persons Diet and Health Study; PUFA: polyunsaturated fatty acids; W: women.

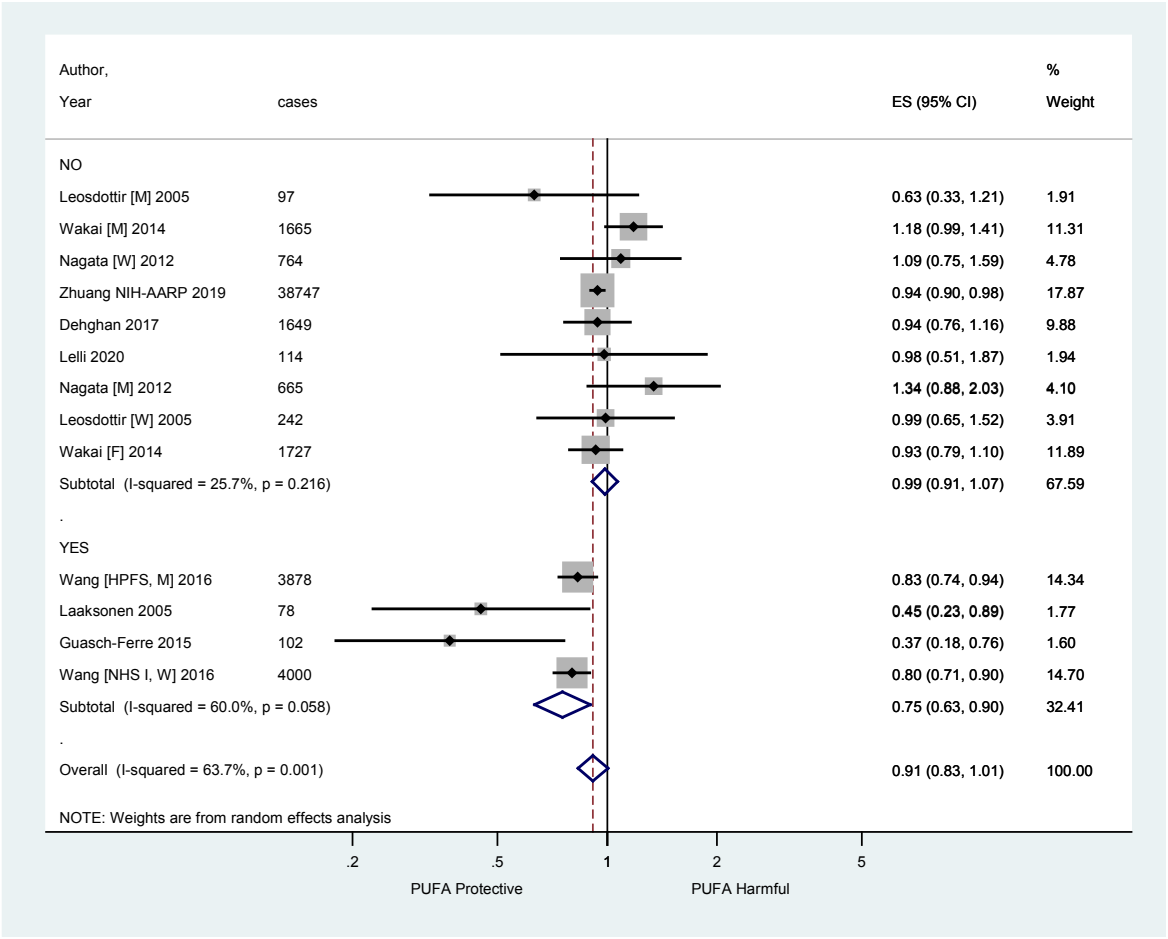
Fig. 86m. Meta-regression of total PUFA and CVD mortality; dyslipidaemia adjustment; Panel A – effect size



The effect size was associated with adjustment for dyslipidaemia (RR=0.80; 95% CI: 0.67 to 0.96; *P*=0.019).

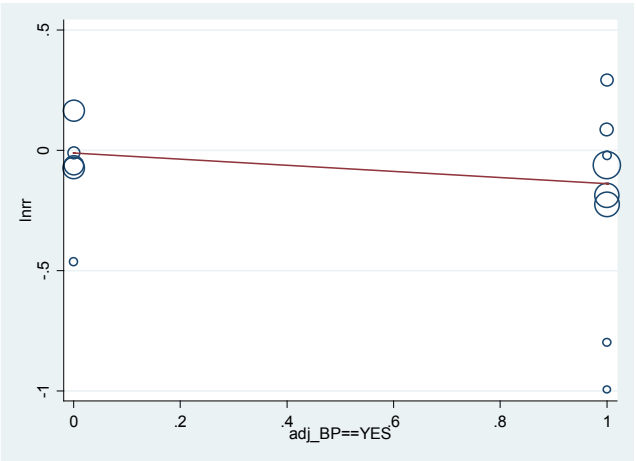
adj_tcorLDL: adjusted for dyslipidaemia; CI: confidence interval; CVD: cardiovascular disease; PUFA: polyunsaturated fatty acids; rr: risk ratio; RR: risk ratio.

Fig. 86n. Meta-regression of total PUFA and CVD mortality; dyslipidaemia adjustment; Panel B – subgroups analysis (yes/no)



CI: confidence interval; CVD: cardiovascular disease; ES: effect size; F: female; HPFS: Health Professionals Follow-up Study; M: male; NHS I: Nurses' Health Study I; NIH-AARP: National Institutes of Health American Association of Retired Persons Diet and Health Study; PUFA: polyunsaturated fatty acids; W: women.

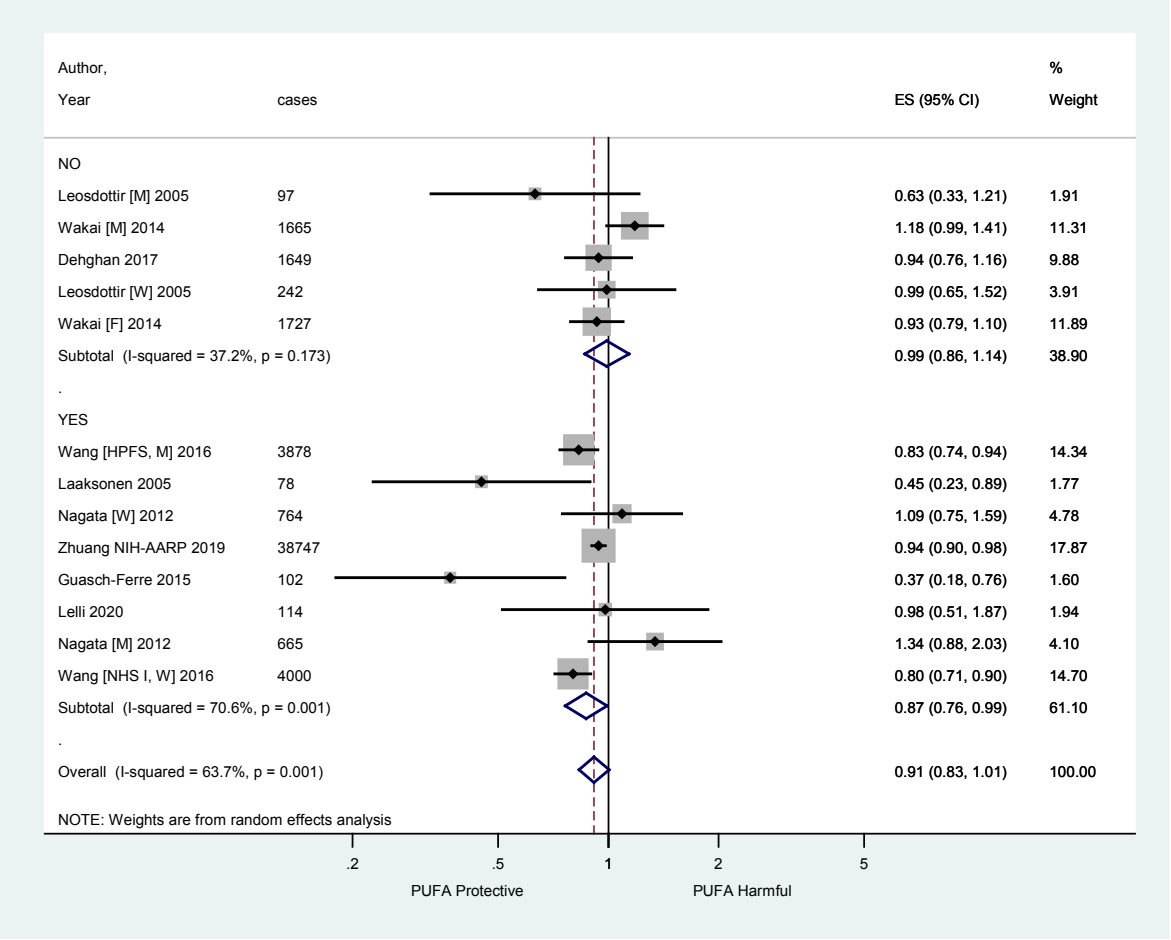
Fig. 86o. Meta-regression of total PUFA and CVD mortality; blood pressure adjustment; Panel A – effect size



The effect size was not associated with adjustment for blood pressure in the final model.

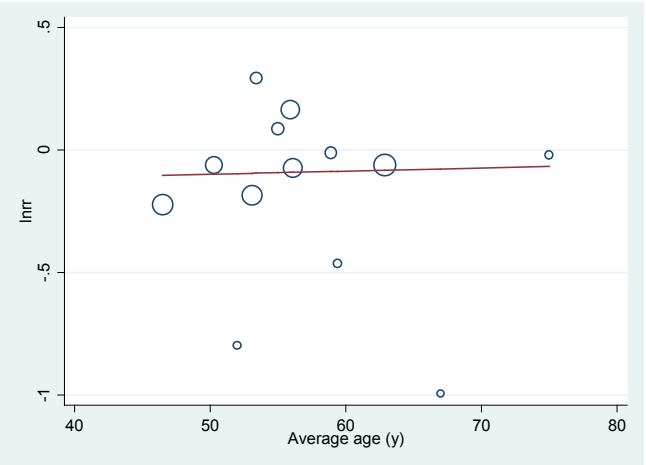
adj_BP: adjusted for blood pressure; CVD: cardiovascular disease; mvRR: multivariable risk ratio; PUFA: polyunsaturated fatty acids; rr: risk ratio.

Fig. 86p. Meta-regression of total PUFA and CVD mortality; blood pressure adjustment; Panel B – subgroup analysis (yes/no, blood pressure)



CI: confidence interval; CVD: cardiovascular disease; ES: effect size; F: female; HPFS: Health Professionals Follow-up Study; M: male; NHS I: Nurses' Health Study I; NIH-AARP: National Institutes of Health American Association of Retired Persons Diet and Health Study; PUFA: polyunsaturated fatty acids; W: women.

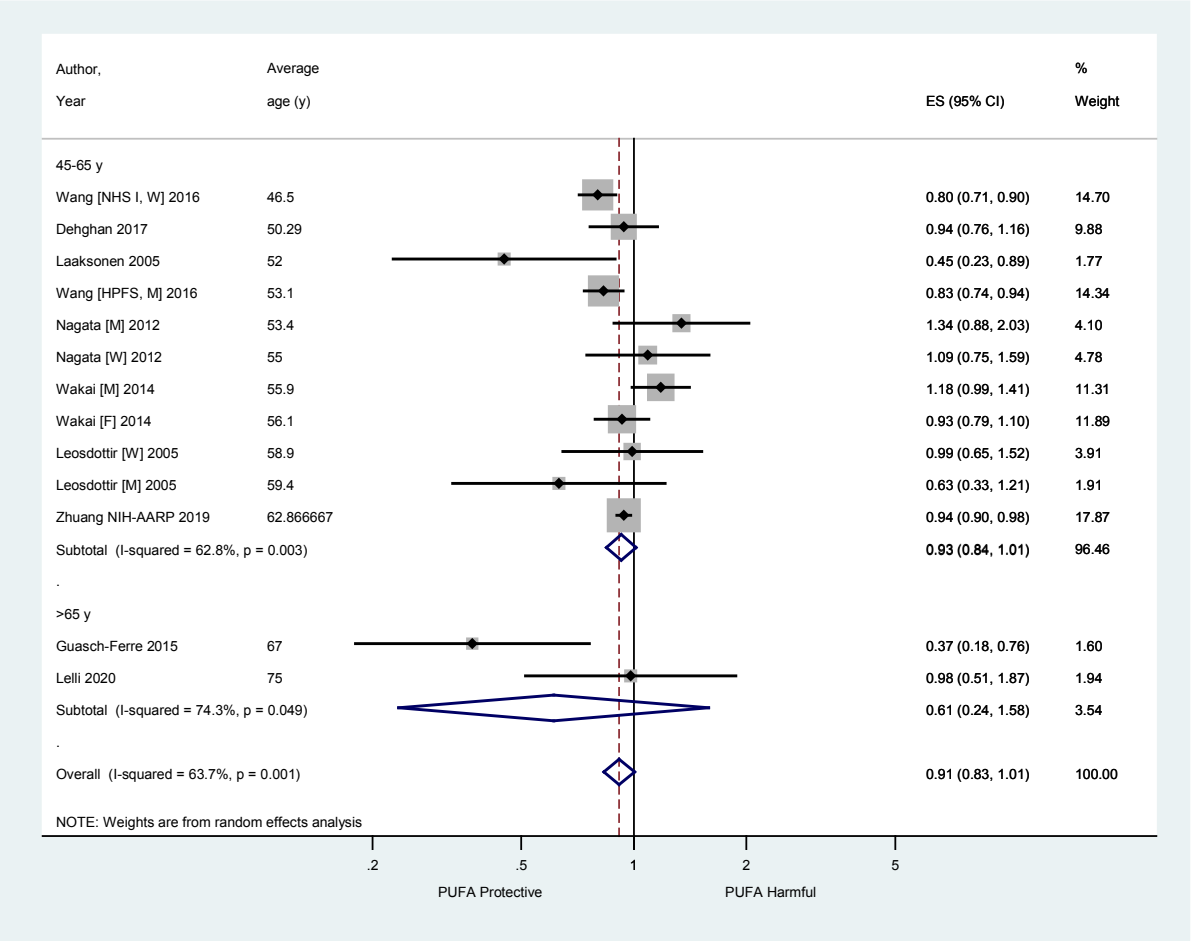
Fig. 86q. Meta-regression of total PUFA and CVD mortality; age; Panel A – effect size



The effect size was not associated with the age of participants in the study (*P*=0.91).

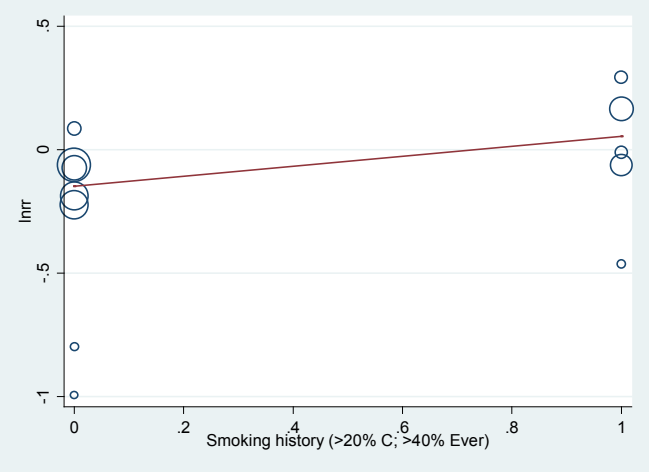
CVD: cardiovascular disease; PUFA: polyunsaturated fatty acids; rr: risk ratio; y: years.

Fig. 86r. Meta-regression of total PUFA and CVD mortality; age; Panel B – subgroup analysis (by age group)



CI: confidence interval; CVD: cardiovascular disease; ES: effect size; F: female; HPFS: Health Professionals Follow-up Study; M: male; NHS I: Nurses' Health Study I; NIH-AARP: National Institutes of Health American Association of Retired Persons Diet and Health Study; PUFA: polyunsaturated fatty acids; W: women; y: years.

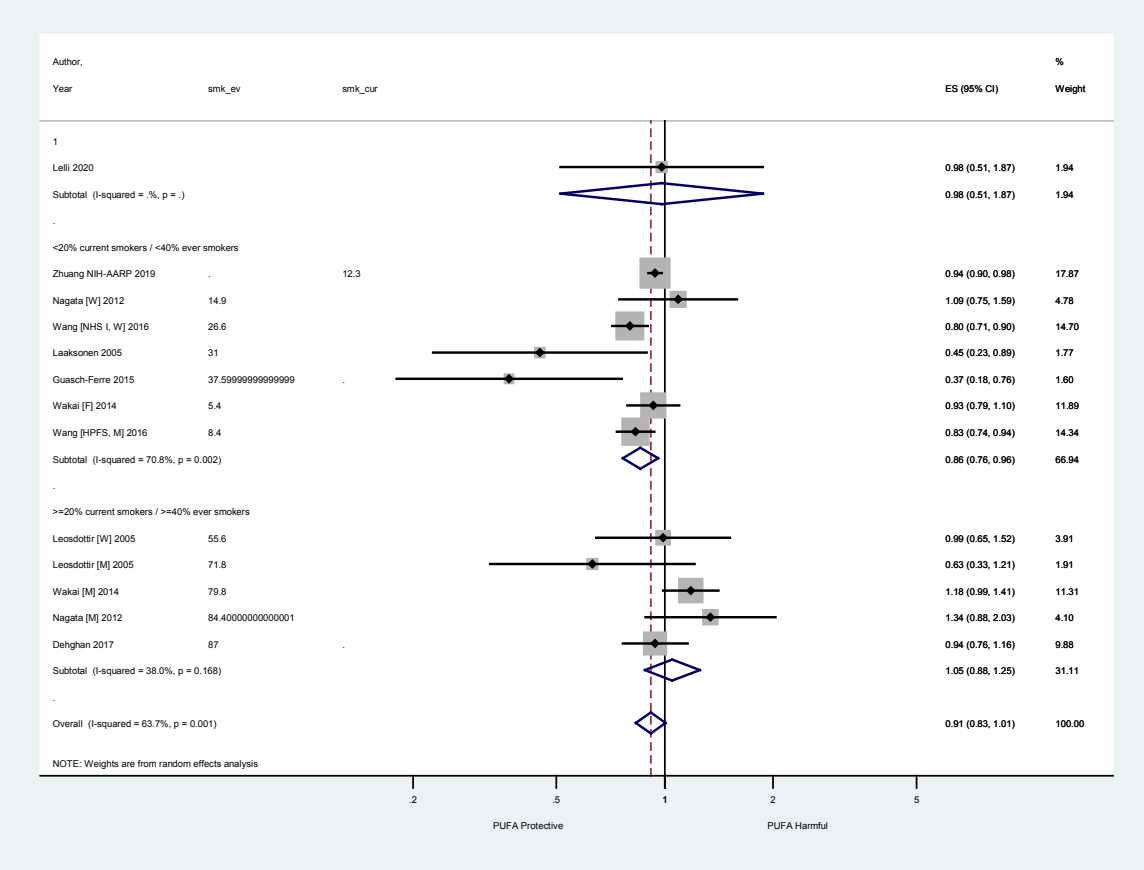
Fig. 86s. Meta-regression of total PUFA and CVD mortality; smoking; Panel A – effect size



The effect size was not associated with adjustment for smoking history of the study sample in the final model (*P*=0.69). High smokers ≥40% current or former (i.e. "ever smoked"), or >20% of current.

C: current; CVD: cardiovascular disease; Ever: ever smoked; PUFA: polyunsaturated fatty acids; rr: risk ratio.

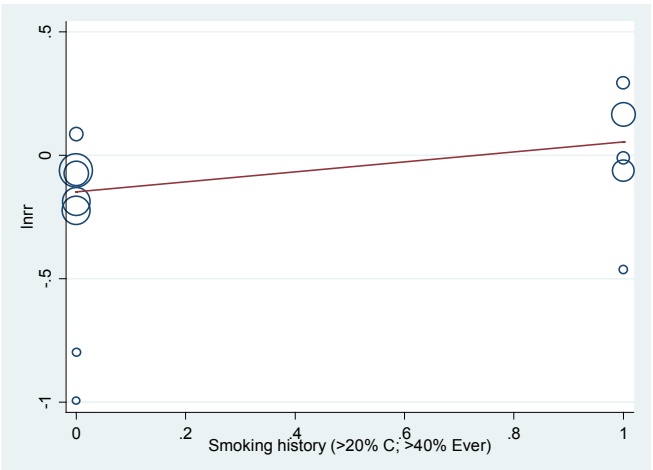
Fig. 86t. Meta-regression of total PUFA and CVD mortality; smoking; Panel B – subgroup analysis (by smoking)



*Lelli missing data on smoking (only reported as mean pack-years)

CI: confidence interval; CVD: cardiovascular disease; ES: effect size; F: female; HPFS: Health Professionals Follow-up Study; M: male; NHS I: Nurses' Health Study I; NIH-AARP: National Institutes of Health American Association of Retired Persons Diet and Health Study; PUFA: polyunsaturated fatty acids; smk_cur: current smokers; smk_ev: ever smoked; W: women.

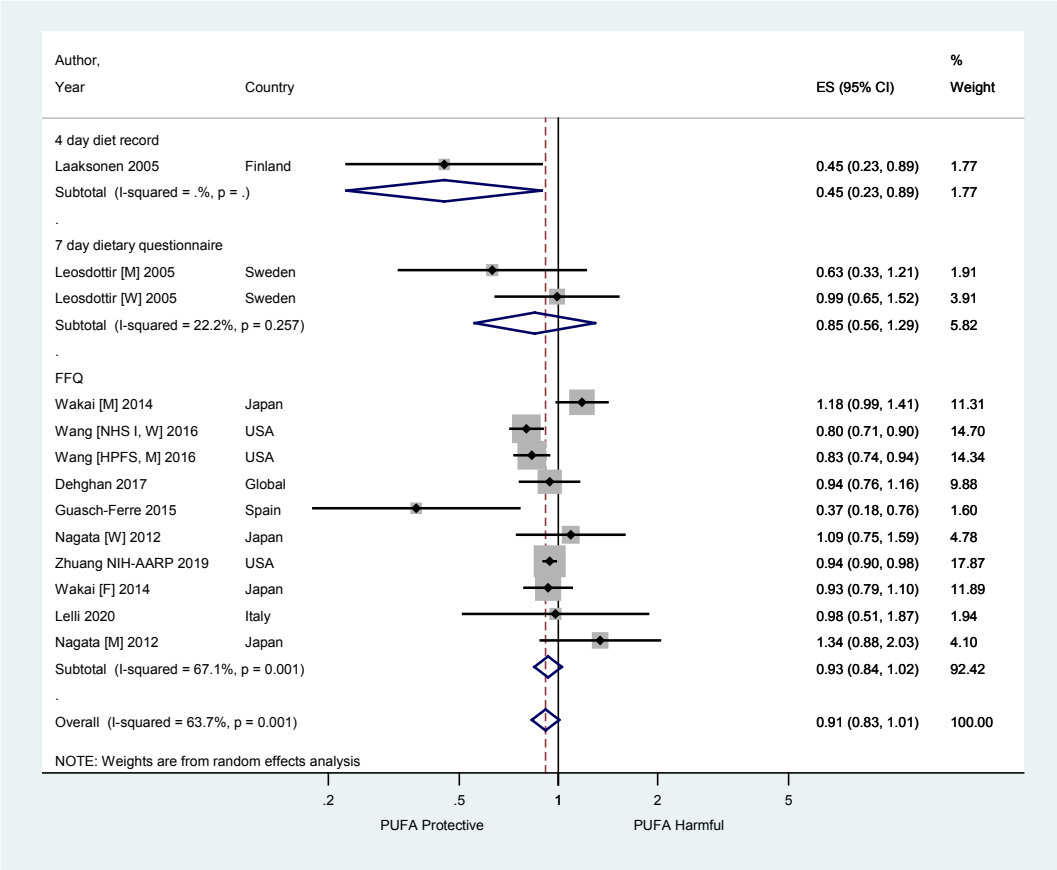
Fig. 86u. Meta-regression of total PUFA and CVD mortality; diet assessment method; Panel A – effect size



There was significant between-method heterogeneity in effect size (Phet by diet method=0.11). Because the predictor variable had more than 2 levels, it is not appropriate to show the continuous meta-regression line; therefore, we present the "by country" estimates separately by country in Panel B (Fig. 86v).

CVD: cardiovascular disease; PUFA: polyunsaturated fatty acids.

Fig. 86v. Meta-regression of total PUFA and CVD mortality; diet assessment method; Panel B – subgroup analysis by diet assessment method



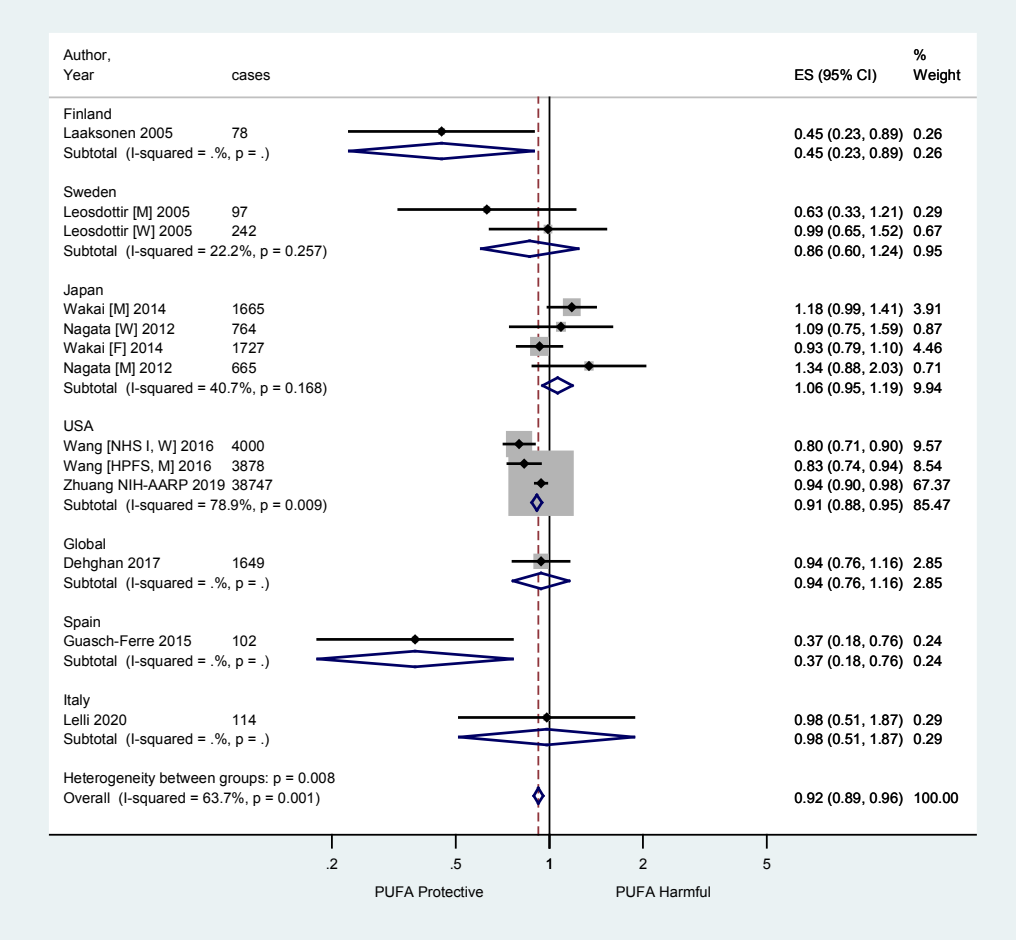
CI: confidence interval; CVD: cardiovascular disease; ES: effect size; F: female; FFQ: food frequency questionnaire; HPFS: Health Professionals Follow-up Study; M: male; NHS I: Nurses' Health Study I; NIH-AARP: National Institutes of Health American Association of Retired Persons Diet and Health Study; PUFA: polyunsaturated fatty acids; USA: United States of America; W: women.

Fig. 86w. Meta-regression of total PUFA and CVD mortality; country of conduct; Panel A – effect size

There was significant between-country heterogeneity in effect size (Phet=0.008). Because the predictor variable had more than 2 levels, it is not appropriate to show the continuous meta-regression line; therefore, we present the "by country" estimates separately by country in Panel B **(Fig. 86x)**.

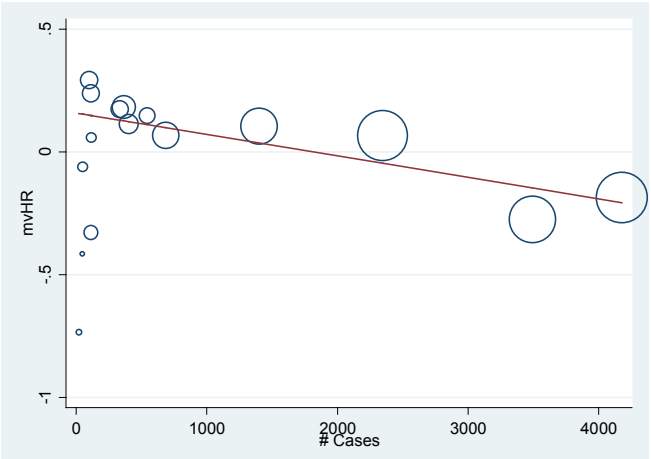
CVD: cardiovascular disease; PUFA: polyunsaturated fatty acids.

Fig. 86x. Meta-regression of total PUFA and CVD mortality; country of conduct; Panel B – subgroup analysis by country



CI: confidence interval; CVD: cardiovascular disease; ES: effect size; F: female; HPFS: Health Professionals Follow-up Study; M: male; NHS I: Nurses' Health Study I; NIH-AARP: National Institutes of Health American Association of Retired Persons Diet and Health Study; PUFA: polyunsaturated fatty acids; USA: United States of America; W: women.

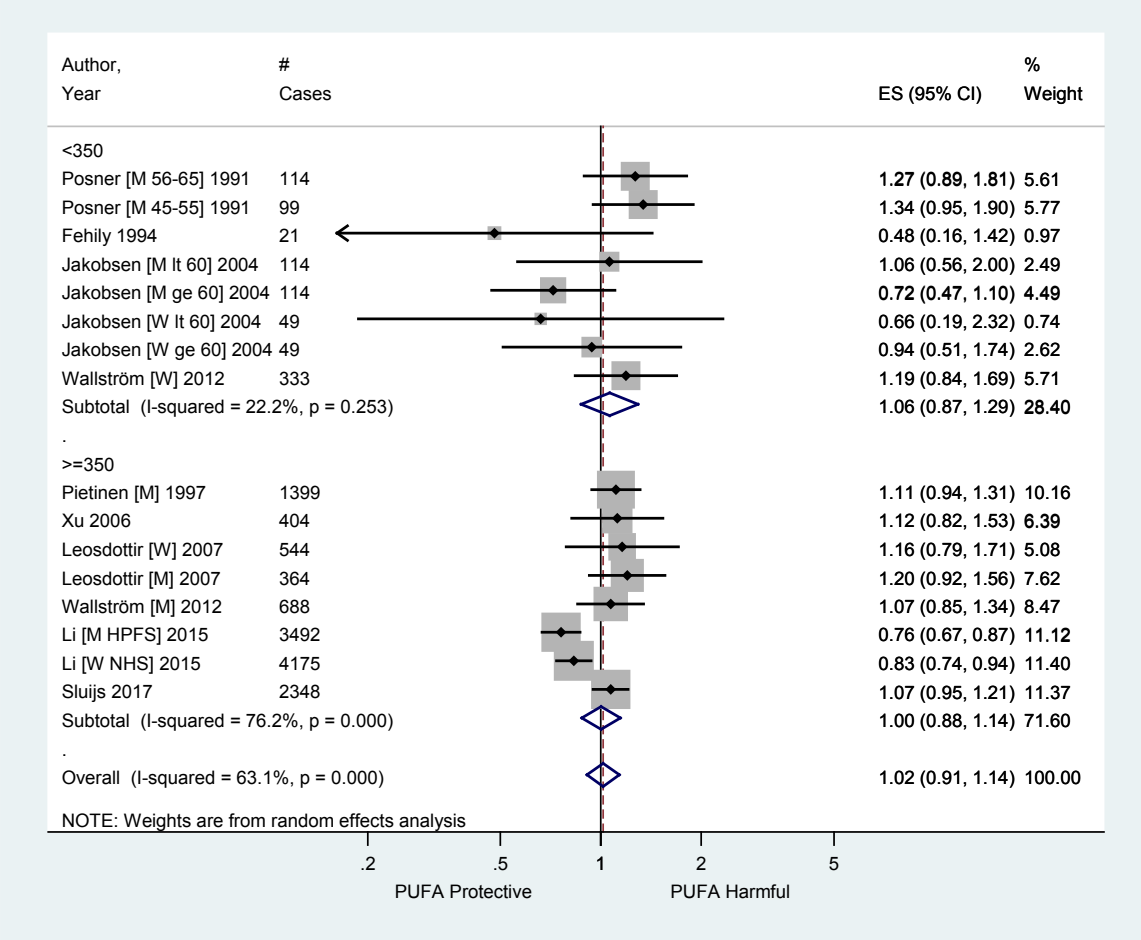
Fig. 87a. Meta-regression of total PUFA and total CHD; number of cases; Panel A – effect size



Each 500-case increase in study size was associated with a 4% decrease in estimate (mvRR: 0.96; 95% CI: 0.93, to 0.98; *P*=0.003).

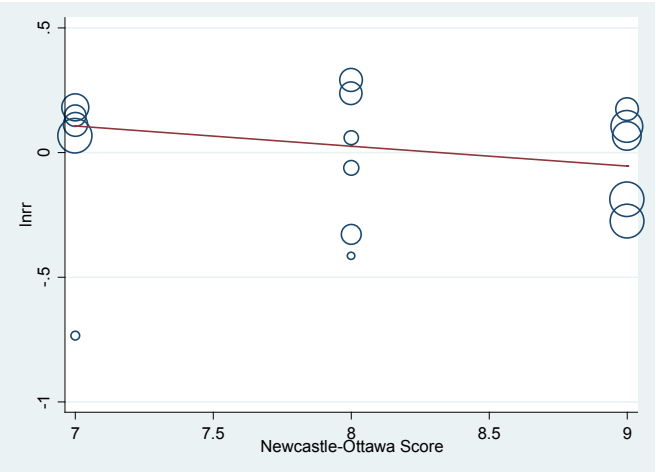
#: number; CHD: coronary heart disease; CI: confidence interval; mvHR: multivariable hazard ratio; mvRR: multivariable risk ratio; PUFA: polyunsaturated fatty acids.

Fig. 87b. Meta-regression of total PUFA and total CHD; number of cases; Panel B – subgroup analysis by number of cases (median=350)



#: number; CHD: coronary heart disease; CI: confidence interval; ES: effect size; ge: greater than or equal to; HPFS: Health Professionals Follow-up Study; lt: less than; M: male; NHS: Nurses' Health Study; PUFA: polyunsaturated fatty acids; W: women.

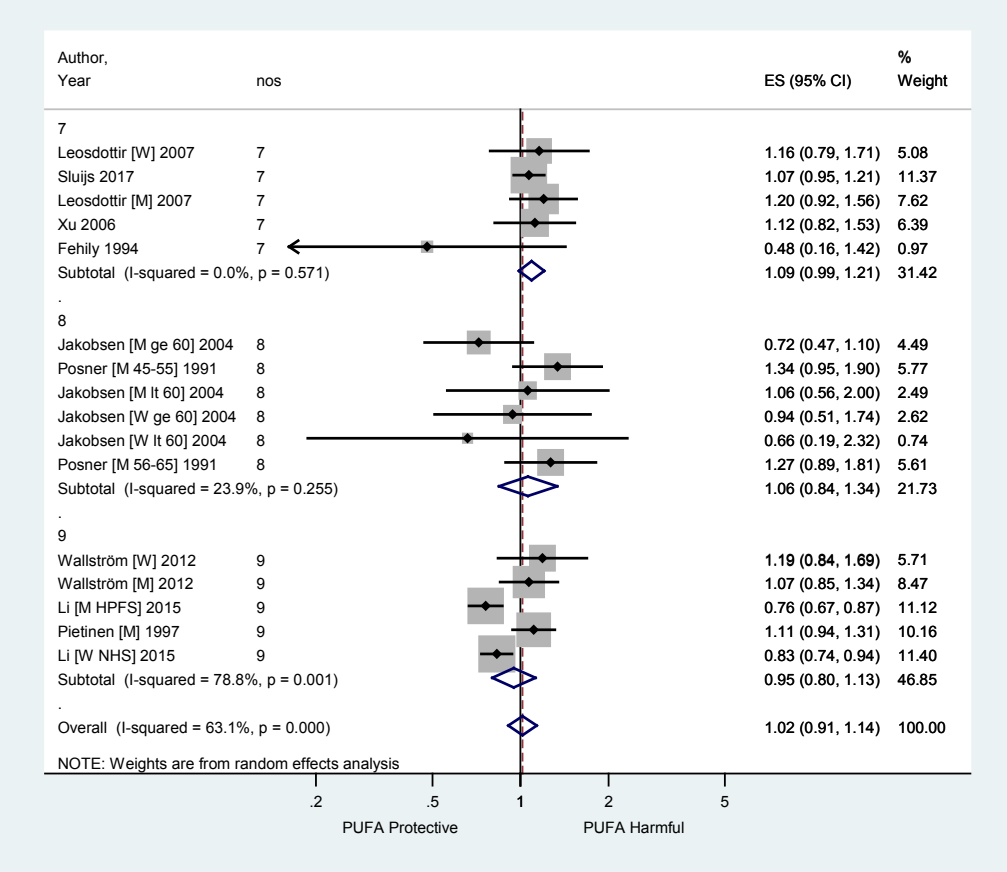
Fig. 87c. Meta-regression of total PUFA and total CHD; NOS assessment; Panel A – effect size



NOS assessment was not a predictor of effect size (P=0.19).

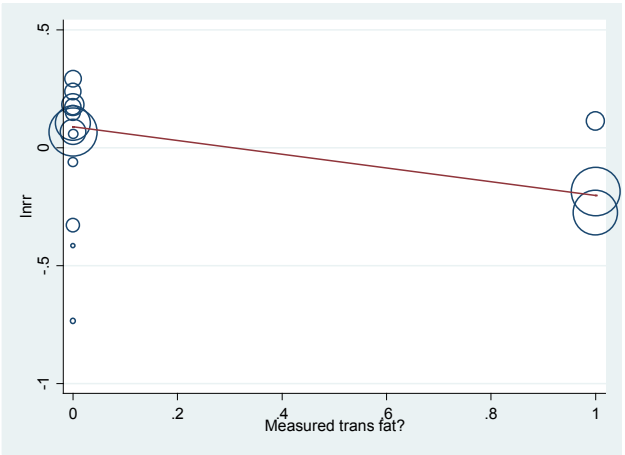
CHD: coronary heart disease; NOS: Newcastle-Ottawa Scale; PUFA: polyunsaturated fatty acids; rr: risk ratio.

Fig. 87d. Meta-regression of total PUFA and total CHD; NOS assessment; Panel B – subgroup analysis (by NOS)



CHD: coronary heart disease; CI: confidence interval; ES: effect size; ge: greater than or equal to; HPFS: Health Professionals Follow-up Study; lt: less than; M: male; NHS: Nurses' Health Study; nos: Newcastle-Ottawa Scale; NOS: Newcastle-Ottawa Scale; PUFA: polyunsaturated fatty acids; W: women.

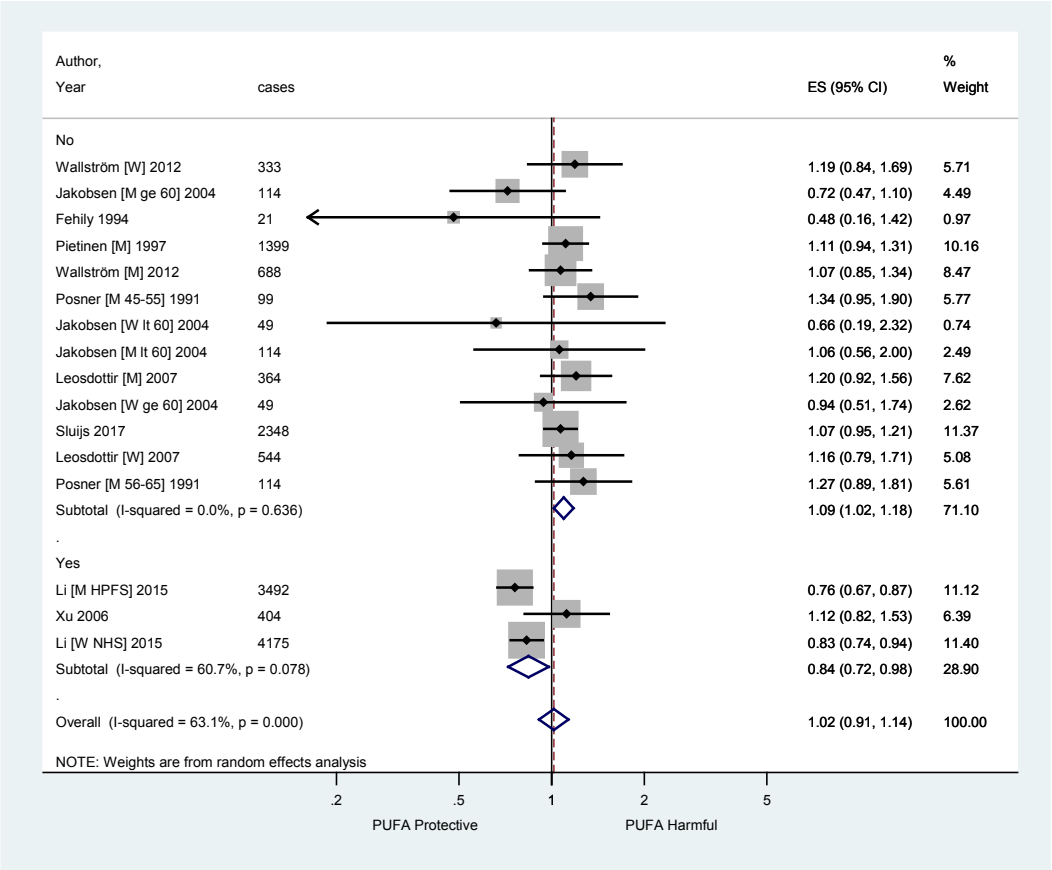
Fig. 87e. Meta-regression of total PUFA and total CHD; TFA assessment; Panel A – effect size



Measurement of TFA was associated with effect size (P<0.0001).

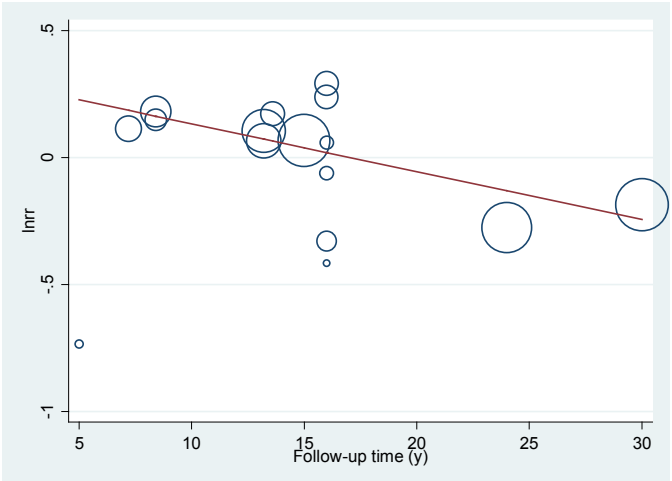
CHD: coronary heart disease; PUFA: polyunsaturated fatty acids; rr: risk ratio; TFA: trans-fatty acids.

Fig. 87f. Meta-regression of total PUFA and total CHD; TFA assessment; Panel B – subgroup analysis (by trans-fat measurement)



CHD: coronary heart disease; CI: confidence interval; ES: effect size; ge: greater than or equal to; HPFS: Health Professionals Follow-up Study; lt: less than; M: male; NHS: Nurses' Health Study; PUFA: polyunsaturated fatty acids; TFA: trans-fatty acids; W: women.

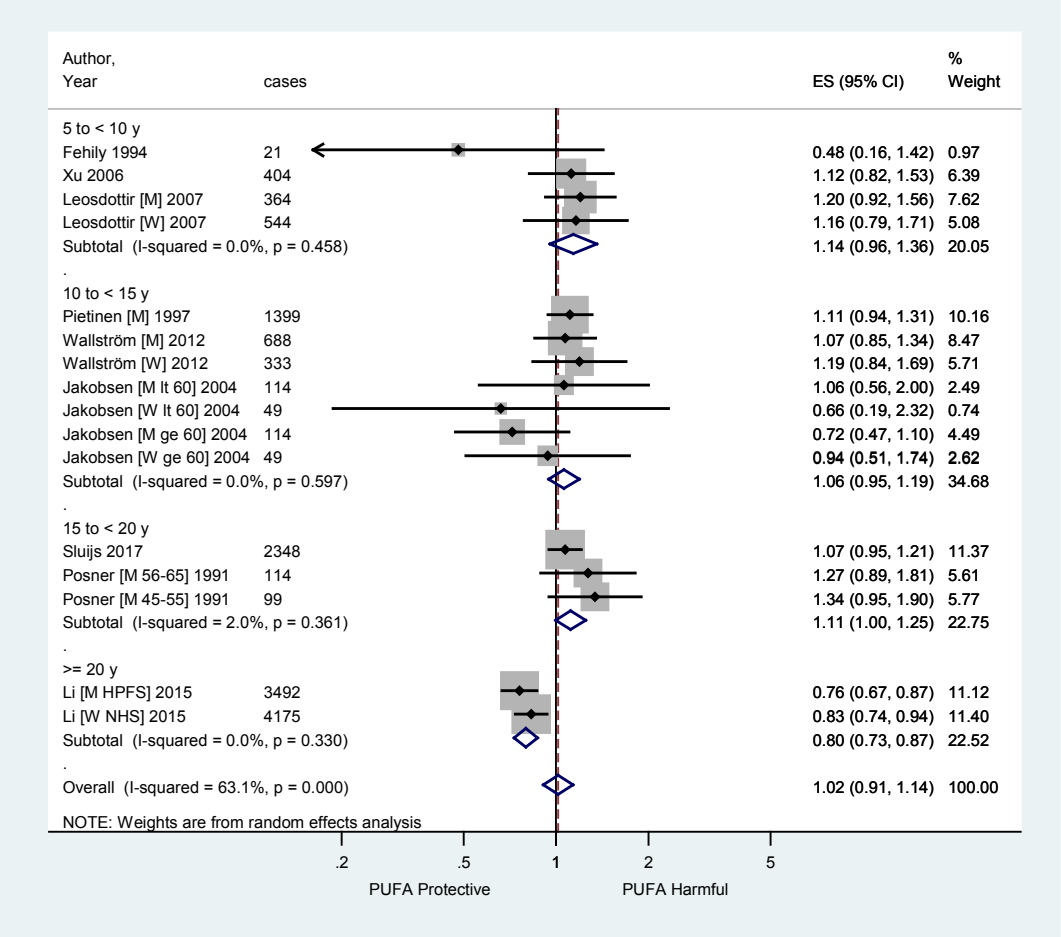
Fig. 87g. Meta-regression of total PUFA and total CHD; follow-up time; Panel A – effect size



Follow-up duration was associated with effect size (*P*=0.002).

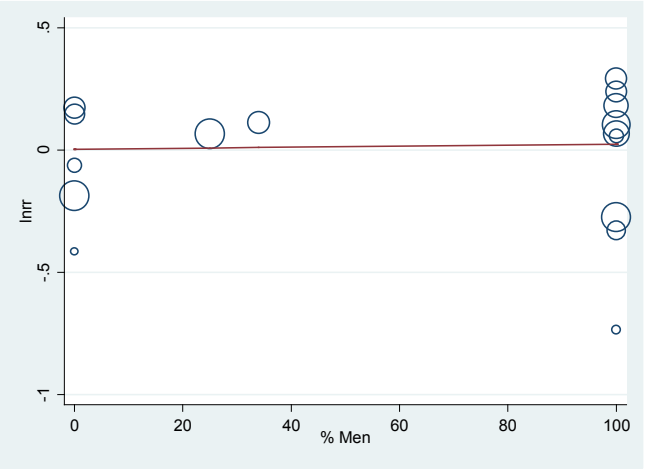
CHD: coronary heart disease; PUFA: polyunsaturated fatty acids; rr: risk ratio; y: years.

Fig. 87h. Meta-regression of total PUFA and total CHD; follow-up time; Panel B – subgroup analysis by follow-up duration



CHD: coronary heart disease; CI: confidence interval; ES: effect size; ge: greater than or equal to; HPFS: Health Professionals Follow-up Study; lt: less than; M: male; NHS: Nurses' Health Study; PUFA: polyunsaturated fatty acids; W: women; y: years.

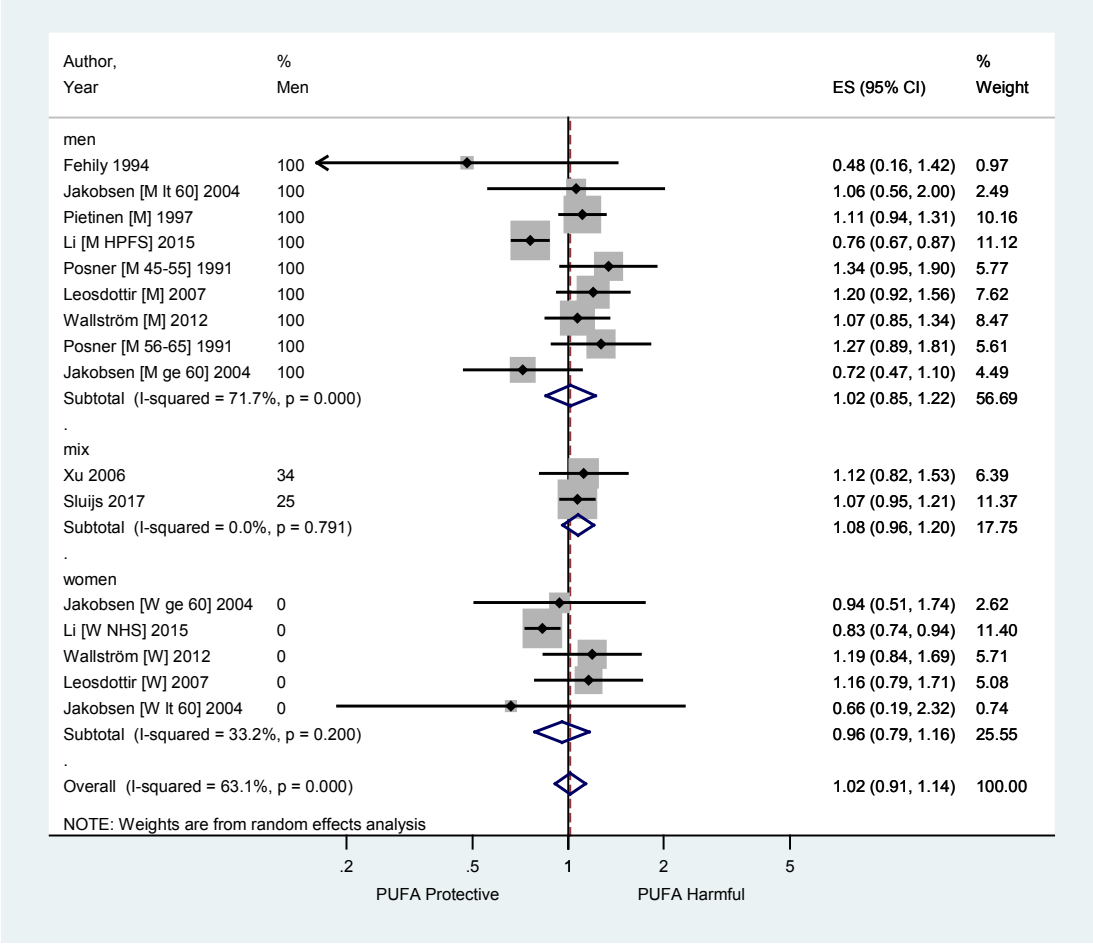
Fig. 87i. Meta-regression of total PUFA and total CHD; sex; Panel A – effect size



Percent men was not a predictor of effect size (P=0.88).

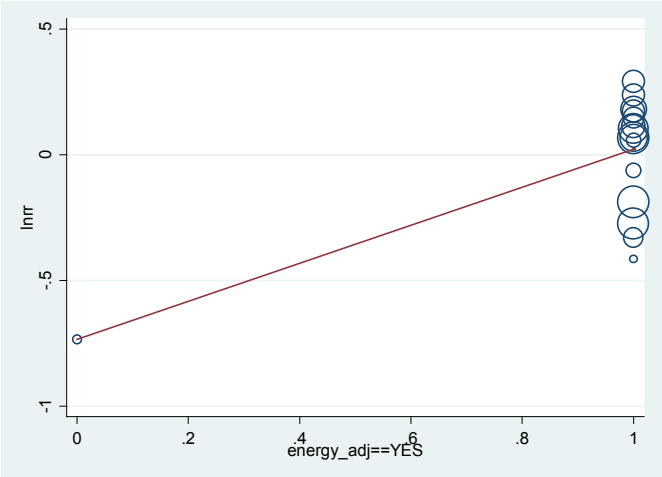
CHD: coronary heart disease; PUFA: polyunsaturated fatty acids; rr: risk ratio.

Fig. 87j. Meta-regression of total PUFA and total CHD; sex; Panel B – subgroup analysis



CHD: coronary heart disease; CI: confidence interval; ES: effect size; ge: greater than or equal to; HPFS: Health Professionals Follow-up Study; lt: less than; M: male; NHS: Nurses' Health Study; PUFA: polyunsaturated fatty acids; W: women.

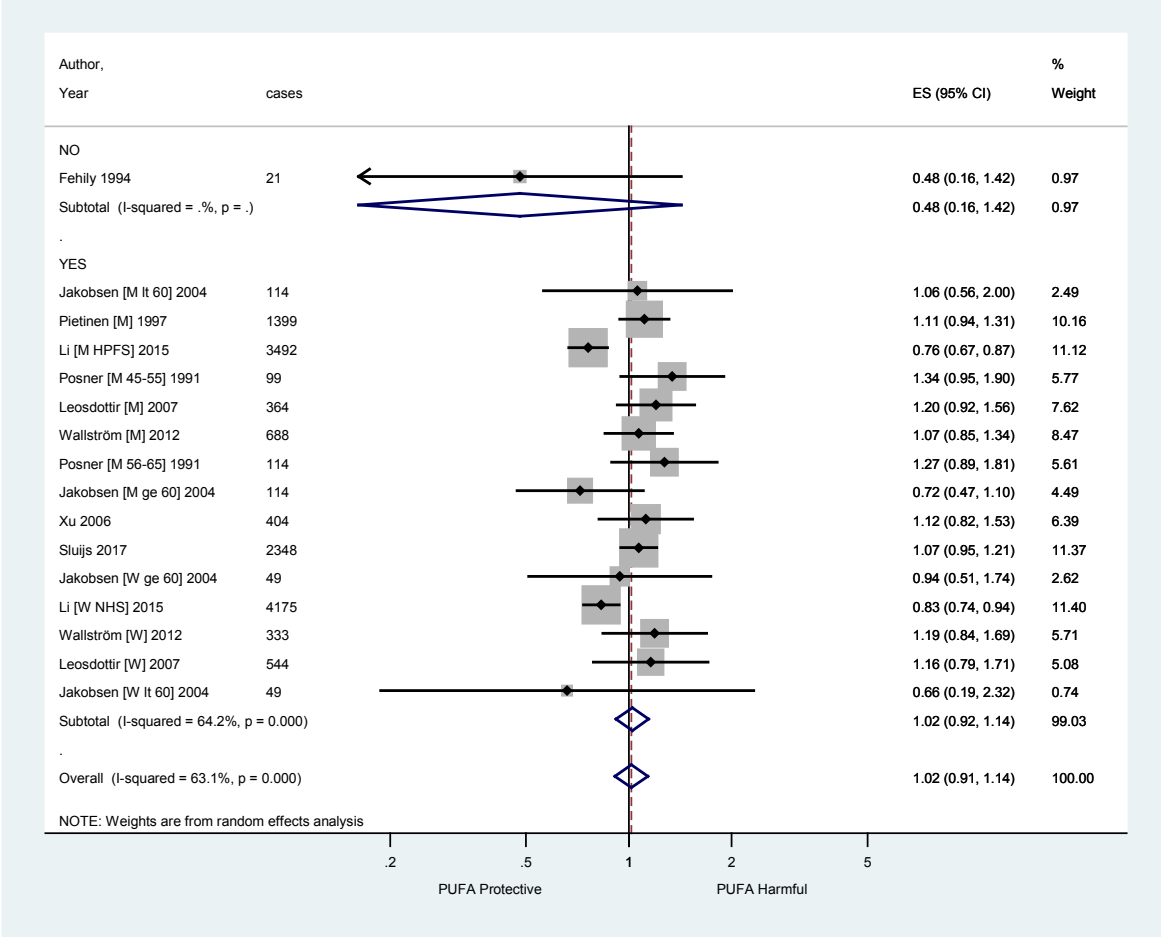
Fig. 87k. Meta-regression of total PUFA and total CHD; energy adjustment; Panel A – effect size



The effect size was not associated with adjustment for energy in the final model (*P*=0.21).

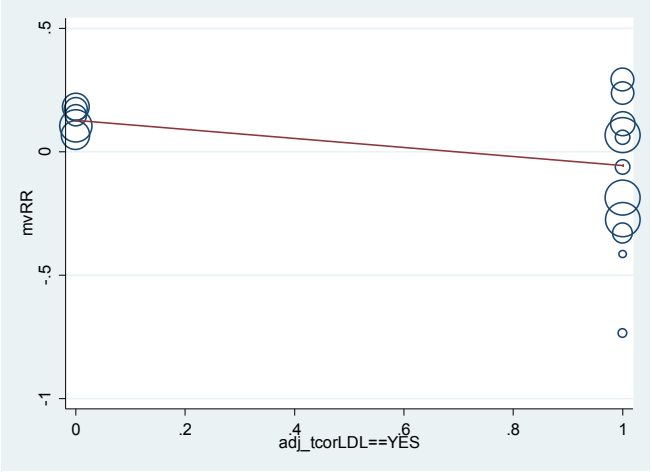
CHD: coronary heart disease; energy_adj: adjusted for energy; PUFA: polyunsaturated fatty acids; rr: risk ratio.

Fig. 87l. Meta-regression of total PUFA and total CHD; energy adjustment; Panel B – subgroup by adjustment for energy



CHD: coronary heart disease; CI: confidence interval; ES: effect size; ge: greater than or equal to; HPFS: Health Professionals Follow-up Study; lt: less than; M: male; NHS: Nurses' Health Study; PUFA: polyunsaturated fatty acids; W: women.

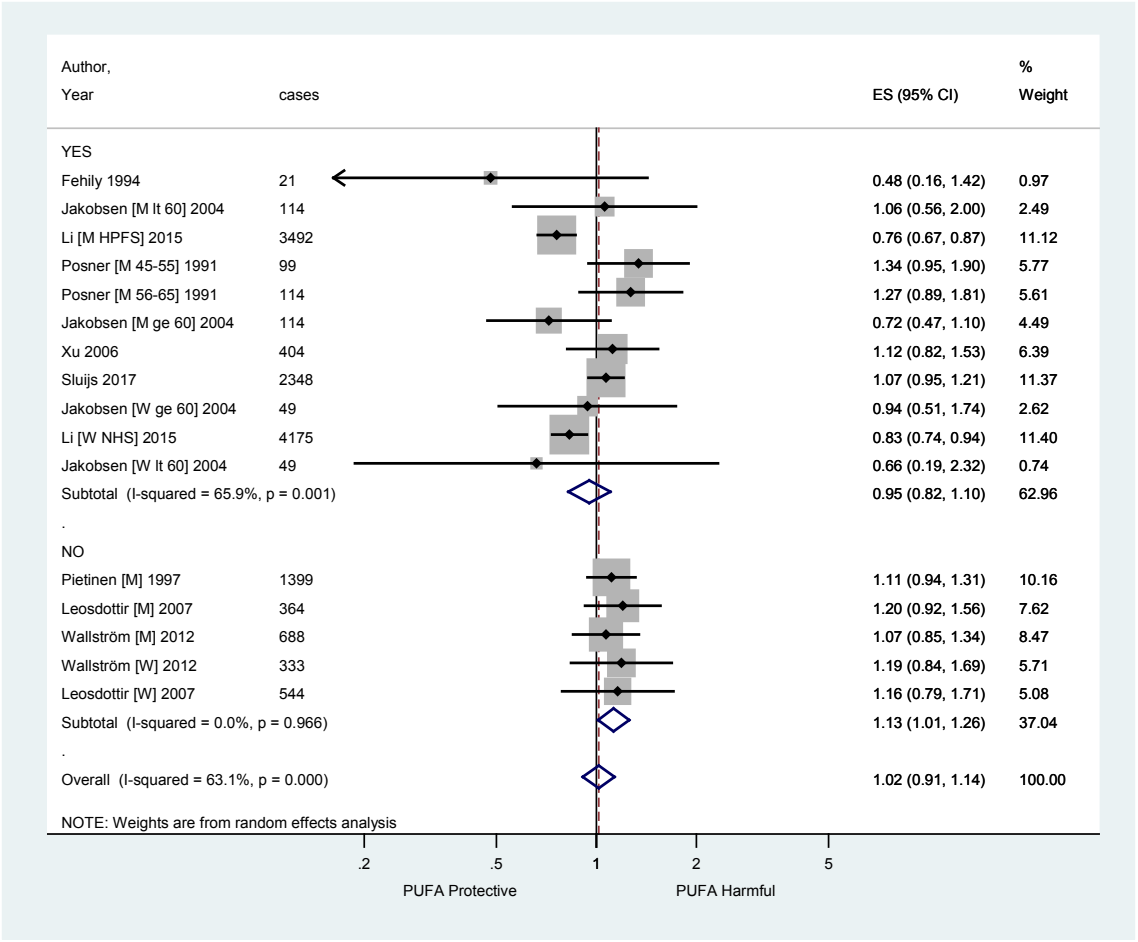
Fig. 87m. Meta-regression of total PUFA and total CHD; dyslipidaemia adjustment; Panel A – effect size



The effect size did not differ by whether or not there was adjustment for dyslipidaemia in the final model (P=0.10).

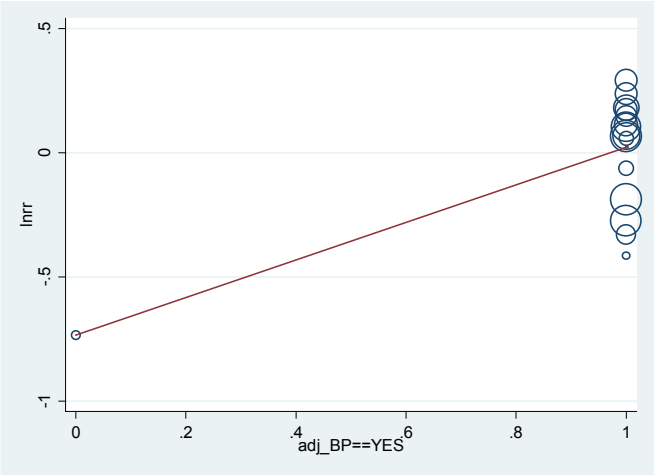
CHD: coronary heart disease; PUFA: polyunsaturated fatty acids.

Fig. 87n. Meta-regression of total PUFA and total CHD; dyslipidaemia adjustment; Panel B – subgroup analysis



CHD: coronary heart disease; CI: confidence interval; ES: effect size; ge: greater than or equal to; HPFS: Health Professionals Follow-up Study; lt: less than; M: male; NHS: Nurses' Health Study; PUFA: polyunsaturated fatty acids; W: women.

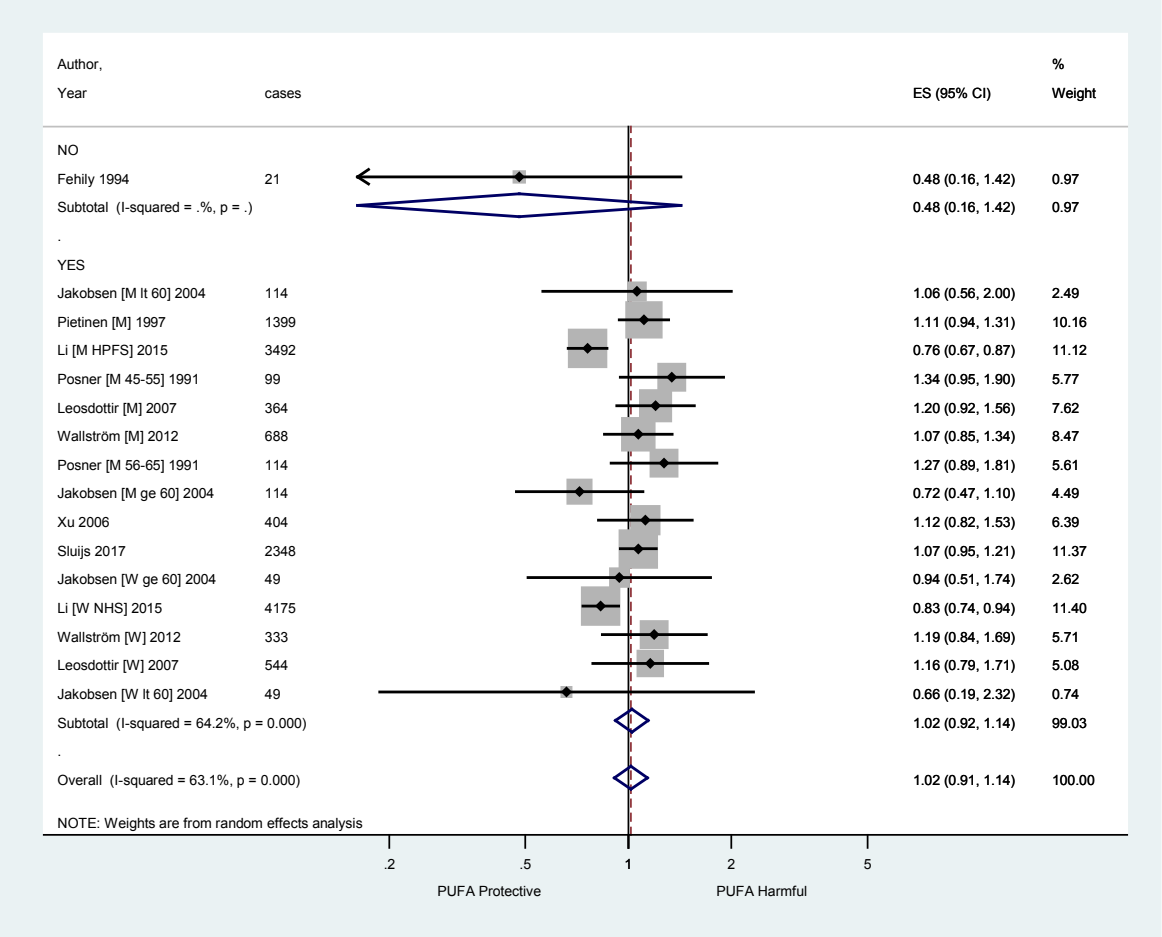
Fig. 87o. Meta-regression of total PUFA and total CHD; blood pressure adjustment; Panel A – effect size



The effect size was not associated with adjustment for blood pressure in the final model (*P*=0.21).

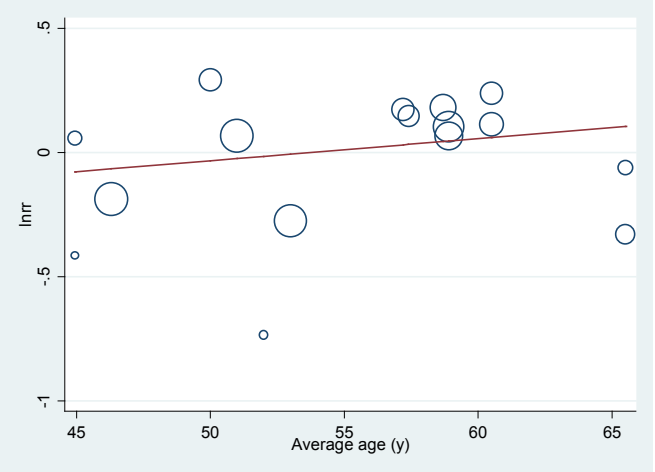
adj_BP: adjusted for blood pressure; CHD: coronary heart disease; PUFA: polyunsaturated fatty acids; rr: risk ratio.

Fig. 87p. Meta-regression of total PUFA and total CHD; blood pressure adjustment; Panel B – subgroup analysis



CHD: coronary heart disease; CI: confidence interval; ES: effect size; ge: greater than or equal to; HPFS: Health Professionals Follow-up Study; lt: less than; M: male; NHS: Nurses' Health Study; PUFA: polyunsaturated fatty acids; W: women.

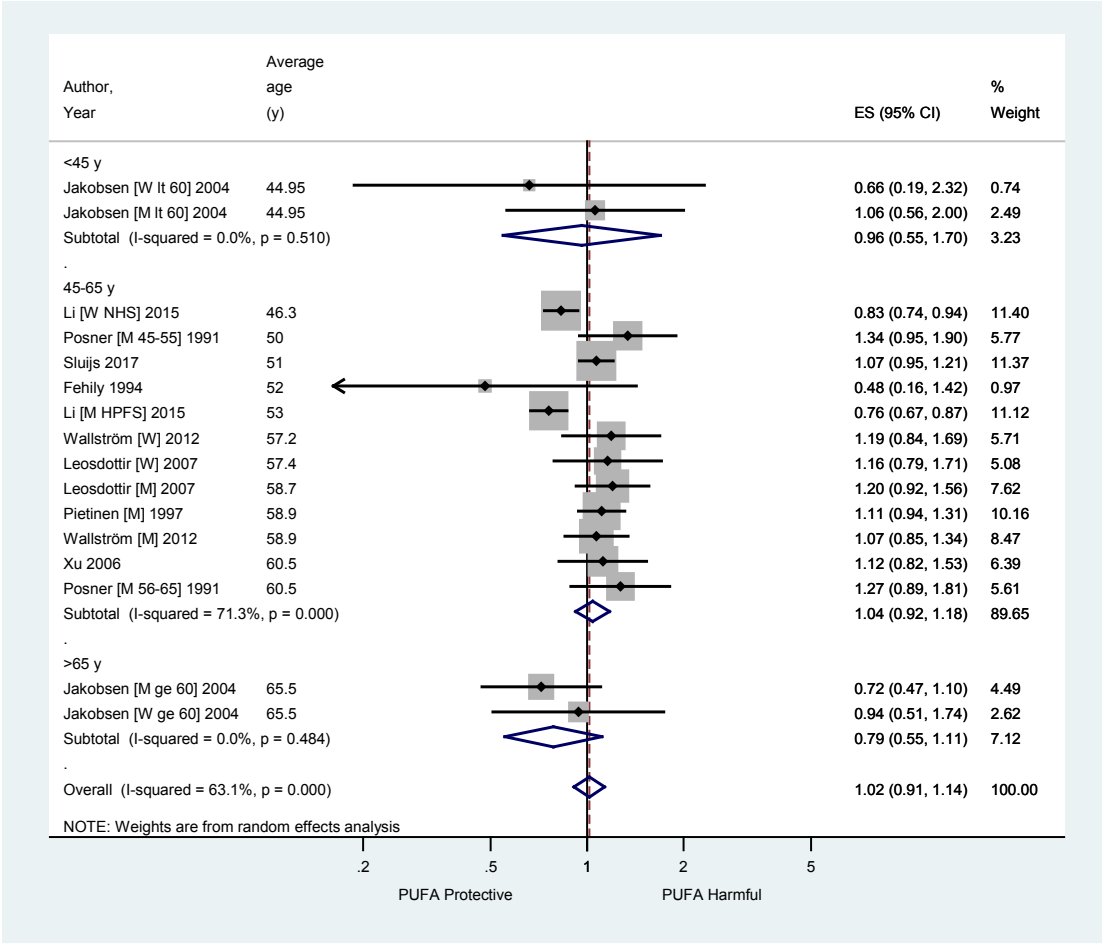
Fig. 87q. Meta-regression of total PUFA and total CHD; age; Panel A – effect size



The effect size was not associated the age of participants (P=0.37).

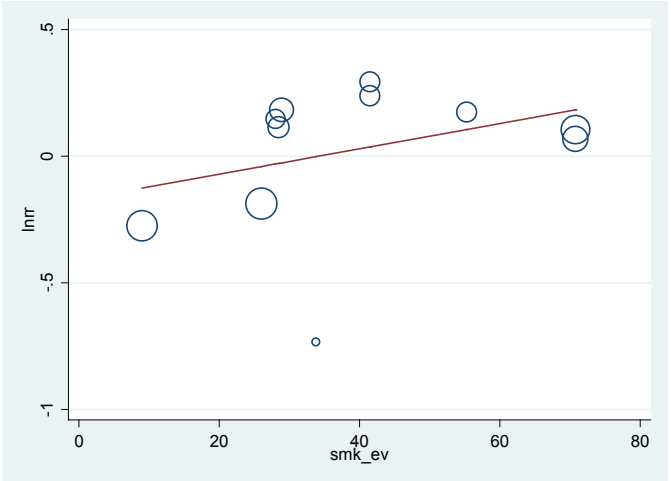
CHD: coronary heart disease; PUFA: polyunsaturated fatty acids; rr: risk ratio; y: years.

Fig. 87r. Meta-regression of total PUFA and total CHD; age; Panel B – subgroup analysis (age group)



CHD: coronary heart disease; CI: confidence interval; ES: effect size; ge: greater than or equal to; HPFS: Health Professionals Follow-up Study; lt: less than; M: male; NHS: Nurses' Health Study; PUFA: polyunsaturated fatty acids; W: women; y: years.

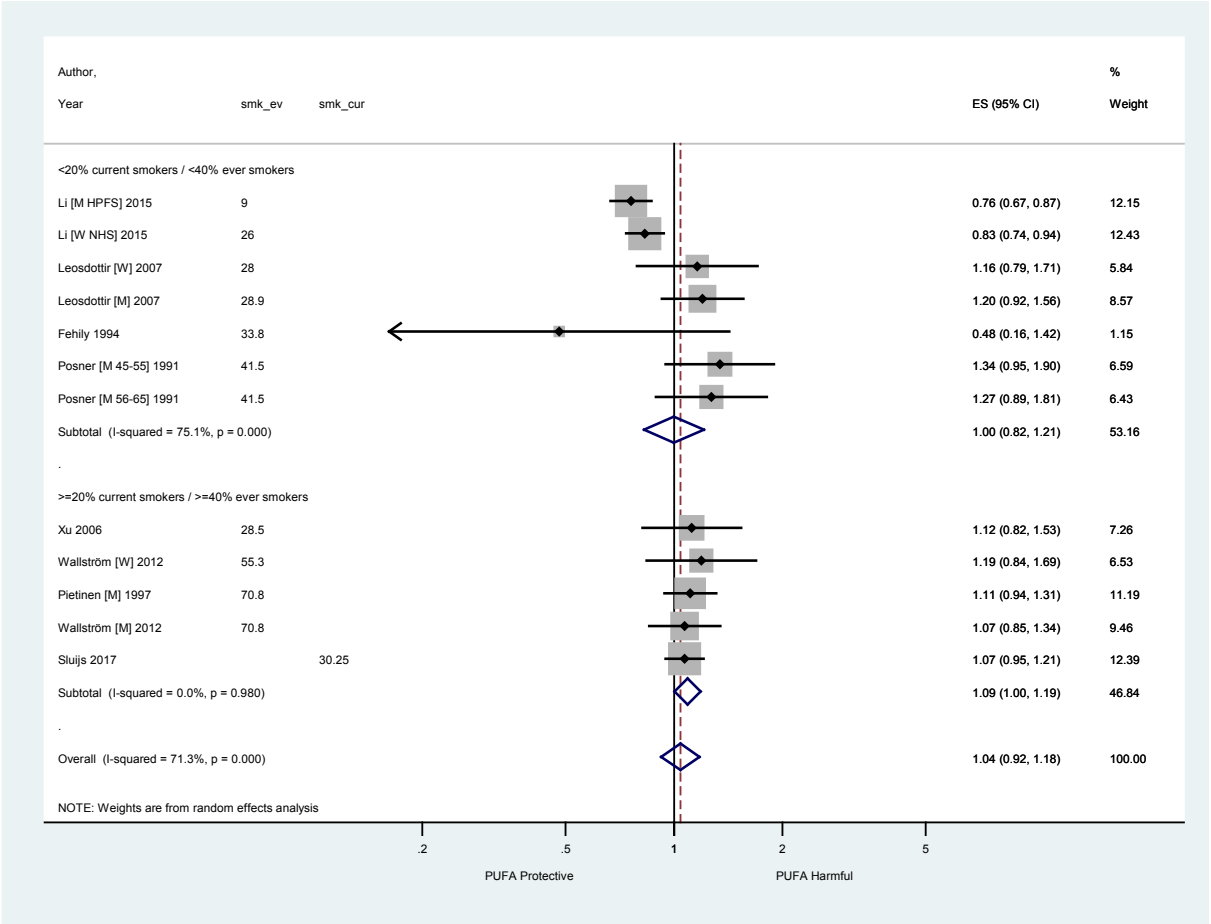
Fig. 87s. Meta-regression of total PUFA and total CHD; smoking; Panel A – effect size



The percentage of participants in studies who were current or ever smokers was associated with effect size (*P*=0.096).

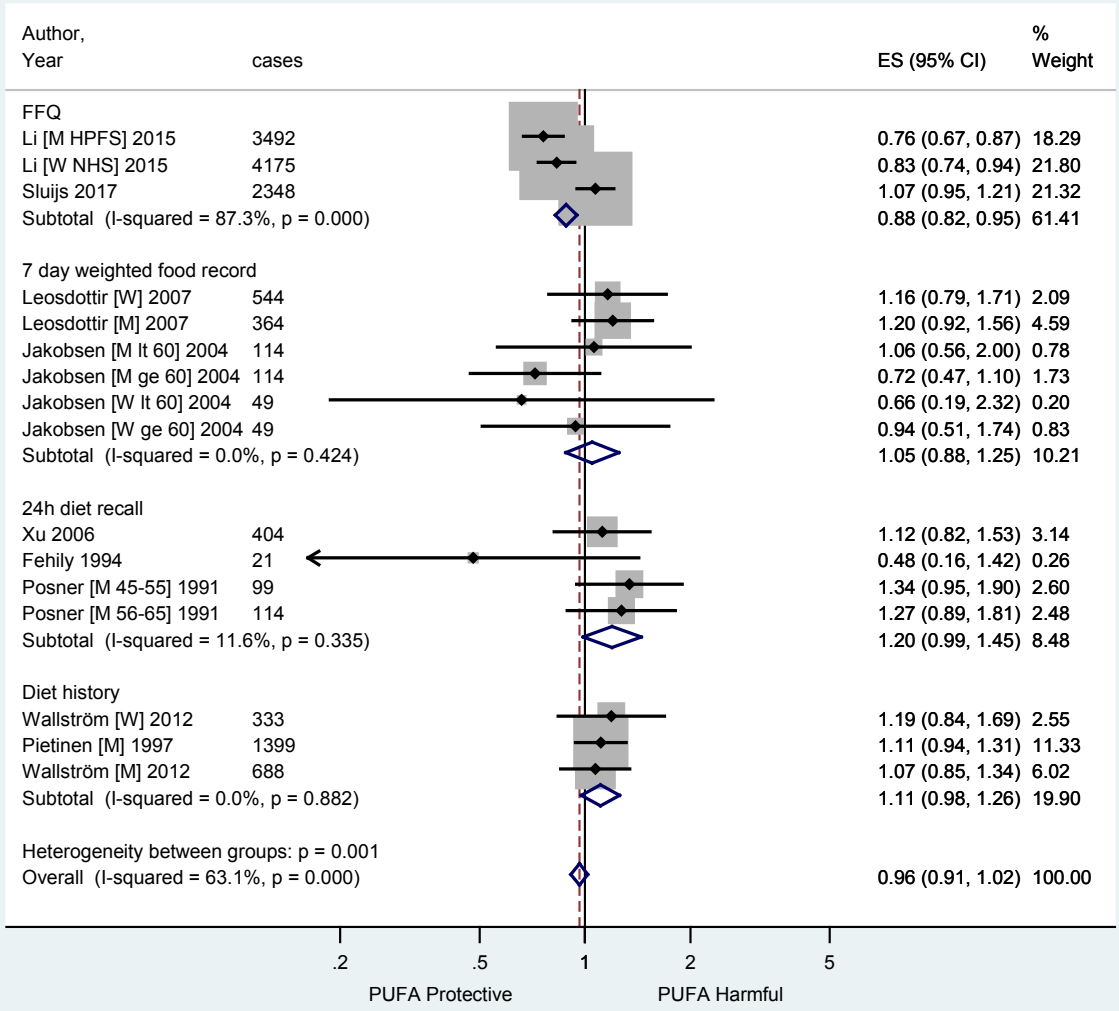
CHD: coronary heart disease; PUFA: polyunsaturated fatty acids; rr: risk ratio; smk_ev: ever smoked.

Fig. 87t. Meta-regression of total PUFA and total CHD; smoking; Panel B – subgroup analysis (smoking status)



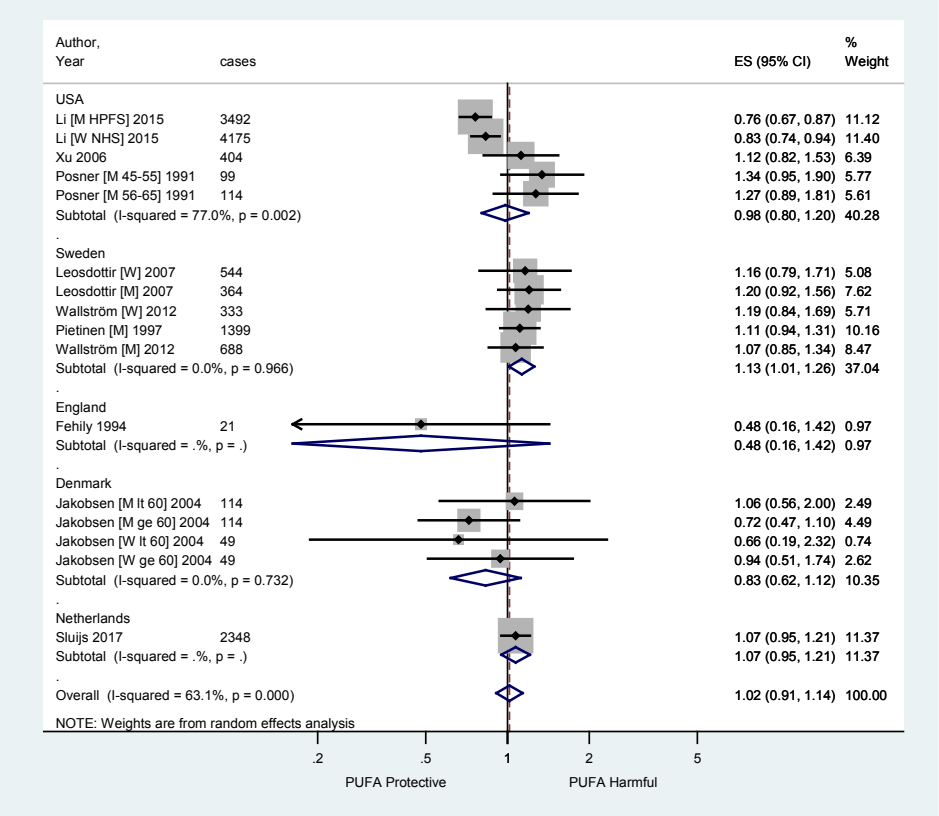
CHD: coronary heart disease; CI: confidence interval; ES: effect size; HPFS: Health Professionals Follow-up Study; M: male; NHS: Nurses' Health Study; PUFA: polyunsaturated fatty acids; smk_cur: current smokers; smk_ev: ever smoked; W: women.

Fig. 87u. Meta-regression of total PUFA and total CHD; diet assessment method; subgroup analysis



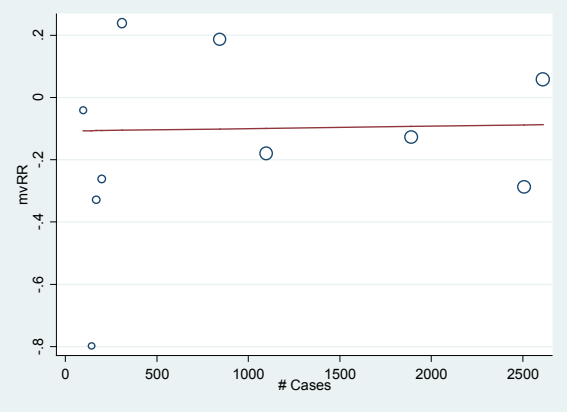
CHD: coronary heart disease; CI: confidence interval; ES: effect size; FFQ: food frequency questionnaire; ge: greater than or equal to; h: hour; HPFS: Health Professionals Follow-up Study; lt: less than; M: male; NHS: Nurses' Health Study; PUFA: polyunsaturated fatty acids; W: women. There was evidence of heterogeneity of effect size by method (P_{het}=0.001). Because the predictor variable had more than 2 levels, it is not appropriate to show the continuous meta-regression line; therefore, we present the "by country" estimates separately.

Fig. 87v. Meta-regression of total PUFA and total CHD; country of conduct; subgroup analysis by country



CHD: coronary heart disease; CI: confidence interval; ES: effect size; ge: greater than or equal to; HPFS: Health Professionals Follow-up Study; lt: less than; M: male; NHS: Nurses' Health Study; PUFA: polyunsaturated fatty acids; USA: United States of America; W: women. There was evidence of heterogeneity of effect size by country (Phet=0.0008). Because the predictor variable had more than 2 levels, it is not appropriate to show the continuous meta-regression line; therefore, we present the "by country" estimates separately.

Fig. 88a. Meta-regression of total PUFA and type 2 diabetes; number of cases; Panel A – effect size[1]

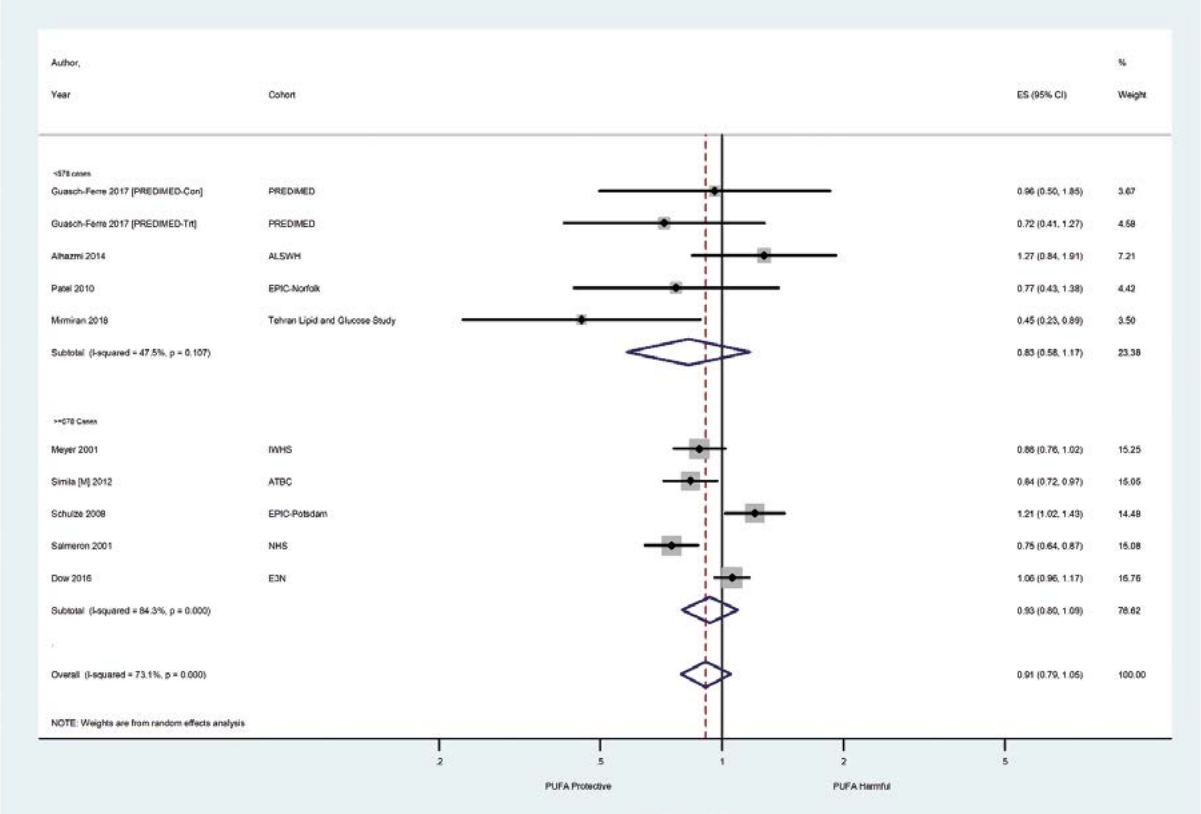


The number of cases in the study was not associated with the effect estimate (*P*=0.93).

#: number; mvRR: multivariable risk ratio; PUFA: polyunsaturated fatty acids.

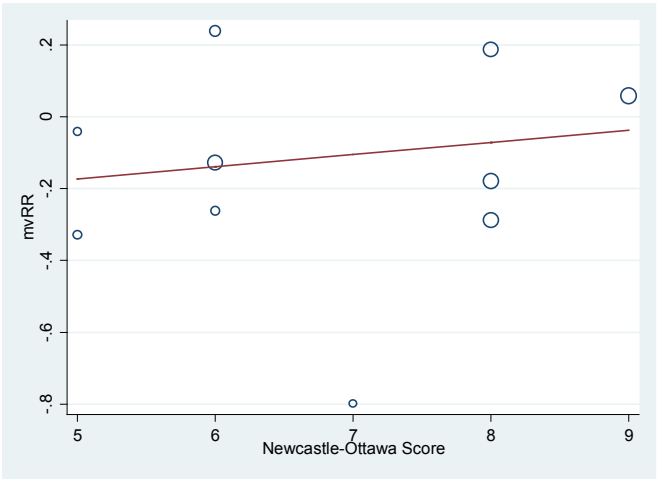
[1] Note: There is no figure for meta-regression of total PUFA and type 2 diabetes, diet assessment. All studies used a food frequency questionnaire for dietary measurement.

Fig. 88b. Meta-regression of total PUFA and type 2 diabetes; number of cases; Panel B – subgroup analysis by number of cases (median=578)



ALSWH: Australian Longitudinal Study on Women's Health; ATBC: Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study; CI: confidence interval; E3N: Etude Epidémiologique auprès de Femmes de la Mutuelle Générale de l'Éducation Nationale; EPIC: European Prospective Investigation into Cancer and Nutrition; ES: effect size; IWHS: Iowa Women's Health Study; M: male; NHS: Nurses' Health Study; PREDIMED: Prevención con Dieta Mediterránea; PREDIMED-Con: Prevención con Dieta Mediterránea (control); PREDIMED-Trt: Prevención con Dieta Mediterránea (treatment); PUFA: polyunsaturated fatty acids.

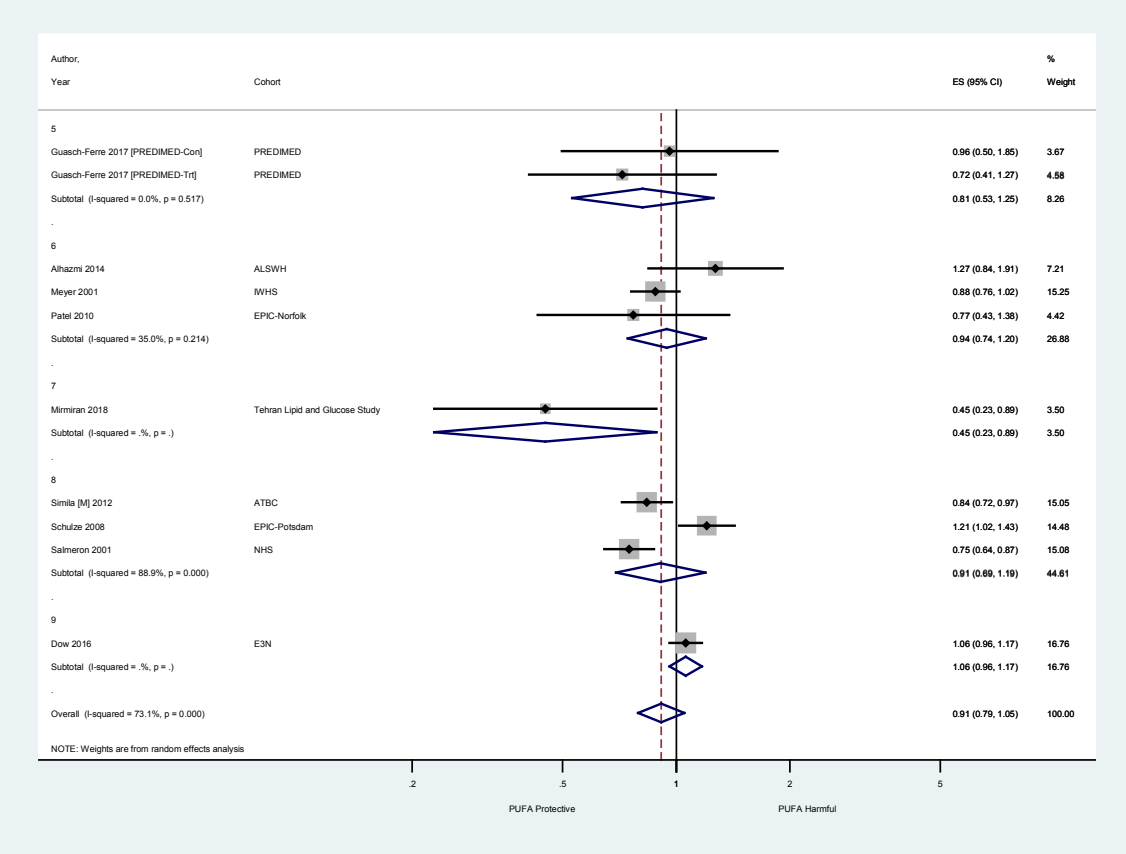
Fig. 88c. Meta-regression of total PUFA and type 2 diabetes; NOS assessment; Panel A – effect size



The effect size was not associated with adjustment for NOS score in the final model (*P*=0.61).

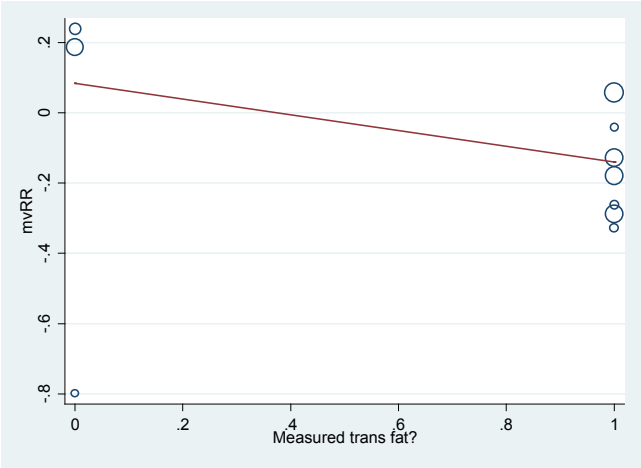
mvRR: multivariable risk ratio; NOS: Newcastle-Ottawa Scale; PUFA: polyunsaturated fatty acids.

Fig. 88d. Meta-regression of total PUFA and type 2 diabetes; NOS assessment; Panel B – subgroup analysis by NOS



ALSWH: Australian Longitudinal Study on Women's Health; ATBC: Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study; CI: confidence interval; E3N: Etude Epidémiologique auprès de Femmes de la Mutuelle Générale de l'Éducation Nationale; EPIC: European Prospective Investigation into Cancer and Nutrition; ES: effect size; IWHS: Iowa Women's Health Study; M: male; NHS: Nurses' Health Study; NOS: Newcastle-Ottawa Scale; PREDIMED: Prevención con Dieta Mediterránea; PREDIMED-Con: Prevención con Dieta Mediterránea (control); PREDIMED-Trt: Prevención con Dieta Mediterránea (treatment); PUFA: polyunsaturated fatty acids.

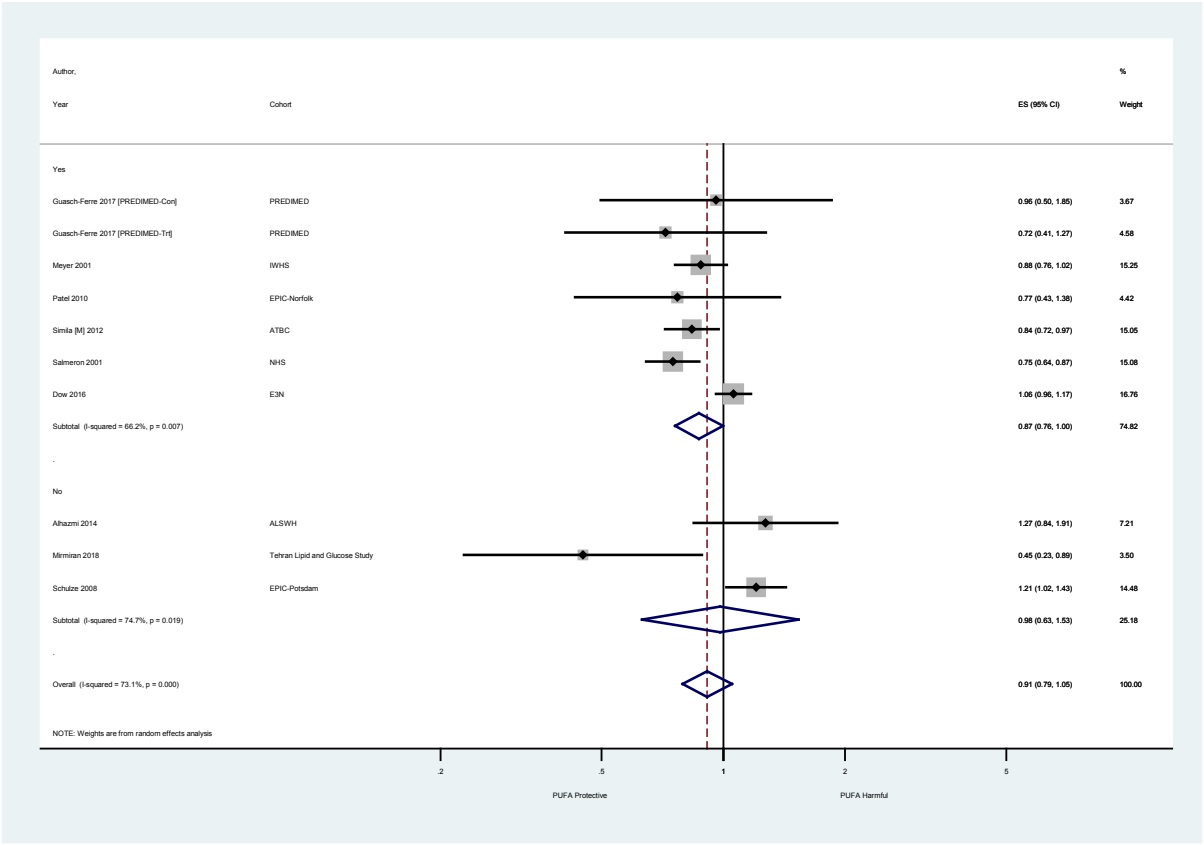
Fig. 88e. Meta-regression of total PUFA and type 2 diabetes; TFA assessment; Panel A – effect size



The effect size was not associated with adjustment for TFA measurement in the final model (*P*=0.21).

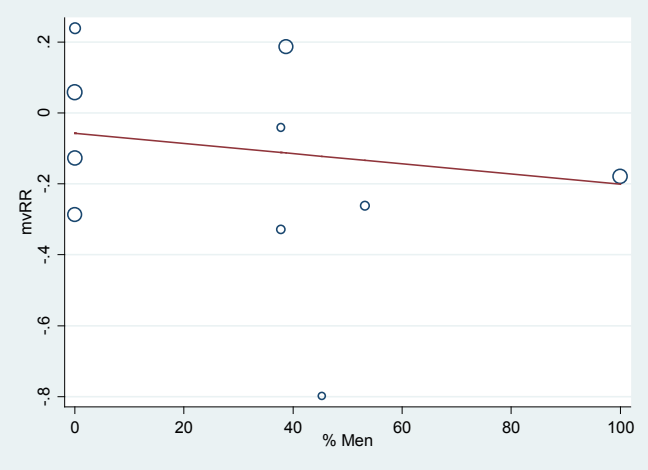
mvRR: multivariable risk ratio; PUFA: polyunsaturated fatty acids; TFA: trans-fatty acids.

Fig. 88f. Meta-regression of total PUFA and type 2 diabetes; TFA assessment; Panel B – subgroup analysis



ALSWH: Australian Longitudinal Study on Women's Health; ATBC: Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study; CI: confidence interval; E3N: Etude Epidémiologique auprès de Femmes de la Mutuelle Générale de l'Éducation Nationale; EPIC: European Prospective Investigation into Cancer and Nutrition; ES: effect size; IWHS: Iowa Women's Health Study; M: male; NHS: Nurses' Health Study; PREDIMED: Prevención con Dieta Mediterránea; PREDIMED-Con: Prevención con Dieta Mediterránea (control); PREDIMED-Trt: Prevención con Dieta Mediterránea (treatment); PUFA: polyunsaturated fatty acids; TFA: trans-fatty acids.

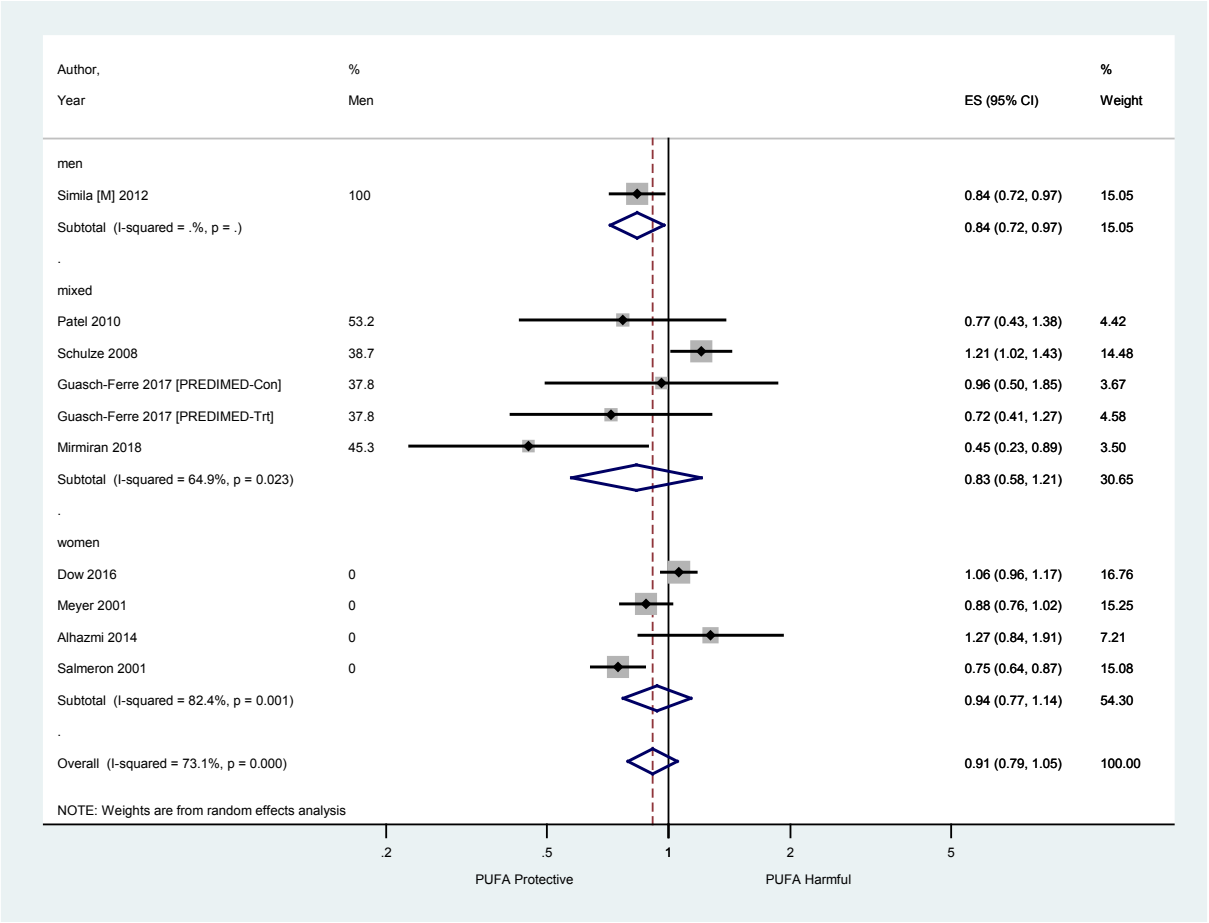
Fig. 88g. Meta-regression of total PUFA and type 2 diabetes; sex; Panel A – effect size



The effect size was not associated with the percentage of men in the study (P=0.55).

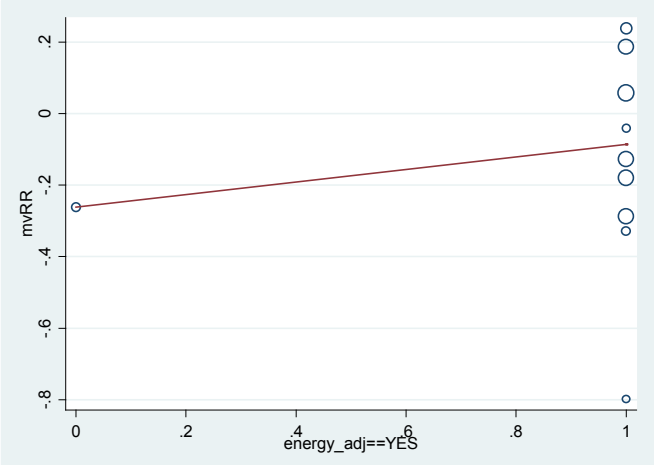
mvRR: multivariable risk ratio; PUFA: polyunsaturated fatty acids.

Fig. 88h. Meta-regression of total PUFA and type 2 diabetes; sex; Panel B – subgroup analysis



CI: confidence interval; ES: effect size; M: male; PREDIMED-Con: Prevención con Dieta Mediterránea (control); PREDIMED-Trt: Prevención con Dieta Mediterránea (treatment); PUFA: polyunsaturated fatty acids.

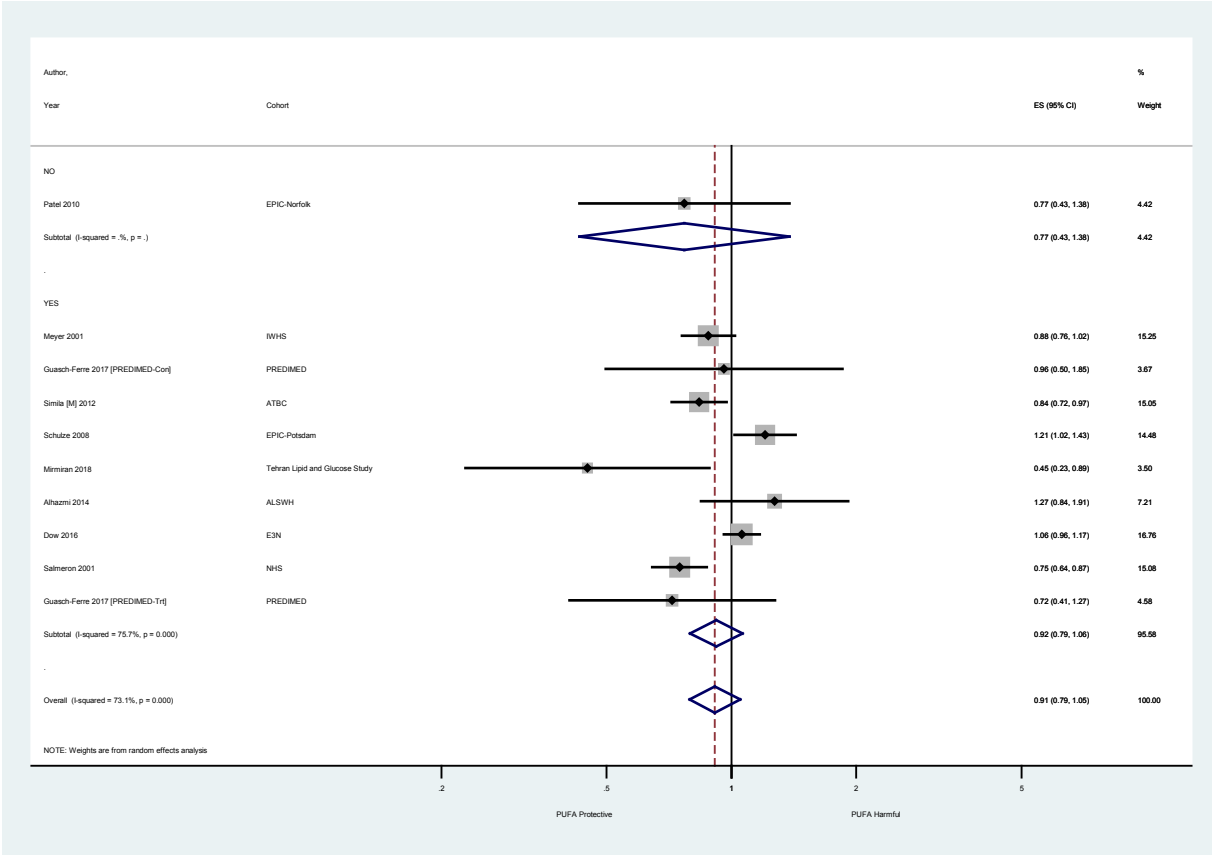
Fig. 88i. Meta-regression of total PUFA and type 2 diabetes; energy adjustment; Panel A – effect size



The effect size was not associated with adjustment for energy in the final model (*P*=0.55).

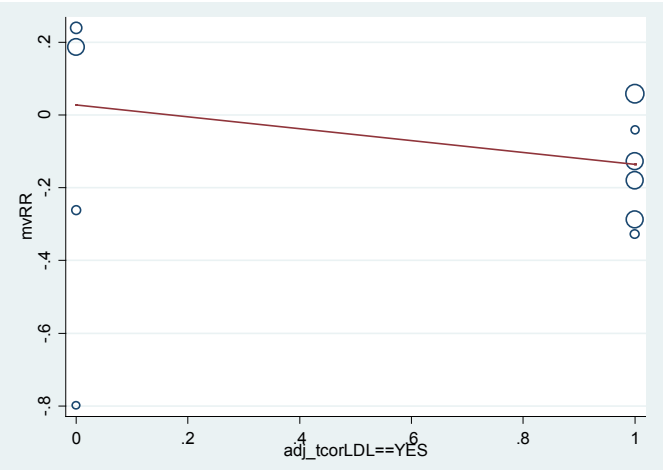
energy_adj: adjusted for energy; mvRR: multivariable risk ratio; PUFA: polyunsaturated fatty acids.

Fig. 88j. Meta-regression of total PUFA and type 2 diabetes; energy adjustment; Panel B – subgroup analysis (by adjustment for energy)



ALSWH: Australian Longitudinal Study on Women's Health; ATBC: Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study; CI: confidence interval; E3N: Etude Epidémiologique auprès de Femmes de la Mutuelle Générale de l'Éducation Nationale; EPIC: European Prospective Investigation into Cancer and Nutrition; ES: effect size; IWHS: Iowa Women's Health Study; M: male; NHS: Nurses' Health Study; PREDIMED: Prevención con Dieta Mediterránea; PREDIMED-Con: Prevención con Dieta Mediterránea (control); PREDIMED-Trt: Prevención con Dieta Mediterránea (treatment); PUFA: polyunsaturated fatty acids.

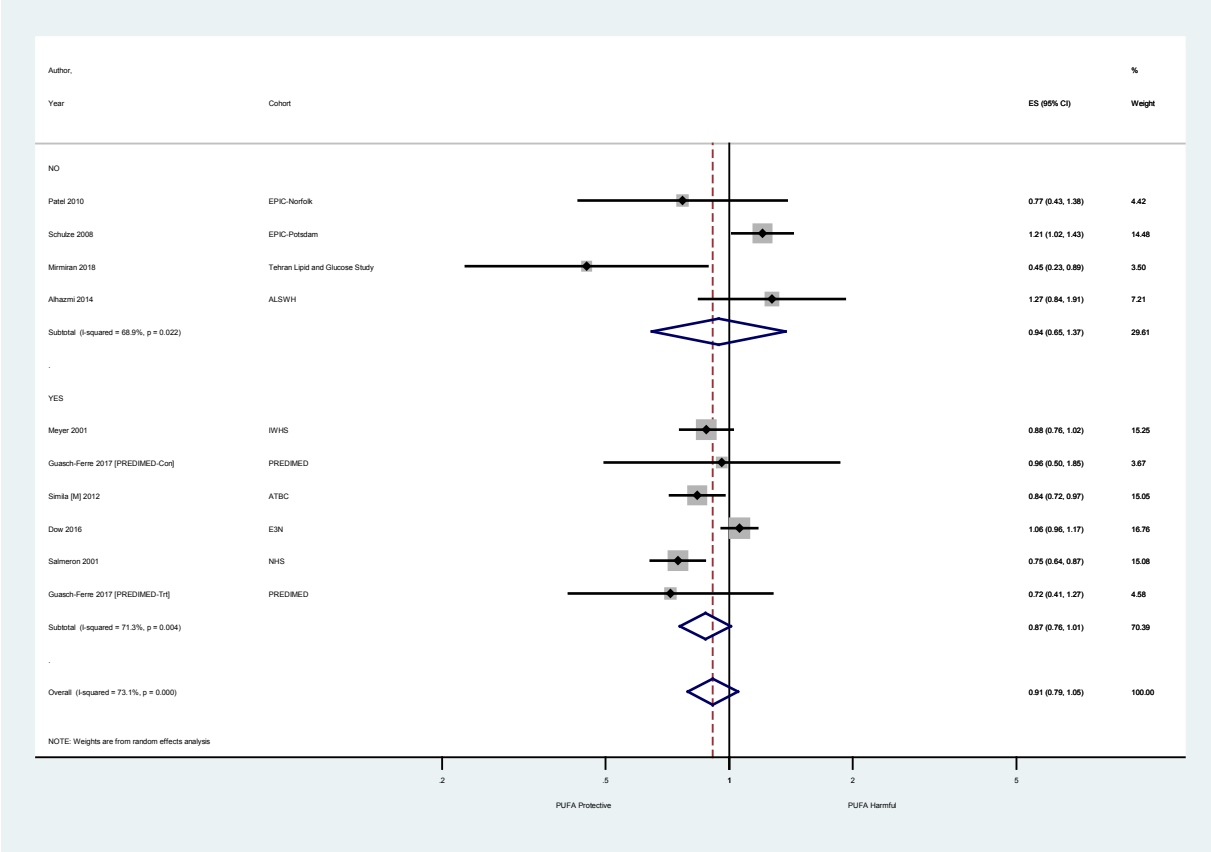
Fig. 88k. Meta-regression of total PUFA and type 2 diabetes; dyslipidaemia adjustment; Panel A – effect size



The effect size was not associated with adjustment for dyslipidaemia in the final model (*P*=0.35).

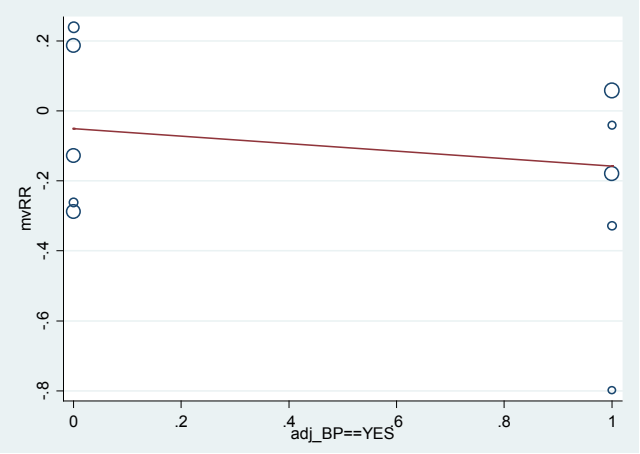
adj_tcorLDL: adjusted for dyslipidaemia; mvRR: multivariable risk ratio; PUFA: polyunsaturated fatty acids.

Fig. 88l. Meta-regression of total PUFA and type 2 diabetes; dyslipidaemia adjustment; Panel B – subgroup analysis (by adjustment for energy)



ALSWH: Australian Longitudinal Study on Women's Health; ATBC: Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study; CI: confidence interval; E3N: Etude Epidémiologique auprès de Femmes de la Mutuelle Générale de l'Éducation Nationale; EPIC: European Prospective Investigation into Cancer and Nutrition; ES: effect size; IWHS: Iowa Women's Health Study; M: male; NHS: Nurses' Health Study; PREDIMED: Prevención con Dieta Mediterránea; PREDIMED-Con: Prevención con Dieta Mediterránea (control); PREDIMED-Trt: Prevención con Dieta Mediterránea (treatment); PUFA: polyunsaturated fatty acids.

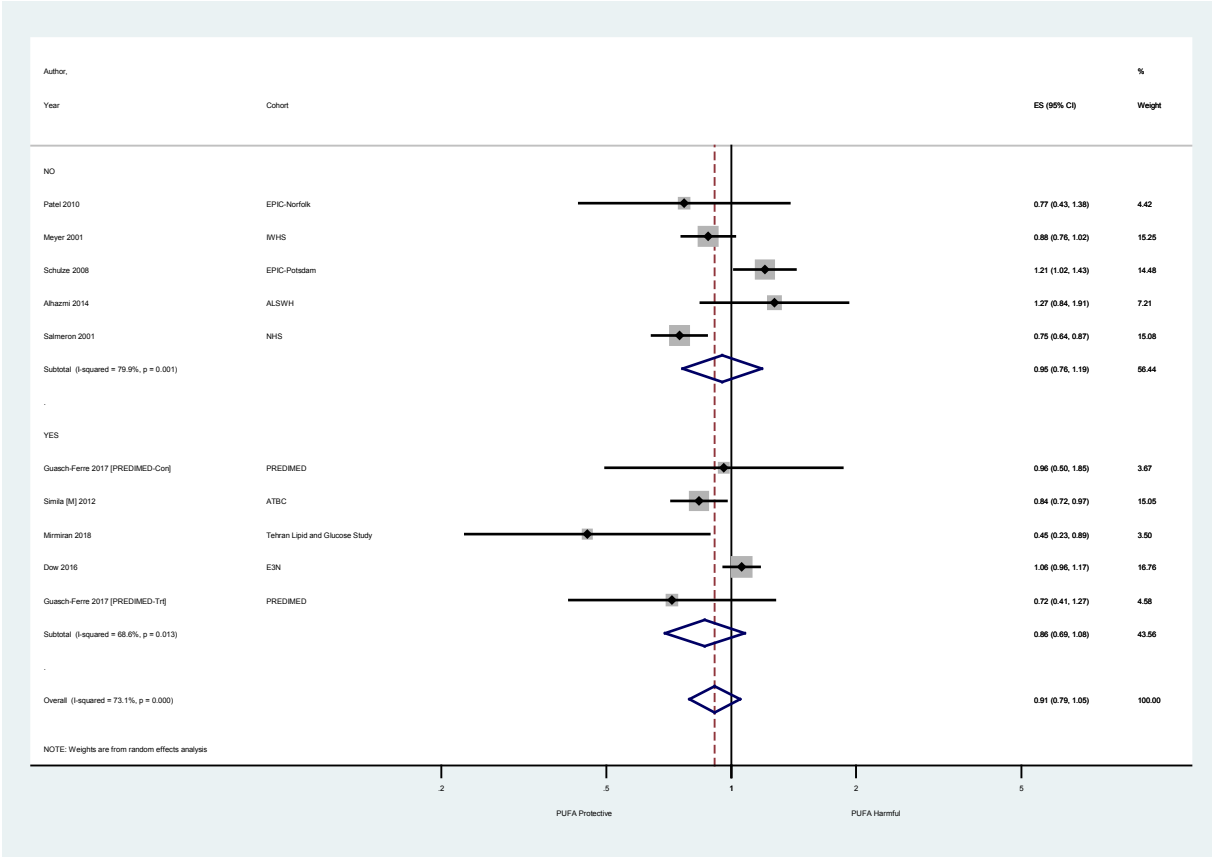
Fig. 88m. Meta-regression of total PUFA and type 2 diabetes; blood pressure adjustment; Panel A – effect size



The effect size was not associated with adjustment for blood pressure/hypertension in the final model (*P*=0.53).

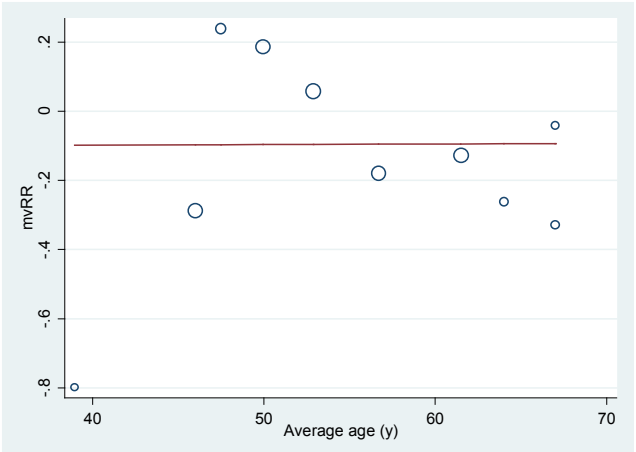
adj_BP: adjusted for blood pressure; mvRR: multivariable risk ratio; PUFA: polyunsaturated fatty acids.

Fig. 88n. Meta-regression of total PUFA and type 2 diabetes; blood pressure adjustment; Panel B – subgroup analysis



ALSWH: Australian Longitudinal Study on Women's Health; ATBC: Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study; CI: confidence interval; E3N: Etude Epidémiologique auprès de Femmes de la Mutuelle Générale de l'Éducation Nationale; EPIC: European Prospective Investigation into Cancer and Nutrition; ES: effect size; IWHS: Iowa Women's Health Study; M: male; NHS: Nurses' Health Study; PREDIMED: Prevención con Dieta Mediterránea; PREDIMED-Con: Prevención con Dieta Mediterránea (control); PREDIMED-Trt: Prevención con Dieta Mediterránea (treatment); PUFA: polyunsaturated fatty acids.

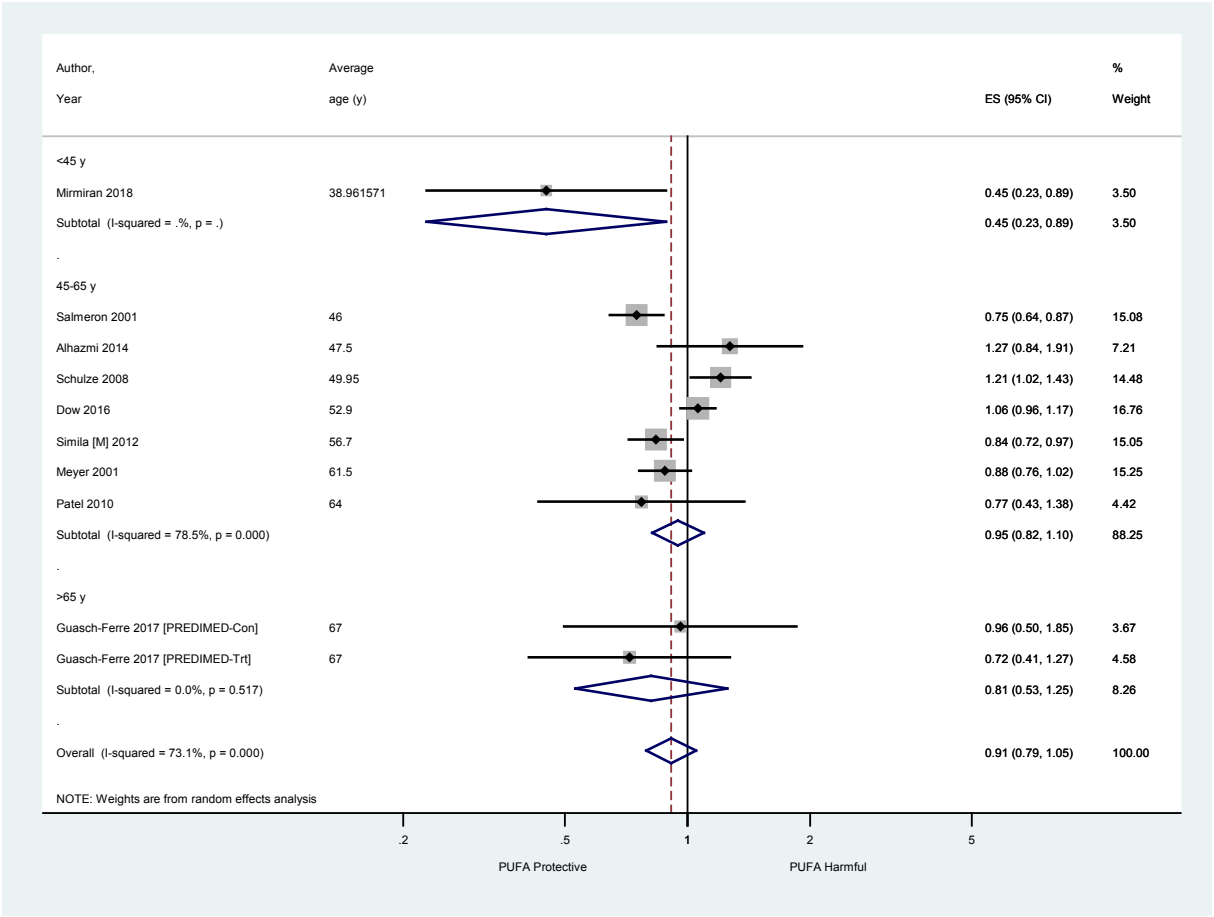
Fig. 88o. Meta-regression of total PUFA and type 2 diabetes; age; Panel A – effect size



The effect size did not depend on the average age of participants in the study (P=0.99).

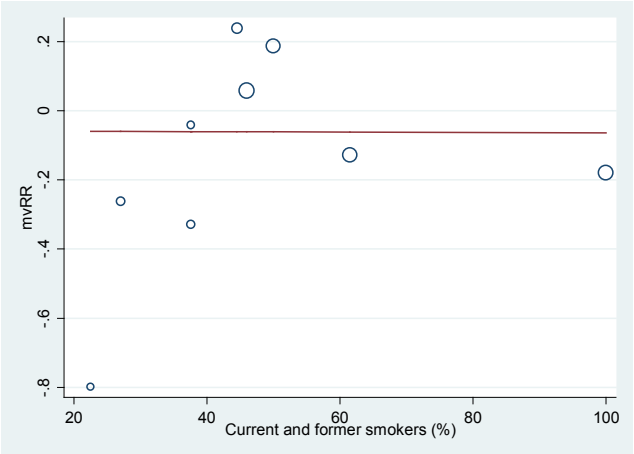
mvRR: multivariable risk ratio; PUFA: polyunsaturated fatty acids; y: years.

Fig. 88p. Meta-regression of total PUFA and type 2 diabetes; age; Panel B – subgroup analysis



CI: confidence interval; ES: effect size; M: male; PREDIMED-Con: Prevención con Dieta Mediterránea (control); PREDIMED-Trt: Prevención con Dieta Mediterránea (treatment); PUFA: polyunsaturated fatty acids; y: years.

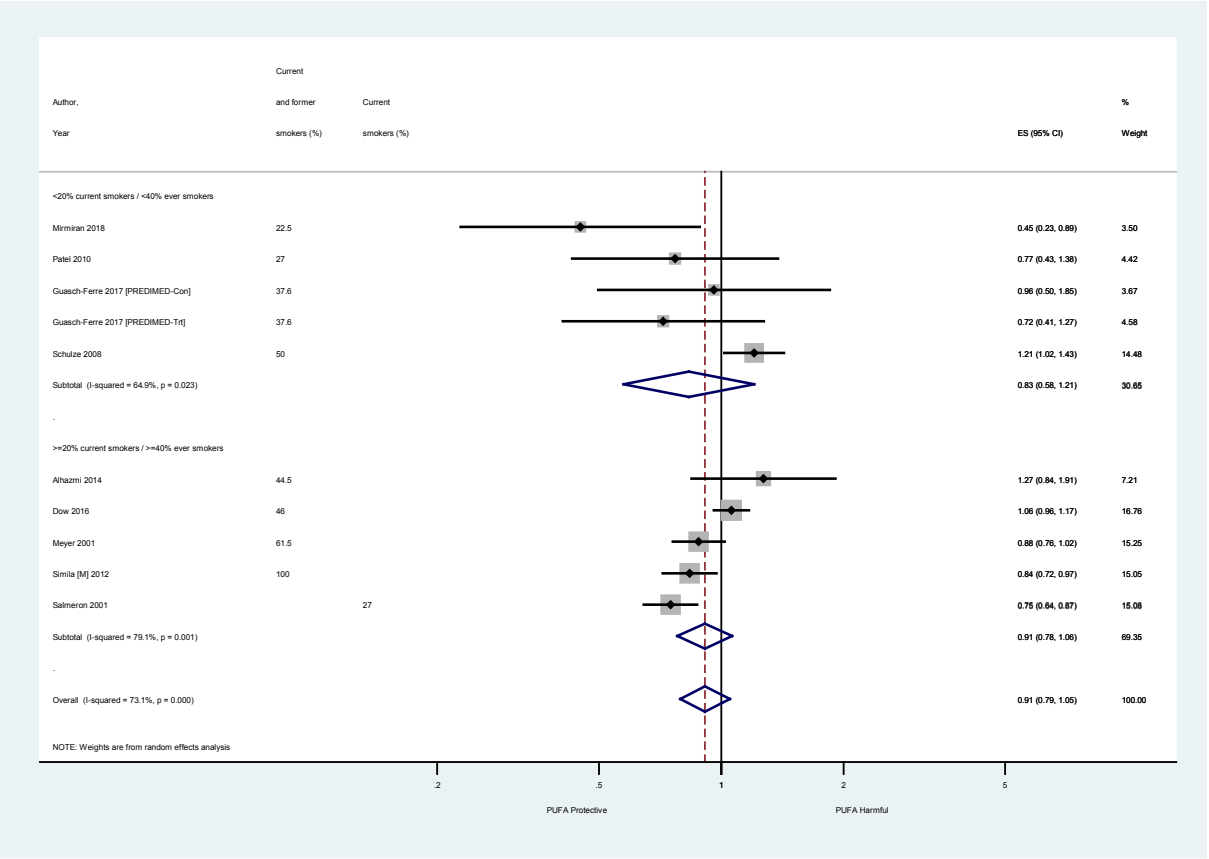
Fig. 88q. Meta-regression of total PUFA and type 2 diabetes; smoking; Panel A – effect size



The effect size did not depend on the proportion of current/former smokers in the study (*P*=0.99).

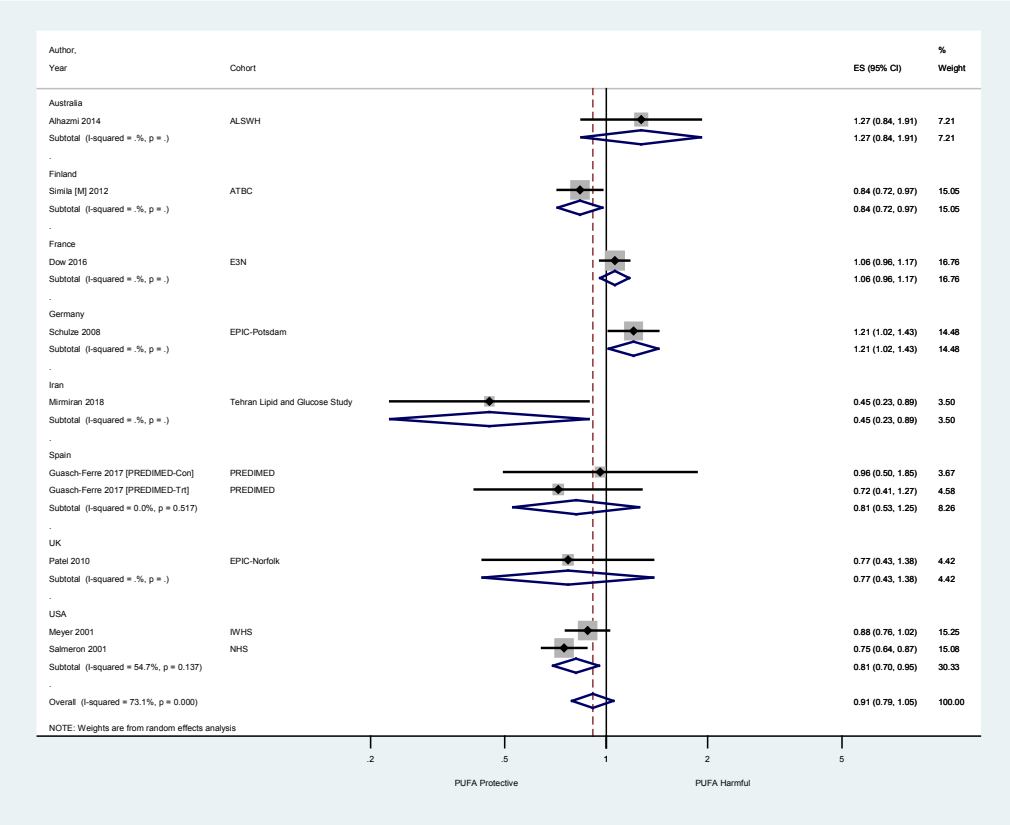
mvRR: multivariable risk ratio; PUFA: polyunsaturated fatty acids.

Fig. 88r. Meta-regression of total PUFA and type 2 diabetes; smoking; Panel B – subgroup analysis



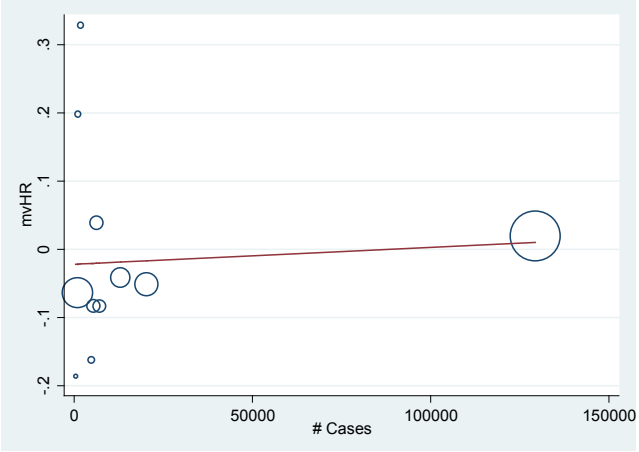
CI: confidence interval; ES: effect size; M: male; PREDIMED-Con: Prevención con Dieta Mediterránea (control); PREDIMED-Trt: Prevención con Dieta Mediterránea (treatment); PUFA: polyunsaturated fatty acids.

Fig. 88s. Meta-regression of total PUFA and type 2 diabetes; country of conduct; subgroup analysis by country



ALSWH: Australian Longitudinal Study on Women's Health; ATBC: Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study; CI: confidence interval; E3N: Etude Epidémiologique auprès de Femmes de la Mutuelle Générale de l'Éducation Nationale; EPIC: European Prospective Investigation into Cancer and Nutrition; ES: effect size; IWHS: Iowa Women's Health Study; M: male; NHS: Nurses' Health Study; PREDIMED: Prevención con Dieta Mediterránea; PREDIMED-Con: Prevención con Dieta Mediterránea (control); PREDIMED-Trt: Prevención con Dieta Mediterránea (treatment); PUFA: polyunsaturated fatty acids; UK: United Kingdom; USA: United States of America. There was no evidence of heterogeneity of effect size by country of conduct (*P*=0.25).

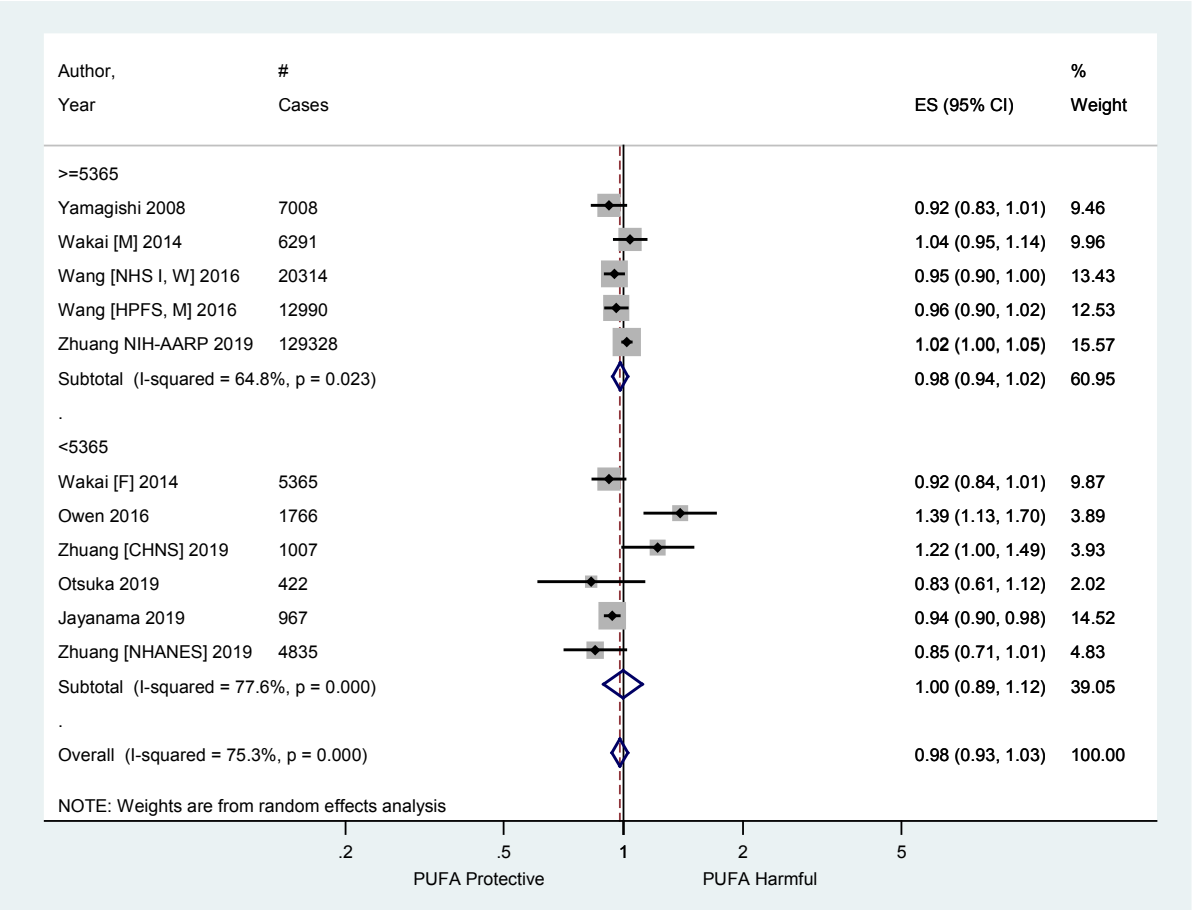
Fig. 89a. Meta-regression of total n-3 PUFA and all-cause mortality; number of cases; Panel A – effect size



The number of cases in the study was not associated with the effect estimate (*P*=0.80).

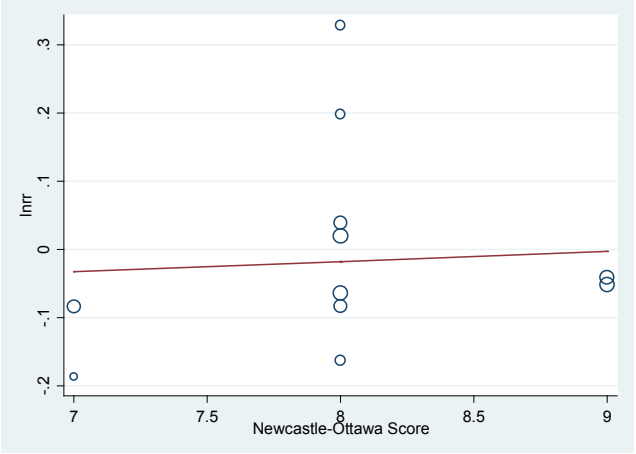
#: number; CI: confidence interval; mvHR: multivariable hazard ratio; mvRR: multivariable risk ratio; PUFA: polyunsaturated fatty acids.

Fig. 89b. Meta-regression of total n-3 PUFA and all-cause mortality; number of cases; Panel B – subgroup analysis by number of cases (median=5365)



#: number; CHNS: China Health and Nutrition Survey; CI: confidence interval; ES: effect size; F: female; HPFS: Health Professionals Follow-up Study; M: male; NHANES: National Health and Nutrition Examination Survey; NHS I: Nurses' Health Study I; NIH-AARP: National Institutes of Health American Association of Retired Persons Diet and Health Study; PUFA: polyunsaturated fatty acids; W: women.

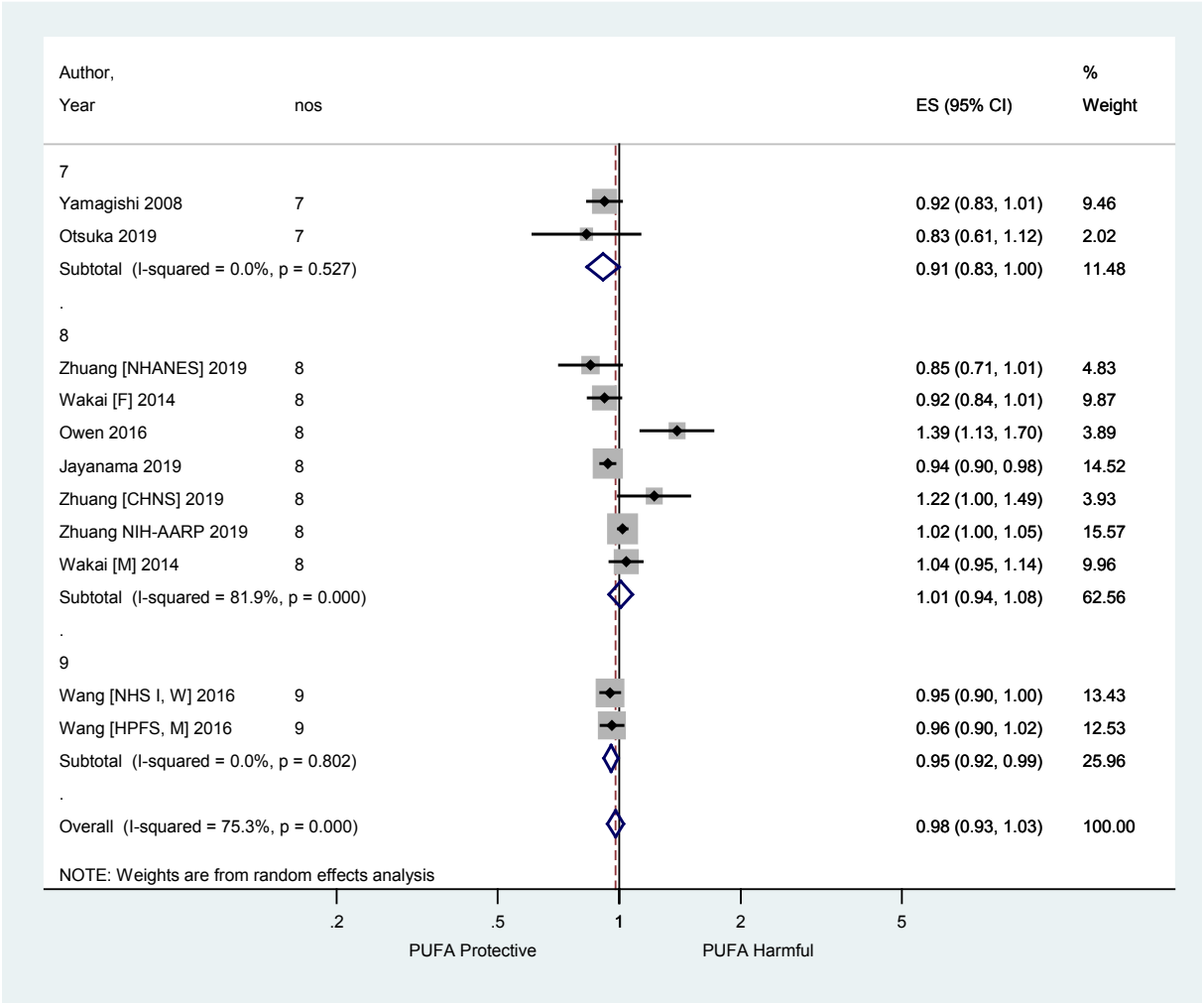
Fig. 89c. Meta-regression of total n-3 PUFA and all-cause mortality; NOS assessment; Panel A – effect size



NOS was associated with effect size estimate (*P*=0.02).

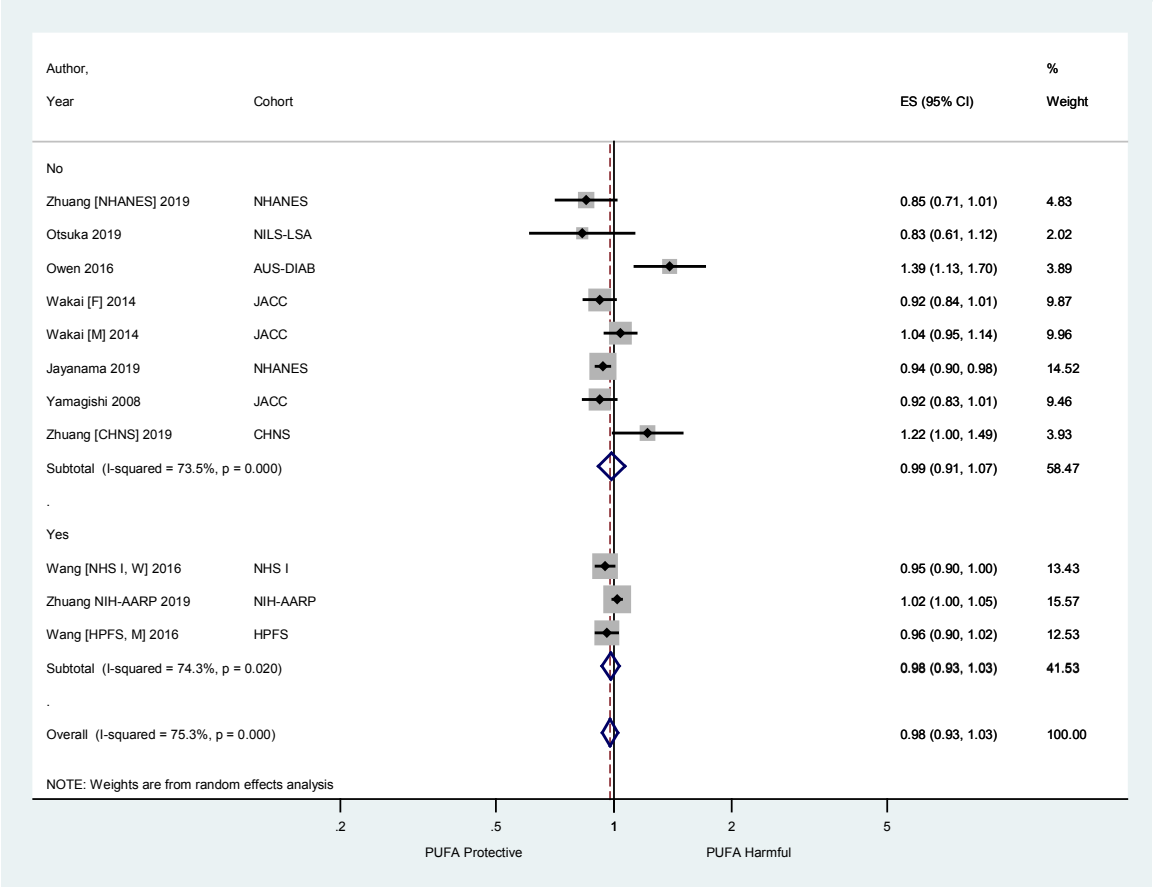
NOS: Newcastle-Ottawa Scale; PUFA: polyunsaturated fatty acids; rr: risk ratio.

Fig. 89d. Meta-regression of total n-3 PUFA and all-cause mortality; NOS assessment; Panel B – subgroup analysis



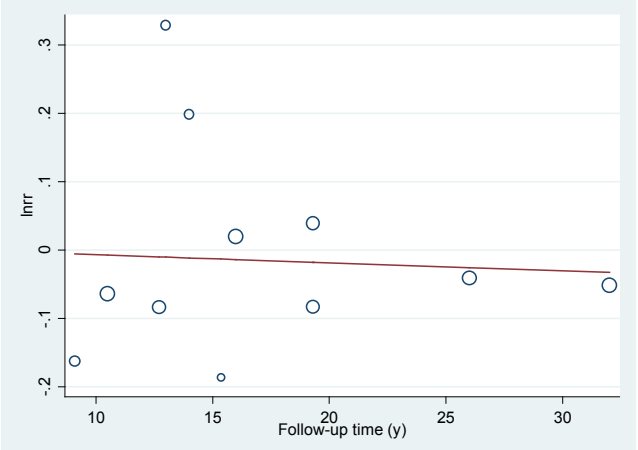
CHNS: China Health and Nutrition Survey; CI: confidence interval; ES: effect size; F: female; HPFS: Health Professionals Follow-up Study; M: male; NHANES: National Health and Nutrition Examination Survey; NHS I: Nurses' Health Study I; NIH-AARP: National Institutes of Health American Association of Retired Persons Diet and Health Study; nos: Newcastle-Ottawa Scale; NOS: Newcastle-Ottawa Scale; PUFA: polyunsaturated fatty acids; W: women.

Fig. 89e. Meta-regression of total n-3 PUFA and all-cause mortality; TFA assessment; subgroup analysis



CHNS: China Health and Nutrition Survey; CI: confidence interval; ES: effect size; F: female; HPFS: Health Professionals Follow-up Study; M: male; NHANES: National Health and Nutrition Examination Survey; NHS I: Nurses' Health Study I; NIH-AARP: National Institutes of Health American Association of Retired Persons Diet and Health Study; PUFA: polyunsaturated fatty acids; TFA: trans-fatty acids; W: women. The effect size was not associated with adjustment for measurement of TFA in the final model (*P*=0.90).

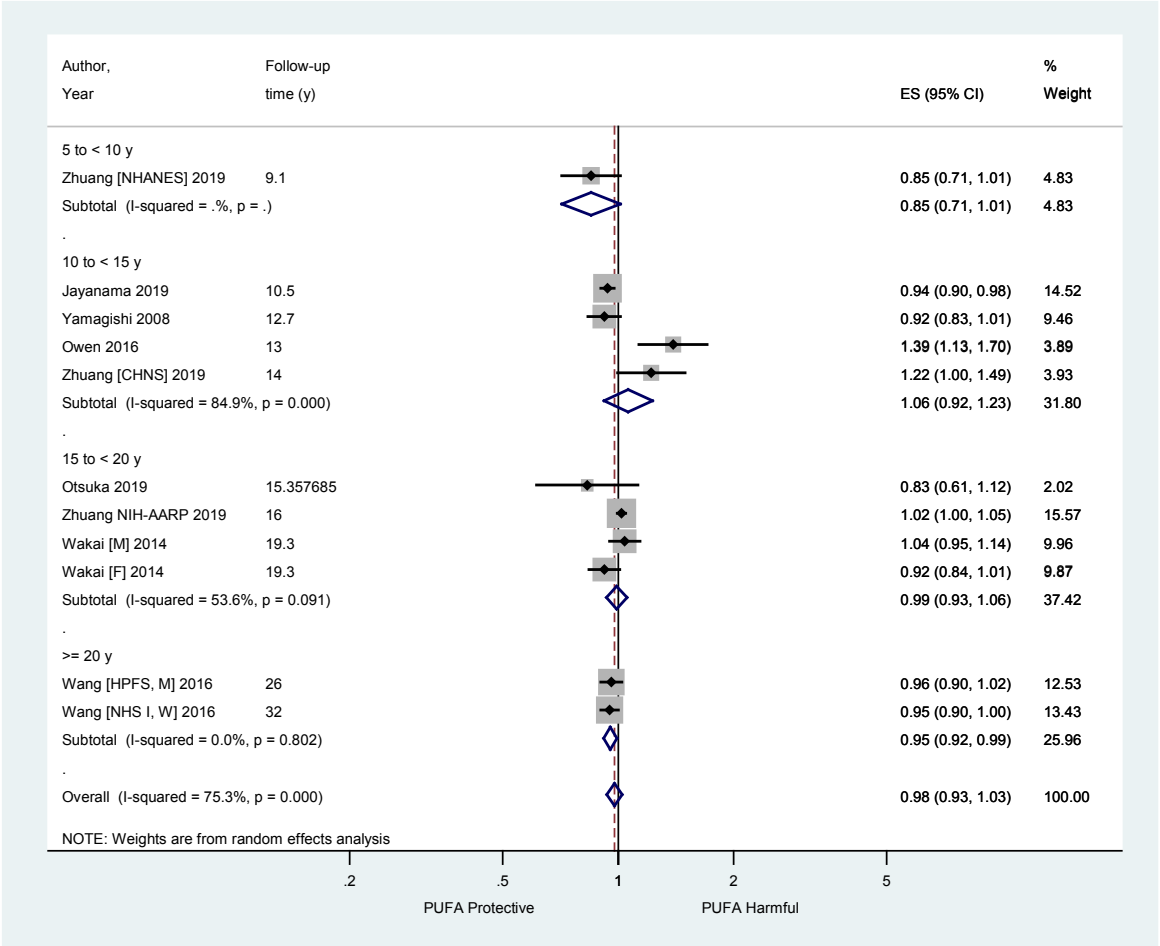
Fig. 89f. Meta-regression of total n-3 PUFA and all-cause mortality; follow-up time; Panel A – effect size



The effect size was not associated with adjustment for duration of follow-up in the final model (*P*=0.84).

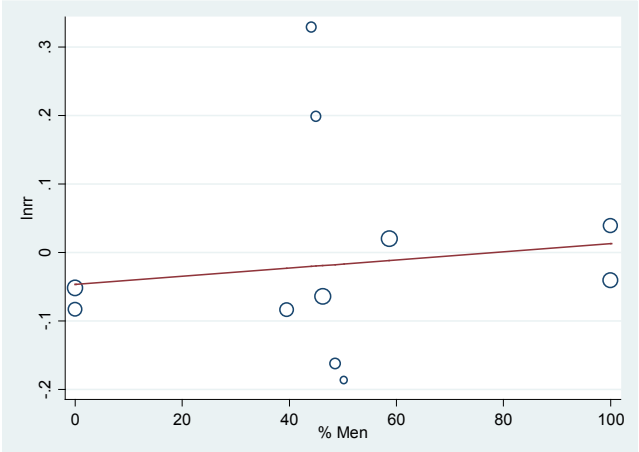
PUFA: polyunsaturated fatty acids; rr: risk ratio; y: years.

Fig. 89g. Meta-regression of total n-3 PUFA and all-cause mortality; follow-up time; Panel B – subgroup analysis



CHNS: China Health and Nutrition Survey; CI: confidence interval; ES: effect size; F: female; HPFS: Health Professionals Follow-up Study; M: male; NHANES: National Health and Nutrition Examination Survey; NHS I: Nurses' Health Study I; NIH-AARP: National Institutes of Health American Association of Retired Persons Diet and Health Study; PUFA: polyunsaturated fatty acids; W: women; y: years.

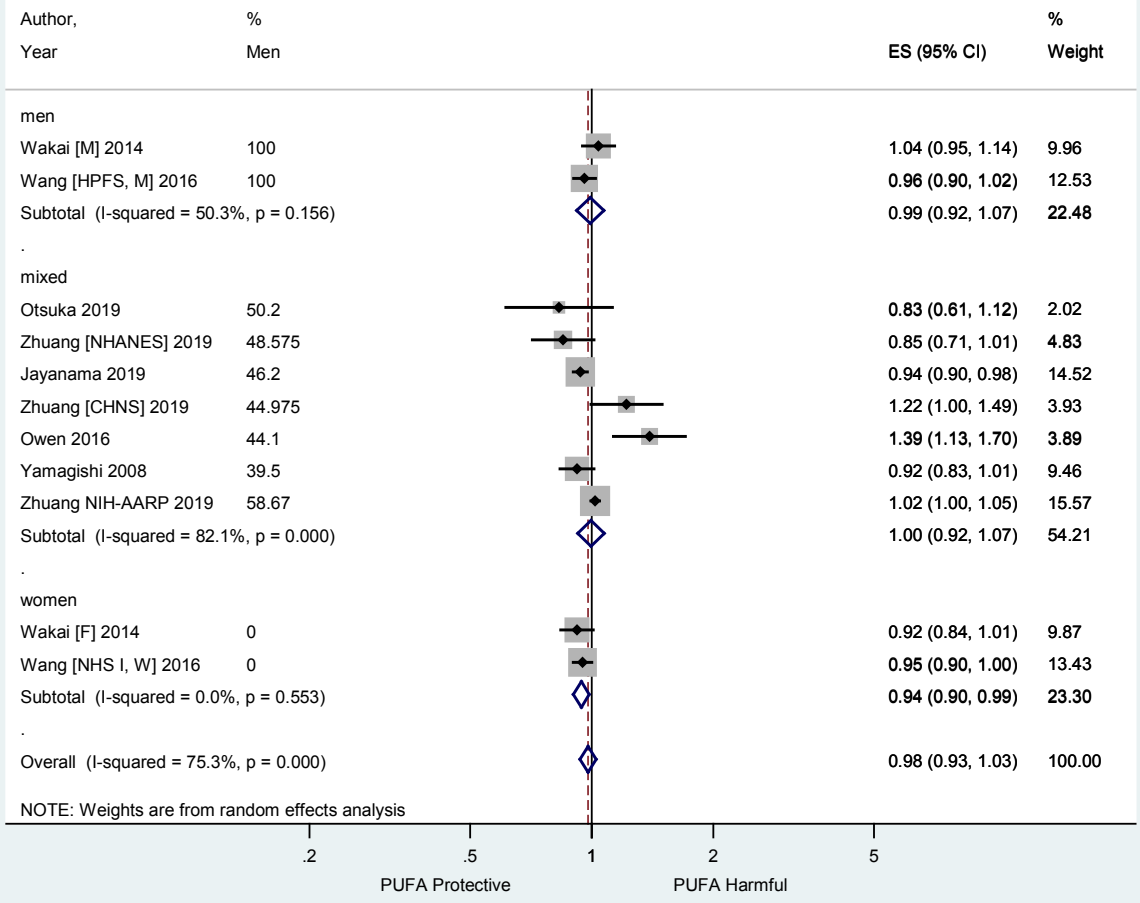
Fig. 89h. Meta-regression of total n-3 PUFA and all-cause mortality; sex; Panel A – effect size



The effect size was not associated with the percentage of men in the study (*P*=0.60).

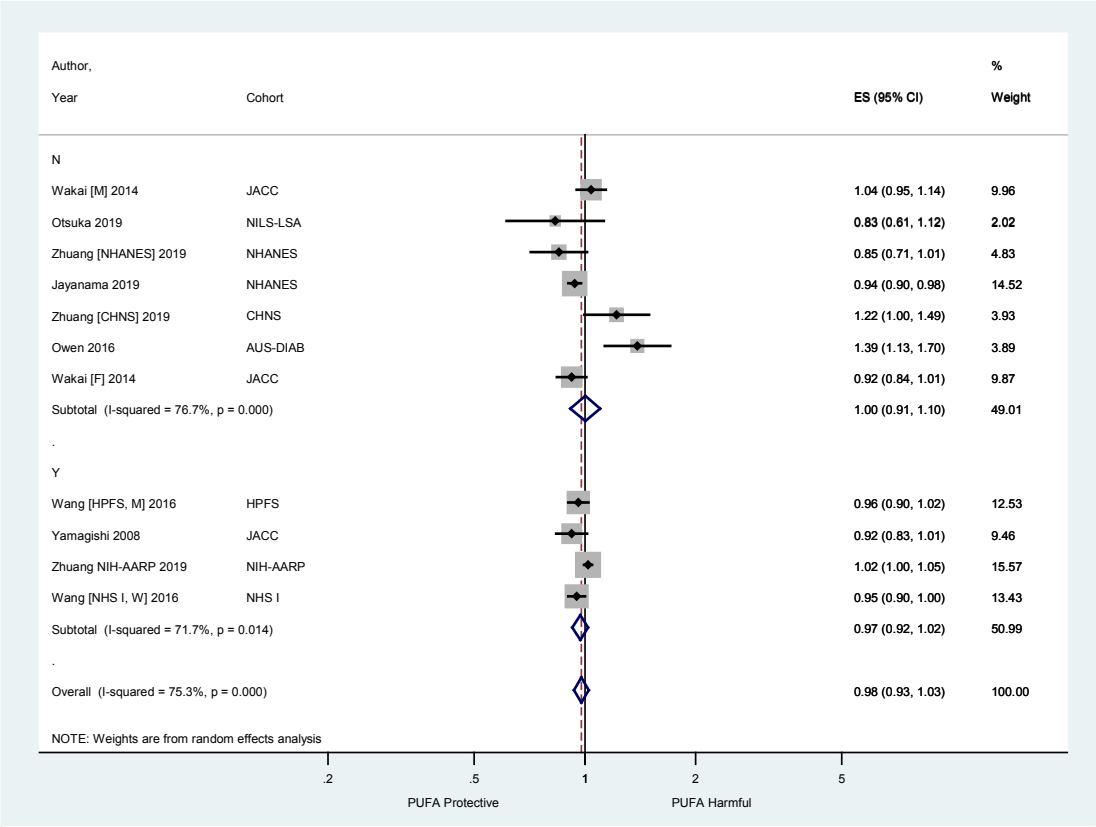
PUFA: polyunsaturated fatty acids; rr: risk ratio.

Fig. 89i. Meta-regression of total n-3 PUFA and all-cause mortality; sex; Panel B – subgroup analysis



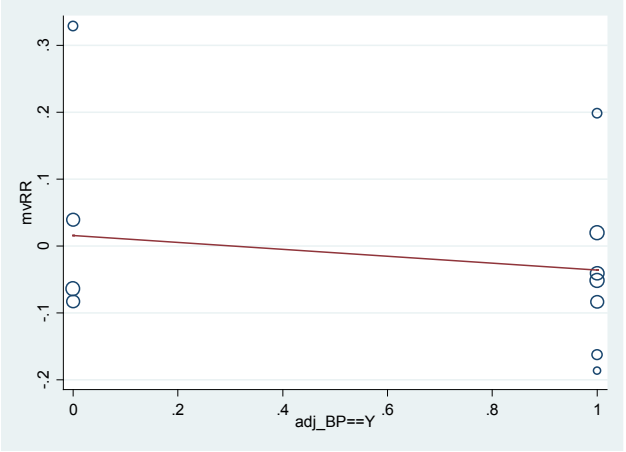
CHNS: China Health and Nutrition Survey; CI: confidence interval; ES: effect size; F: female; HPFS: Health Professionals Follow-up Study; M: male; NHANES: National Health and Nutrition Examination Survey; NHS I: Nurses' Health Study I; NIH-AARP: National Institutes of Health American Association of Retired Persons Diet and Health Study; PUFA: polyunsaturated fatty acids; W: women.

Fig. 89j. Meta-regression of total n-3 PUFA and all-cause mortality; dyslipidaemia adjustment; subgroup analysis



AUS-DIAB: Australian Diabetes, Obesity and Lifestyle Study; CHNS: China Health and Nutrition Survey; CI: confidence interval; ES: effect size; F: female; HPFS: Health Professionals Follow-up Study; JACC: Japan Collaborative Cohort; M: male; N: no; NHANES: National Health and Nutrition Examination Survey; NHS I: Nurses' Health Study I; NIH-AARP: National Institutes of Health American Association of Retired Persons Diet and Health Study; NILS-LSA: National Institute for Longevity Sciences-Longitudinal Study of Aging; PUFA: polyunsaturated fatty acids; W: women; Y: yes.
The effect size was not associated with whether or not there was adjustment for a measure of dyslipidaemia in the final model (P=0.64).

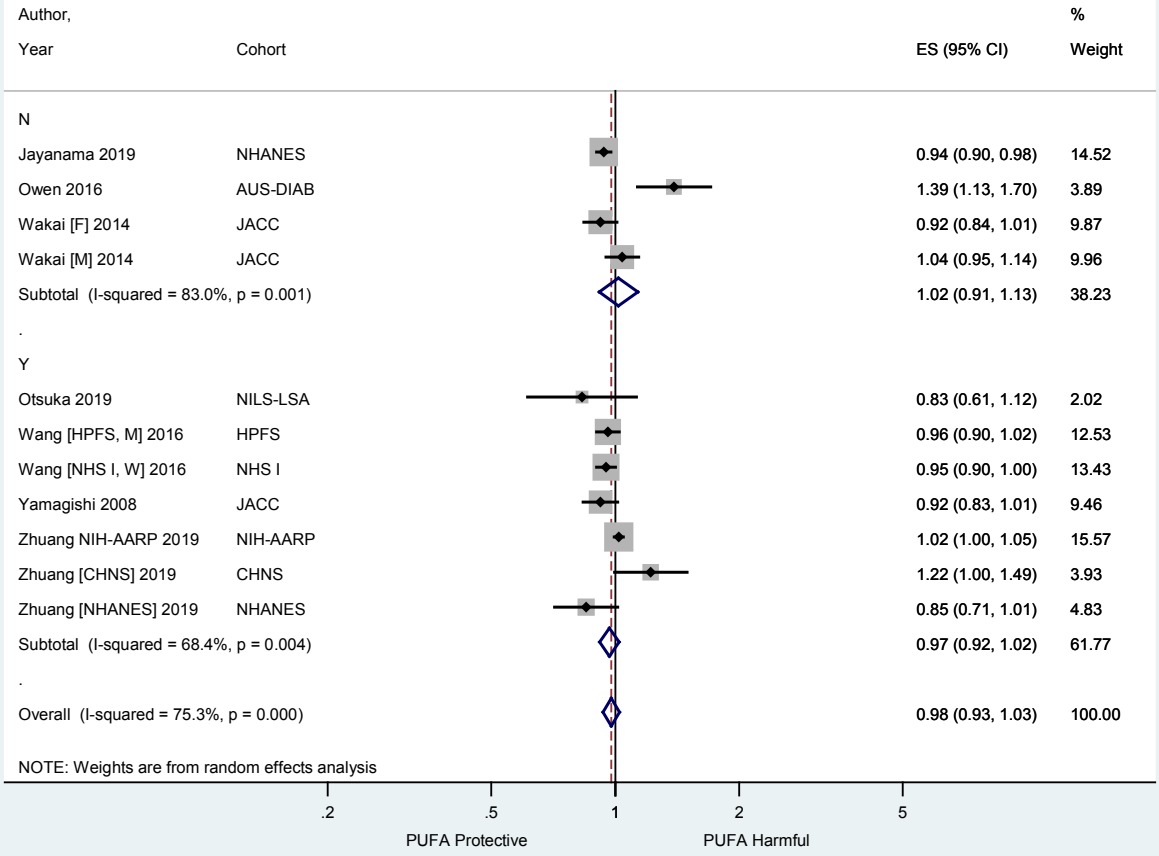
Fig. 89k. Meta-regression of total n-3 PUFA and all-cause mortality; blood pressure adjustment; Panel A – effect size



The effect size was not associated with adjustment for a measure of hypertension in the final model (P=0.52).

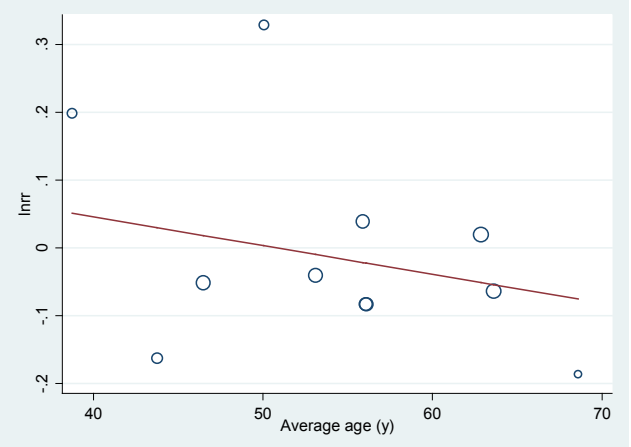
PUFA: polyunsaturated fatty acids.

Fig. 89l. Meta-regression of total n-3 PUFA and all-cause mortality; blood pressure adjustment; Panel B – subgroup analysis



AUS-DIAB: Australian Diabetes, Obesity and Lifestyle Study; CHNS: China Health and Nutrition Survey; CI: confidence interval; ES: effect size; F: female; HPFS: Health Professionals Follow-up Study; JACC: Japan Collaborative Cohort; M: male; N: no; NHANES: National Health and Nutrition Examination Survey; NHS I: Nurses' Health Study I; NIH-AARP: National Institutes of Health American Association of Retired Persons Diet and Health Study; NILS-LSA: National Institute for Longevity Sciences-Longitudinal Study of Aging; PUFA: polyunsaturated fatty acids; W: women; Y: yes.

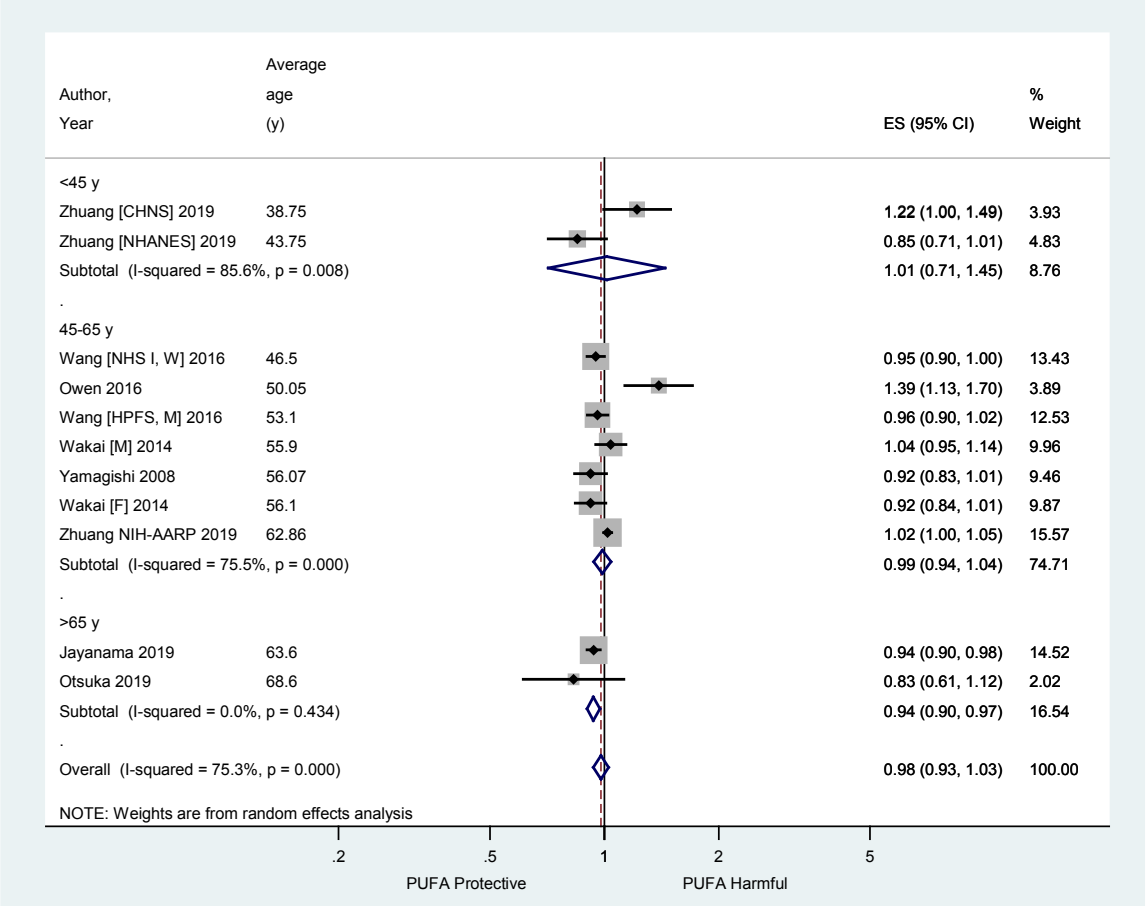
Fig. 89m. Meta-regression of total n-3 PUFA and all-cause mortality; age; Panel A – effect size



The effect estimate was not associated with the average age of participants (P=0.41).

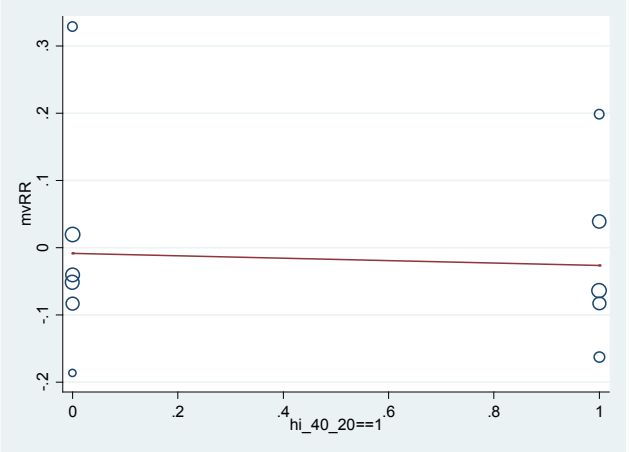
PUFA: polyunsaturated fatty acids; rr: risk ratio; y: years.

Fig. 89n. Meta-regression of total n-3 PUFA and all-cause mortality; age; Panel B – subgroup analysis



CHNS: China Health and Nutrition Survey; CI: confidence interval; ES: effect size; F: female; HPFS: Health Professionals Follow-up Study; M: male; NHANES: National Health and Nutrition Examination Survey; NHS I: Nurses' Health Study I; NIH-AARP: National Institutes of Health American Association of Retired Persons Diet and Health Study; PUFA: polyunsaturated fatty acids; W: women; y: years.

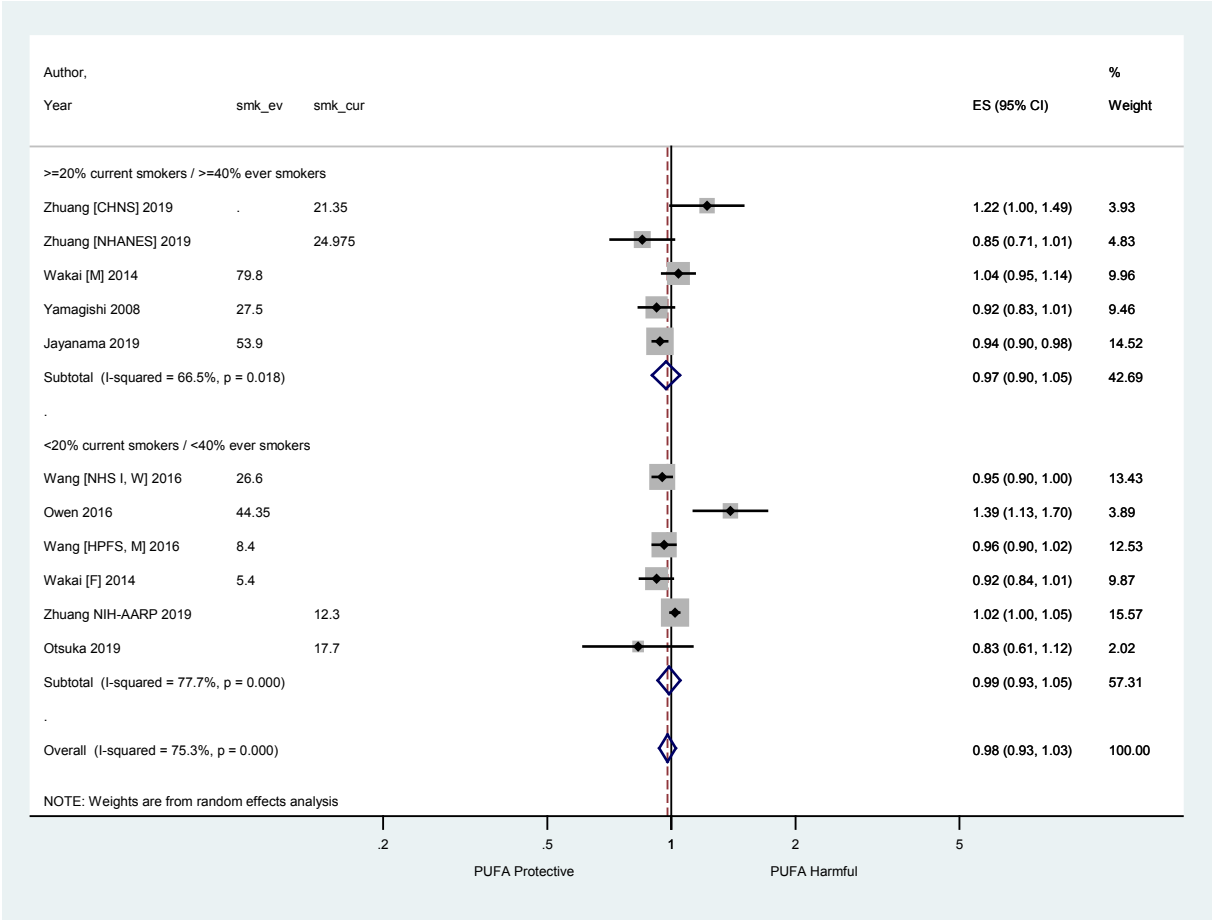
Fig. 89o. Meta-regression of total n-3 PUFA and all-cause mortality; smoking; Panel A – effect size



The effect of total n-3 PUFA on all-cause mortality did not depend on the% of smokers in the study (*P*=0.83).

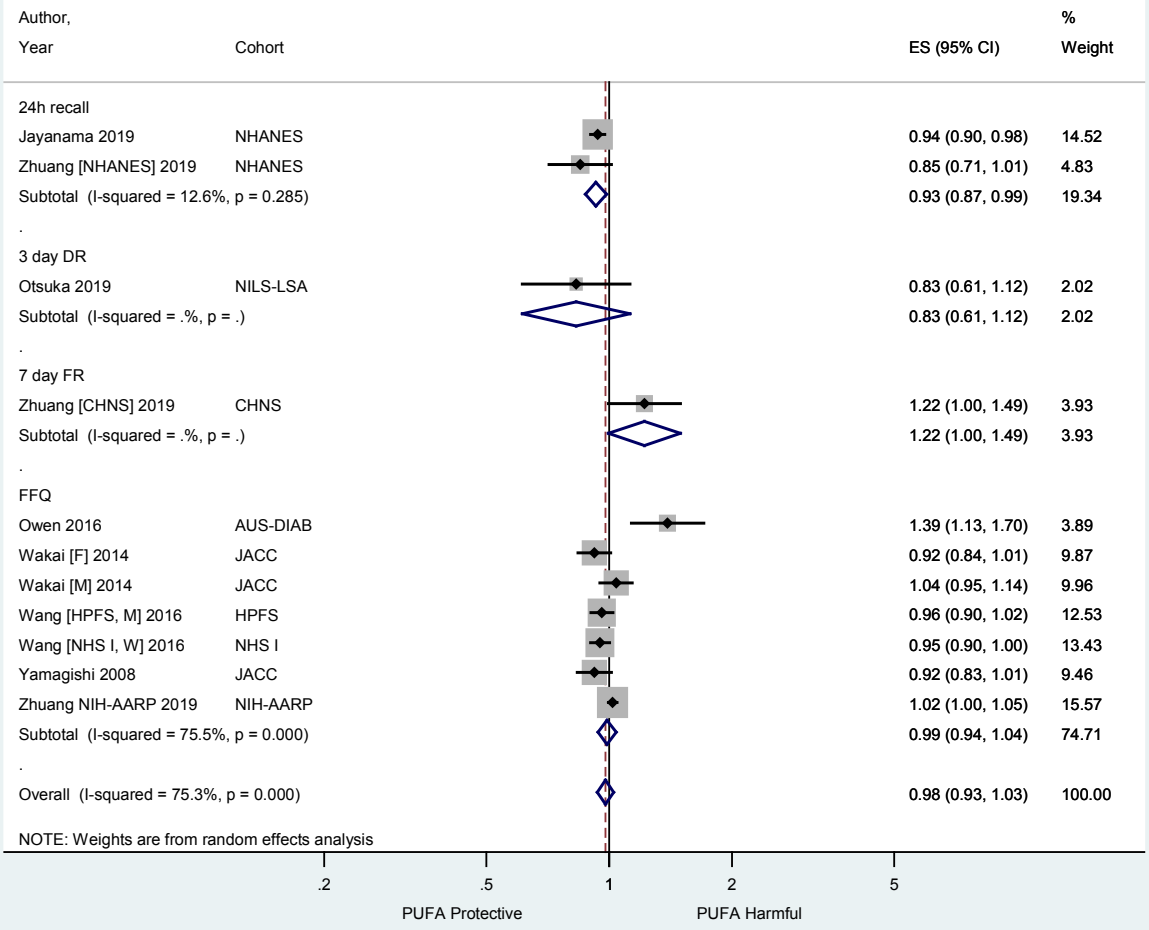
mvRR: multivariable risk ratio; PUFA: polyunsaturated fatty acids.

Fig. 89p. Meta-regression of total n-3 PUFA and all-cause mortality; smoking; Panel B – subgroup analysis



CHNS: China Health and Nutrition Survey; CI: confidence interval; ES: effect size; F: female; HPFS: Health Professionals Follow-up Study; M: male; NHANES: National Health and Nutrition Examination Survey; NHS I: Nurses' Health Study I; NIH-AARP: National Institutes of Health American Association of Retired Persons Diet and Health Study; PUFA: polyunsaturated fatty acids; smk_cur: current smokers; smk_ev: ever smoked; W: women.

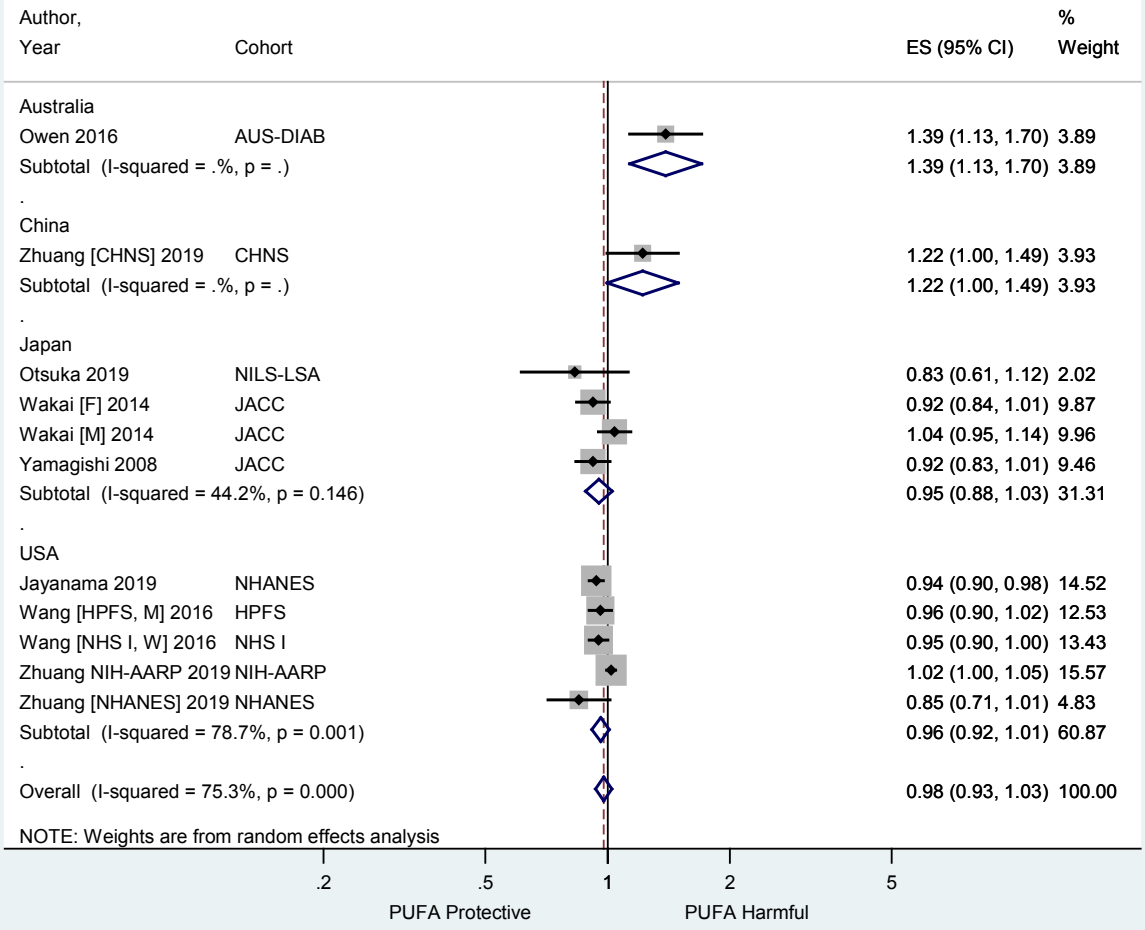
Fig. 89q. Meta-regression of total n-3 PUFA and all-cause mortality; diet assessment method; subgroup analysis



AUS-DIAB: Australian Diabetes, Obesity and Lifestyle Study; CHNS: China Health and Nutrition Survey; CI: confidence interval; DR: dietary record; ES: effect size; F: female; FFQ: food frequency questionnaire; FR: food record; h: hour; HPFS: Health Professionals Follow-up Study; JACC: Japan Collaborative Cohort; M: male; NHANES: National Health and Nutrition Examination Survey; NHS I: Nurses' Health Study I; NIH-AARP: National Institutes of Health American Association of Retired Persons Diet and Health Study; NILS-LSA: National Institute for Longevity Sciences-Longitudinal Study of Aging; PUFA: polyunsaturated fatty acids; W: women.

The effect of total n-3 PUFA on all-cause mortality did not depend on diet assessment method (P=0.38). Because the predictor variable had more than 2 levels, it is not appropriate to show the continuous meta-regression line; therefore, we present the "by assessment method" estimates separately.

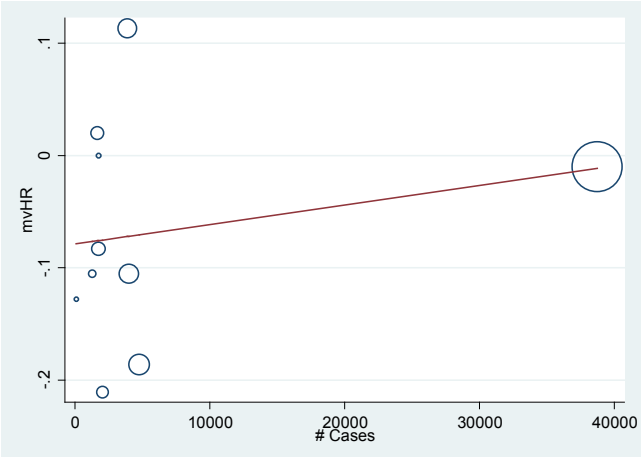
Fig. 89r. Meta-regression of total n-3 PUFA and all-cause mortality; country of conduct; subgroup analysis



AUS-DIAB: Australian Diabetes, Obesity and Lifestyle Study; CHNS: China Health and Nutrition Survey; CI: confidence interval; ES: effect size; F: female; HPFS: Health Professionals Follow-up Study; JACC: Japan Collaborative Cohort; M: male; NHANES: National Health and Nutrition Examination Survey; NHS I: Nurses' Health Study I; NIH-AARP: National Institutes of Health American Association of Retired Persons Diet and Health Study; NILS-LSA: National Institute for Longevity Sciences-Longitudinal Study of Aging; PUFA: polyunsaturated fatty acids; USA: United States of America; W: women.

The effect size was associated with country of study (*P*=0.03). Because the predictor variable had more than 2 levels, it is not appropriate to show the continuous meta-regression line; therefore, we present the "by country" estimates separately.

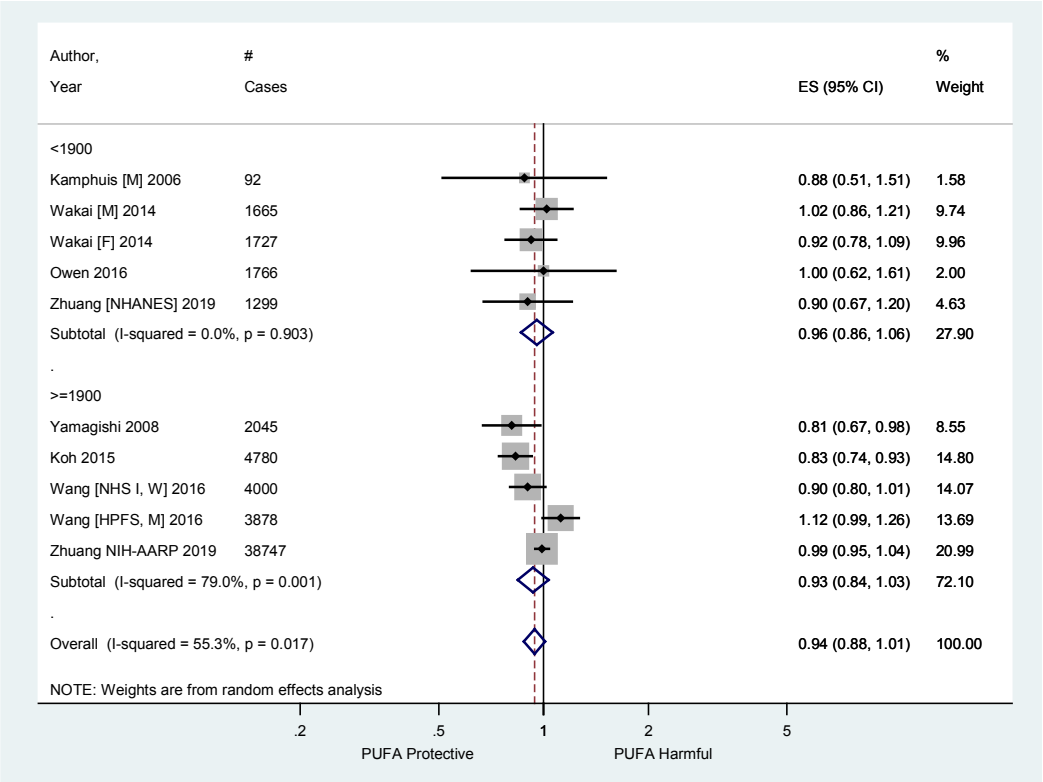
Fig. 90a.[1] Meta-regression of n-3 PUFA and cardiovascular mortality; number of cases; Panel A – effect size



The number of cases in the study was not associated with the effect estimate (*P*=0.59).

#: number; CI: confidence interval; mvHR: multivariable hazard ratio; mvRR: multivariable risk ratio; PUFA: polyunsaturated fatty acids.

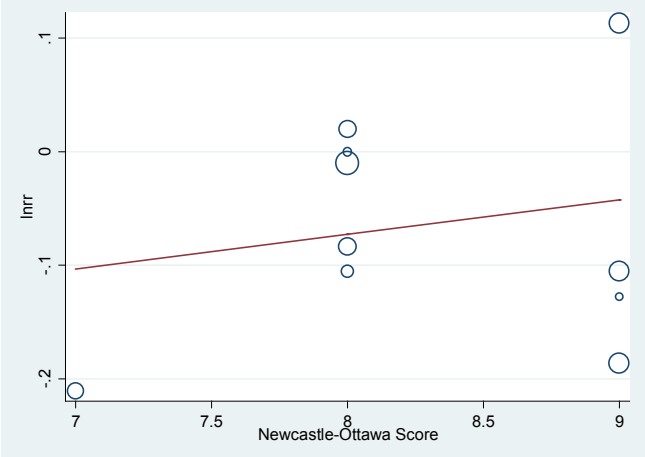
Fig. 90b. Meta-regression of n-3 PUFA and cardiovascular mortality; number of cases; Panel B – subgroup analysis by number of cases (median=1900)



#: number; CI: confidence interval; ES: effect size; F: female; HPFS: Health Professionals Follow-up Study; M: male; NHANES: National Health and Nutrition Examination Survey; NHS I: Nurses' Health Study I; NIH-AARP: National Institutes of Health American Association of Retired Persons Diet and Health Study; PUFA: polyunsaturated fatty acids; W: women.

[1] Note: There is no figure for meta-regression of n-3 PUFA and cardiovascular mortality, energy adjustment. All studies adjusted for total energy.

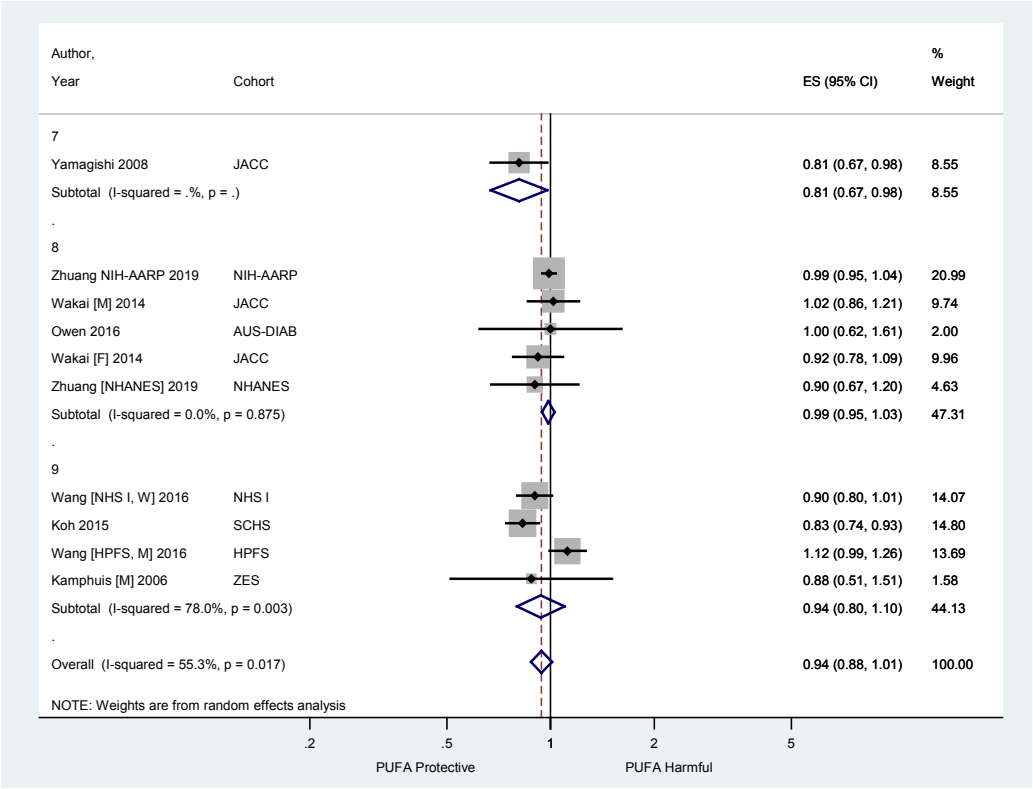
Fig. 90c. Meta-regression of n-3 PUFA and cardiovascular mortality; NOS assessment; Panel A – effect size



NOS was not associated with association estimate (*P*=0.65).

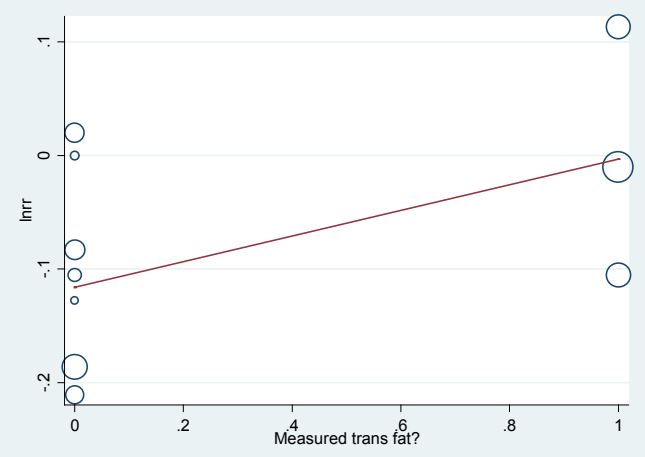
NOS: Newcastle-Ottawa Scale; PUFA: polyunsaturated fatty acids; rr: risk ratio.

Fig. 90d. Meta-regression of n-3 PUFA and cardiovascular mortality; NOS assessment; Panel B – subgroup analysis



AUS-DIAB: Australian Diabetes, Obesity and Lifestyle Study; CI: confidence interval; ES: effect size; F: female; HPFS: Health Professionals Follow-up Study; JACC: Japan Collaborative Cohort; M: male; NHANES: National Health and Nutrition Examination Survey; NHS I: Nurses' Health Study I; NIH-AARP: National Institutes of Health American Association of Retired Persons Diet and Health Study; NOS: Newcastle-Ottawa Scale; PUFA: polyunsaturated fatty acids; SCHS: Singapore Chinese Health Study; W: women; ZES: Zutphen Elderly Study.

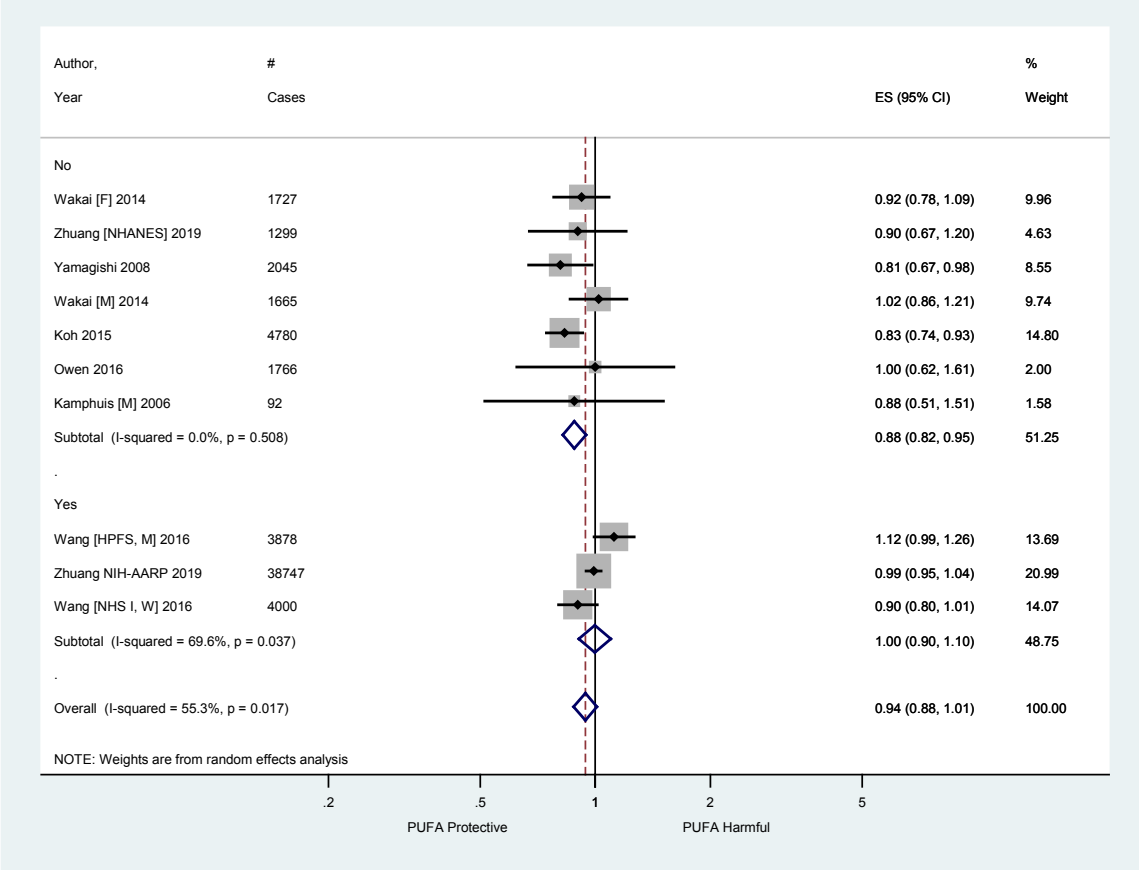
Fig. 90e. Meta-regression of n-3 PUFA and cardiovascular mortality; TFA assessment; Panel A – effect size



The association estimate was not associated with adjustment for measurement of TFA (*P*=0.13).

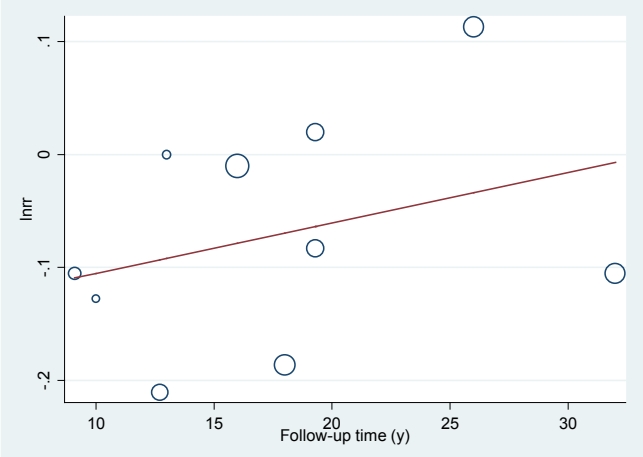
PUFA: polyunsaturated fatty acids; rr: risk ratio; TFA: trans-fatty acids.

Fig. 90f. Meta-regression of n-3 PUFA and cardiovascular mortality; TFA assessment; Panel B – subgroup analysis



#: number; CI: confidence interval; ES: effect size; F: female; HPFS: Health Professionals Follow-up Study; M: male; NHANES: National Health and Nutrition Examination Survey; NHS I: Nurses' Health Study I; NIH-AARP: National Institutes of Health American Association of Retired Persons Diet and Health Study; PUFA: polyunsaturated fatty acids; TFA: trans-fatty acids; W: women.

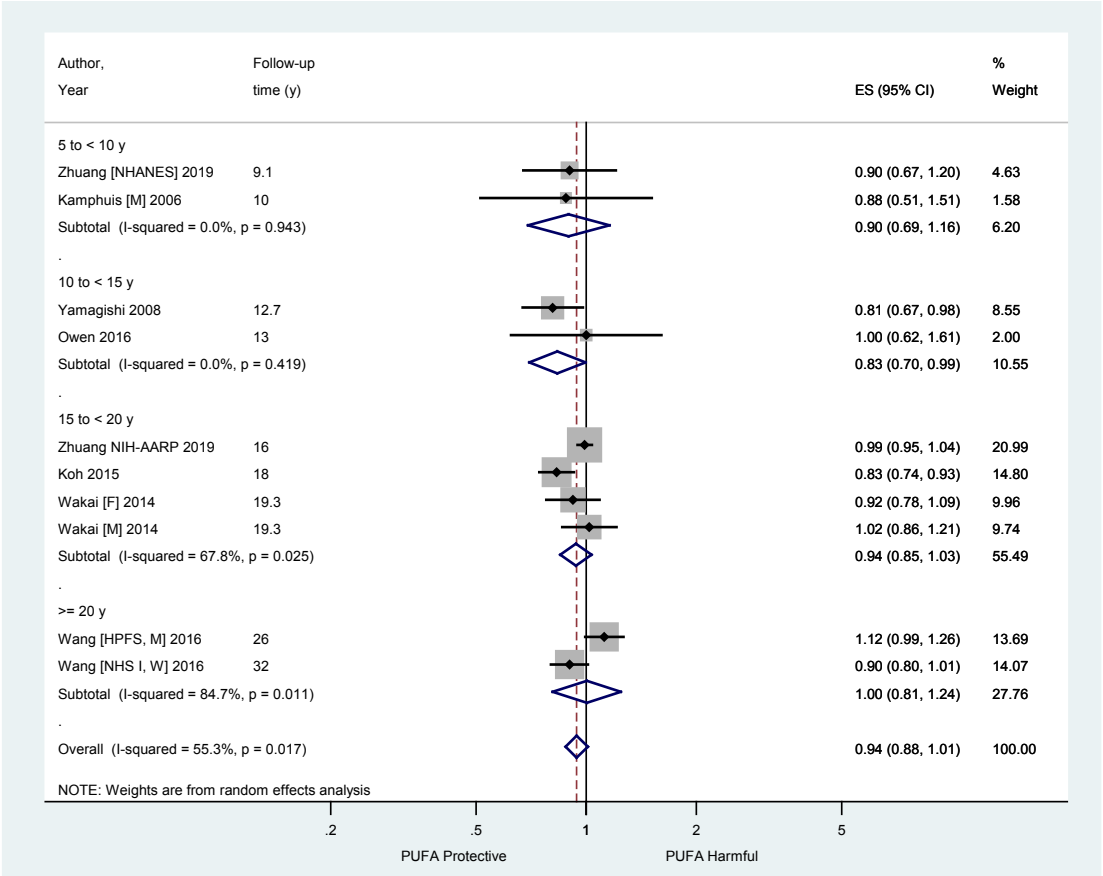
Fig. 90g. Meta-regression of n-3 PUFA and cardiovascular mortality; follow-up time; Panel A – effect size



The association estimate was not associated with follow-up time (*P*=0.50).

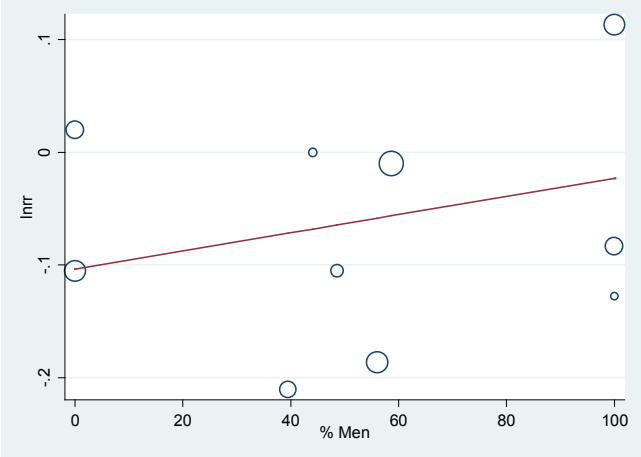
PUFA: polyunsaturated fatty acids; rr: risk ratio; y: years.

Fig. 90h. Meta-regression of n-3 PUFA and cardiovascular mortality; follow-up time; Panel B – subgroup analysis



CI: confidence interval; ES: effect size; F: female; HPFS: Health Professionals Follow-up Study; M: male; NHANES: National Health and Nutrition Examination Survey; NHS I: Nurses' Health Study I; NIH-AARP: National Institutes of Health American Association of Retired Persons Diet and Health Study; PUFA: polyunsaturated fatty acids; W: women; y: years.

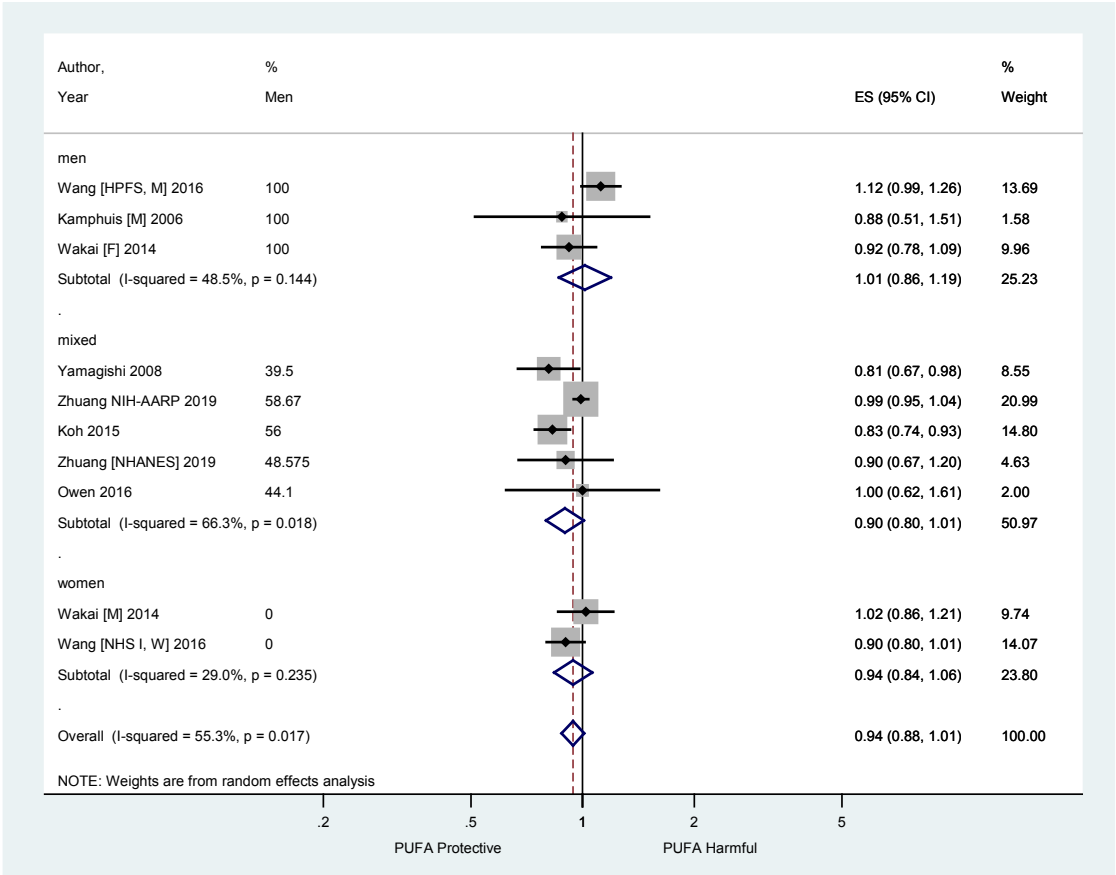
Fig. 90i. Meta-regression of n-3 PUFA and cardiovascular mortality; sex; Panel A – effect size



The association estimate was not associated with the percentage of men in the study (P=0.48).

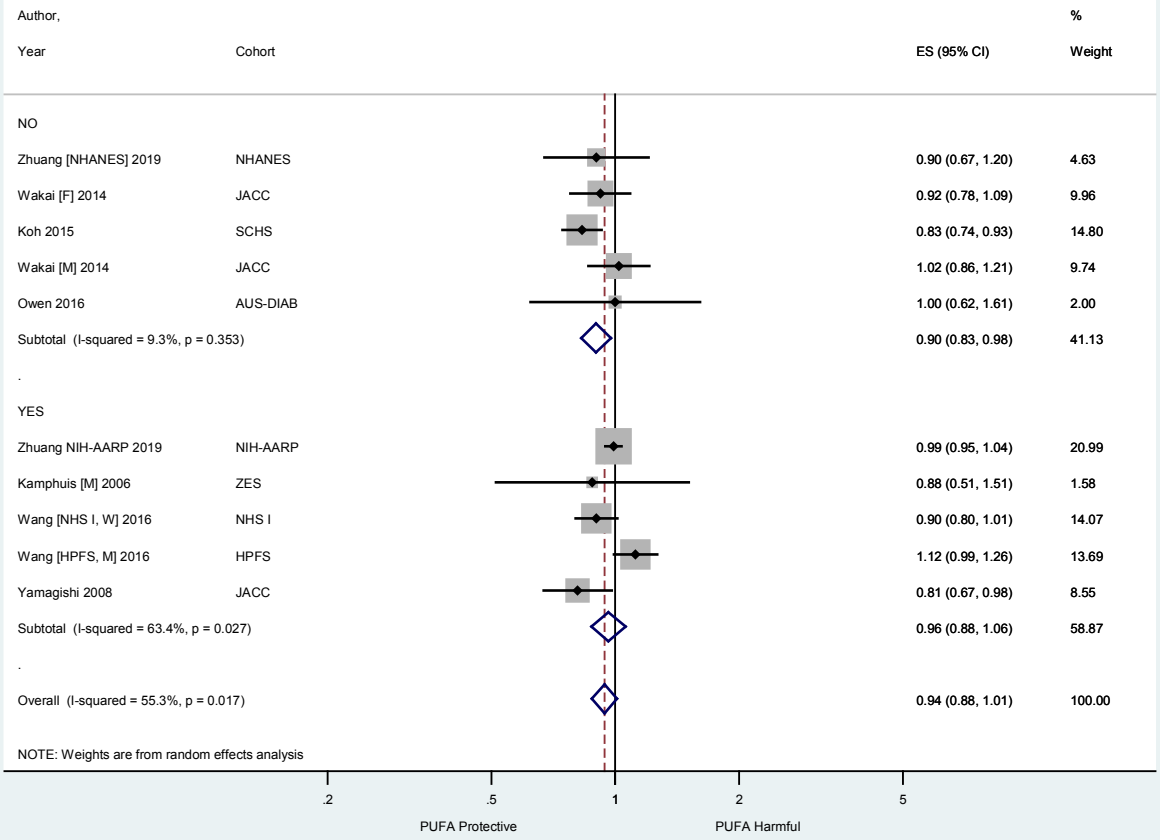
PUFA: polyunsaturated fatty acids; rr: risk ratio.

Fig. 90j. Meta-regression of n-3 PUFA and cardiovascular mortality; sex; Panel B – subgroup analysis (sex)



CI: confidence interval; ES: effect size; F: female; HPFS: Health Professionals Follow-up Study; M: male; NHANES: National Health and Nutrition Examination Survey; NHS I: Nurses' Health Study I; NIH-AARP: National Institutes of Health American Association of Retired Persons Diet and Health Study; PUFA: polyunsaturated fatty acids; W: women.

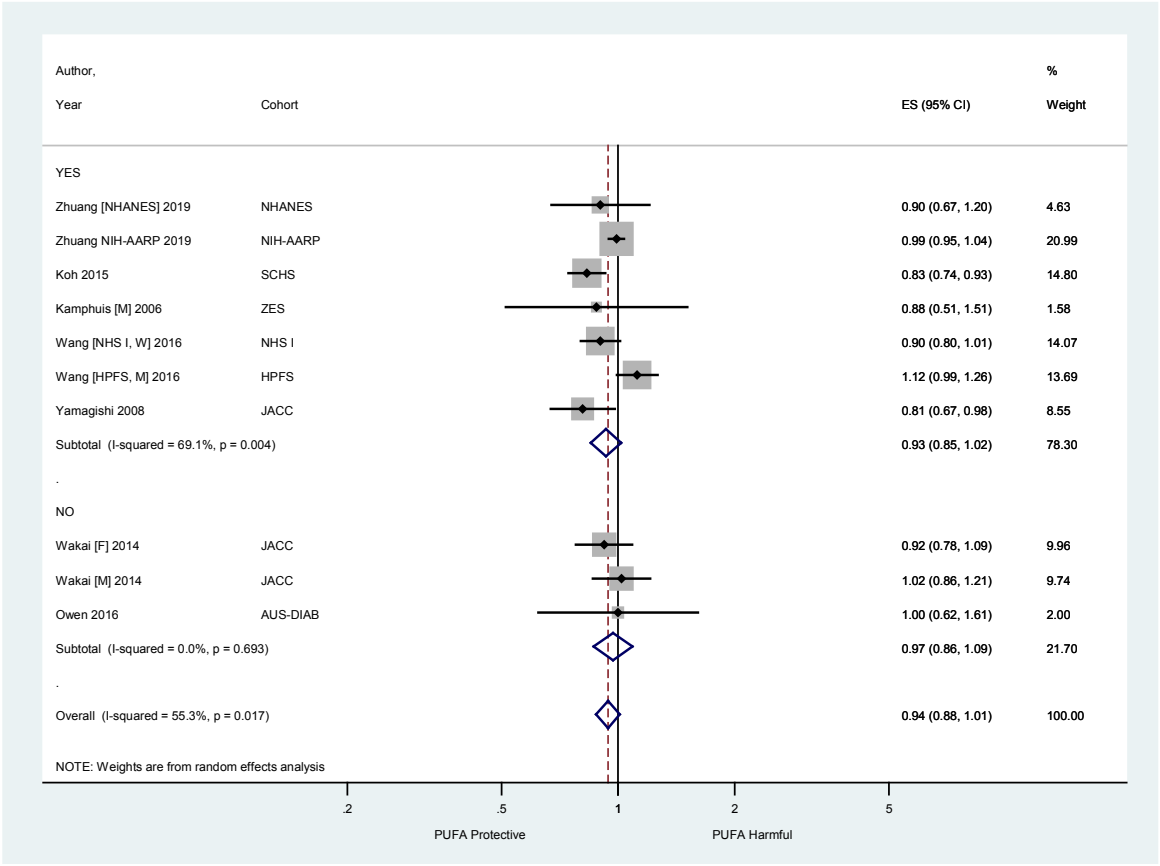
Fig. 90k. Meta-regression of n-3 PUFA and cardiovascular mortality; dyslipidaemia adjustment; subgroup analysis



AUS-DIAB: Australian Diabetes, Obesity and Lifestyle Study; CI: confidence interval; ES: effect size; F: female; HPFS: Health Professionals Follow-up Study; JACC: Japan Collaborative Cohort; M: male; NHANES: National Health and Nutrition Examination Survey; NHS I: Nurses' Health Study I; NIH-AARP: National Institutes of Health American Association of Retired Persons Diet and Health Study; PUFA: polyunsaturated fatty acids; SCHS: Singapore Chinese Health Study; W: women; ZES: Zutphen Elderly Study.

Association estimates were not associated with adjustment for dyslipidaemia in the final model (P=0.51).

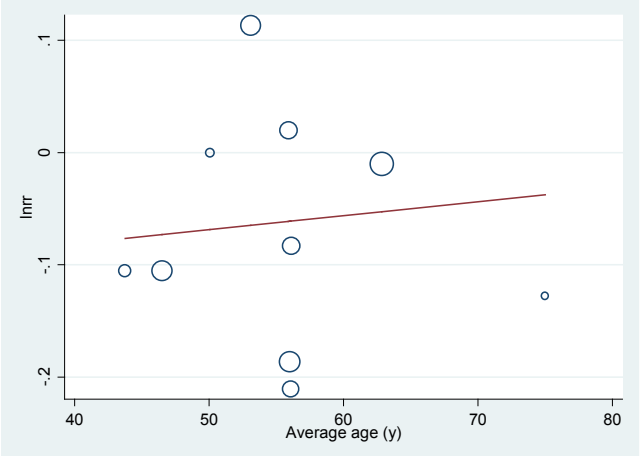
Fig. 90l. Meta-regression of n-3 PUFA and cardiovascular mortality; blood pressure adjustment; subgroup analysis



AUS-DIAB: Australian Diabetes, Obesity and Lifestyle Study; CI: confidence interval; ES: effect size; F: female; HPFS: Health Professionals Follow-up Study; JACC: Japan Collaborative Cohort; M: male; NHANES: National Health and Nutrition Examination Survey; NHS I: Nurses' Health Study I; NIH-AARP: National Institutes of Health American Association of Retired Persons Diet and Health Study; PUFA: polyunsaturated fatty acids; SCHS: Singapore Chinese Health Study; W: women; ZES: Zutphen Elderly Study.

Association estimates were not associated with adjustment for blood pressure in the final model (*P*=0.66).

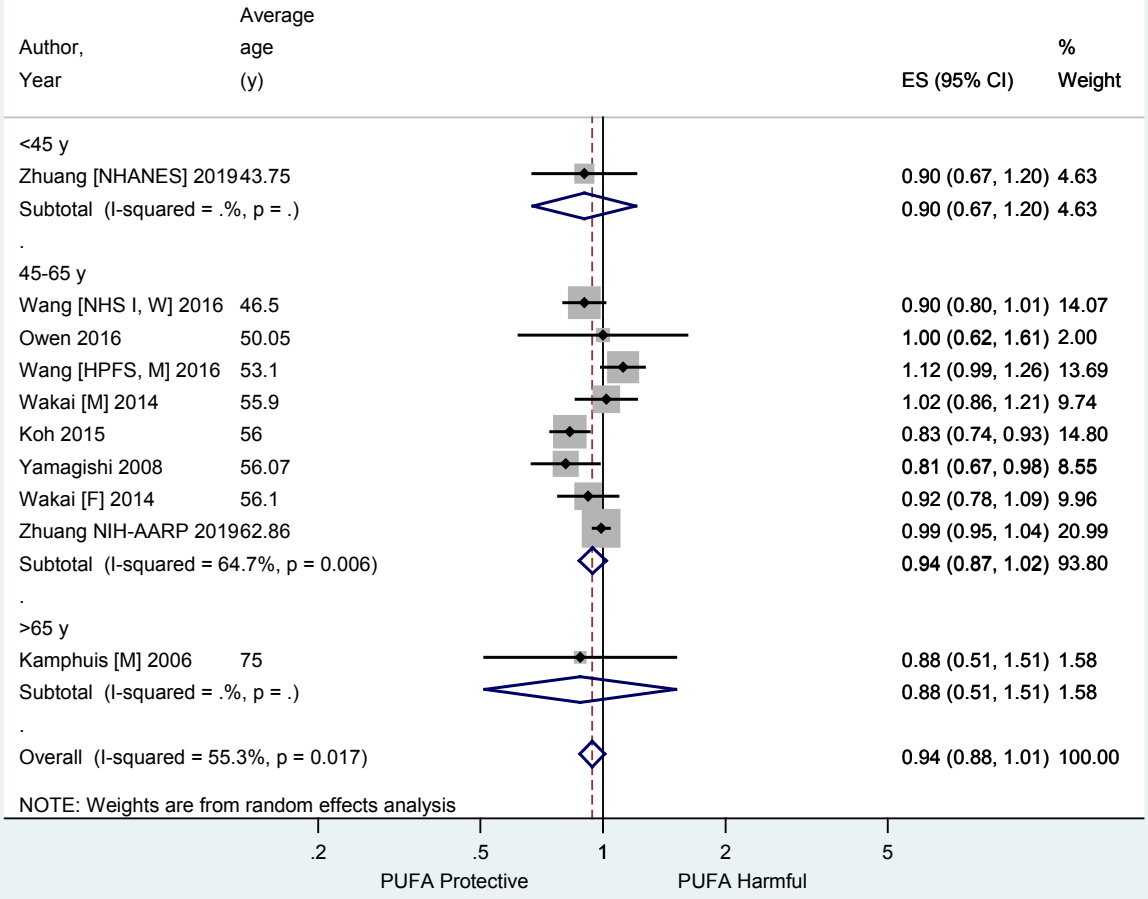
Fig. 90m. Meta-regression of n-3 PUFA and cardiovascular mortality; age; Panel A – effect size



The association estimate was not associated with the average age of the study population (*P*=0.86).

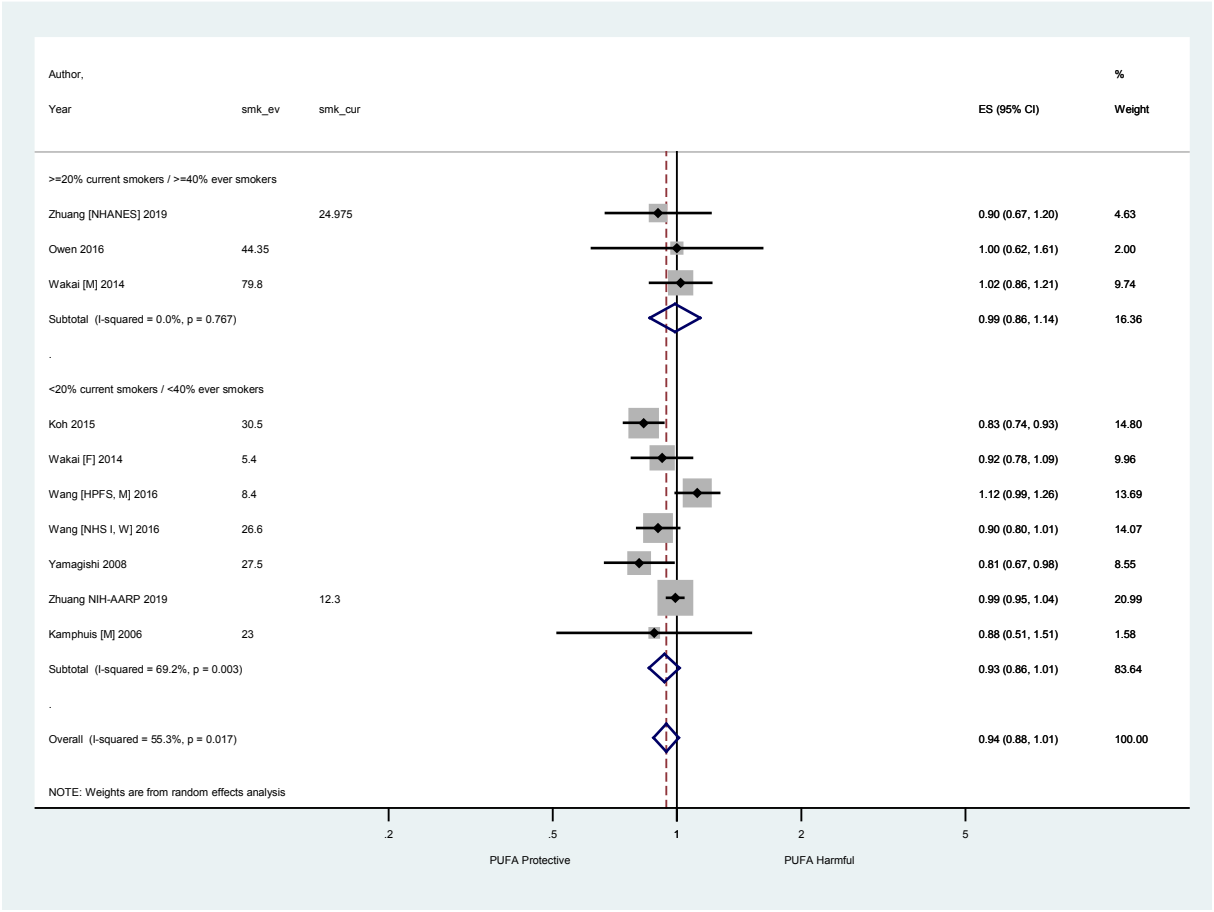
PUFA: polyunsaturated fatty acids; rr: risk ratio; y: years.

Fig. 90n. Meta-regression of n-3 PUFA and cardiovascular mortality; age; Panel B – subgroup analysis



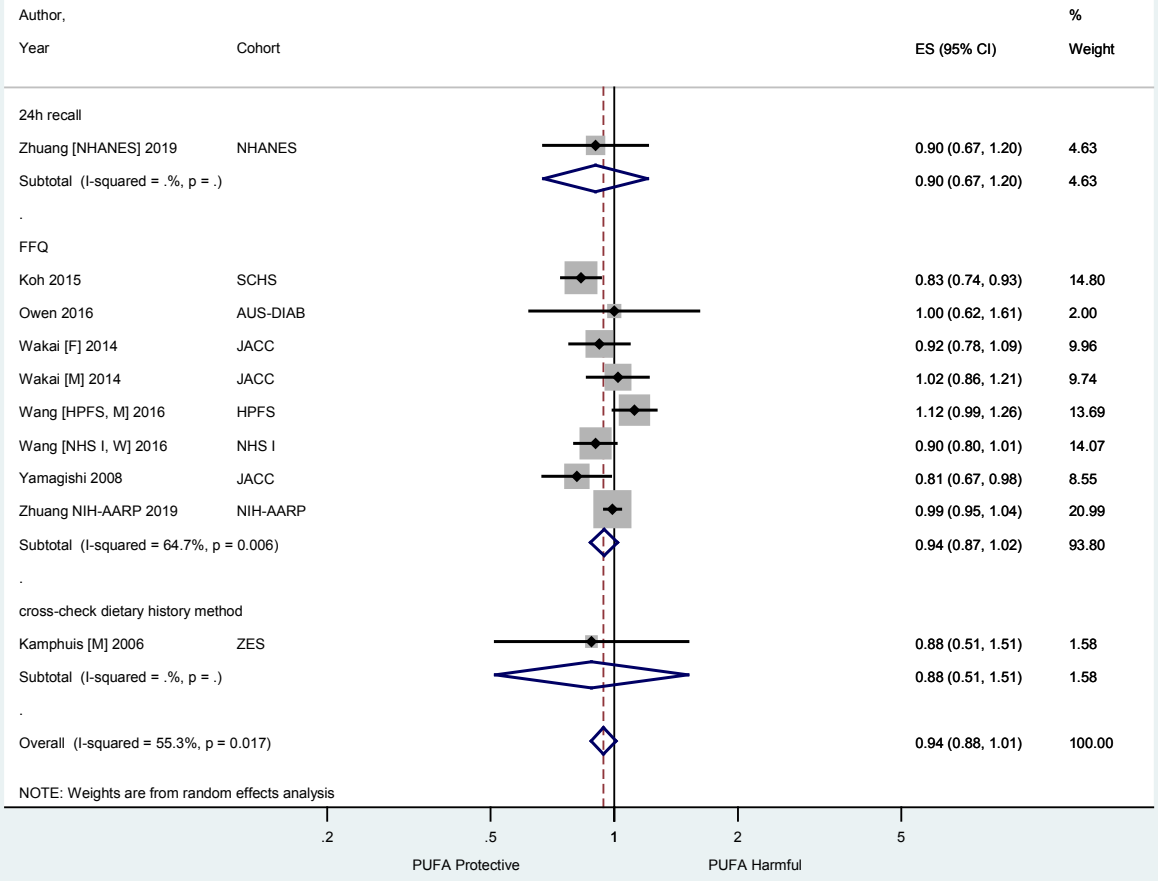
CI: confidence interval; ES: effect size; F: female; HPFS: Health Professionals Follow-up Study; M: male; NHANES: National Health and Nutrition Examination Survey; NHS I: Nurses' Health Study I; NIH-AARP: National Institutes of Health American Association of Retired Persons Diet and Health Study; PUFA: polyunsaturated fatty acids; W: women; y: years.

Fig. 90o. Meta-regression of n-3 PUFA and cardiovascular mortality; smoking



CI: confidence interval; ES: effect size; F: female; HPFS: Health Professionals Follow-up Study; M: male; NHANES: National Health and Nutrition Examination Survey; NHS I: Nurses' Health Study I; NIH-AARP: National Institutes of Health American Association of Retired Persons Diet and Health Study; PUFA: polyunsaturated fatty acids; smk_cur: current smokers; smk_ev: ever smoked; W: women. In the continuous meta-regression analysis, the association estimate was not associated with the proportion of smokers in the study (*P*=0.94).

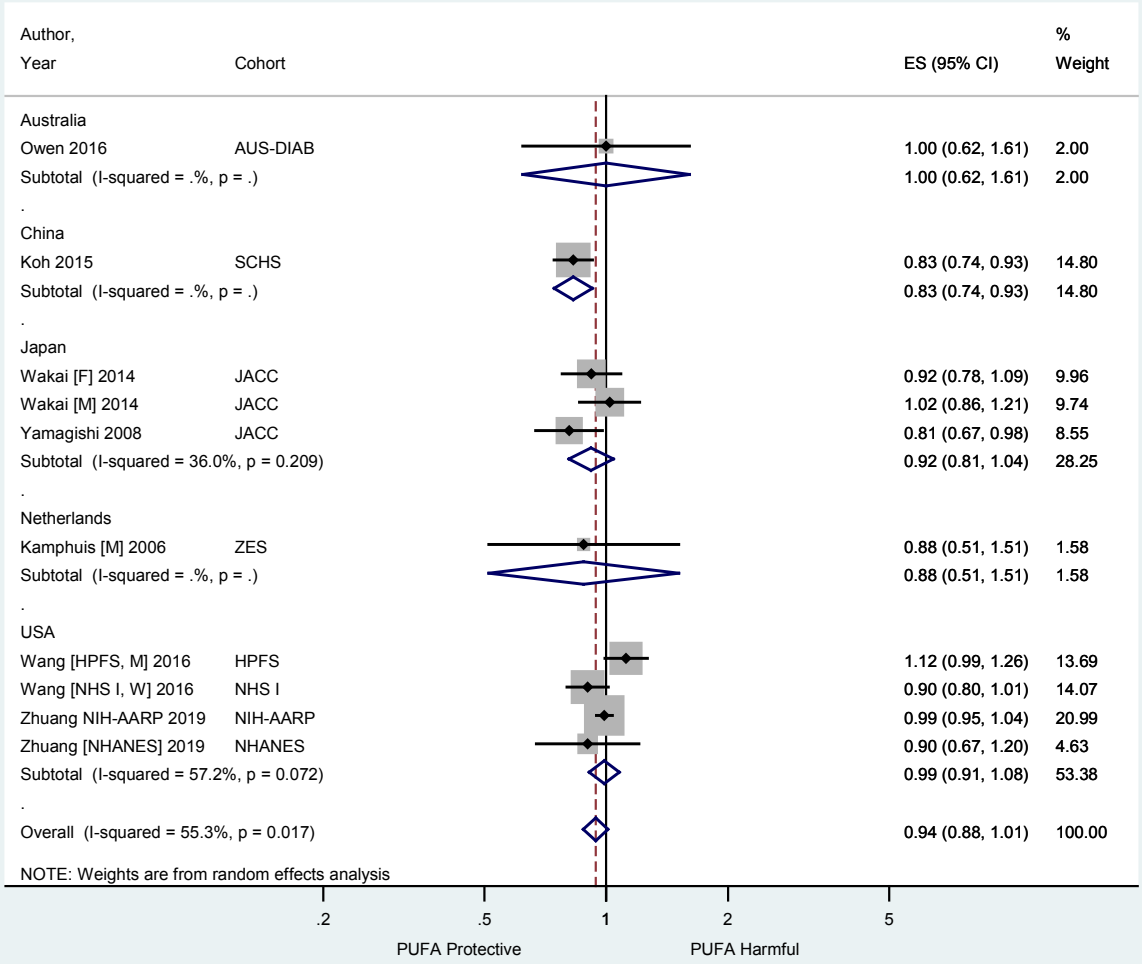
Fig. 90p. Meta-regression of n-3 PUFA and cardiovascular mortality; diet assessment method; subgroup analysis



AUS-DIAB: Australian Diabetes, Obesity and Lifestyle Study; CI: confidence interval; ES: effect size; F: female; FFQ: food frequency questionnaire; h: hour; HPFS: Health Professionals Follow-up Study; JACC: Japan Collaborative Cohort; M: male; NHANES: National Health and Nutrition Examination Survey; NHS I: Nurses' Health Study I; NIH-AARP: National Institutes of Health American Association of Retired Persons Diet and Health Study; PUFA: polyunsaturated fatty acids; SCHS: Singapore Chinese Health Study; W: women; ZES: Zutphen Elderly Study.

In the continuous meta-regression analysis, the effect size was not associated with adjustment for dietary assessment method in the final model (P=0.94). Because the predictor variable had more than 2 levels, it is not appropriate to show the continuous meta-regression line; therefore, we present the "by method" estimates separately.

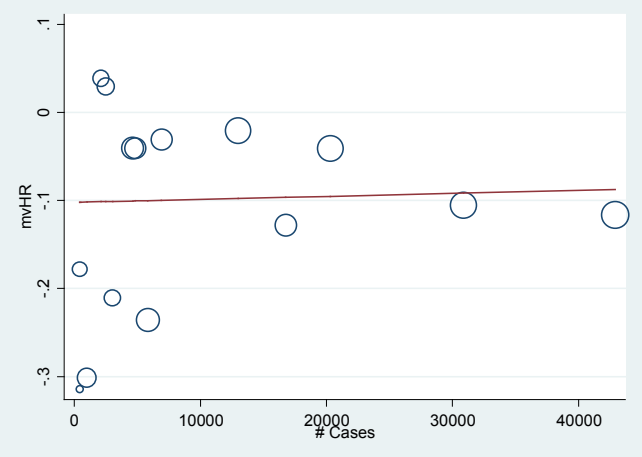
Fig. 90q. Meta-regression of n-3 PUFA and cardiovascular mortality; country of conduct; subgroup analysis



AUS-DIAB: Australian Diabetes, Obesity and Lifestyle Study; CI: confidence interval; ES: effect size; F: female; HPFS: Health Professionals Follow-up Study; JACC: Japan Collaborative Cohort; M: male; NHANES: National Health and Nutrition Examination Survey; NHS I: Nurses' Health Study I; NIH-AARP: National Institutes of Health American Association of Retired Persons Diet and Health Study; PUFA: polyunsaturated fatty acids; SCHS: Singapore Chinese Health Study; USA: United States of America; W: women; ZES: Zutphen Elderly Study.

The effect size was not associated with adjustment for country of conduct in the final model (P=0.58). Because the predictor variable had more than 2 levels, it is not appropriate to show the continuous meta-regression line; therefore, we present the "by country" estimates separately.

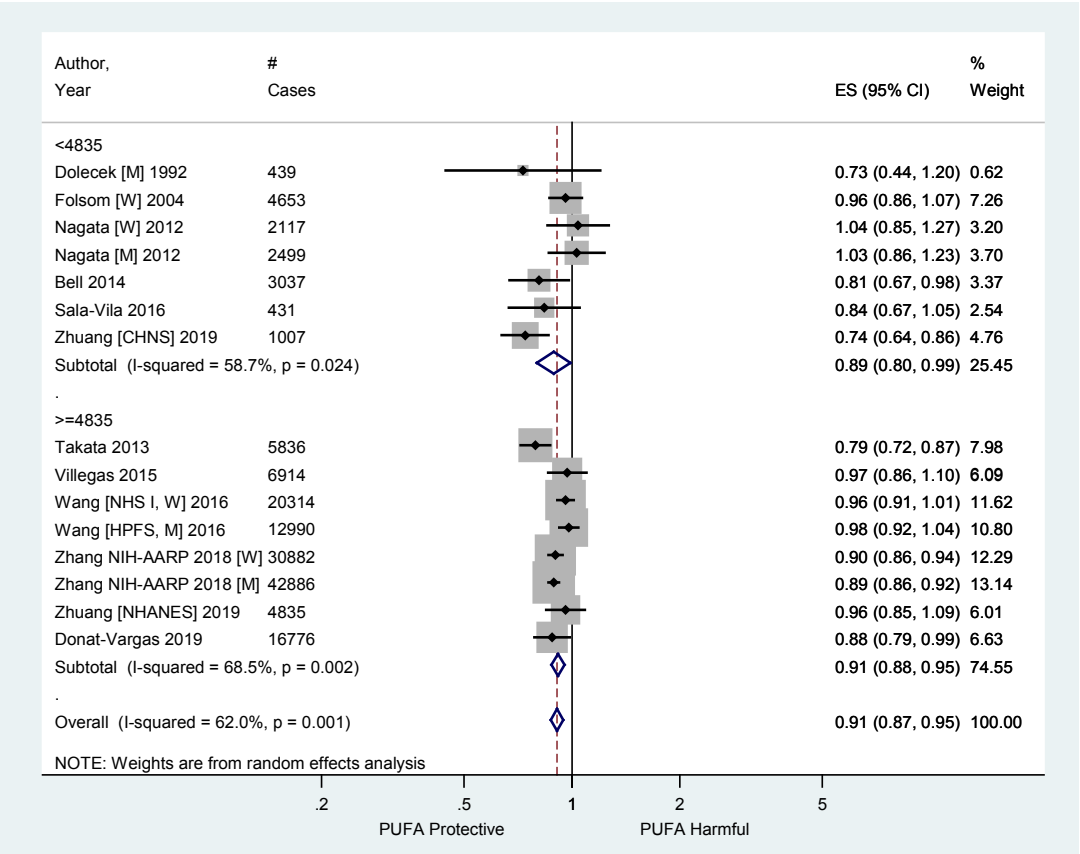
Fig. 91a. Meta-regression of long-chain n-3 PUFA and all-cause mortality; number of cases; Panel A – effect size



The number of cases in the study was not associated with the effect estimate (*P*=0.86).

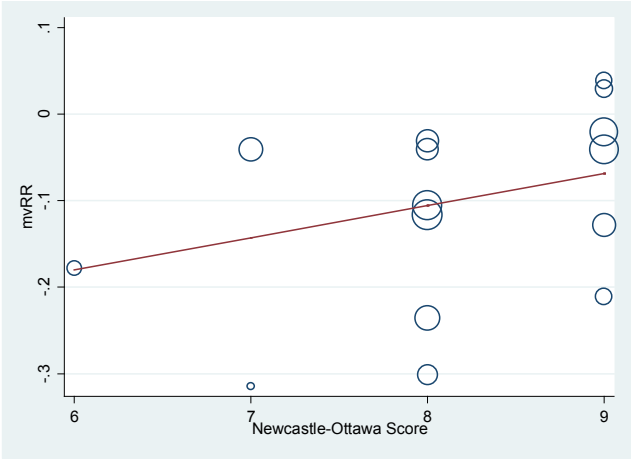
#: number; CI: confidence interval; mvHR: multivariable hazard ratio; mvRR: multivariable risk ratio; PUFA: polyunsaturated fatty acids.

Fig. 91b. Meta-regression of long-chain n-3 PUFA and all-cause mortality; number of cases; Panel B – subgroup analysis by number of cases (median=4835)



#: number; CHNS: China Health and Nutrition Survey; CI: confidence interval; ES: effect size; HPFS: Health Professionals Follow-up Study; M: male; NHANES: National Health and Nutrition Examination Survey; NHS I: Nurses' Health Study I; NIH-AARP: National Institutes of Health American Association of Retired Persons Diet and Health Study; PUFA: polyunsaturated fatty acids; W: women.

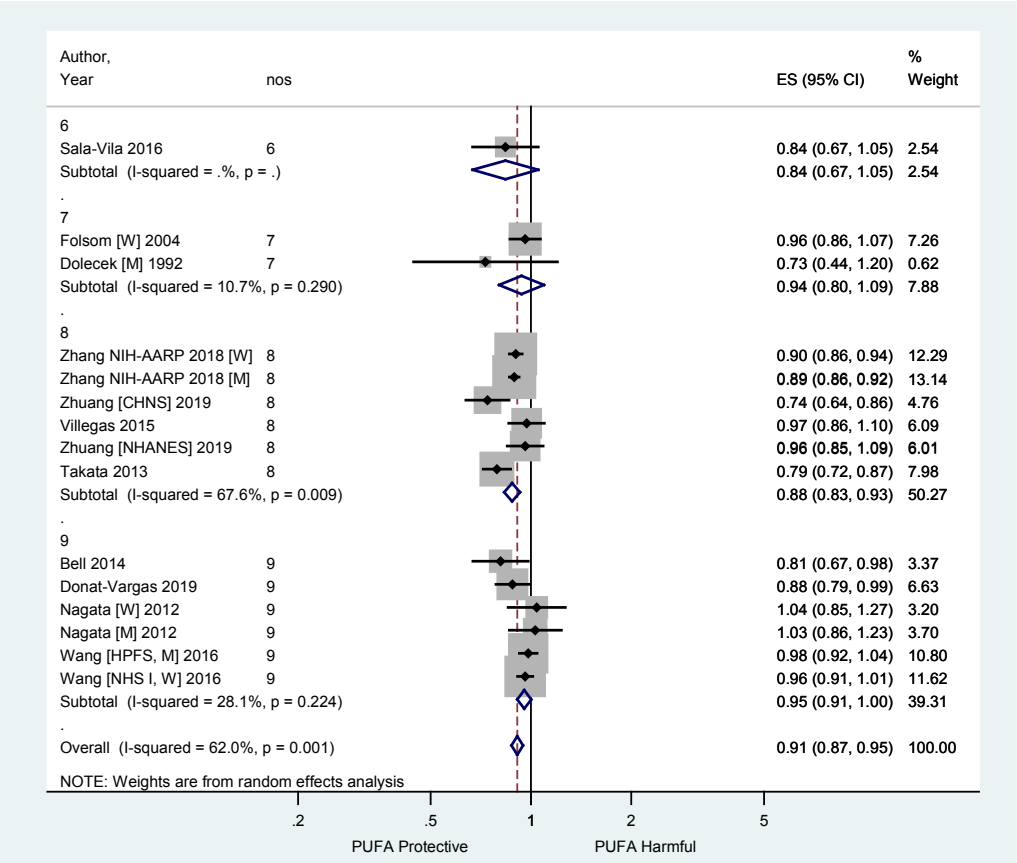
Fig. 91c. Meta-regression of long-chain n-3 PUFA and all-cause mortality; NOS assessment; Panel A – effect size



Effect size was not associated with NOS score (*P*=0.26).

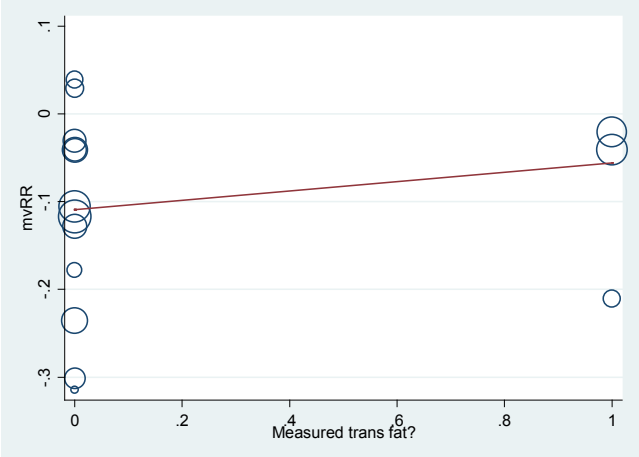
mvRR: multivariable risk ratio; NOS: Newcastle-Ottawa Scale; PUFA: polyunsaturated fatty acids.

Fig. 91d. Meta-regression of long-chain n-3 PUFA and all-cause mortality; NOS assessment; Panel B – subgroup analysis by NOS score



CHNS: China Health and Nutrition Survey; CI: confidence interval; ES: effect size; HPFS: Health Professionals Follow-up Study; M: male; NHANES: National Health and Nutrition Examination Survey; NHS I: Nurses' Health Study I; NIH-AARP: National Institutes of Health American Association of Retired Persons Diet and Health Study; nos: Newcastle-Ottawa Scale; NOS: Newcastle-Ottawa Scale; PUFA: polyunsaturated fatty acids; W: women.

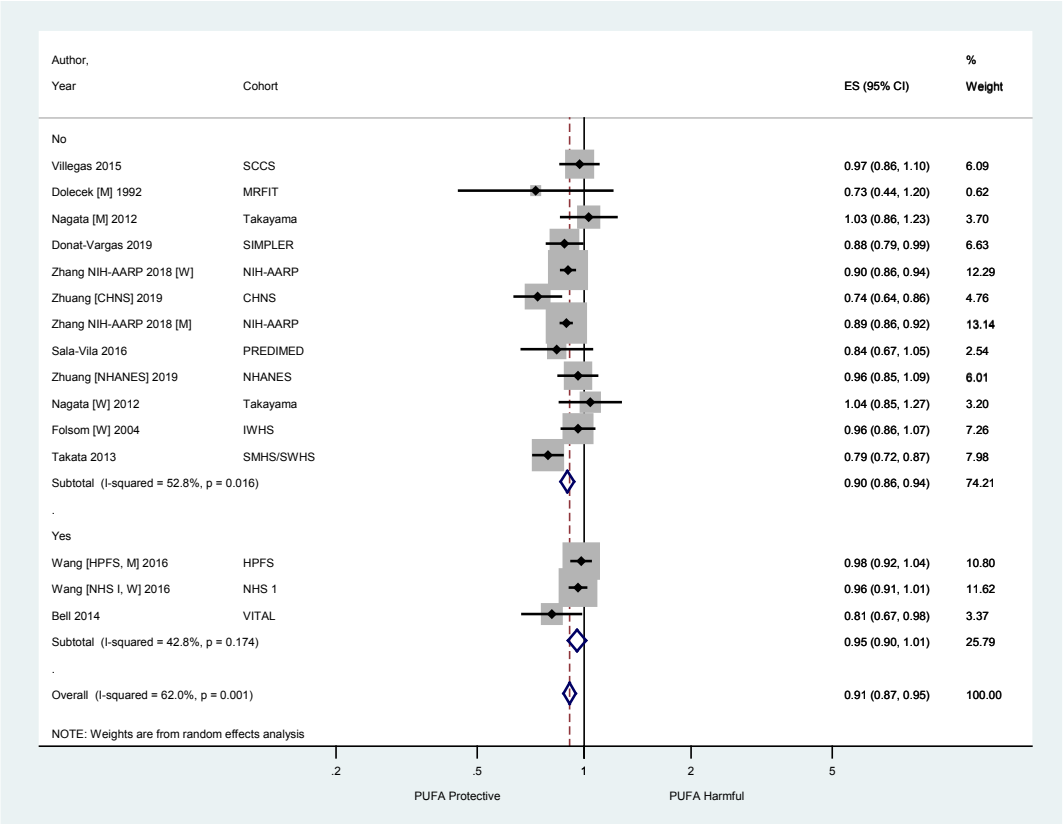
Fig. 91e. Meta-regression of long-chain n-3 PUFA and all-cause mortality; TFA assessment; Panel A – effect size



Effect size was not associated with adjustment for measurement of TFA in the final model (P=0.34).

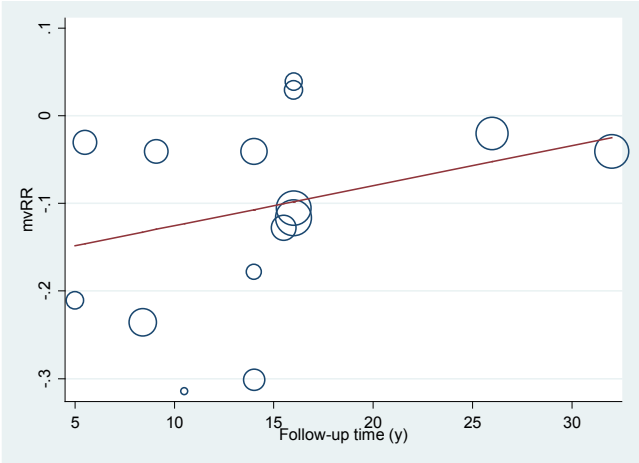
mvRR: multivariable risk ratio; PUFA: polyunsaturated fatty acids; TFA: trans-fatty acids.

Fig. 91f. Meta-regression of long-chain n-3 PUFA and all-cause mortality; TFA assessment; Panel B – subgroup analysis by TFA measurement



CHNS: China Health and Nutrition Survey; CI: confidence interval; ES: effect size; HPFS: Health Professionals Follow-up Study; IWHS: Iowa Women's Health Study; M: male; MRFIT: Multiple Risk Factor Intervention Trial; NHANES: National Health and Nutrition Examination Survey; NHS I: Nurses' Health Study I; NIH-AARP: National Institutes of Health American Association of Retired Persons Diet and Health Study; PREDIMED: Prevención con Dieta Mediterránea; PUFA: polyunsaturated fatty acids; SCCS: Southern Community Cohort Study; SIMPLER: Swedish Infrastructure for Medical Population-based Life-course and Environmental Research; SMHS: Shanghai Men's Health Study; SWHS: Shanghai Women's Health Study; TFA: trans-fatty acids; VITAL: Vitamins and Lifestyle Study; W: women.

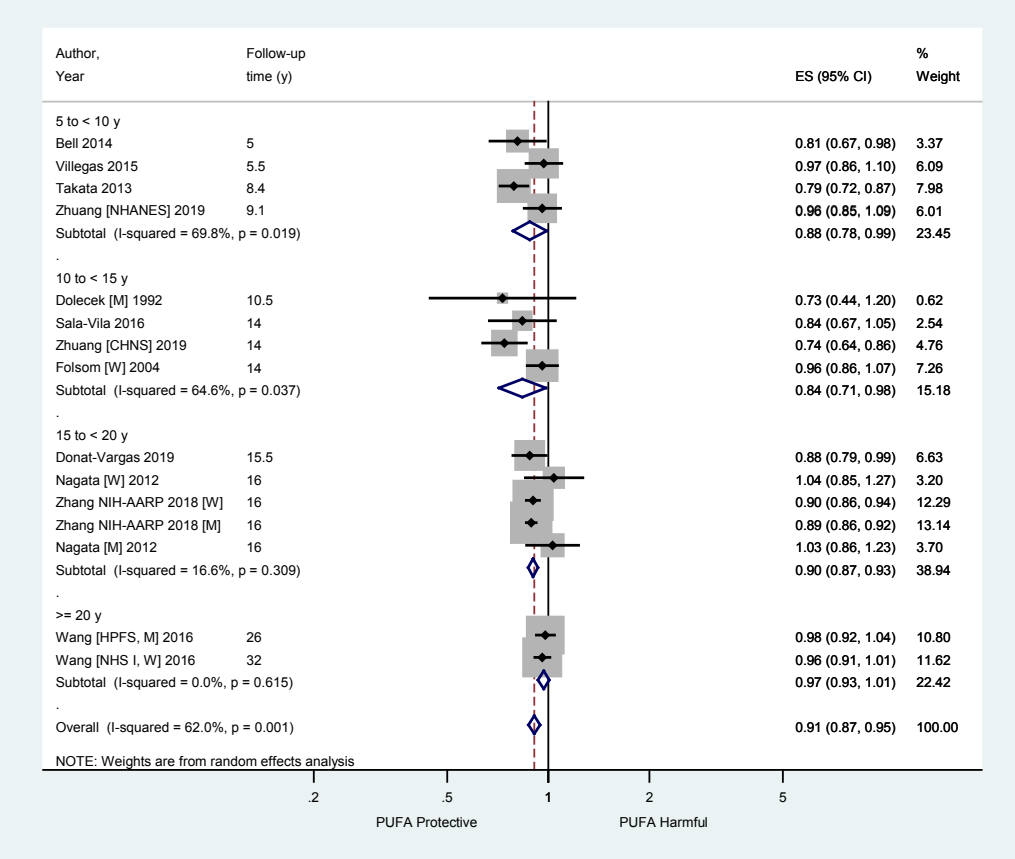
Fig. 91g. Meta-regression of long-chain n-3 PUFA and all-cause mortality; follow-up time; Panel A – effect size



Effect size was not associated with follow-up duration (*P*=0.23).

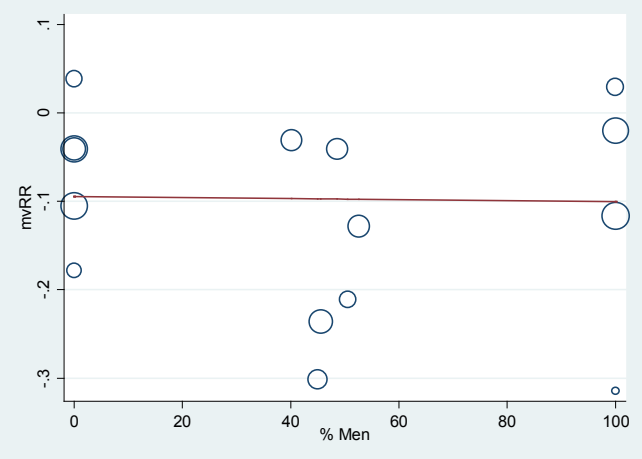
mvRR: multivariable risk ratio; PUFA: polyunsaturated fatty acids; y: years.

Fig. 91h. Meta-regression of long-chain n-3 PUFA and all-cause mortality; follow-up time; Panel B – subgroup analysis by duration of follow-up



CHNS: China Health and Nutrition Survey; CI: confidence interval; ES: effect size; HPFS: Health Professionals Follow-up Study; M: male; NHANES: National Health and Nutrition Examination Survey; NHS I: Nurses' Health Study I; NIH-AARP: National Institutes of Health American Association of Retired Persons Diet and Health Study; PUFA: polyunsaturated fatty acids; W: women; y: years.

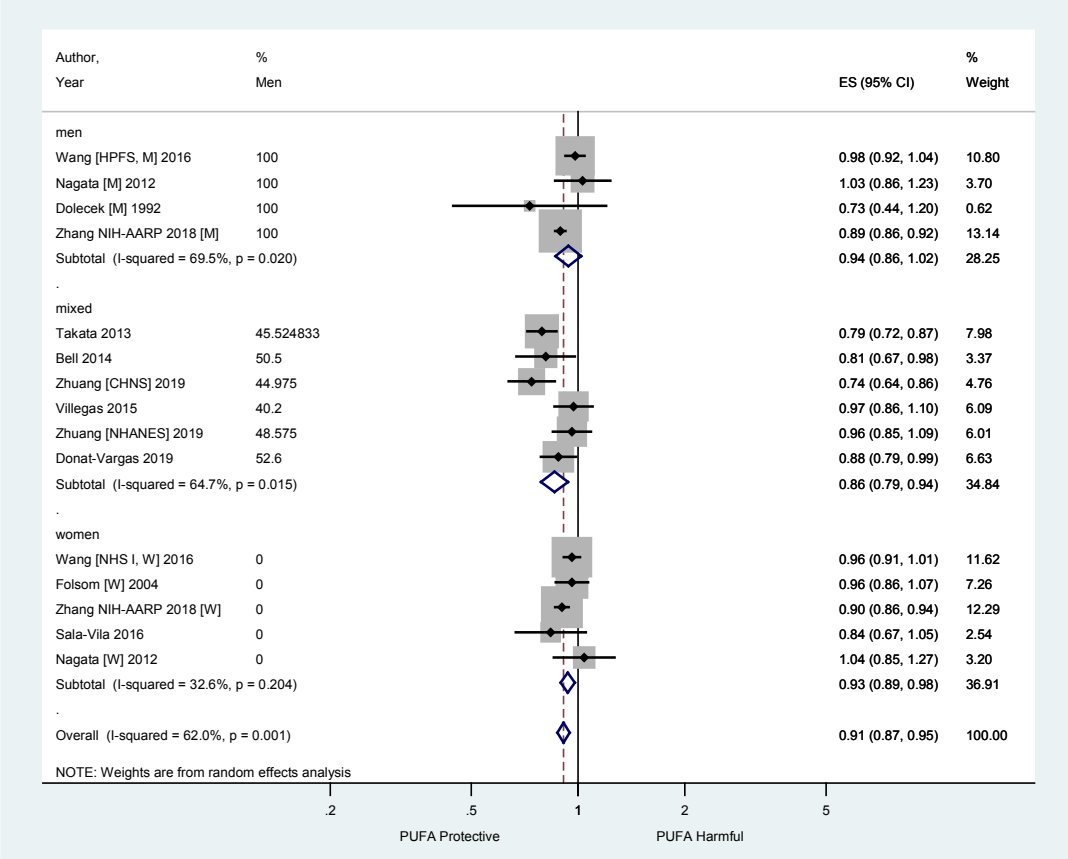
Fig. 91i. Meta-regression of long-chain n-3 PUFA and all-cause mortality; sex; Panel A – effect size



The effect size was not associated with the percentage of men in the study (*P*=0.93).

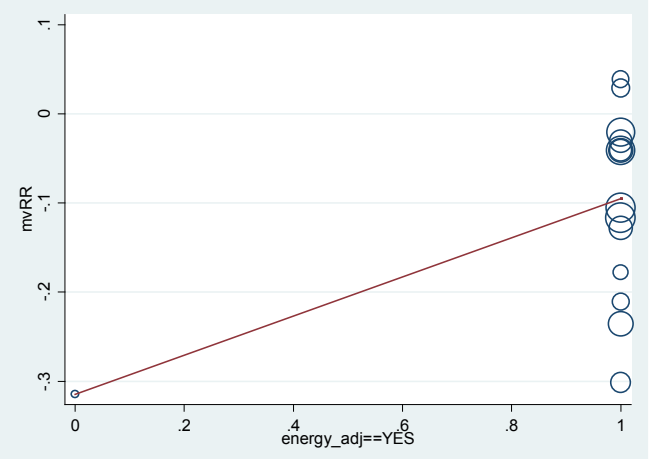
mvRR: multivariable risk ratio; PUFA: polyunsaturated fatty acids.

Fig. 91j. Meta-regression of long-chain n-3 PUFA and all-cause mortality; sex; Panel B – subgroup analysis by sex



CHNS: China Health and Nutrition Survey; CI: confidence interval; ES: effect size; HPFS: Health Professionals Follow-up Study; M: male; NHANES: National Health and Nutrition Examination Survey; NHS I: Nurses' Health Study I; NIH-AARP: National Institutes of Health American Association of Retired Persons Diet and Health Study; PUFA: polyunsaturated fatty acids; W: women.

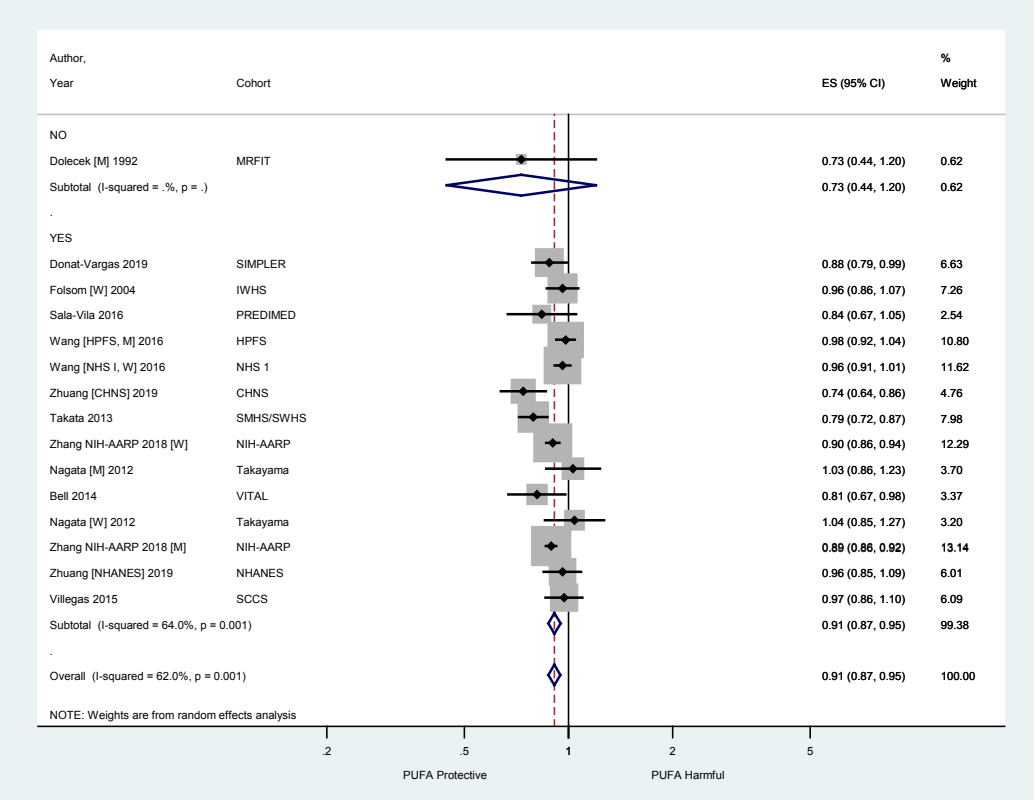
Fig. 91k. Meta-regression of long-chain n-3 PUFA and all-cause mortality; energy adjustment; Panel A – effect size



Effect size was not associated with energy adjustment (yes or no) (P=0.46).

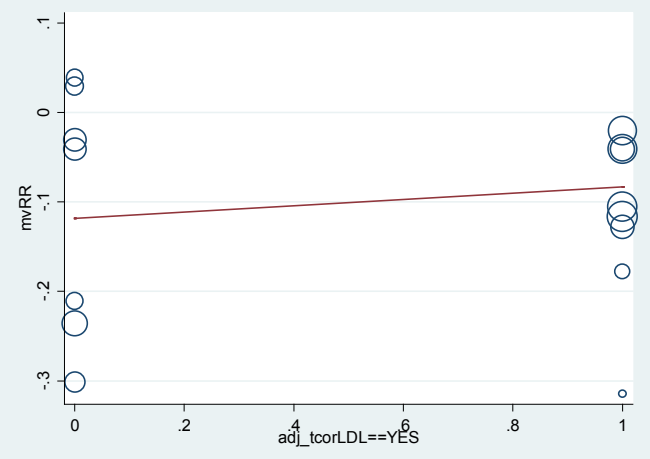
energy_adj: adjusted for energy; mvRR: multivariable risk ratio; PUFA: polyunsaturated fatty acids.

Fig. 91l. Meta-regression of long-chain n-3 PUFA and all-cause mortality; energy adjustment; Panel B – subgroup analysis by adjustment for energy



CHNS: China Health and Nutrition Survey; CI: confidence interval; ES: effect size; HPFS: Health Professionals Follow-up Study; IWHS: Iowa Women's Health Study; M: male; MRFIT: Multiple Risk Factor Intervention Trial; NHANES: National Health and Nutrition Examination Survey; NHS I: Nurses' Health Study I; NIH-AARP: National Institutes of Health American Association of Retired Persons Diet and Health Study; PREDIMED: Prevención con Dieta Mediterránea; PUFA: polyunsaturated fatty acids; SCCS: Southern Community Cohort Study; SIMPLER: Swedish Infrastructure for Medical Population-based Life-course and Environmental Research; SMHS: Shanghai Men's Health Study; SWHS: Shanghai Women's Health Study; VITAL: Vitamins and Lifestyle Study; W: women.

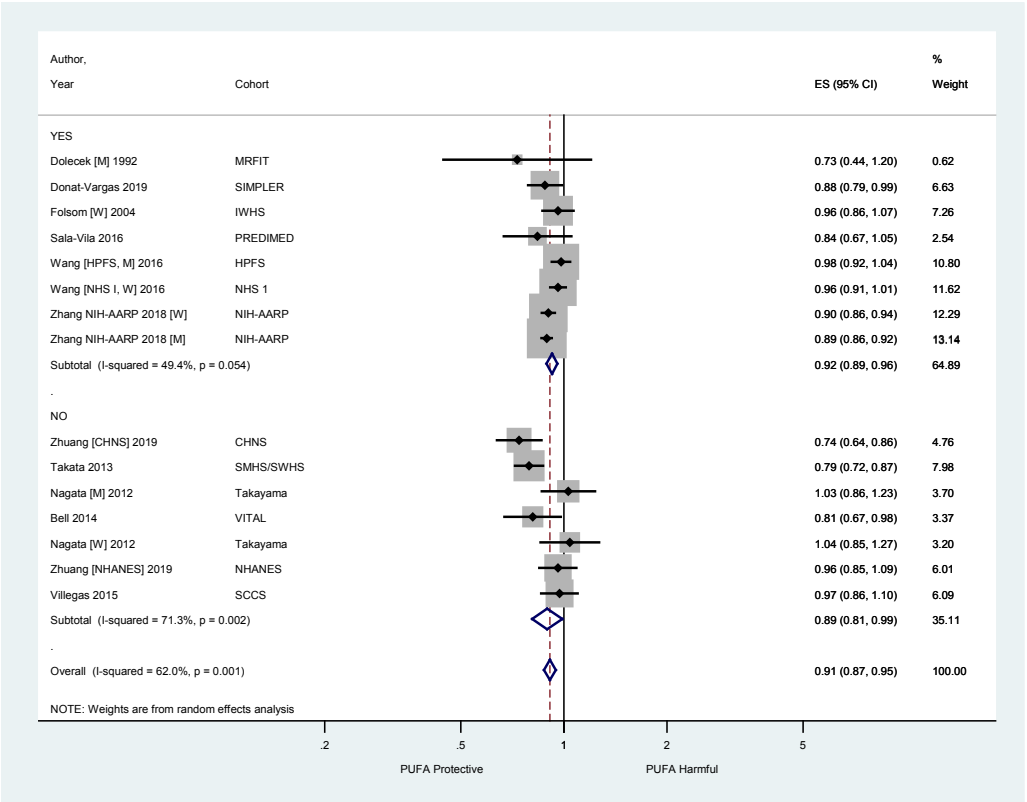
Fig. 91m. Meta-regression of long-chain n-3 PUFA and all-cause mortality; dyslipidaemia adjustment; Panel A – effect size



Effect size was not associated with adjustment for dyslipidaemia (yes or no) (P=0.49).

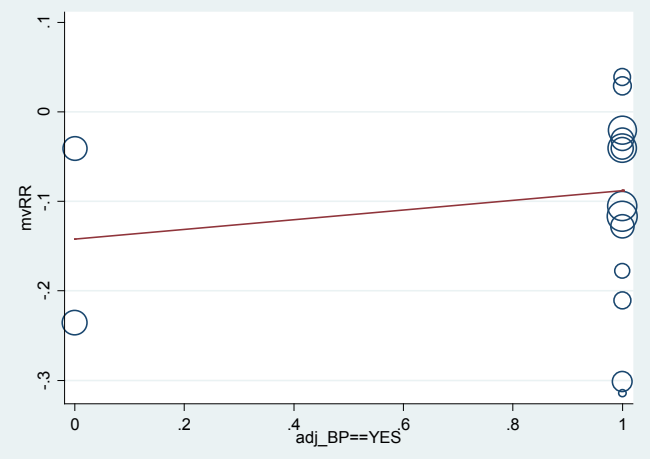
adj_tcorLDL: adjusted for dyslipidaemia; mvRR: multivariable risk ratio; PUFA: polyunsaturated fatty acids.

Fig. 91n. Meta-regression of long-chain n-3 PUFA and all-cause mortality; dyslipidaemia adjustment; Panel B – subgroup analysis by adjustment for dyslipidaemia



CHNS: China Health and Nutrition Survey; CI: confidence interval; ES: effect size; HPFS: Health Professionals Follow-up Study; IWHS: Iowa Women's Health Study; M: male; MRFIT: Multiple Risk Factor Intervention Trial; NHANES: National Health and Nutrition Examination Survey; NHS I: Nurses' Health Study I; NIH-AARP: National Institutes of Health American Association of Retired Persons Diet and Health Study; PREDIMED: Prevención con Dieta Mediterránea; PUFA: polyunsaturated fatty acids; SCCS: Southern Community Cohort Study; SIMPLER: Swedish Infrastructure for Medical Population-based Life-course and Environmental Research; SMHS: Shanghai Men's Health Study; SWHS: Shanghai Women's Health Study; VITAL: Vitamins and Lifestyle Study; W: women.

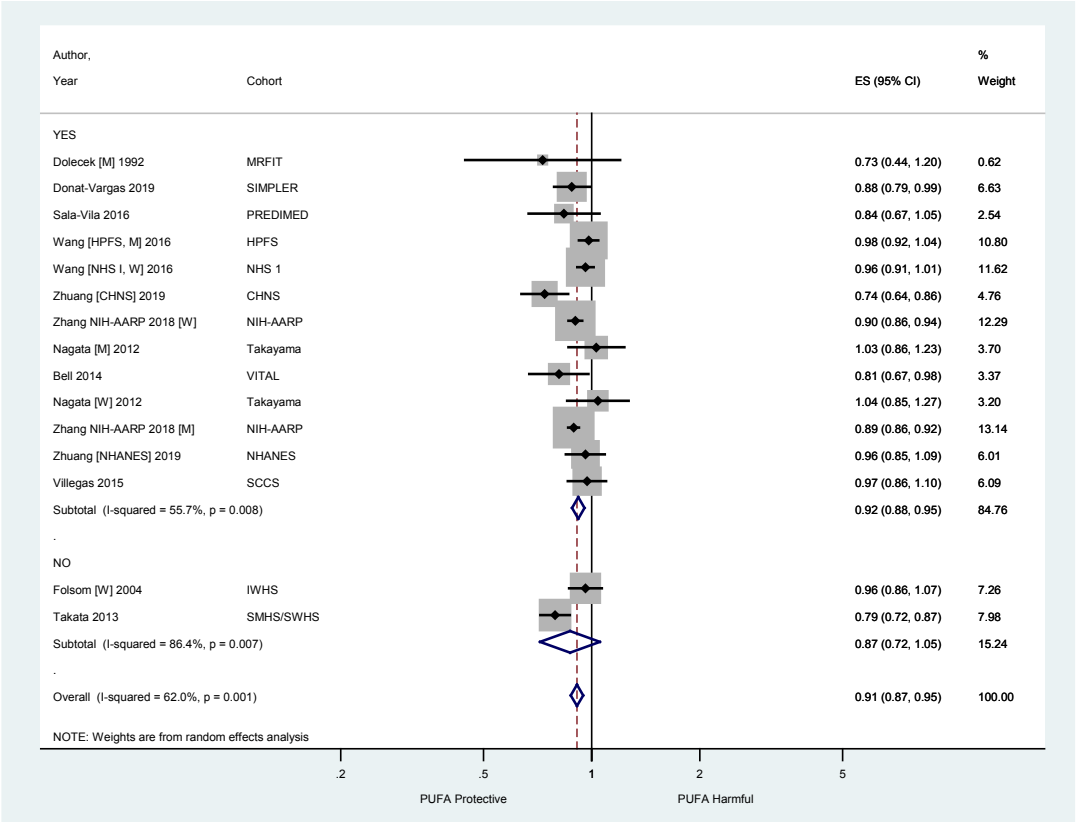
Fig. 91o. Meta-regression of long-chain n-3 PUFA and all-cause mortality; blood pressure adjustment; Panel A – effect size



Effect size was not associated with adjustment for hypertension (yes or no) (P=0.43).

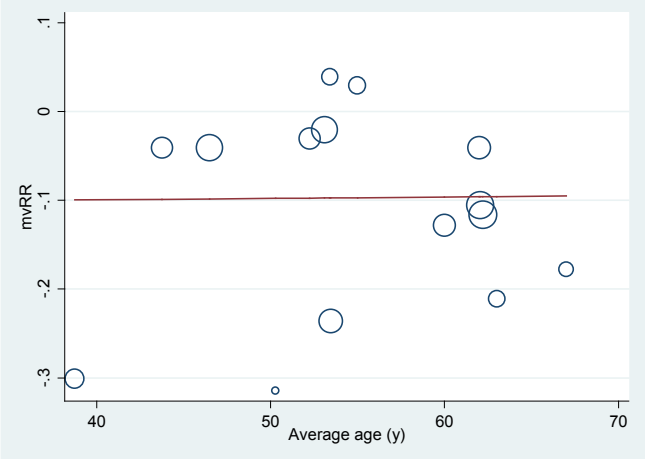
adj_BP: adjusted for blood pressure; mvRR: multivariable risk ratio; PUFA: polyunsaturated fatty acids.

Fig. 91p. Meta-regression of long-chain n-3 PUFA and all-cause mortality; blood pressure adjustment; Panel B – subgroup analysis by adjustment for blood pressure or measure of hypertension



CHNS: China Health and Nutrition Survey; CI: confidence interval; ES: effect size; HPFS: Health Professionals Follow-up Study; IWHS: Iowa Women's Health Study; M: male; MRFIT: Multiple Risk Factor Intervention Trial; NHANES: National Health and Nutrition Examination Survey; NHS I: Nurses' Health Study I; NIH-AARP: National Institutes of Health American Association of Retired Persons Diet and Health Study; PREDIMED: Prevención con Dieta Mediterránea; PUFA: polyunsaturated fatty acids; SCCS: Southern C-based Life-course and Environmental Research; SMHS: Shanghai Men's Health Study; SWHS: Shanghai Women's Health Study; VITAL: Vitamins and Lifestyle Study; W: women.

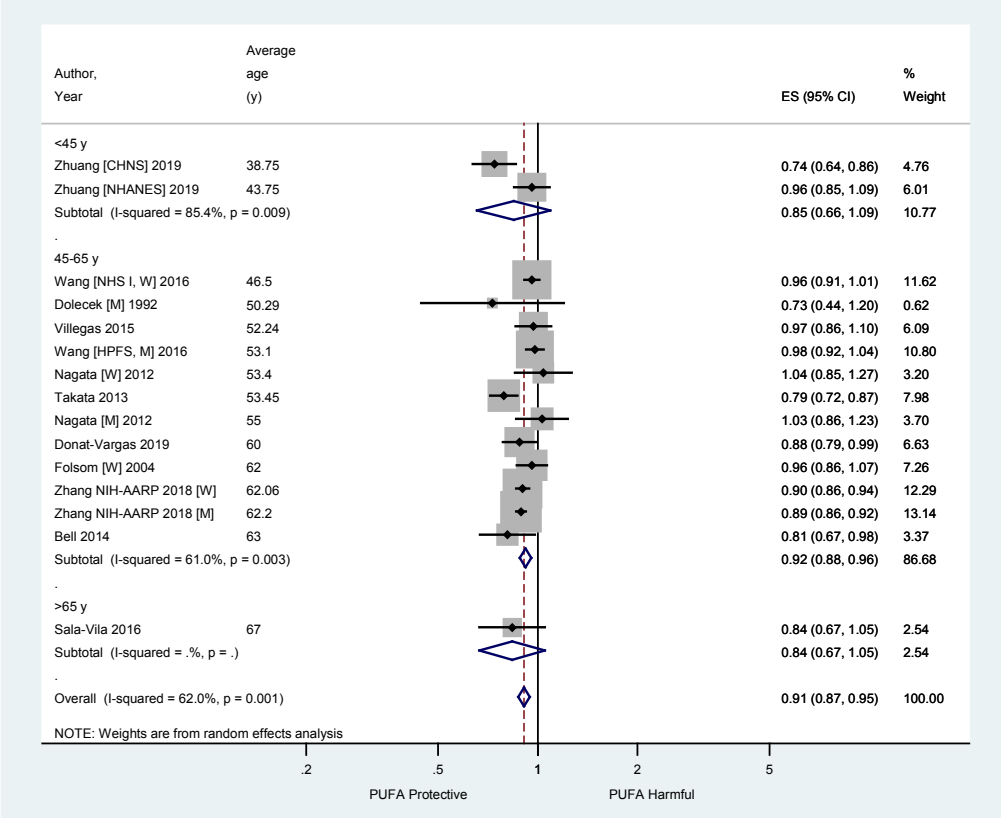
Fig. 91q. Meta-regression of long-chain n-3 PUFA and all-cause mortality; adjustment for age; Panel A – effect size



The effect estimate was not associated with average age of the participants (*P*=0.96).

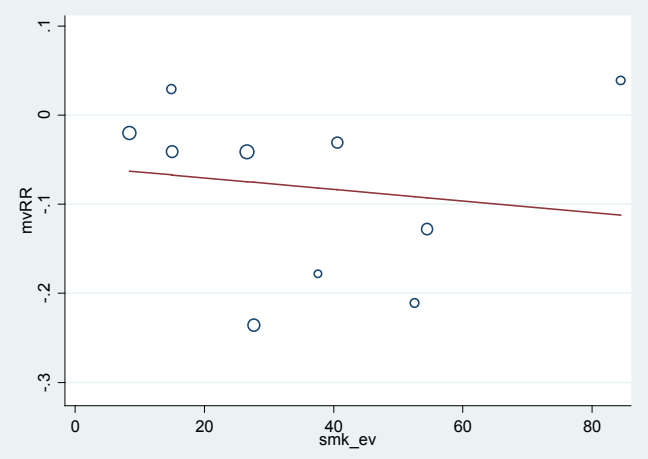
mvRR: multivariable risk ratio; PUFA: polyunsaturated fatty acids; y: years.

Fig. 91r. Meta-regression of long-chain n-3 PUFA and all-cause mortality; adjustment for age; Panel B – subgroup analysis by age



CHNS: China Health and Nutrition Survey; CI: confidence interval; ES: effect size; HPFS: Health Professionals Follow-up Study; M: male; NHANES: National Health and Nutrition Examination Survey; NHS I: Nurses' Health Study I; NIH-AARP: National Institutes of Health American Association of Retired Persons Diet and Health Study; PUFA: polyunsaturated fatty acids; W: women; y: years.

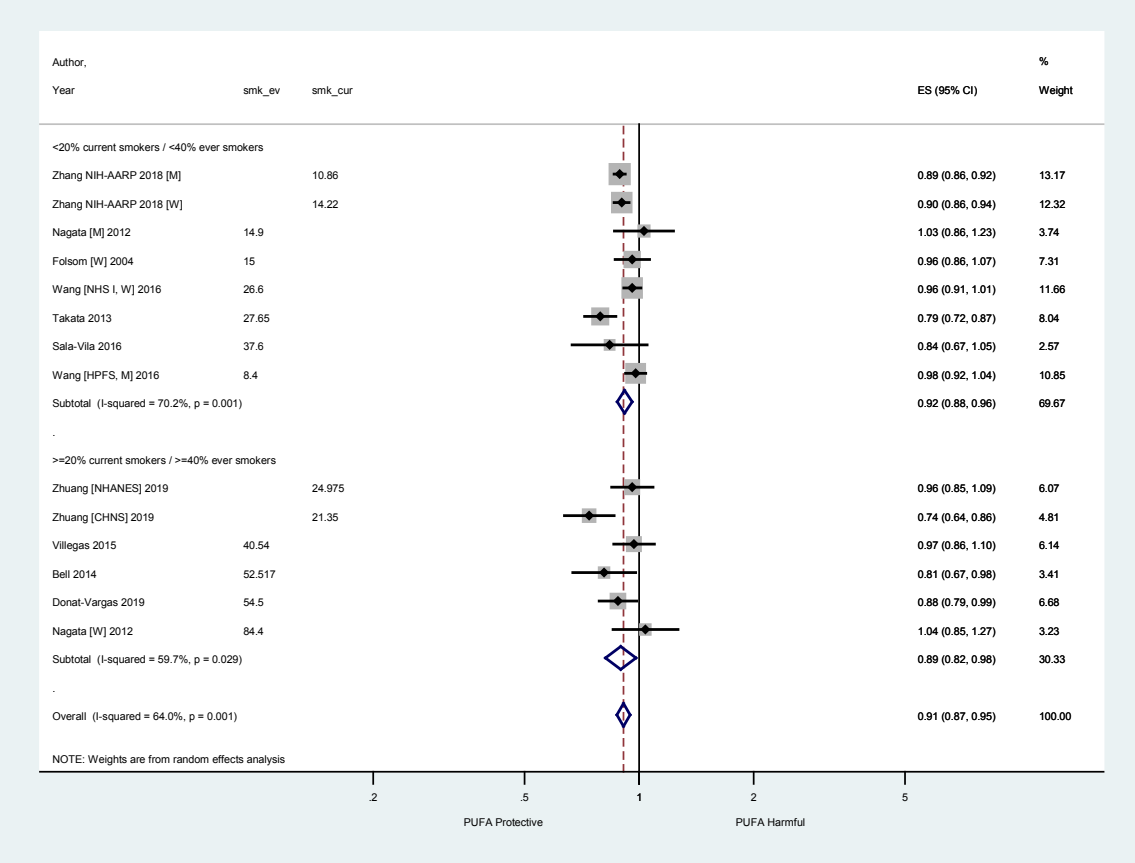
Fig. 91s. Meta-regression of long-chain n-3 PUFA and all-cause mortality; smoking; Panel A – effect size



The effect estimate was not associated with the frequency of smoking in the study (*P*=0.68).

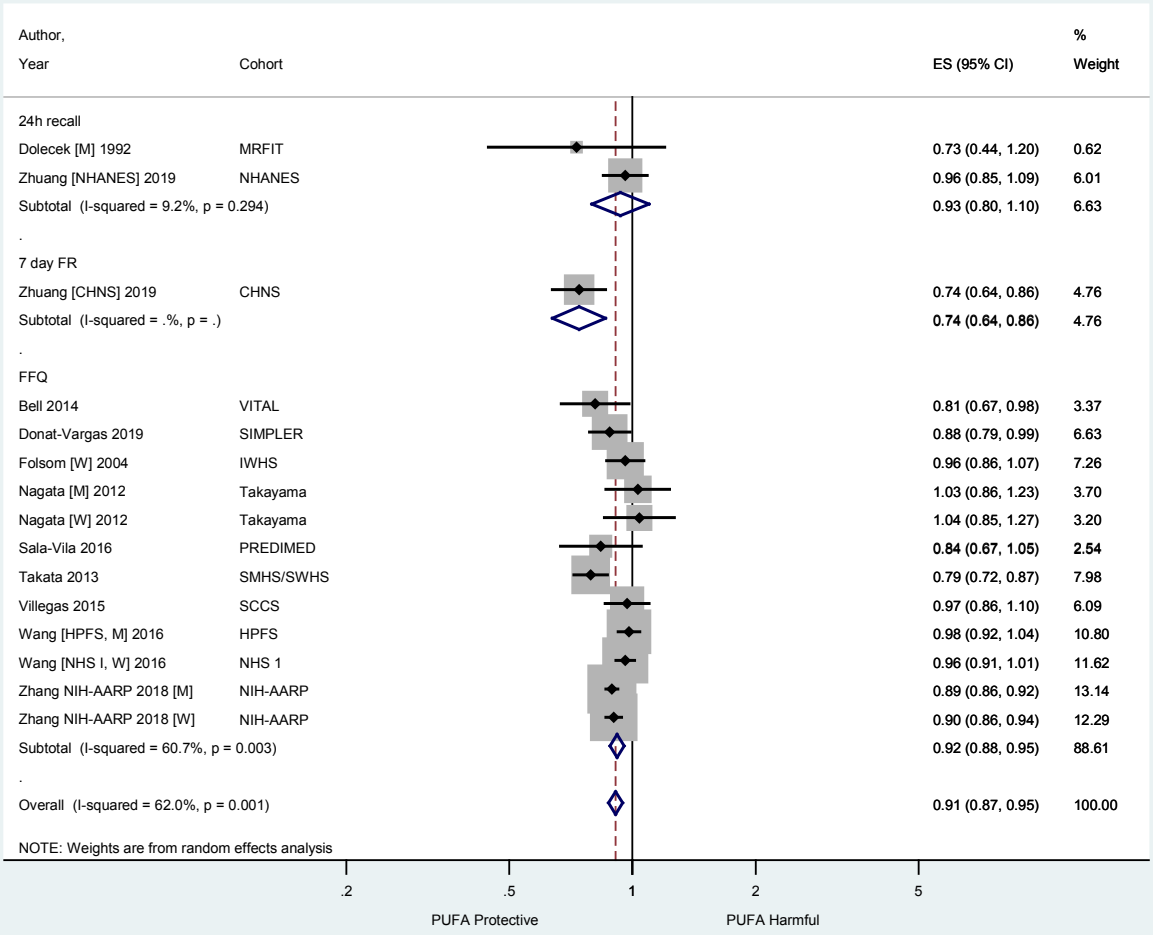
mvRR: multivariable risk ratio; PUFA: polyunsaturated fatty acids; smk_ev: ever smoked.

Fig. 91t. Meta-regression of long-chain n-3 PUFA and all-cause mortality; smoking; Panel B – subgroup analysis by smoking status



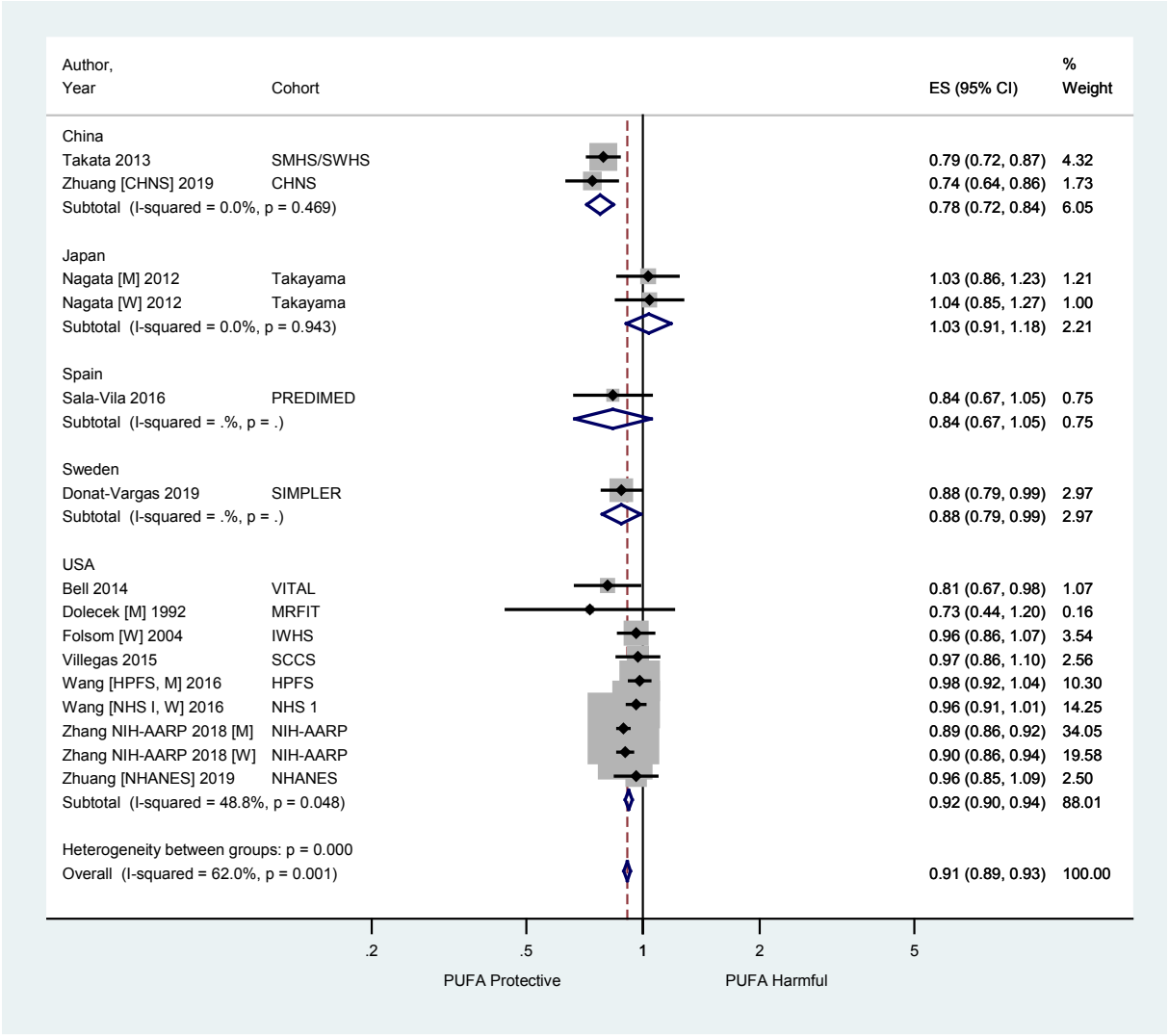
CHNS: China Health and Nutrition Survey; CI: confidence interval; ES: effect size; HPFS: Health Professionals Follow-up Study; M: male; NHANES: National Health and Nutrition Examination Survey; NHS I: Nurses' Health Study I; NIH-AARP: National Institutes of Health American Association of Retired Persons Diet and Health Study; PUFA: polyunsaturated fatty acids; smk_cur: current smokers; smk_ev: ever smoked; W: women.

Fig. 91u. Meta-regression of long-chain n-3 PUFA and all-cause mortality; diet assessment method; subgroup analysis by diet assessment method



CHNS: China Health and Nutrition Survey; CI: confidence interval; ES: effect size; FFQ: food frequency questionnaire; FR: food record; h: hour; HPFS: Health Professionals Follow-up Study; IWHS: Iowa Women's Health Study; M: male; MRFIT: Multiple Risk Factor Intervention Trial; NHANES: National Health and Nutrition Examination Survey; NHS I: Nurses' Health Study I; NIH-AARP: National Institutes of Health American Association of Retired Persons Diet and Health Study; PREDIMED: Prevención con Dieta Mediterránea; PUFA: polyunsaturated fatty acids; SCCS: Southern Community Cohort Study; SIMPLER: Swedish Infrastructure for Medical Population-based Life-course and Environmental Research; SMHS: Shanghai Men's Health Study; SWHS: Shanghai Women's Health Study; VITAL: Vitamins and Lifestyle Study; W: women. Effect estimate differed by diet assessment method (Phet=0.02).

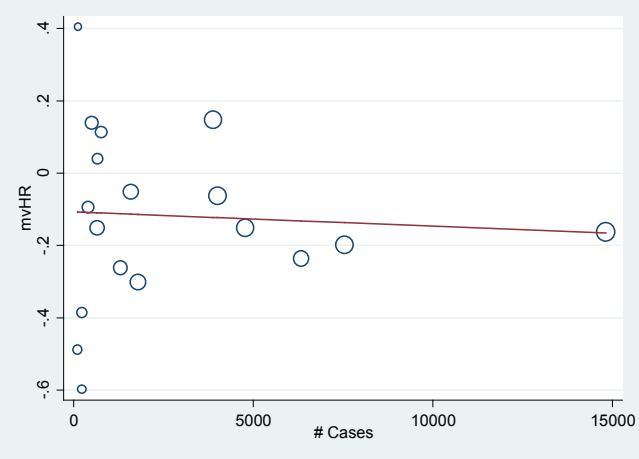
Fig. 91v. Meta-regression of long-chain n-3 PUFA and all-cause mortality; country of conduct; subgroup analysis by country



CHNS: China Health and Nutrition Survey; CI: confidence interval; ES: effect size; HPFS: Health Professionals Follow-up Study; IWHS: Iowa Women's Health Study; M: male; MRFIT: Multiple Risk Factor Intervention Trial; NHANES: National Health and Nutrition Examination Survey; NHS I: Nurses' Health Study I; NIH-AARP: National Institutes of Health American Association of Retired Persons Diet and Health Study; PREDIMED: Prevención con Dieta Mediterránea; PUFA: polyunsaturated fatty acids; SCCS: Southern Community Cohort Study; SIMPLER: Swedish Infrastructure for Medical Population-based Life-course and Environmental Research; SMHS: Shanghai Men's Health Study; SWHS: Shanghai Women's Health Study; USA: United States of America; VITAL: Vitamins and Lifestyle Study; W: women.

Effect estimate differed by country of conduct (Phet<0.0001).

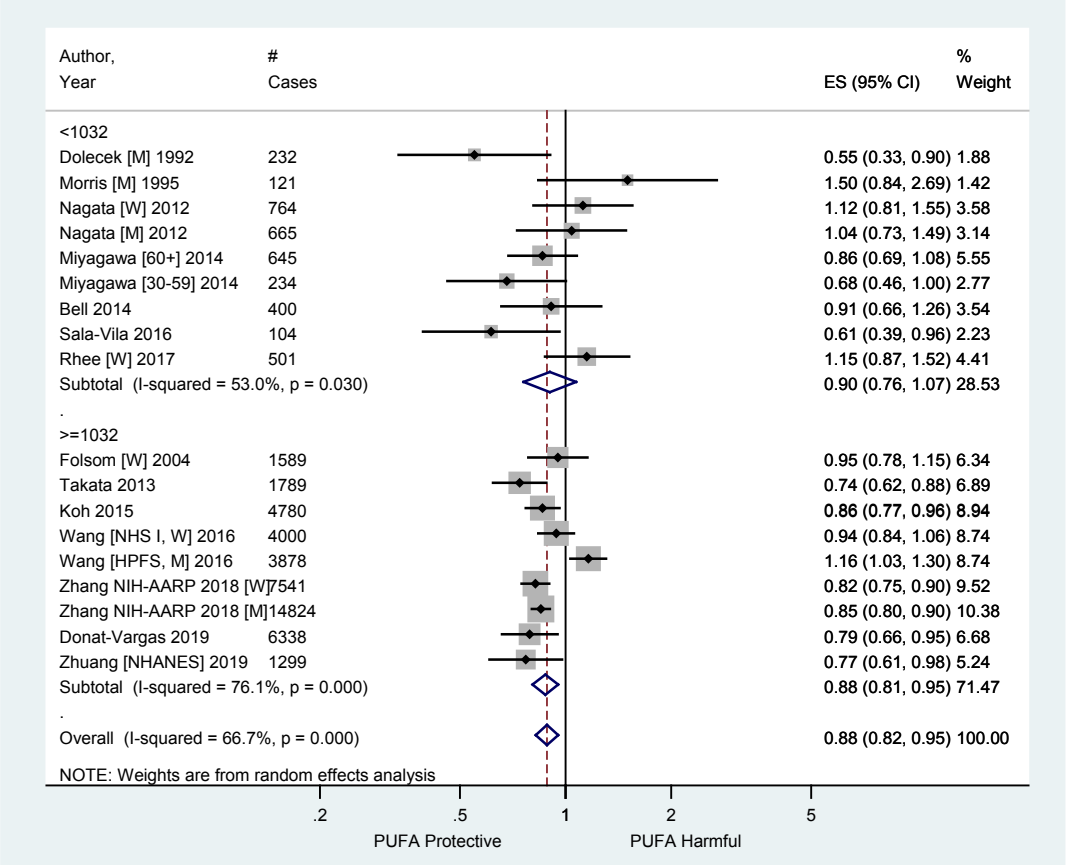
Fig. 92a. Meta-regression of long-chain n-3 PUFA and CVD mortality; number of cases; Panel A – effect size



The number of cases in the study was not associated with the effect estimate (*P*=0.71).

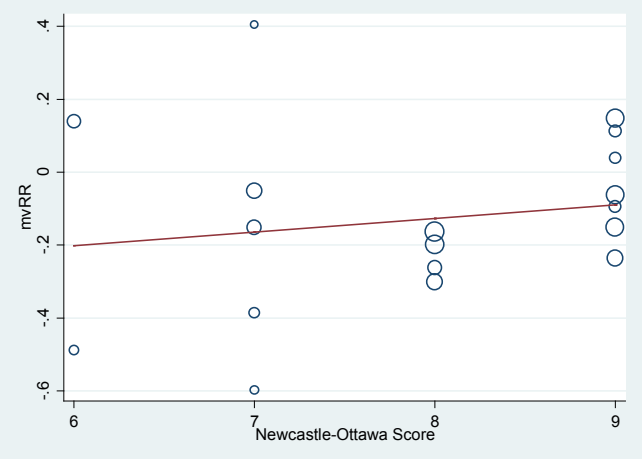
#: number; CI: confidence interval; CVD: cardiovascular disease; mvHR: multivariable hazard ratio; mvRR: multivariable risk ratio; PUFA: polyunsaturated fatty acids.

Fig. 92b. Meta-regression of long-chain n-3 PUFA and CVD mortality; number of cases; Panel B – subgroup analysis by number of cases (median=1032)



#: number; CI: confidence interval; CVD: cardiovascular disease; ES: effect size; HPFS: Health Professionals Follow-up Study; M: male; NHANES: National Health and Nutrition Examination Survey; NHS I: Nurses' Health Study I; NIH-AARP: National Institutes of Health American Association of Retired Persons Diet and Health Study; PUFA: polyunsaturated fatty acids; W: women.

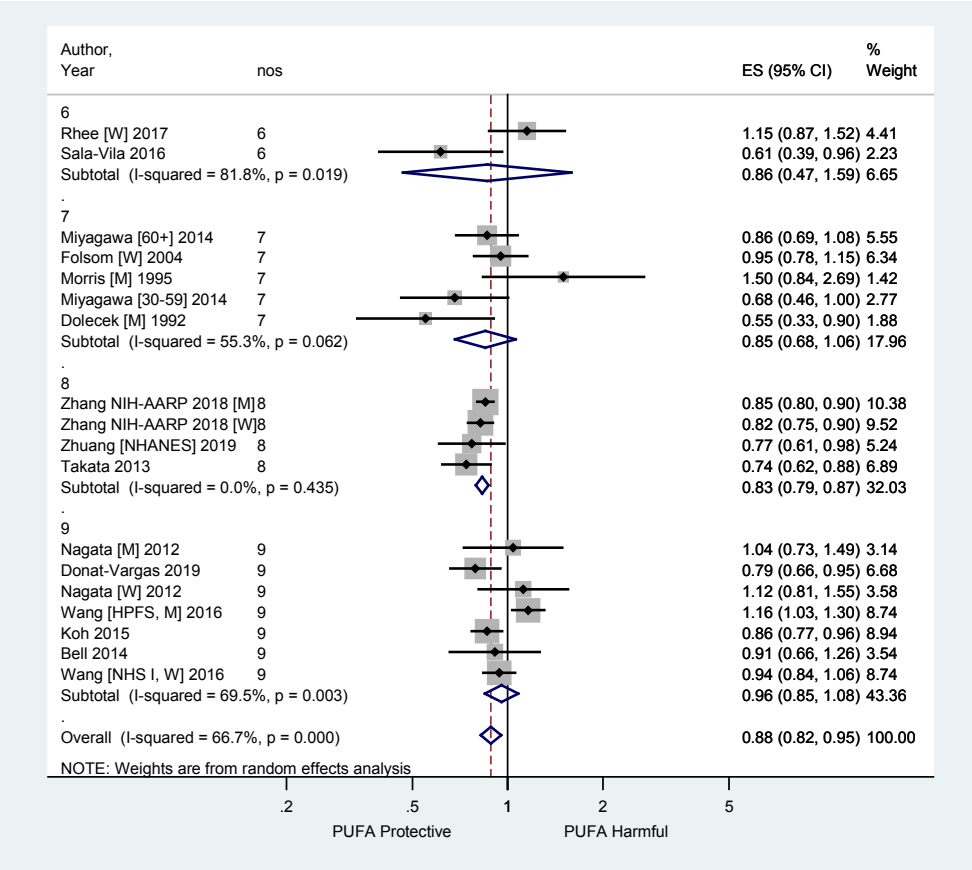
Fig. 92c. Meta-regression of long-chain n-3 PUFA and CVD mortality; NOS assessment; Panel A – effect size



The effect size was not associated with the NOS quality score (P=0.43).

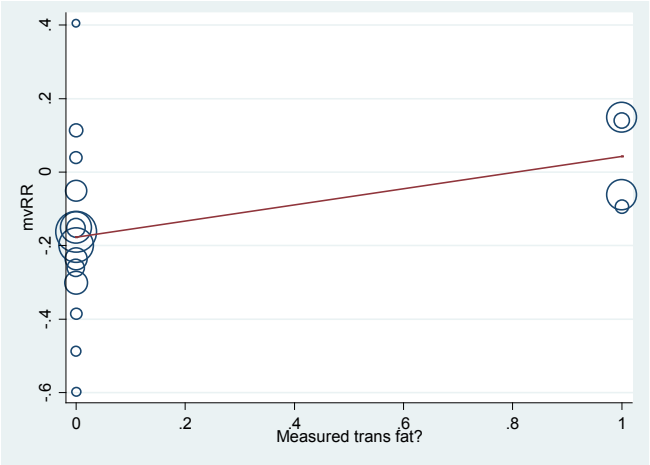
CVD: cardiovascular disease; mvRR: multivariable risk ratio; NOS: Newcastle-Ottawa Scale; PUFA: polyunsaturated fatty acids.

Fig. 92d. Meta-regression of long-chain n-3 PUFA and CVD mortality; NOS assessment; Panel B – subgroup analysis by NOS score



CI: confidence interval; CVD: cardiovascular disease; ES: effect size; HPFS: Health Professionals Follow-up Study; M: male; NHANES: National Health and Nutrition Examination Survey; NHS I: Nurses' Health Study I; NIH-AARP: National Institutes of Health American Association of Retired Persons Diet and Health Study; nos: Newcastle-Ottawa Scale; NOS: Newcastle-Ottawa Scale; PUFA: polyunsaturated fatty acids; W: women.

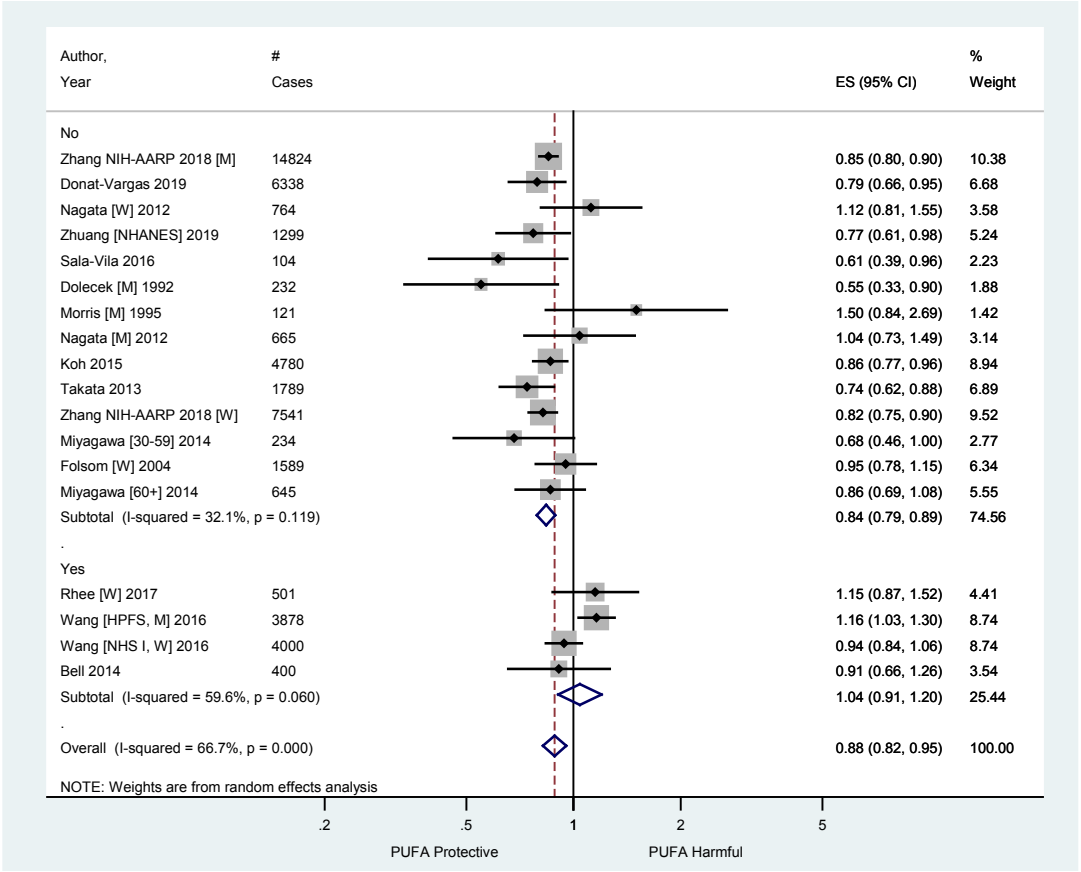
Fig. 92e. Meta-regression of long-chain n-3 PUFA and CVD mortality; TFA assessment; Panel A – effect size



TFA assessment was associated with effect size (*P*=0.004).

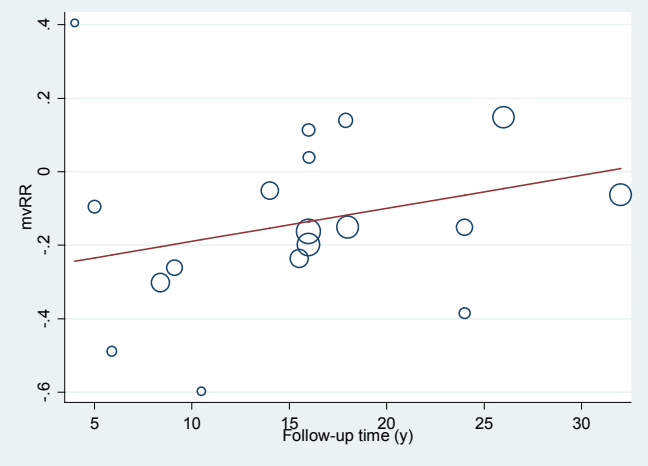
CVD: cardiovascular disease; mvRR: multivariable risk ratio; PUFA: polyunsaturated fatty acids; TFA: trans-fatty acids.

Fig. 92f. Meta-regression of long-chain n-3 PUFA and CVD mortality; TFA assessment; Panel B – subgroup analysis (yes/no)



#: number; CI: confidence interval; CVD: cardiovascular disease; ES: effect size; HPFS: Health Professionals Follow-up Study; M: male; NHANES: National Health and Nutrition Examination Survey; NHS I: Nurses' Health Study I; NIH-AARP: National Institutes of Health American Association of Retired Persons Diet and Health Study; PUFA: polyunsaturated fatty acids; TFA: trans-fatty acids; W: women.

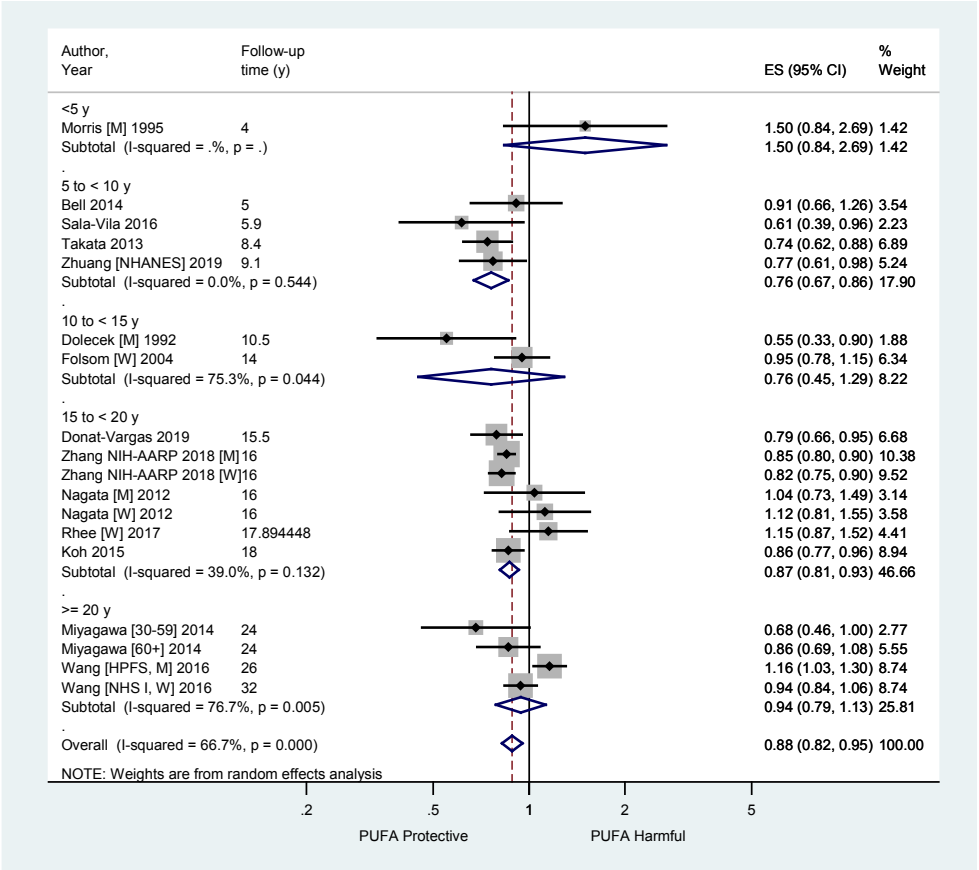
Fig. 92g. Meta-regression of long-chain n-3 PUFA and CVD mortality; follow-up time; Panel A – effect size



The effect size was not associated with adjustment for follow-up time in the final model (*P*=0.12).

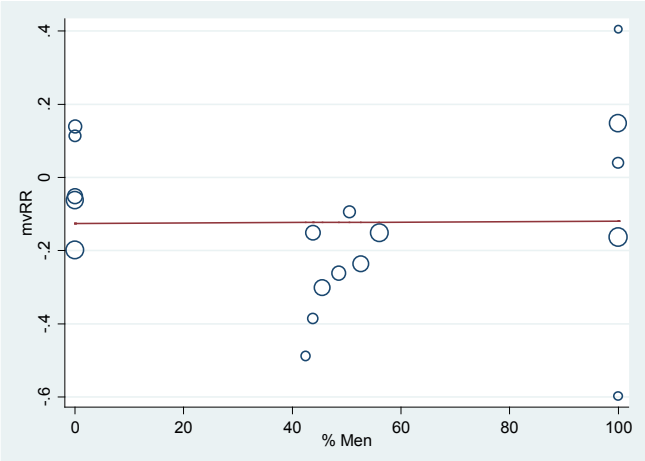
CVD: cardiovascular disease; mvRR: multivariable risk ratio; PUFA: polyunsaturated fatty acids; y: years.

Fig. 92h. Meta-regression of long-chain n-3 PUFA and CVD mortality; follow-up time; Panel B – subgroup analysis by follow-up time



CI: confidence interval; CVD: cardiovascular disease; ES: effect size; HPFS: Health Professionals Follow-up Study; M: male; NHANES: National Health and Nutrition Examination Survey; NHS I: Nurses' Health Study I; NIH-AARP: National Institutes of Health American Association of Retired Persons Diet and Health Study; PUFA: polyunsaturated fatty acids; W: women; y: years.

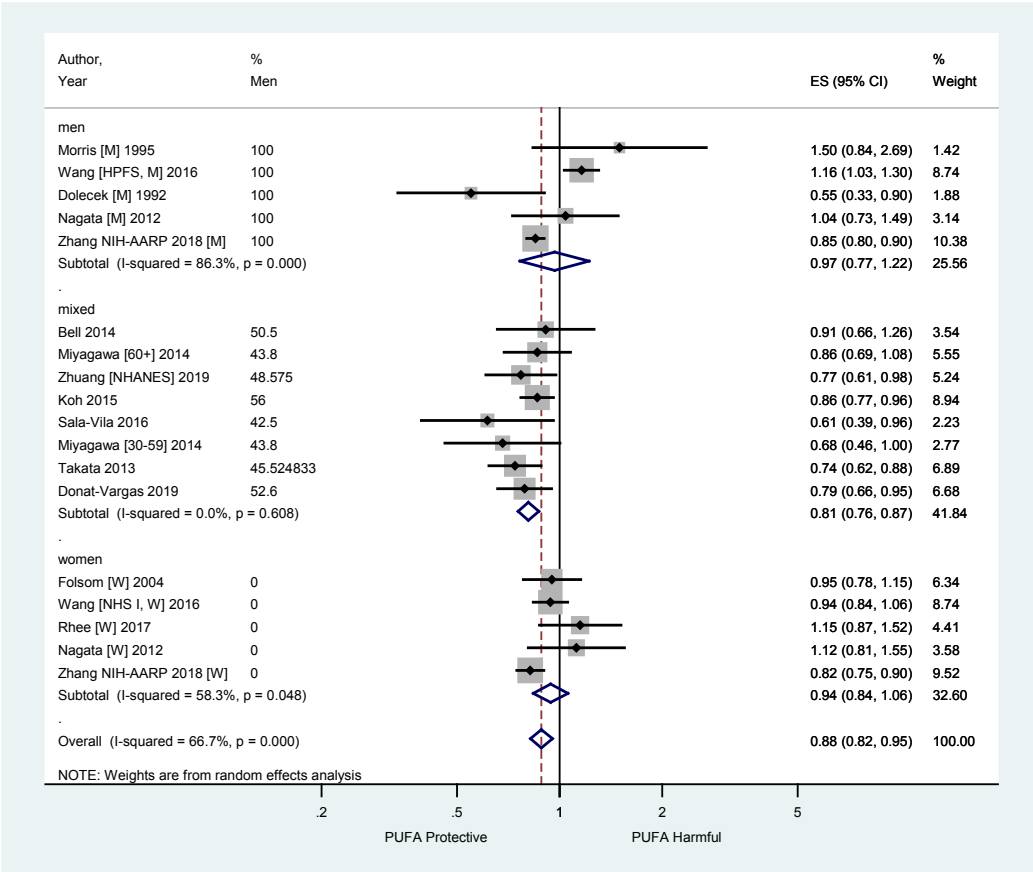
Fig. 92i. Meta-regression of long-chain n-3 PUFA and CVD mortality; sex; Panel A – effect size



The effect size was not associated with the percentage of men in the study (*P*=0.96).

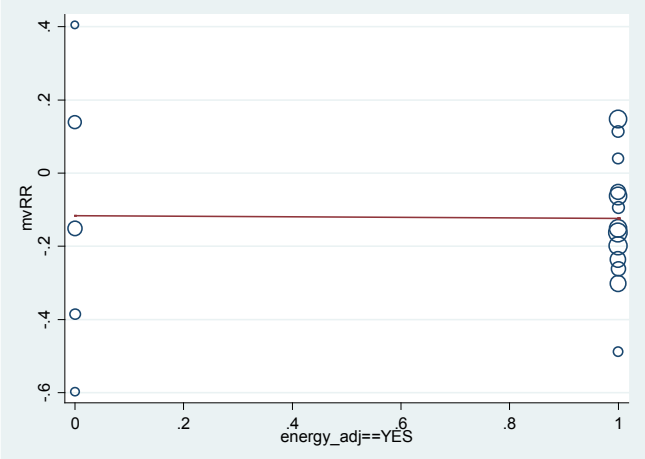
CVD: cardiovascular disease; mvRR: multivariable risk ratio; PUFA: polyunsaturated fatty acids.

Fig. 92j. Meta-regression of long-chain n-3 PUFA and CVD mortality; sex; Panel B – subgroup analysis by sex



CI: confidence interval; CVD: cardiovascular disease; ES: effect size; HPFS: Health Professionals Follow-up Study; M: male; NHANES: National Health and Nutrition Examination Survey; NHS I: Nurses' Health Study I; NIH-AARP: National Institutes of Health American Association of Retired Persons Diet and Health Study; PUFA: polyunsaturated fatty acids; W: women.

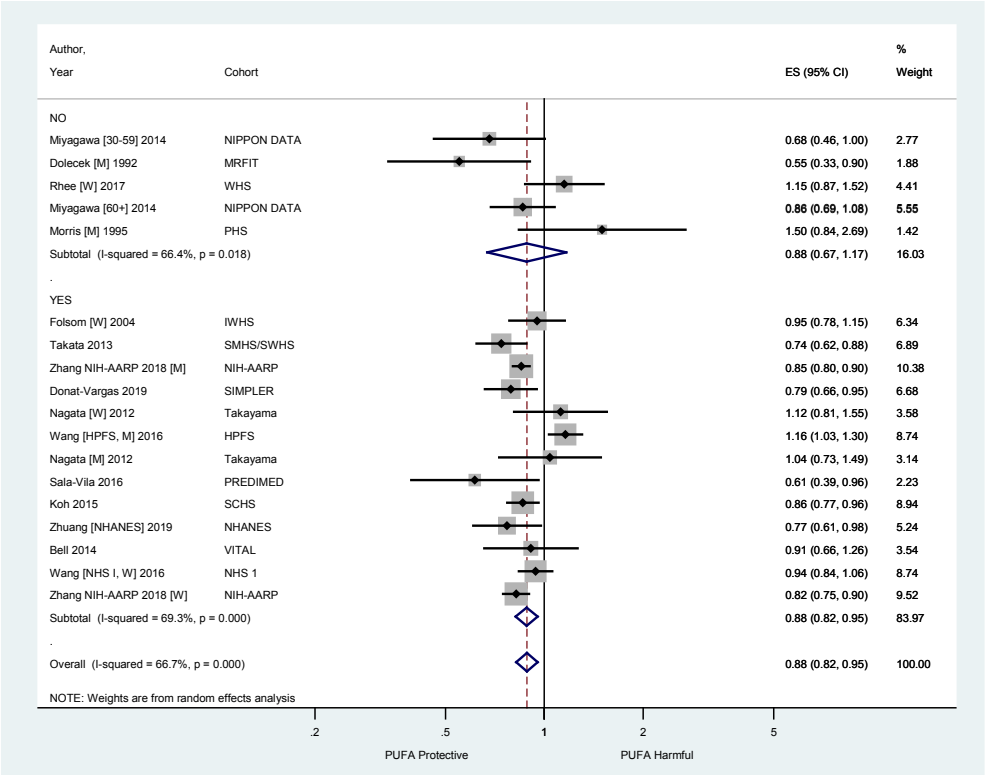
Fig. 92k. Meta-regression of long-chain n-3 PUFA and CVD mortality; energy adjustment; Panel A – effect size



The effect size was not associated with adjustment for energy in the final model (*P*=0.95).

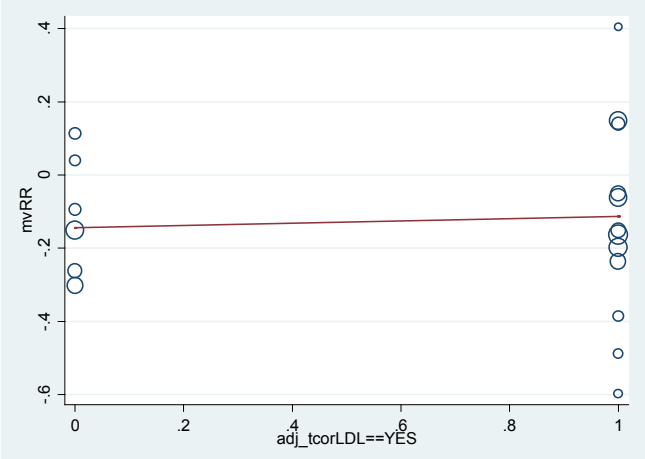
CVD: cardiovascular disease; energy_adj: adjusted for energy; mvRR: multivariable risk ratio; PUFA: polyunsaturated fatty acids.

Fig. 92l. Meta-regression of long-chain n-3 PUFA and CVD mortality; energy adjustment; Panel B – subgroup analysis (yes/no)



CI: confidence interval; CVD: cardiovascular disease; ES: effect size; HPFS: Health Professionals Follow-up Study; IWHS: Iowa Women's Health Study; M: male; MRFIT: Multiple Risk Factor Intervention Trial; NHANES: National Health and Nutrition Examination Survey; NHS I: Nurses' Health Study I; NIH-AARP: National Institutes of Health American Association of Retired Persons Diet and Health Study; NIPPON DATA: The National Integrated Project for Prospective Observation Of Non-communicable Disease and its Trends in the Aged; PHS: Physicians' Health Study; PREDIMED: Prevención con Dieta Mediterránea; PUFA: polyunsaturated fatty acids; SCHS: Singapore Chinese Health Study; SIMPLER: Swedish Infrastructure for Medical Population-based Life-course and Environmental Research; SMHS: Shanghai Men's Health Study; SWHS: Shanghai Women's Health Study; VITAL: Vitamins and Lifestyle Study; W: women; WHS: Women's Health Study.

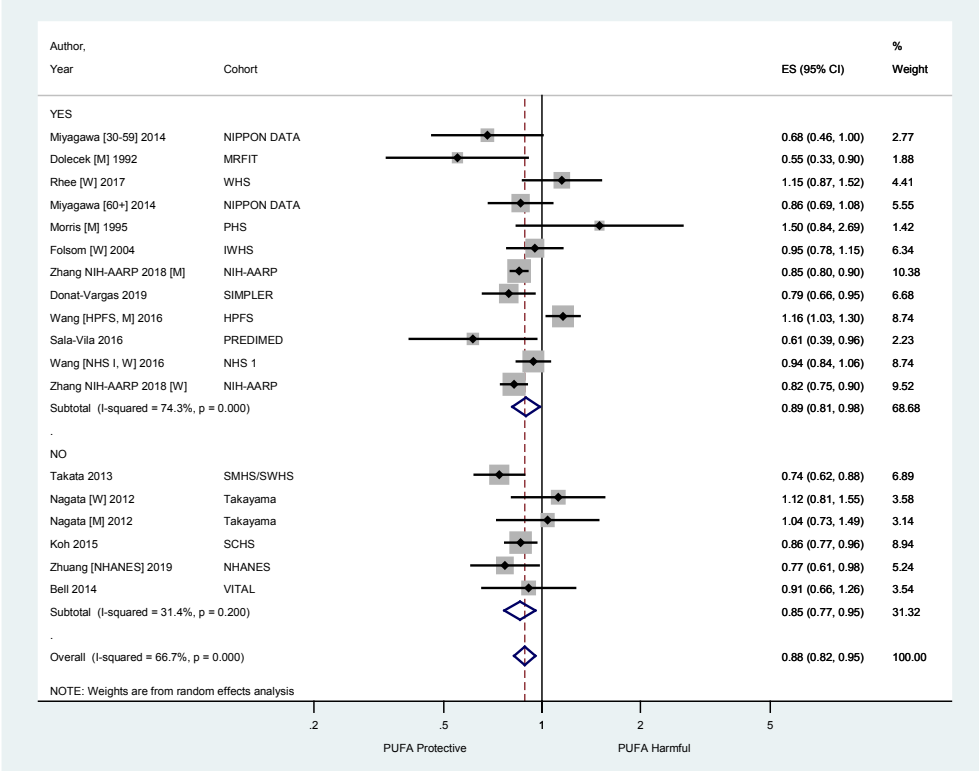
Fig. 92m. Meta-regression of long-chain n-3 PUFA and CVD mortality; dyslipidaemia adjustment; Panel A – effect size



The effect size was not associated with adjustment for a measure of dyslipidaemia in the final model (*P*=0.75).

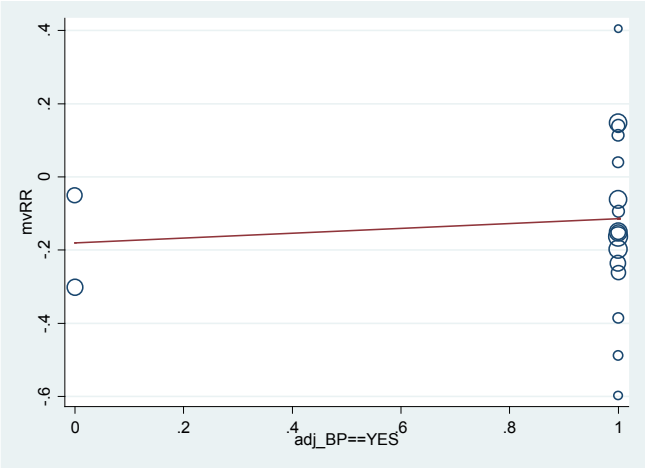
adj_tcorLDL: adjusted for dyslipidaemia; CVD: cardiovascular disease; mvRR: multivariable risk ratio; PUFA: polyunsaturated fatty acids.

Fig. 92n. Meta-regression of long-chain n-3 PUFA and CVD mortality; dyslipidaemia adjustment; Panel B – subgroup analysis (yes/no)



CI: confidence interval; CVD: cardiovascular disease; ES: effect size; HPFS: Health Professionals Follow-up Study; IWHS: Iowa Women's Health Study; M: male; MRFIT: Multiple Risk Factor Intervention Trial; NHANES: National Health and Nutrition Examination Survey; NHS I: Nurses' Health Study I; NIH-AARP: National Institutes of Health American Association of Retired Persons Diet and Health Study; NIPPON DATA: The National Integrated Project for Prospective Observation Of Non-communicable Disease and its Trends in the Aged; PHS: Physicians' Health Study; PREDIMED: Prevención con Dieta Mediterránea; PUFA: polyunsaturated fatty acids; SCHS: Singapore Chinese Health Study; SIMPLER: Swedish Infrastructure for Medical Population-based Life-course and Environmental Research; SMHS: Shanghai Men's Health Study; SWHS: Shanghai Women's Health Study; VITAL: Vitamins and Lifestyle Study; W: women; WHS: Women's Health Study.

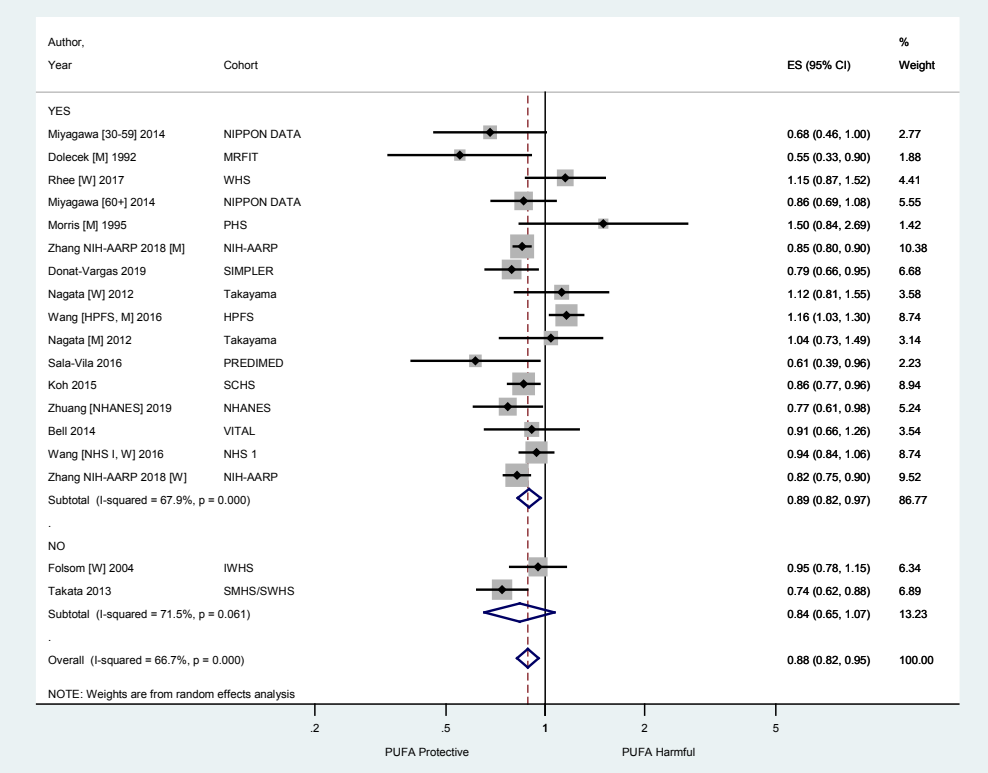
Fig. 92o. Meta-regression of long-chain n-3 PUFA and CVD mortality; blood pressure adjustment; Panel A – effect size



The effect size was not associated with whether or not there was adjustment for a measure of blood pressure in the final model (*P*=0.62).

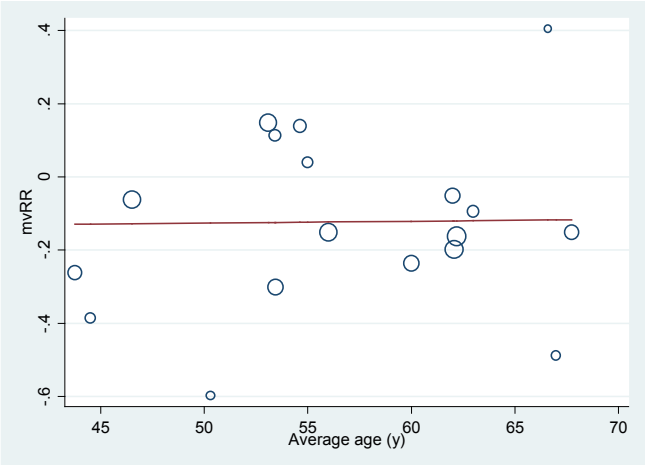
adj_BP: adjusted for blood pressure; CVD: cardiovascular disease; mvRR: multivariable risk ratio; PUFA: polyunsaturated fatty acids.

Fig. 92p. Meta-regression of long-chain n-3 PUFA and CVD mortality; blood pressure adjustment; Panel B – subgroup analysis (yes/no)



CI: confidence interval; CVD: cardiovascular disease; ES: effect size; HPFS: Health Professionals Follow-up Study; IWHS: Iowa Women's Health Study; M: male; MRFIT: Multiple Risk Factor Intervention Trial; NHANES: National Health and Nutrition Examination Survey; NHS I: Nurses' Health Study I; NIH-AARP: National Institutes of Health American Association of Retired Persons Diet and Health Study; NIPPON DATA: The National Integrated Project for Prospective Observation Of Non-communicable Disease and its Trends in the Aged; PHS: Physicians' Health Study; PREDIMED: Prevención con Dieta Mediterránea; PUFA: polyunsaturated fatty acids; SCHS: Singapore Chinese Health Study; SIMPLER: Swedish Infrastructure for Medical Population-based Life-course and Environmental Research; SMHS: Shanghai Men's Health Study; SWHS: Shanghai Women's Health Study; VITAL: Vitamins and Lifestyle Study; W: women; WHS: Women's Health Study.

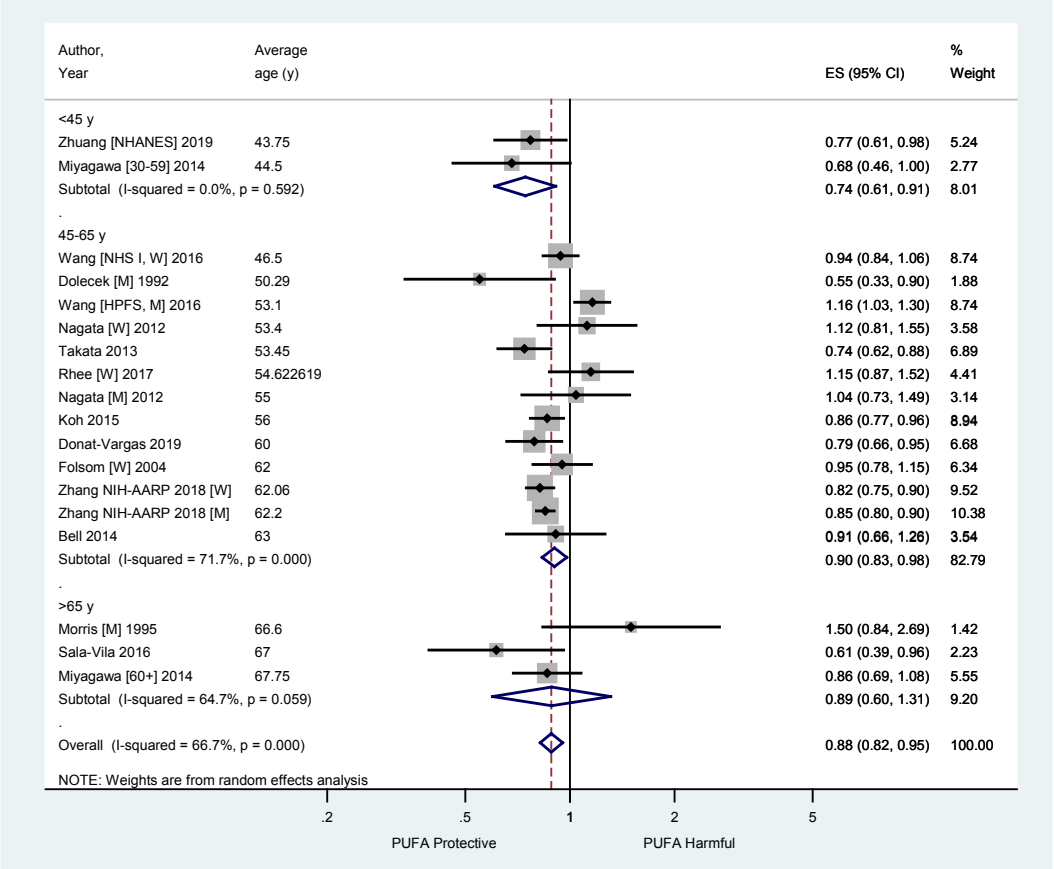
Fig. 92q. Meta-regression of long-chain n-3 PUFA and CVD mortality; age; Panel A – effect size



The effect size was not associated with adjustment for average age of the study sample in the final model (*P*=0.94).

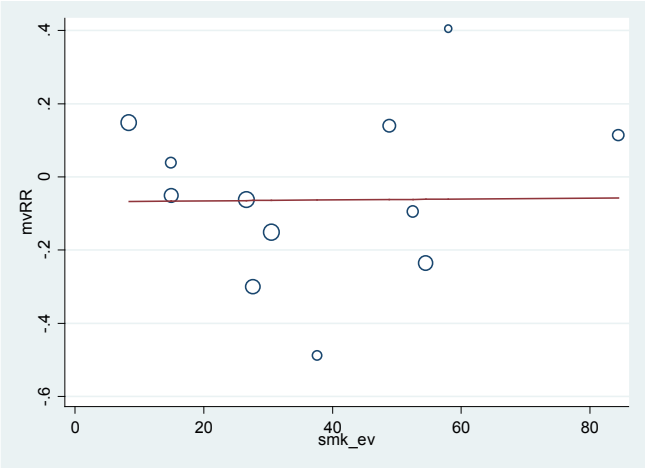
CVD: cardiovascular disease; mvRR: multivariable risk ratio; PUFA: polyunsaturated fatty acids; y: years.

Fig. 92r. Meta-regression of long-chain n-3 PUFA and CVD mortality; age; Panel B – subgroup analysis (age group)



CI: confidence interval; CVD: cardiovascular disease; ES: effect size; HPFS: Health Professionals Follow-up Study; M: male; NHANES: National Health and Nutrition Examination Survey; NHS I: Nurses' Health Study I; NIH-AARP: National Institutes of Health American Association of Retired Persons Diet and Health Study; PUFA: polyunsaturated fatty acids; W: women; y: years.

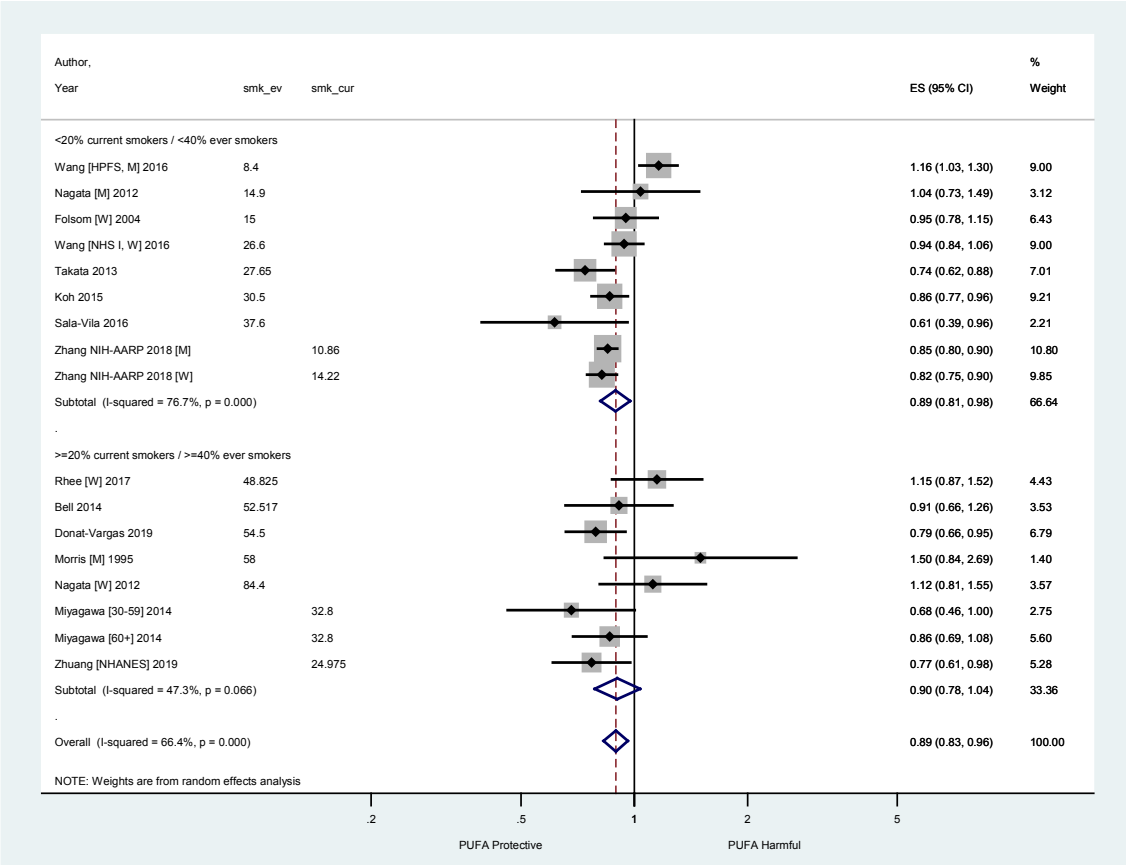
Fig. 92s. Meta-regression of long-chain n-3 PUFA and CVD mortality; smoking; Panel A – effect size



The effect size was not associated with adjustment for smoking history of the study sample in the final model (*P*=0.96). High smokers ≥40% current/former or >20% current.

CVD: cardiovascular disease; mvRR: multivariable risk ratio; PUFA: polyunsaturated fatty acids; smk_ev: ever smoked.

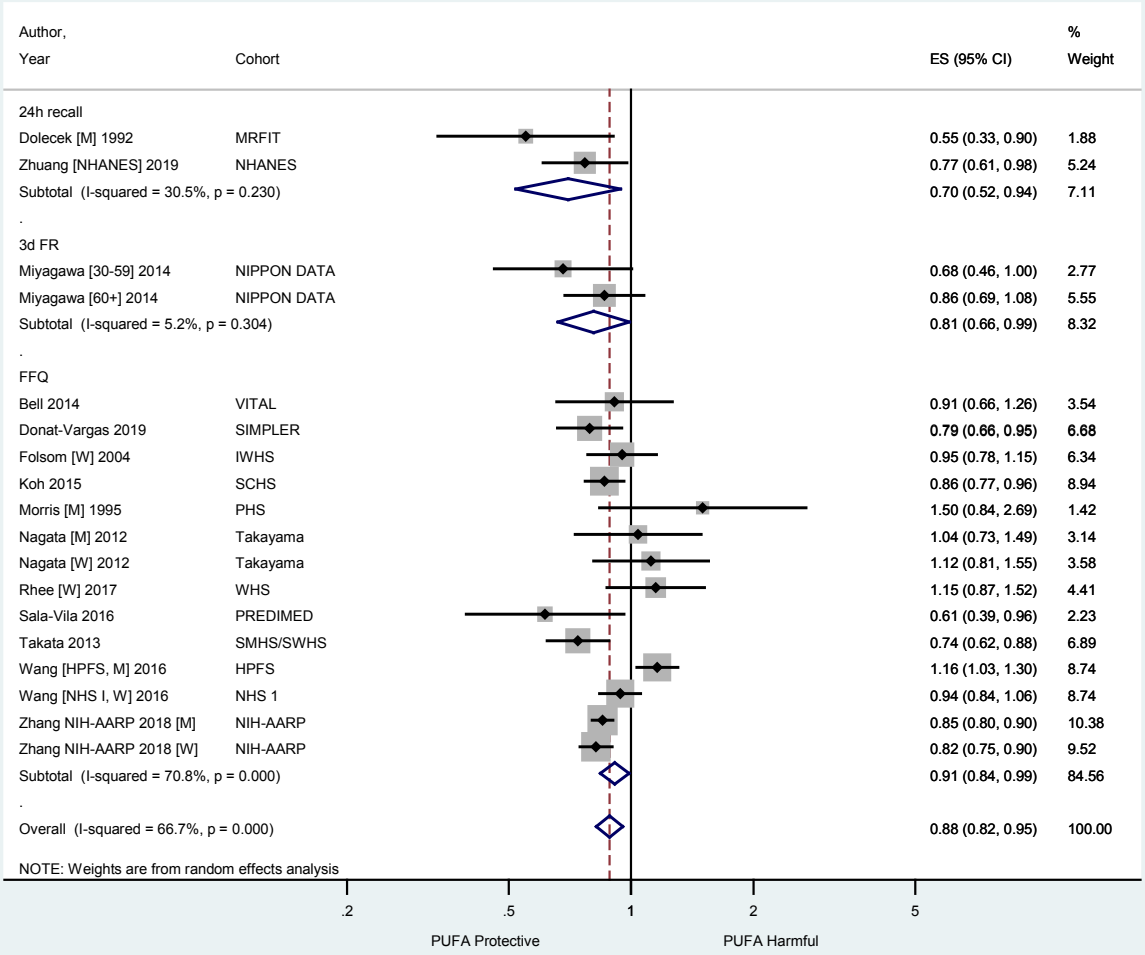
Fig. 92t. Meta-regression of long-chain n-3 PUFA and CVD mortality; smoking; Panel B – subgroup analysis by smoking status



*Smoking data not available for one study (Dolocek, 1992).

CI: confidence interval; CVD: cardiovascular disease; ES: effect size; HPFS: Health Professionals Follow-up Study; M: male; NHANES: National Health and Nutrition Examination Survey; NHS I: Nurses' Health Study I; NIH-AARP: National Institutes of Health American Association of Retired Persons Diet and Health Study; PUFA: polyunsaturated fatty acids; smk_cur: current smokers; smk_ev: ever smoked; W: women.

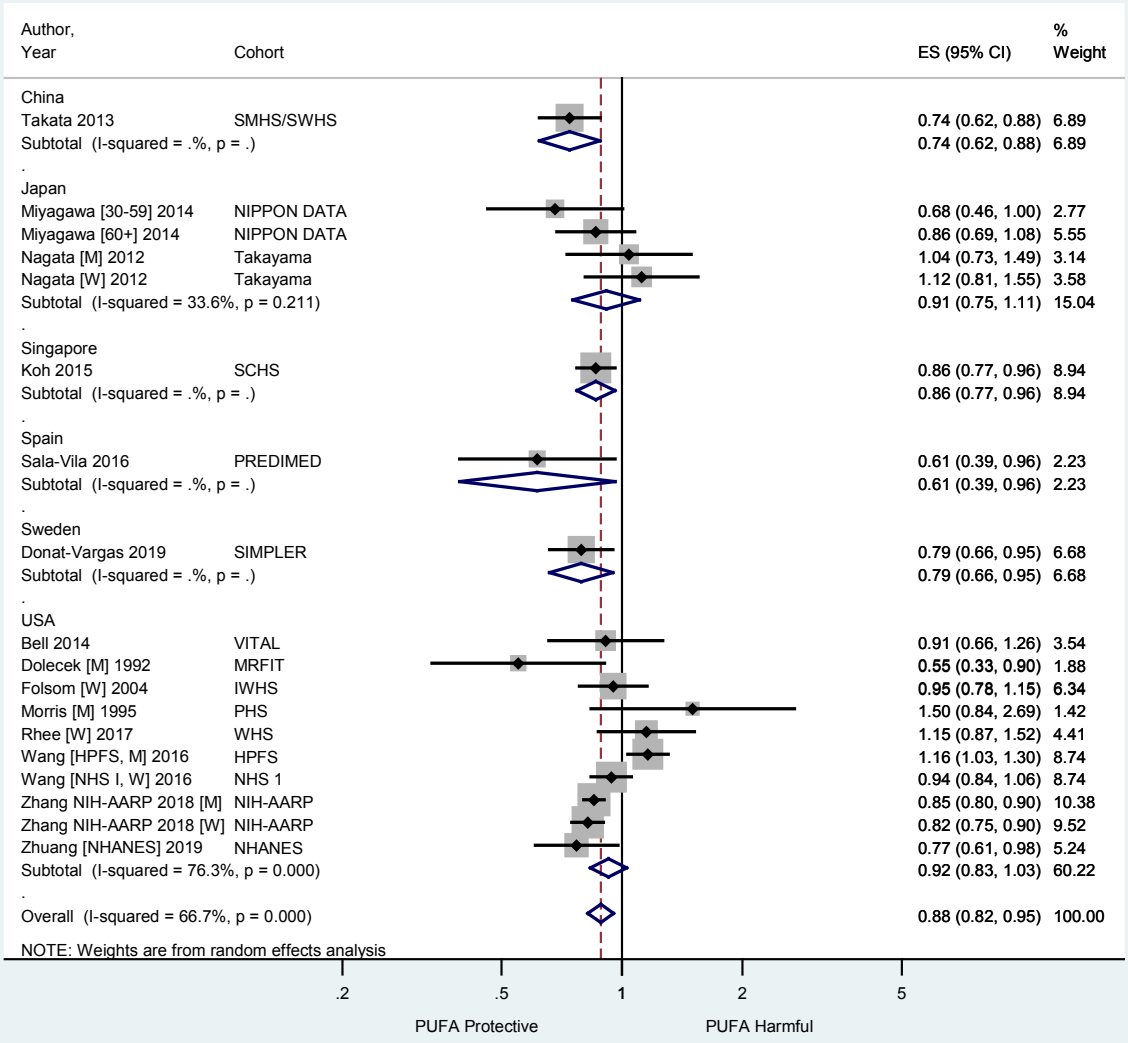
Fig. 92u. Meta-regression of long-chain n-3 PUFA and CVD mortality; diet assessment method; subgroup analysis



CI: confidence interval; CVD: cardiovascular disease; d: day; ES: effect size; FFQ: food frequency questionnaire; FR: food record; h: hour; HPFS: Health Professionals Follow-up Study; IWHS: Iowa Women's Health Study; M: male; MRFIT: Multiple Risk Factor Intervention Trial; NHANES: National Health and Nutrition Examination Survey; NHS I: Nurses' Health Study I; NIH-AARP: National Institutes of Health American Association of Retired Persons Diet and Health Study; NIPPON DATA: The National Integrated Project for Prospective Observation Of Non-communicable Disease and its Trends in the Aged; PHS: Physicians' Health Study; PREDIMED: Prevención con Dieta Mediterránea; PUFA: polyunsaturated fatty acids; SCHS: Singapore Chinese Health Study; SIMPLER: Swedish Infrastructure for Medical Population-based Life-course and Environmental Research; SMHS: Shanghai Men's Health Study; SWHS: Shanghai Women's Health Study; VITAL: Vitamins and Lifestyle Study; W: women; WHS: Women's Health Study.

The effect size was not associated with diet assessment method (P_{het}=0.22). Because the predictor variable had more than 2 levels, it is not appropriate to show the continuous meta-regression line; therefore, we present the "by country" estimates separately.

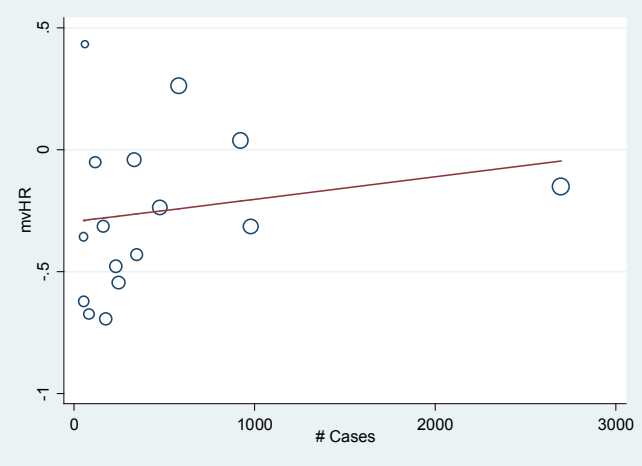
Fig. 92v. Meta-regression of long-chain n-3 PUFA and CVD mortality; country of conduct; subgroup analysis



CI: confidence interval; CVD: cardiovascular disease; ES: effect size; HPFS: Health Professionals Follow-up Study; IWHS: Iowa Women's Health Study; M: male; MRFIT: Multiple Risk Factor Intervention Trial; NHANES: National Health and Nutrition Examination Survey; NHS I: Nurses' Health Study I; NIH-AARP: National Institutes of Health American Association of Retired Persons Diet and Health Study; NIPPON DATA: The National Integrated Project for Prospective Observation Of Non-communicable Disease and its Trends in the Aged; PHS: Physicians' Health Study; PREDIMED: Prevención con Dieta Mediterránea; PUFA: polyunsaturated fatty acids; SCHS: Singapore Chinese Health Study; SIMPLER: Swedish Infrastructure for Medical Population-based Life-course and Environmental Research; SMHS: Shanghai Men's Health Study; SWHS: Shanghai Women's Health Study; USA: United States of America; VITAL: Vitamins and Lifestyle Study; W: women; WHS: Women's Health Study.

There was evidence of heterogeneity of effect size by country of conduct (P_{het}=0.60). Because the predictor variable had more than 2 levels, it is not appropriate to show the continuous meta-regression line; therefore, we present the "by country" estimates separately.

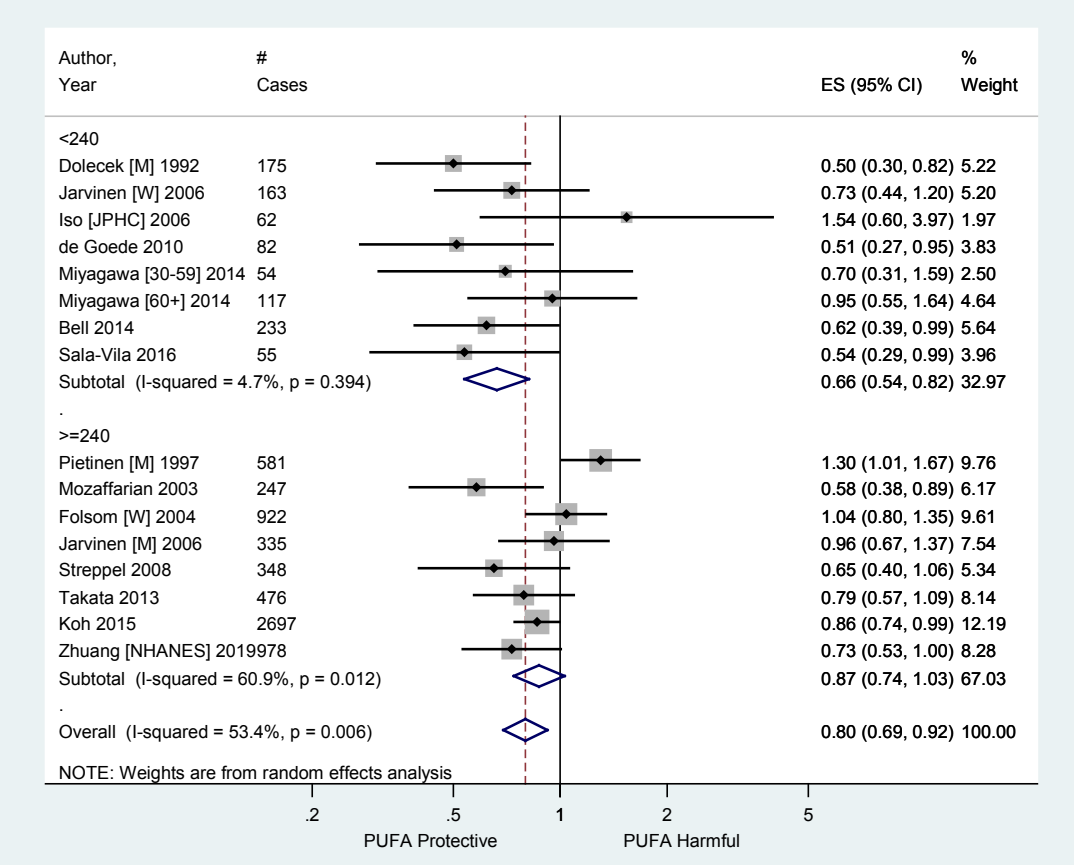
Fig. 93a. Meta-regression of long-chain n-3 PUFA and CHD mortality; number of cases; Panel A – effect size



The number of cases in the study was not associated with the effect estimate (*P*=0.38).

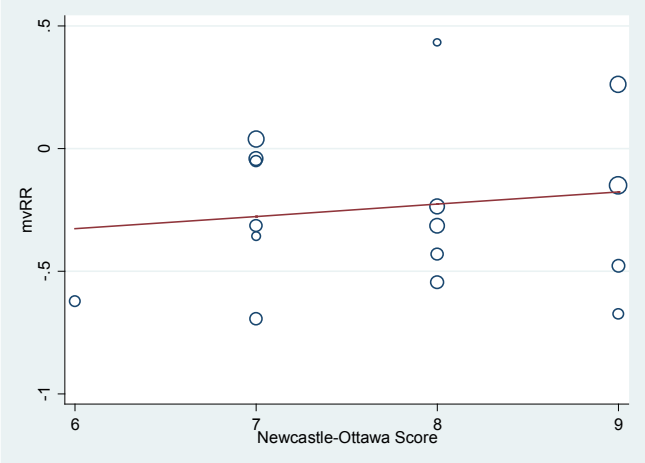
#: number; CHD: coronary heart disease; CI: confidence interval; mvHR: multivariable hazard ratio; mvRR: multivariable risk ratio; PUFA: polyunsaturated fatty acids.

Fig. 93b. Meta-regression of long-chain n-3 PUFA and CHD mortality; number of cases; Panel B – subgroup analysis by number of cases (median=240)



#: number; CHD: coronary heart disease; CI: confidence interval; ES: effect size; JPHC: Japan Public Health Center; M: male; NHANES: National Health and Nutrition Examination Survey; PUFA: polyunsaturated fatty acids; W: women.

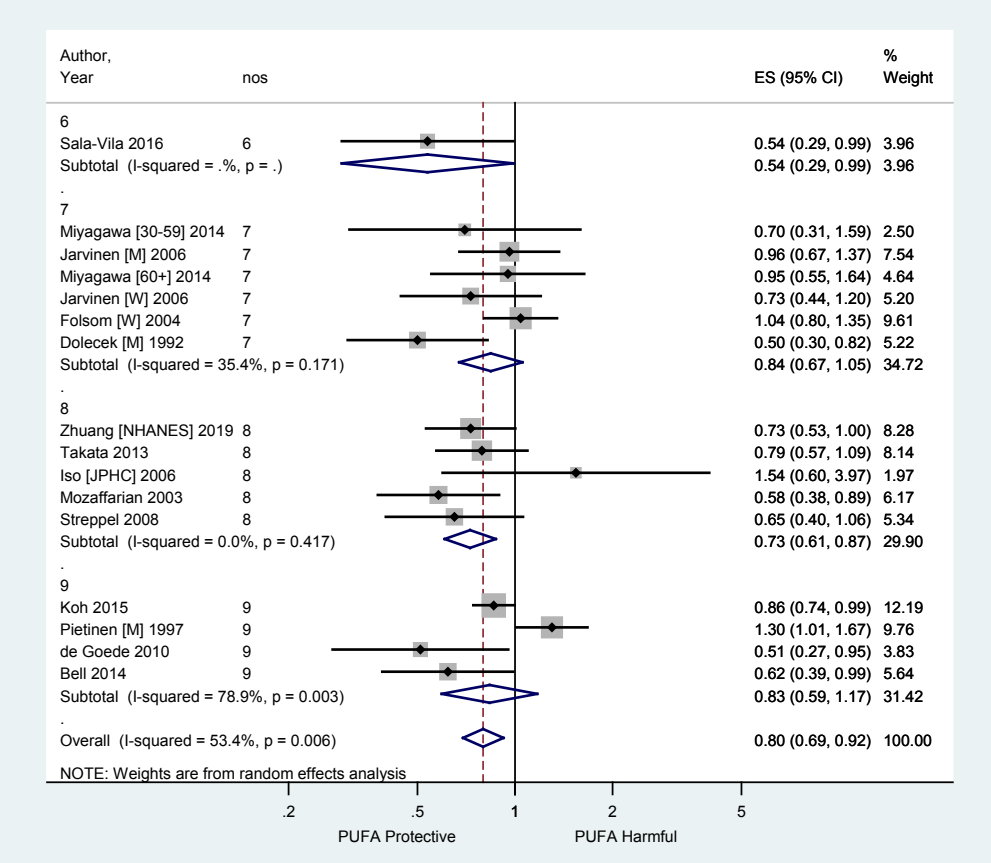
Fig. 93c. Meta-regression of long-chain n-3 PUFA and CHD mortality; NOS assessment; Panel A – effect size



The effect size was not associated with the NOS quality score (P=0.57).

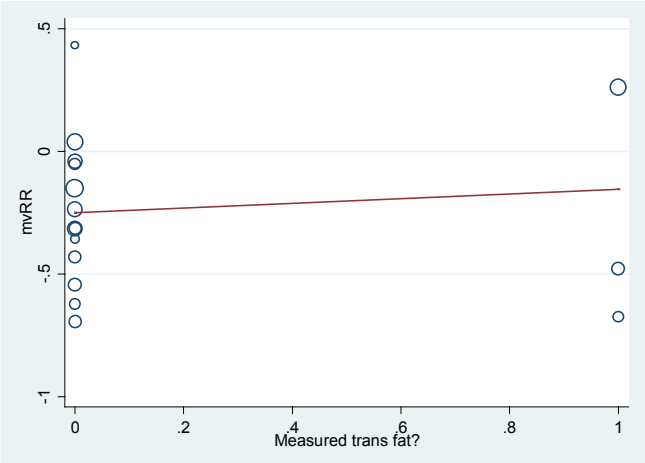
CHD: coronary heart disease; mvRR: multivariable risk ratio; NOS: Newcastle-Ottawa Scale; PUFA: polyunsaturated fatty acids.

Fig. 93d. Meta-regression of long-chain n-3 PUFA and CHD mortality; NOS assessment; Panel B – subgroup analysis by NOS score



CHD: coronary heart disease; CI: confidence interval; ES: effect size; JPHC: Japan Public Health Center; M: male; NHANES: National Health and Nutrition Examination Survey; nos: Newcastle-Ottawa Scale; NOS: Newcastle-Ottawa Scale; PUFA: polyunsaturated fatty acids; W: women.

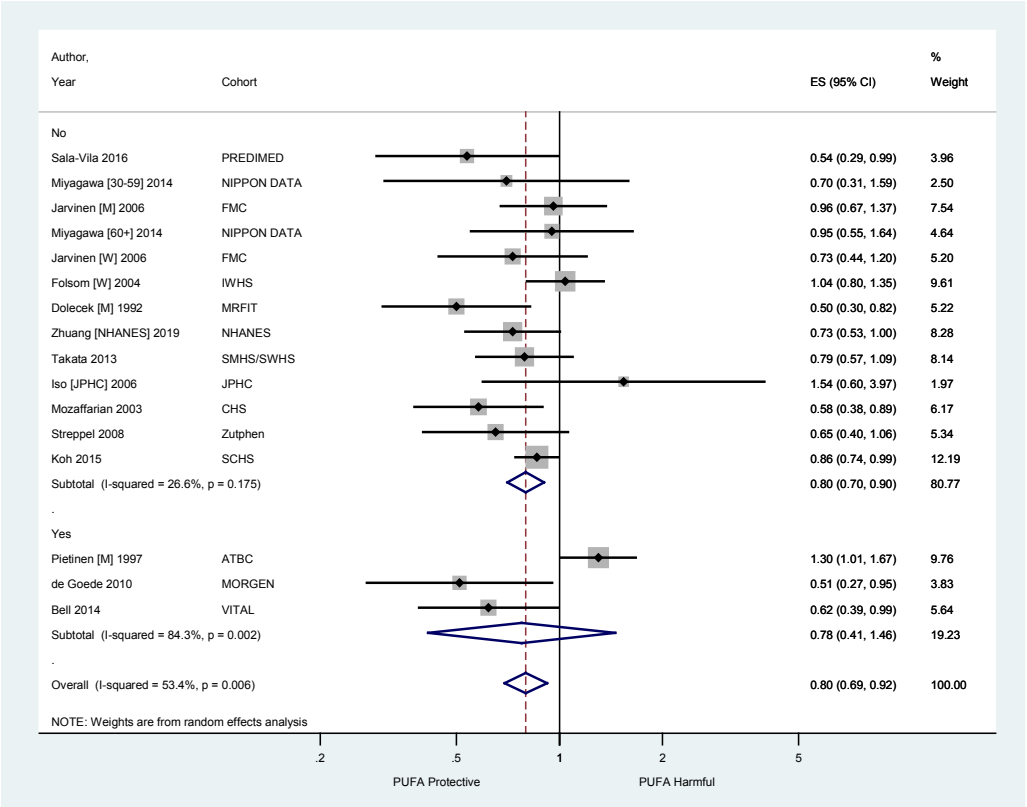
Fig. 93e. Meta-regression of long-chain n-3 PUFA and CHD mortality; TFA assessment; Panel A – effect size



The effect size was not associated with adjustment for TFA assessment in the final model (*P*=0.63).

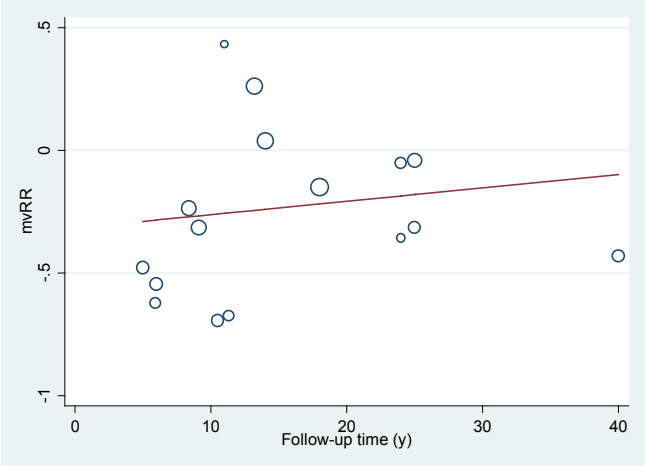
CHD: coronary heart disease; mvRR: multivariable risk ratio; PUFA: polyunsaturated fatty acids; TFA: trans-fatty acids.

Fig. 93f. Meta-regression of long-chain n-3 PUFA and CHD mortality; TFA assessment; Panel B – subgroup analysis (yes/no)



ATBC: Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study; CHD: coronary heart disease; CHS: Cardiovascular Health Study; CI: confidence interval; ES: effect size; FMC: Finnish Mobile Health Clinic; IWHS: Iowa Women's Health Study; JPHC: Japan Public Health Center; M: male; MORGEN: Monitoring Project on Risk Factors for Chronic Diseases; MRFIT: Multiple Risk Factor Intervention Trial; NHANES: National Health and Nutrition Examination Survey; NIPPON DATA: The National Integrated Project for Prospective Observation Of Non-communicable Disease and its Trends in the Aged; PREDIMED: Prevención con Dieta Mediterránea; PUFA: polyunsaturated fatty acids; SCHS: Singapore Chinese Health Study; SMHS: Shanghai Men's Health Study; SWHS: Shanghai Women's Health Study; TFA: trans-fatty acids; VITAL: Vitamins and Lifestyle Study; W: women.

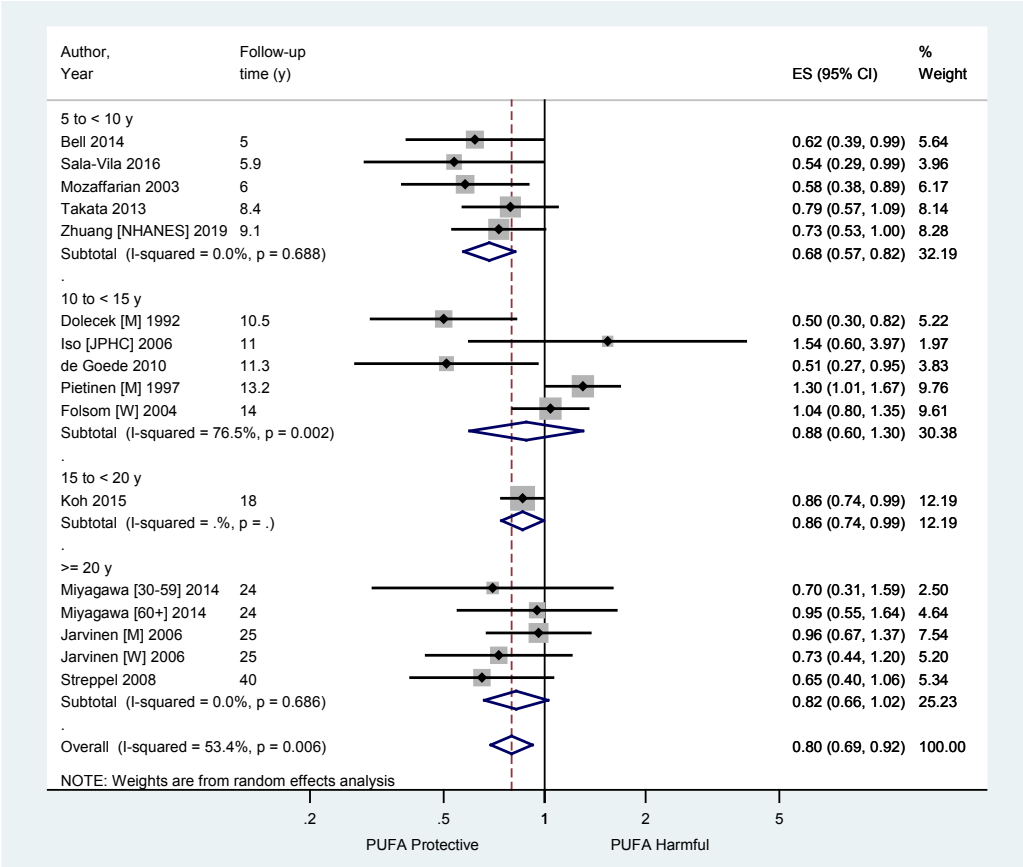
Fig. 93g. Meta-regression of long-chain n-3 PUFA and CHD mortality; follow-up time; Panel A – effect size



The effect size was not associated with adjustment for follow-up time in the final model (P=0.55).

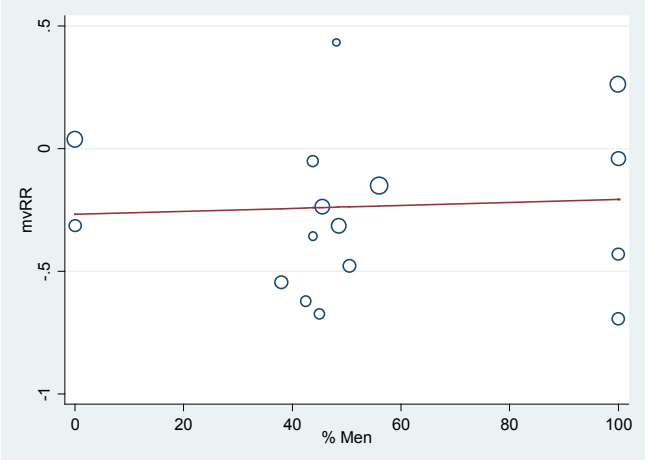
CHD: coronary heart disease; mvRR: multivariable risk ratio; PUFA: polyunsaturated fatty acids; y: years.

Fig. 93h. Meta-regression of long-chain n-3 PUFA and CHD mortality; follow-up time; Panel B – subgroup analysis



CHD: coronary heart disease; CI: confidence interval; ES: effect size; JPHC: Japan Public Health Center; M: male; NHANES: National Health and Nutrition Examination Survey; PUFA: polyunsaturated fatty acids; W: women; y: years.

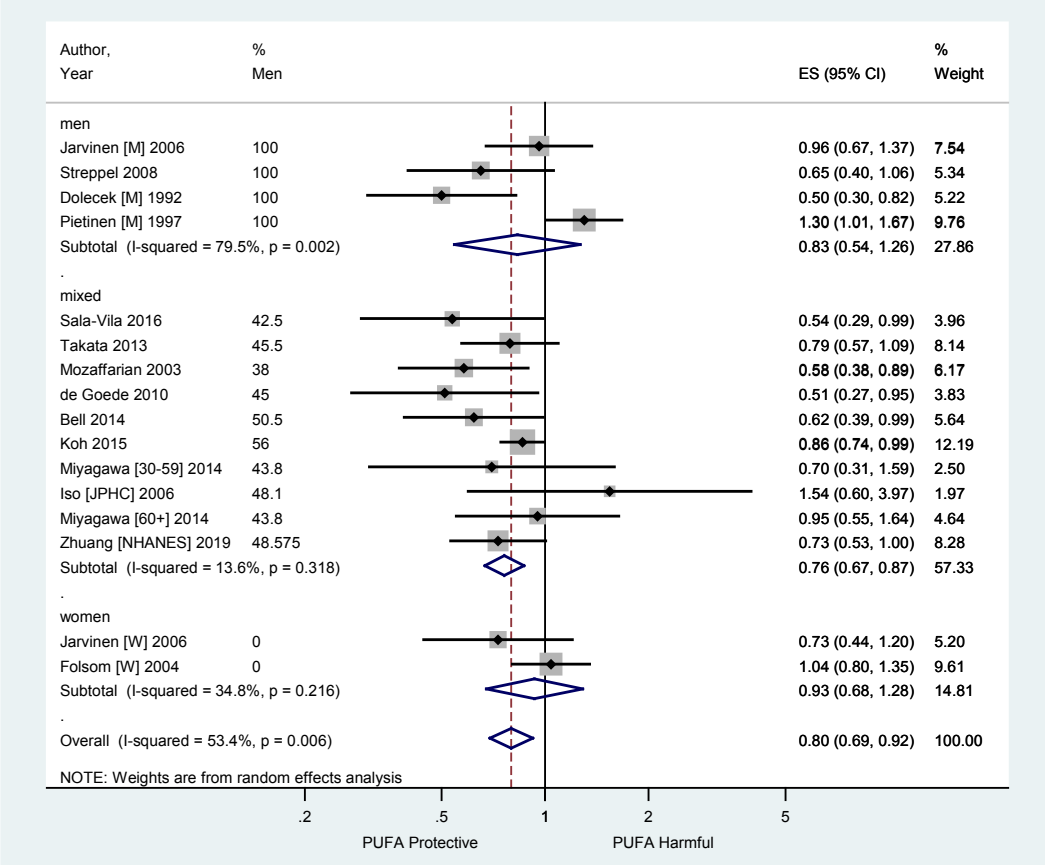
Fig. 93i. Meta-regression of long-chain n-3 PUFA and CHD mortality; sex; Panel A – effect size



The effect size was not associated with adjustment for the percentage of men in the study in the final model (*P*=0.80).

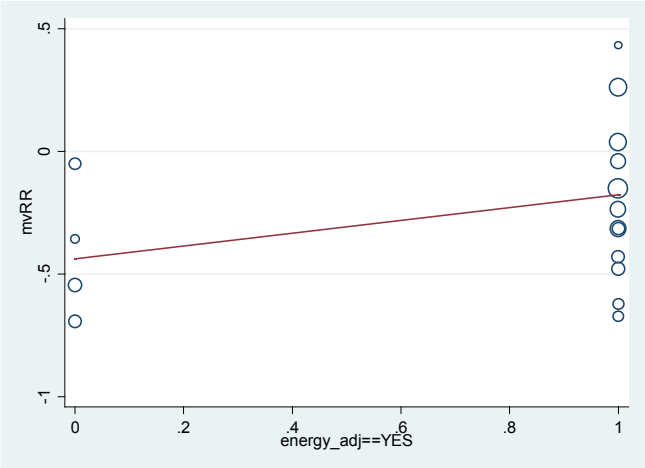
CHD: coronary heart disease; mvRR: multivariable risk ratio; PUFA: polyunsaturated fatty acids.

Fig. 93j. Meta-regression of long-chain n-3 PUFA and CHD mortality; sex; Panel B – subgroup analysis



CHD: coronary heart disease; CI: confidence interval; ES: effect size; JPHC: Japan Public Health Center; M: male; NHANES: National Health and Nutrition Examination Survey; PUFA: polyunsaturated fatty acids; W: women.

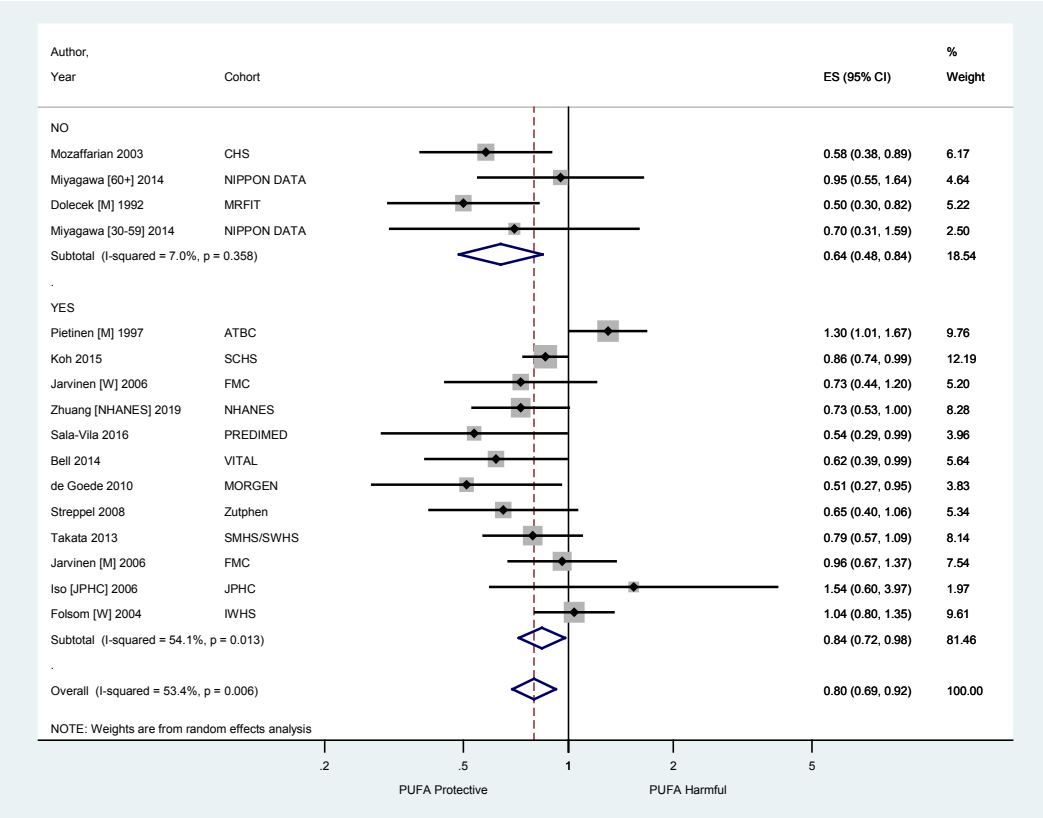
Fig. 93k. Meta-regression of long-chain n-3 PUFA and CHD mortality; energy adjustment; Panel A – effect size



The effect size was not associated with adjustment for energy in the final model (*P*=0.18).

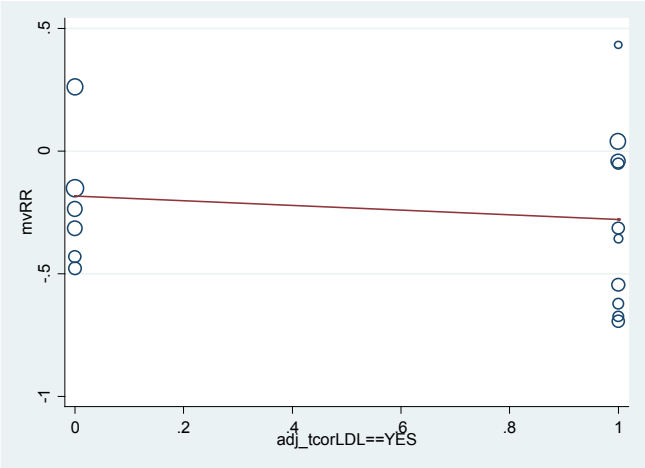
CHD: coronary heart disease; energy_adj: adjusted for energy; mvRR: multivariable risk ratio; PUFA: polyunsaturated fatty acids.

Fig. 93l. Meta-regression of long-chain n-3 PUFA and CHD mortality; energy adjustment; Panel B – subgroup analysis (yes/no)



ATBC: Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study; CHD: coronary heart disease; CHS: Cardiovascular Health Study; CI: confidence interval; ES: effect size; FMC: Finnish Mobile Health Clinic; IWHS: Iowa Women's Health Study; JPHC: Japan Public Health Center; M: male; MORGEN: Monitoring Project on Risk Factors for Chronic Diseases; MRFIT: Multiple Risk Factor Intervention Trial; NHANES: National Health and Nutrition Examination Survey; NIPPON DATA: The National Integrated Project for Prospective Observation Of Non-communicable Disease and its Trends in the Aged; PREDIMED: Prevención con Dieta Mediterránea; PUFA: polyunsaturated fatty acids; SCHS: Singapore Chinese Health Study; SMHS: Shanghai Men's Health Study; SWHS: Shanghai Women's Health Study; VITAL: Vitamins and Lifestyle Study; W: women.

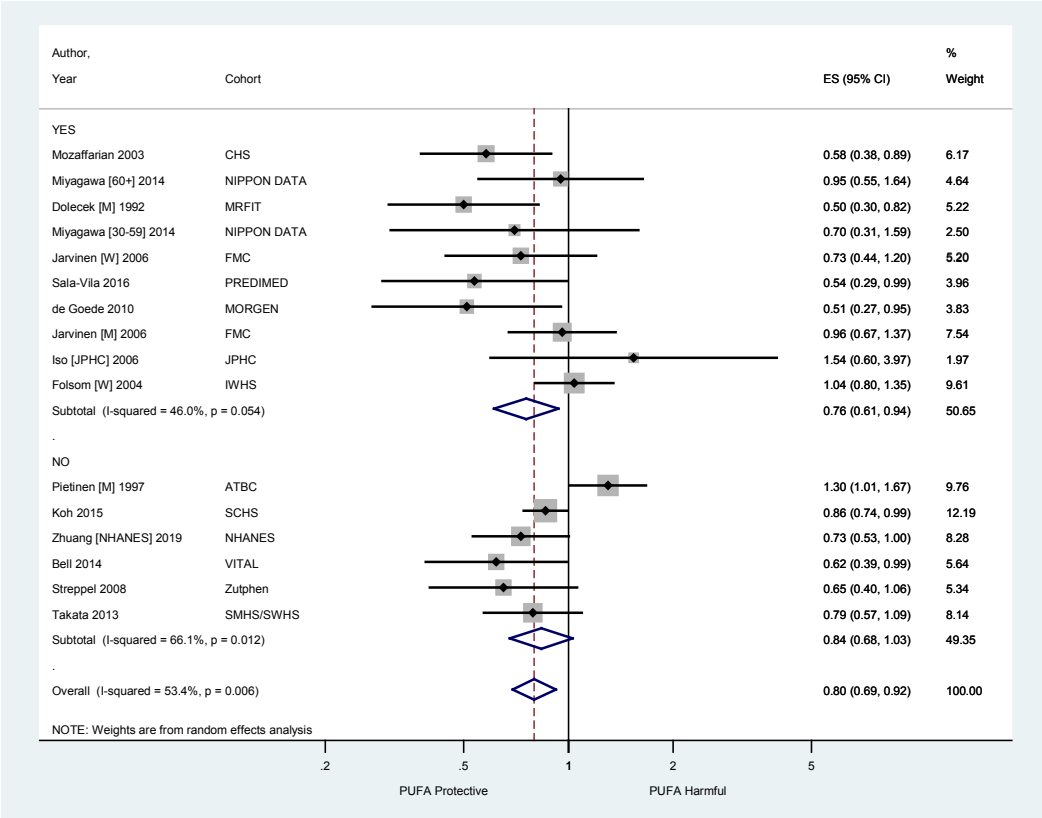
Fig. 93m. Meta-regression of long-chain n-3 PUFA and CHD mortality; dyslipidaemia adjustment; Panel A – effect size



The effect size was not associated with adjustment for a measure of dyslipidaemia in the final model (*P*=0.55).

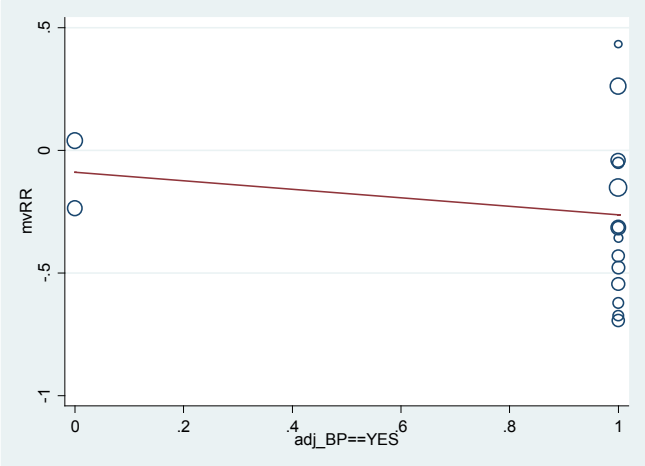
adj_tcorLDL: adjusted for dyslipidaemia; CHD: coronary heart disease; mvRR: multivariable risk ratio; PUFA: polyunsaturated fatty acids.

Fig. 93n. Meta-regression of long-chain n-3 PUFA and CHD mortality; dyslipidaemia adjustment; Panel B – subgroup analysis (yes/no)



ATBC: Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study; CHD: coronary heart disease; CHS: Cardiovascular Health Study; CI: confidence interval; ES: effect size; FMC: Finnish Mobile Health Clinic; IWHS: Iowa Women's Health Study; JPHC: Japan Public Health Center; M: male; MORGEN: Monitoring Project on Risk Factors for Chronic Diseases; MRFIT: Multiple Risk Factor Intervention Trial; NHANES: National Health and Nutrition Examination Survey; NIPPON DATA: The National Integrated Project for Prospective Observation Of Non-communicable Disease and its Trends in the Aged; PREDIMED: Prevención con Dieta Mediterránea; PUFA: polyunsaturated fatty acids; SCHS: Singapore Chinese Health Study; SMHS: Shanghai Men's Health Study; SWHS: Shanghai Women's Health Study; VITAL: Vitamins and Lifestyle Study; W: women.

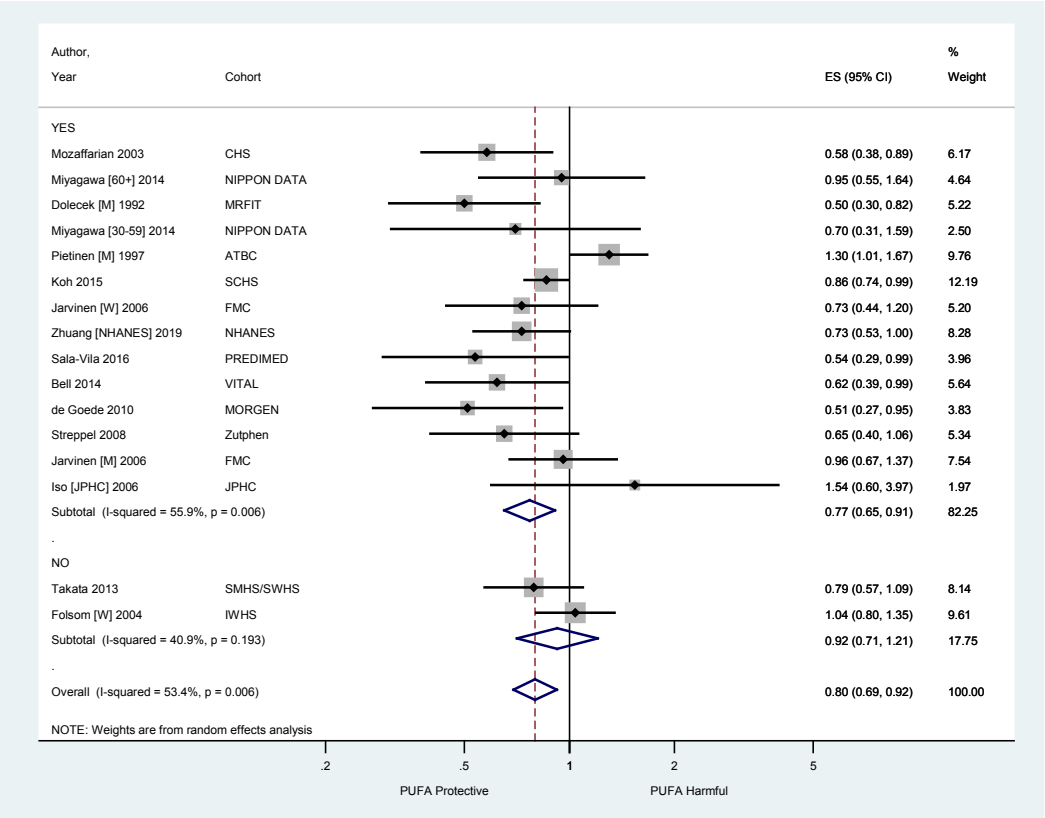
Fig. 93o. Meta-regression of long-chain n-3 PUFA and CHD mortality; blood pressure adjustment; Panel A – effect size



The effect size was not associated with adjustment for a measure of blood pressure in the final model (*P*=0.41).

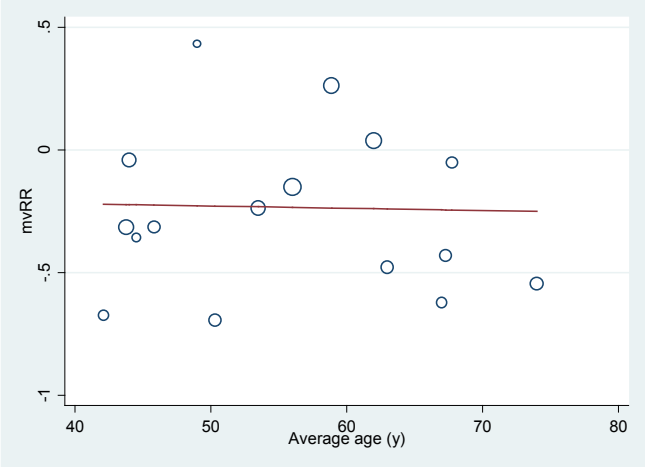
adj_BP: adjusted for blood pressure; CHD: coronary heart disease; mvRR: multivariable risk ratio; PUFA: polyunsaturated fatty acids.

Fig. 93p. Meta-regression of long-chain n-3 PUFA and CHD mortality; blood pressure adjustment; Panel B – subgroup analysis (yes/no)



ATBC: Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study; CHD: coronary heart disease; CHS: Cardiovascular Health Study; CI: confidence interval; ES: effect size; FMC: Finnish Mobile Health Clinic; IWHS: Iowa Women's Health Study; JPHC: Japan Public Health Center; M: male; MORGEN: Monitoring Project on Risk Factors for Chronic Diseases; MRFIT: Multiple Risk Factor Intervention Trial; NHANES: National Health and Nutrition Examination Survey; NIPPON DATA: The National Integrated Project for Prospective Observation Of Non-communicable Disease and its Trends in the Aged; PREDIMED: Prevención con Dieta Mediterránea; PUFA: polyunsaturated fatty acids; SCHS: Singapore Chinese Health Study; SMHS: Shanghai Men's Health Study; SWHS: Shanghai Women's Health Study; VITAL: Vitamins and Lifestyle Study; W: women.

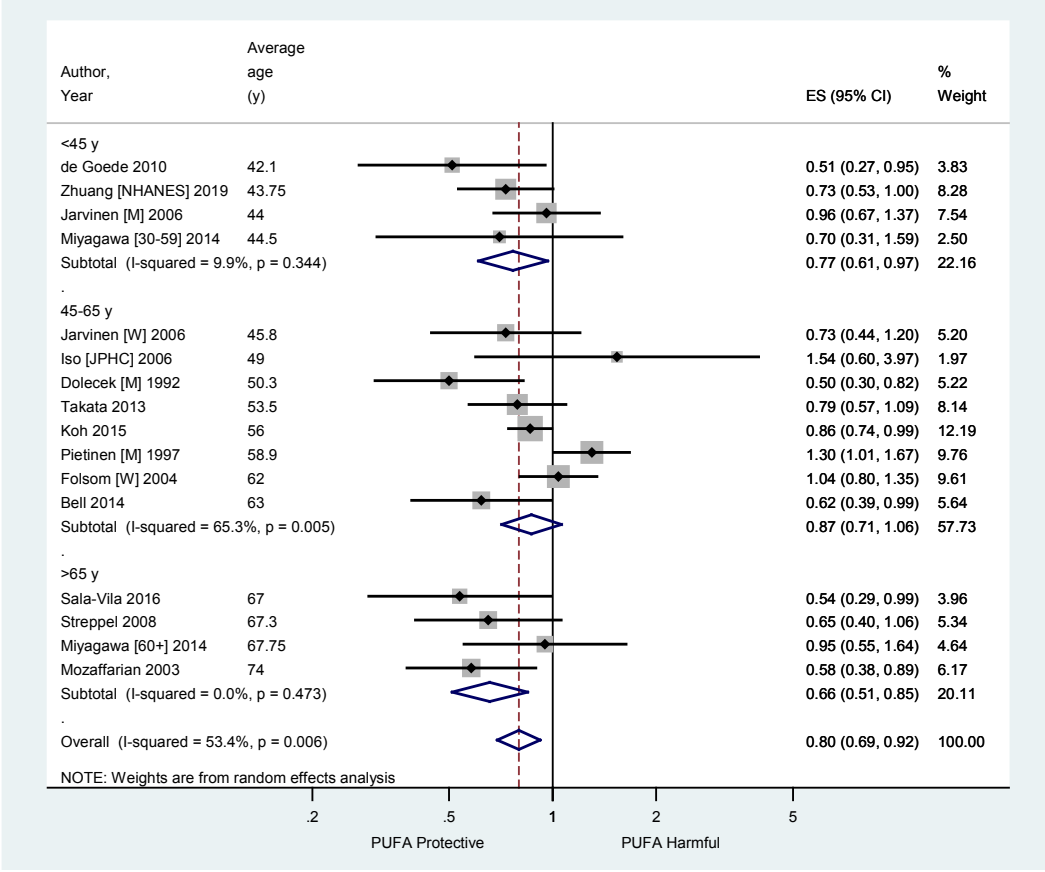
Fig. 93q. Meta-regression of long-chain n-3 PUFA and CHD mortality; age; Panel A – effect size



The effect size was not associated with adjustment for average age of the study sample in the final model (*P*=0.91).

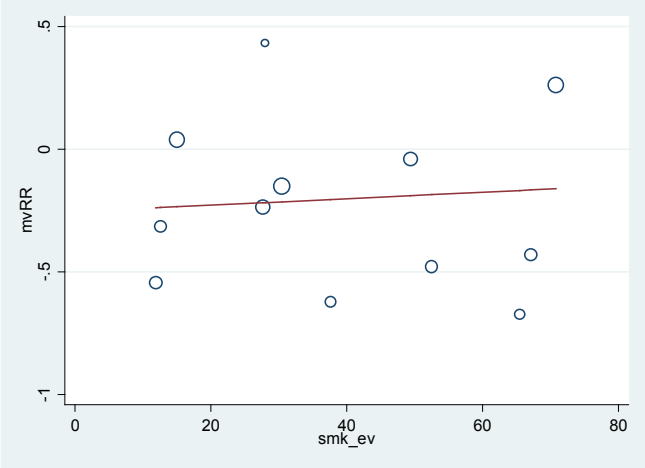
CHD: coronary heart disease; mvRR: multivariable risk ratio; PUFA: polyunsaturated fatty acids; y: years.

Fig. 93r. Meta-regression of long-chain n-3 PUFA and CHD mortality; age; Panel B – subgroup analysis (age group)



CHD: coronary heart disease; CI: confidence interval; ES: effect size; JPHC: Japan Public Health Center; M: male; NHANES: National Health and Nutrition Examination Survey; PUFA: polyunsaturated fatty acids; W: women; y: years.

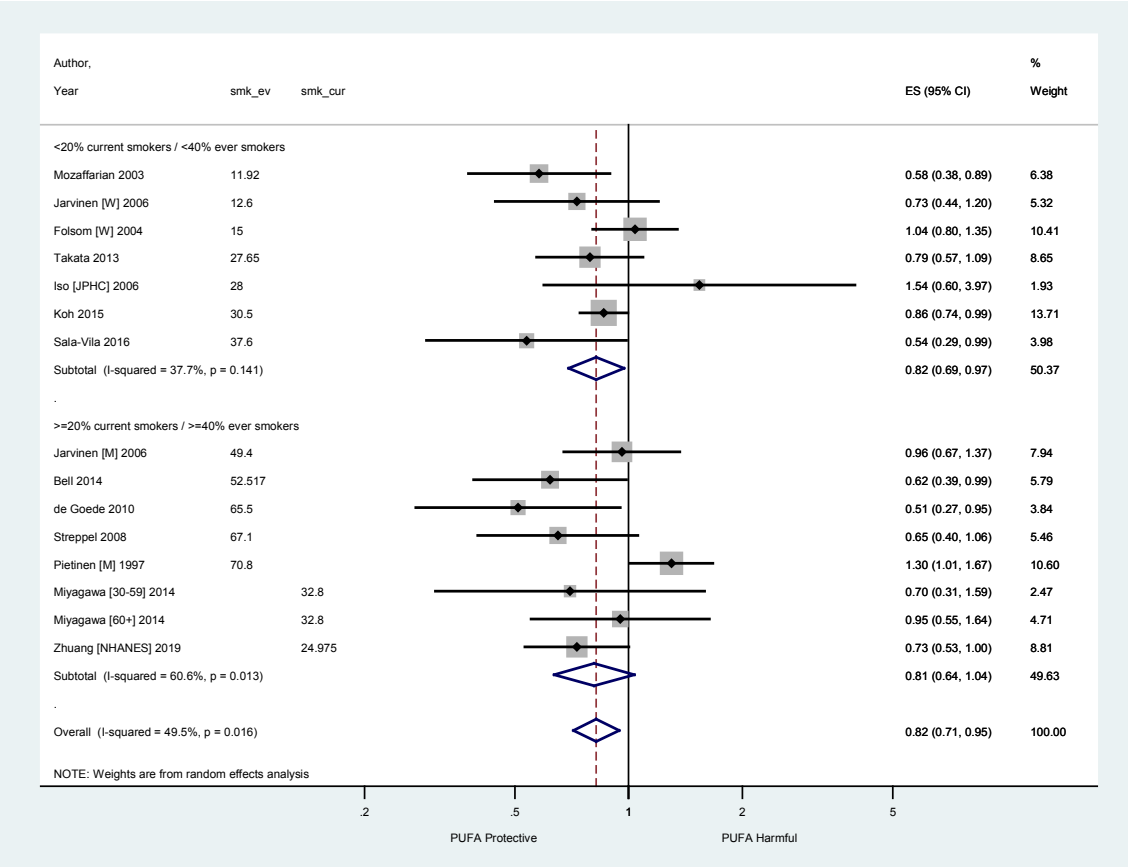
Fig. 93s. Meta-regression of long-chain n-3 PUFA and CHD mortality; smoking; Panel A – effect size



The effect size was not associated with adjustment for smoking history of the study sample in the final model (*P*=0.77). High smokers ≥40% current/former or >20% current.

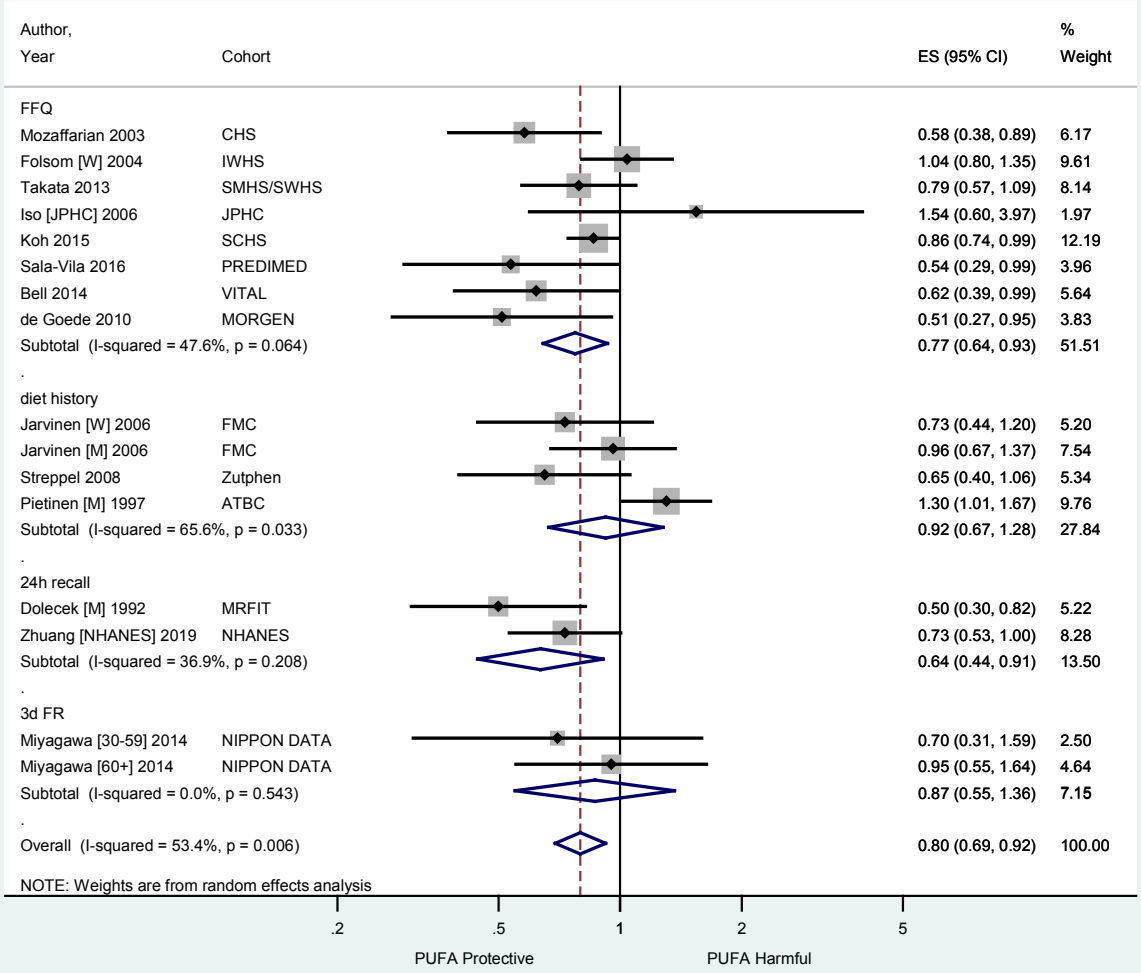
CHD: coronary heart disease; mvRR: multivariable risk ratio; PUFA: polyunsaturated fatty acids; smk_ev: ever smoked.

Fig. 93t. Meta-regression of long-chain n-3 PUFA and CHD mortality; smoking; Panel B – subgroup analysis



CHD: coronary heart disease; CI: confidence interval; ES: effect size; JPHC: Japan Public Health Center; M: male; NHANES: National Health and Nutrition Examination Survey; PUFA: polyunsaturated fatty acids; smk_cur: current smokers; smk_ev: ever smoked; W: women.

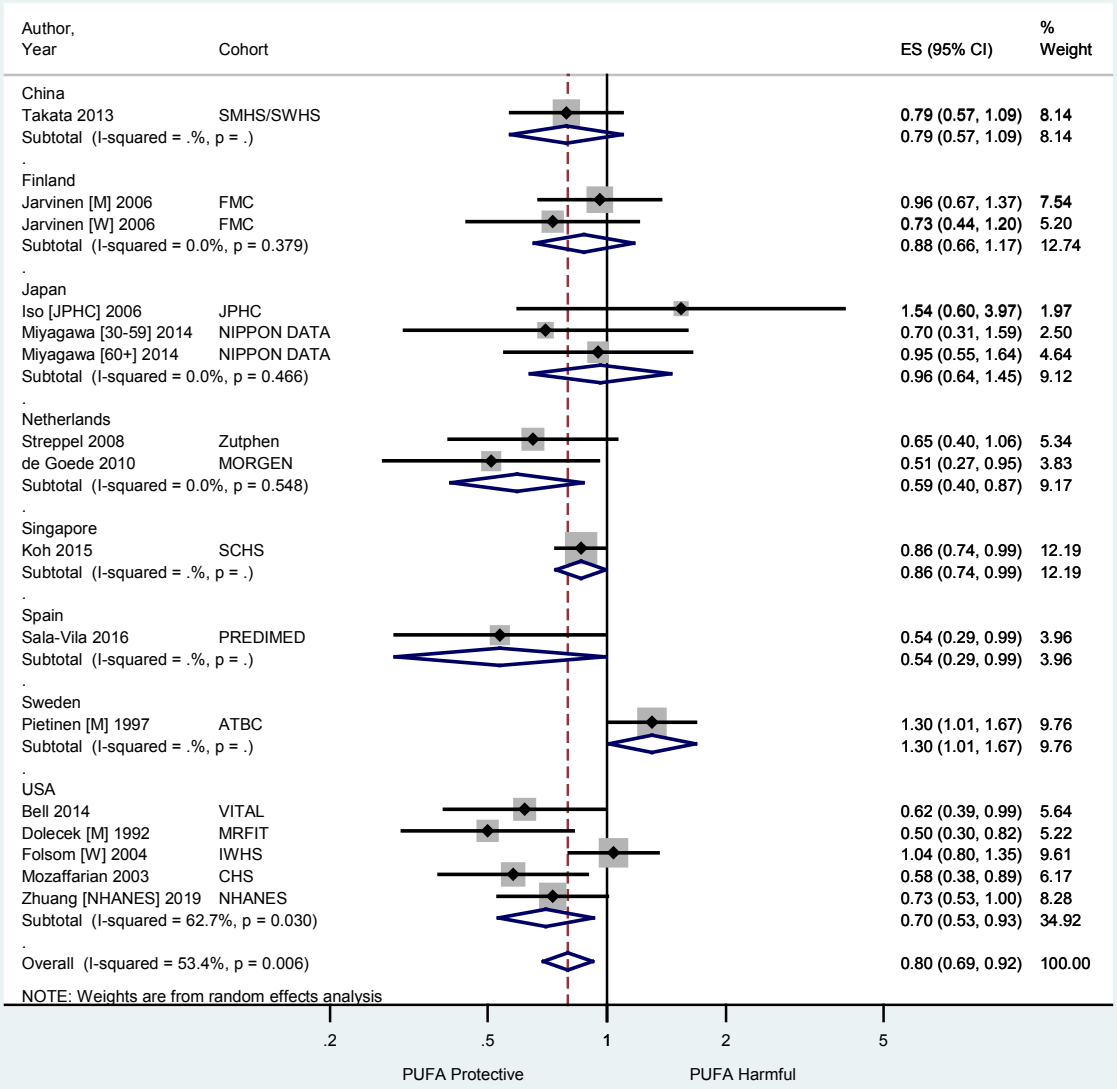
Fig. 93u. Meta-regression of long-chain n-3 PUFA and CHD mortality; diet assessment method; subgroup analysis



ATBC: Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study; CHD: coronary heart disease; CHS: Cardiovascular Health Study; CI: confidence interval; d: day; ES: effect size; FFQ: food frequency questionnaire; FMC: Finnish Mobile Health Clinic; FR: food record; h: hour; IWHS: Iowa Women's Health Study; JPHC: Japan Public Health Center; M: male; MORGEN: Monitoring Project on Risk Factors for Chronic Diseases; MRFIT: Multiple Risk Factor Intervention Trial; NHANES: National Health and Nutrition Examination Survey; NIPPON DATA: The National Integrated Project for Prospective Observation Of Non-communicable Disease and its Trends in the Aged; PREDIMED: Prevención con Dieta Mediterránea; PUFA: polyunsaturated fatty acids; SCHS: Singapore Chinese Health Study; SMHS: Shanghai Men's Health Study; SWHS: Shanghai Women's Health Study; VITAL: Vitamins and Lifestyle Study; W: women.

The effect size estimate was associated with adjustment for diet assessment method in the final model (Phet=0.04). Because the predictor variable had more than 2 levels, it is not appropriate to show the continuous meta-regression line; therefore, we present the "by country" estimates separately.

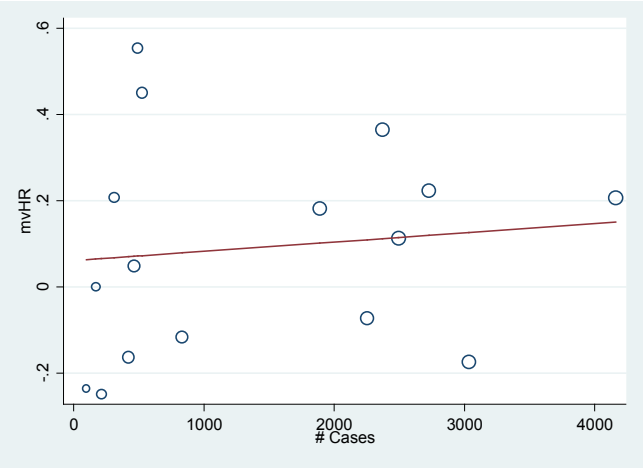
Fig. 93v. Meta-regression of long-chain n-3 PUFA and CHD mortality; country of conduct; subgroup analysis by country



ATBC: Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study; CHD: coronary heart disease; CHS: Cardiovascular Health Study; CI: confidence interval; ES: effect size; FMC: Finnish Mobile Health Clinic; IWHS: Iowa Women's Health Study; JPHC: Japan Public Health Center; M: male; MORGEN: Monitoring Project on Risk Factors for Chronic Diseases; MRFIT: Multiple Risk Factor Intervention Trial; NHANES: National Health and Nutrition Examination Survey; NIPPON DATA: The National Integrated Project for Prospective Observation Of Non-communicable Disease and its Trends in the Aged; PREDIMED: Prevención con Dieta Mediterránea; PUFA: polyunsaturated fatty acids; SCHS: Singapore Chinese Health Study; SMHS: Shanghai Men's Health Study; SWHS: Shanghai Women's Health Study; USA: United States of America; VITAL: Vitamins and Lifestyle Study; W: women.

There was evidence of heterogeneity of effect size by country of conduct (P_{het}=0.009). Because the predictor variable had more than 2 levels, it is not appropriate to show the continuous meta-regression line; therefore, we present the "by country" estimates separately.

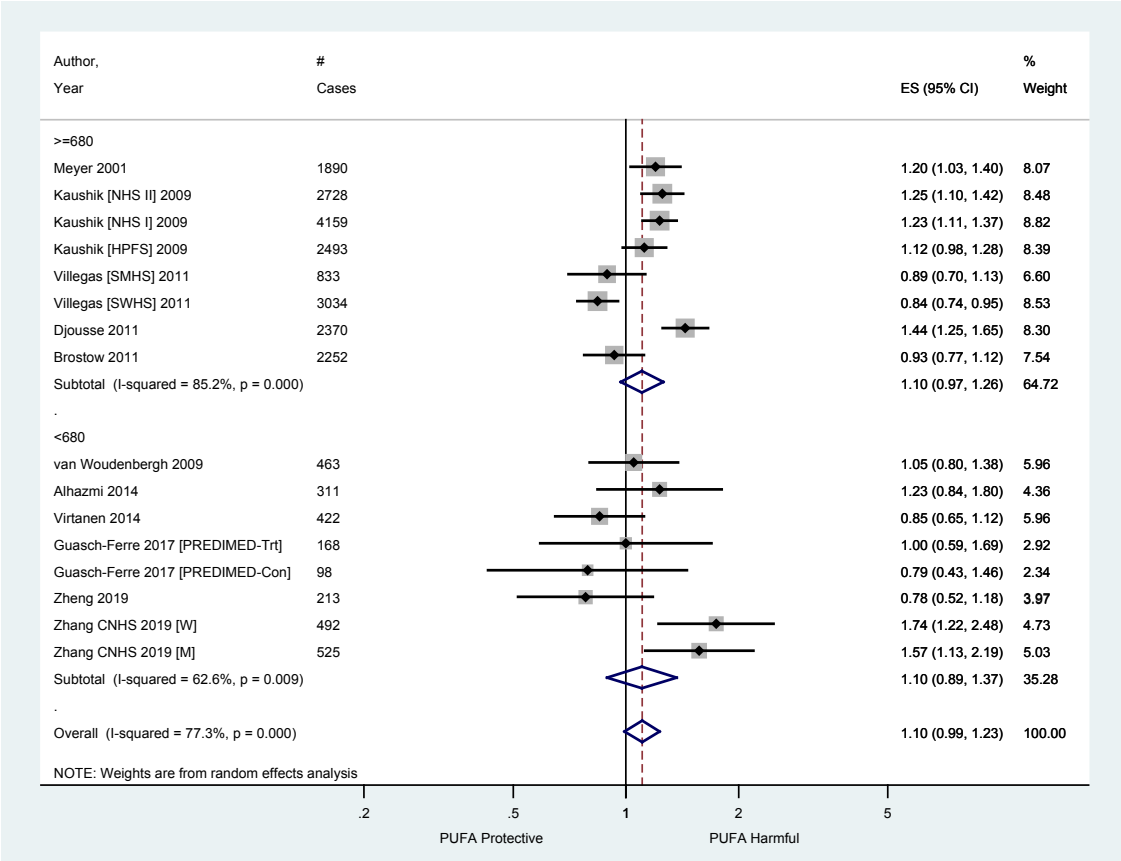
Fig. 94a. Meta-regression of long-chain n-3 PUFA and type 2 diabetes; number of cases; Panel A– effect size



The number of cases in the study was not associated with the effect estimate (*P*=0.66).

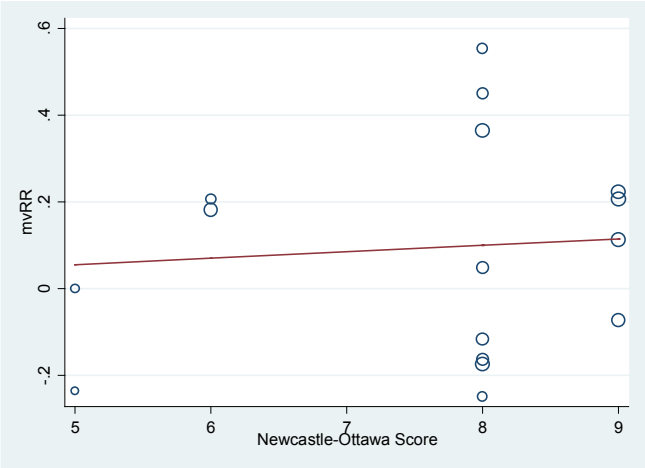
#: number; CI: confidence interval; mvHR: multivariable hazard ratio; mvRR: multivariable risk ratio; PUFA: polyunsaturated fatty acids.

Fig. 94b. Meta-regression of long-chain n-3 PUFA and type 2 diabetes; number of cases; Panel B – subgroup analysis by number of cases (median=680)



#: number; CHNS: China Health and Nutrition Survey; CI: confidence interval; ES: effect size; HPFS: Health Professionals Follow-up Study; M: male; NHS I: Nurses' Health Study I; NHS II: Nurses' Health Study II; PREDIMED-Con: Prevención con Dieta Mediterránea (control); PREDIMED-Trt: Prevención con Dieta Mediterránea (treatment); PUFA: polyunsaturated fatty acids; SMHS: Shanghai Men's Health Study; SWHS: Shanghai Women's Health Study; W: women.

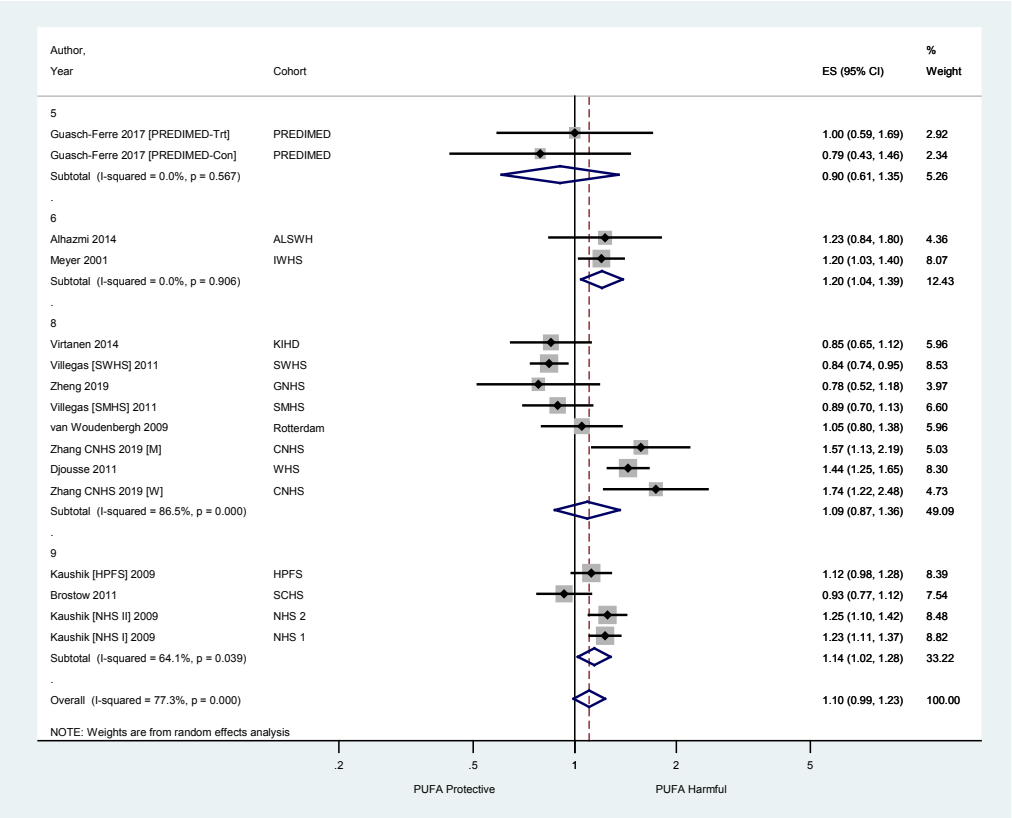
Fig. 94c. Meta-regression of long-chain n-3 PUFA and type 2 diabetes; NOS assessment; Panel A – effect size



The effect size was not associated with the NOS quality score (P=0.78).

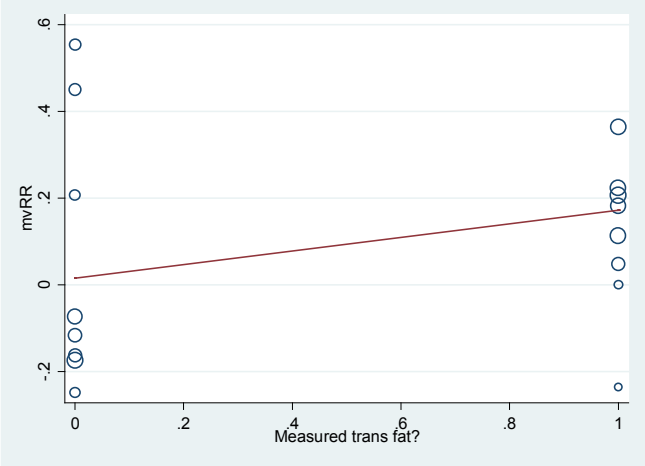
mvRR: multivariable risk ratio; NOS: Newcastle-Ottawa Scale; PUFA: polyunsaturated fatty acids.

Fig. 94d. Meta-regression of long-chain n-3 PUFA and type 2 diabetes; NOS assessment; Panel B – subgroup analysis by NOS score



ALSWH: Australian Longitudinal Study on Women's Health; CHNS: China Health and Nutrition Survey; CI: confidence interval; ES: effect size; GNHS: Guangzhou Nutrition and Health Study; HPFS: Health Professionals Follow-up Study; IWHS: Iowa Women's Health Study; KIHD: Kuopio Ischemic Heart Disease Risk Factor Study; M: male; NHS I: Nurses' Health Study I; NHS II: Nurses' Health Study II; NOS: Newcastle-Ottawa Scale; PREDIMED: Prevención con Dieta Mediterránea; PREDIMED-Con: Prevención con Dieta Mediterránea (control); PREDIMED-Trt: Prevención con Dieta Mediterránea (treatment); PUFA: polyunsaturated fatty acids; SCHS: Singapore Chinese Health Study; SMHS: Shanghai Men's Health Study; SWHS: Shanghai Women's Health Study; W: women; WHS: Women's Health Study.

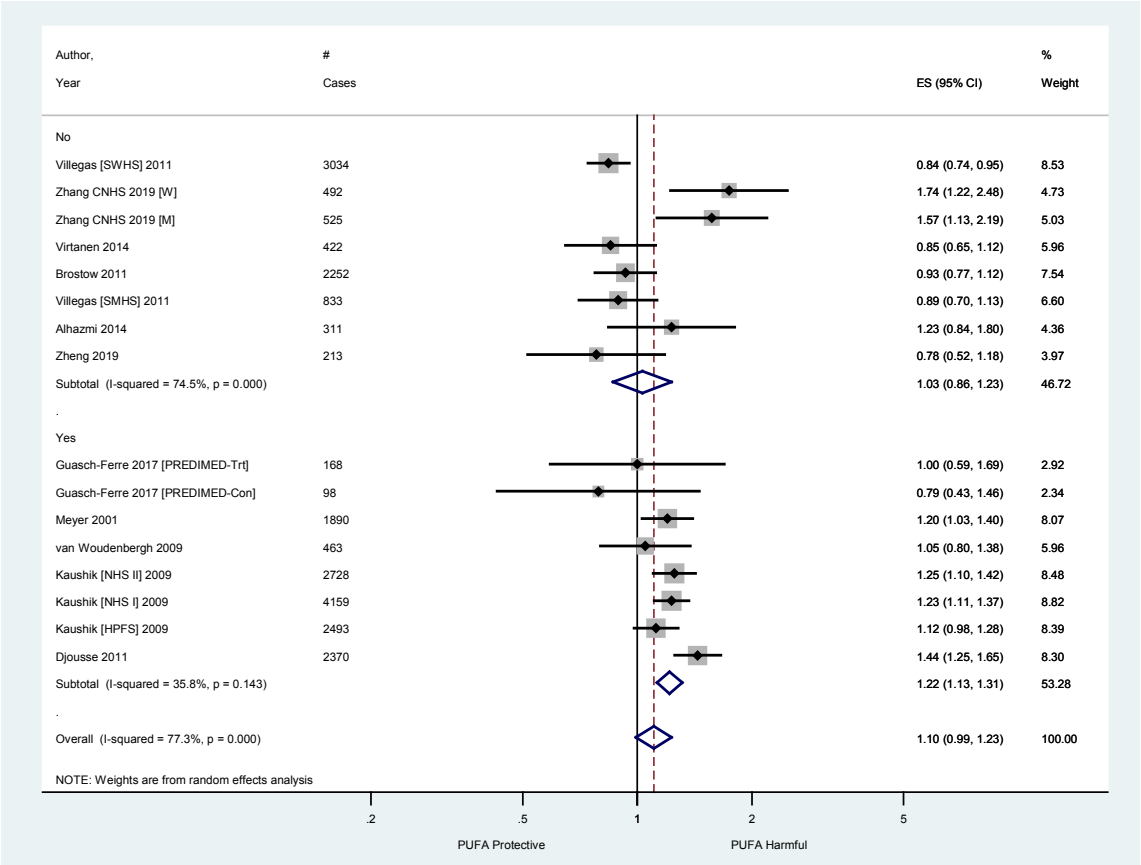
Fig. 94e. Meta-regression of long-chain n-3 PUFA and type 2 diabetes; TFA assessment; Panel A – effect size



The effect size was not associated with adjustment for TFA assessment in the final model (*P*=0.18).

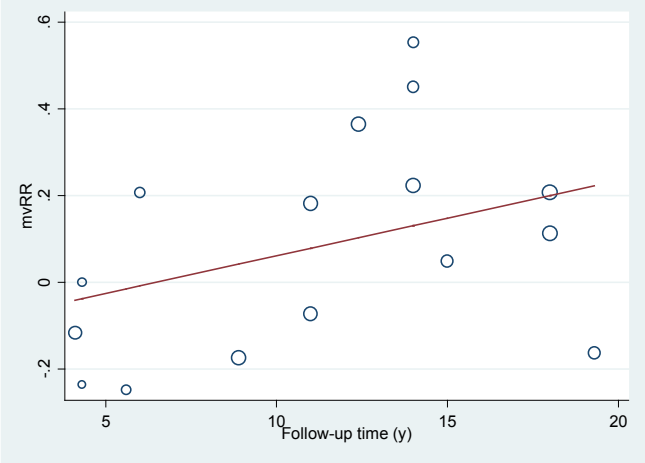
mvRR: multivariable risk ratio; PUFA: polyunsaturated fatty acids; TFA: trans-fatty acids.

Fig. 94f. Meta-regression of long-chain n-3 PUFA and type 2 diabetes; TFA assessment; Panel B – subgroup analysis (yes/no)



#: number; CHNS: China Health and Nutrition Survey; CI: confidence interval; ES: effect size; HPFS: Health Professionals Follow-up Study; M: male; NHS I: Nurses' Health Study I; NHS II: Nurses' Health Study II; PREDIMED-Con: Prevención con Dieta Mediterránea (control); PREDIMED-Trt: Prevención con Dieta Mediterránea (treatment); PUFA: polyunsaturated fatty acids; SMHS: Shanghai Men's Health Study; SWHS: Shanghai Women's Health Study; TFA: trans-fatty acids; W: women.

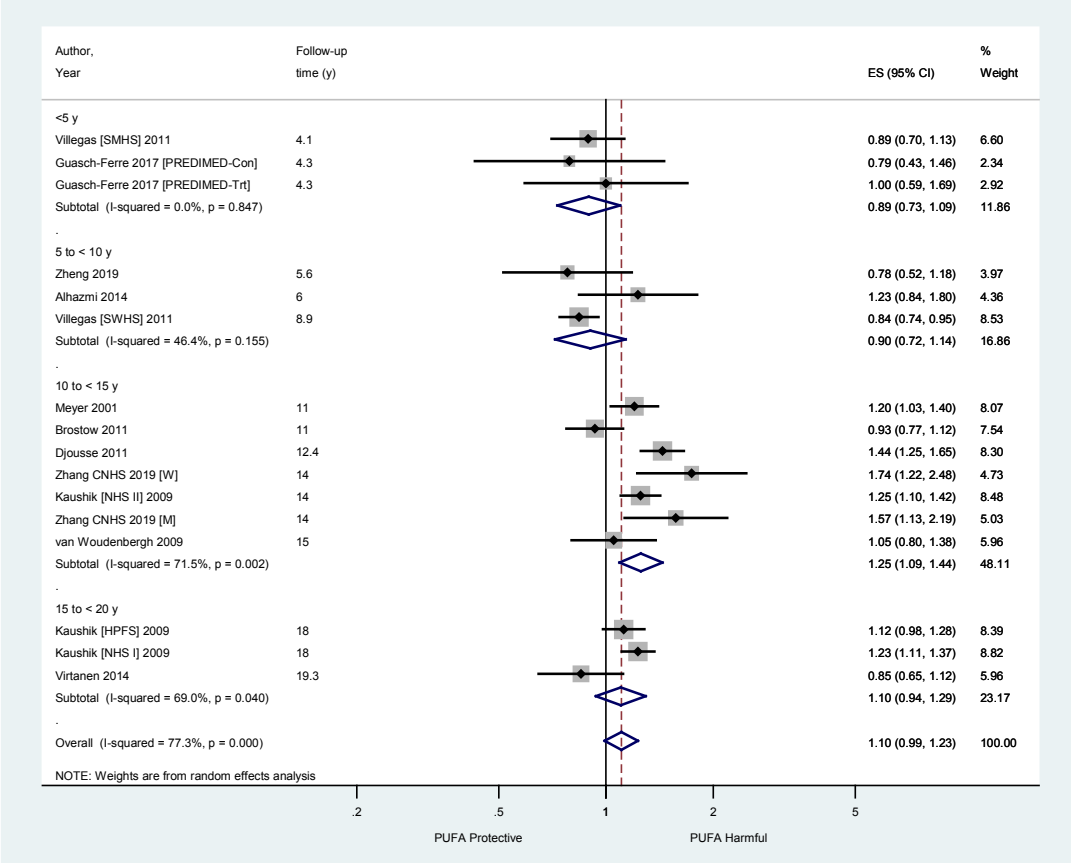
Fig. 94g. Meta-regression of long-chain n-3 PUFA and type 2 diabetes; follow-up time; Panel A – effect size



The effect size was not associated with adjustment for follow-up time in the final model (*P*=0.16).

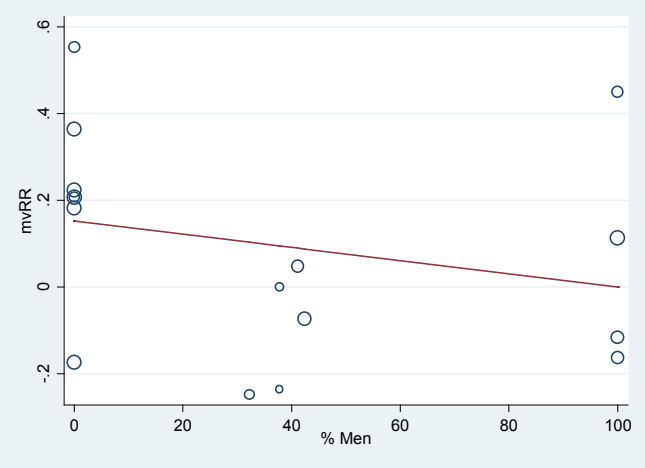
mvRR: multivariable risk ratio; PUFA: polyunsaturated fatty acids; y: years.

Fig. 94h. Meta-regression of long-chain n-3 PUFA and type 2 diabetes; follow-up time; Panel B – subgroup analysis



CHNS: China Health and Nutrition Survey; CI: confidence interval; ES: effect size; HPFS: Health Professionals Follow-up Study; M: male; NHS I: Nurses' Health Study I; NHS II: Nurses' Health Study II; PREDIMED-Con: Prevención con Dieta Mediterránea (control); PREDIMED-Trt: Prevención con Dieta Mediterránea (treatment); PUFA: polyunsaturated fatty acids; SMHS: Shanghai Men's Health Study; SWHS: Shanghai Women's Health Study; W: women; y: years.

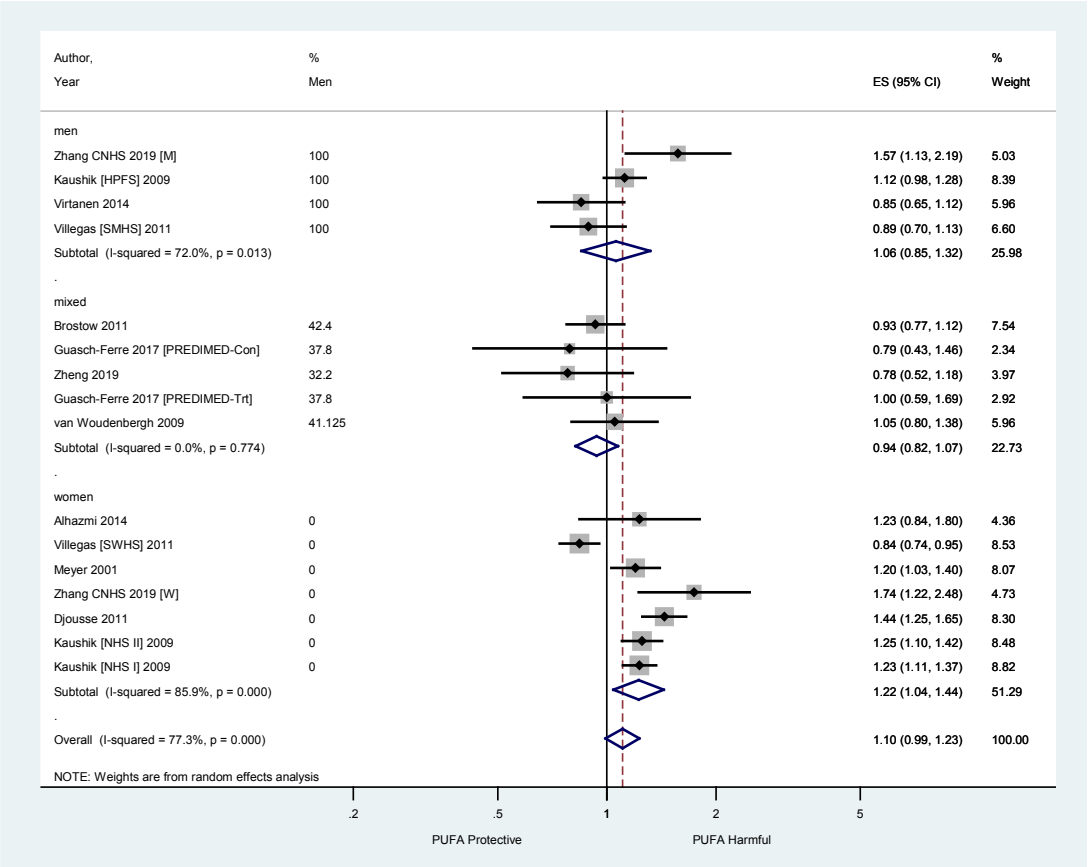
Fig. 94i. Meta-regression of long-chain n-3 PUFA and type 2 diabetes; sex; Panel A – effect size



The effect size was not associated with the sex distribution of the cohort (% men)(*P*=0.76).

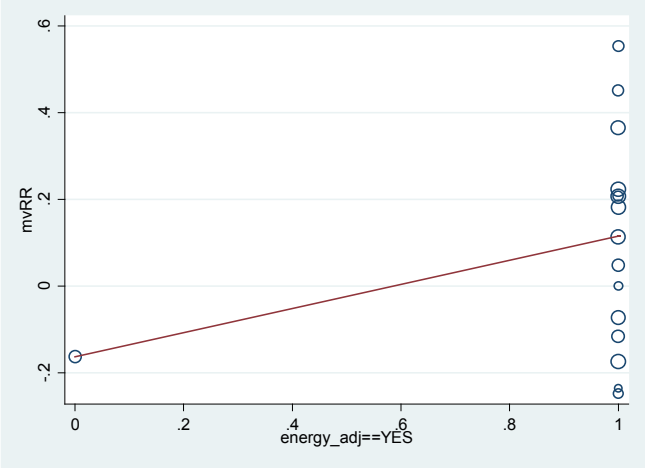
mvRR: multivariable risk ratio; PUFA: polyunsaturated fatty acids.

Fig. 94j. Meta-regression of long-chain n-3 PUFA and type 2 diabetes; sex; Panel B – subgroup analysis



CHNS: China Health and Nutrition Survey; CI: confidence interval; ES: effect size; HPFS: Health Professionals Follow-up Study; M: male; NHS I: Nurses' Health Study I; NHS II: Nurses' Health Study II; PREDIMED-Con: Prevención con Dieta Mediterránea (control); PREDIMED-Trt: Prevención con Dieta Mediterránea (treatment); PUFA: polyunsaturated fatty acids; SMHS: Shanghai Men's Health Study; SWHS: Shanghai Women's Health Study; W: women.

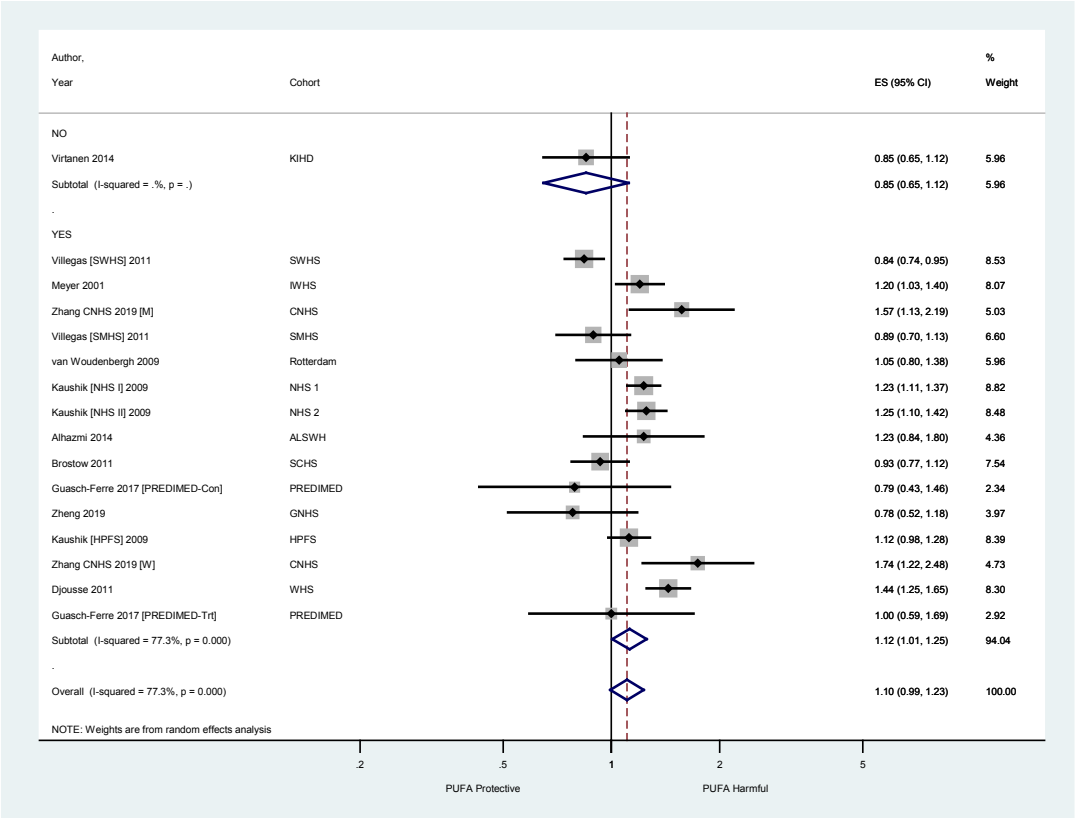
Fig. 94k. Meta-regression of long-chain n-3 PUFA and type 2 diabetes; energy adjustment; Panel A – effect size



The effect size was not associated with adjustment for energy in the final model (*P*=0.26).

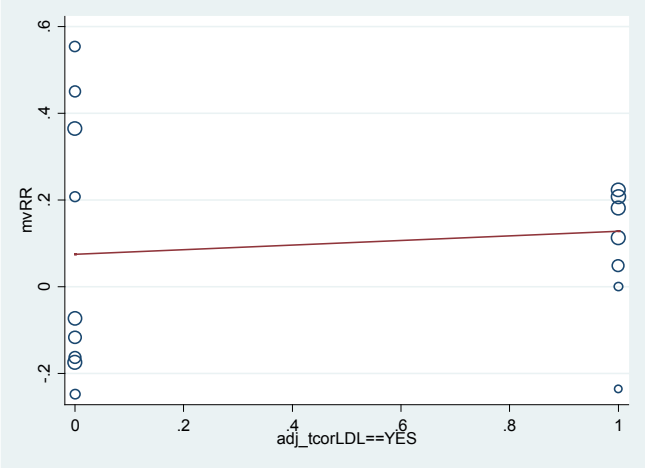
energy_adj: adjusted for energy; mvRR: multivariable risk ratio; PUFA: polyunsaturated fatty acids.

Fig. 94l. Meta-regression of long-chain n-3 PUFA and type 2 diabetes; energy adjustment; Panel B – subgroup analysis (yes/no)



ALSWH: Australian Longitudinal Study on Women's Health; CHNS: China Health and Nutrition Survey; CI: confidence interval; ES: effect size; GNHS: Guangzhou Nutrition and Health Study; HPFS: Health Professionals Follow-up Study; IWHS: Iowa Women's Health Study; KIHD: Kuopio Ischemic Heart Disease Risk Factor Study; M: male; NHS I: Nurses' Health Study I; NHS II: Nurses' Health Study II; PREDIMED: Prevención con Dieta Mediterránea; PREDIMED-Con: Prevención con Dieta Mediterránea (control); PREDIMED-Trt: Prevención con Dieta Mediterránea (treatment); PUFA: polyunsaturated fatty acids; SCHS: Singapore Chinese Health Study; SMHS: Shanghai Men's Health Study; SWHS: Shanghai Women's Health Study; W: women; WHS: Women's Health Study.

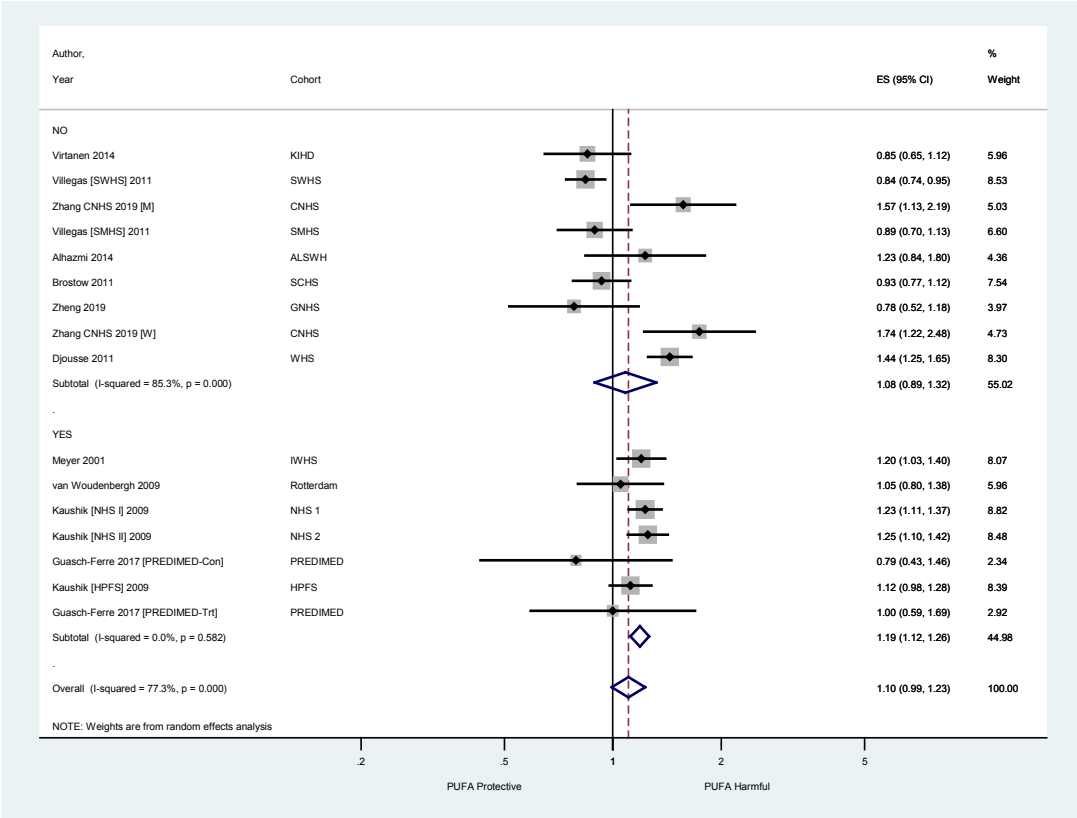
Fig. 94m. Meta-regression of long-chain n-3 PUFA and type 2 diabetes; dyslipidaemia adjustment; Panel A – effect size



The effect size was not associated with adjustment for inclusion of a measure of dyslipidaemia in the final model (*P*=0.67).

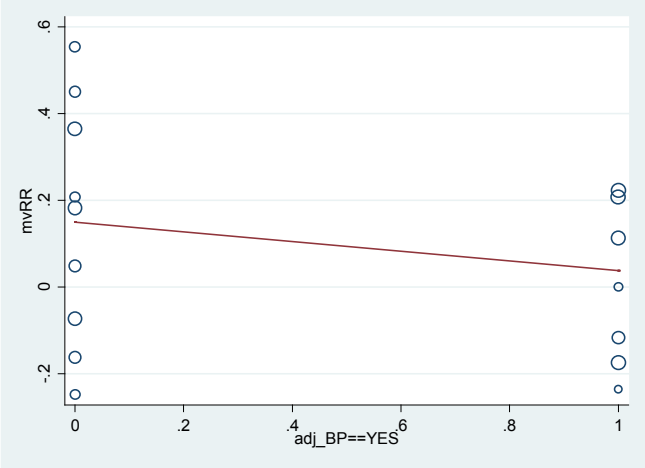
adj_tcorLDL: adjusted for dyslipidaemia; mvRR: multivariable risk ratio; PUFA: polyunsaturated fatty acids.

Fig. 94n. Meta-regression of long-chain n-3 PUFA and type 2 diabetes; dyslipidaemia adjustment; Panel B – subgroup analysis (yes/no)



ALSWH: Australian Longitudinal Study on Women's Health; CHNS: China Health and Nutrition Survey; CI: confidence interval; ES: effect size; GNHS: Guangzhou Nutrition and Health Study; HPFS: Health Professionals Follow-up Study; IWHS: Iowa Women's Health Study; KIHD: Kuopio Ischemic Heart Disease Risk Factor Study; M: male; NHS I: Nurses' Health Study I; NHS II: Nurses' Health Study II; PREDIMED: Prevención con Dieta Mediterránea; PREDIMED-Con: Prevención con Dieta Mediterránea (control); PREDIMED-Trt: Prevención con Dieta Mediterránea (treatment); PUFA: polyunsaturated fatty acids; SCHS: Singapore Chinese Health Study; SMHS: Shanghai Men's Health Study; SWHS: Shanghai Women's Health Study; W: women; WHS: Women's Health Study.

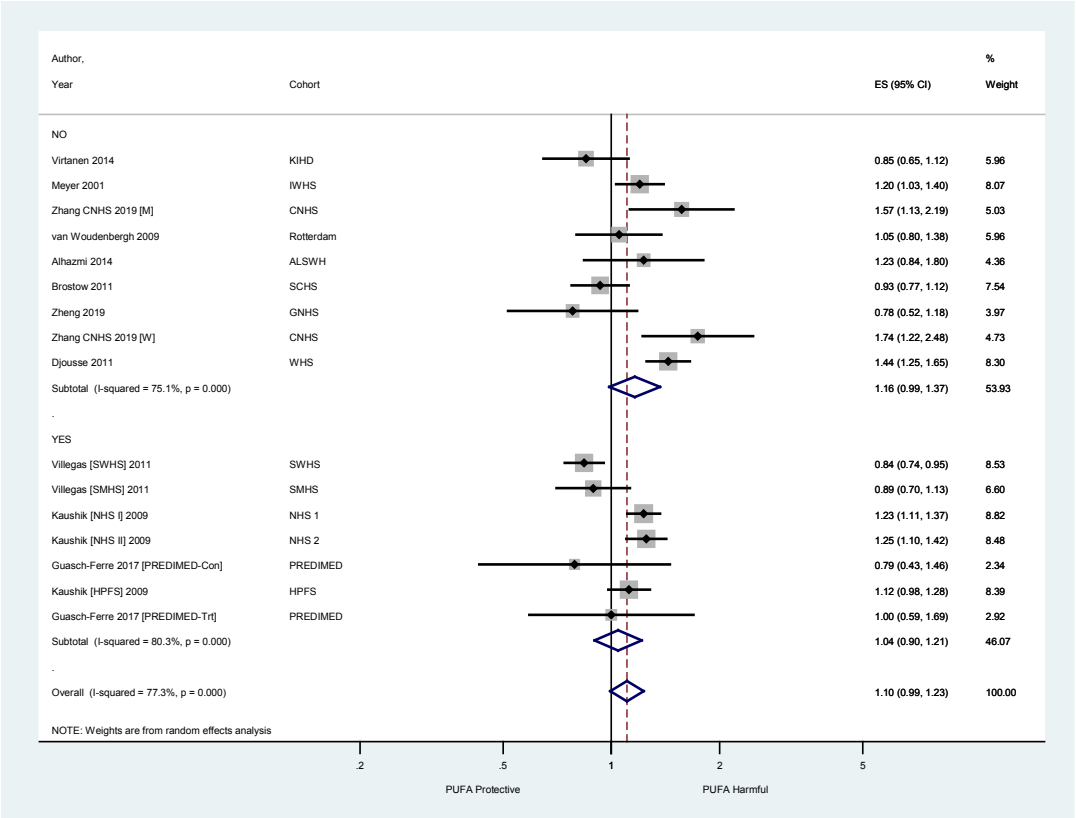
Fig. 94o. Meta-regression of long-chain n-3 PUFA and type 2 diabetes; blood pressure adjustment; Panel A – effect size



The effect size was not associated with adjustment for inclusion of a measure of blood pressure in the final model (*P*=0.35).

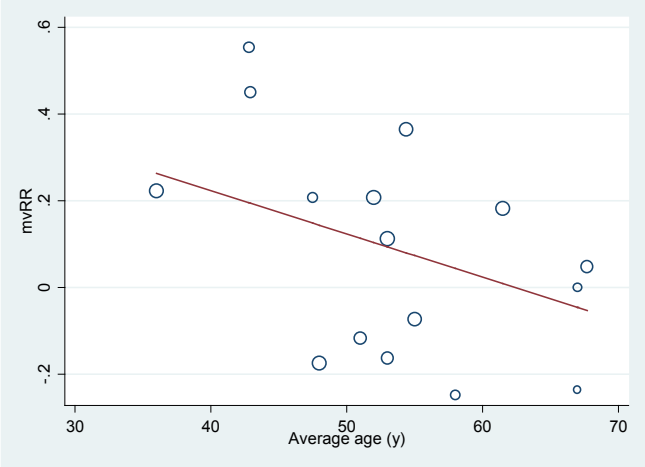
adj_BP: adjusted for blood pressure; mvRR: multivariable risk ratio; PUFA: polyunsaturated fatty acids.

Fig. 94p. Meta-regression of long-chain n-3 PUFA and type 2 diabetes; blood pressure adjustment; Panel B – subgroup analysis (yes/no)



ALSWH: Australian Longitudinal Study on Women's Health; CHNS: China Health and Nutrition Survey; CI: confidence interval; ES: effect size; GNHS: Guangzhou Nutrition and Health Study; HPFS: Health Professionals Follow-up Study; IWHS: Iowa Women's Health Study; KIHD: Kuopio Ischemic Heart Disease Risk Factor Study; M: male; NHS I: Nurses' Health Study I; NHS II: Nurses' Health Study II; PREDIMED: Prevención con Dieta Mediterránea; PREDIMED-Con: Prevención con Dieta Mediterránea (control); PREDIMED-Trt: Prevención con Dieta Mediterránea (treatment); PUFA: polyunsaturated fatty acids; SCHS: Singapore Chinese Health Study; SMHS: Shanghai Men's Health Study; SWHS: Shanghai Women's Health Study; W: women; WHS: Women's Health Study.

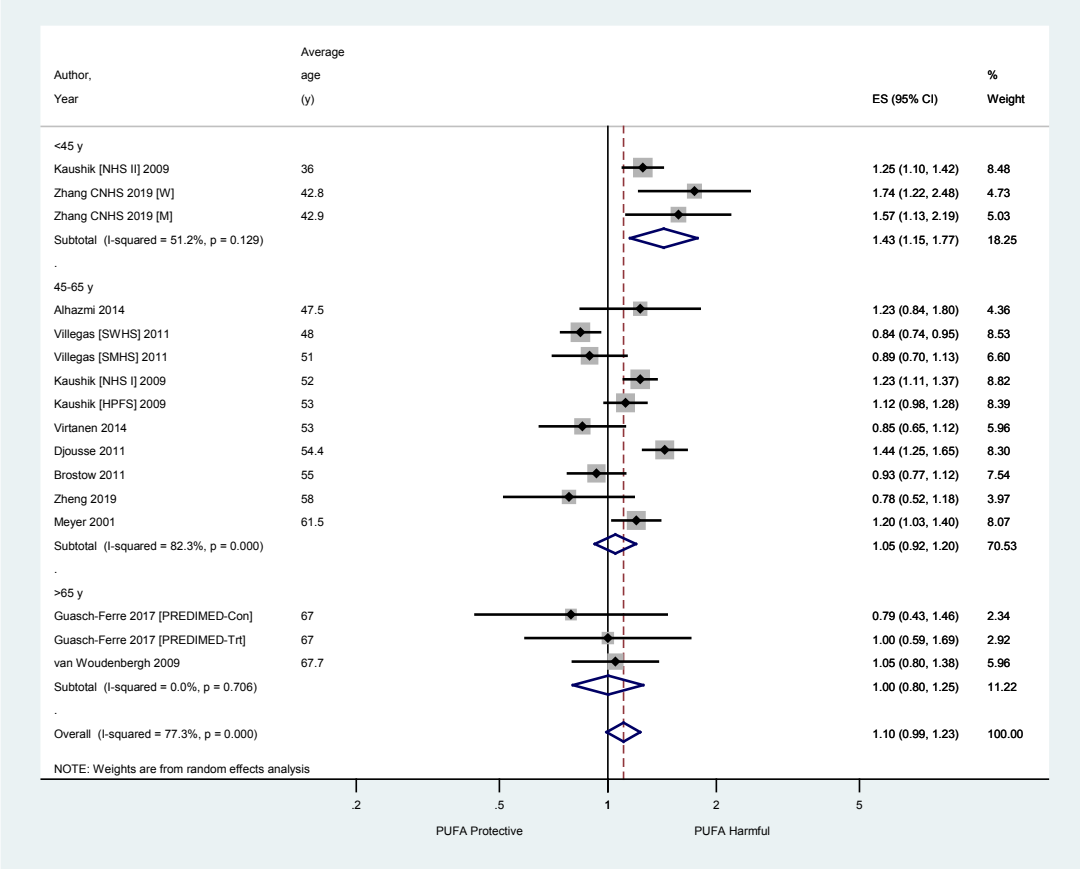
Fig. 94q. Meta-regression of long-chain n-3 PUFA and type 2 diabetes; age; Panel A – effect size



The effect size was not associated with adjustment for average age of the study sample in the final model (*P*=0.17).

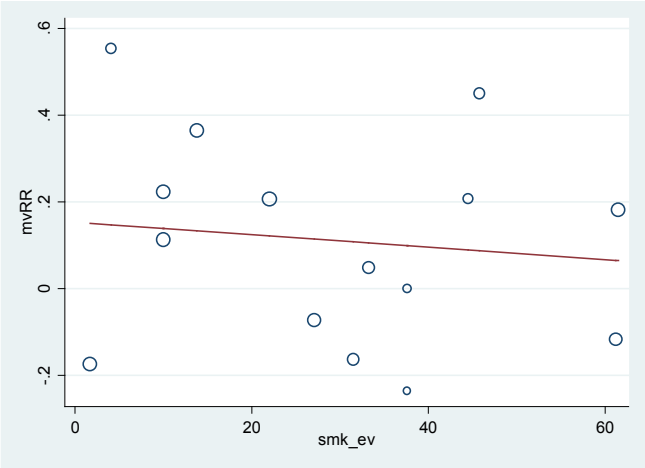
mvRR: multivariable risk ratio; PUFA: polyunsaturated fatty acids; y: years.

Fig. 94r. Meta-regression of long-chain n-3 PUFA and type 2 diabetes; age; Panel B – subgroup analysis (age group)



CHNS: China Health and Nutrition Survey; CI: confidence interval; ES: effect size; HPFS: Health Professionals Follow-up Study; M: male; NHS I: Nurses' Health Study I; NHS II: Nurses' Health Study II; PREDIMED-Con: Prevención con Dieta Mediterránea (control); PREDIMED-Trt: Prevención con Dieta Mediterránea (treatment); PUFA: polyunsaturated fatty acids; SMHS: Shanghai Men's Health Study; SWHS: Shanghai Women's Health Study; W: women; y: years.

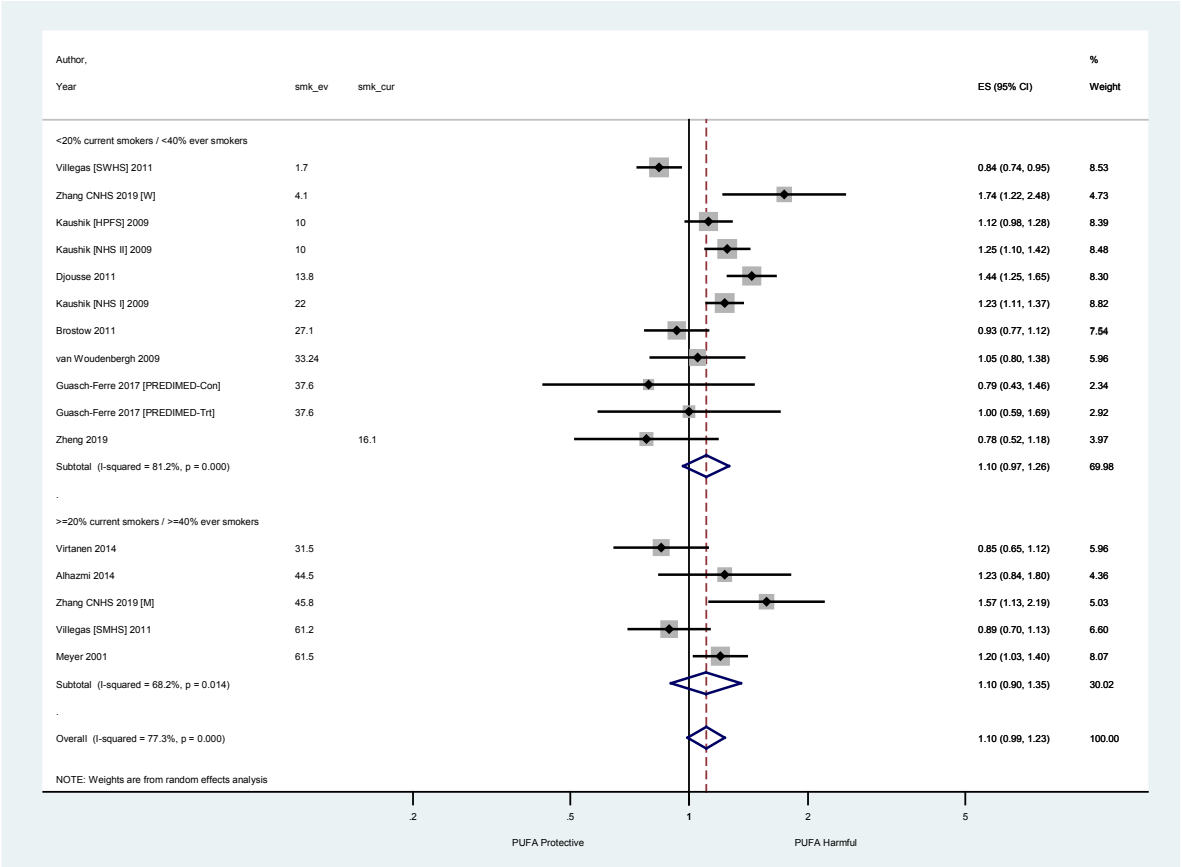
Fig. 94s. Meta-regression of long-chain n-3 PUFA and type 2 diabetes; smoking; Panel A – effect size



The effect size was not associated with adjustment for smoking history of the study sample in the final model (*P*=0.65). High smokers ≥40% current/former or >20% current.

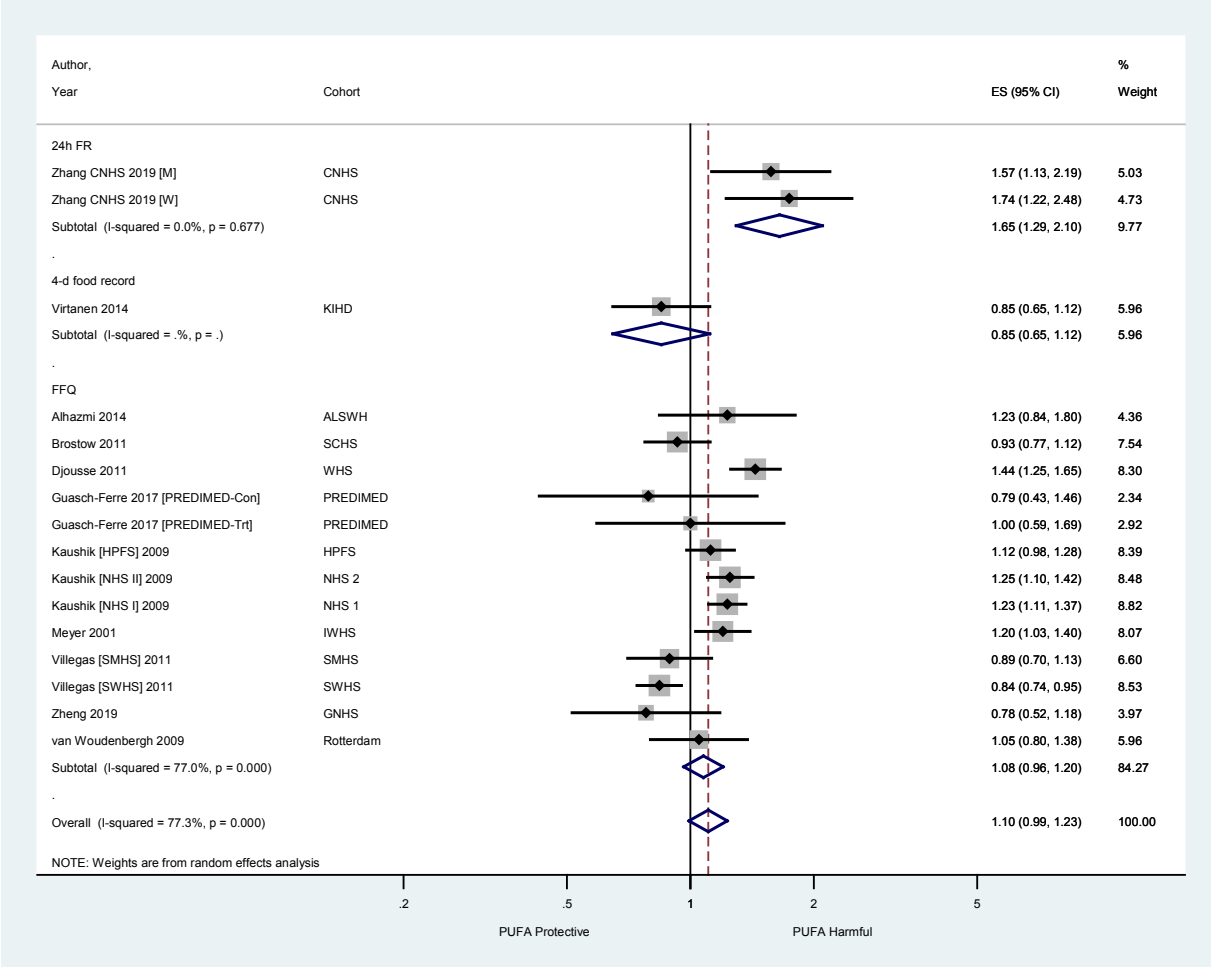
mvRR: multivariable risk ratio; PUFA: polyunsaturated fatty acids; smk_ev: ever smoked.

Fig. 94t. Meta-regression of long-chain n-3 PUFA and type 2 diabetes; smoking; Panel B – subgroup analysis



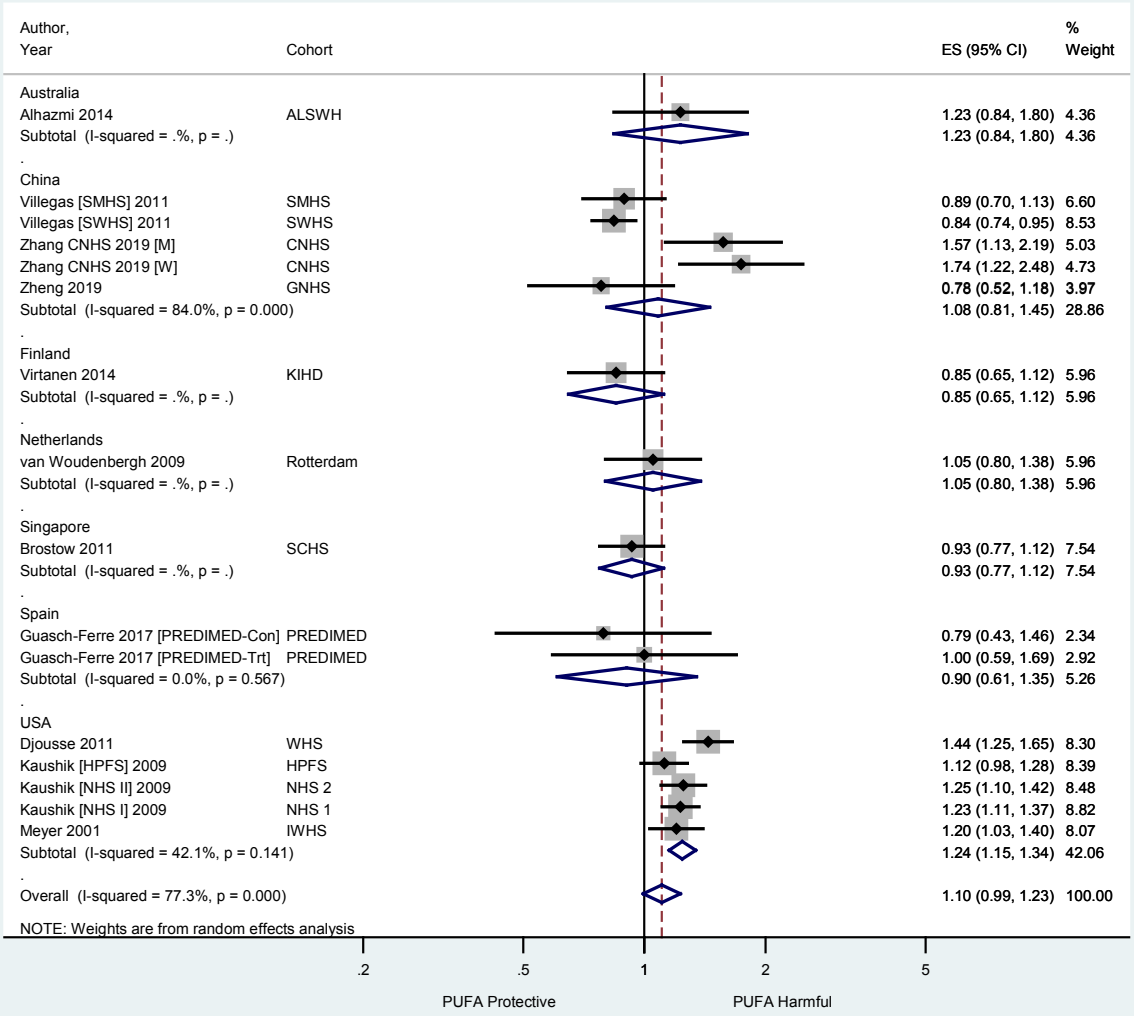
CHNS: China Health and Nutrition Survey; CI: confidence interval; ES: effect size; HPFS: Health Professionals Follow-up Study; M: male; NHS I: Nurses' Health Study I; NHS II: Nurses' Health Study II; PREDIMED-Con: Prevención con Dieta Mediterránea (control); PREDIMED-Trt: Prevención con Dieta Mediterránea (treatment); PUFA: polyunsaturated fatty acids; SMHS: Shanghai Men's Health Study; smk_cur: current smokers; smk_ev: ever smoked; SWHS: Shanghai Women's Health Study; W: women.

Fig. 94u. Meta-regression of long-chain n-3 PUFA and type 2 diabetes; diet assessment method; subgroup analysis



ALSWH: Australian Longitudinal Study on Women's Health; CHNS: China Health and Nutrition Survey; CI: confidence interval; d: day; ES: effect size; FFQ: food frequency questionnaire; FR: food record; GNHS: Guangzhou Nutrition and Health Study; h: hour; HPFS: Health Professionals Follow-up Study; IWHS: Iowa Women's Health Study; KIHD: Kuopio Ischemic Heart Disease Risk Factor Study; M: male; NHS I: Nurses' Health Study I; NHS II: Nurses' Health Study II; PREDIMED: Prevención con Dieta Mediterránea; PREDIMED-Con: Prevención con Dieta Mediterránea (control); PREDIMED-Trt: Prevención con Dieta Mediterránea (treatment); PUFA: polyunsaturated fatty acids; SCHS: Singapore Chinese Health Study; SMHS: Shanghai Men's Health Study; SWHS: Shanghai Women's Health Study; W: women; WHS: Women's Health Study. Diet assessment method was associated with effect size (P_{het}=0.001). Because the predictor variable had more than 2 levels, it is not appropriate to show the continuous meta-regression line; therefore, we present the "by method" estimates separately.

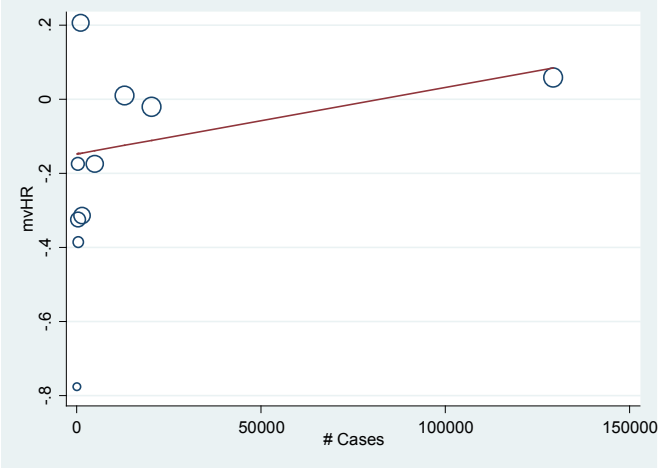
Fig. 94v. Meta-regression of long-chain n-3 PUFA and type 2 diabetes; country of conduct; subgroup analysis



ALSWH: Australian Longitudinal Study on Women's Health; CHNS: China Health and Nutrition Survey; CI: confidence interval; ES: effect size; GNHS: Guangzhou Nutrition and Health Study; HPFS: Health Professionals Follow-up Study; IWHS: Iowa Women's Health Study; KIHD: Kuopio Ischemic Heart Disease Risk Factor Study; M: male; NHS I: Nurses' Health Study I; NHS II: Nurses' Health Study II; PREDIMED: Prevención con Dieta Mediterránea; PREDIMED-Con: Prevención con Dieta Mediterránea (control); PREDIMED-Trt: Prevención con Dieta Mediterránea (treatment); PUFA: polyunsaturated fatty acids; SCHS: Singapore Chinese Health Study; SMHS: Shanghai Men's Health Study; SWHS: Shanghai Women's Health Study; USA: United States of America; W: women; WHS: Women's Health Study.

There was evidence of heterogeneity of effect size by country of conduct (P_{het}=0.001). Because the predictor variable had more than 2 levels, it is not appropriate to show the continuous meta-regression line; therefore, we present the "by country" estimates separately.

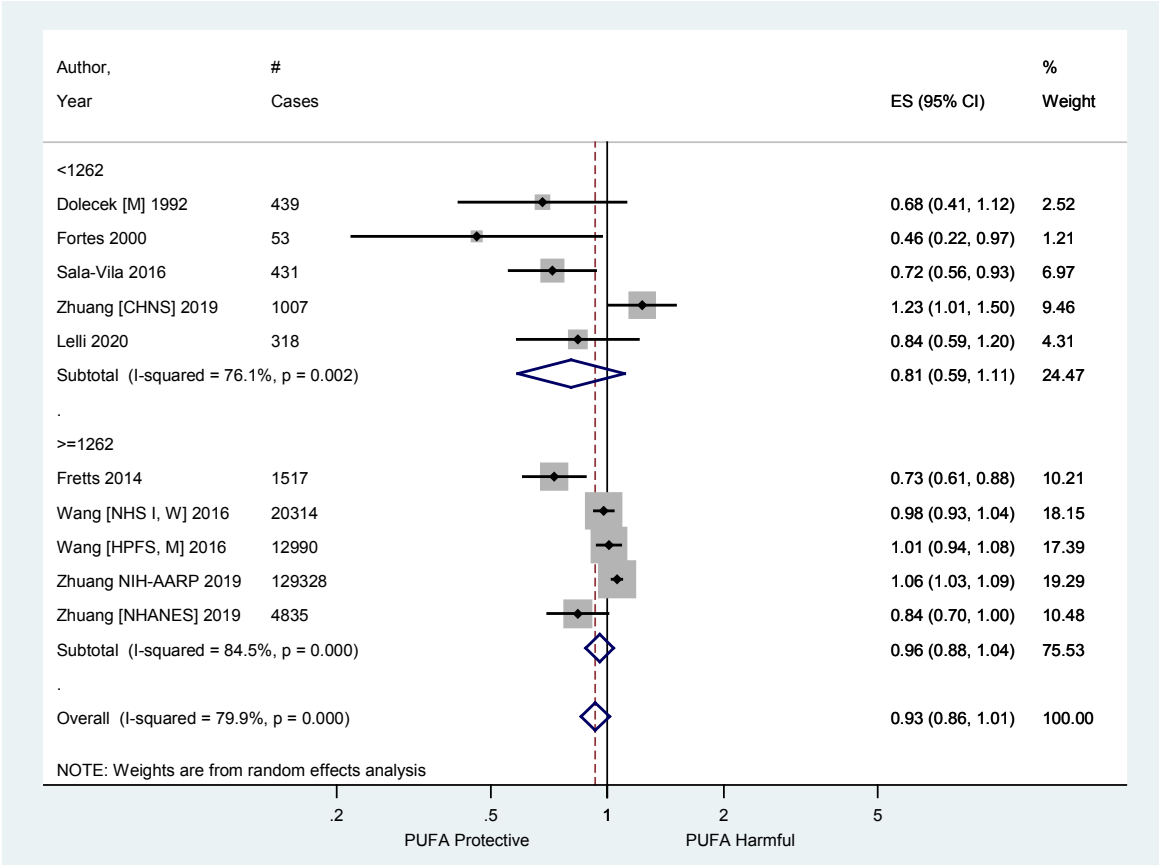
Fig. 95a. Meta-regression of ALA and all-cause mortality; number of cases; Panel A – effect size



The number of cases in the study was not associated with the effect estimate (*P*=0.27).

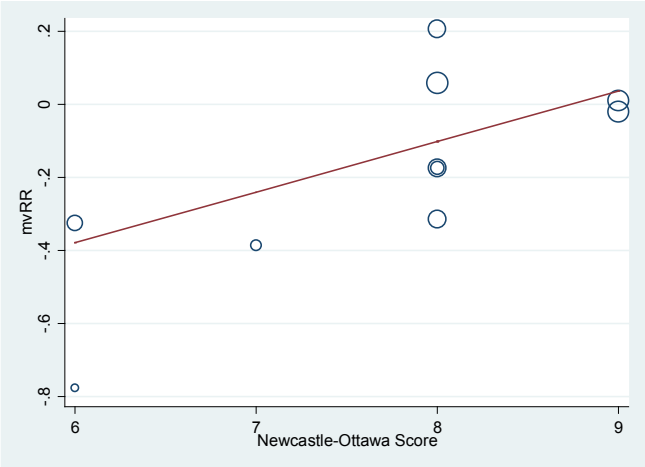
#: number; ALA: alpha-linolenic acid; CI: confidence interval; mvHR: multivariable hazard ratio; mvRR: multivariable risk ratio.

Fig. 95b. Meta-regression of ALA and all-cause mortality; number of cases; Panel B – subgroup analysis by number of cases (*n*=1262)



#: number; ALA: alpha-linolenic acid; CHNS: China Health and Nutrition Survey; CI: confidence interval; ES: effect size; HPFS: Health Professionals Follow-up Study; M: male; NHANES: National Health and Nutrition Examination Survey; NHS I: Nurses' Health Study I; NIH-AARP: National Institutes of Health American Association of Retired Persons Diet and Health Study; PUFA: polyunsaturated fatty acids; W: women.

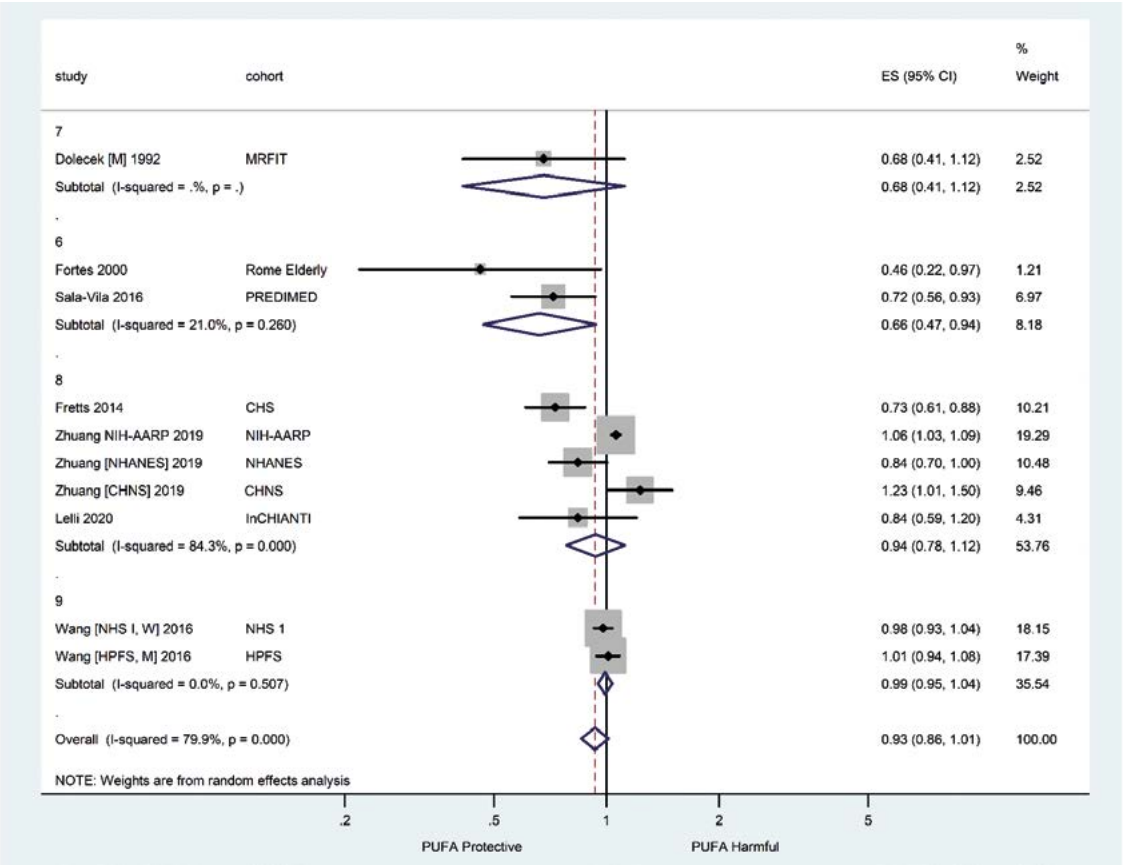
Fig. 95c. Meta-regression of ALA and all-cause mortality; NOS assessment; Panel A – effect size



There was an association between NOS assessment and effect size (*P*=0.069).

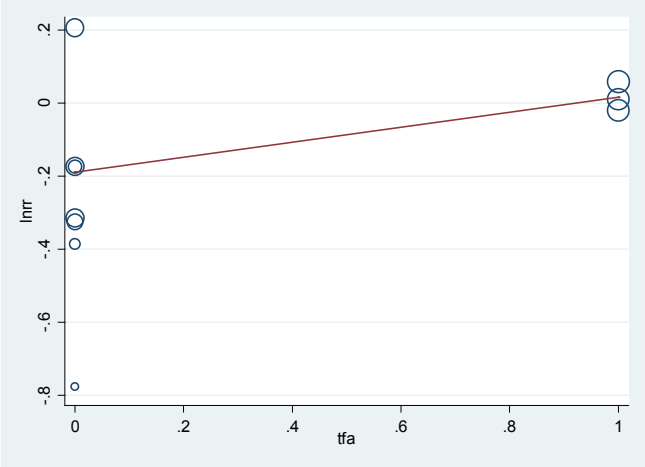
ALA: alpha-linolenic acid; mvRR: multivariable risk ratio; NOS: Newcastle-Ottawa Scale.

Fig. 95d. Meta-regression of ALA and all-cause mortality; NOS assessment; Panel B – subgroup analysis by NOS score



ALA: alpha-linolenic acid; CHNS: China Health and Nutrition Survey; CHS: Cardiovascular Health Study; CI: confidence interval; CNHS : China Health and Nutrition Survey; ES: effect size; HPFS: Health Professionals Follow-up Study; InCHIANTI: Invecchiare in Chianti; M: male; MRFIT: Multiple Risk Factor Intervention Trial; NHANES: National Health and Nutrition Examination Survey; NHS I: Nurses' Health Study I; NIH-AARP: National Institutes of Health American Association of Retired Persons Diet and Health Study; NOS: Newcastle-Ottawa Scale; PREDIMED: Prevención con Dieta Mediterránea; PUFA: polyunsaturated fatty acids; W: women.

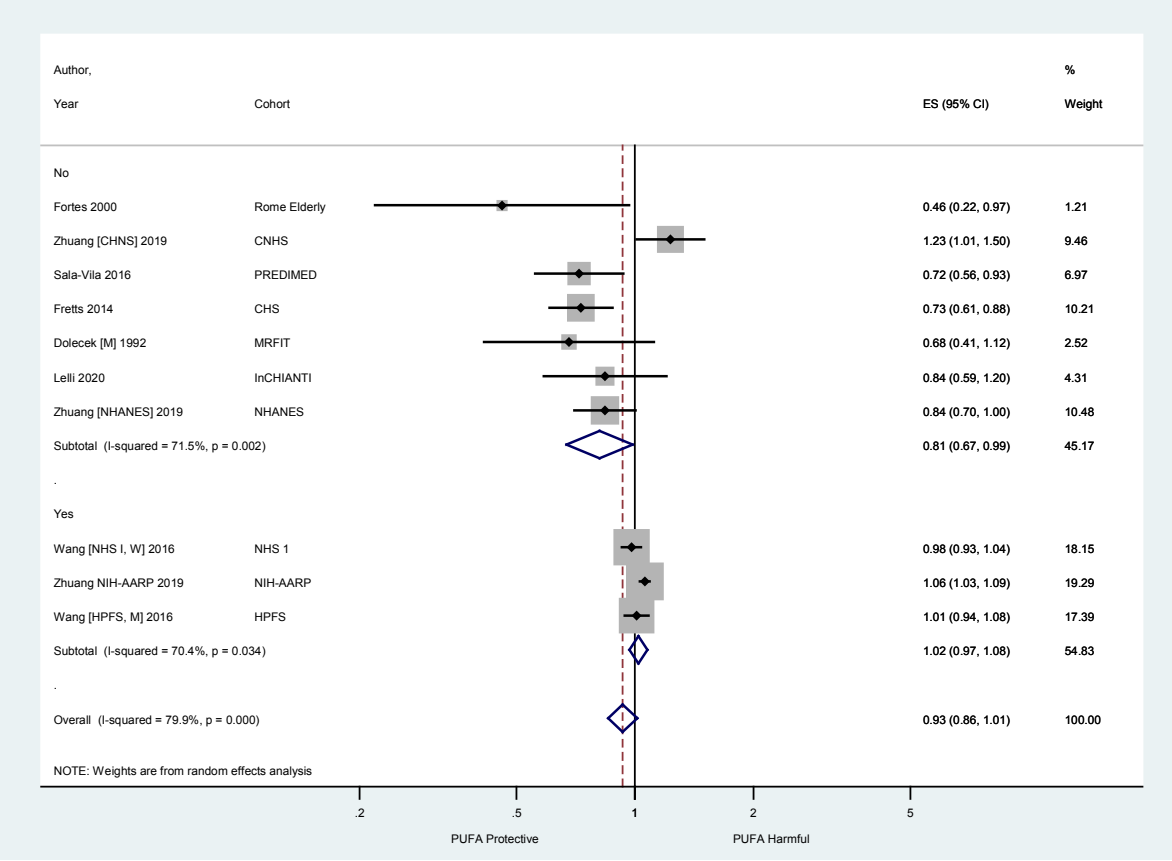
Fig. 95e. Meta-regression of ALA and all-cause mortality; TFA assessment; Panel A – effect size



The effect size was not associated with adjustment for TFA assessment in the final model (*P*=0.12).

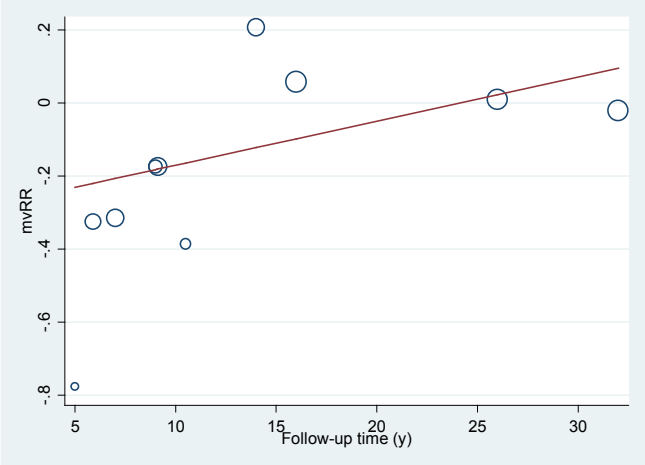
ALA: alpha-linolenic acid; rr: risk ratio; tfa: trans-fatty acids; TFA: trans-fatty acid.

Fig. 95f. Meta-regression of ALA and all-cause mortality; TFA assessment; Panel B – subgroup analysis (yes/no)



ALA: alpha-linolenic acid; CHNS: China Health and Nutrition Survey; CHS: Cardiovascular Health Study; CI: confidence interval; CNHS: China Health and Nutrition Survey; ES: effect size; HPFS: Health Professionals Follow-up Study; InCHIANTI: Invecchiare in Chianti; M: male; MRFIT: Multiple Risk Factor Intervention Trial; NHANES: National Health and Nutrition Examination Survey; NHS I: Nurses' Health Study I; NIH-AARP: National Institutes of Health American Association of Retired Persons Diet and Health Study; PREDIMED: Prevención con Dieta Mediterránea; PUFA: polyunsaturated fatty acids; TFA: trans-fatty acids; W: women.

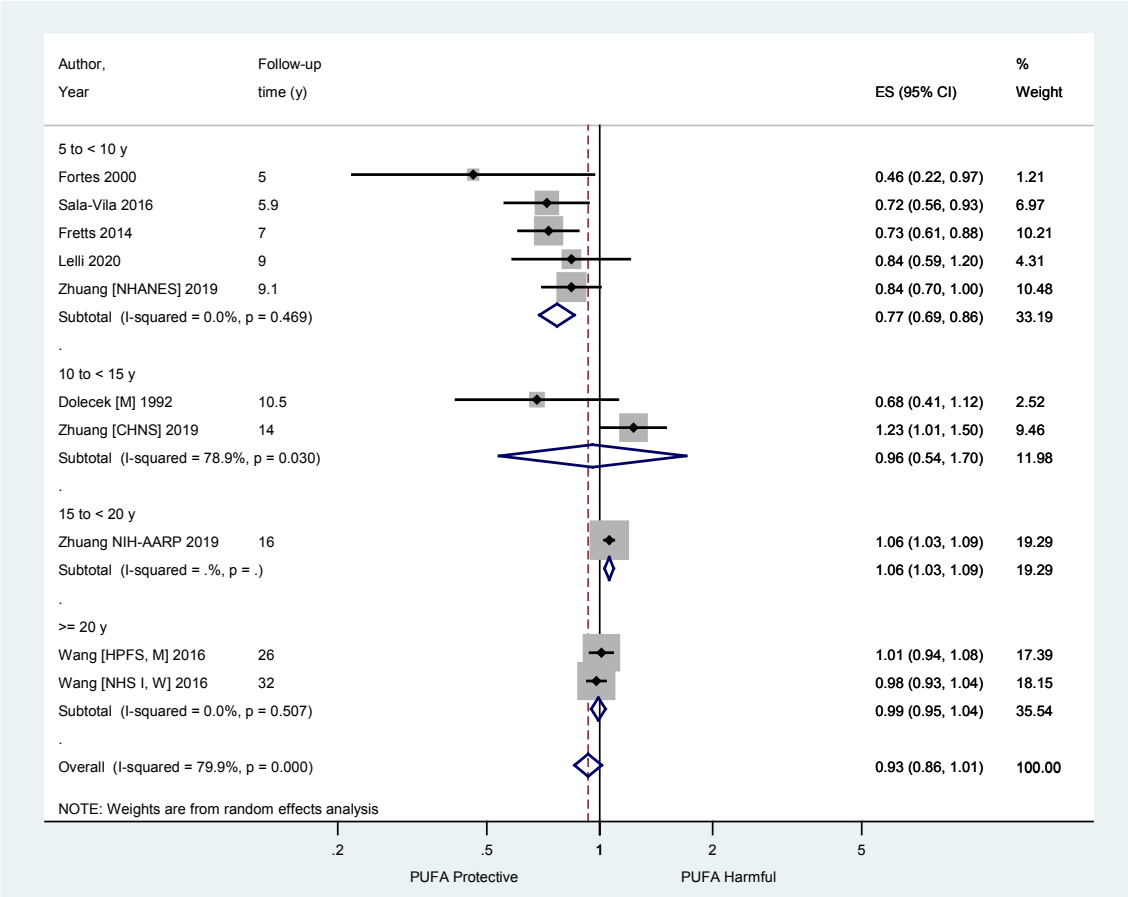
Fig. 95g. Meta-regression of ALA and all-cause mortality; follow-up time; Panel A – effect size



There was an association between follow-up time and effect size (P=0.098).

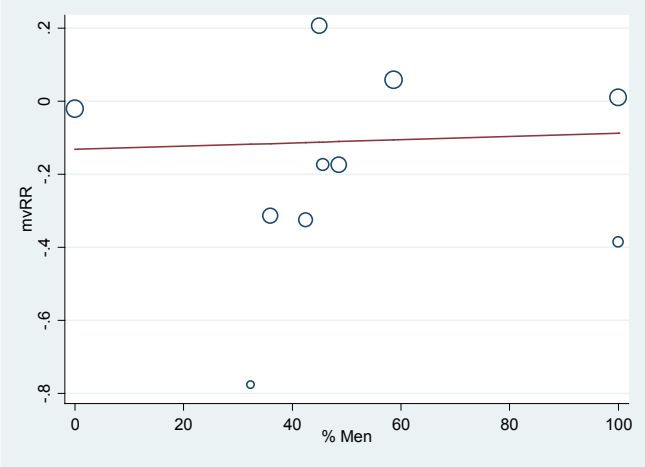
ALA: alpha-linolenic acid; mvRR: multivariable risk ratio; y: years.

Fig. 95h. Meta-regression of ALA and all-cause mortality; follow-up time; Panel B – subgroup analysis



ALA: alpha-linolenic acid; CHNS: China Health and Nutrition Survey; CI: confidence interval; ES: effect size; HPFS: Health Professionals Follow-up Study; M: male; NHANES: National Health and Nutrition Examination Survey; NHS I: Nurses' Health Study I; NIH-AARP: National Institutes of Health American Association of Retired Persons Diet and Health Study; PUFA: polyunsaturated fatty acids; W: women; y: years.

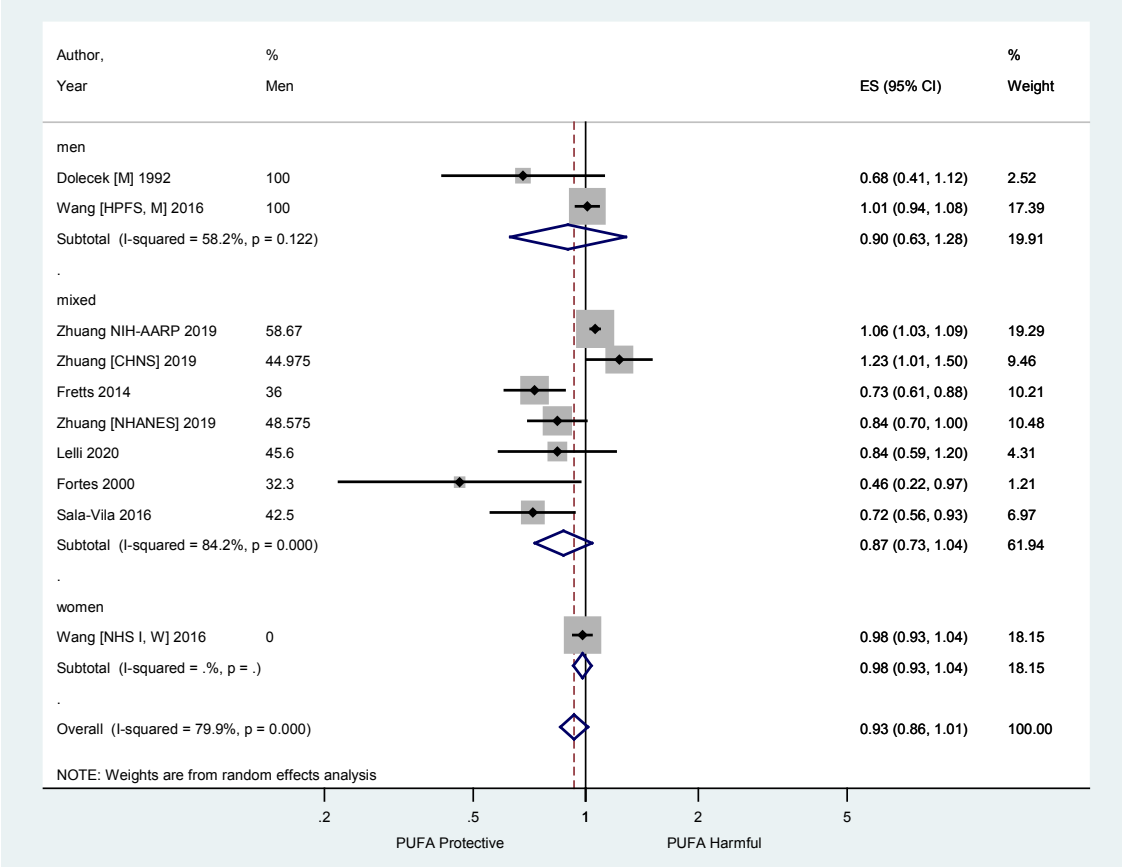
Fig. 95i. Meta-regression of ALA and all-cause mortality; sex; Panel A – effect size



The effect size was not associated with adjustment for the percentage of men in the study in the final model (*P*=0.88).

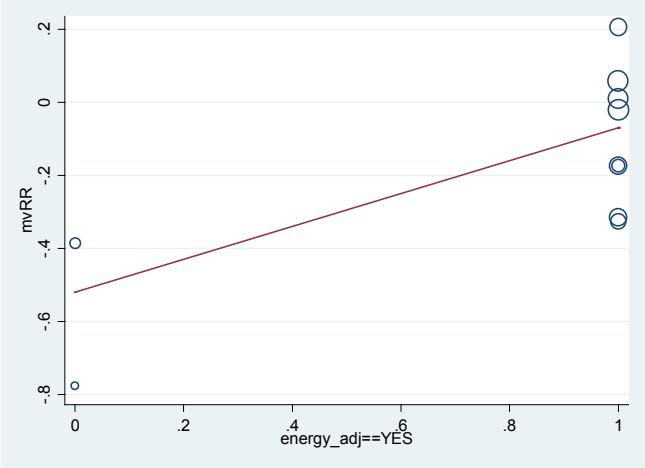
ALA: alpha-linolenic acid; mvRR: multivariable risk ratio.

Fig. 95j. Meta-regression of ALA and all-cause mortality; sex; Panel B – subgroup analysis



ALA: alpha-linolenic acid; CHNS: China Health and Nutrition Survey; CI: confidence interval; ES: effect size; HPFS: Health Professionals Follow-up Study; M: male; NHANES: National Health and Nutrition Examination Survey; NHS I: Nurses' Health Study I; NIH-AARP: National Institutes of Health American Association of Retired Persons Diet and Health Study; PUFA: polyunsaturated fatty acids; W: women.

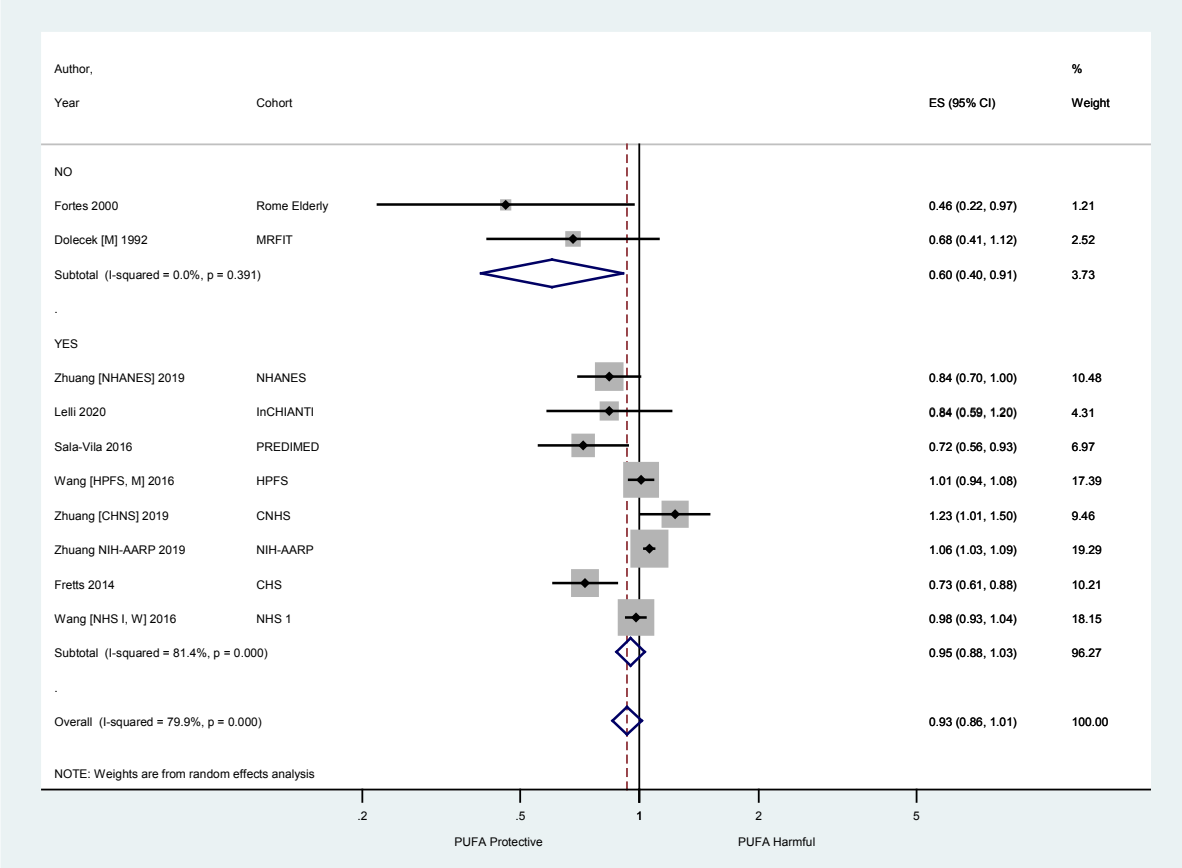
Fig. 95k. Meta-regression of ALA and all-cause mortality; energy adjustment; Panel A – effect size



The effect size was not associated with adjustment for energy in the final model (*P*=0.11).

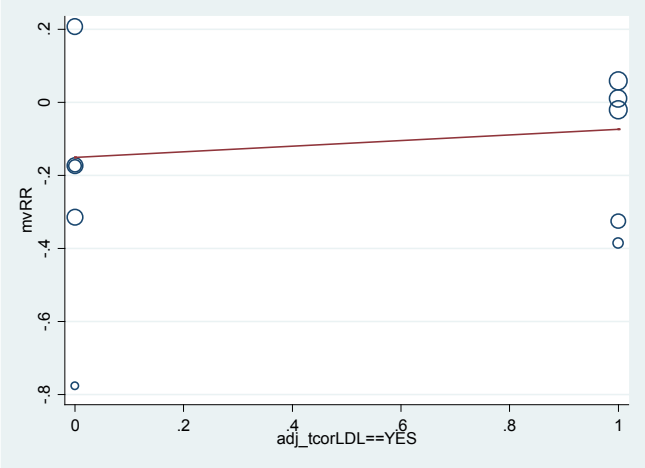
ALA: alpha-linolenic acid; energy_adj: adjusted for energy; mvRR: multivariable risk ratio.

Fig. 95l. Meta-regression of ALA and all-cause mortality; energy adjustment; Panel B – subgroup analysis (yes/no)



ALA: alpha-linolenic acid; CHNS: China Health and Nutrition Survey; CHS: Cardiovascular Health Study; CI: confidence interval; CNHS: China Health and Nutrition Survey; ES: effect size; HPFS: Health Professionals Follow-up Study; InCHIANTI: Invecchiare in Chianti; M: male; MRFIT: Multiple Risk Factor Intervention Trial; NHANES: National Health and Nutrition Examination Survey; NHS I: Nurses' Health Study I; NIH-AARP: National Institutes of Health American Association of Retired Persons Diet and Health Study; PREDIMED: Prevención con Dieta Mediterránea; PUFA: polyunsaturated fatty acids; W: women.

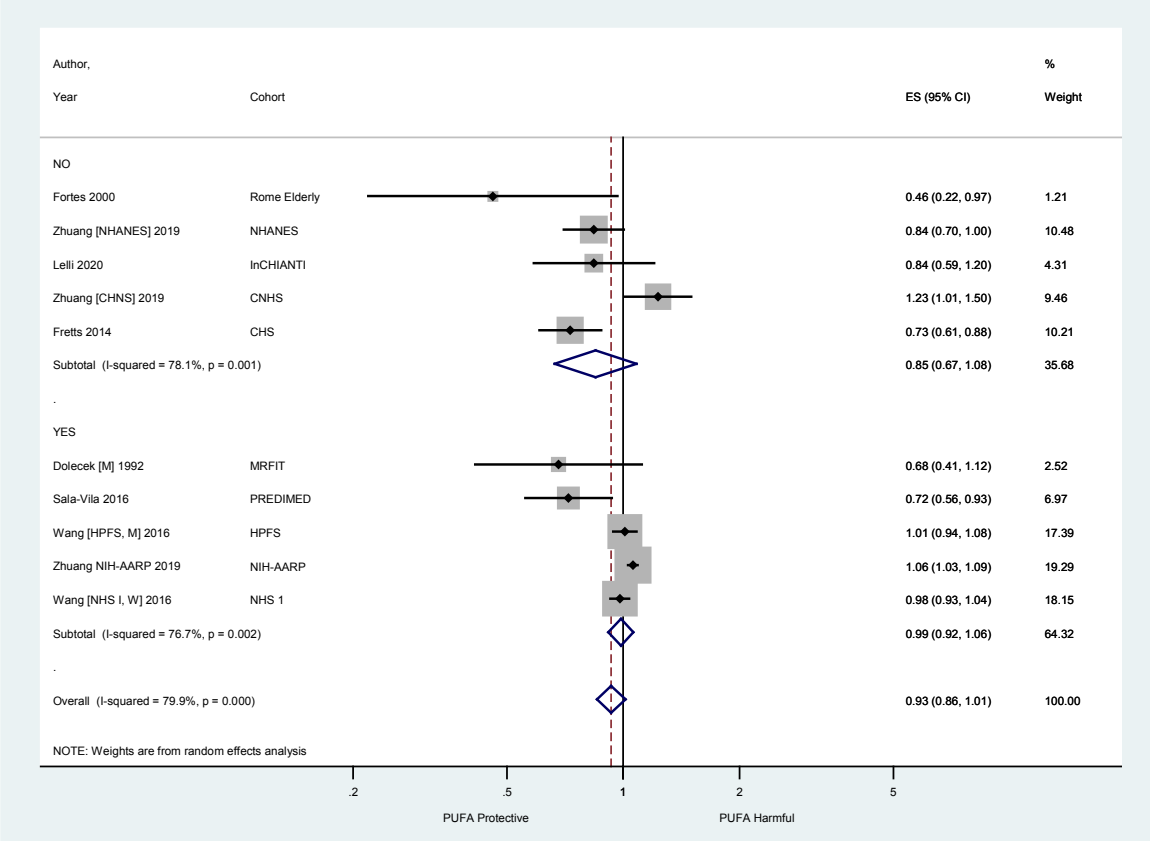
Fig. 95m. Meta-regression of ALA and all-cause mortality; dyslipidaemia adjustment; Panel A – effect size



The effect size was not associated with adjustment for a measure of dyslipidaemia in the final model (*P*=0.61).

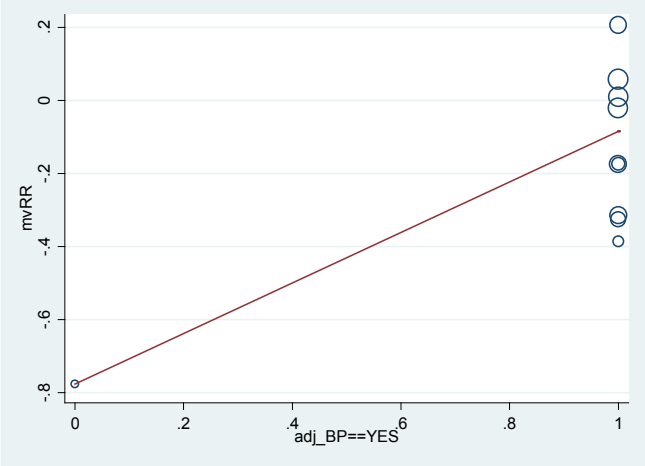
adj_tcorLDL: adjusted for dyslipidaemia; ALA: alpha-linolenic acid; mvRR: multivariable risk ratio.

Fig. 95n. Meta-regression of ALA and all-cause mortality; dyslipidaemia adjustment; Panel B – subgroup analysis (yes/no)



ALA: alpha-linolenic acid; CHNS: China Health and Nutrition Survey; CHS: Cardiovascular Health Study; CI: confidence interval; CNHS: China Health and Nutrition Survey; ES: effect size; HPFS: Health Professionals Follow-up Study; InCHIANTI: Invecchiare in Chianti; M: male; MRFIT: Multiple Risk Factor Intervention Trial; NHANES: National Health and Nutrition Examination Survey; NHS I: Nurses' Health Study I; NIH-AARP: National Institutes of Health American Association of Retired Persons Diet and Health Study; PREDIMED: Prevención con Dieta Mediterránea; PUFA: polyunsaturated fatty acids; W: women.

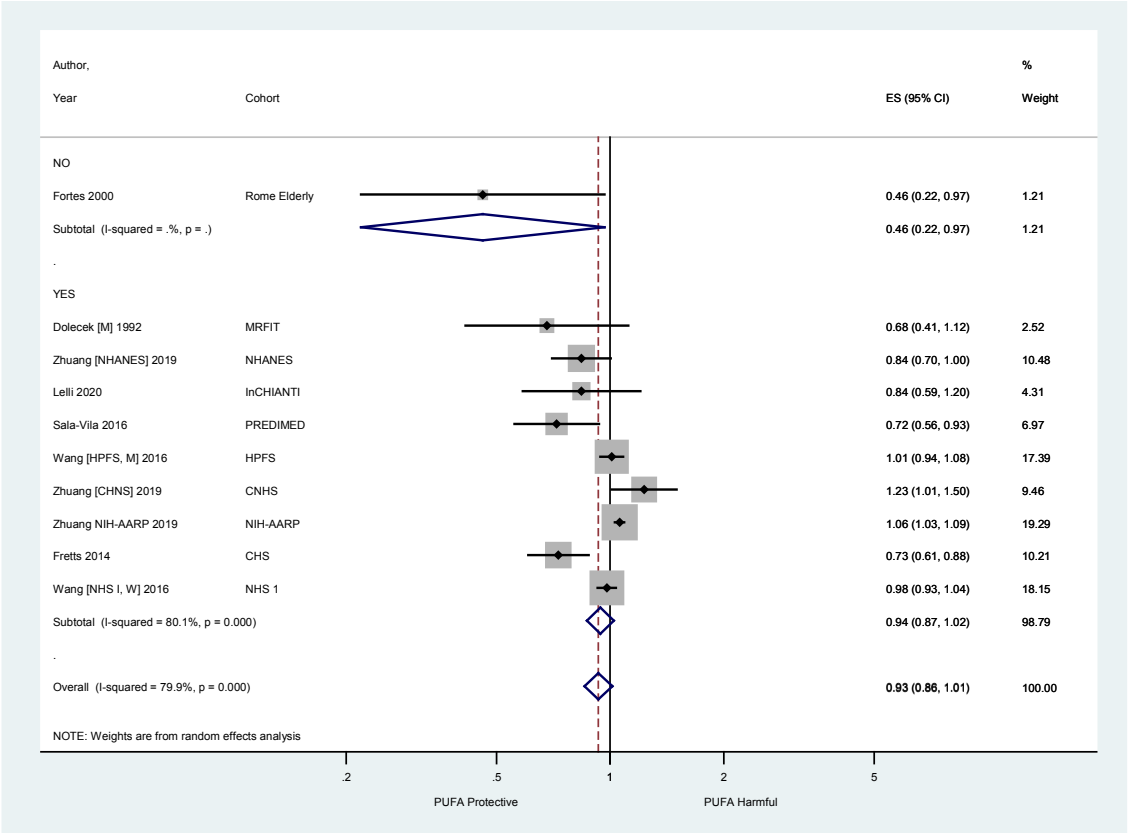
Fig. 95o. Meta-regression of ALA and all-cause mortality; blood pressure adjustment; Panel A – effect size



The effect size was not associated with adjustment for a measure of blood pressure in the final model (*P*=0.14).

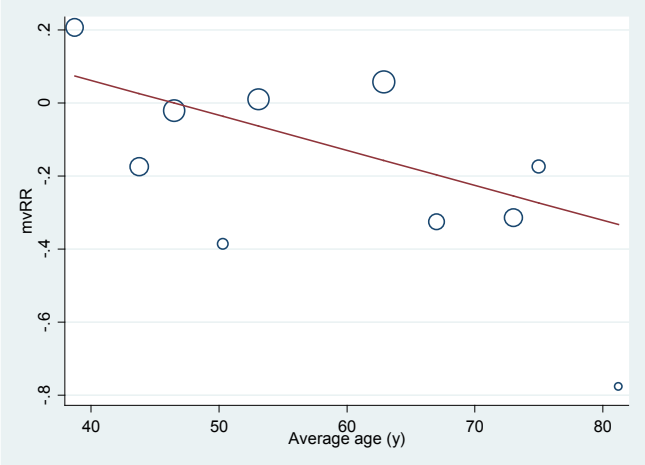
adj_BP: adjusted for blood pressure; ALA: alpha-linolenic acid; mvRR: multivariable risk ratio.

Fig. 95p. Meta-regression of ALA and all-cause mortality; blood pressure adjustment; Panel B – subgroup analysis (yes/no)



ALA: alpha-linolenic acid; CHNS: China Health and Nutrition Survey; CHS: Cardiovascular Health Study; CI: confidence interval; CNHS: China Health and Nutrition Survey; ES: effect size; HPFS: Health Professionals Follow-up Study; InCHIANTI: Invecchiare in Chianti; M: male; MRFIT: Multiple Risk Factor Intervention Trial; NHANES: National Health and Nutrition Examination Survey; NHS I: Nurses' Health Study I; NIH-AARP: National Institutes of Health American Association of Retired Persons Diet and Health Study; PREDIMED: Prevención con Dieta Mediterránea; PUFA: polyunsaturated fatty acids; W: women.

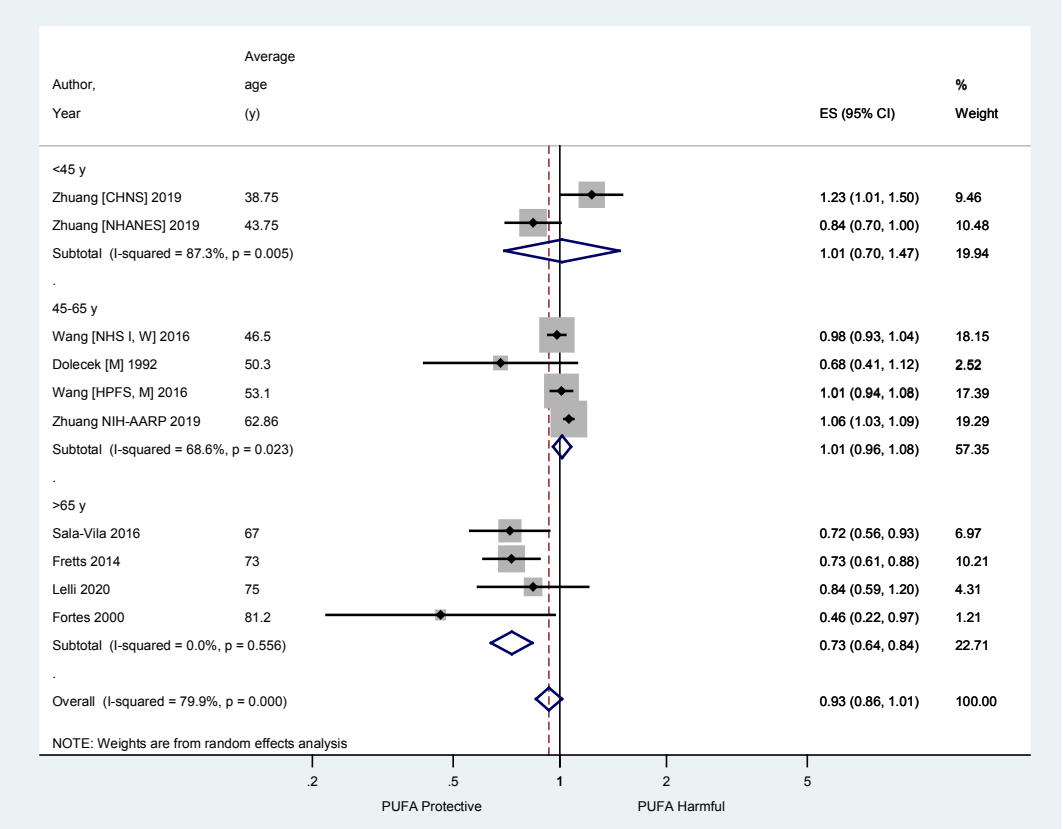
Fig. 95q. Meta-regression of ALA and all-cause mortality; age; Panel A – effect size



There was an association between effect size and average age of the study sample (*P*=0.072).

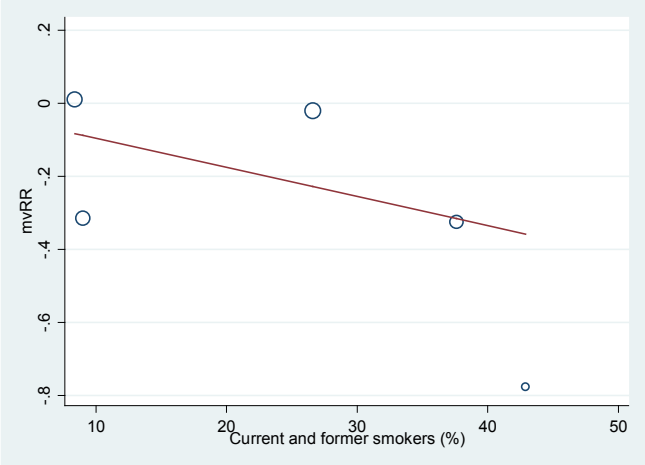
ALA: alpha-linolenic acid; mvRR: multivariable risk ratio; y: years.

Fig. 95r. Meta-regression of ALA and all-cause mortality; age; Panel B – subgroup analysis (age group)



ALA: alpha-linolenic acid; CHNS: China Health and Nutrition Survey; CI: confidence interval; ES: effect size; HPFS: Health Professionals Follow-up Study; M: male; NHANES: National Health and Nutrition Examination Survey; NHS I: Nurses' Health Study I; NIH-AARP: National Institutes of Health American Association of Retired Persons Diet and Health Study; PUFA: polyunsaturated fatty acids; W: women; y: years.

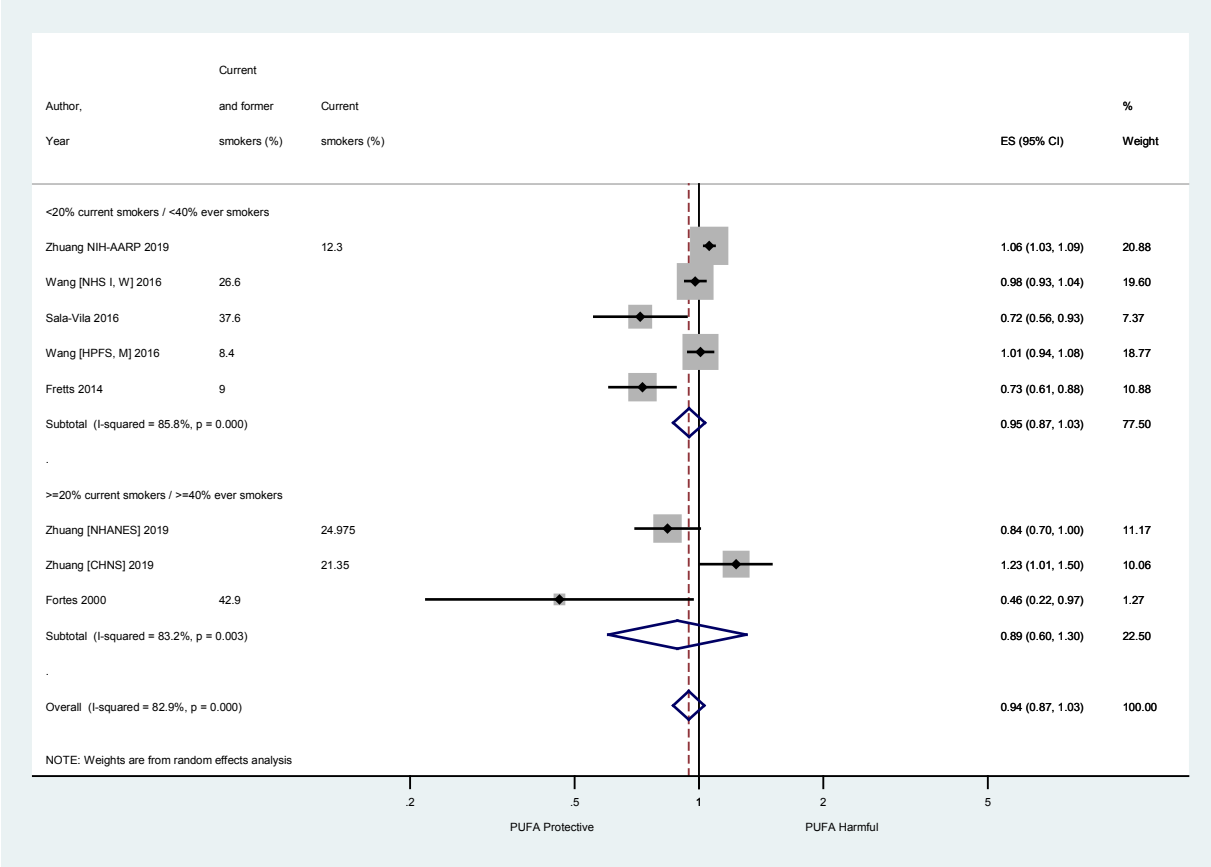
Fig. 95s. Meta-regression of ALA and all-cause mortality; smoking; Panel A – effect size



The effect size was not associated with adjustment for smoking history of the study sample in the final model (*P*=0.80). High smokers ≥40% current/former or >20% current.

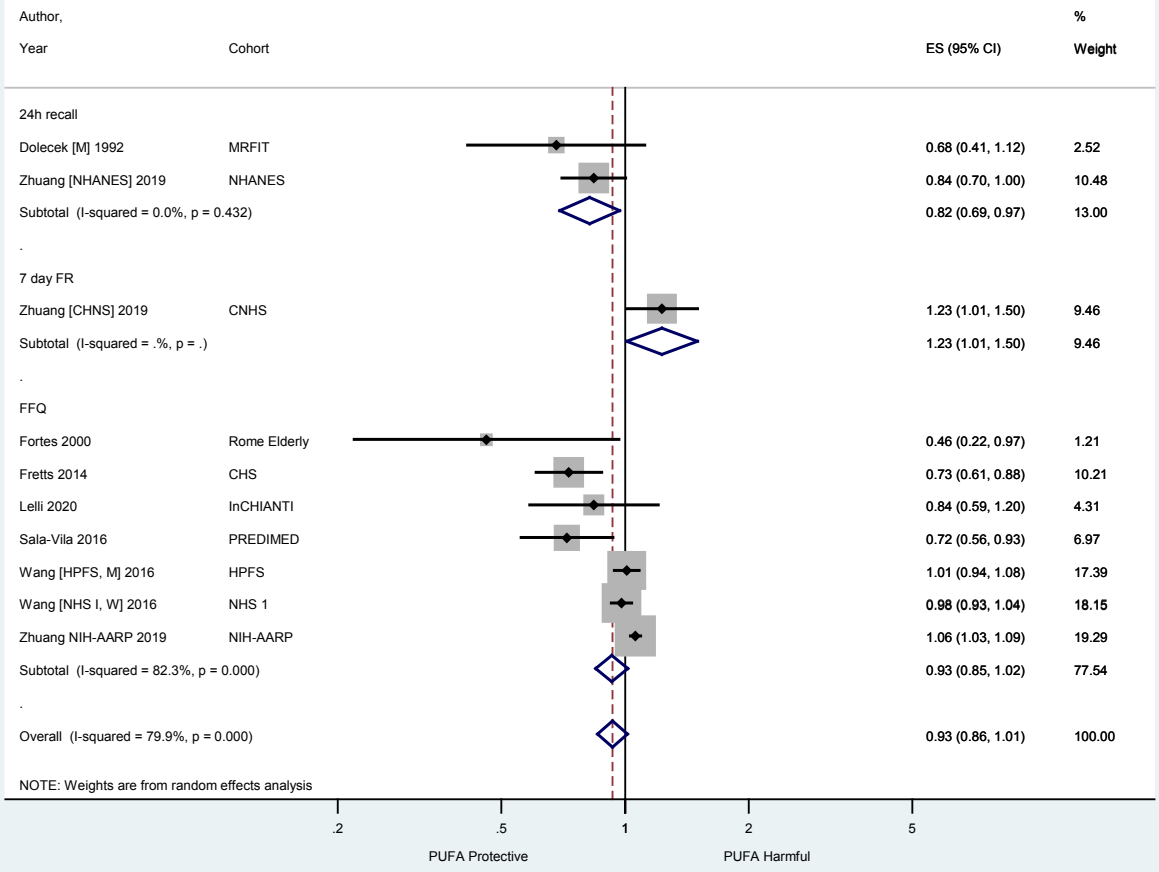
ALA: alpha-linolenic acid; mvRR: multivariable risk ratio.

Fig. 95t. Meta-regression of ALA and all-cause mortality; smoking; Panel B – subgroup analysis



ALA: alpha-linolenic acid; CHNS: China Health and Nutrition Survey; CI: confidence interval; ES: effect size; HPFS: Health Professionals Follow-up Study; M: male; NHANES: National Health and Nutrition Examination Survey; NHS I: Nurses' Health Study I; NIH-AARP: National Institutes of Health American Association of Retired Persons Diet and Health Study; PUFA: polyunsaturated fatty acids; W: women.

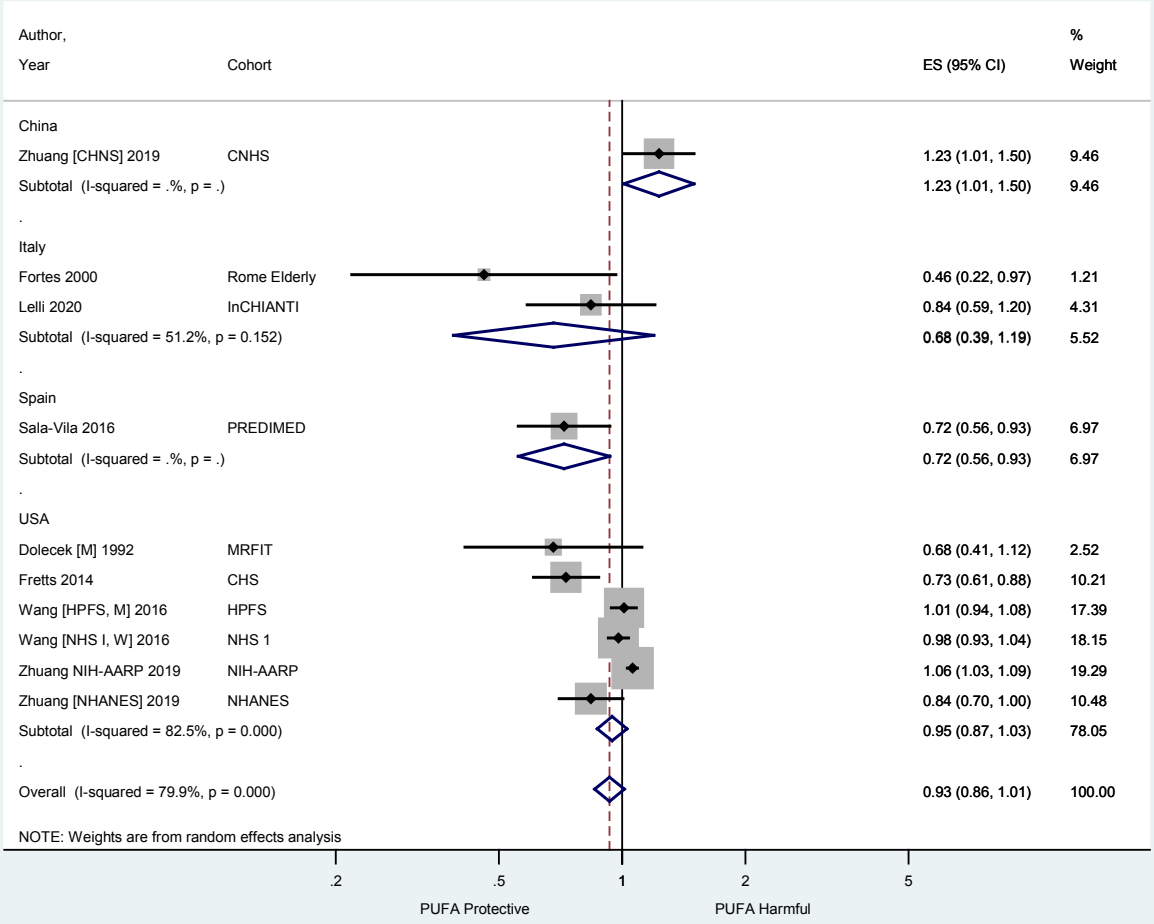
Fig. 95u. Meta-regression of ALA and all-cause mortality; diet assessment method; subgroup analysis



ALA: alpha-linolenic acid; CHNS: China Health and Nutrition Survey; CHS: Cardiovascular Health Study; CI: confidence interval; CNHS: China Health and Nutrition Survey; ES: effect size; FFQ: food frequency questionnaire; FR: food record; h: hour; HPFS: Health Professionals Follow-up Study; InCHIANTI: Invecchiare in Chianti; M: male; MRFIT: Multiple Risk Factor Intervention Trial; NHANES: National Health and Nutrition Examination Survey; NHS I: Nurses' Health Study I; NIH-AARP: National Institutes of Health American Association of Retired Persons Diet and Health Study; PREDIMED: Prevención con Dieta Mediterránea; PUFA: polyunsaturated fatty acids; W: women.

There was an association between effect size and diet assessment method (P_{het}=0.006). Because the predictor variable had more than 2 levels, it is not appropriate to show the continuous meta-regression line; therefore, we present the "by assessment method" estimates separately.

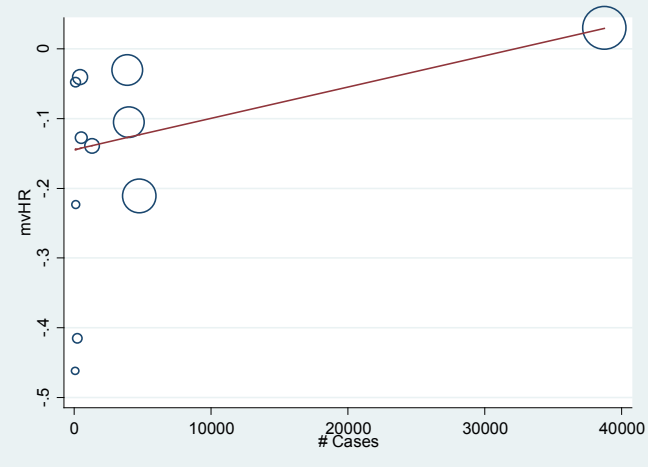
Fig. 95v. Meta-regression of ALA and all-cause mortality; country of conduct; subgroup analysis



ALA: alpha-linolenic acid; CHNS: China Health and Nutrition Survey; CHS: Cardiovascular Health Study; CI: confidence interval; CNHS: China Health and Nutrition Survey; ES: effect size; HPFS: Health Professionals Follow-up Study; InCHIANTI: Invecchiare in Chianti; M: male; MRFIT: Multiple Risk Factor Intervention Trial; NHANES: National Health and Nutrition Examination Survey; NHS I: Nurses' Health Study I; NIH-AARP: National Institutes of Health American Association of Retired Persons Diet and Health Study; PREDIMED: Prevención con Dieta Mediterránea; PUFA: polyunsaturated fatty acids; USA: United States of America; W: women.

There was evidence of heterogeneity of effect size by country of conduct (P_{het}=0.003). Because the predictor variable had more than 2 levels, it is not appropriate to show the continuous meta-regression line; therefore, we present the "by country" estimates separately.

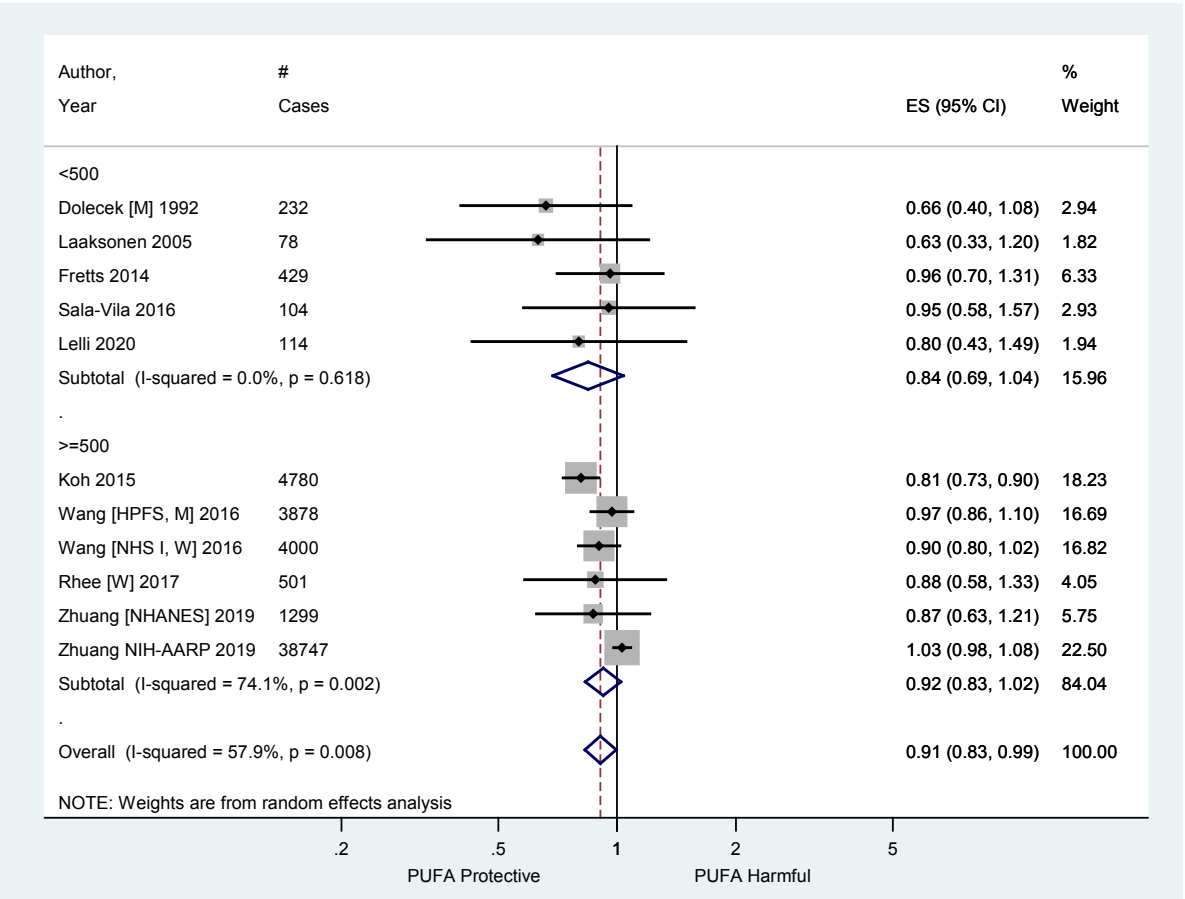
Fig. 96a. Meta-regression of ALA and CVD mortality; number of cases; Panel A – effect size



The number of cases in the study was associated with the effect estimate (*P*=0.053).

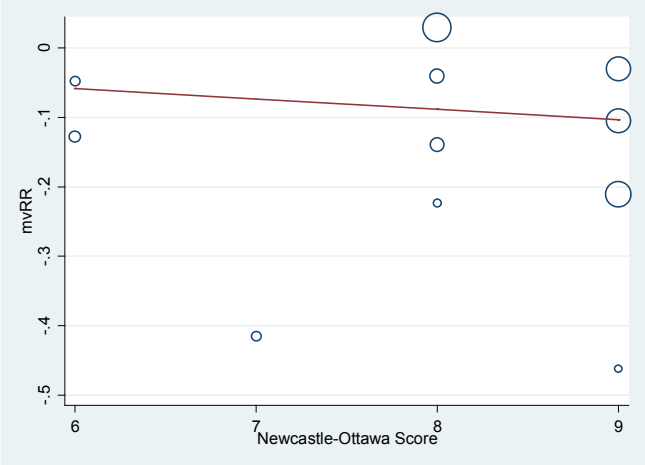
#: number; ALA: alpha-linolenic acid; CI: confidence interval; CVD: cardiovascular disease; mvHR: multivariable hazard ratio; mvRR: multivariable risk ratio.

Fig. 96b. Meta-regression of ALA and CVD mortality; number of cases; Panel B – subgroup analysis by number of cases (median *n*=500)



#: number; ALA: alpha-linolenic acid; CI: confidence interval; CVD: cardiovascular disease; ES: effect size; HPFS: Health Professionals Follow-up Study; M: male; NHANES: National Health and Nutrition Examination Survey; NHS I: Nurses' Health Study I; NIH-AARP: National Institutes of Health American Association of Retired Persons Diet and Health Study; PUFA: polyunsaturated fatty acids; W: women.

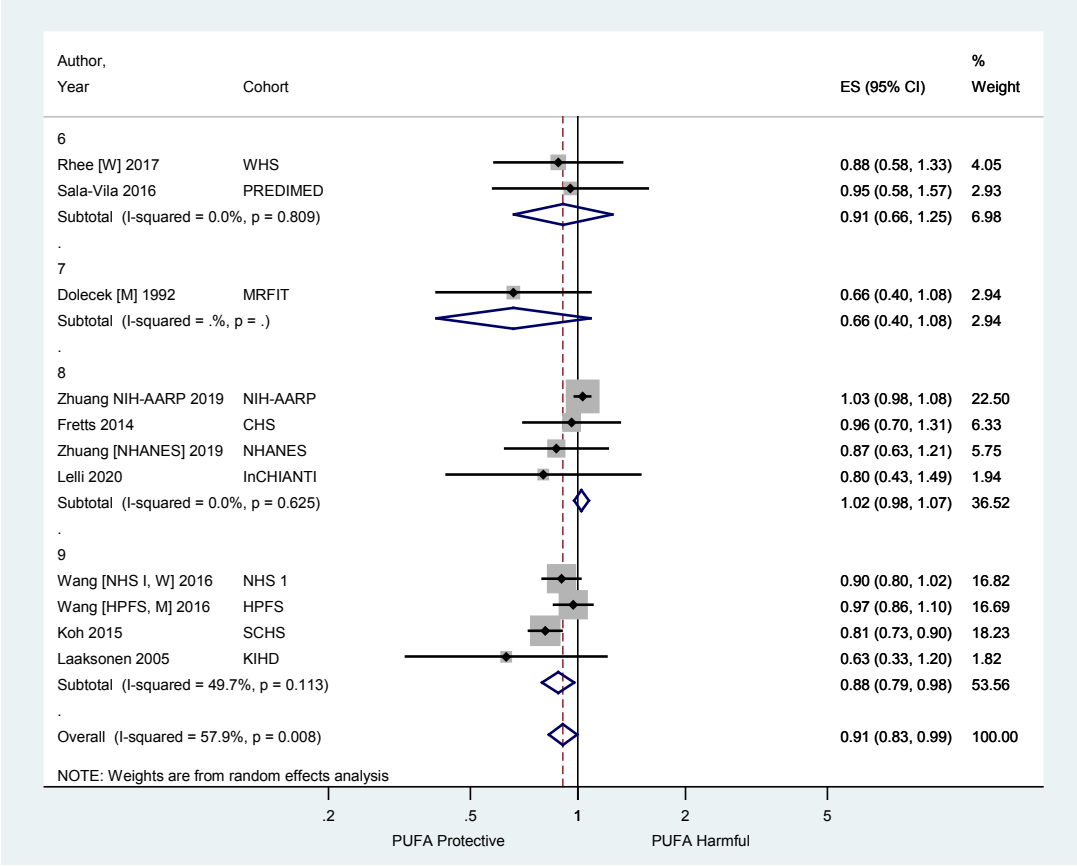
Fig. 96c. Meta-regression of ALA and CVD mortality; NOS assessment; Panel A – effect size



The effect size was not associated with the NOS quality score (P=0.79).

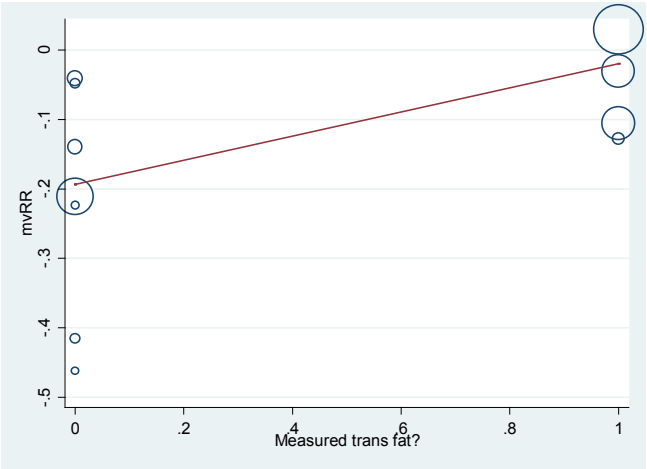
ALA: alpha-linolenic acid; CVD: cardiovascular disease; mvRR: multivariable risk ratio; NOS: Newcastle-Ottawa Scale.

Fig. 96d. Meta-regression of ALA and CVD mortality; NOS assessment; Panel B – subgroup analysis by NOS score



ALA: alpha-linolenic acid; CHS: Cardiovascular Health Study; CI: confidence interval; CVD: cardiovascular disease; ES: effect size; HPFS: Health Professionals Follow-up Study; InCHIANTI: Invecchiare in Chianti; KIHD: Kuopio Ischemic Heart Disease Risk Factor Study; M: male; MRFIT: Multiple Risk Factor Intervention Trial; NHANES: National Health and Nutrition Examination Survey; NHS I: Nurses' Health Study I; NIH-AARP: National Institutes of Health American Association of Retired Persons Diet and Health Study; NOS: Newcastle-Ottawa Scale; PREDIMED: Prevención con Dieta Mediterránea; PUFA: polyunsaturated fatty acids; SCHS: Singapore Chinese Health Study; W: women; WHS: Women's Health Study.

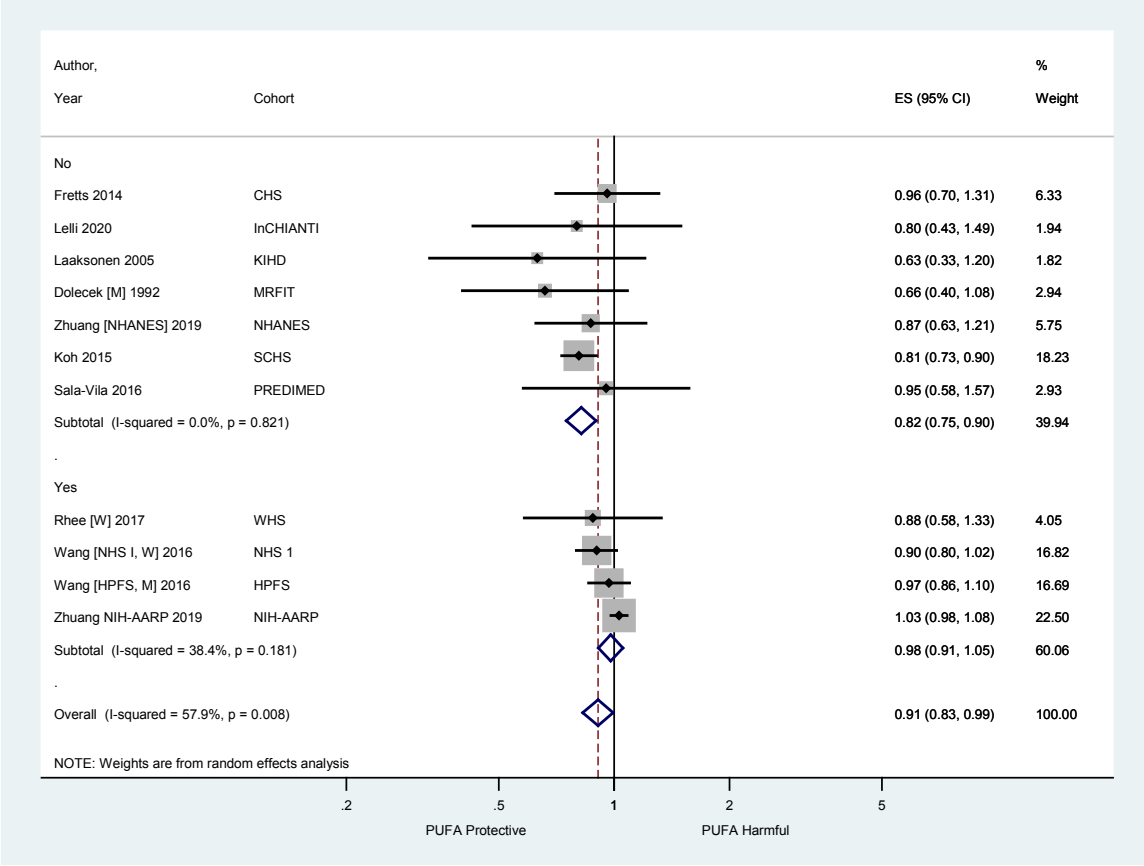
Fig. 96e. Meta-regression of ALA and CVD mortality; TFA assessment; Panel A – effect size



TFA assessment was associated with effect size (*P*=0.028).

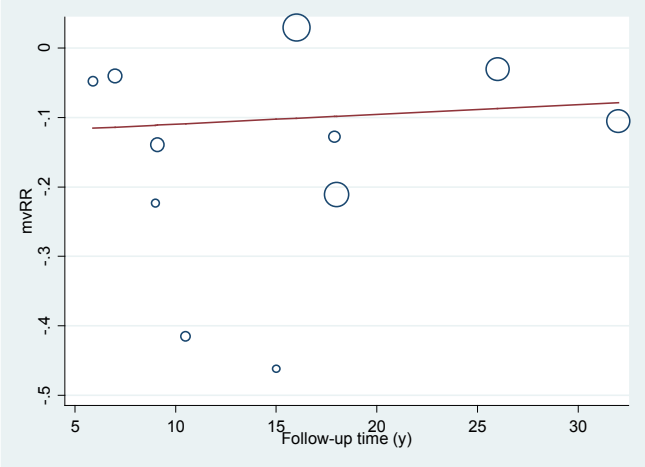
ALA: alpha-linolenic acid; CVD: cardiovascular disease; mvRR: multivariable risk ratio; TFA: trans-fatty acids.

Fig. 96f. Meta-regression of ALA and CVD mortality; TFA assessment; Panel B – subgroup analysis (yes/no)



ALA: alpha-linolenic acid; CHS: Cardiovascular Health Study; CI: confidence interval; CVD: cardiovascular disease; ES: effect size; HPFS: Health Professionals Follow-up Study; InCHIANTI: Invecchiare in Chianti; KIHD: Kuopio Ischemic Heart Disease Risk Factor Study; M: male; MRFIT: Multiple Risk Factor Intervention Trial; NHANES: National Health and Nutrition Examination Survey; NHS I: Nurses' Health Study I; NIH-AARP: National Institutes of Health American Association of Retired Persons Diet and Health Study; PREDIMED: Prevención con Dieta Mediterránea; PUFA: polyunsaturated fatty acids; SCHS: Singapore Chinese Health Study; TFA: trans-fatty acids; W: women; WHS: Women's Health Study.

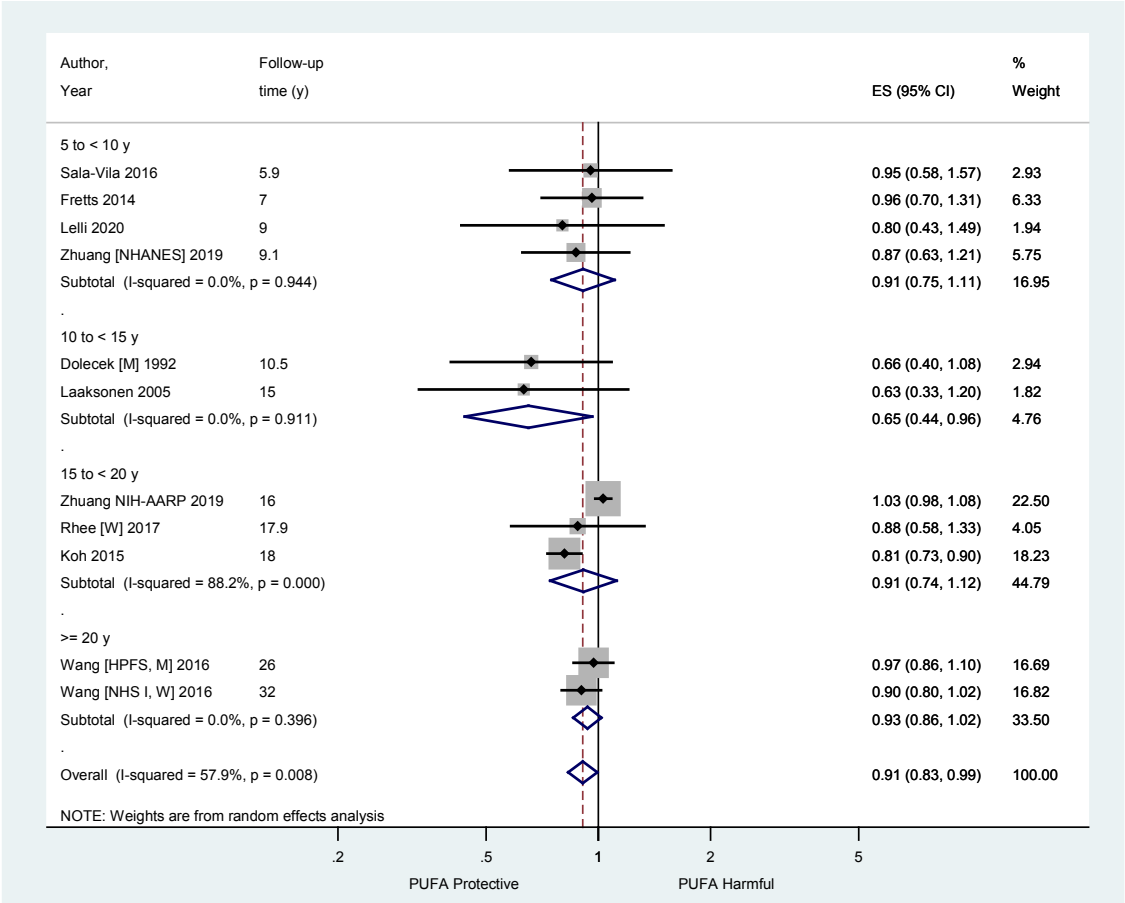
Fig. 96g. Meta-regression of ALA and CVD mortality; follow-up time; Panel A – effect size



Follow-up time was not associated with effect size (P=0.81).

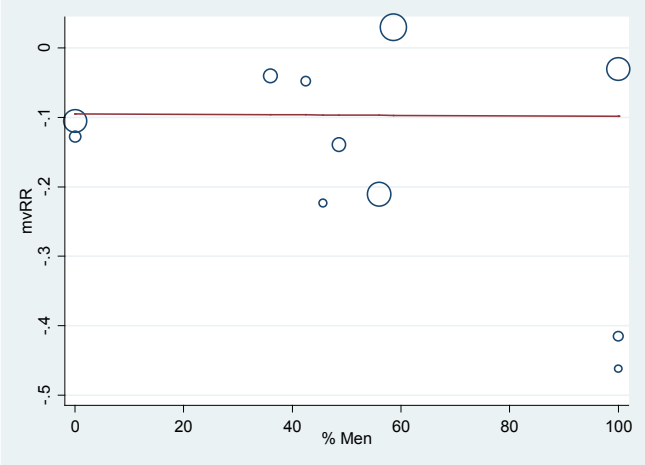
ALA: alpha-linolenic acid; CVD: cardiovascular disease; mvRR: multivariable risk ratio; y: years.

Fig. 96h. Meta-regression of ALA and CVD mortality; follow-up time; Panel B – subgroup analysis



ALA: alpha-linolenic acid; CI: confidence interval; CVD: cardiovascular disease; ES: effect size; HPFS: Health Professionals Follow-up Study; M: male; NHANES: National Health and Nutrition Examination Survey; NHS I: Nurses' Health Study I; NIH-AARP: National Institutes of Health American Association of Retired Persons Diet and Health Study; PUFA: polyunsaturated fatty acids; W: women; y: years.

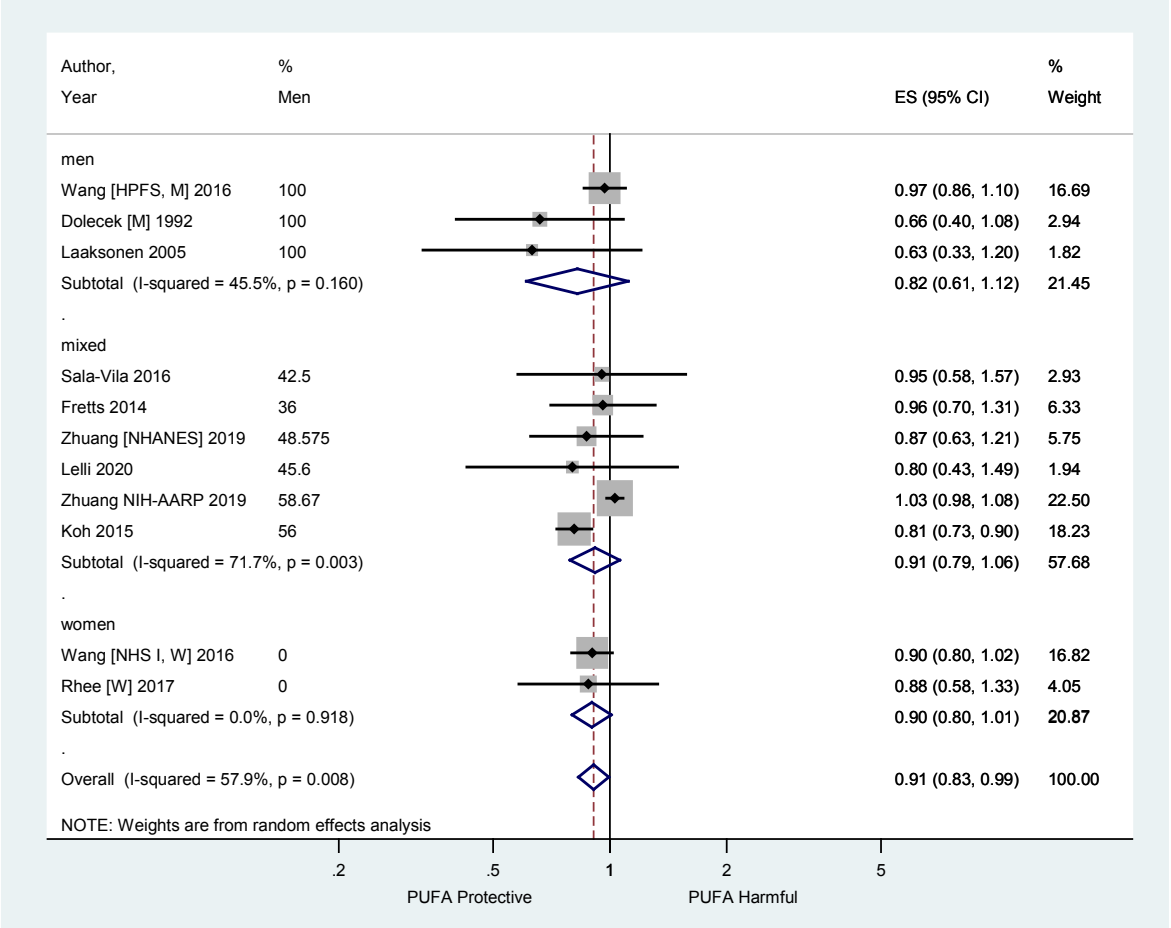
Fig. 96i. Meta-regression of ALA and CVD mortality; sex; Panel A – effect size



The effect size was not associated with adjustment for follow-up time and the percentage of men in the study in the final model (*P*=0.98).

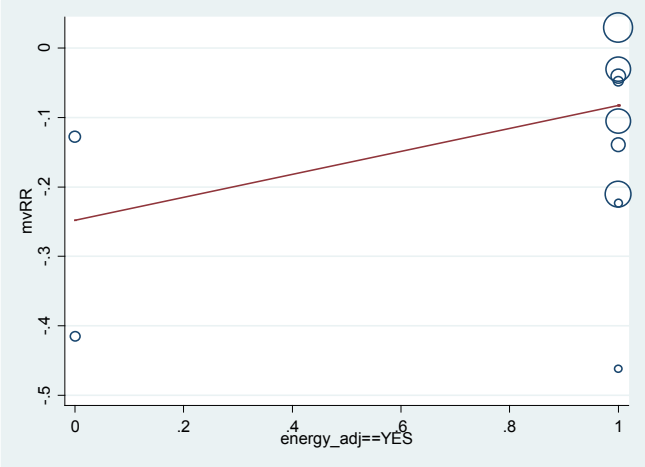
ALA: alpha-linolenic acid; CVD: cardiovascular disease; mvRR: multivariable risk ratio.

Fig. 96j. Meta-regression of ALA and CVD mortality; sex; Panel B – subgroup analysis



ALA: alpha-linolenic acid; CI: confidence interval; CVD: cardiovascular disease; ES: effect size; HPFS: Health Professionals Follow-up Study; M: male; NHANES: National Health and Nutrition Examination Survey; NHS I: Nurses' Health Study I; NIH-AARP: National Institutes of Health American Association of Retired Persons Diet and Health Study; PUFA: polyunsaturated fatty acids; W: women.

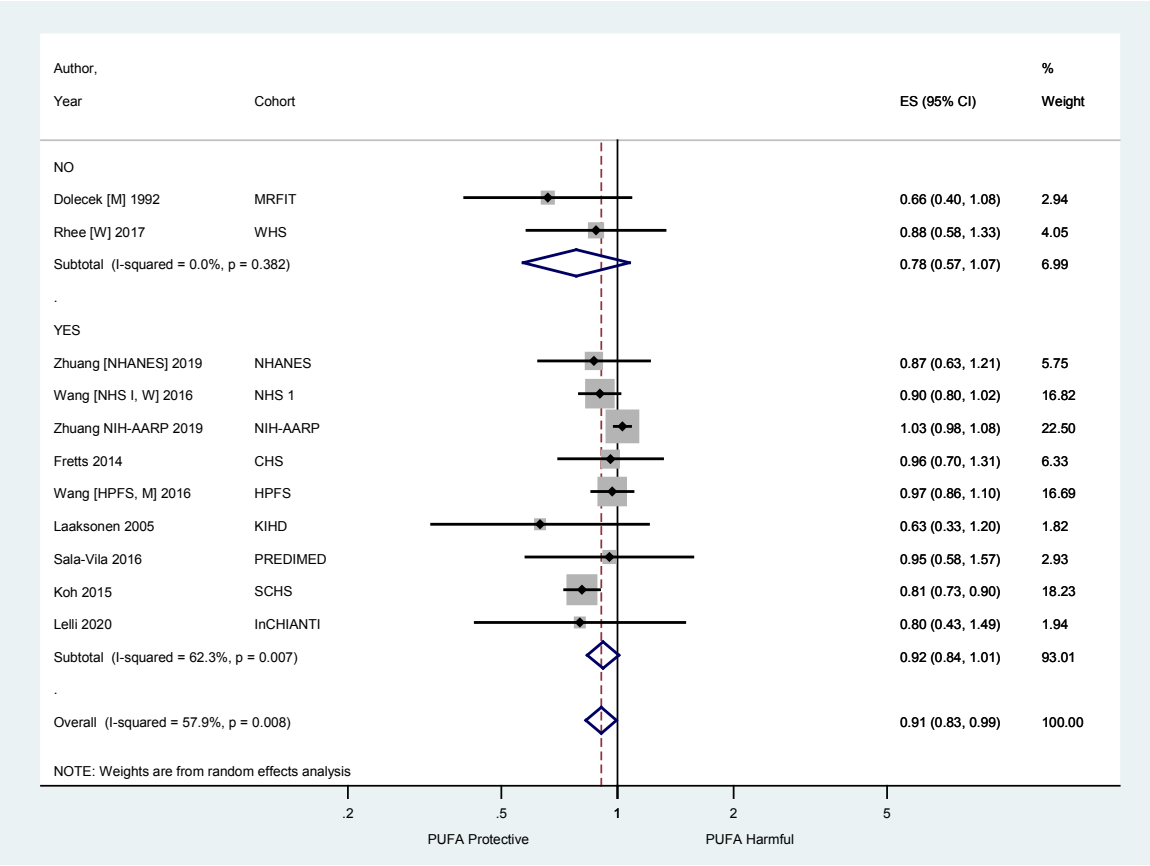
Fig. 96k. Meta-regression of ALA and CVD mortality; energy adjustment; Panel A – effect size



The effect size was not associated with adjustment for energy in the final model (*P*=0.38).

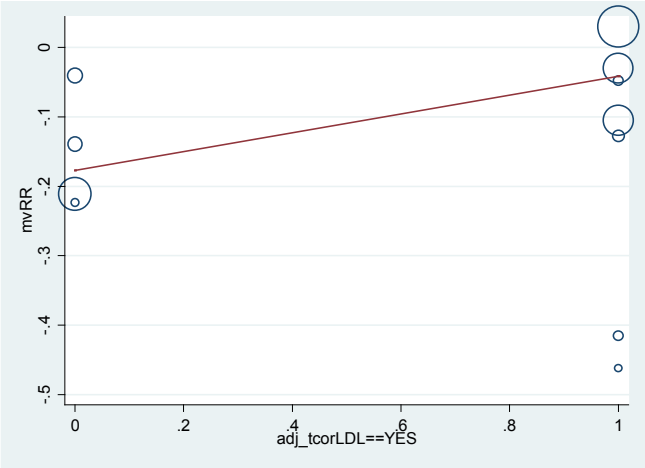
ALA: alpha-linolenic acid; energy_adj: adjusted for energy; CVD: cardiovascular disease; mvRR: multivariable risk ratio.

Fig. 96l. Meta-regression of ALA and CVD mortality; energy adjustment; Panel B – subgroup analysis (yes/no)



ALA: alpha-linolenic acid; CHS: Cardiovascular Health Study; CI: confidence interval; CVD: cardiovascular disease; ES: effect size; HPFS: Health Professionals Follow-up Study; InCHIANTI: Invecchiare in Chianti; KIHD: Kuopio Ischemic Heart Disease Risk Factor Study; M: male; MRFIT: Multiple Risk Factor Intervention Trial; NHANES: National Health and Nutrition Examination Survey; NHS I: Nurses' Health Study I; NIH-AARP: National Institutes of Health American Association of Retired Persons Diet and Health Study; PREDIMED: Prevención con Dieta Mediterránea; PUFA: polyunsaturated fatty acids; SCHS: Singapore Chinese Health Study; W: women; WHS: Women's Health Study.

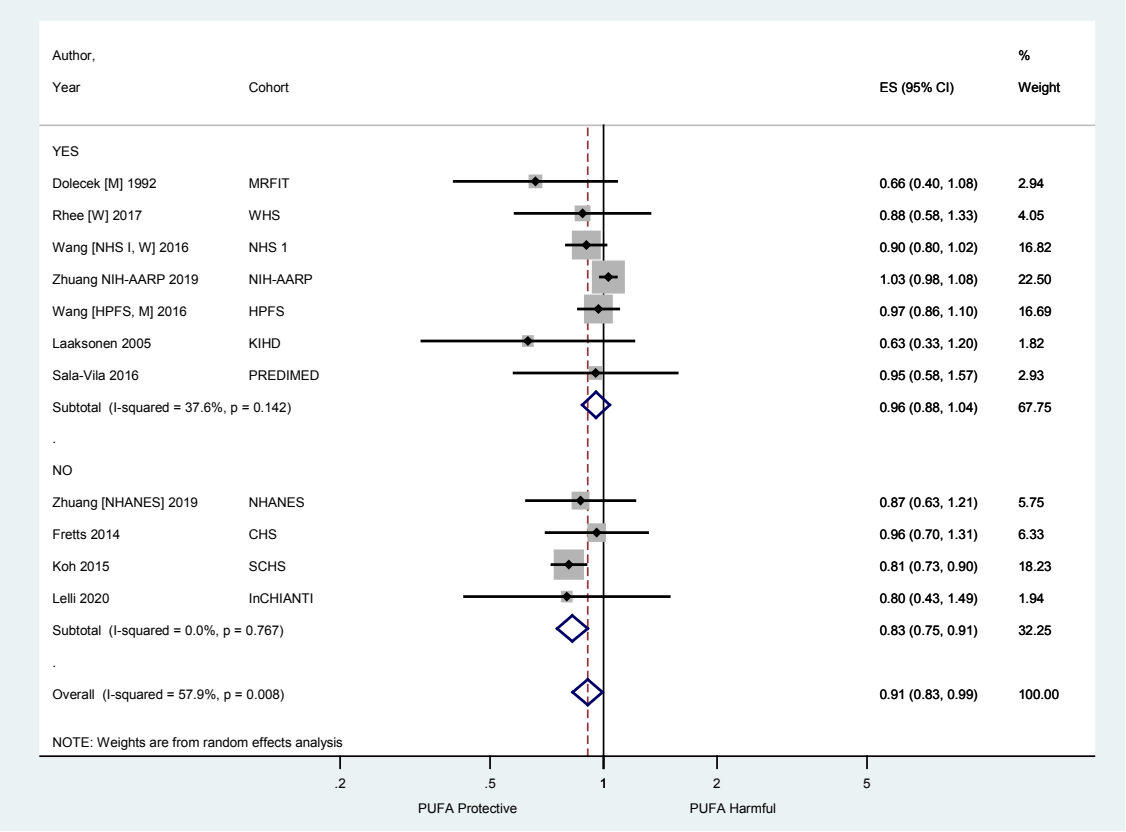
Fig. 96m. Meta-regression of ALA and CVD mortality; dyslipidaemia adjustment; Panel A – effect size



The effect size was associated with adjustment for a measure of dyslipidaemia in the final model (*P*=0.11).

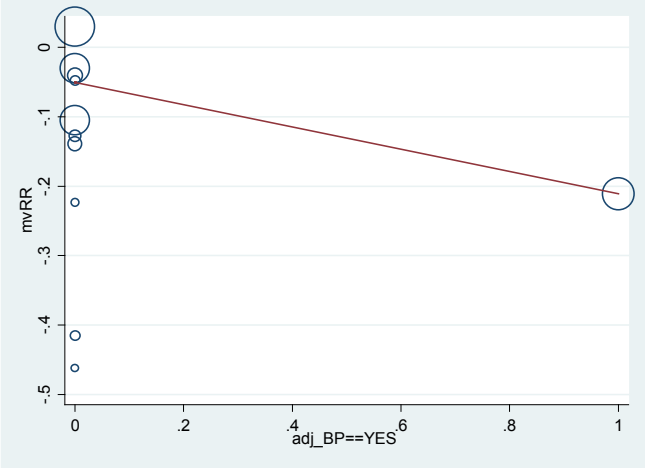
adj_tcorLDL: adjusted for dyslipidaemia; ALA: alpha-linolenic acid; CVD: cardiovascular disease; mvRR: multivariable risk ratio.

Fig. 96n. Meta-regression of ALA and CVD mortality; dyslipidaemia adjustment; Panel B – subgroup analysis (yes/no)



ALA: alpha-linolenic acid; CHS: Cardiovascular Health Study; CI: confidence interval; CVD: cardiovascular disease; ES: effect size; HPFS: Health Professionals Follow-up Study; InCHIANTI: Invecchiare in Chianti; KIHD: Kuopio Ischemic Heart Disease Risk Factor Study; M: male; MRFIT: Multiple Risk Factor Intervention Trial; NHANES: National Health and Nutrition Examination Survey; NHS I: Nurses' Health Study I; NIH-AARP: National Institutes of Health American Association of Retired Persons Diet and Health Study; PREDIMED: Prevención con Dieta Mediterránea; PUFA: polyunsaturated fatty acids; SCHS: Singapore Chinese Health Study; W: women; WHS: Women's Health Study.

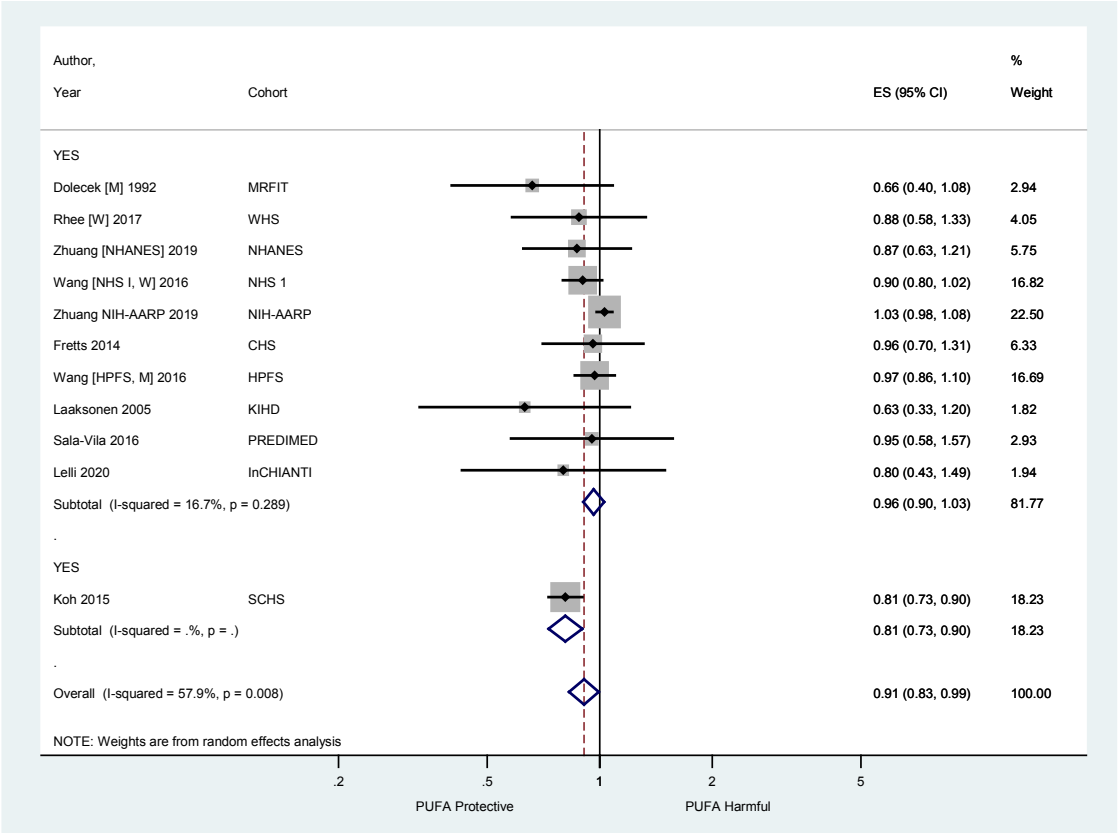
Fig. 96o. Meta-regression of ALA and CVD mortality; blood pressure adjustment; Panel A – effect size



The effect size was not associated with adjustment for a measure of blood pressure in the final model (*P*=0.11).

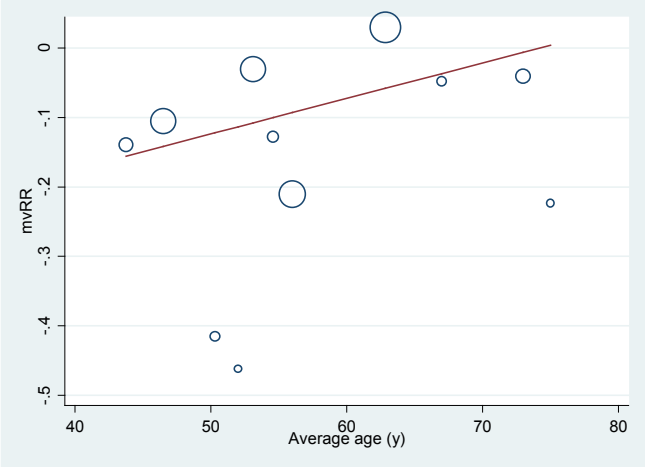
adj_BP: adjusted for blood pressure; ALA: alpha-linolenic acid; CVD: cardiovascular disease; mvRR: multivariable risk ratio.

Fig. 96p. Meta-regression of ALA and CVD mortality; blood pressure adjustment; Panel B – subgroup analysis (yes/no)



ALA: alpha-linolenic acid; CHS: Cardiovascular Health Study; CI: confidence interval; CVD: cardiovascular disease; ES: effect size; HPFS: Health Professionals Follow-up Study; InCHIANTI: Invecchiare in Chianti; KIHD: Kuopio Ischemic Heart Disease Risk Factor Study; M: male; MRFIT: Multiple Risk Factor Intervention Trial; NHANES: National Health and Nutrition Examination Survey; NHS I: Nurses' Health Study I; NIH-AARP: National Institutes of Health American Association of Retired Persons Diet and Health Study; PREDIMED: Prevención con Dieta Mediterránea; PUFA: polyunsaturated fatty acids; SCHS: Singapore Chinese Health Study; W: women; WHS: Women's Health Study.

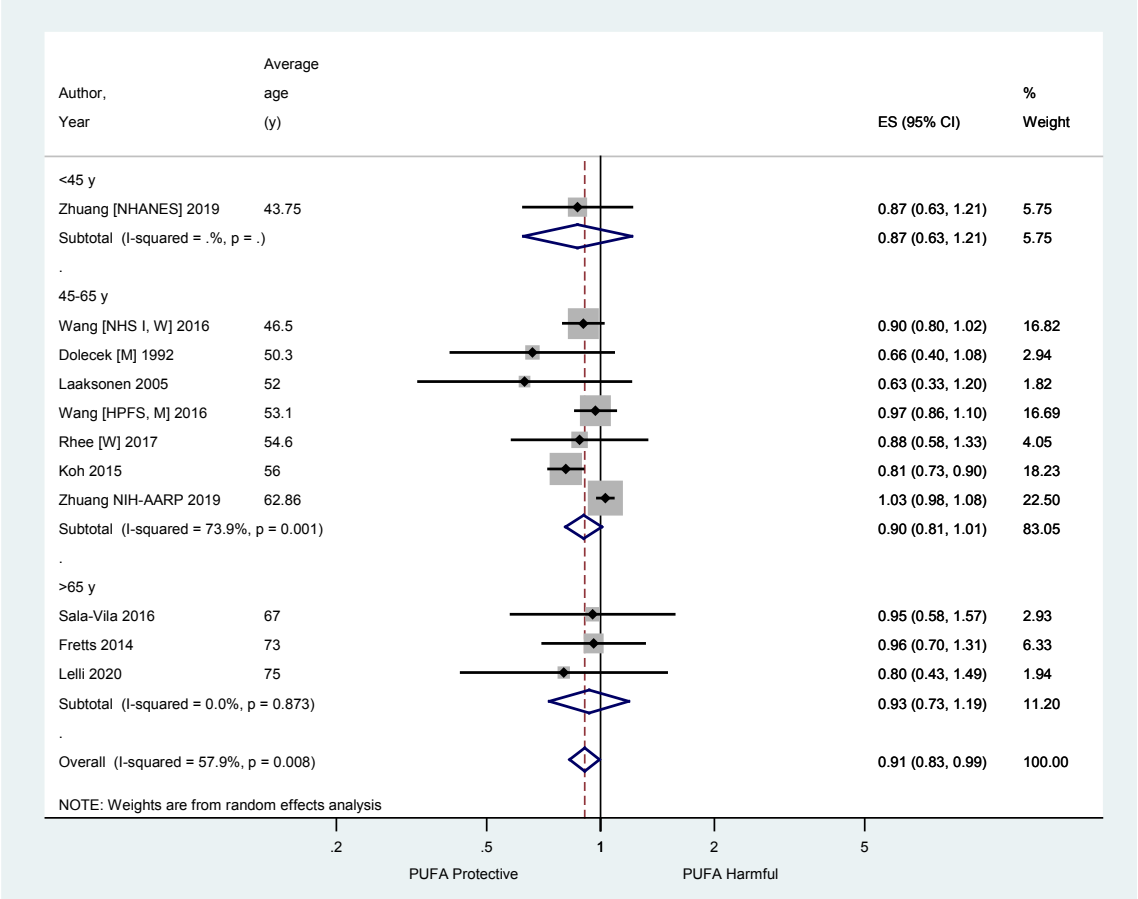
Fig. 96q. Meta-regression of ALA and CVD mortality; age; Panel A – effect size



The effect size was not associated with adjustment for average age of the study sample in the final model (P=0.36).

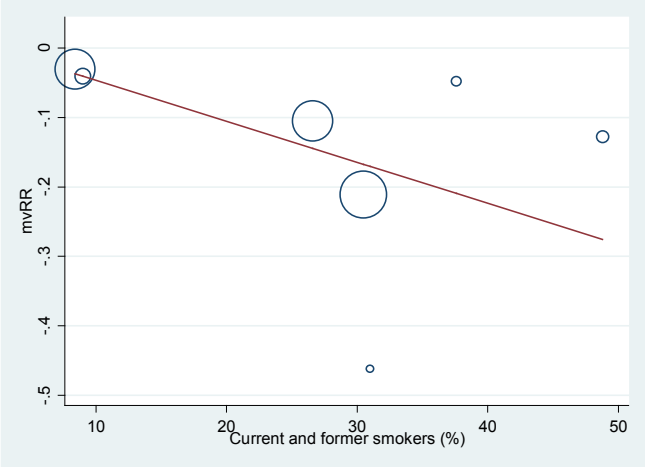
ALA: alpha-linolenic acid; CVD: cardiovascular disease; mvRR: multivariable risk ratio; y: years.

Fig. 96r. Meta-regression of ALA and CVD mortality; age; Panel B – subgroup analysis (age group)



ALA: alpha-linolenic acid; CI: confidence interval; CVD: cardiovascular disease; ES: effect size; HPFS: Health Professionals Follow-up Study; M: male; NHANES: National Health and Nutrition Examination Survey; NHS I: Nurses' Health Study I; NIH-AARP: National Institutes of Health American Association of Retired Persons Diet and Health Study; PUFA: polyunsaturated fatty acids; W: women; y: years.

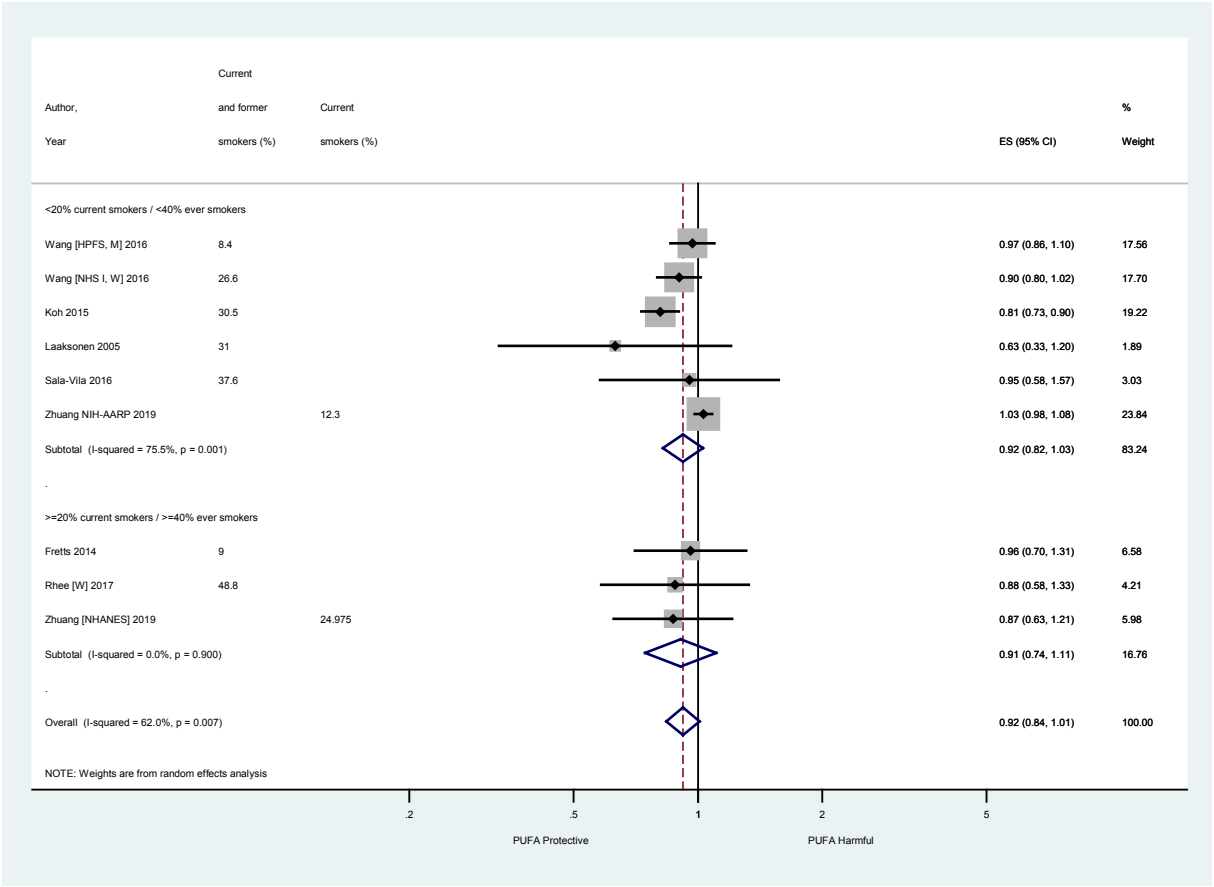
Fig. 96s. Meta-regression of ALA and CVD mortality; smoking; Panel A – effect size



The effect size was not associated with adjustment for smoking history of the study sample in the final model (*P*=0.12). High smokers ≥40% current/former or >20% current.

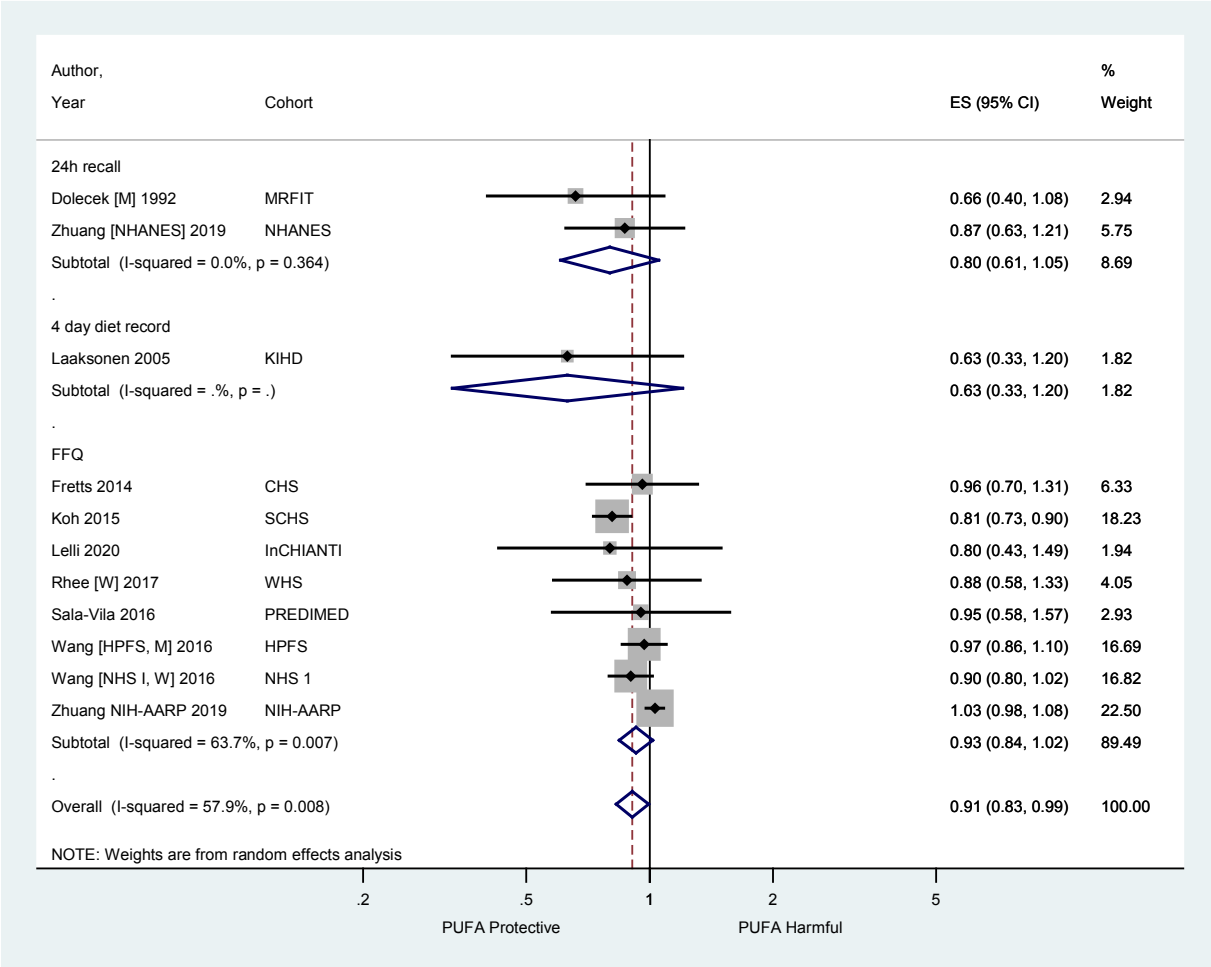
ALA: alpha-linolenic acid; CVD: cardiovascular disease; mvRR: multivariable risk ratio.

Fig. 96t. Meta-regression of ALA and CVD mortality; smoking; Panel B – subgroup analysis



ALA: alpha-linolenic acid; CI: confidence interval; CVD: cardiovascular disease; ES: effect size; HPFS: Health Professionals Follow-up Study; M: male; NHANES: National Health and Nutrition Examination Survey; NHS I: Nurses' Health Study I; NIH-AARP: National Institutes of Health American Association of Retired Persons Diet and Health Study; PUFA: polyunsaturated fatty acids; W: women.

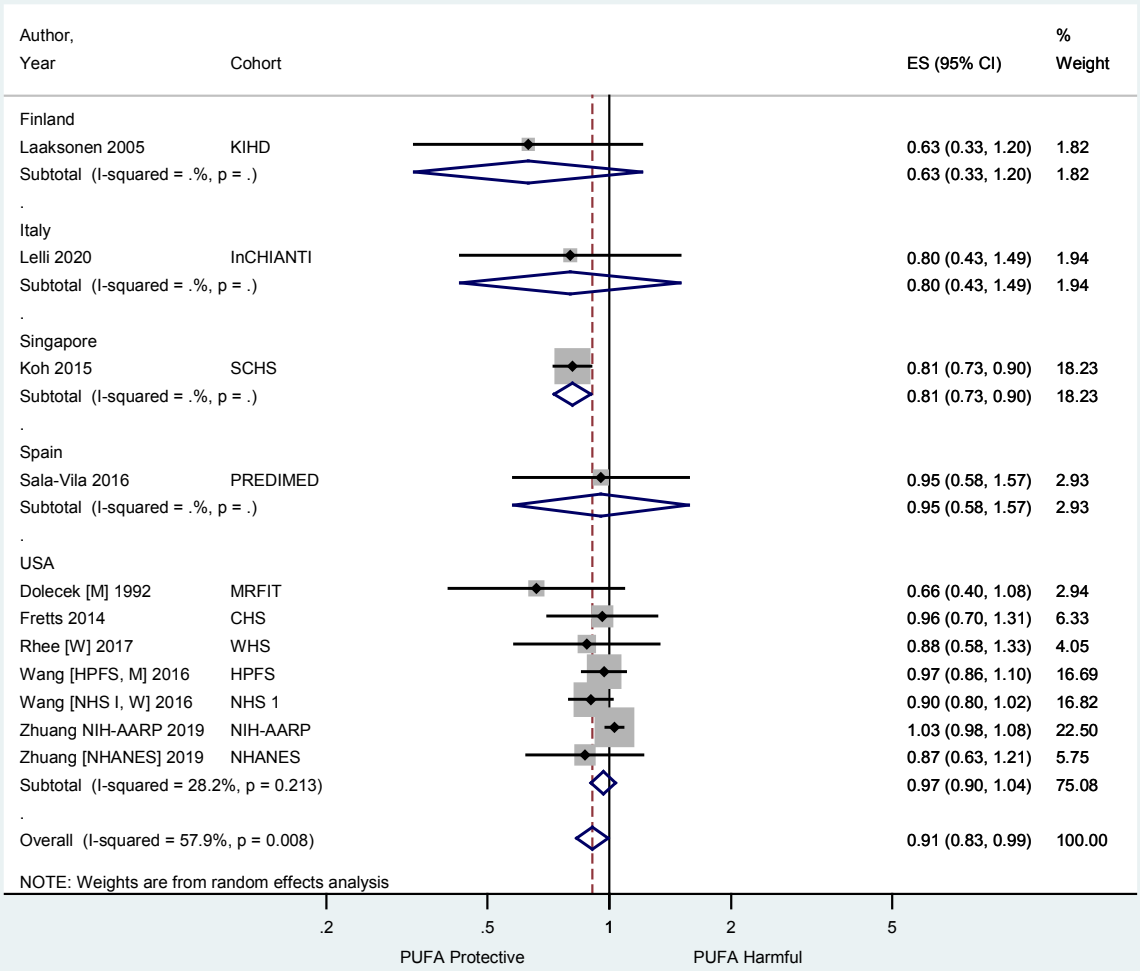
Fig. 96u. Meta-regression of ALA and CVD mortality; diet assessment method; subgroup analysis



ALA: alpha-linolenic acid; CHS: Cardiovascular Health Study; CI: confidence interval; CVD: cardiovascular disease; ES: effect size; FFQ: food frequency questionnaire; h: hour; HPFS: Health Professionals Follow-up Study; InCHIANTI: Invecchiare in Chianti; KIHD: Kuopio Ischemic Heart Disease Risk Factor Study; M: male; MRFIT: Multiple Risk Factor Intervention Trial; NHANES: National Health and Nutrition Examination Survey; NHS I: Nurses' Health Study I; NIH-AARP: National Institutes of Health American Association of Retired Persons Diet and Health Study; PREDIMED: Prevención con Dieta Mediterránea; PUFA: polyunsaturated fatty acids; SCHS: Singapore Chinese Health Study; W: women; WHS: Women's Health Study.

There was evidence of heterogeneity of effect size by method of diet assessment (P_{het}=0.003). Because the predictor variable had more than 2 levels, it is not appropriate to show the continuous meta-regression line; therefore, we present the "by country" estimates separately.

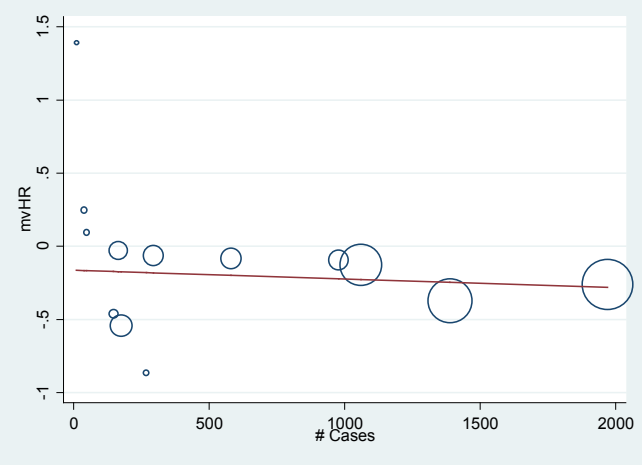
Fig. 96v. Meta-regression of ALA and CVD mortality; country of conduct; subgroup analysis



ALA: alpha-linolenic acid; CHS: Cardiovascular Health Study; CI: confidence interval; CVD: cardiovascular disease; ES: effect size; HPFS: Health Professionals Follow-up Study; InCHIANTI: Invecchiare in Chianti; KIHD: Kuopio Ischemic Heart Disease Risk Factor Study; M: male; MRFIT: Multiple Risk Factor Intervention Trial; NHANES: National Health and Nutrition Examination Survey; NHS I: Nurses' Health Study I; NIH-AARP: National Institutes of Health American Association of Retired Persons Diet and Health Study; PREDIMED: Prevención con Dieta Mediterránea; PUFA: polyunsaturated fatty acids; SCHS: Singapore Chinese Health Study; USA: United States of America; W: women; WHS: Women's Health Study.

There was no evidence of heterogeneity of effect size by country of conduct (P_{het}=0.35). Because the predictor variable had more than 2 levels, it is not appropriate to show the continuous meta-regression line; therefore, we present the "by country" estimates separately.

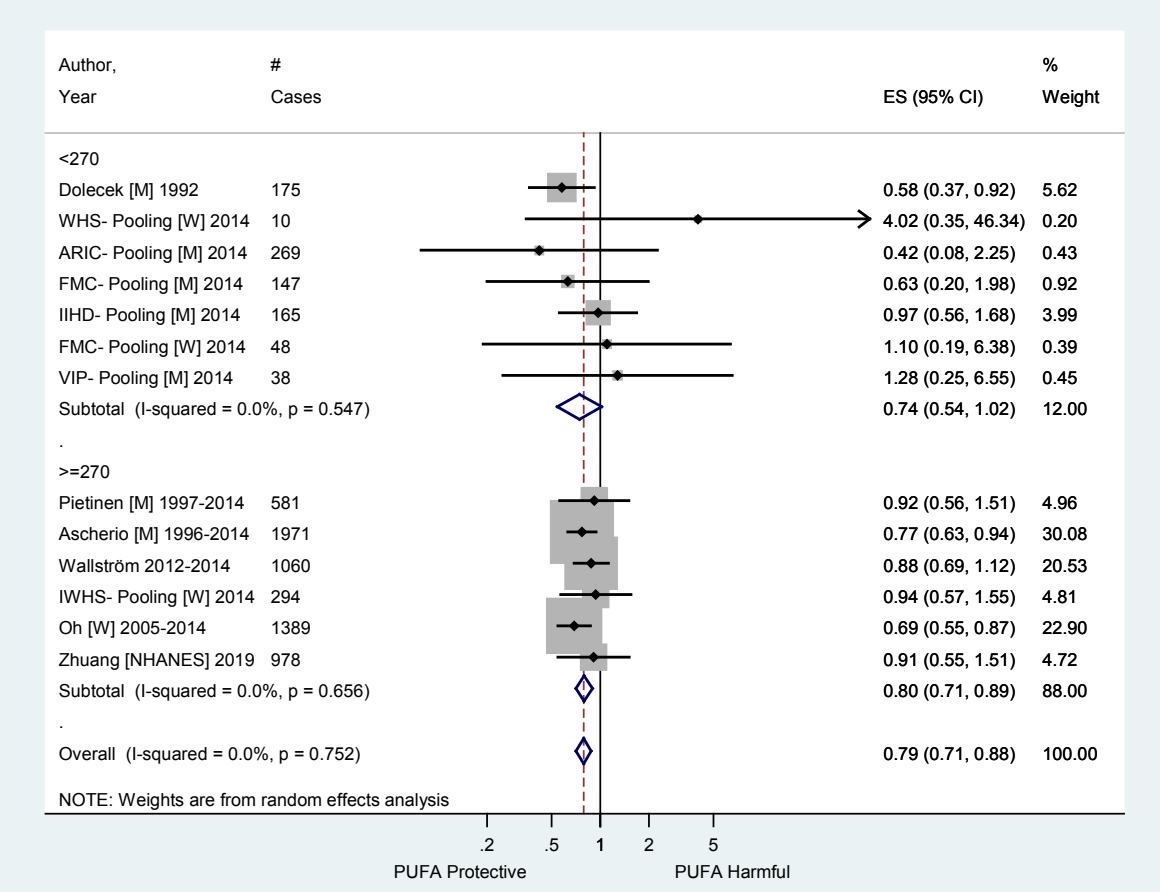
Fig. 97a. Meta-regression of LA and CHD mortality; number of cases; Panel A – effect size



The number of cases in the study was not associated with the effect estimate (*P*=0.53)

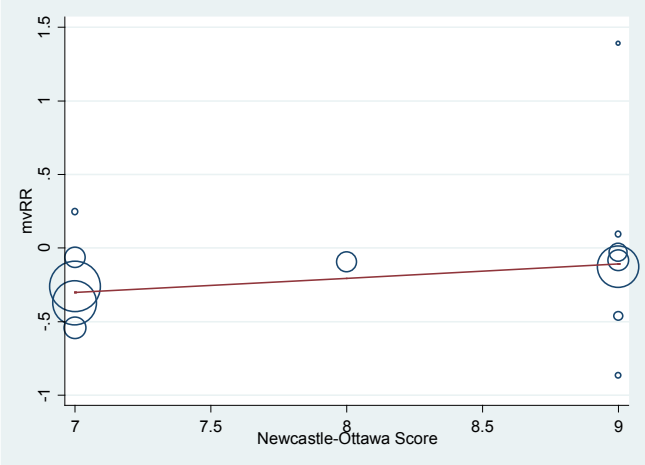
#: number; CHD: coronary heart disease; CI: confidence interval; LA: linoleic acid; mvHR: multivariable hazard ratio; mvRR: multivariable risk ratio.

Fig. 97b. Meta-regression of LA and CHD mortality; number of cases; Panel B – subgroup analysis by number of cases (median *n*=270)



#: number; ARIC: Atherosclerosis Risk in Communities; CHD: coronary heart disease; CI: confidence interval; ES: effect size; FMC: Finnish Mobile Health Clinic; IIHD: Israeli Ischemic Heart Disease; IWHS: Iowa Women's Health Study; LA: linoleic acid; M: male; NHANES: National Health and Nutrition Examination Survey; PUFA: polyunsaturated fatty acids; VIP: Västerbotten Intervention Program; W: women; WHS: Women's Health Study.

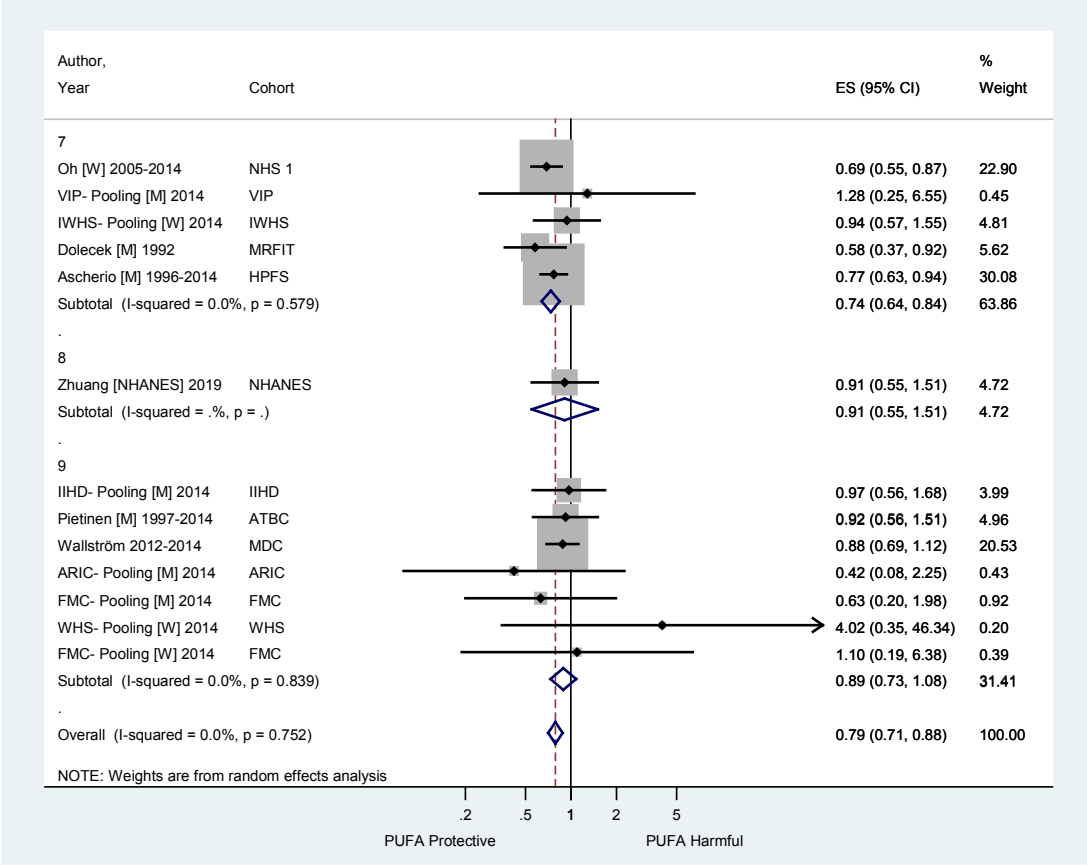
Fig. 97c. Meta-regression of LA and CHD mortality; NOS assessment; Panel A – effect size



The effect size was not associated with the NOS quality score (P=0.14).

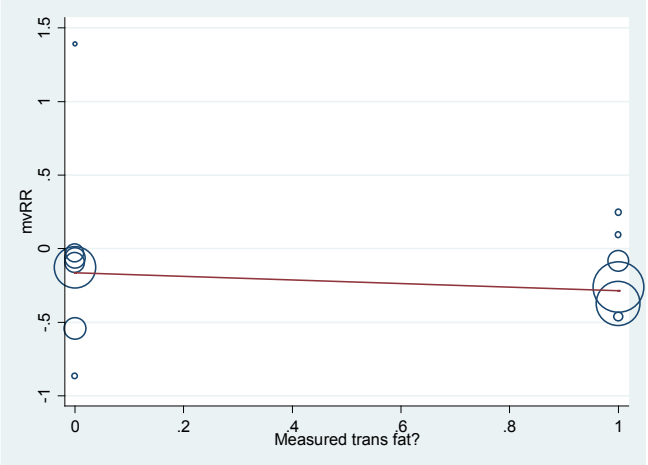
CHD: coronary heart disease; LA: linoleic acid; mvRR: multivariable risk ratio; NOS: Newcastle-Ottawa Scale.

Fig. 97d. Meta-regression of LA and CHD mortality; NOS assessment; Panel B – subgroup analysis by NOS score



ARIC: Atherosclerosis Risk in Communities; ATBC: Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study; CHD: coronary heart disease; CI: confidence interval; ES: effect size; FMC: Finnish Mobile Health Clinic; HPFS: Health Professionals Follow-up Study; IIHD: Israeli Ischemic Heart Disease; IWHS: Iowa Women's Health Study; LA: linoleic acid; M: male; MDC: Malmö Diet and Cancer; MRFIT: Multiple Risk Factor Intervention Trial; NHANES: National Health and Nutrition Examination Survey; NHS 1: Nurses' Health Study 1; NOS: Newcastle-Ottawa Scale; PUFA: polyunsaturated fatty acids; VIP: Västerbotten Intervention Program; W: women; WHS: Women's Health Study.

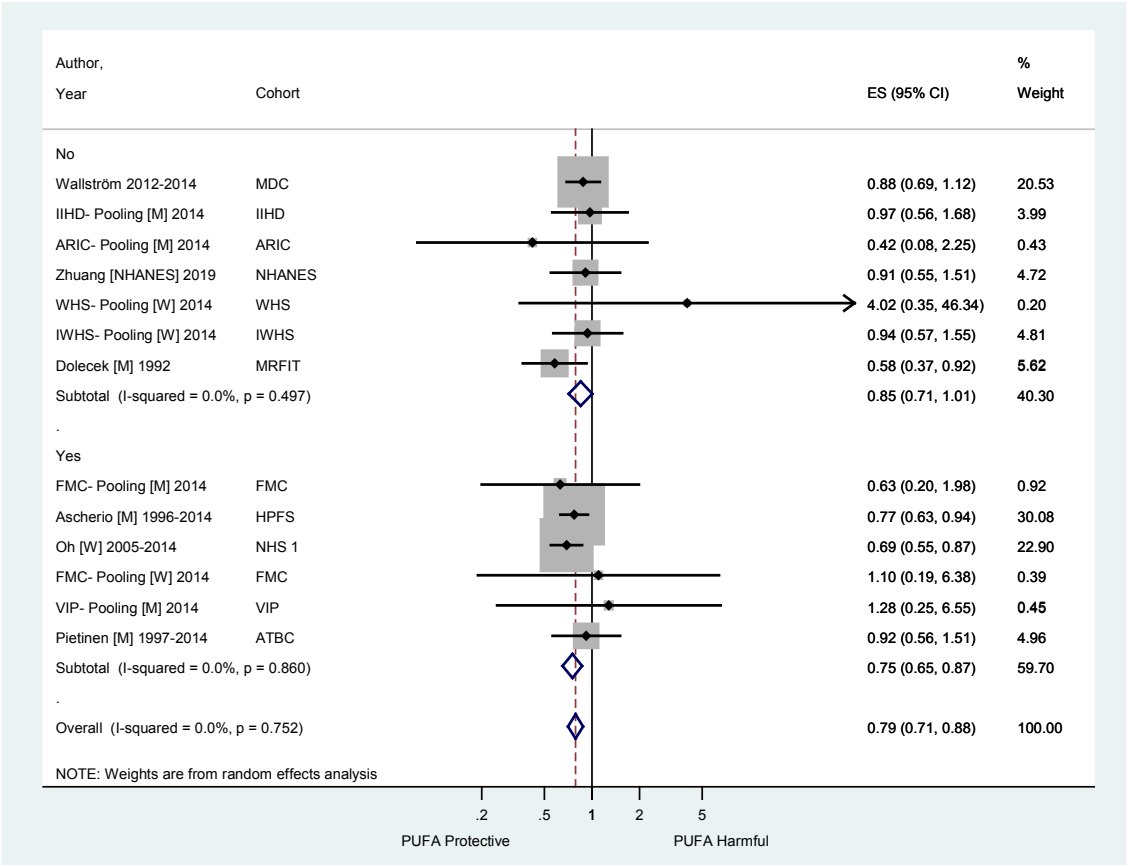
Fig. 97e. Meta-regression of LA and CHD mortality; TFA assessment; Panel A – effect size



The effect size was not associated with adjustment for TFA assessment in the final model (*P*=0.31).

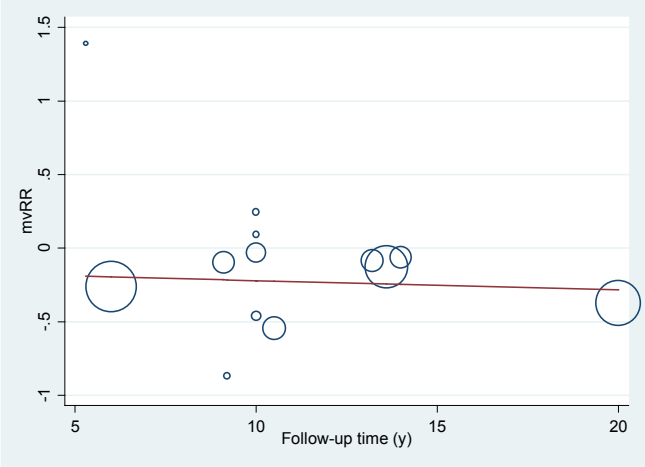
CHD: coronary heart disease; LA: linoleic acid; mvRR: multivariable risk ratio; TFA: trans-fatty acids.

Fig. 97f. Meta-regression of LA and CHD mortality; TFA assessment; Panel B – subgroup analysis (yes/no)



ARIC: Atherosclerosis Risk in Communities; ATBC: Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study; CHD: coronary heart disease; CI: confidence interval; ES: effect size; FMC: Finnish Mobile Health Clinic; HPFS: Health Professionals Follow-up Study; IIHD: Israeli Ischemic Heart Disease; IWHS: Iowa Women's Health Study; LA: linoleic acid; M: male; MDC: Malmö Diet and Cancer; MRFIT: Multiple Risk Factor Intervention Trial; NHANES: National Health and Nutrition Examination Survey; NHS 1: Nurses' Health Study 1; PUFA: polyunsaturated fatty acids; TFA: trans-fatty acids; VIP: Västerbotten Intervention Program; W: women; WHS: Women's Health Study.

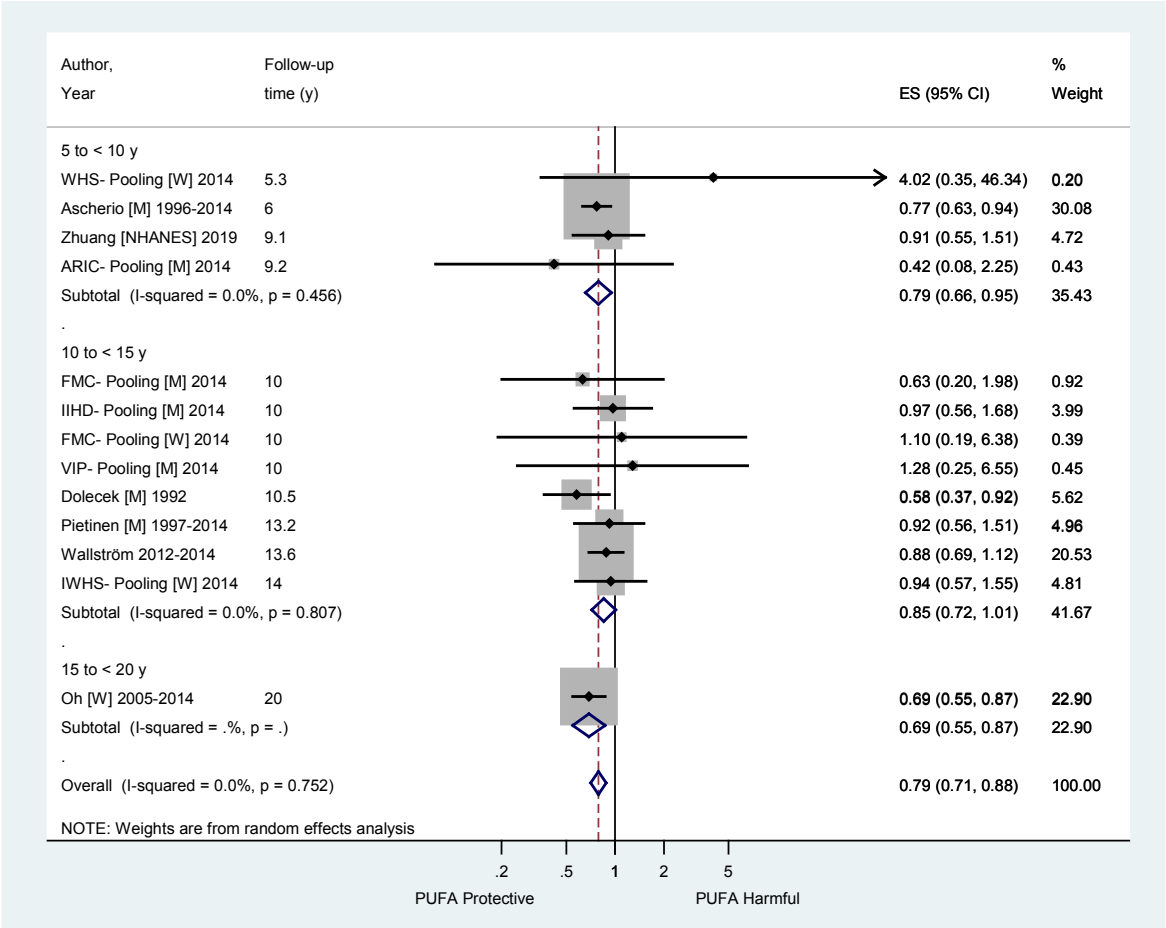
Fig. 97g. Meta-regression of LA and CHD mortality; follow-up time; Panel A – effect size



The effect size was not associated with adjustment for follow-up time in the final model (*P*=0.59).

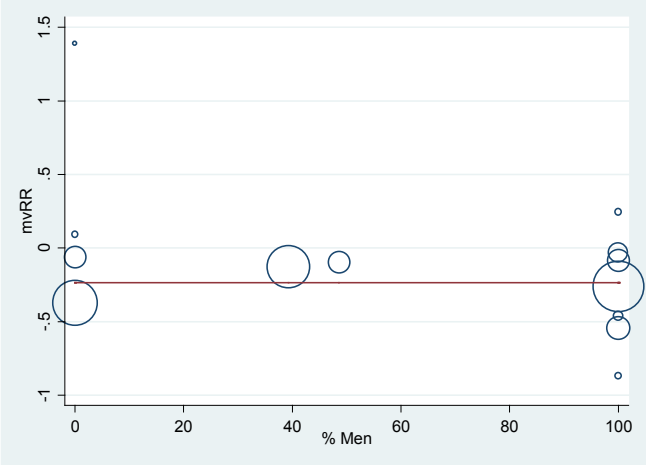
CHD: coronary heart disease; LA: linoleic acid; mvRR: multivariable risk ratio; y: years.

Fig. 97h. Meta-regression of LA and CHD mortality; follow-up time; Panel B – subgroup analysis



ARIC: Atherosclerosis Risk in Communities; CHD: coronary heart disease; CI: confidence interval; ES: effect size; FMC: Finnish Mobile Health Clinic; IIHD: Israeli Ischemic Heart Disease; IWHS: Iowa Women's Health Study; LA: linoleic acid; M: male; NHANES: National Health and Nutrition Examination Survey; PUFA: polyunsaturated fatty acids; VIP: Västerbotten Intervention Program; W: women; WHS: Women's Health Study; y: years.

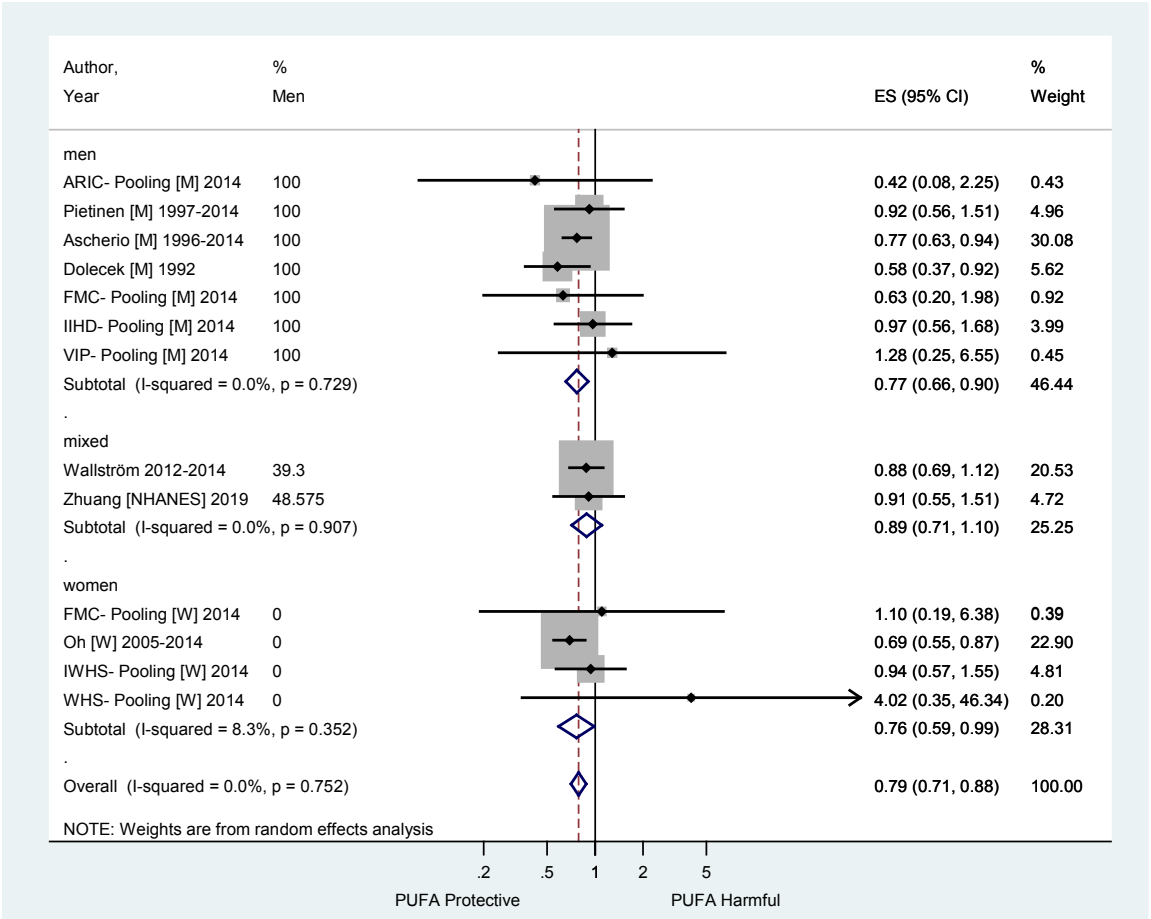
Fig. 97i. Meta-regression of LA and CHD mortality; sex; Panel A – effect size



The effect size was not associated with adjustment for follow-up time and percentage of men in the study in the final model (*P*=0.99).

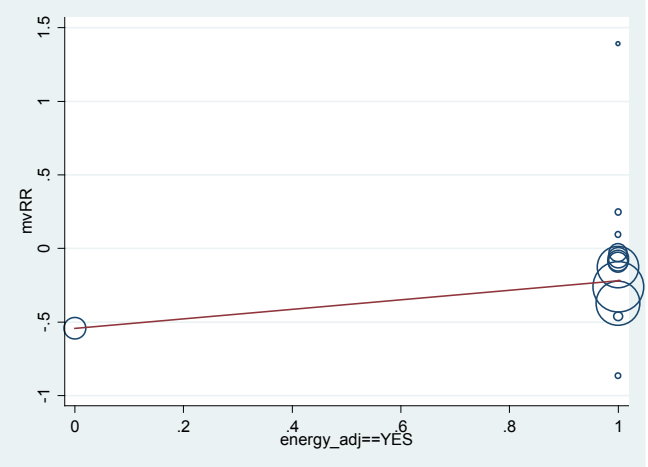
CHD: coronary heart disease; LA: linoleic acid; mvRR: multivariable risk ratio.

Fig. 97j. Meta-regression of LA and CHD mortality; sex; Panel B – subgroup analysis



ARIC: Atherosclerosis Risk in Communities; CHD: coronary heart disease; CI: confidence interval; ES: effect size; FMC: Finnish Mobile Health Clinic; IIHD: Israeli Ischemic Heart Disease; IWHS: Iowa Women's Health Study; LA: linoleic acid; M: male; NHANES: National Health and Nutrition Examination Survey; PUFA: polyunsaturated fatty acids; VIP: Västerbotten Intervention Program; W: women; WHS: Women's Health Study.

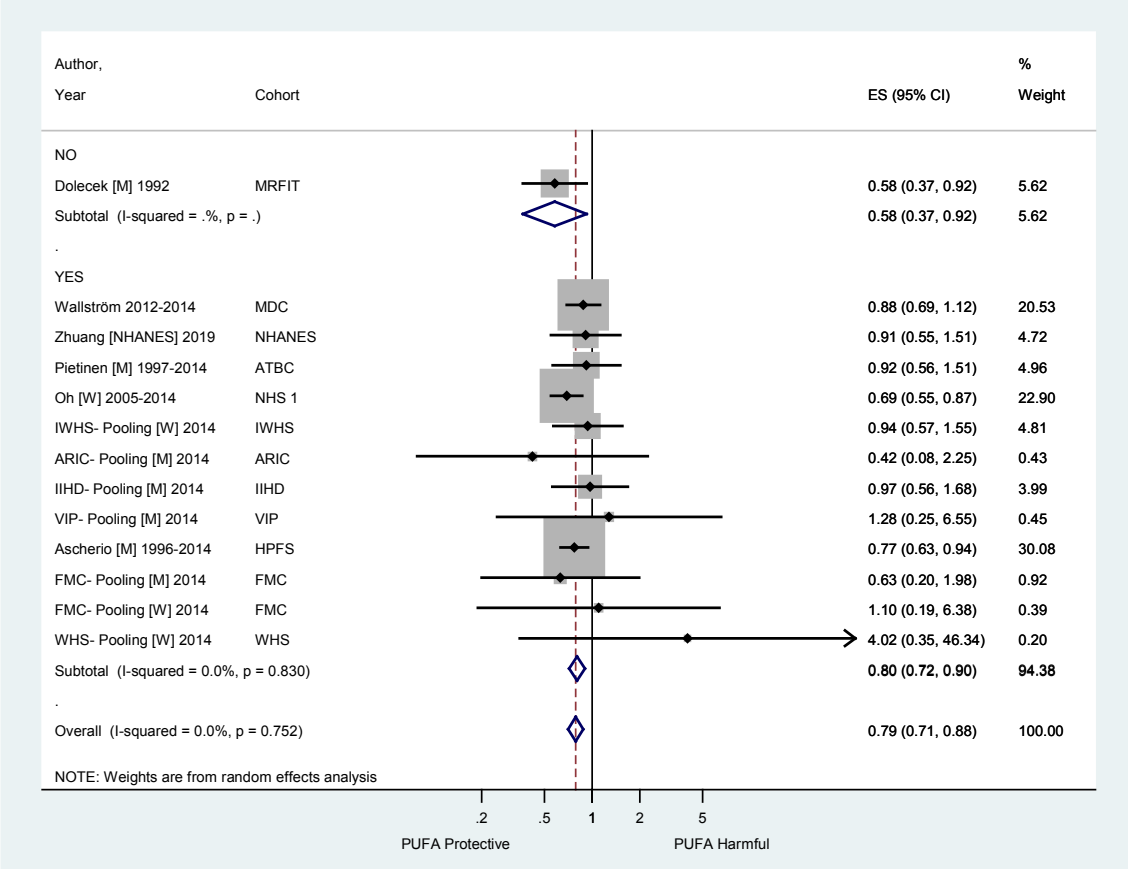
Fig. 97k. Meta-regression of LA and CHD mortality; energy adjustment; Panel A – effect size



The effect size was not associated with adjustment for energy in the final model (*P*=0.21).

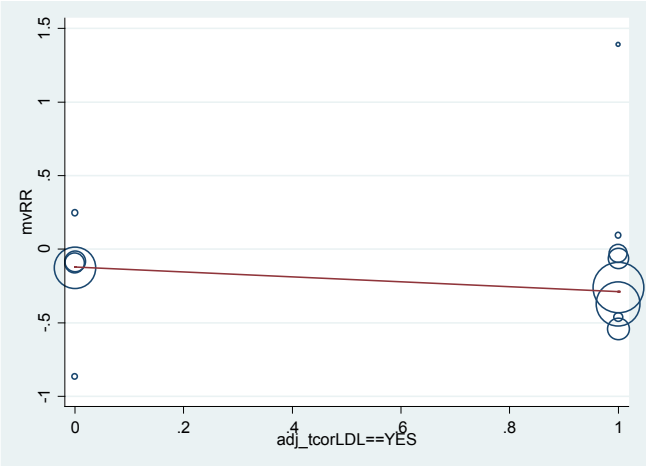
CHD: coronary heart disease; energy_adj: adjusted for energy; LA: linoleic acid; mvRR: multivariable risk ratio.

Fig. 97l. Meta-regression of LA and CHD mortality; energy adjustment; Panel B – subgroup analysis (yes/no)



ARIC: Atherosclerosis Risk in Communities; ATBC: Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study; CHD: coronary heart disease; CI: confidence interval; ES: effect size; FMC: Finnish Mobile Health Clinic; HPFS: Health Professionals Follow-up Study; IIHD: Israeli Ischemic Heart Disease; IWHS: Iowa Women's Health Study; LA: linoleic acid; M: male; MDC: Malmö Diet and Cancer; MRFIT: Multiple Risk Factor Intervention Trial; NHANES: National Health and Nutrition Examination Survey; NHS 1: Nurses' Health Study 1; PUFA: polyunsaturated fatty acids; VIP: Västerbotten Intervention Program; W: women; WHS: Women's Health Study.

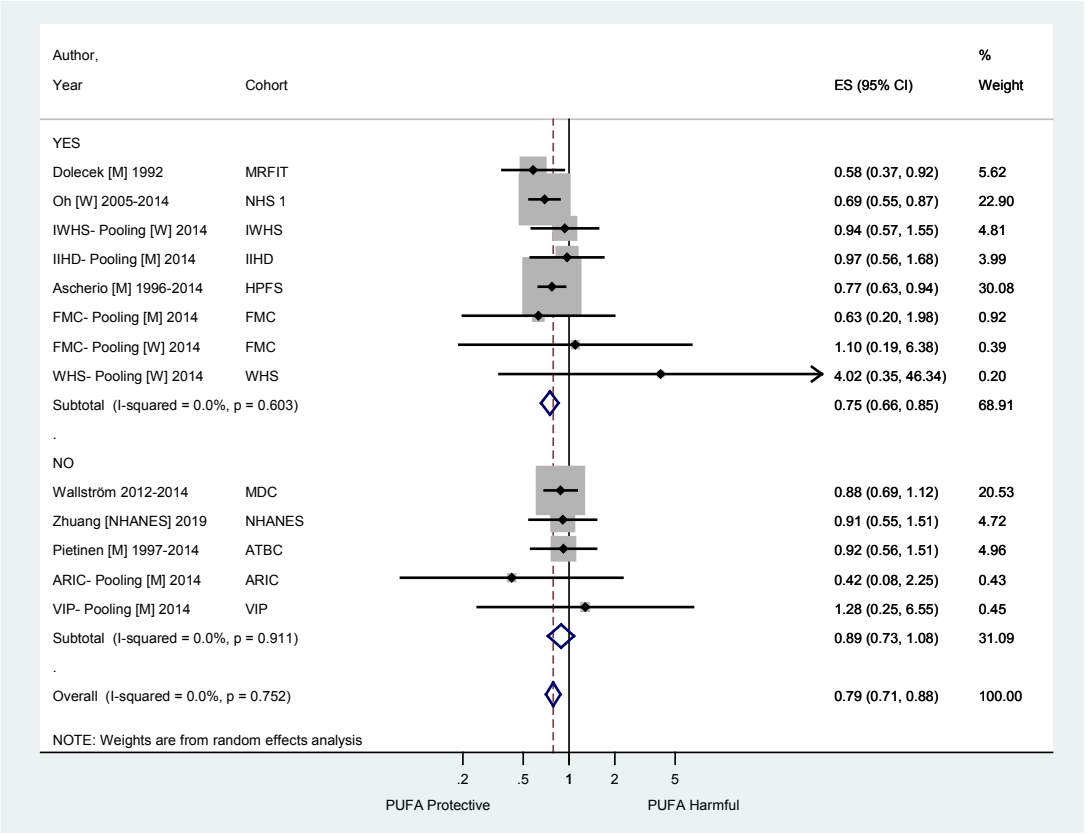
Fig. 97m. Meta-regression of LA and CHD mortality; dyslipidaemia adjustment; Panel A – effect size



The effect size was not associated with adjustment for a measure of dyslipidaemia in the final model (*P*=0.19).

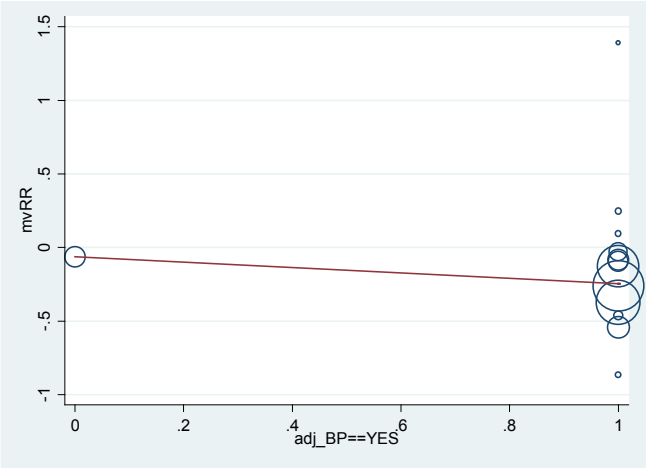
adj_tcorLDL: adjusted for dyslipidaemia; CHD: coronary heart disease; LA: linoleic acid; mvRR: multivariable risk ratio.

Fig. 97n. Meta-regression of LA and CHD mortality; dyslipidaemia adjustment; Panel B – subgroup analysis (yes/no)



ARIC: Atherosclerosis Risk in Communities; ATBC: Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study; CHD: coronary heart disease; CI: confidence interval; ES: effect size; FMC: Finnish Mobile Health Clinic; HPFS: Health Professionals Follow-up Study; IIHD: Israeli Ischemic Heart Disease; IWHS: Iowa Women's Health Study; LA: linoleic acid; M: male; MDC: Malmö Diet and Cancer; MRFIT: Multiple Risk Factor Intervention Trial; NHANES: National Health and Nutrition Examination Survey; NHS 1: Nurses' Health Study 1; PUFA: polyunsaturated fatty acids; VIP: Västerbotten Intervention Program; W: women; WHS: Women's Health Study.

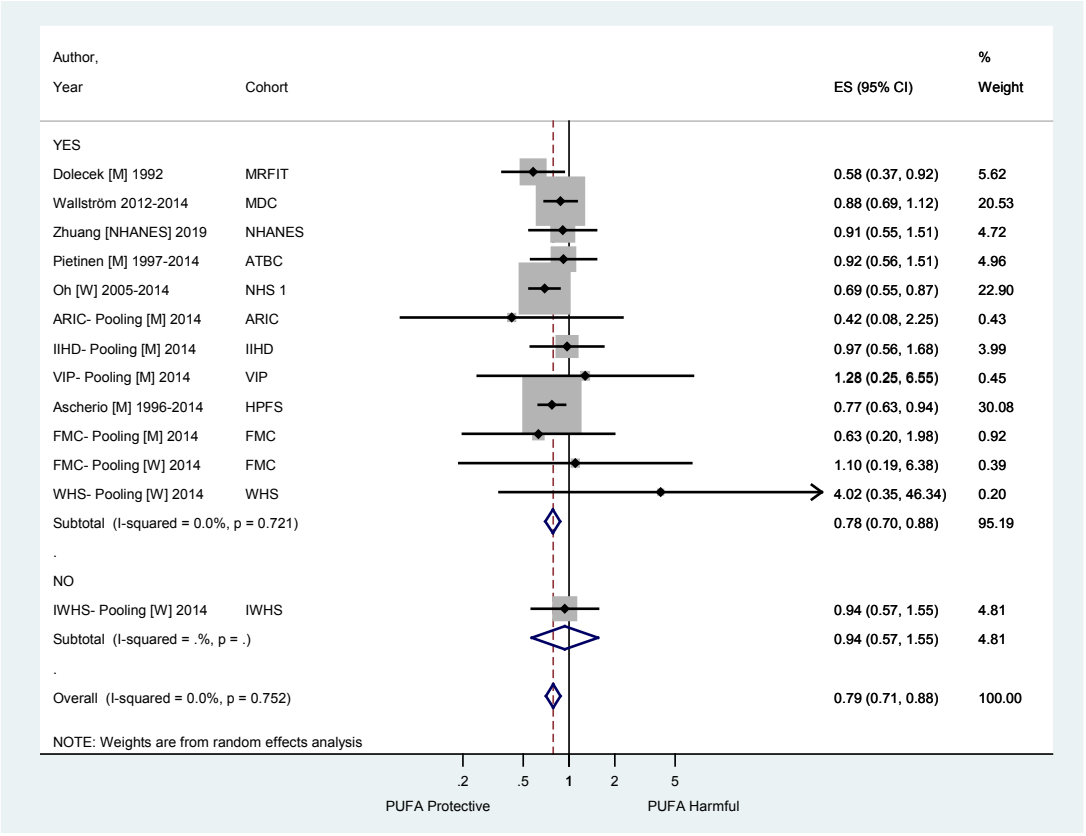
Fig. 97o. Meta-regression of LA and CHD mortality; blood pressure adjustment; Panel A – effect size



The effect size was not associated with adjustment for a measure of blood pressure in the final model (*P*=0.50).

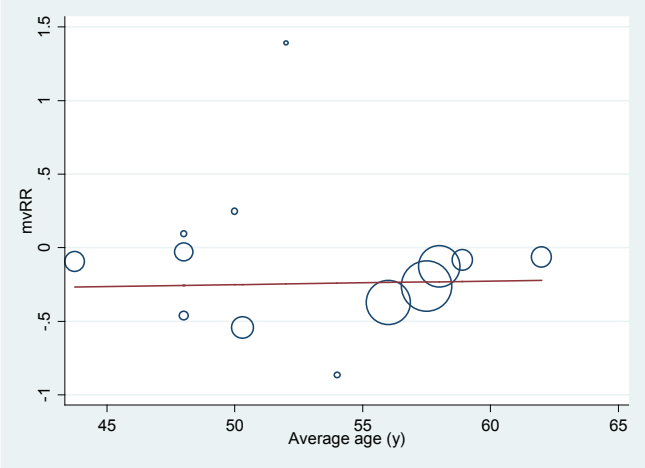
adj_BP: adjusted for blood pressure; CHD: coronary heart disease; LA: linoleic acid; mvRR: multivariable risk ratio.

Fig. 97p. Meta-regression of LA and CHD mortality; blood pressure adjustment; Panel B – subgroup analysis (yes/no)



ARIC: Atherosclerosis Risk in Communities; ATBC: Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study; CHD: coronary heart disease; CI: confidence interval; ES: effect size; FMC: Finnish Mobile Health Clinic; HPFS: Health Professionals Follow-up Study; IIHD: Israeli Ischemic Heart Disease; IWHS: Iowa Women's Health Study; LA: linoleic acid; M: male; MDC: Malmö Diet and Cancer; MRFIT: Multiple Risk Factor Intervention Trial; NHANES: National Health and Nutrition Examination Survey; NHS 1: Nurses' Health Study 1; PUFA: polyunsaturated fatty acids; VIP: Västerbotten Intervention Program; W: women; WHS: Women's Health Study.

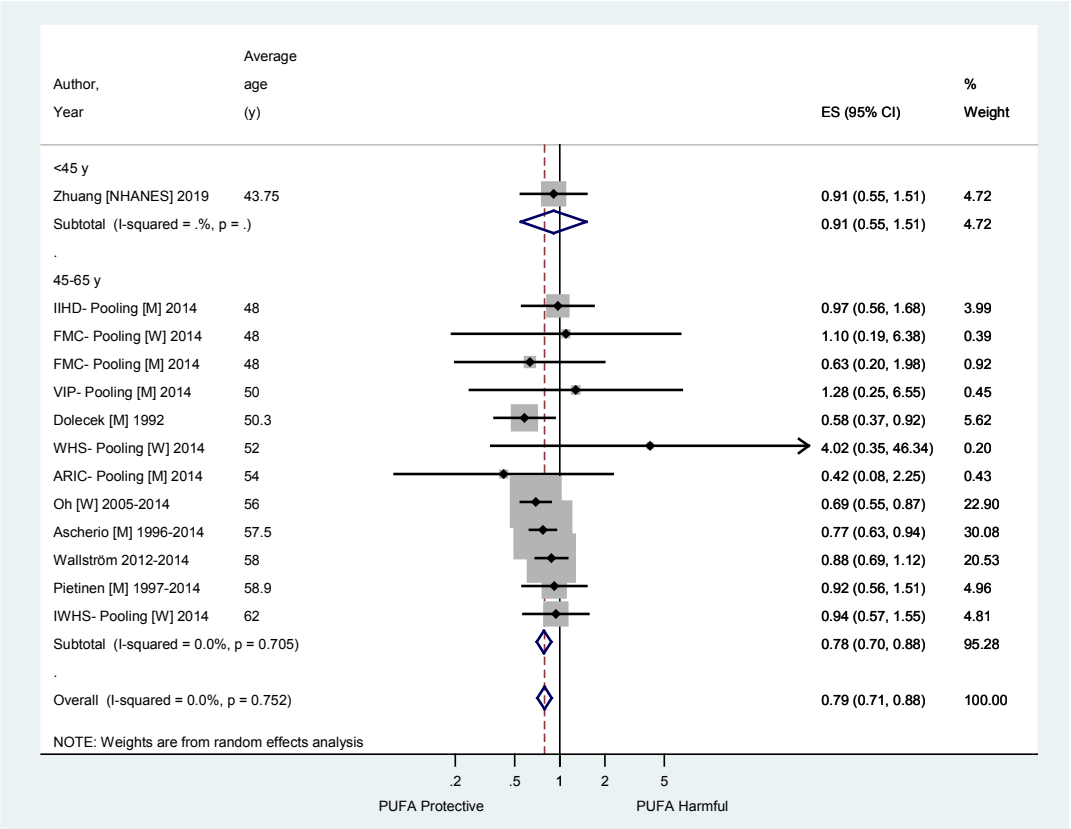
Fig. 97q. Meta-regression of LA and CHD mortality; age; Panel A – effect size



The effect size was not associated with adjustment for average age of the study sample in the final model (*P*=0.86).

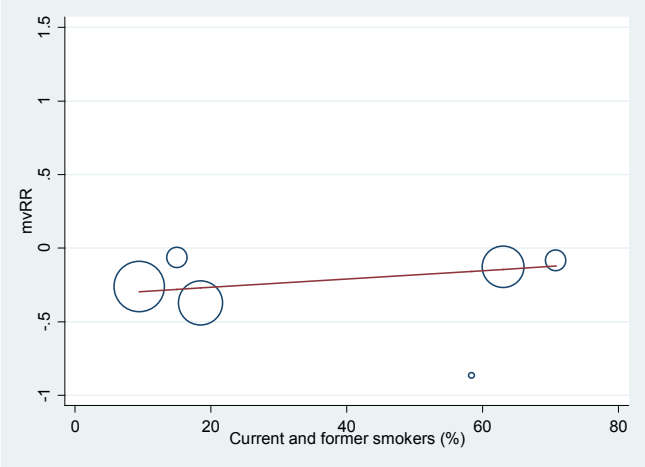
CHD: coronary heart disease; LA: linoleic acid; mvRR: multivariable risk ratio; y: years.

Fig. 97r. Meta-regression of LA and CHD mortality; age; Panel B – subgroup analysis (age group)



ARIC: Atherosclerosis Risk in Communities; CHD: coronary heart disease; CI: confidence interval; ES: effect size; FMC: Finnish Mobile Health Clinic; IIHD: Israeli Ischemic Heart Disease; IWHS: Iowa Women's Health Study; LA: linoleic acid; M: male; NHANES: National Health and Nutrition Examination Survey; PUFA: polyunsaturated fatty acids; VIP: Västerbotten Intervention Program; W: women; WHS: Women's Health Study; y: years.

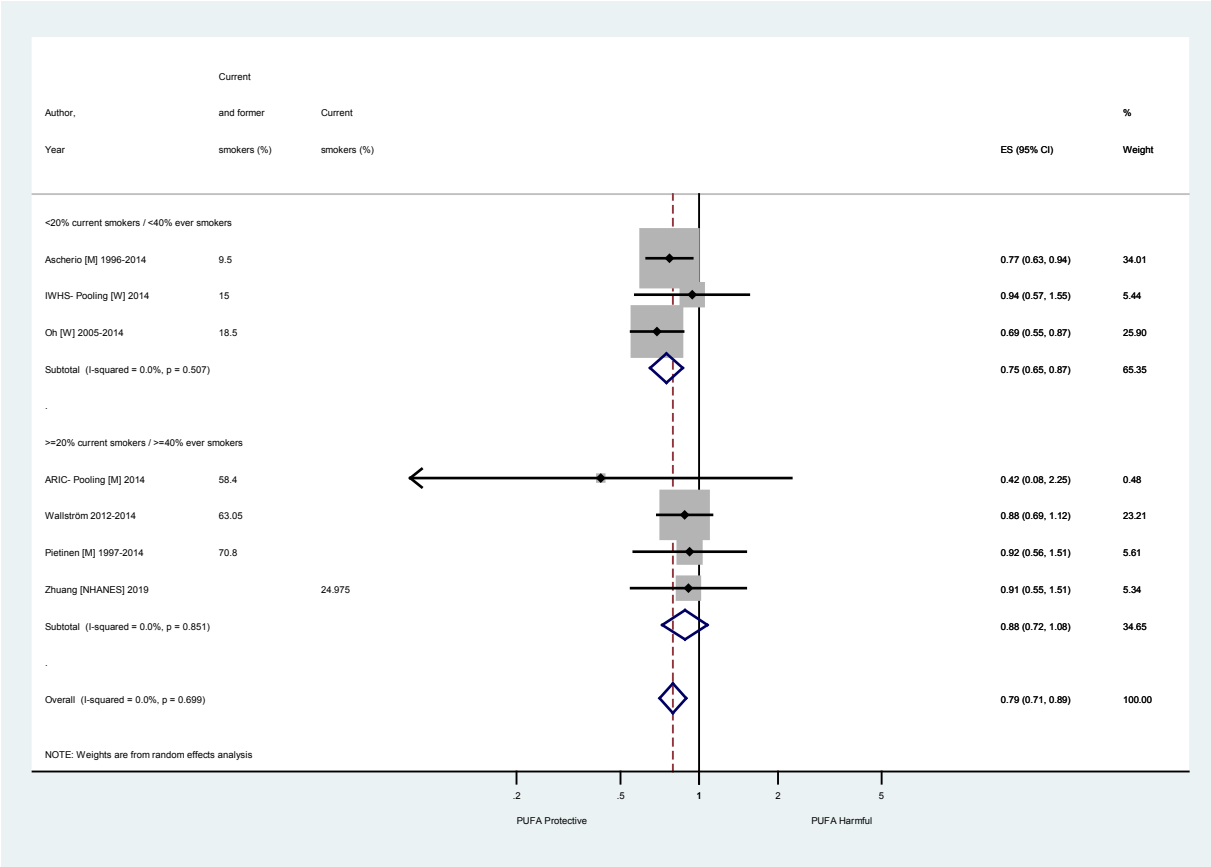
Fig. 97s. Meta-regression of LA and CHD mortality; smoking; Panel A – effect size



The effect size was not associated with adjustment for smoking history of the study sample in the final model (*P*=0.33). High smokers ≥40% current/former or >20% current.

CHD: coronary heart disease; LA: linoleic acid; mvRR: multivariable risk ratio.

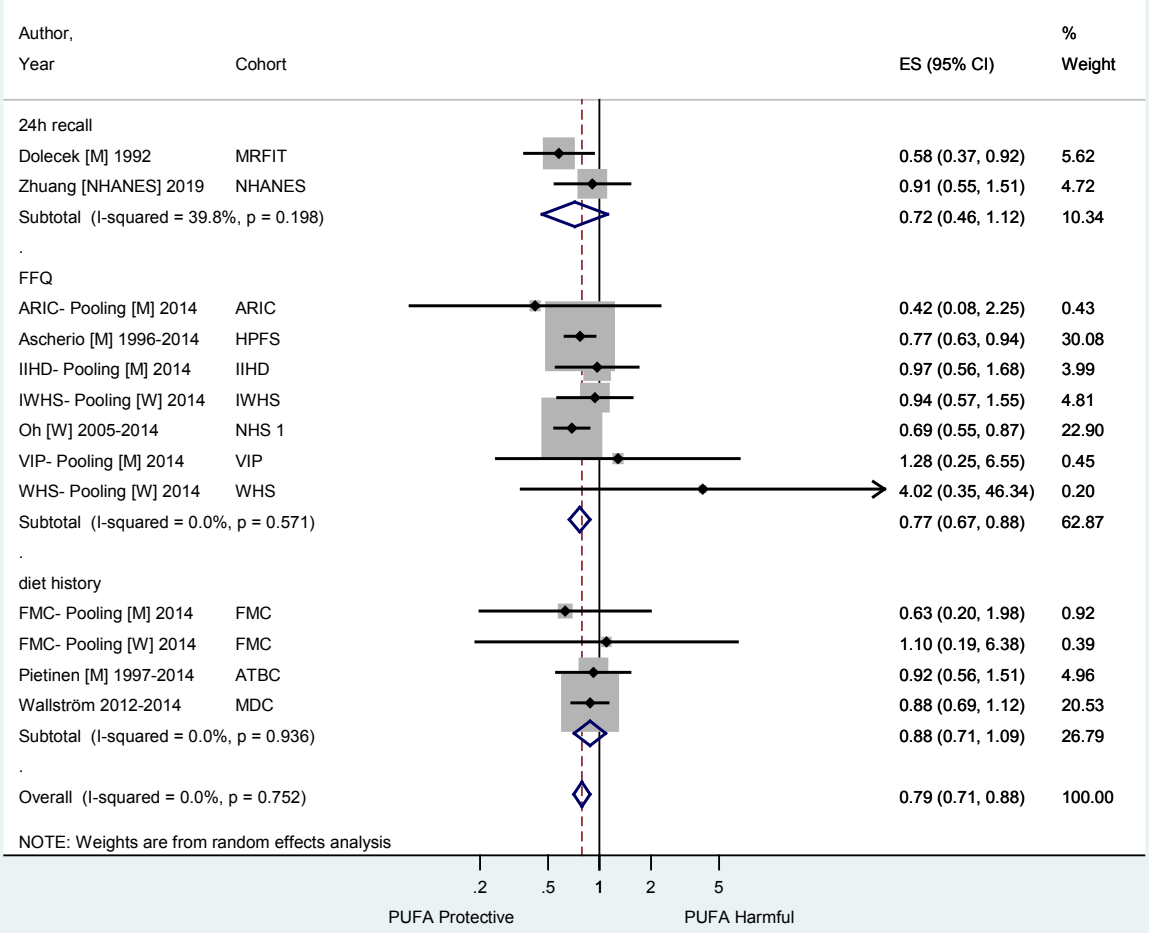
Fig. 97t. Meta-regression of LA and CHD mortality; smoking; Panel B – subgroup analysis



Smoking not reported in all studies.

ARIC: Atherosclerosis Risk in Communities; CHD: coronary heart disease; CI: confidence interval; ES: effect size; IWHS: Iowa Women's Health Study; LA: linoleic acid; M: male; NHANES: National Health and Nutrition Examination Survey; PUFA: polyunsaturated fatty acids; W: women.

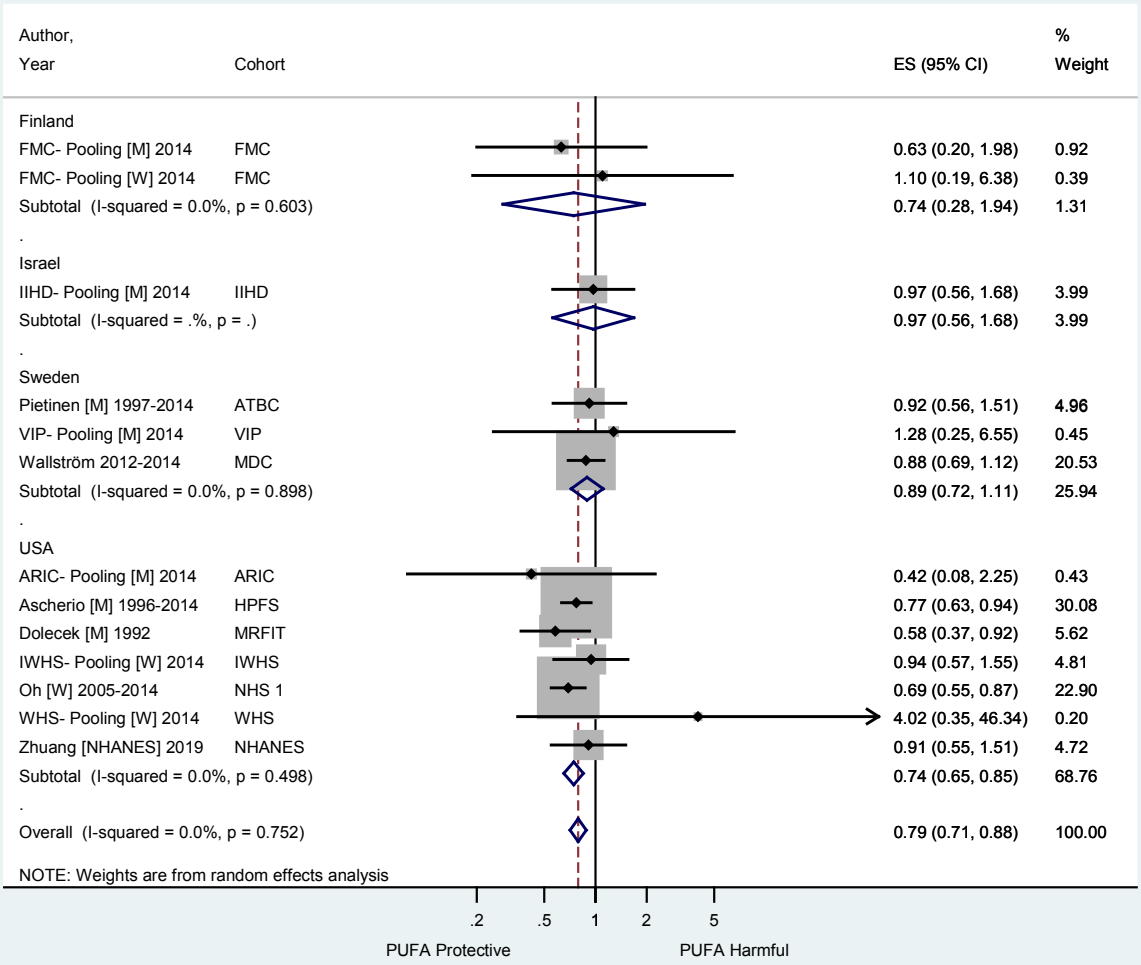
Fig. 97u. Meta-regression of LA and CHD mortality; diet assessment method; subgroup analysis



ARIC: Atherosclerosis Risk in Communities; ATBC: Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study; CHD: coronary heart disease; CI: confidence interval; ES: effect size; FFQ: food frequency questionnaire; FMC: Finnish Mobile Health Clinic; h: hour; HPFS: Health Professionals Follow-up Study; IIHD: Israeli Ischemic Heart Disease; IWHS: Iowa Women's Health Study; LA: linoleic acid; M: male; MDC: Malmö Diet and Cancer; MRFIT: Multiple Risk Factor Intervention Trial; NHANES: National Health and Nutrition Examination Survey; NHS 1: Nurses' Health Study 1; PUFA: polyunsaturated fatty acids; VIP: Västerbotten Intervention Program; W: women; WHS: Women's Health Study.

The effect size was not associated with adjustment for diet assessment method in the final model (P_{het}=0.49). Because the predictor variable had more than 2 levels, it is not appropriate to show the continuous meta-regression line; therefore, we present the "by diet assessment method" estimates separately.

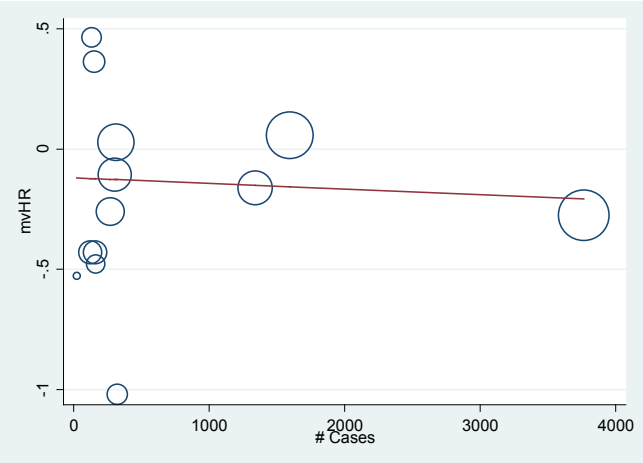
Fig. 97v. Meta-regression of LA and CHD mortality; country of conduct; subgroup analysis



ARIC: Atherosclerosis Risk in Communities; ATBC: Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study; CHD: coronary heart disease; CI: confidence interval; ES: effect size; FMC: Finnish Mobile Health Clinic; HPFS: Health Professionals Follow-up Study; IIHD: Israeli Ischemic Heart Disease; IWHS: Iowa Women's Health Study; LA: linoleic acid; M: male; MDC: Malmö Diet and Cancer; MRFIT: Multiple Risk Factor Intervention Trial; NHANES: National Health and Nutrition Examination Survey; NHS 1: Nurses' Health Study 1; PUFA: polyunsaturated fatty acids; USA: United States of America; VIP: Västerbotten Intervention Program; W: women; WHS: Women's Health Study.

There was no evidence of heterogeneity of effect size by country of conduct (P_{het}=0.50). Because the predictor variable had more than 2 levels, it is not appropriate to show the continuous meta-regression line; therefore, we present the "by country" estimates separately.

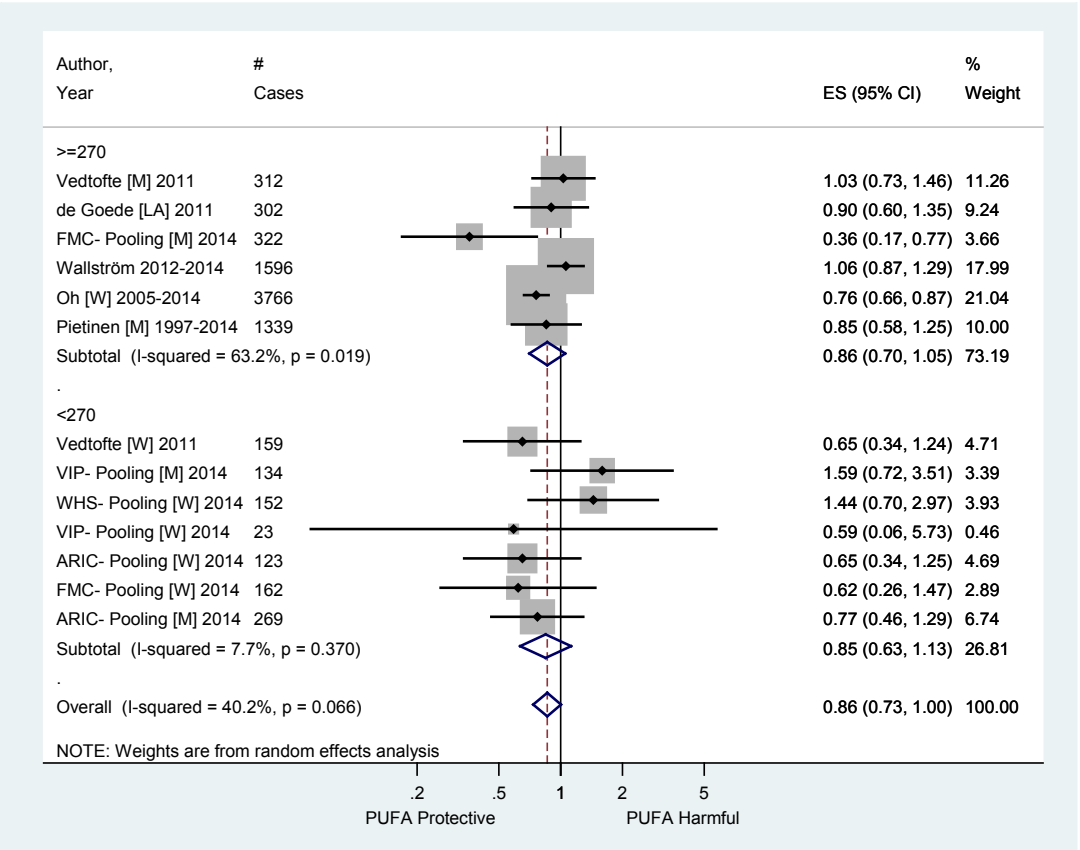
Fig. 98a.[1] Meta-regression of LA and total CHD; number of cases; Panel A – effect size



The number of cases in the study was not associated with the effect estimate (*P*=0.71).

#: number; CHD: coronary heart disease; CI: confidence interval; LA: linoleic acid; mvHR: multivariable hazard ratio; mvRR: multivariable risk ratio;

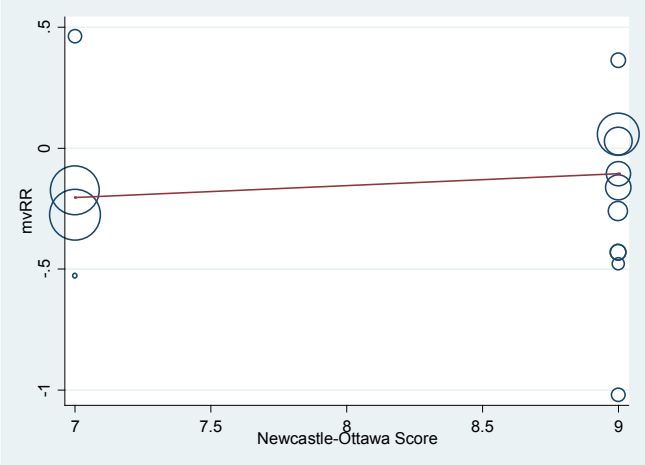
Fig. 98b. Meta-regression of LA and total CHD; number of cases; Panel B – subgroup analysis by cases (median *n*=270)



#: number; ALA: alpha-linolenic acid; ARIC: Atherosclerosis Risk in Communities; CHD: coronary heart disease; CI: confidence interval; ES: effect size; FMC: Finnish Mobile Health Clinic; LA: linoleic acid; M: male; PUFA: polyunsaturated fatty acids; VIP: Västerbotten Intervention Program; W: women; WHS: Women's Health Study.

[1] Note: There is no figure for meta-regression of LA and total CHD, energy adjustment because all studies adjusted for total energy intake.

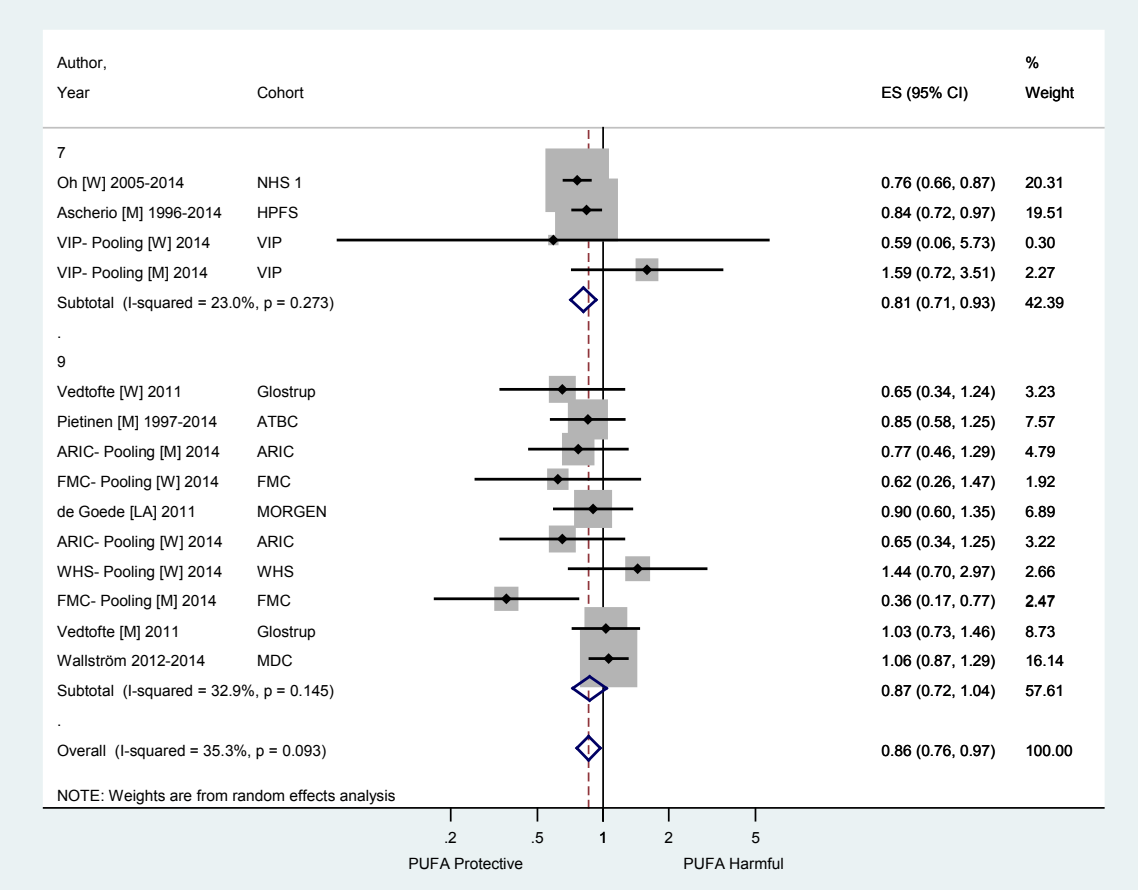
Fig. 98c. Meta-regression of LA and total CHD; NOS assessment; Panel A – effect size



The effect size was not associated with the NOS quality score (P=0.42).

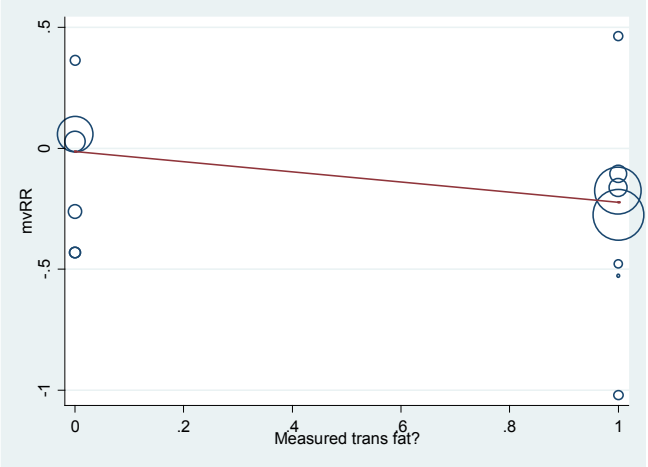
CHD: coronary heart disease; LA: linoleic acid; mvRR: multivariable risk ratio; NOS: Newcastle-Ottawa Scale.

Fig. 98d. Meta-regression of LA and total CHD; NOS assessment; Panel B – subgroup analysis by NOS score



ALA: alpha-linolenic acid; ARIC: Atherosclerosis Risk in Communities; ATBC: Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study; CHD: coronary heart disease; CI: confidence interval; ES: effect size; FMC: Finnish Mobile Health Clinic; HPFS: Health Professionals Follow-up Study; LA: linoleic acid; M: male; MDC: Malmö Diet and Cancer; MORGEN: Monitoring Project on Risk Factors for Chronic Diseases; NHS 1: Nurses' Health Study 1; NOS: Newcastle-Ottawa Scale; PUFA: polyunsaturated fatty acids; VIP: Västerbotten Intervention Program; W: women; WHS: Women's Health Study.

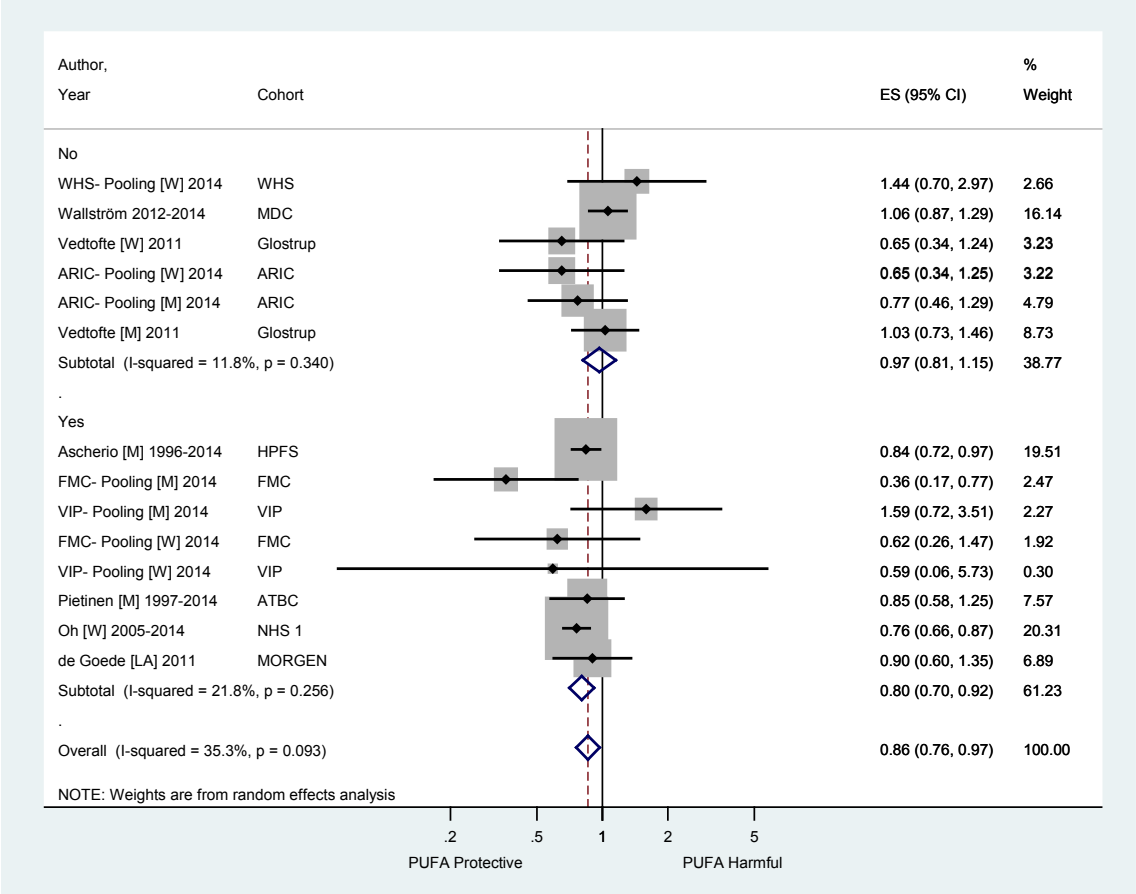
Fig. 98e. Meta-regression of LA and total CHD; TFA assessment; Panel A – effect size



TFA assessment was associated with effect size (*P*=0.055).

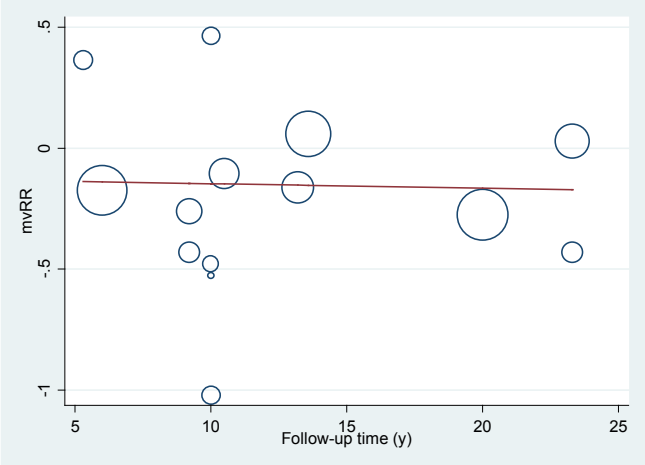
CHD: coronary heart disease; LA: linoleic acid; mvRR: multivariable risk ratio; TFA: trans-fatty acids.

Fig. 98f. Meta-regression of LA and total CHD; TFA assessment; Panel B – subgroup analysis (yes/no)



ALA: alpha-linolenic acid; ARIC: Atherosclerosis Risk in Communities; ATBC: Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study; CHD: coronary heart disease; CI: confidence interval; ES: effect size; FMC: Finnish Mobile Health Clinic; HPFS: Health Professionals Follow-up Study; LA: linoleic acid; M: male; MDC: Malmö Diet and Cancer; MORGEN: Monitoring Project on Risk Factors for Chronic Diseases; NHS 1: Nurses' Health Study 1; PUFA: polyunsaturated fatty acids; TFA: trans-fatty acids; VIP: Västerbotten Intervention Program; W: women; WHS: Women's Health Study.

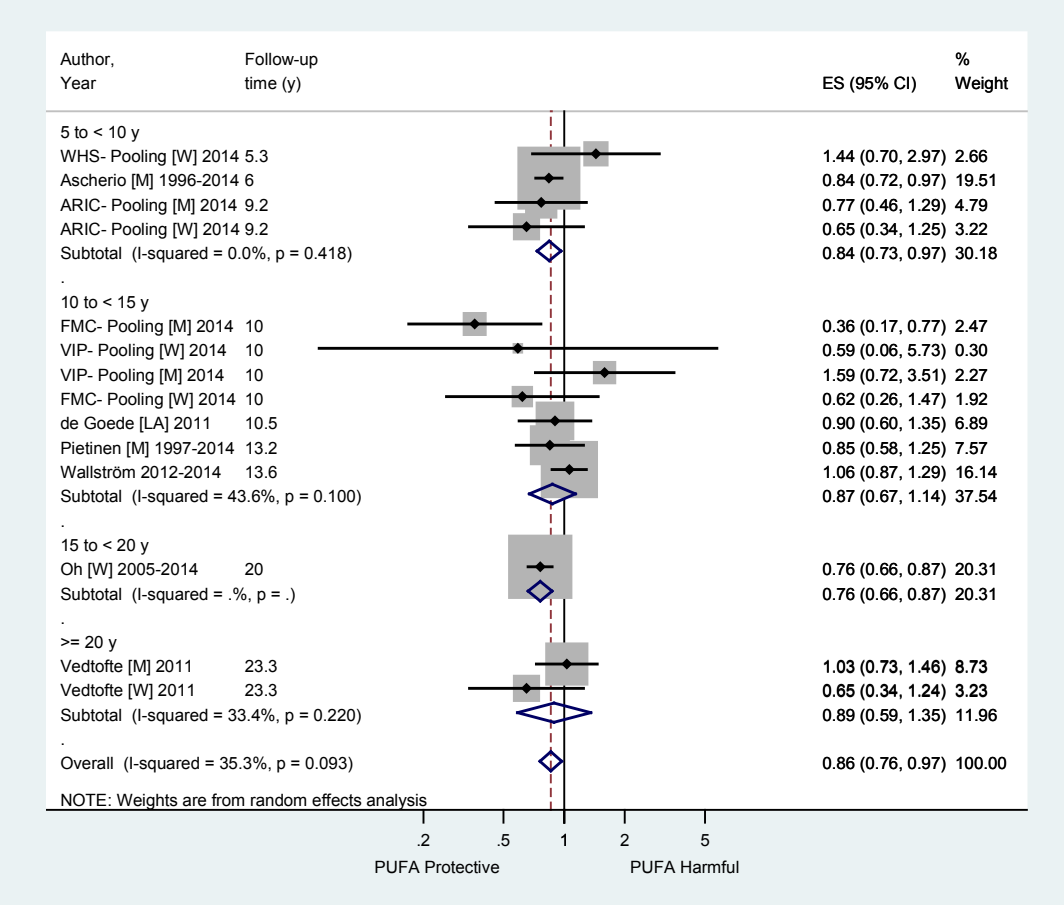
Fig. 98g. Meta-regression of LA and total CHD; follow-up time; Panel A – effect size



The effect size was not associated with adjustment for follow-up time in the final model (*P*=0.87).

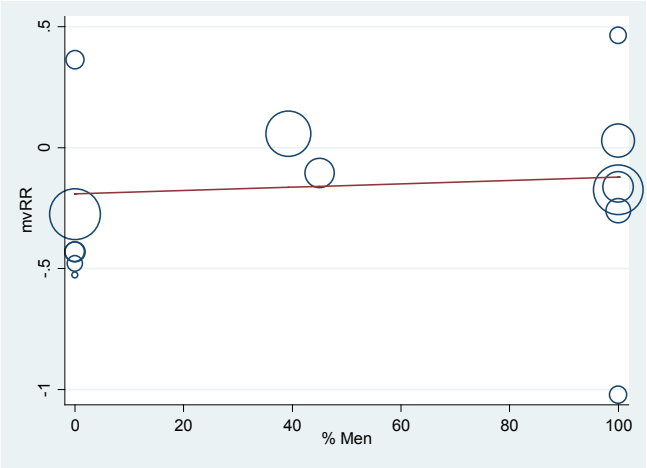
CHD: coronary heart disease; LA: linoleic acid; mvRR: multivariable risk ratio; y: years.

Fig. 98h. Meta-regression of LA and total CHD; follow-up time; Panel B – subgroup analysis



ALA: alpha-linolenic acid; ARIC: Atherosclerosis Risk in Communities; CHD: coronary heart disease; CI: confidence interval; ES: effect size; FMC: Finnish Mobile Health Clinic; LA: linoleic acid; M: male; PUFA: polyunsaturated fatty acids; VIP: Västerbotten Intervention Program; W: women; WHS: Women's Health Study; y: years.

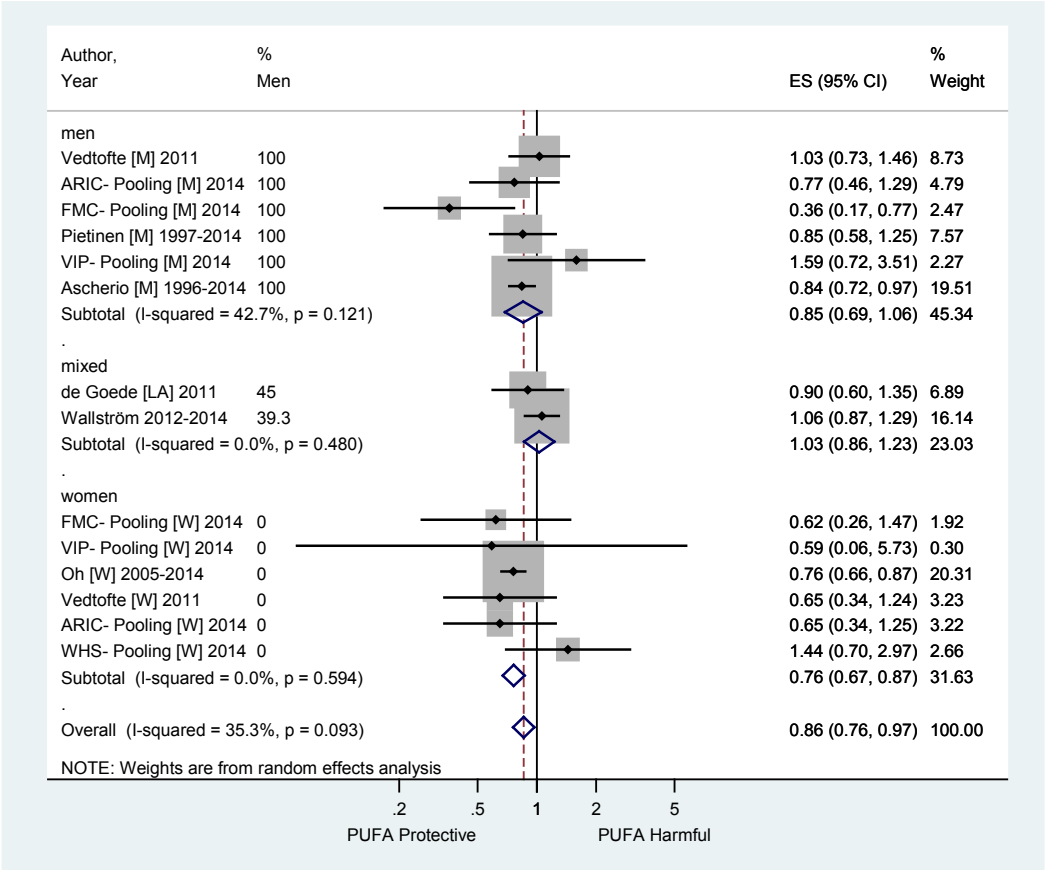
Fig. 98i. Meta-regression of LA and total CHD; sex; Panel A – effect size



The effect size was not associated with adjustment for and percentage of men in the study in the final model (*P*=0.66).

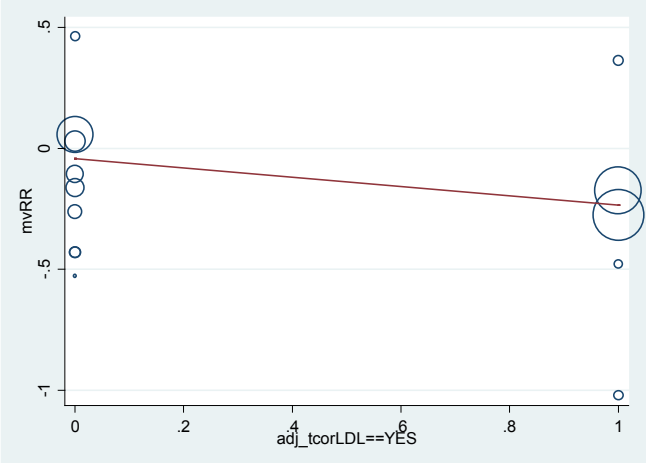
CHD: coronary heart disease; LA: linoleic acid; mvRR: multivariable risk ratio.

Fig. 98j. Meta-regression of LA and total CHD; sex; Panel B – subgroup analysis



ALA: alpha-linolenic acid; ARIC: Atherosclerosis Risk in Communities; CHD: coronary heart disease; CI: confidence interval; ES: effect size; FMC: Finnish Mobile Health Clinic; LA: linoleic acid; M: male; PUFA: polyunsaturated fatty acids; VIP: Västerbotten Intervention Program; W: women; WHS: Women's Health Study.

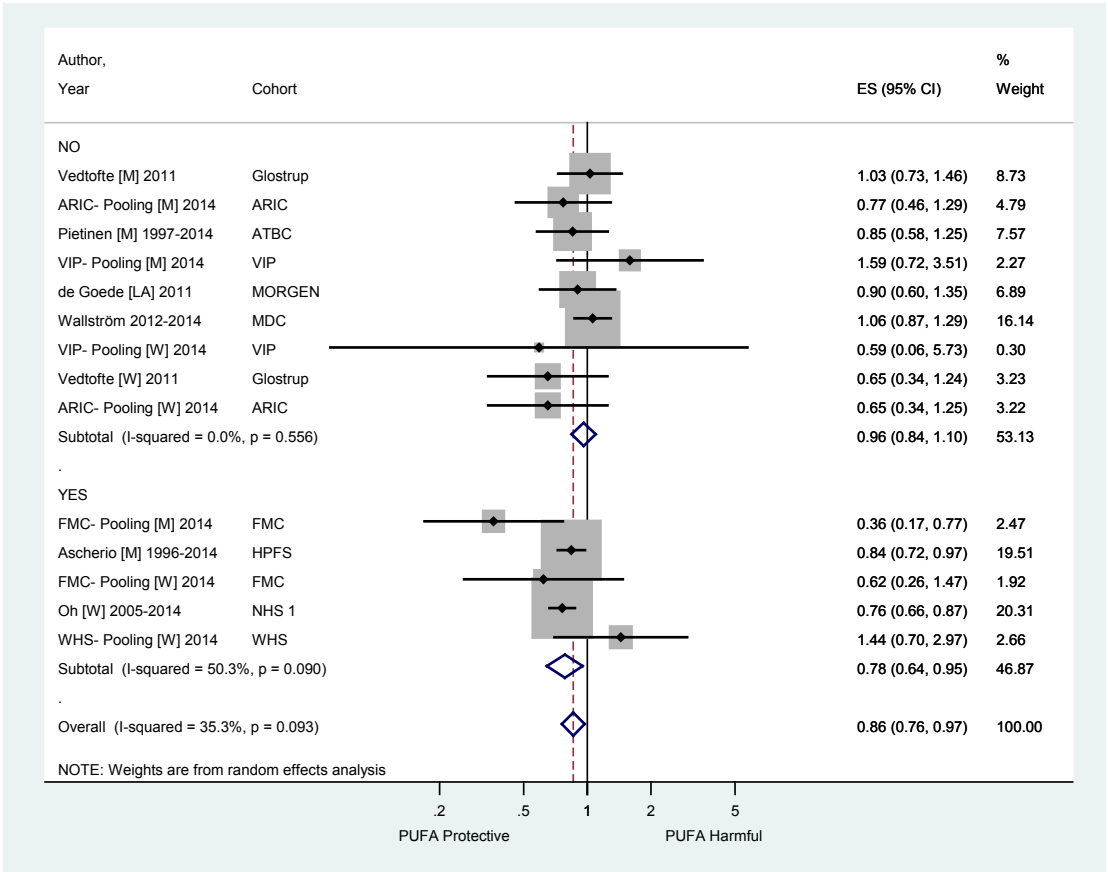
Fig. 98k. Meta-regression of LA and total CHD; dyslipidaemia adjustment; Panel A – effect size



The effect size was associated with adjustment for measure of dyslipidaemia in the final model (*P*=0.066).

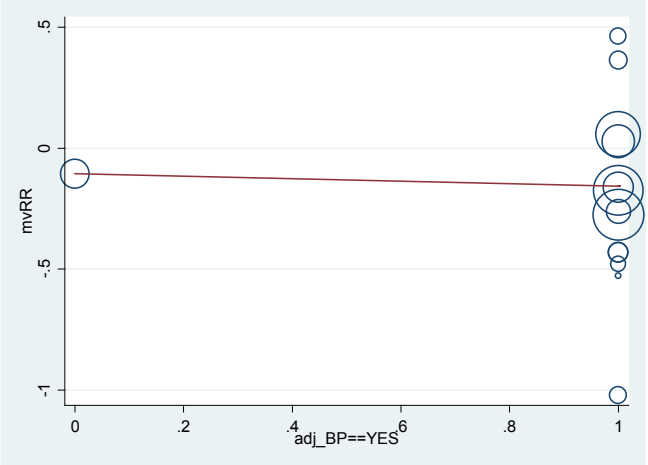
adj_tcorLDL: adjusted for dyslipidaemia; CHD: coronary heart disease; LA: linoleic acid; mvRR: multivariable risk ratio.

Fig. 98l. Meta-regression of LA and total CHD; dyslipidaemia adjustment; Panel B – subgroup analysis (yes/no)



ALA: alpha-linolenic acid; ARIC: Atherosclerosis Risk in Communities; ATBC: Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study; CHD: coronary heart disease; CI: confidence interval; ES: effect size; FMC: Finnish Mobile Health Clinic; HPFS: Health Professionals Follow-up Study; LA: linoleic acid; M: male; MDC: Malmö Diet and Cancer; MORGEN: Monitoring Project on Risk Factors for Chronic Diseases; NHS 1: Nurses' Health Study 1; PUFA: polyunsaturated fatty acids; VIP: Västerbotten Intervention Program; W: women; WHS: Women's Health Study.

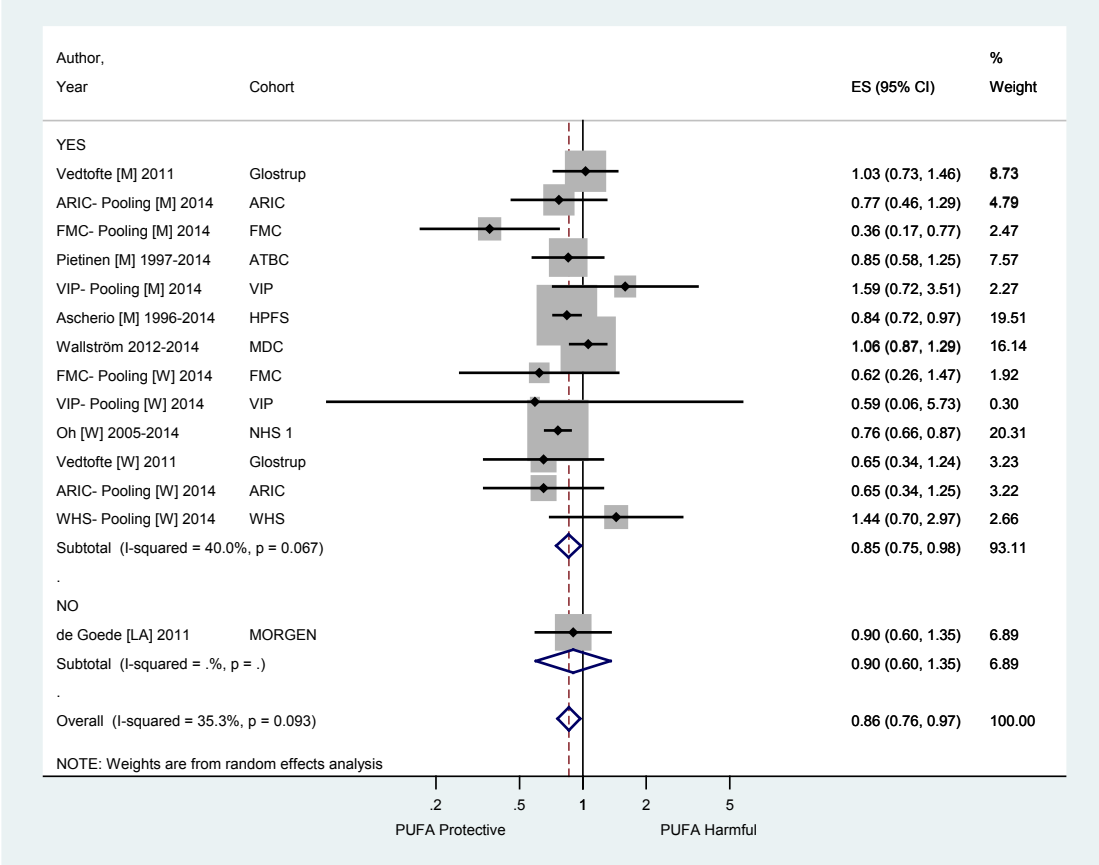
Fig. 98m. Meta-regression of LA and total CHD; blood pressure adjustment; Panel A – effect size



The effect size was not associated with adjustment for a measure of blood pressure in the final model (*P*=0.39).

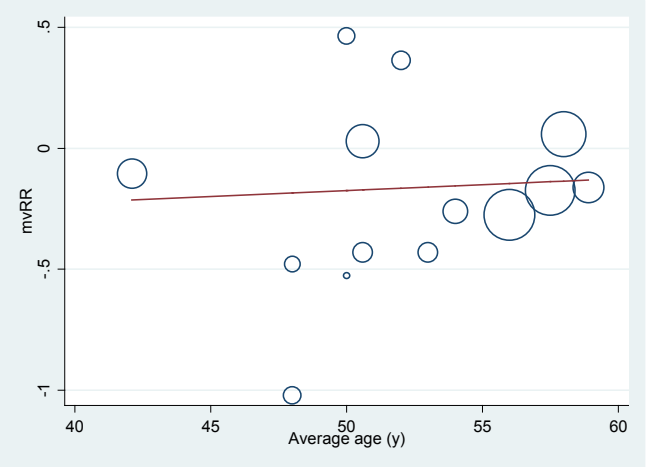
adj_BP: adjusted for blood pressure; CHD: coronary heart disease; LA: linoleic acid; mvRR: multivariable risk ratio.

Fig. 98n. Meta-regression of LA and total CHD; blood pressure adjustment; Panel B – subgroup analysis (yes/no)



ALA: alpha-linolenic acid; ARIC: Atherosclerosis Risk in Communities; ATBC: Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study; CHD: coronary heart disease; CI: confidence interval; ES: effect size; FMC: Finnish Mobile Health Clinic; HPFS: Health Professionals Follow-up Study; LA: linoleic acid; M: male; MDC: Malmö Diet and Cancer; MORGEN: Monitoring Project on Risk Factors for Chronic Diseases; NHS 1: Nurses' Health Study 1; PUFA: polyunsaturated fatty acids; VIP: Västerbotten Intervention Program; W: women; WHS: Women's Health Study.

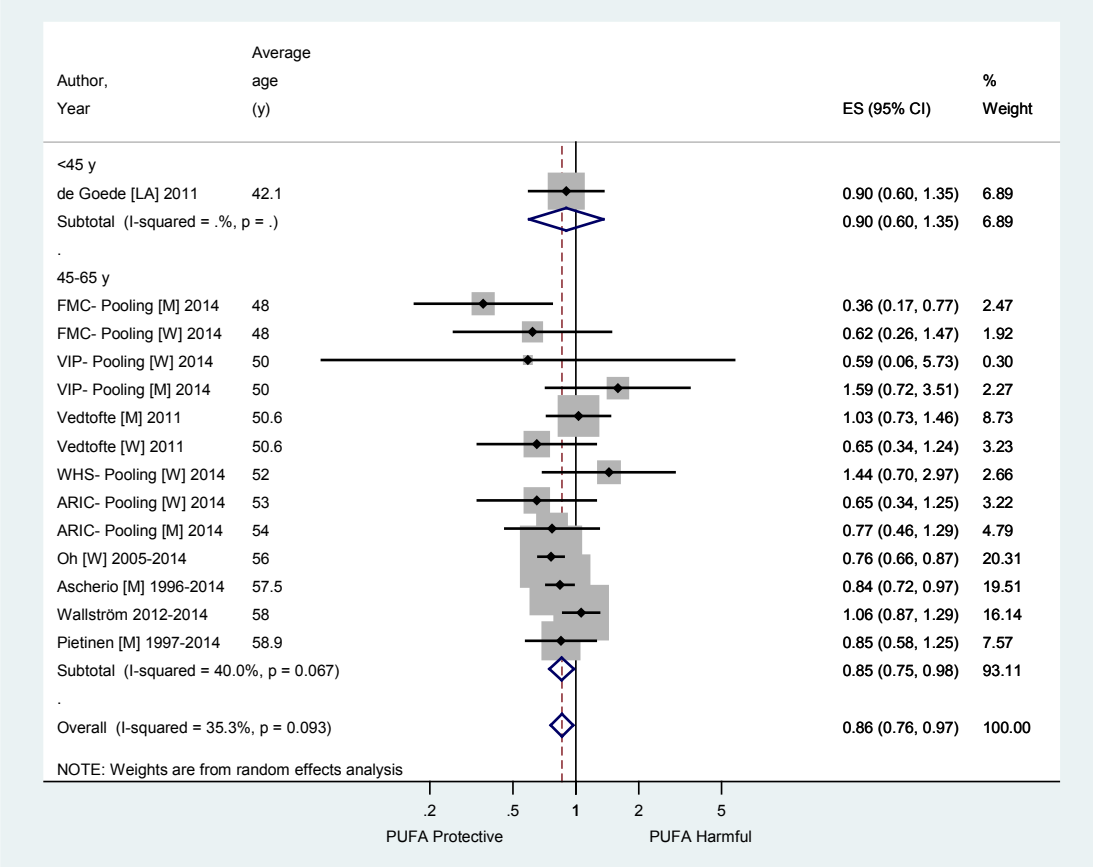
Fig. 98o. Meta-regression of LA and total CHD; age; Panel A – effect size



The effect size was not associated with adjustment for average age of the study sample in the final model (*P*=0.75).

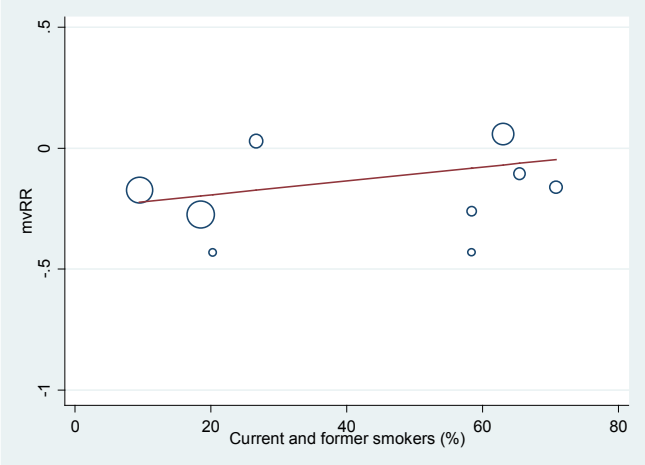
CHD: coronary heart disease; LA: linoleic acid; mvRR: multivariable risk ratio; y: years.

Fig. 98p. Meta-regression of LA and total CHD; age; Panel B – subgroup analysis (age group)



ALA: alpha-linolenic acid; ARIC: Atherosclerosis Risk in Communities; CHD: coronary heart disease; CI: confidence interval; ES: effect size; FMC: Finnish Mobile Health Clinic; LA: linoleic acid; M: male; PUFA: polyunsaturated fatty acids; VIP: Västerbotten Intervention Program; W: women; WHS: Women's Health Study; y: years.

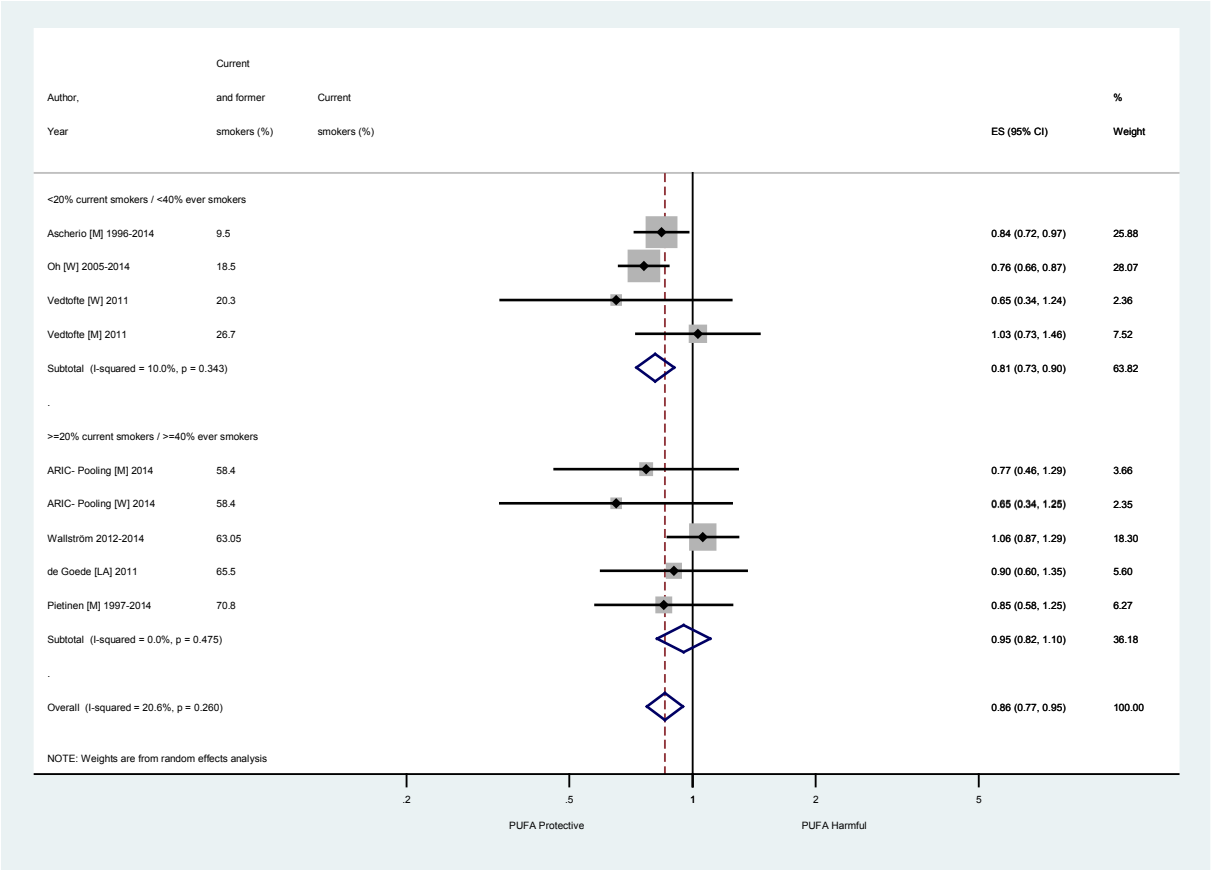
Fig. 98q. Meta-regression of LA and total CHD; smoking history; Panel A – effect size



The effect size was not associated with adjustment for smoking history of the study sample in the final model (*P*=0.75). High smokers ≥40% current/former or >20% current.

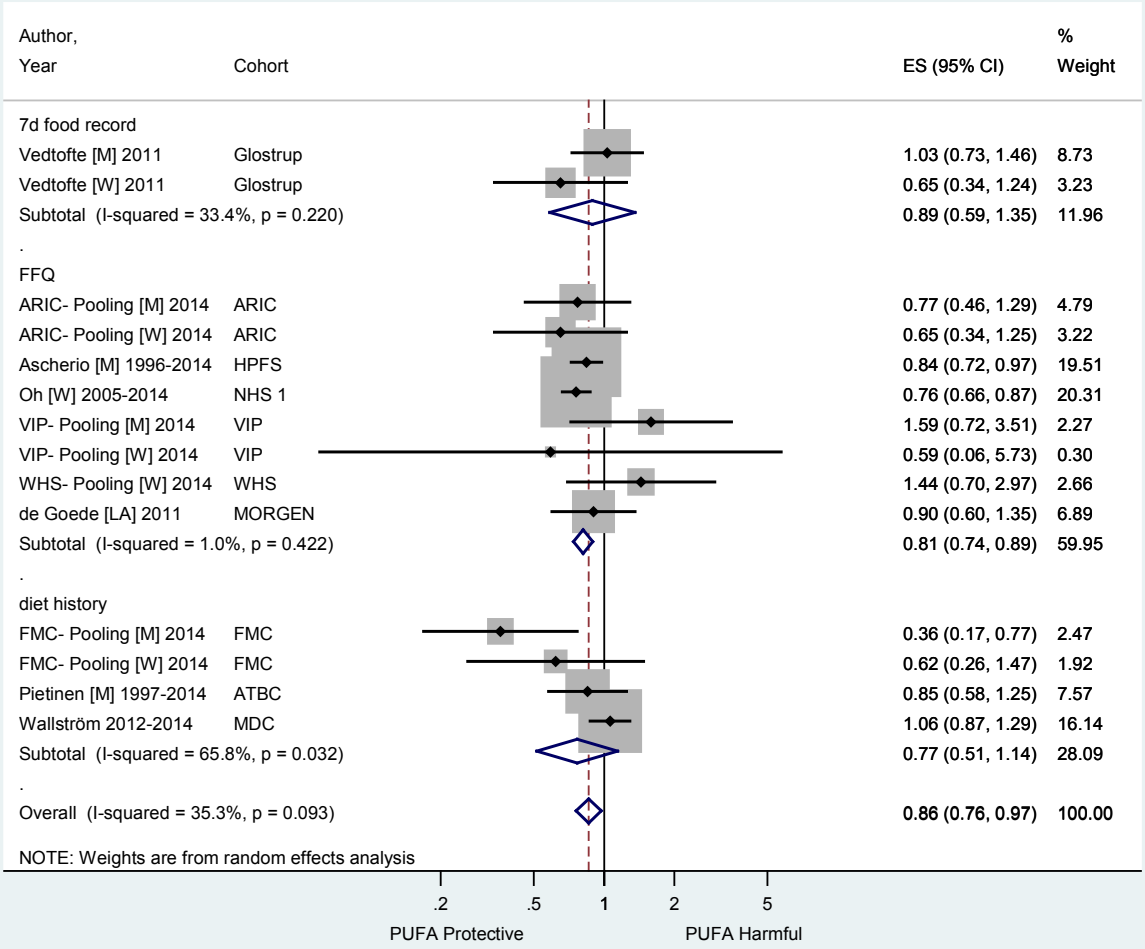
CHD: coronary heart disease; LA: linoleic acid; mvRR: multivariable risk ratio.

Fig. 98r. Meta-regression of LA and total CHD; smoking history; Panel B – subgroup analysis



ALA: alpha-linolenic acid; ARIC: Atherosclerosis Risk in Communities; CHD: coronary heart disease; CI: confidence interval; ES: effect size; LA: linoleic acid; M: male; PUFA: polyunsaturated fatty acids; W: women.

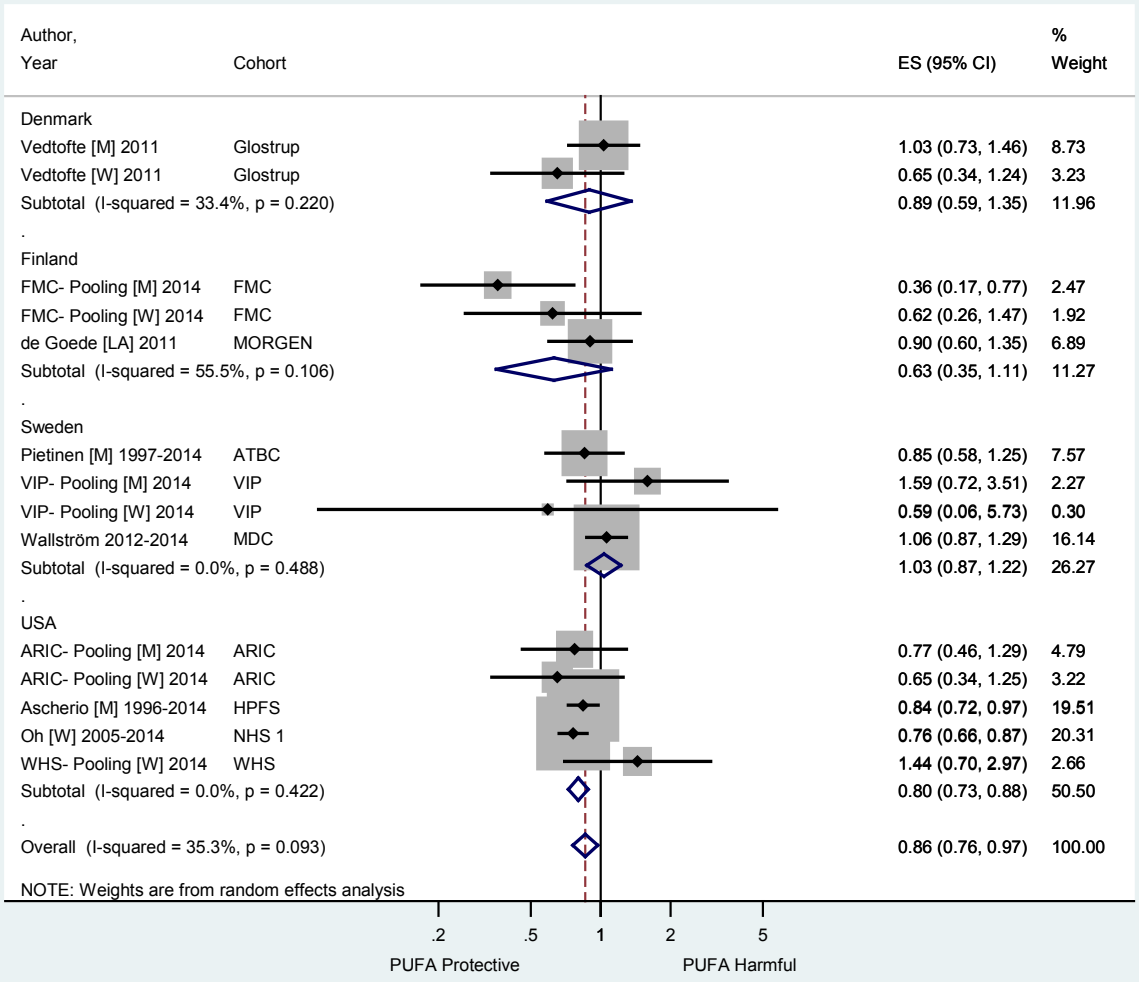
Fig. 98s. Meta-regression of LA and total CHD; diet assessment method; subgroup analysis



ALA: alpha-linolenic acid; ARIC: Atherosclerosis Risk in Communities; ATBC: Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study; CHD: coronary heart disease; CI: confidence interval; d: day; ES: effect size; FFQ: food frequency questionnaire; FMC: Finnish Mobile Health Clinic; HPFS: Health Professionals Follow-up Study; LA: linoleic acid; M: male; MDC: Malmö Diet and Cancer; MORGEN: Monitoring Project on Risk Factors for Chronic Diseases; NHS 1: Nurses' Health Study 1; PUFA: polyunsaturated fatty acids; VIP: Västerbotten Intervention Program; W: women; WHS: Women's Health Study.

The effect size was not associated with adjustment for diet assessment method in the final model (P_{het}=0.91). Because the predictor variable had more than 2 levels, it is not appropriate to show the continuous meta-regression line; therefore, we present the "by country" estimates separately.

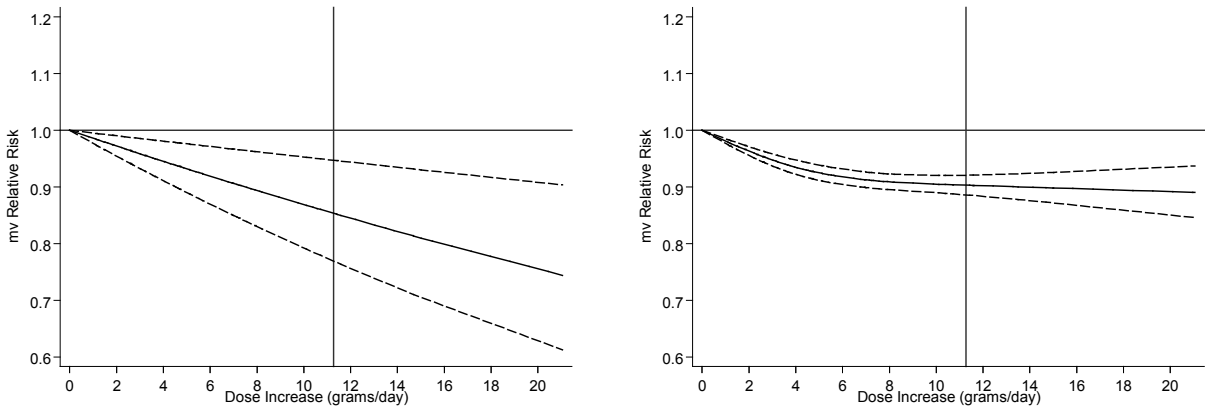
Fig. 98t. Meta-regression of LA and total CHD; country of conduct; subgroup analysis



ALA: alpha-linolenic acid; ARIC: Atherosclerosis Risk in Communities; ATBC: Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study; CHD: coronary heart disease; CI: confidence interval; ES: effect size; FMC: Finnish Mobile Health Clinic; HPFS: Health Professionals Follow-up Study; LA: linoleic acid; M: male; MDC: Malmö Diet and Cancer; MORGEN: Monitoring Project on Risk Factors for Chronic Diseases; NHS 1: Nurses' Health Study 1; PUFA: polyunsaturated fatty acids; USA: United States of America; VIP: Västerbotten Intervention Program; W: women; WHS: Women's Health Study.

There was no evidence of heterogeneity of effect size by country of conduct (P_{het}=0.16). Because the predictor variable had more than 2 levels, it is not appropriate to show the continuous meta-regression line; therefore, we present the "by country" estimates separately.

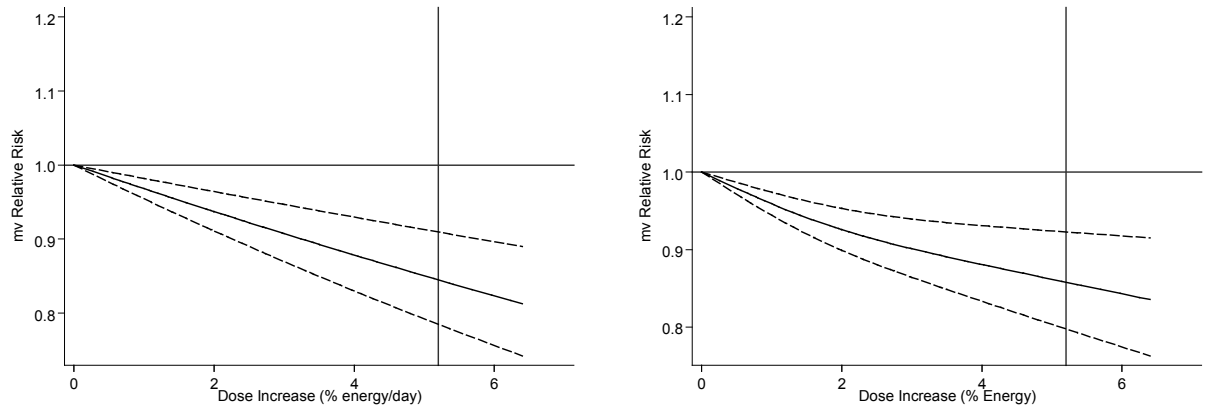
Fig. 99. Dose–response association between total PUFA (g/day) and most-adjusted RR of all-cause mortality from 15 studies, assuming linearity (*P*<0.0001 for goodness-of-fit[1]) (left), and using non-linear, cubic spline approach (right), with knots at 0, 3.7 and 10.7 g/day



Assuming linearity, a 10 g/day increase in PUFA was associated with a 13% decrease in risk of all-cause mortality (mvRR: 0.87; 95% CI: 0.79 to 0.95). ***Horizontal line represents a RR=1.0; vertical line represents the median PUFA intake in the studied populations (11.3 g/day).***

CI: confidence interval; mv: multivariable; mvRR: multivariable risk ratio; PUFA: polyunsaturated fatty acids; RR: risk ratio.

Fig. 100. Dose–response association between total PUFA (%E) and most-adjusted RR of all-cause mortality from 15 studies, assuming linearity (*P*=0.01 for goodness-of-fit) (left), and using non-linear, cubic spline approach (right), with knots at 0, 1.6 and 4.0% energy

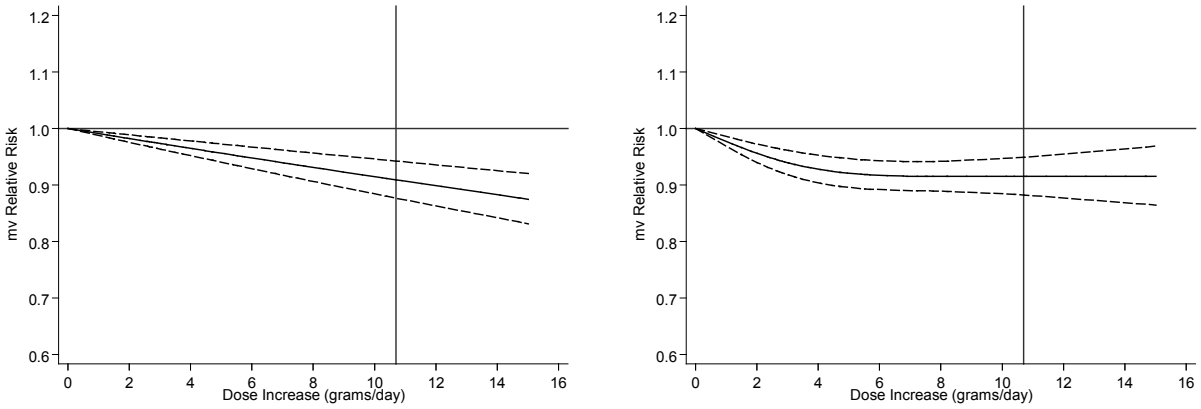


Assuming linearity, a 5% increase in energy from PUFA was associated with a 15% reduction in all-cause mortality (mvRR: 0.85; 95% CI: 0.79 to 0.91). *Horizontal line represents a RR=1.0; vertical line represents the median PUFA intake in the studied populations (5.2%E).*

CI: confidence interval; E: energy; mv: multivariable; mvRR: multivariable risk ratio; PUFA: polyunsaturated fatty acids; RR: risk ratio.

[1] If *P*<0.05, the interpretation is that a straight line is not a good fit to the data; if P>0.05 then a straight line is an adequate fit.

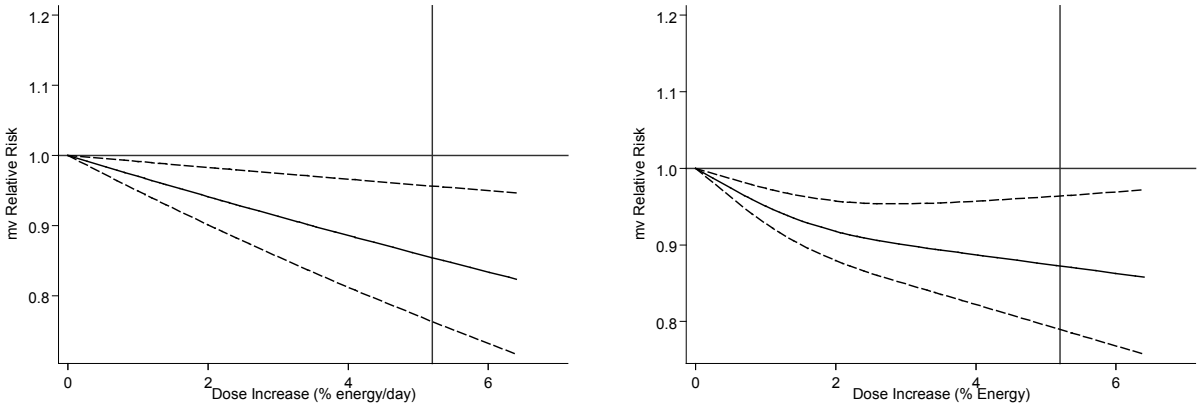
Fig. 101. Dose–response association between total PUFA (g/day) and most-adjusted RR of CVD mortality from nine studies, assuming linearity (*P*=0.005 for goodness-of-fit) (left), and using non-linear, cubic spline approach (right), with knots at 0, 3.0 and 8.2 g/day



Assuming linearity, a 10 g/day increase in total PUFA was associated with a 9% decrease in risk of CVD mortality (mvRR: 0.91; 95% CI: 0.88 to 0.95). *The dose–response effect seems to stabilize beyond 8 g/day. Horizontal line represents a RR=1.0; vertical line represents the median PUFA intake in the studied populations (10.7 g/day).*

CI: confidence interval; CVD: cardiovascular disease; mv: multivariable; mvRR: multivariable risk ratio; PUFA: polyunsaturated fatty acids; RR: risk ratio.

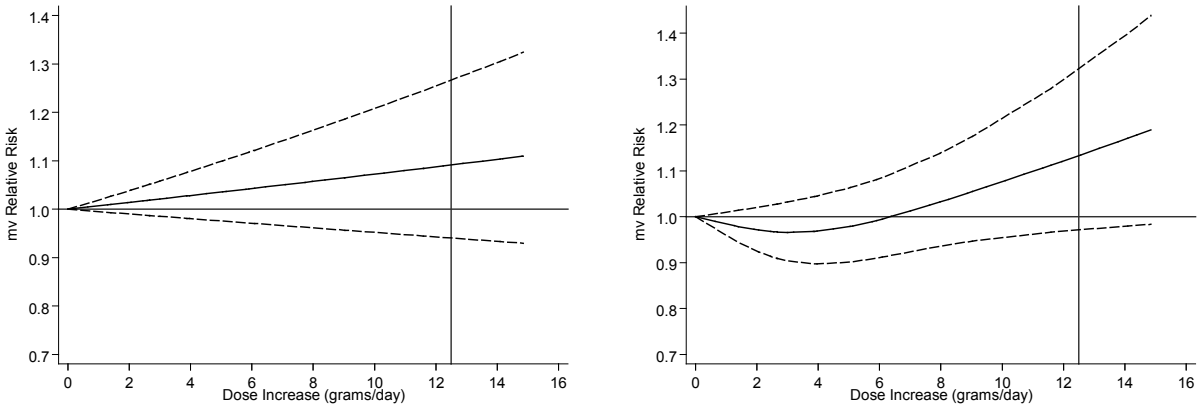
Fig. 102. Dose–response association between total PUFA (%E) and most-adjusted RR of CVD mortality in nine studies, assuming linearity (*P*=0.13 for goodness-of-fit) (left), and using non-linear, cubic spline approach (right), with knots at 0, 1.6 and 4.0% energy



Assuming linearity, a 5% increase in energy from total PUFA was associated with a 14% decrease in risk of CVD mortality (mvRR: 0.86; 95% CI: 0.77 to 0.96). *Horizontal line represents a RR=1.0; vertical line represents the median PUFA intake in the studied populations (5.2%E).*

CI: confidence interval; CVD: cardiovascular disease; E: energy; mv: multivariable; mvRR: multivariable risk ratio; PUFA: polyunsaturated fatty acids; RR: risk ratio.

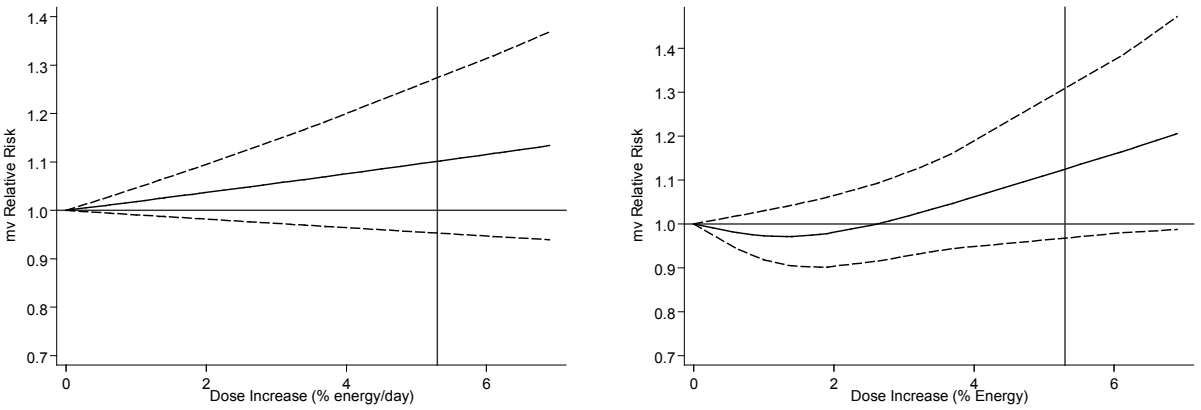
Fig. 103. Dose–response association between total PUFA (g/day) and most-adjusted RR of CHD mortality in seven studies, assuming linearity (P=0.09 for goodness-of-fit) (left), and using non-linear, cubic spline approach (right), with knots at 0, 2.7 and 8.0 g/day



Assuming linearity, a 10 g/day increase in total PUFA was associated with a 7% increased risk of CHD mortality (mvRR: 1.07; 95% CI: 0.95 to 1.21). *Horizontal line represents a RR=1.0; vertical line represents the median PUFA intake in the studied populations (12.5 g/day).*

CHD: coronary heart disease; CI: confidence interval; mv: multivariable; mvRR: multivariable risk ratio; PUFA: polyunsaturated fatty acids; RR: risk ratio.

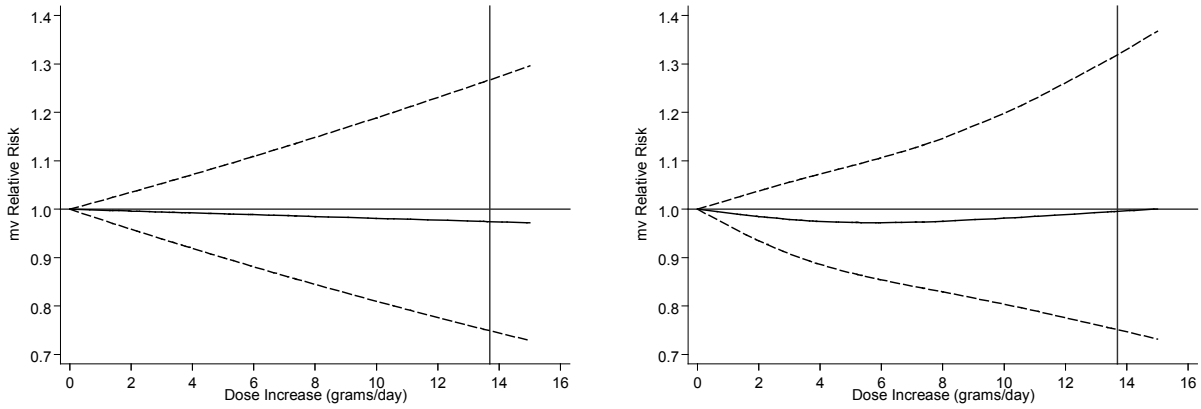
Fig. 104. Dose–response association between total PUFA (%E) and most-adjusted RR of CHD mortality in seven studies, assuming linearity (*P*=0.10 for goodness-of-fit) (left), and using non-linear, cubic spline approach (right), with knots at 0, 1.0 and 3.4% energy



Assuming linearity, a 5% increase in energy from total PUFA was associated with a 10% increased risk of CHD mortality (mvRR: 1.10; 95% CI: 0.96 to 1.26). *Horizontal line represents a RR=1.0; vertical line represents the median PUFA intake in the studied populations (5.5%E).*

CHD: coronary heart disease; CI: confidence interval; E: energy; mv: multivariable; mvRR: multivariable risk ratio; PUFA: polyunsaturated fatty acids; RR: risk ratio.

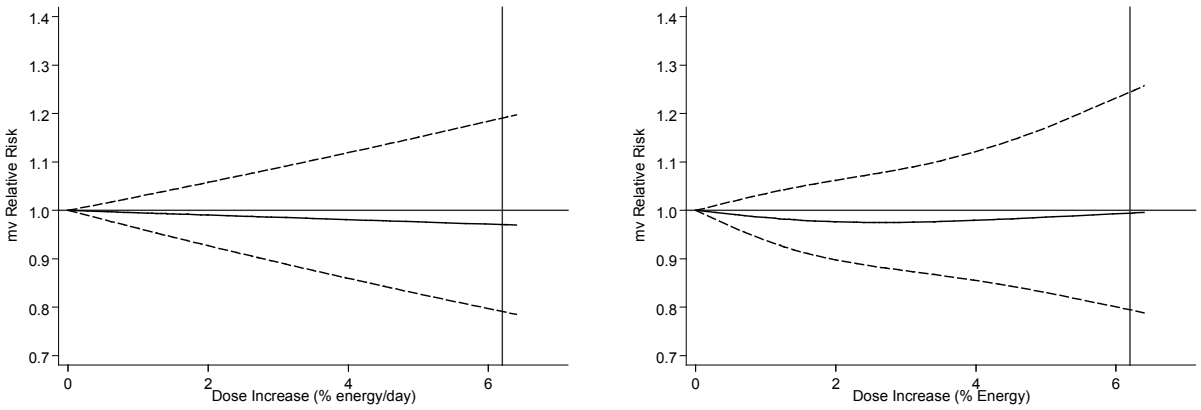
Fig. 105. Dose–response association between total PUFA (g/day) and most-adjusted RR of total CHD in 15 studies, assuming linearity (*P*=0.26 for goodness-of-fit) (left), and using non-linear, cubic spline approach (right), with knots at 0, 3.5 and 11.1 g/day



There was no evidence of a dose–response association between total PUFA and total CHD (mvRR: 0.98; 95% CI: 0.81 to 1.19 per 10 g). *Horizontal line represents a RR=1.0; vertical line represents the median PUFA intake in the studied populations (13.7 g/day).*

CHD: coronary heart disease; CI: confidence interval; mv: multivariable; mvRR: multivariable risk ratio; PUFA: polyunsaturated fatty acids; RR: risk ratio.

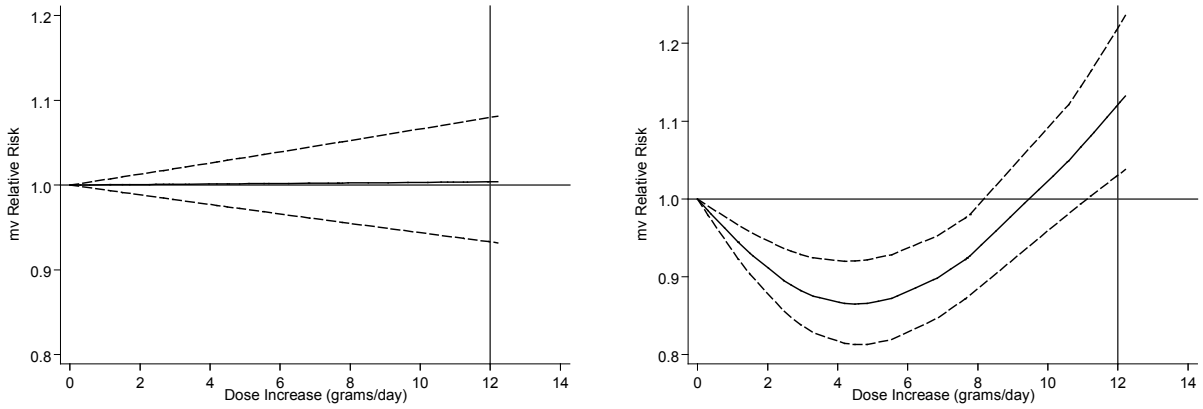
Fig. 106. Dose–response association between total PUFA (%E) and most-adjusted RR of total CHD in 15 studies, assuming linearity (*P*=0.10 for goodness-of-fit) (left), and using non-linear, cubic spline approach (right), with knots at 0, 1.5 and 5.0% energy



There was no evidence of a dose–response association between total PUFA and total CHD (mvRR: 0.98; 95% CI: 0.83 to 1.15 per 5%). *Horizontal line represents a RR=1.0; vertical line represents the median PUFA intake in the studied populations (6.2%E).*

CHD: coronary heart disease; CI: confidence interval; E: energy; mv: multivariable; mvRR: multivariable risk ratio; PUFA: polyunsaturated fatty acids; RR: risk ratio.

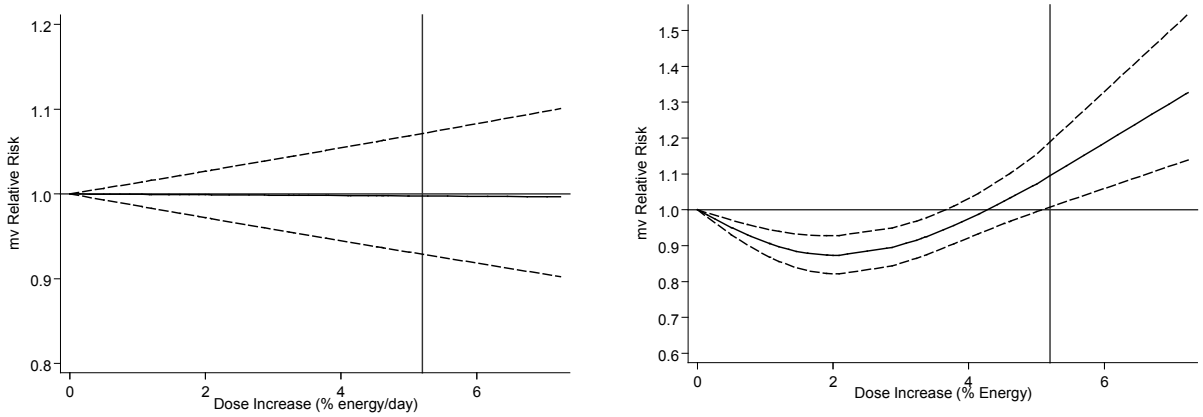
Fig. 107. Dose–response association between total PUFA (g/day) and most-adjusted RR of type 2 diabetes in eight studies, assuming linearity (*P*=0.0002 for goodness-of-fit) (left), and using non-linear, cubic spline approach (right), with knots at 0, 3.3 and 10.6 g/day



There was no evidence of a dose–response association between total PUFA and type 2 diabetes (mvRR: 1.00; 95% CI: 0.94 to 1.07 per 10 g). *Horizontal line represents a RR=1.0; vertical line represents the median PUFA intake in the studied populations (12.0 g/day).*

CI: confidence interval; mv: multivariable; mvRR: multivariable risk ratio; PUFA: polyunsaturated fatty acids; RR: risk ratio.

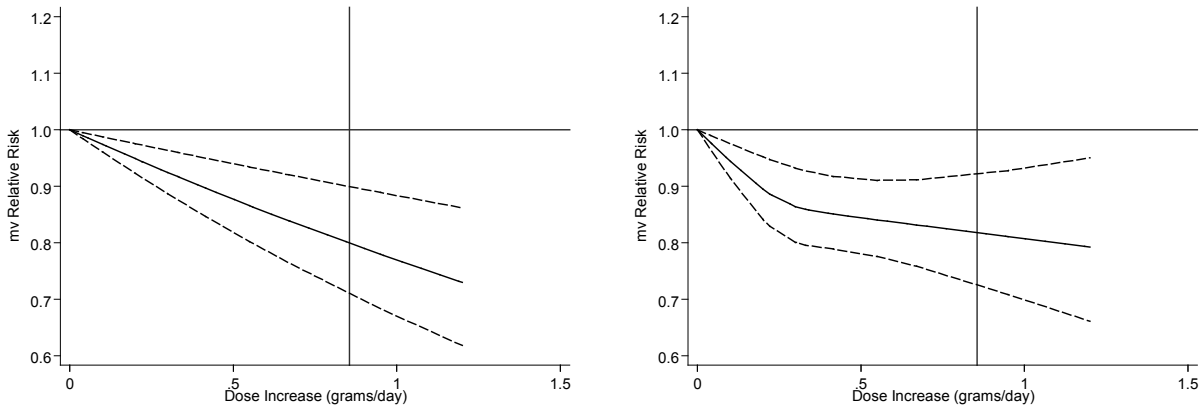
Fig. 108. Dose–response association between total PUFA (%E) and most-adjusted RR of type 2 diabetes in eight studies, assuming linearity (*P*=0.0002 for goodness-of-fit) (left), and using non-linear, cubic spline approach (right), with knots at 0, 3.3 and 10.6% energy



There was no evidence of a dose–response association between total PUFA and type 2 diabetes (mvRR: 1.00; 95% CI: 0.94 to 1.07 per 5%). *Horizontal line represents a RR=1.0; vertical line represents the median PUFA intake in the studied populations (5.2%E).*

CI: confidence interval; E: energy; mv: multivariable; mvRR: multivariable risk ratio; PUFA: polyunsaturated fatty acids; RR: risk ratio.

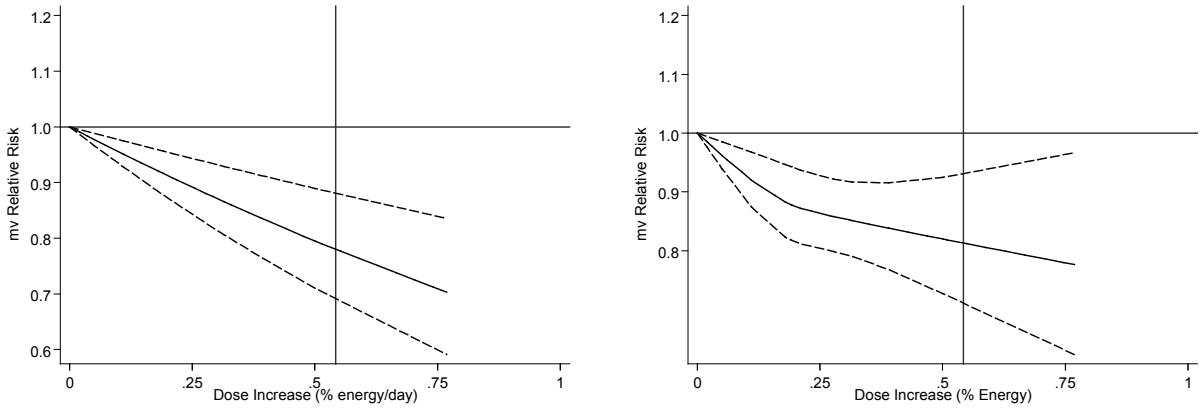
Fig. 109. Dose–response association between total n-3 PUFA (g/day) and most-adjusted RR of CHD mortality in three studies, assuming linearity (*P*=0.39 for goodness-of-fit) (left), and using non-linear, cubic spline approach (right), with knots at 101, 261 and 415 mg/day



Assuming linearity, a 1 g/day increase in n-3 PUFA was associated with a 23% decrease in risk of CHD mortality (mvRR: 0.77; 95% CI: 0.67 to 0.88). *Horizontal line represents a RR=1.0; vertical line represents the median n-3 PUFA intake in the studied populations (855 mg/day).*

CHD: coronary heart disease; CI: confidence interval; mv: multivariable; mvRR: multivariable risk ratio; PUFA: polyunsaturated fatty acids; RR: risk ratio.

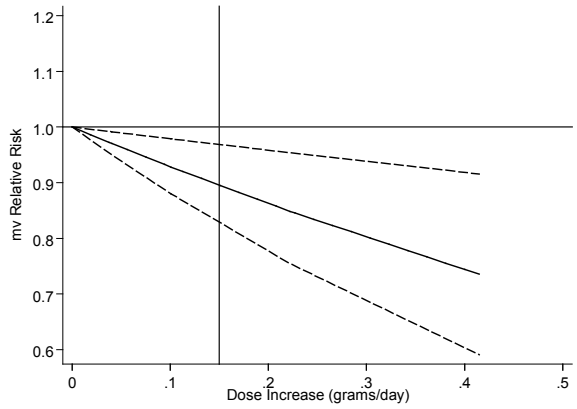
Fig. 110. Dose–response association between total n-3 PUFA (%E) and most-adjusted RR of CHD mortality, assuming linearity (*P*=0.56 for goodness-of-fit) (left), and using non-linear, cubic spline approach (right), with knots at 101, 261 and 415 mg/day



Assuming linearity, a 0.5% increase in energy from n-3 PUFA was associated with a 21% decrease in risk of CHD mortality (mvRR: 0.79; 95% CI: 0.71 to 0.89). *Horizontal line represents a RR=1.0; vertical line represents the median n-3 PUFA intake in the studied populations (0.6%E).*

CHD: coronary heart disease; CI: confidence interval; E: energy; mv: multivariable; mvRR: multivariable risk ratio; PUFA: polyunsaturated fatty acids; RR: risk ratio.

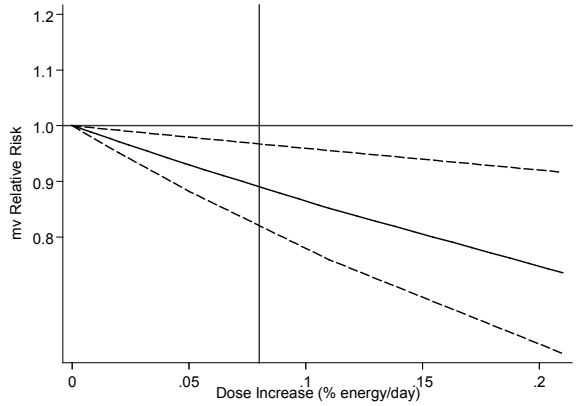
Fig. 111. Dose–response association (fixed-effect) between total n-3 PUFA (g/day) and non-fatal myocardial infarction in one study, assuming linearity (*P*=0.76 for goodness-of-fit)



Assuming linearity, a 1 g/day increase in n-3 PUFA was associated with a 52% decrease in non-fatal myocardial infarction (mvRR: 0.48; 95% CI: 0.28 to 0.81). *Horizontal line represents a RR=1.0; vertical line represents the median n-3 PUFA intake in the studied populations (0.15 g/day).*

CI: confidence interval; mv: multivariable; mvRR: multivariable risk ratio; PUFA: polyunsaturated fatty acids; RR: risk ratio.

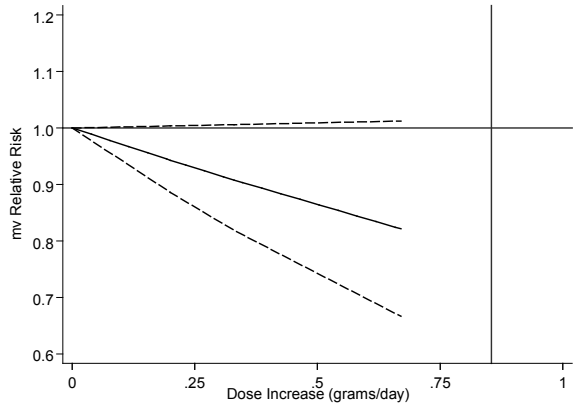
Fig. 112. Dose–response association (fixed-effect) between total n-3 PUFA (%E) and non-fatal myocardial infarction in one study, assuming linearity (*P*=0.85 for goodness-of-fit)



Assuming linearity, a 0.5% increase in energy from n-3 PUFA was associated with a 52% decrease in non-fatal myocardial infarction (mvRR: 0.48; 95% CI: 0.28 to 0.81). *Horizontal line represents a RR=1.0; vertical line represents the median n-3 PUFA intake in the studied populations (0.08%E).*

CI: confidence interval; E: energy; mv: multivariable; mvRR: multivariable risk ratio; PUFA: polyunsaturated fatty acids; RR: risk ratio.

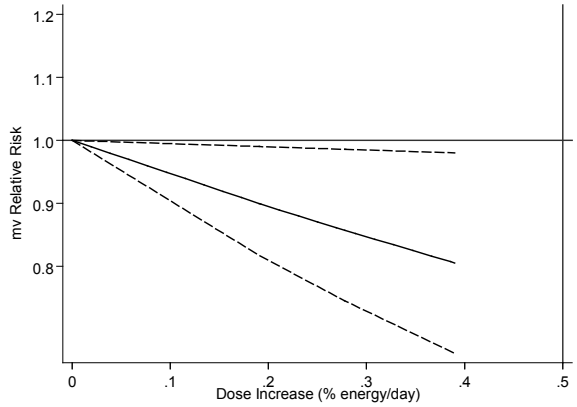
Fig. 113. Dose–response association (fixed-effect) between total n-3 PUFA (g/day) and fatal stroke in one study, assuming linearity (*P*=0.41 for goodness-of-fit)



Assuming linearity, a 1 g/day increase in n-3 PUFA was associated with a 25% decrease in risk of fatal stroke (mvRR: 0.75; 95% CI: 0.55 to 1.01). *Horizontal line represents a RR=1.0; vertical line represents the median n-3 PUFA intake in the studied populations (0.86 g/day).*

CI: confidence interval; mv: multivariable; mvRR: multivariable risk ratio; PUFA: polyunsaturated fatty acids; RR: risk ratio.

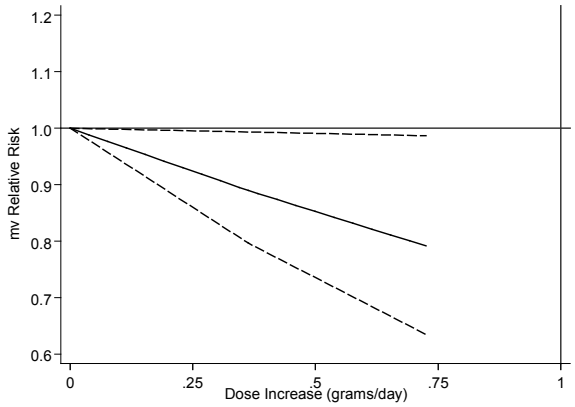
Fig. 114. Dose–response association (fixed-effect) between total n-3 PUFA (%E) and fatal stroke in one study, assuming linearity (*P*=0.78 for goodness-of-fit)



Assuming linearity, a 0.5% increase in energy from n-3 PUFA was associated with a 24% decrease in risk of fatal stroke (mvRR: 0.76; 95% CI: 0.59 to 0.97). *Horizontal line represents a RR=1.0; vertical line represents the median n-3 PUFA intake in the studied populations (0.5%E).*

CI: confidence interval; E: energy; mv: multivariable; mvRR: multivariable risk ratio; PUFA: polyunsaturated fatty acids; RR: risk ratio.

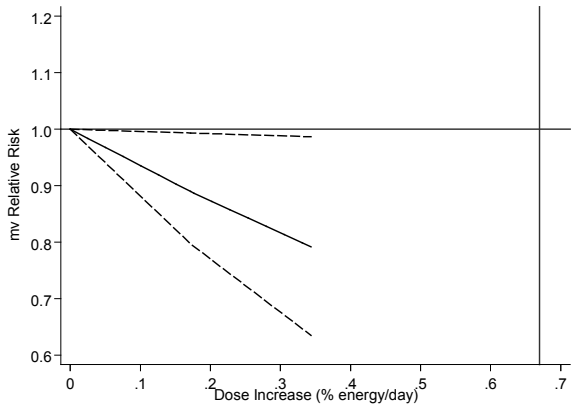
Fig. 115. Dose–response association (fixed-effect) between total n-3 PUFA (g/day) and cognitive decline in one study, assuming linearity (*P*=0.81 for goodness-of-fit)



Assuming linearity, a 1 g/day increase in n-3 PUFA was associated with a 28% decrease in risk of cognitive decline (mvRR: 0.72; 95% CI: 0.53 to 0.98). *Horizontal line represents a RR=1.0; vertical line represents the median n-3 PUFA intake in the studied populations (1.4 g/day).*

CI: confidence interval; mv: multivariable; mvRR: multivariable risk ratio; PUFA: polyunsaturated fatty acids; RR: risk ratio.

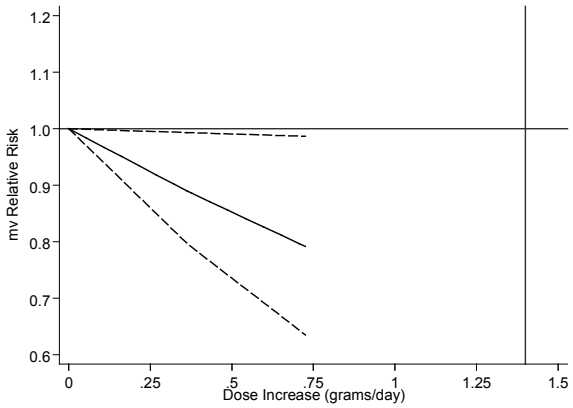
Fig. 116. Dose–response association (fixed-effect) between total n-3 PUFA (%E) and cognitive decline in one study, assuming linearity (*P*=0.81 for goodness-of-fit)



Assuming linearity, a 0.5% increase in energy from n-3 PUFA was associated with a 29% decrease in risk of cognitive decline (mvRR: 0.71; 95% CI: 0.51 to 0.98). *Horizontal line represents a RR=1.0; vertical line represents the median n-3 PUFA intake in the studied populations (0.67%E).*

CI: confidence interval; E: energy; mv: multivariable; mvRR: multivariable risk ratio; PUFA: polyunsaturated fatty acids; RR: risk ratio.

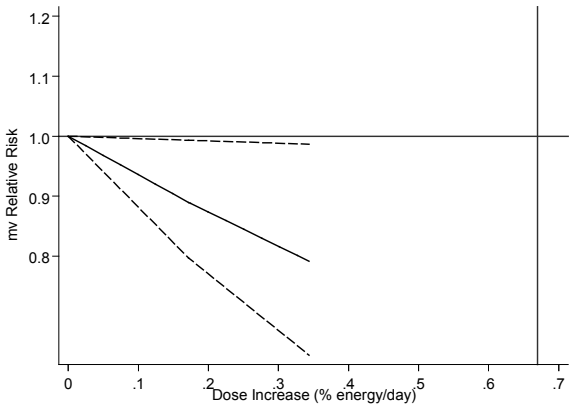
Fig. 117. Dose–response association (fixed-effect) between total n-3 PUFA (g/day) and depression in one study, assuming linearity (*P*=0.81 for goodness-of-fit)



Assuming linearity, a 1 g/day increase in n-3 PUFA was associated with a 28% decrease in risk of depression (mvRR: 0.72; 95% CI: 0.53 to 0.98). *Horizontal line represents a RR=1.0; vertical line represents the median n-3 PUFA intake in the studied populations (1.4 g/day).*

CI: confidence interval; mv: multivariable; mvRR: multivariable risk ratio; PUFA: polyunsaturated fatty acids; RR: risk ratio.

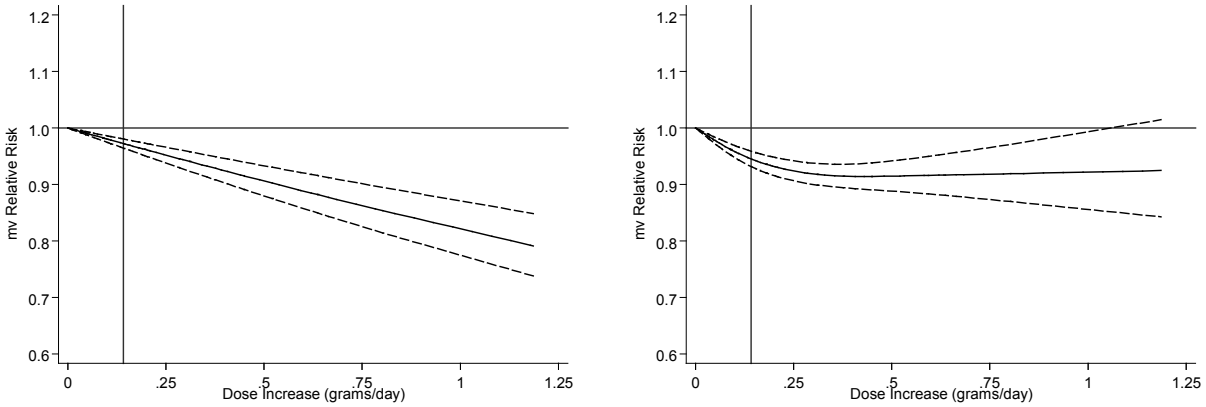
Fig. 118. Dose–response association (fixed-effect) between total n-3 PUFA (%E) and depression in one study, assuming linearity (*P*=0.81 for goodness-of-fit)



Assuming linearity, a 0.5% increase in energy from n-3 PUFA was associated with a 29% decrease in risk of depression (mvRR: 0.71; 95% CI: 0.52 to 0.98). *Horizontal line represents a RR=1.0; vertical line represents the median n-3 PUFA intake in the studied populations (0.67%E).*

CI: confidence interval; E: energy; mv: multivariable; mvRR: multivariable risk ratio; PUFA: polyunsaturated fatty acids; RR: risk ratio.

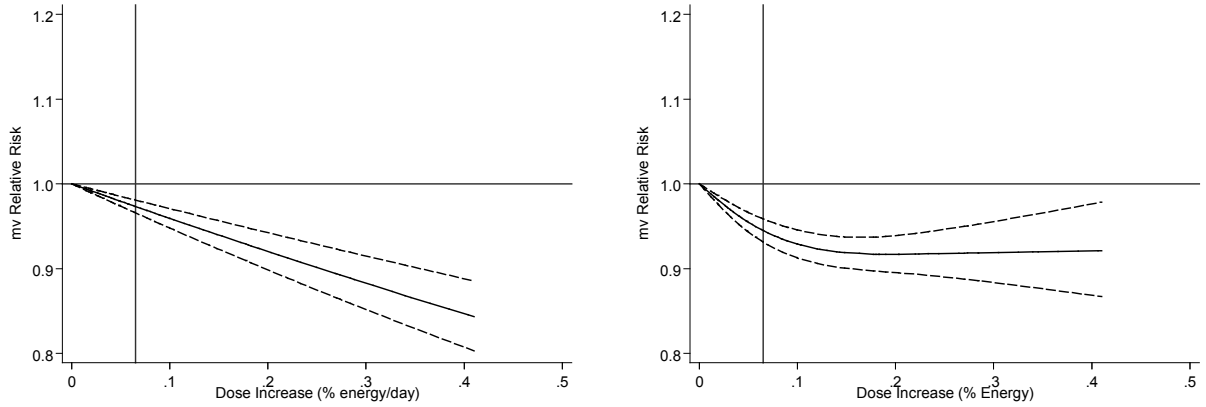
Fig. 119. Dose–response association between long-chain n-3 PUFA (g/day) and most-adjusted RR of all-cause mortality in 15 studies, assuming linearity (*P*<0.0001 for goodness-of-fit) (left), and using non-linear, cubic spline approach (right), with knots at 0, 0.09 and 0.521 g/day



Assuming linearity, a 0.5 g/day increase in long chain n-3 PUFA was associated with a 9% decrease in risk of all-cause mortality (mvRR: 0.91; 95% CI: 0.88 to 0.93). *Horizontal line represents a RR=1.0; vertical line represents the median long-chain n-3 PUFA intake in the studied populations (0.14 g/day).*

CI: confidence interval; mv: multivariable; mvRR: multivariable risk ratio; PUFA: polyunsaturated fatty acids; RR: risk ratio.

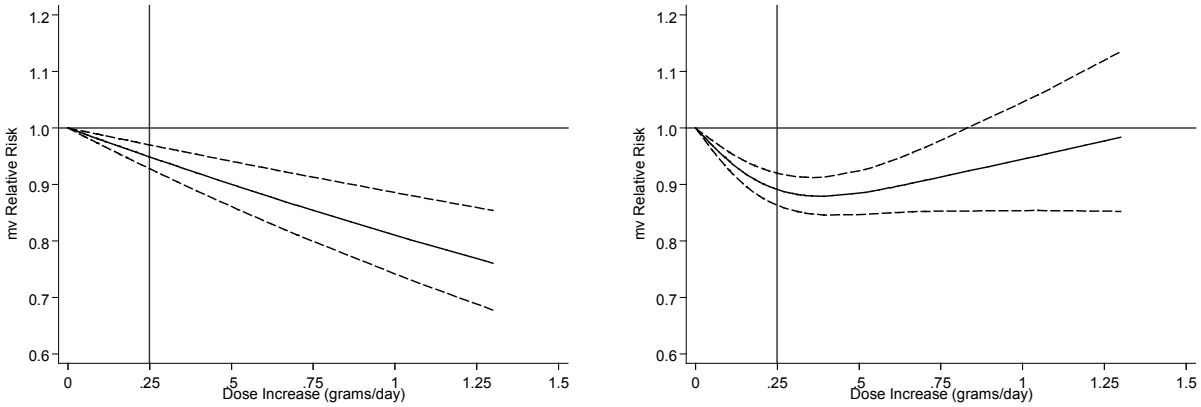
Fig. 120. Dose–response association between long-chain n-3 PUFA (%E) and most-adjusted RR of all-cause mortality in 15 studies, assuming linearity (*P*<0.0001 for goodness-of-fit) (left), and using non-linear, cubic spline approach (right), with knots at 0, 0.042 and 0.22% energy



Assuming linearity, a 0.1% increase in energy from long chain n-3 PUFA was associated with a 4% decrease in risk of all-cause mortality (mvRR: 0.96; 95% CI: 0.95 to 0.97). *Horizontal line represents a RR=1.0; vertical line represents the median long-chain n-3 PUFA intake in the studied populations (0.065%E).*

CI: confidence interval; E: energy; mv: multivariable; mvRR: multivariable risk ratio; PUFA: polyunsaturated fatty acids; RR: risk ratio.

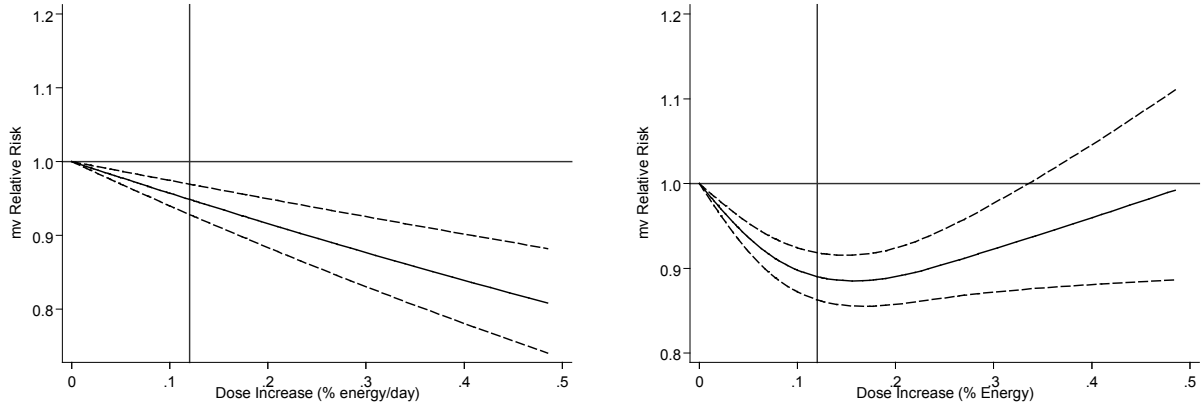
Fig. 121a. Dose–response association between long-chain n-3 PUFA (g/day) and most-adjusted RR of CVD mortality in 15 studies, assuming linearity (*P*<0.0001 for goodness-of-fit) (left), and using non-linear, cubic spline approach (right), with knots at 0, 0.144 and 0.620 g/day



Assuming linearity, a 0.5 g/day increase in long chain n-3 PUFA was associated with a 10% decrease in risk of CVD mortality (mvRR: 0.90; 95% CI: 0.86 to 0.94). *Horizontal line represents a RR=1.0; vertical line represents the median long-chain n-3 PUFA intake in the studied populations (249 mg/day).*

CI: confidence interval; CVD: cardiovascular disease; mv: multivariable; mvRR: multivariable risk ratio; PUFA: polyunsaturated fatty acids; RR: risk ratio.

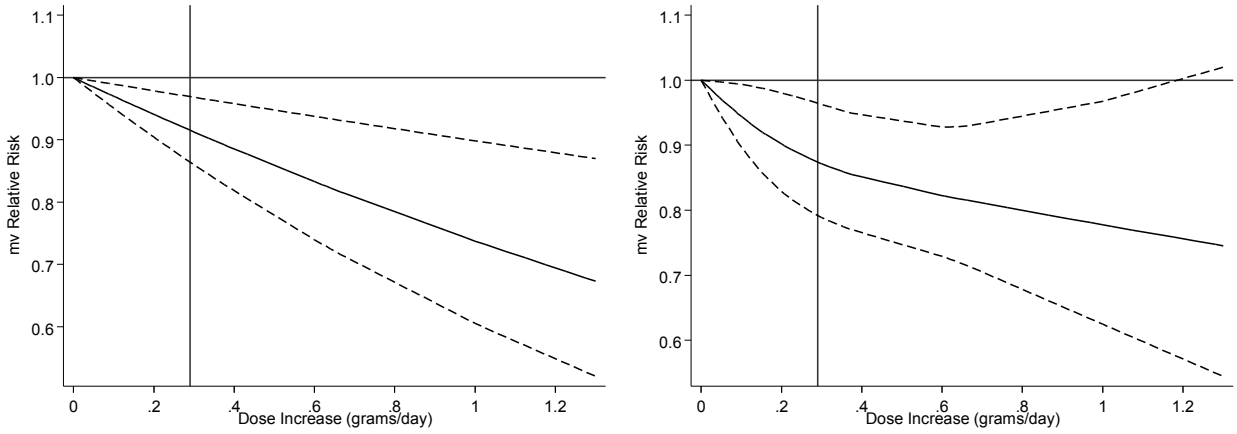
Fig. 121b. Dose–response association between long-chain n-3 PUFA (%E) and most-adjusted RR of CVD mortality in 15 studies, assuming linearity (*P*<0.0001 for goodness-of-fit) (left), and using non-linear, cubic spline approach with knots at 0, 0.067 and 0.265% (right)



Assuming linearity, a 0.1% increase in energy from long chain n-3 PUFA was associated with a 4% decrease in risk of CVD mortality (mvRR: 0.96; 95% CI: 0.94 to 0.97). *Horizontal line represents a RR=1.0; vertical line represents the median long-chain n-3 PUFA intake in the studied populations (0.12%E).*

CI: confidence interval; CVD: cardiovascular disease; E: energy; mv: multivariable; mvRR: multivariable risk ratio; PUFA: polyunsaturated fatty acids; RR: risk ratio.

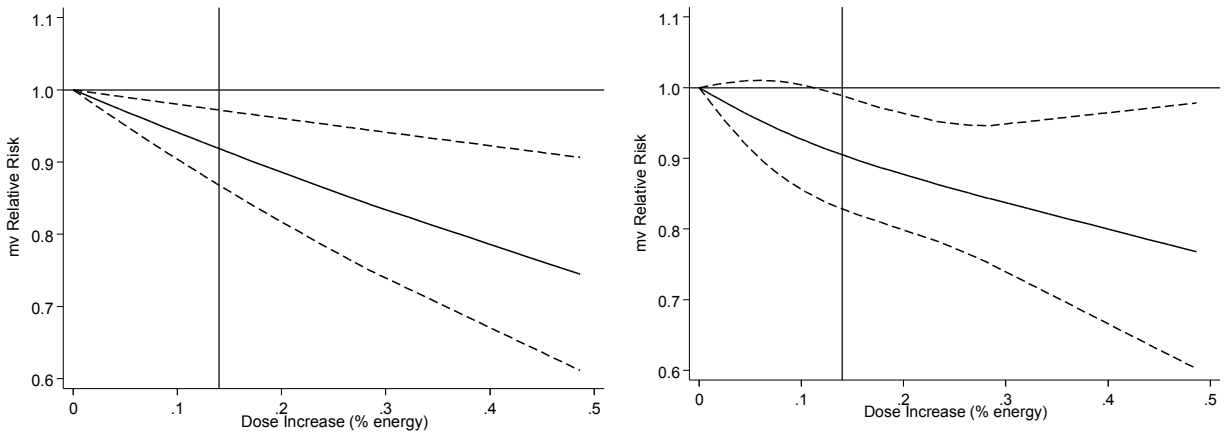
Fig. 122. Dose–response association between long-chain n-3 PUFA (g/day) and most-adjusted RR of CHD mortality in nine studies, assuming linearity (*P*<0.02 for goodness-of-fit) (left), and using non-linear, cubic spline approach (right), with knots at 0, 0.144 and 0.620 g/day



Assuming linearity, a 0.5 g/day increase in long chain n-3 PUFA was associated with a 14% decrease in risk of CHD mortality (mvRR: 0.86; 95% CI: 0.78 to 0.95). *Horizontal line represents a RR=1.0; vertical line represents the median long-chain n-3 PUFA intake in the studied populations (290 mg/day).*

CHD: coronary heart disease; CI: confidence interval; mv: multivariable; mvRR: multivariable risk ratio; PUFA: polyunsaturated fatty acids; RR: risk ratio.

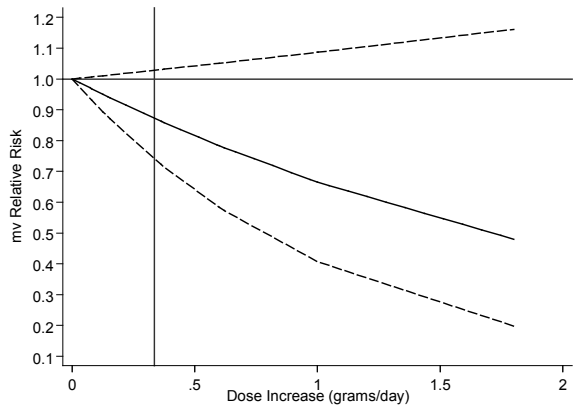
Fig. 123. Dose–response association between long-chain n-3 PUFA (%E) and most-adjusted RR of CHD mortality in nine studies, assuming linearity (*P*<0.02 for linearity) (left), and using non-linear, cubic spline approach with knots at 0, 0.067 and 0.265% (right)



Assuming linearity, a 0.5% increase in energy from long chain n-3 PUFA was associated with a 26% decrease in risk of CHD mortality (mvRR: 0.74; 95% CI: 0.60 to 0.90). *Horizontal line represents a RR=1.0; vertical line represents the median long-chain n-3 PUFA intake in the studied populations (0.14%E).*

CHD: coronary heart disease; CI: confidence interval; E: energy; mv: multivariable; mvRR: multivariable risk ratio; PUFA: polyunsaturated fatty acids; RR: risk ratio.

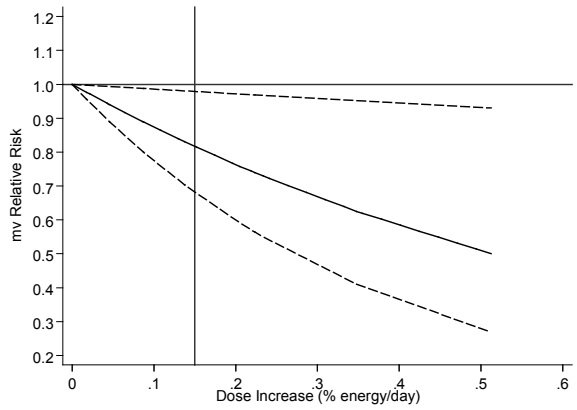
Fig. 124. Dose–response association between long-chain n-3 PUFA (g/day) and sudden cardiac death in four studies, assuming linearity (*P*=0.24 for goodness-of-fit)



Assuming linearity, a 0.5 g/day increase in long-chain n-3 PUFA was associated with an 18% decrease in risk of sudden cardiac death (mvRR: 0.82; 95% CI: 0.64 to 1.05). *Horizontal line represents a RR=1.0; vertical line represents the median n-3 PUFA intake in the studied populations (0.36 g/day).*

CI: confidence interval; mv: multivariable; mvRR: multivariable risk ratio; PUFA: polyunsaturated fatty acids; RR: risk ratio.

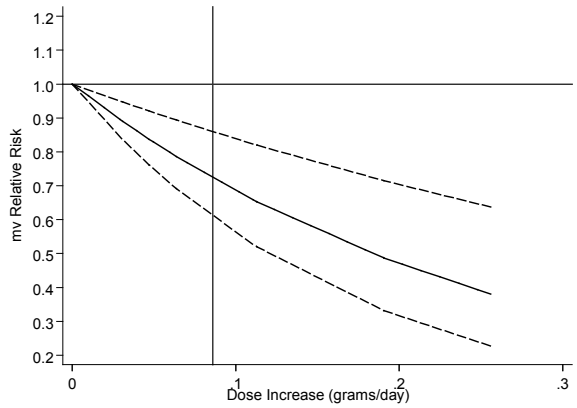
Fig. 125. Dose–response association between long-chain n-3 PUFA (%E) and sudden cardiac death in four studies, assuming linearity (*P*=0.24 for goodness-of-fit)



Assuming linearity, a 0.1% increase in energy from long-chain n-3 PUFA was associated with a 13% decrease in risk of sudden cardiac death (mvRR: 0.87; 95% CI: 0.77 to 0.99). *Horizontal line represents a RR=1.0; vertical line represents the median n-3 PUFA intake in the studied populations (0.15%E).*

CI: confidence interval; E: energy; mv: multivariable; mvRR: multivariable risk ratio; PUFA: polyunsaturated fatty acids; RR: risk ratio.

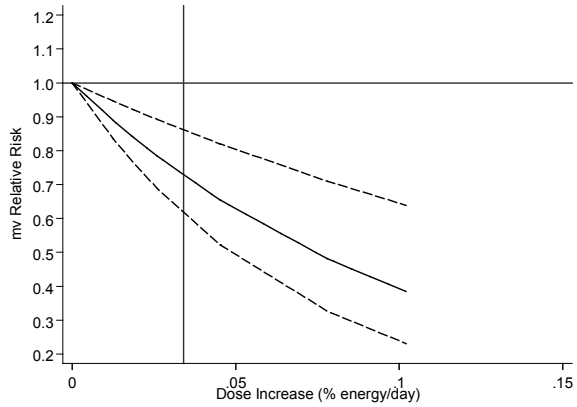
Fig. 126. Dose–response association between long-chain n-3 PUFA (g/day) and fatal myocardial infarction in two studies, assuming linearity (*P*=0.28 for goodness-of-fit)



Assuming linearity, a 0.5 g/day increase in long-chain n-3 PUFA was associated with an 85% decrease in risk of fatal myocardial infarction (mvRR: 0.15; 95% CI: 0.05 to 0.41). *Horizontal line represents a RR=1.0; vertical line represents the median n-3 PUFA intake in the studied populations (0.09 g/day).*

CI: confidence interval; mv: multivariable; mvRR: multivariable risk ratio; PUFA: polyunsaturated fatty acids; RR: risk ratio.

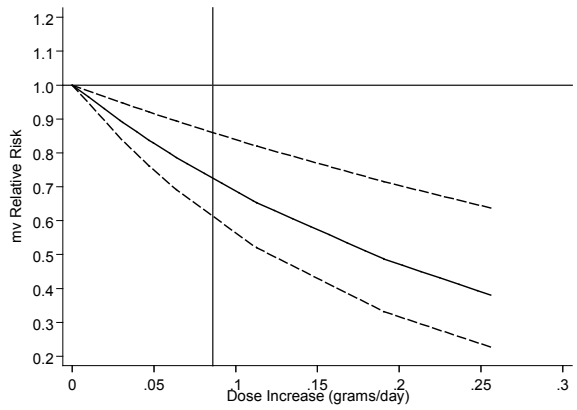
Fig. 127. Dose–response association between long-chain n-3 PUFA (%E) and fatal myocardial infarction in two studies, assuming linearity (*P*=0.29 for goodness-of-fit)



Assuming linearity, a 0.1% increase in energy from long-chain n-3 PUFA was associated with a 61% decrease in risk of fatal myocardial infarction (mvRR: 0.39; 95% CI: 0.24 to 0.64). *Horizontal line represents a RR=1.0; vertical line represents the median n-3 PUFA intake in the studied populations (0.034%E).*

CI: confidence interval; E: energy; mv: multivariable; mvRR: multivariable risk ratio; PUFA: polyunsaturated fatty acids; RR: risk ratio.

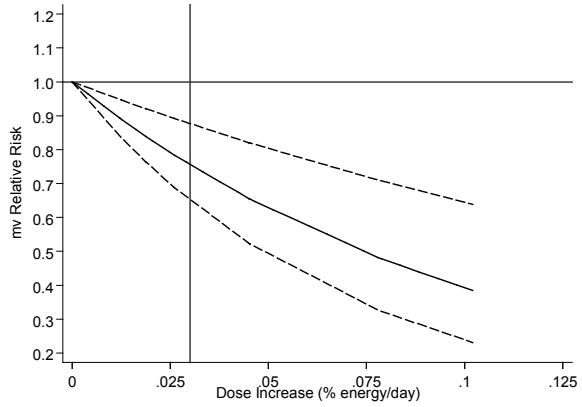
Fig. 128. Dose–response association between long-chain n-3 PUFA (g/day) and fatal arrythmia in two studies, assuming linearity (*P*=0.28 for goodness-of-fit)



Assuming linearity, a 0.5 g/day increase in long-chain n-3 PUFA was associated with an 85% decrease in risk of fatal arrythmia (mvRR: 0.15; 95% CI: 0.06 to 0.41). *Horizontal line represents a RR=1.0; vertical line represents the median n-3 PUFA intake in the studied populations (0.086 g/day).*

CI: confidence interval; mv: multivariable; mvRR: multivariable risk ratio; PUFA: polyunsaturated fatty acids; RR: risk ratio.

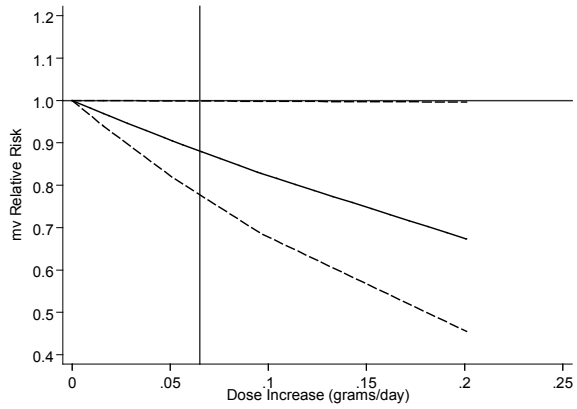
Fig. 129. Dose–response association between long-chain n-3 PUFA (%E) and fatal arrythmia in two studies, assuming linearity (*P*=0.28 for goodness-of-fit)



Assuming linearity, a 0.1% increase in energy from long-chain n-3 PUFA was associated with a 61% decrease in risk of fatal arrythmia (mvRR: 0.39; 95% CI: 0.24 to 0.64). *Horizontal line represents a RR=1.0; vertical line represents the median n-3 PUFA intake in the studied populations (0.03%E).*

CI: confidence interval; E: energy; mv: multivariable; mvRR: multivariable risk ratio; PUFA: polyunsaturated fatty acids; RR: risk ratio.

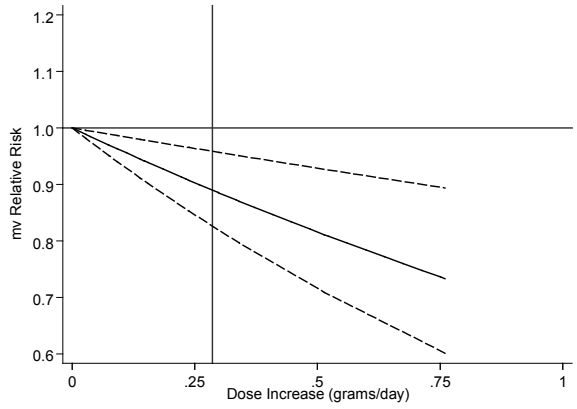
Fig. 130. Dose–response association between long-chain n-3 PUFA (g/day) and fatal ischaemic stroke in two studies, assuming linearity (*P*=0.08 for goodness-of-fit)



Too few points for cubic spline modelling. Assuming linearity, a 0.5 g/day increase in long-chain n-3 PUFA was associated with a 63% decrease in risk of fatal ischaemic stroke (mvRR: 0.37; 95% CI: 0.14 to 0.99). *Horizontal line represents a RR=1.0; vertical line represents the median long-chain n-3 PUFA intake in the studied populations (0.07 g/day).*

CI: confidence interval; mv: multivariable; mvRR: multivariable risk ratio; PUFA: polyunsaturated fatty acids; RR: risk ratio.

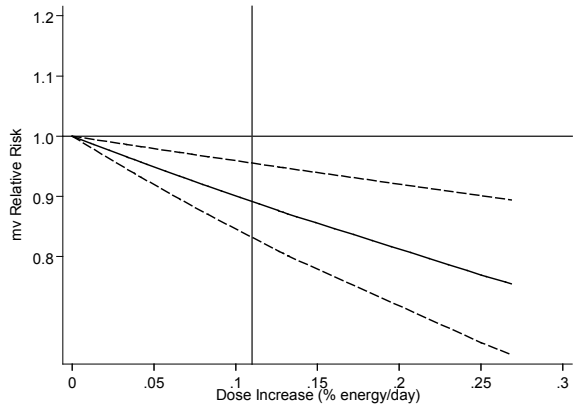
Fig. 131. Dose–response association between long-chain n-3 PUFA (g/day) and heart failure in three studies, assuming linearity (*P*=0.32 for goodness-of-fit)



Assuming linearity, a 0.5 g/day increase in long-chain n-3 PUFA was associated with an 18% decrease in risk of heart failure (mvRR: 0.82; 95% CI: 0.72 to 0.93). *Horizontal line represents a RR=1.0; vertical line represents the median long-chain n-3 PUFA intake in the studied populations (0.286 g/day).*

CI: confidence interval; d:day; mv: multivariable; mvRR: multivariable risk ratio; PUFA: polyunsaturated fatty acids; RR: risk ratio.

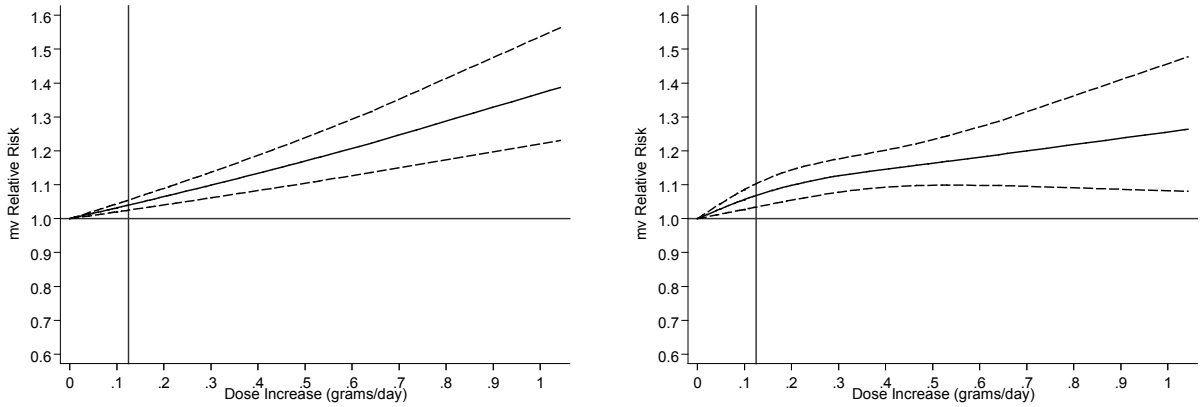
Fig. 132. Dose–response association between long-chain n-3 PUFA (%E) and heart failure in three studies, assuming linearity (*P*=0.40 for goodness-of-fit)



Assuming linearity, a 0.1% increase in energy from long-chain n-3 PUFA was associated with a 10% decrease in risk of heart failure (mvRR: 0.90; 95% CI: 0.85 to 0.96). *Horizontal line represents a RR=1.0; vertical line represents the median n-3 PUFA intake in the studied populations (0.11%E).*

CI: confidence interval; E: energy; mv: multivariable; mvRR: multivariable risk ratio; PUFA: polyunsaturated fatty acids; RR: risk ratio.

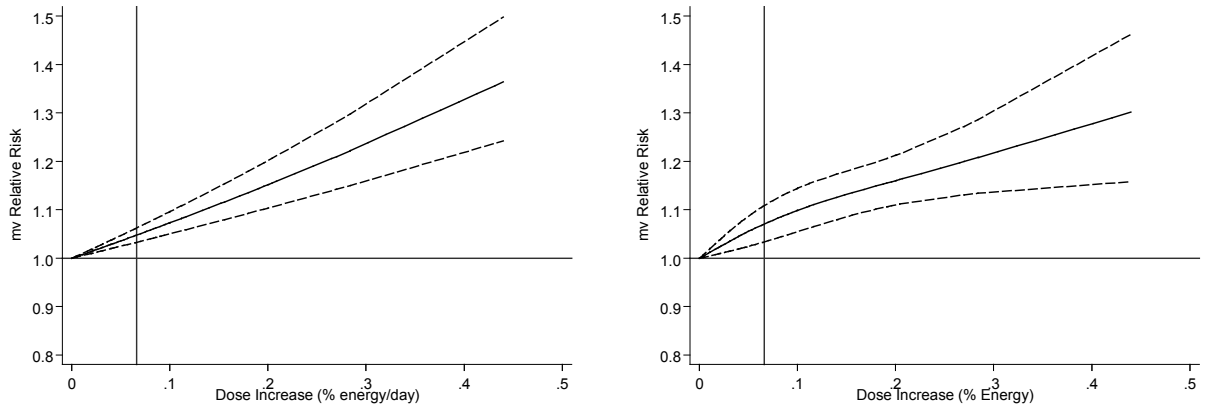
Fig. 133. Dose–response association between long-chain n-3 PUFA (g/day) and most-adjusted RR of type 2 diabetes in 15 studies, assuming linearity (*P*<0.0001 for goodness-of-fit) (left), and using non-linear, cubic spline approach (right), with knots at 0, 0.09 and 0.433 g/day



Assuming linearity, a 0.5 g/day increase in long chain n-3 PUFA was associated with a 17% increase in risk of type 2 diabetes (mvRR: 1.17; 95% CI: 1.10 to 1.24). *Horizontal line represents a RR=1.0; vertical line represents the median long-chain n-3 PUFA intake in the studied populations (125 mg/day).*

CI: confidence interval; mv: multivariable; mvRR: multivariable risk ratio; PUFA: polyunsaturated fatty acids; RR: risk ratio.

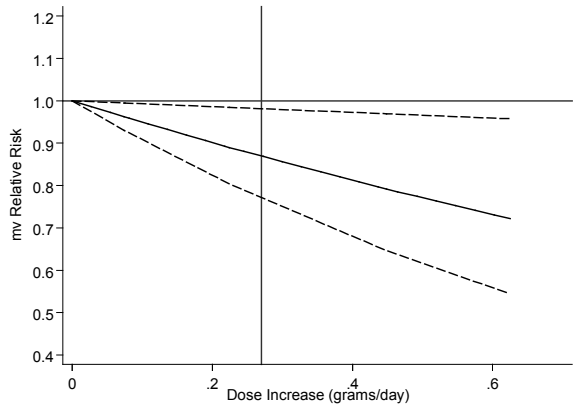
Fig. 134. Dose–response association between long-chain n-3 PUFA (%E) and most-adjusted RR of type 2 diabetes in 15 studies, assuming linearity (*P*<0.0001 for linearity) (left), and using non-linear, cubic spline approach (right), with knots at 0, 0.04 and 0.20% energy



Assuming linearity, a 0.1% increase in energy from long chain n-3 PUFA was associated with a 7% increase in risk of type 2 diabetes (mvRR: 1.07; 95% CI: 1.05 to 1.10). *Horizontal line represents a RR=1.0; vertical line represents the median long-chain n-3 PUFA intake in the studied populations (0.066%E).*

CI: confidence interval; E: energy; mv: multivariable; mvRR: multivariable risk ratio; PUFA: polyunsaturated fatty acids; RR: risk ratio.

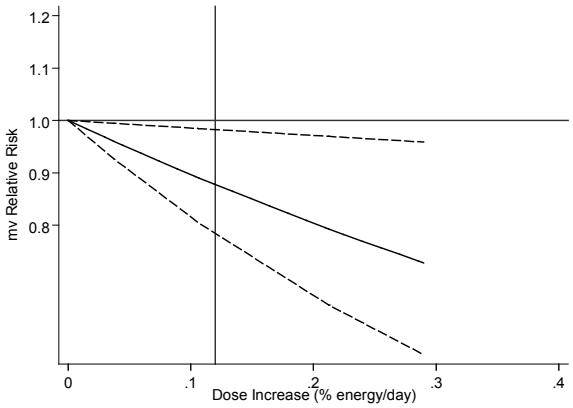
Fig. 135. Dose–response association between long-chain n-3 PUFA (g/day) and cognitive decline in three studies, assuming linearity (*P*=0.36 for goodness-of-fit)



Assuming linearity, a 0.5 g/day increase in long-chain n-3 PUFA was associated with a 23% decrease in risk of cognitive decline (mvRR: 0.77; 95% CI: 0.61 to 0.97). *Horizontal line represents a RR=1.0; vertical line represents the median long-chain n-3 PUFA intake in the studied populations (0.270 g/day).*

CI: confidence interval; mv: multivariable; mvRR: multivariable risk ratio; PUFA: polyunsaturated fatty acids; RR: risk ratio.

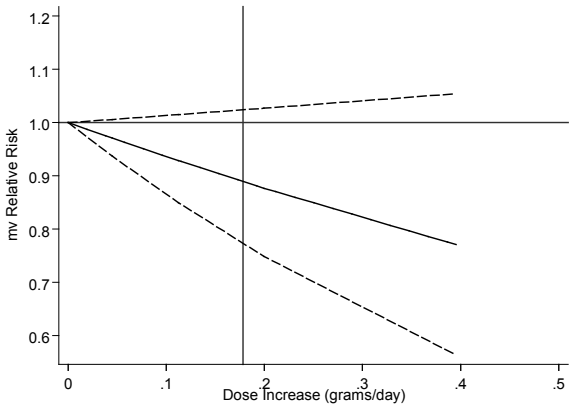
Fig. 136. Dose–response association between long-chain n-3 PUFA (%E) and cognitive decline in three studies, assuming linearity (*P*=0.36 for goodness-of-fit)



Assuming linearity, a 0.1% increase in energy from long-chain n-3 PUFA was associated with an 11% decrease in risk of cognitive decline (mvRR: 0.89; 95% CI: 0.81 to 0.99). *Horizontal line represents a RR=1.0; vertical line represents the median long-chain n-3 PUFA intake in the studied populations (0.124%E).*

CI: confidence interval; E: energy; mv: multivariable; mvRR: multivariable risk ratio; PUFA: polyunsaturated fatty acids; RR: risk ratio.

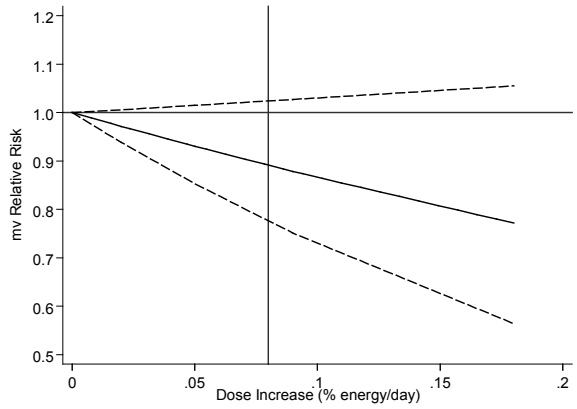
Fig. 137. Dose–response association between long-chain n-3 PUFA (g/day) and ulcerative colitis in one study, assuming linearity (*P*=0.57 for goodness-of-fit)



Assuming linearity, a 0.5 g/day increase in long-chain n-3 PUFA was associated with a 29% decrease in risk of ulcerative colitis (mvRR: 0.71; 95% CI: 0.48 to 1.07). *Horizontal line represents a RR=1.0; vertical line represents the median long-chain n-3 PUFA intake in the studied populations (0.178 g/day).*

CI: confidence interval; mv: multivariable; mvRR: multivariable risk ratio; PUFA: polyunsaturated fatty acids; RR: risk ratio.

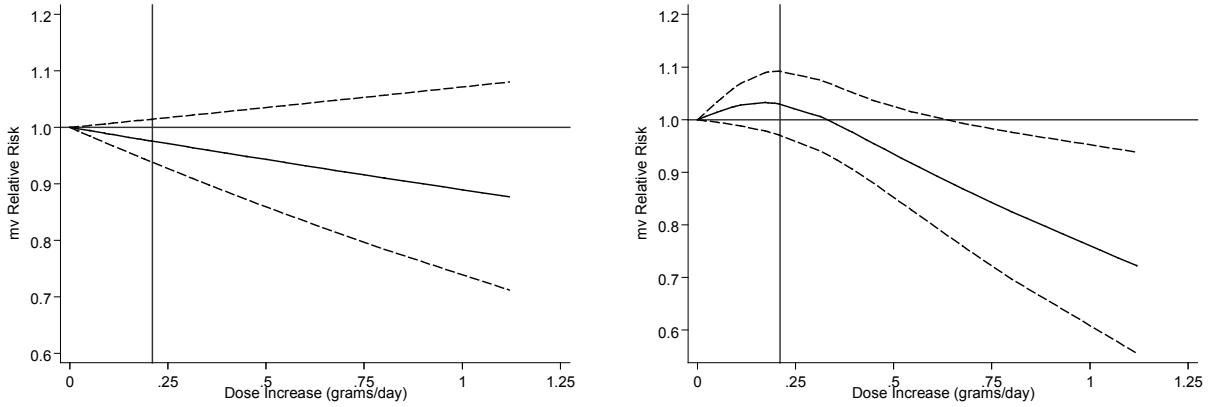
Fig. 138. Dose–response association between long-chain n-3 PUFA (%E) and ulcerative colitis in one study, assuming linearity (*P*=0.57 for goodness-of-fit)



Assuming linearity, a 0.1% increase in energy from long-chain n-3 PUFA was associated with a 13% decrease in risk of ulcerativ colitis (mvRR: 0.87; 95% CI: 0.72 to 1.03). H*orizontal line represents a RR=1.0; vertical line represents the median long-chain n-3 PUFA intake in the studied populations (0.08%E).*

CI: confidence interval; E: energy; mv: multivariable; mvRR: multivariable risk ratio; PUFA: polyunsaturated fatty acids; RR: risk ratio.

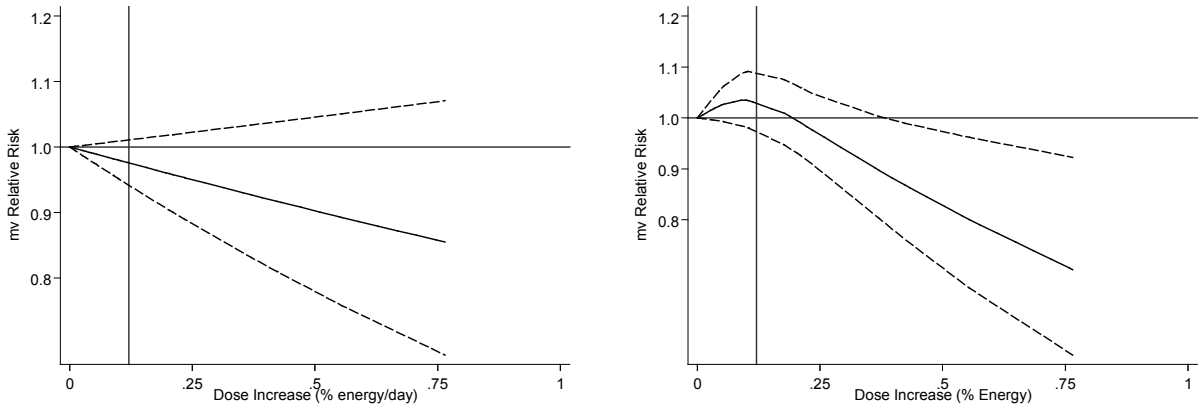
Fig. 139. Dose–response association between long-chain n-3 PUFA (g/day) and breast cancer in six studies, assuming linearity (*P*=0.059 for goodness-of-fit) (left), and using non-linear, cubic spline approach (right), with knots at 0, 0.14 and 0.45 g/day



Assuming linearity, a 0.1% increase in energy from long-chain n-3 PUFA was associated with a 13% decrease in risk of Assuming linearity, a 0.5 g/day increase in long-chain n-3 PUFA was associated with a 6% decrease in risk of breast cancer (mvRR: 0.94; 95% CI: 0.86 to 1.04). *Horizontal line represents a RR=1.0; vertical line represents the median long-chain n-3 PUFA intake in the studied populations (0.210 g/day).*

CI: confidence interval; mv: multivariable; mvRR: multivariable risk ratio; PUFA: polyunsaturated fatty acids; RR: risk ratio.

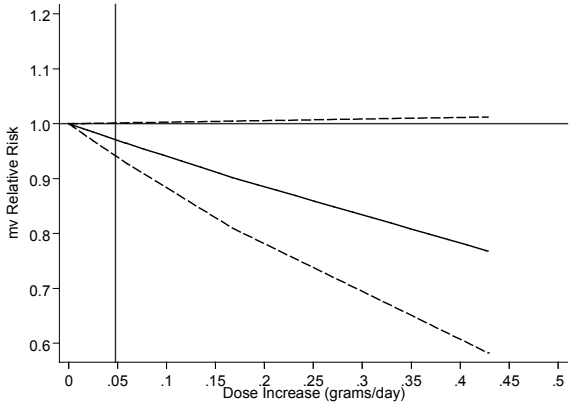
Fig. 140. Dose–response association between long-chain n-3 PUFA (%E) and breast cancer in six studies, assuming linearity (*P*=0.045 for goodness-of-fit) (left), and using non-linear, cubic spline approach (right), with knots at 0, 0.07 and 0.23% energy



Assuming linearity, a 0.1% increase in energy from long-chain n-3 PUFA was associated with a 2% decrease in risk of breast cancer (mvRR: 0.98; 95% CI: 0.95 to 1.01). *Horizontal line represents a RR=1.0; vertical line represents the median long-chain n-3 PUFA intake in the studied populations (0.12%E).*

CI: confidence interval; E: energy; mv: multivariable; mvRR: multivariable risk ratio; PUFA: polyunsaturated fatty acids; RR: risk ratio.

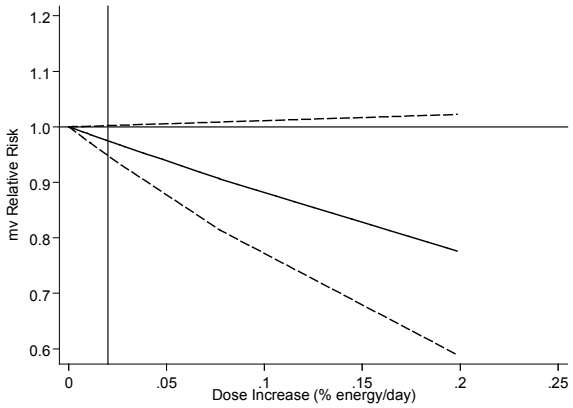
Fig. 141. Dose–response association between EPA (g/day) and all-cause mortality in two studies, assuming linearity (*P*=0.059 for goodness-of-fit)



Too few points for cubic spline modelling. Assuming linearity, a 0.5 g/day increase in EPA was associated with a 27% decrease in risk of all-cause mortality (mvRR: 0.73; 95% CI: 0.53 to 1.01). *Horizontal* line represents a RR=1.0; vertical line represents the median EPA intake in the studied populations (0.0475 g/day).

CI: confidence interval; EPA: eicosapentaenoic acid; mv: multivariable; mvRR: multivariable risk ratio; RR: risk ratio.

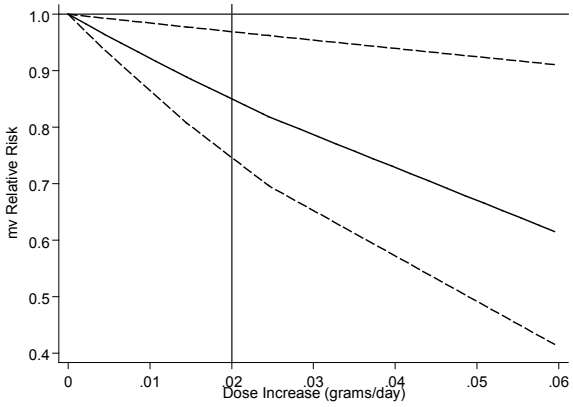
Fig. 142. Dose–response association between EPA (%E) and all-cause mortality in two studies, assuming linearity (*P*=0.059 for goodness-of-fit)



Too few points for cubic spline modelling. Assuming linearity, a 0.1% increase in energy from EPA was associated with a 12% decrease in risk of all-cause mortality (mvRR: 0.88; 95% CI: 0.77 to 1.01). *Horizontal line represents a RR=1.0; vertical line represents the median EPA intake in the studied populations (0.02%E).*

CI: confidence interval; E: energy; EPA: eicosapentaenoic acid; mv: multivariable; mvRR: multivariable risk ratio; RR: risk ratio.

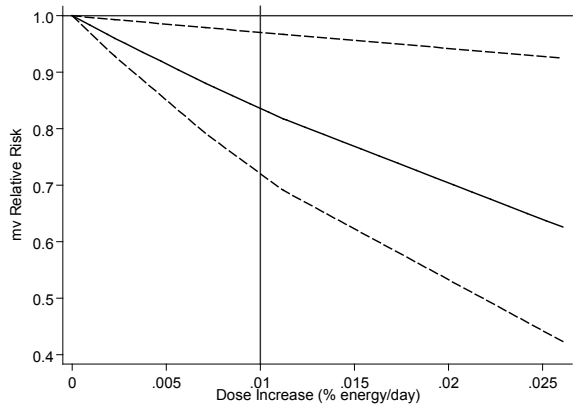
Fig. 143. Dose–response association between EPA (g/day) and fatal ischaemic stroke in one study, assuming linearity (*P*=0.34 for goodness-of-fit)



Assuming linearity, a 0.5 g/day increase in EPA was associated with a 99% decrease in risk of fatal ischaemic stroke (mvRR: 0.02; 95% CI: 0.0006 to 0.4568). *Horizontal line represents a RR=1.0; vertical line represents the median EPA intake in the studied populations (0.02 g/day).*

CI: confidence interval; EPA: eicosapentaenoic acid; mv: multivariable; mvRR: multivariable risk ratio; RR: risk ratio.

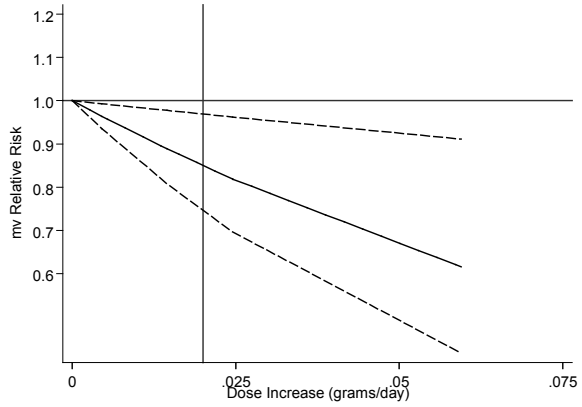
Fig. 144. Dose–response association between EPA (%E) and fatal ischaemic stroke in one study, assuming linearity (*P*=0.34 for goodness-of-fit)



Assuming linearity, a 0.1% increase in energy from EPA was associated with an 83% decrease in risk of fatal ischaemic stroke (mvRR: 0.17; 95% CI: 0.04 to 0.74). *Horizontal line represents a RR=1.0; vertical line represents the median EPA intake in the studied populations (0.01%E).*

CI: confidence interval; E: energy; EPA: eicosapentaenoic acid; mv: multivariable; mvRR: multivariable risk ratio; RR: risk ratio.

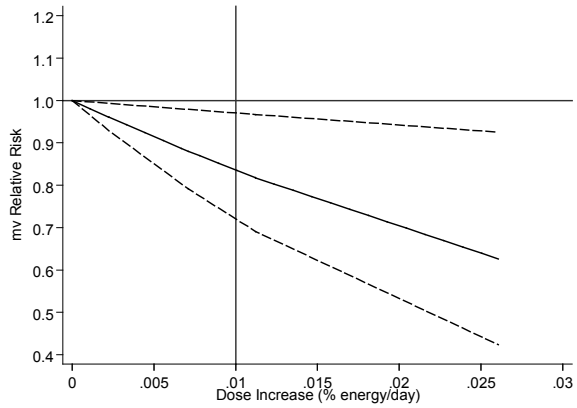
Fig. 145. Dose–response association between EPA (g/day) and total myocardial infarction in one study, assuming linearity (*P*=0.35 for goodness-of-fit)



Too few points for cubic spline modelling. Assuming linearity, a 0.5 g increase in EPA was associated with a 98% decrease in risk of mortality (mvRR: 0.02; 95% CI: 0.0006 to 0.46). *Horizontal line represents a RR=1.0; vertical line represents the median EPA intake in the studied populations (0.02 g/day).*

CI: confidence interval; EPA: eicosapentaenoic acid; mv: multivariable; mvRR: multivariable risk ratio; RR: risk ratio.

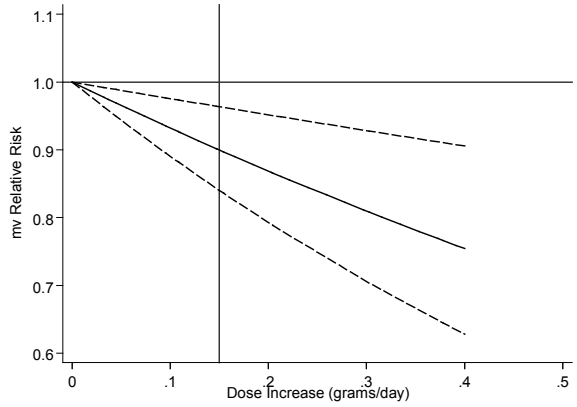
Fig. 146. Dose–response association between EPA (%E) and total myocardial infarction in one study, assuming linearity (*P*=0.30 for goodness-of-fit)



Assuming linearity, a 0.1% increase in energy from EPA was associated with an 83% decrease in risk of total myocardial infarction (mvRR: 0.17; 95% CI: 0.04 to 0.74). *Horizontal line represents a RR=1.0; vertical line represents the median EPA intake in the studied populations (0.01%E).*

CI: confidence interval; E: energy; EPA: eicosapentaenoic acid; mv: multivariable; mvRR: multivariable risk ratio; RR: risk ratio.

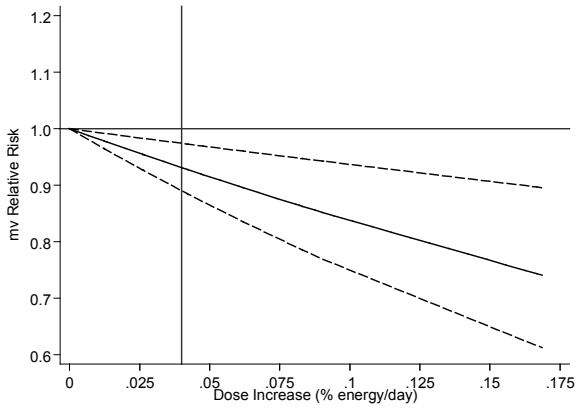
Fig. 147. Dose–response association between EPA (g/day) and depression in four studies, assuming linearity (*P*=0.56 for goodness-of-fit)



Assuming linearity, a 0.5 g increase in EPA was associated with a 30% decrease in risk of depression (mvRR: 0.70; 95% CI: 0.56 to 0.88). *Horizontal line represents a RR=1.0; vertical line represents the median EPA intake in the studied populations (0.15 g/day).*

CI: confidence interval; EPA: eicosapentaenoic acid; mv: multivariable; mvRR: multivariable risk ratio; RR: risk ratio.

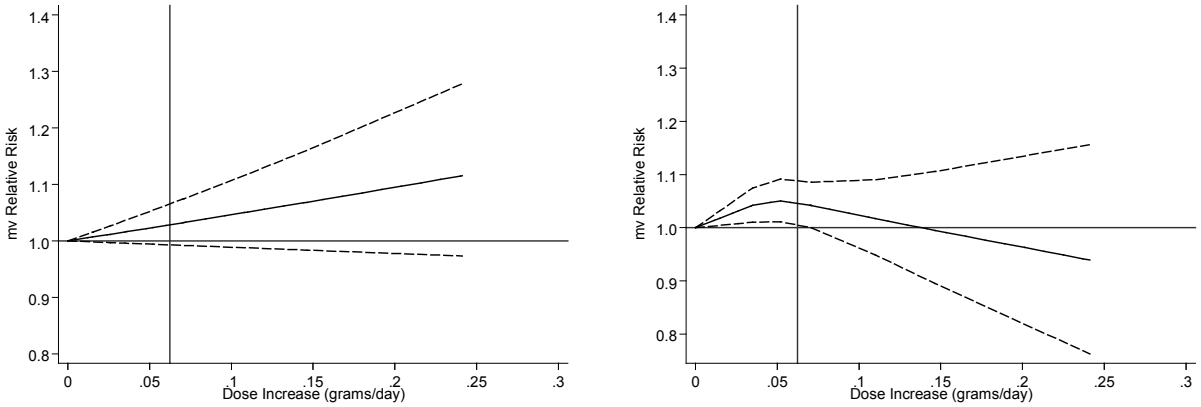
Fig. 148. Dose–response association between EPA (%E) and depression in four studies, assuming linearity (*P*=0.60 for goodness-of-fit)



Assuming linearity, a 0.1% increase in energy from EPA was associated with a 16% decrease in risk of depression (mvRR: 0.84; 95% CI: 0.75 to 0.94). *Horizontal line represents a RR=1.0; vertical line represents the median EPA intake in the studied populations (0.04%E).*

CI: confidence interval; E: energy; EPA: eicosapentaenoic acid; mv: multivariable; mvRR: multivariable risk ratio; RR: risk ratio.

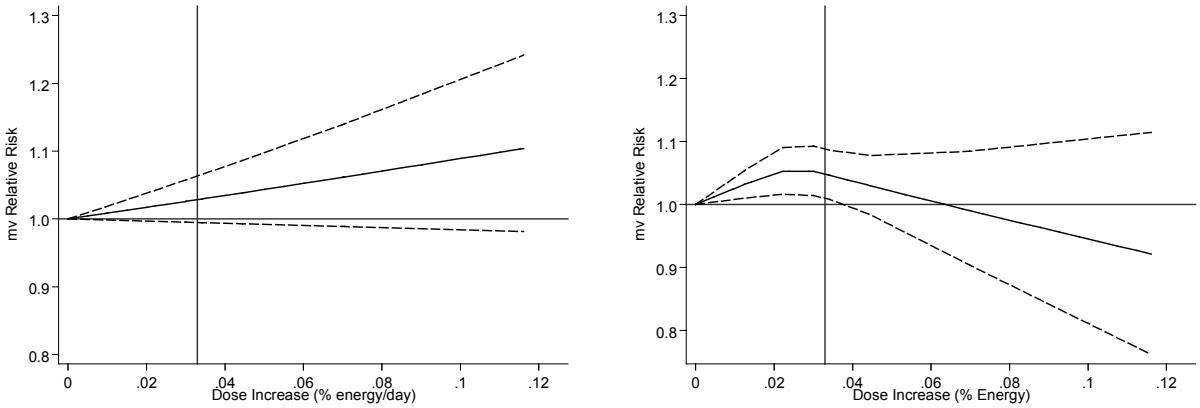
Fig. 149. Dose–response association between EPA (g/day) and breast cancer in three studies, assuming linearity (*P*<0.007 for goodness-of-fit) (left), and using non-linear, cubic spline approach (right), with knots at 0.026, 0.043 and 0.070 g/day



Assuming linearity, a 0.5 g/day increase in EPA was associated with a 25% increase in risk of breast cancer (mvRR: 1.25; 95% CI: 0.95 to 1.66). *Horizontal line represents a RR=1.0; vertical line represents the median EPA intake in the studied populations (0.062 g/day).*

CI: confidence interval; EPA: eicosapentaenoic acid; mv: multivariable; mvRR: multivariable risk ratio; RR: risk ratio.

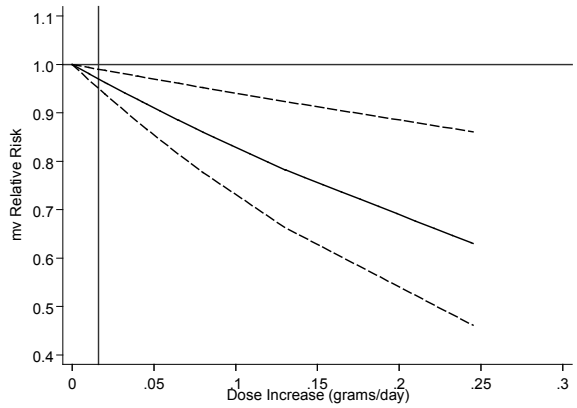
Fig. 150. Dose–response association between EPA (%E) and breast cancer in three studies, assuming linearity (*P*<0.007 for goodness-of-fit) (left), and using non-linear, cubic spline approach (right), with knots at 0.012, 0.026 and 0.034% energy



Assuming linearity, a 0.1% increase in energy from EPA was associated with a 9% increase in risk of breast cancer (mvRR: 1.09; 95% CI: 0.98 to 1.20). *Horizonta*l line represents a RR=1.0; vertical line represents the median EPA intake in the studied populations (0.033%E).

CI: confidence interval; E: energy; EPA: eicosapentaenoic acid; mv: multivariable; mvRR: multivariable risk ratio; RR: risk ratio.

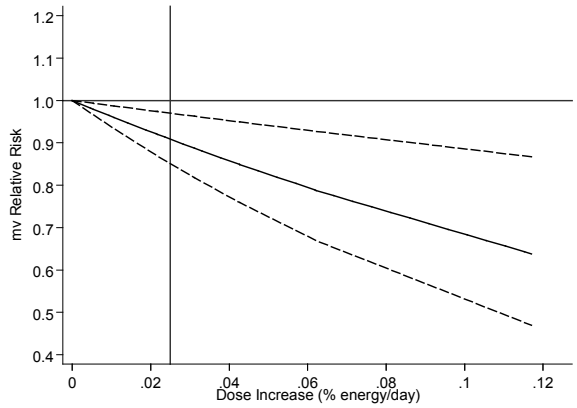
Fig. 151. Dose–response association between EPA (g/day) and post-menopausal breast cancer, assuming linearity (*P*=0.46 for goodness-of-fit)



Assuming linearity, a 0.5 g increase in EPA was associated with a 61% decrease in risk of post-menopausal breast cancer (mvRR: 0.39; 95% CI: 0.21 to 0.74). *Horizontal line represents a RR=1.0; vertical line represents the median EPA intake in the studied populations (0.015 g/day).*

CI: confidence interval; EPA: eicosapentaenoic acid; mv: multivariable; mvRR: multivariable risk ratio; RR: risk ratio.

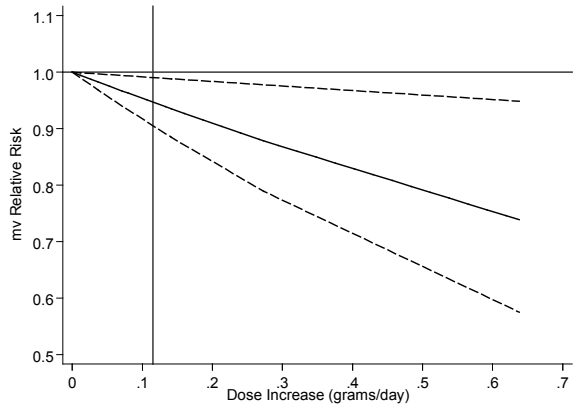
Fig. 152. Dose–response association between EPA (%E) and post-menopausal breast cancer, assuming linearity (*P*=0.44 for goodness-of-fit)



Assuming linearity, a 0.1% increase in energy from EPA was associated with a 32% decrease in risk of post-menopausal breast cancer (mvRR: 0.68; 95% CI: 0.52 to 0.89). *Horizontal line represents a RR=1.0; vertical line represents the median EPA intake in the studied populations (0.025%E).*

CI: confidence interval; E: energy; EPA: eicosapentaenoic acid; mv: multivariable; mvRR: multi 9variable risk ratio; RR: risk ratio.

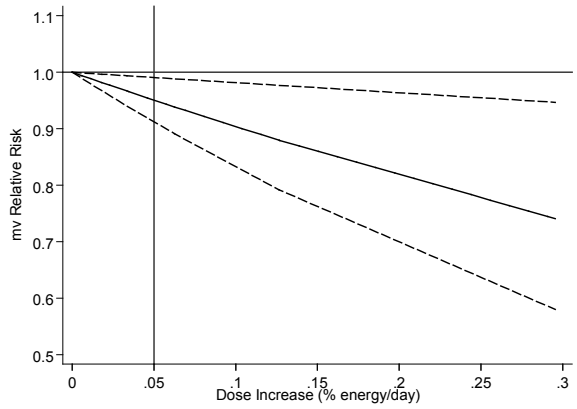
Fig. 153. Dose–response association between DHA (g/day) and all-cause mortality in two studies, assuming linearity (*P*<0.0001 for goodness-of-fit)



Too few points for cubic spline modelling. Assuming linearity, a 0.5 g increase in DHA was associated with a 21% decrease in risk of all-cause mortality (mvRR: 0.79; 95% CI: 0.65 to 0.96). *Horizontal line represents a RR=1.0; vertical line represents the median DHA intake in the studied populations (0.115 g/day).*

CI: confidence interval; DHA: docosahexaenoic acid; mv: multivariable; mvRR: multivariable risk ratio; RR: risk ratio.

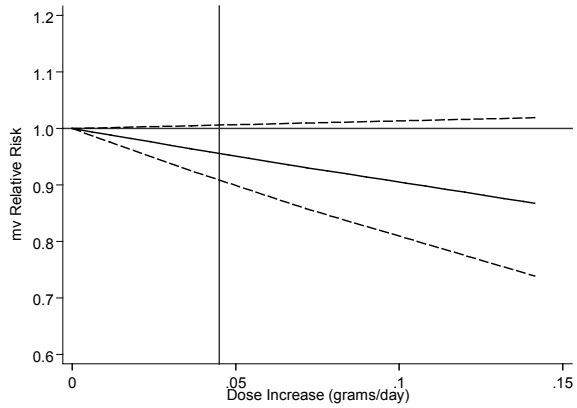
Fig. 154. Dose–response association between DHA (%E) and all-cause mortality in two studies, assuming linearity (*P*<0.0001 for goodness-of-fit)



Too few points for cubic spline modelling. Assuming linearity, a 0.1% increase in energy from DHA was associated with a 10% decrease in risk of all-cause mortality (mvRR: 0.90; 95% CI: 0.83 to 0.98). *Horizontal line represents a RR=1.0; vertical line represents the median DHA intake in the studied populations (0.05%E).*

CI: confidence interval; DHA: docosahexaenoic acid; E: energy; mv: multivariable; mvRR: multivariable risk ratio; RR: risk ratio.

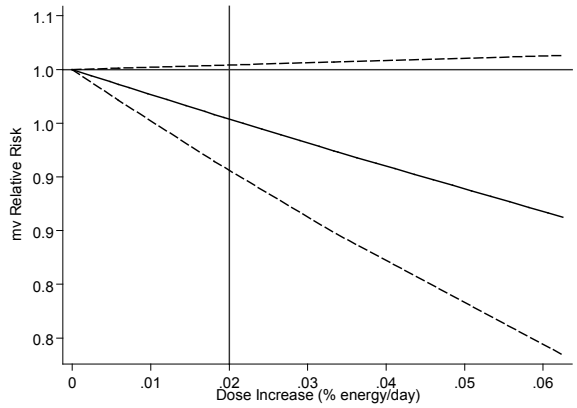
Fig. 155. Dose–response association between DHA (g/day) and CVD mortality in one study, assuming linearity (*P*<0.0028 for goodness-of-fit)



Too few points for cubic spline modelling. Assuming linearity, a 0.5-g increase in DHA was associated with a 39% decrease in risk of CVD mortality (mvRR: 0.61; 95% CI: 0.34 to 1.07). *Horizontal line represents a RR=1.0; vertical line represents the median DHA intake in the studied populations (0.045 g/day).*

CI: confidence interval; CVD: cardiovascular disease; DHA: docosahexaenoic acid; mv: multivariable; mvRR: multivariable risk ratio; RR: risk ratio.

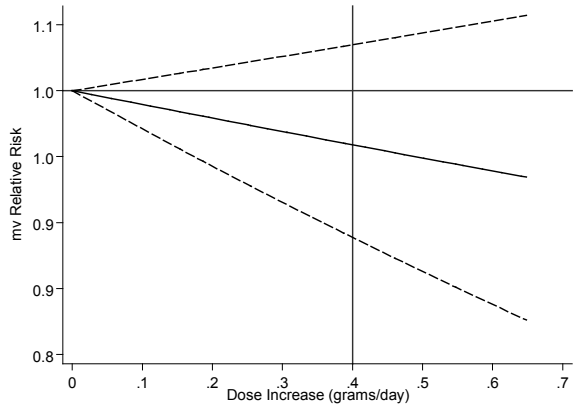
Fig. 156. Dose–response association between DHA (%E) and CVD mortality in one study, assuming linearity (*P*<0.0032 for goodness-of-fit)



Too few points for cubic spline modelling. Assuming linearity, a 0.1% increase in energy from DHA was associated with a 21% decrease in risk of CVD mortality (mvRR: 0.79; 95% CI: 0.61 to 1.02). *Horizontal line represents a RR=1.0; vertical line represents the median DHA intake in the studied populations (0.02%E).*

CI: confidence interval; CVD: cardiovascular disease; DHA: docosahexaenoic acid; E: energy; mv: multivariable; mvRR: multivariable risk ratio; RR: risk ratio.

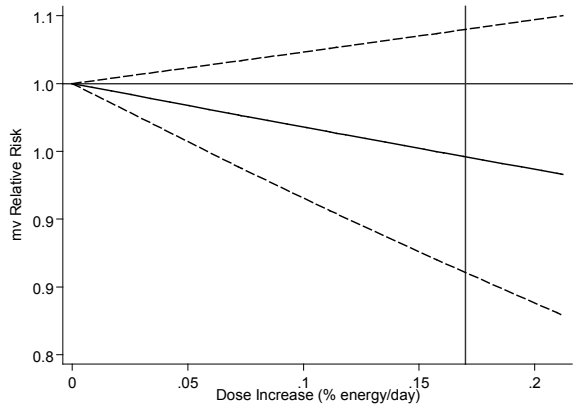
Fig. 157. Dose–response association between DHA (g/day) and total myocardial infarction in two studies, assuming linearity (*P*=0.61 for goodness-of-fit



Assuming linearity, a 0.5 g/day increase in DHA was associated with a 5% decrease in risk of total myocardial infarction (mvRR: 0.95; 95% CI: 0.86 to 1.04). *Horizontal line represents a RR=1.0; vertical line represents the median DHA intake in the studied populations (0.40 g/day).*

CI: confidence interval; DHA: docosahexaenoic acid; mv: multivariable; mvRR: multivariable risk ratio; RR: risk ratio.

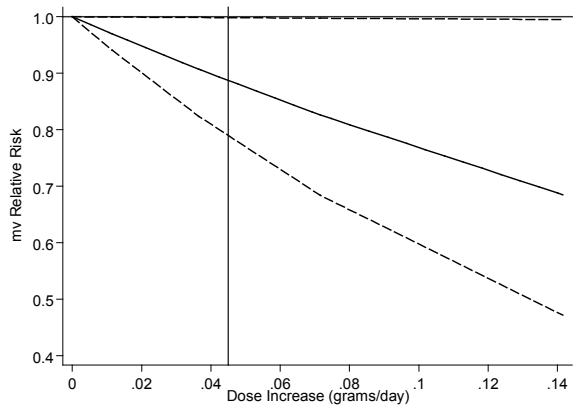
Fig. 158. Dose–response association between DHA (%E) and total myocardial infarction in two studies, assuming linearity (*P*=0.62 for goodness-of-fit



Assuming linearity, a 0.1% increase in energy from DHA was associated with a 3% decrease in risk of total myocardial infarction (mvRR: 0.97; 95% CI: 0.91 to 1.02). *Horizontal line represents a RR=1.0; vertical line represents the median DHA intake in the studied populations (0.17%E).*

CI: confidence interval; DHA: docosahexaenoic acid; E: energy; mv: multivariable; mvRR: multivariable risk ratio; RR: risk ratio.

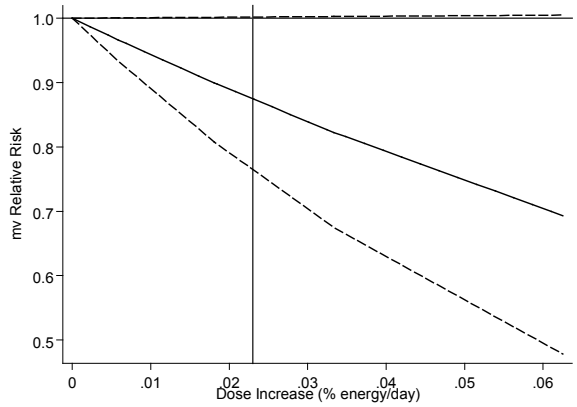
Fig. 159. Dose–response association between DHA (g/day) and fatal ischaemic stroke in one study, assuming linearity (*P*=0.12 for goodness-of-fit)



Assuming linearity, a 0.5 g/day increase in DHA was associated with a 74% decrease in risk of fatal ischaemic stroke (mvRR: 0.26; 95% CI: 0.07 to 0.98). *Horizontal line represents a RR=1.0; vertical line represents the median DHA intake in the studied populations (0.045 g/day).*

CI: confidence interval; DHA: docosahexaenoic acid; mv: multivariable; mvRR: multivariable risk ratio; RR: risk ratio.

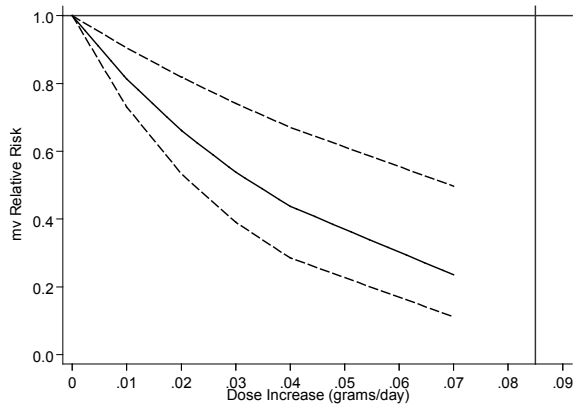
Fig. 160. Dose–response association between DHA (%E) and fatal ischaemic stroke in one study, assuming linearity (*P*=0.11 for goodness-of-fit)



Assuming linearity, a 0.1% increase in energy from DHA was associated with a 44% decrease in risk of fatal ischaemic stroke (mvRR: 0.56; 95% CI: 0.31 to 1.007). *Horizontal line represents a RR=1.0; vertical line represents the median DHA intake in the studied populations (0.023%E).*

CI: confidence interval; DHA: docosahexaenoic acid; E: energy; mv: multivariable; mvRR: multivariable risk ratio; RR: risk ratio.

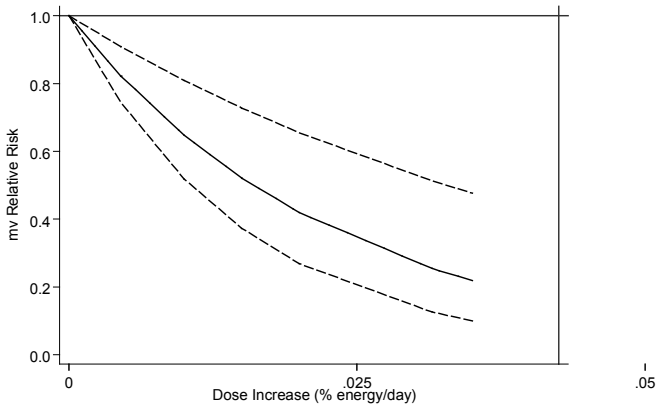
Fig. 161. Dose–response association between DHA (g/day) and dementia in two studies, assuming linearity (*P*=0.001 for goodness-of-fit)



Too few points for cubic spline modelling. Assuming linearity, a 0.5 g/day increase in DHA was associated with a 99% decrease in risk of dementia (mvRR: 0.00003; 95% CI: 1.5 x 10−7 to 0.07). *Horizontal line represents a RR=1.0; vertical line represents the median DHA intake in the studied populations (0.085 g/day).*

CI: confidence interval; DHA: docosahexaenoic acid; mv: multivariable; mvRR: multivariable risk ratio; RR: risk ratio.

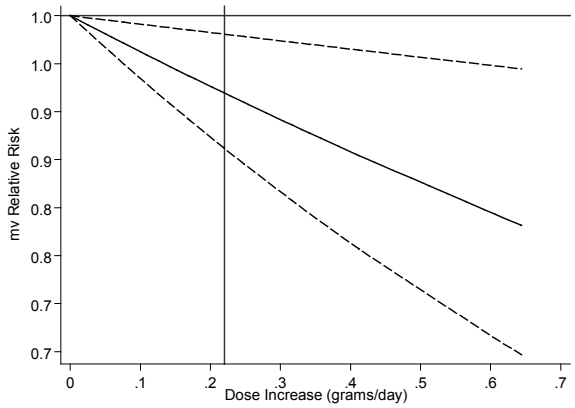
Fig. 162. Dose–response association between DHA (%E) and dementia in two studies, assuming linearity (*P*=0.001 for goodness-of-fit)



Too few points for cubic spline modelling. Assuming linearity, a 0.5 g/day increase in DHA was associated with a 99% decrease in risk of dementia (mvRR: 0.012; 95% CI: 0.0014 to 0.12). *Horizontal line represents a RR=1.0; vertical line represents the median DHA intake in the studied populations (0.0425 g/day).*

CI: confidence interval; DHA: docosahexaenoic acid; E: energy; mv: multivariable; mvRR: multivariable risk ratio; RR: risk ratio.

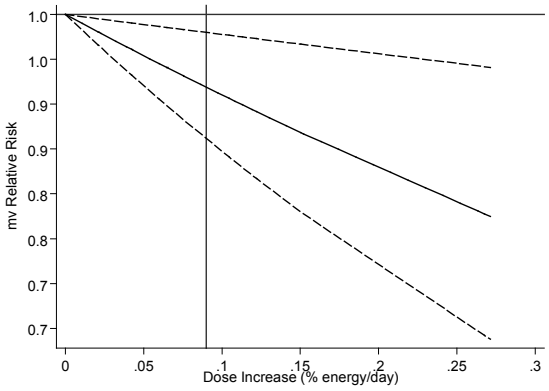
Fig. 163. Dose–response association between DHA (g/day) and depression in four studies, assuming linearity (*P*=0.53 for goodness-of-fit)



Too few points for cubic spline modelling. Assuming linearity, a 0.5 g/day increase in DHA was associated with a 17% decrease in risk of depression (mvRR: 0.83; 95% CI: 0.71 to 0.96). *Horizontal line represents a RR=1.0; vertical line represents the median DHA intake in the studied populations (0.22 g/day).*

CI: confidence interval; DHA: docosahexaenoic acid; mv: multivariable; mvRR: multivariable risk ratio; RR: risk ratio.

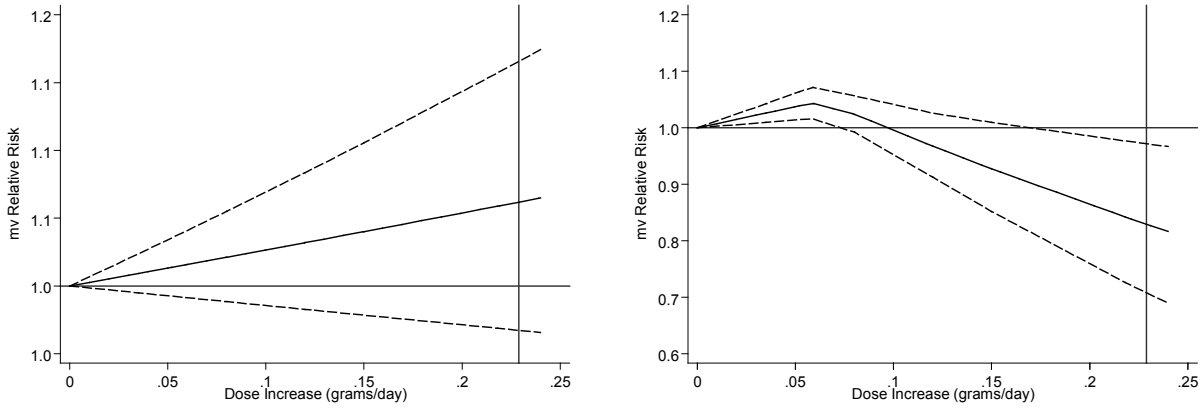
Fig. 164. Dose–response association between DHA (%E) and depression in four studies, assuming linearity (*P*=0.53 for goodness-of-fit)



Assuming linearity, a 0.1% increase in energy from DHA was associated with a 9% decrease in risk of depression (mvRR: 0.91; 95% CI: 0.85 to 0.98). *Horizontal line represents a RR=1.0; vertical line represents the median DHA intake in the studied populations (0.09%E).*

CI: confidence interval; DHA: docosahexaenoic acid; E: energy; mv: multivariable; mvRR: multivariable risk ratio; RR: risk ratio.

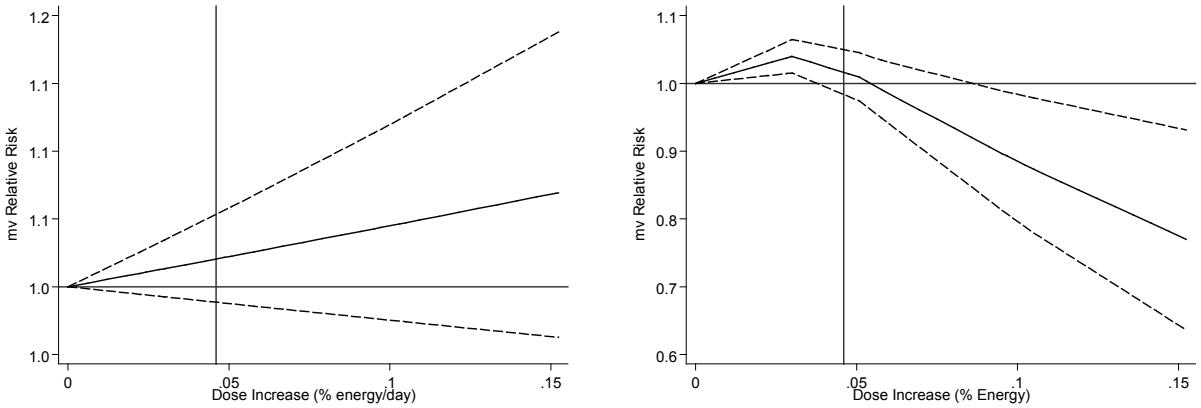
Fig. 165. Dose–response association between DHA (g/day) and breast cancer in three studies, assuming linearity (*P*=0.0075 for goodness-of-fit) (left), and using non-linear, cubic spline approach (right), with knots at 0.05, 0.06 and 0.08 g/day



Assuming linearity, a 0.5 g/day increase in DHA was associated with a 14% increase in risk of breast cancer (mvRR: 1.14; 95% CI: 0.93 to 1.40). *Horizontal line represents a RR=1.0; vertical line represents the median DHA intake in the studied populations (0.229 g/day).*

CI: confidence interval; DHA: docosahexaenoic acid; mv: multivariable; mvRR: multivariable risk ratio; RR: risk ratio.

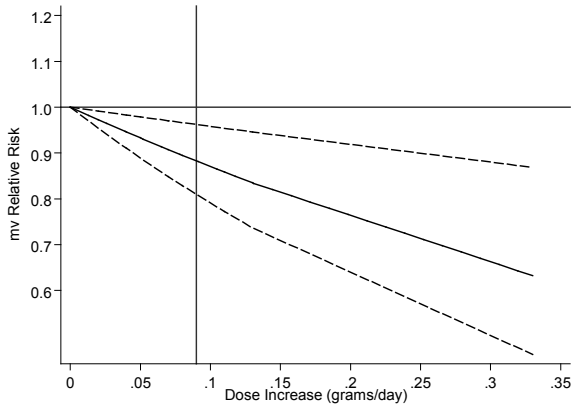
Fig. 166. Dose–response association between DHA (%E) and breast cancer in three studies, assuming linearity (*P*=0.0058 for goodness-of-fit) (left), and using non-linear, cubic spline approach (right), with knots at 0.02, 0.03 and 0.05% energy



Assuming linearity, a 0.1% increase in energy from DHA was associated with a 4% increase in risk of breast cancer (mvRR: 1.04; 95% CI: 0.98 to 1.12). *Horizontal line represents a RR=1.0; vertical line represents the median DHA intake in the studied populations (0.046%E).*

CI: confidence interval; DHA: docosahexaenoic acid; E: energy; mv: multivariable; mvRR: multivariable risk ratio; RR: risk ratio.

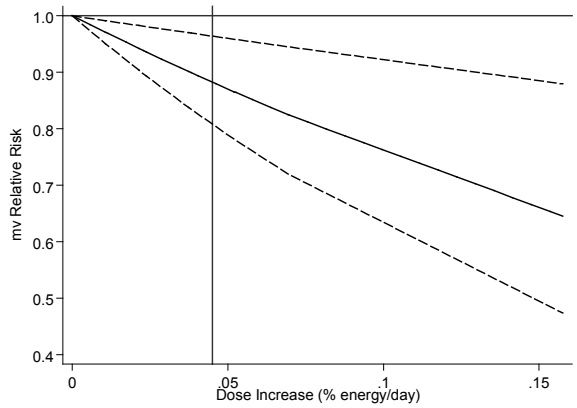
Fig. 167. Dose–response association between DHA (g/day) and post-menopausal breast cancer in three studies, assuming linearity (*P*=0.33 for goodness-of-fit)



Assuming linearity, a 0.5 g/day increase in DHA was associated with a 50% decrease in risk of post-menopausal breast cancer (mvRR: 0.50; 95% CI: 0.31 to 0.81). *Horizontal line represents a RR=1.0; vertical line represents the median DHA intake in the studied populations (0.09 g/day).*

CI: confidence interval; DHA: docosahexaenoic acid; mv: multivariable; mvRR: multivariable risk ratio; RR: risk ratio.

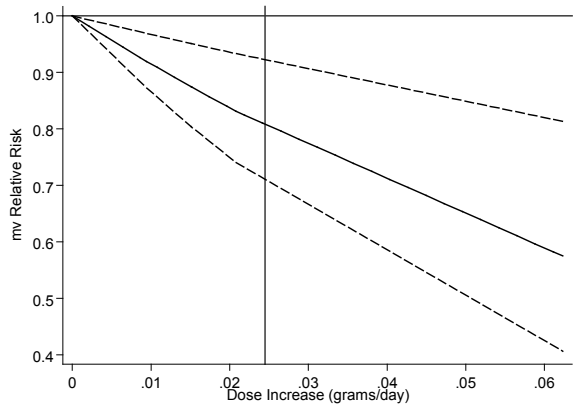
Fig. 168. Dose–response association between DHA (%E) and post-menopausal breast cancer in three studies, assuming linearity (*P*=0.33 for goodness-of-fit)



Assuming linearity, a 0.1% increase in energy from DHA was associated with a 24% decrease in risk of post-menopausal breast cancer (mvRR: 0.76; 95% CI: 0.62 to 0.92). *Horizontal line represents a RR=1.0; vertical line represents the median DHA intake in the studied populations (0.045%E).*

CI: confidence interval; DHA: docosahexaenoic acid; E: energy; mv: multivariable; mvRR: multivariable risk ratio; RR: risk ratio.

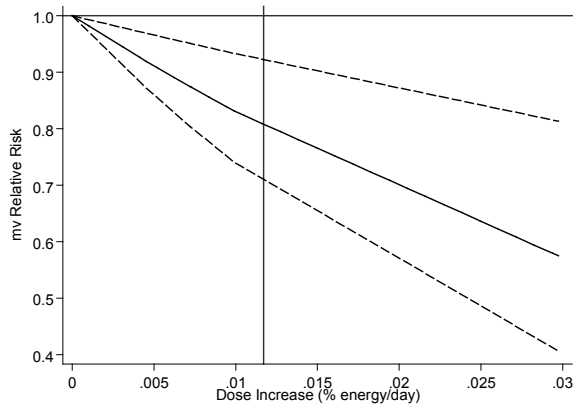
Fig. 169. Dose–response association between DPA (g/day) and post-menopausal breast cancer, assuming linearity (*P*=0.75 for goodness-of-fit)



Assuming linearity, a 0.05 g/day increase in DPA was associated with a 36% decrease in risk of post-menopausal breast cancer (mvRR: 0.64; 95% CI: 0.49 to 0.85). *Horizontal line represents a RR=1.0; vertical line represents the median DPA intake in the studied populations (0.025 g/day).*

CI: confidence interval; DPA: docosapentaenoic acid; mv: multivariable; mvRR: multivariable risk ratio; RR: risk ratio.

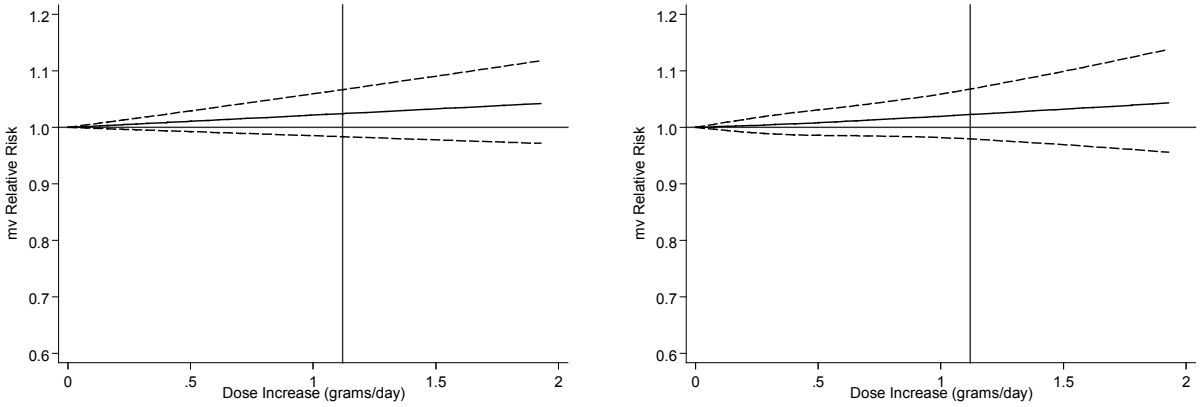
Fig. 170. Dose–response association between DPA (%E) and post-menopausal breast cancer, assuming linearity (*P*=0.75 for goodness-of-fit)



Assuming linearity, a 0.02% increase in energy from DPA was associated with a 31% decrease in risk of post-menopausal breast cancer (mvRR: 0.69; 95% CI: 0.55 to 0.87). *Horizontal line represents a RR=1.0; vertical line represents the median DPA intake in the studied populations (0.011%E).*

CI: confidence interval; DPA: docosapentaenoic acid; E: energy; mv: multivariable; mvRR: multivariable risk ratio; RR: risk ratio.

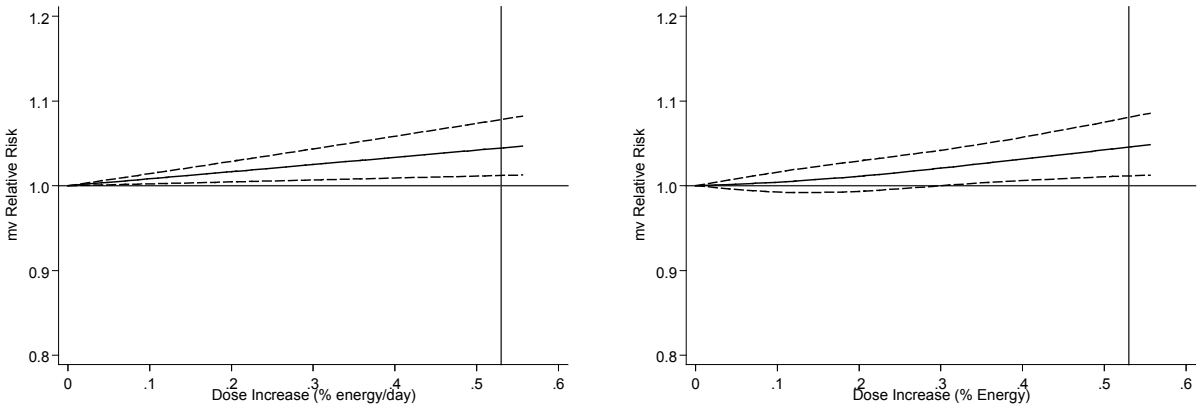
Fig. 171. Dose–response association between ALA (g/day) and most-adjusted RR of all-cause mortality in eight studies, assuming linearity (*P*<0.0005 for goodness-of-fit) (left), and using non-linear, cubic spline approach (right), with knots at 0, 0.3 and 1.1 g/day



Assuming linearity, a 0.5 g/day increase in ALA was associated with a 1% increased risk of all-cause mortality (mvRR: 1.01; 95% CI: 0.99 to 1.03). *Horizontal line represents a RR=1.0; vertical line represents the median ALA intake in the studied populations (1.12 g/day).*

ALA: alpha-linolenic acid; CI: confidence interval; mv: multivariable; mvRR: multivariable risk ratio; RR: risk ratio.

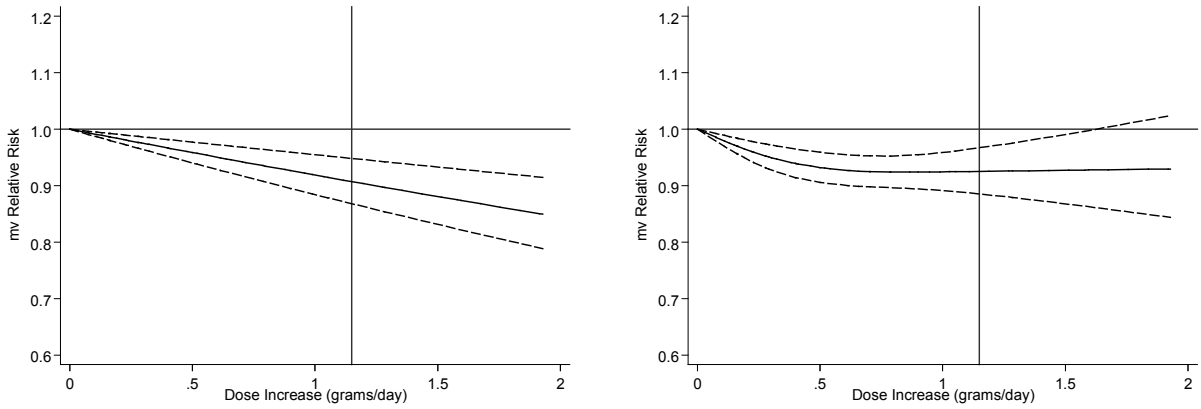
Fig. 172. Dose–response association between ALA (%E) and most-adjusted RR of all-cause mortality in eight studies, assuming linearity (*P*<0.00001 for goodness-of-fit) (left), and using non-linear, cubic spline approach (right), with knots at 0, 0.12 and 0.36% energy



Assuming linearity, a 0.2% increase in energy from ALA was associated with a 2% increased risk of all-cause mortality (mvRR: 1.02; 95% CI: 1.00 to 1.03). *Horizontal line represents a RR=1.0; vertical line represents the median ALA intake in the studied populations (0.53%E).*

ALA: alpha-linolenic acid; CI: confidence interval; E: energy; mv: multivariable; mvRR: multivariable risk ratio; RR: risk ratio.

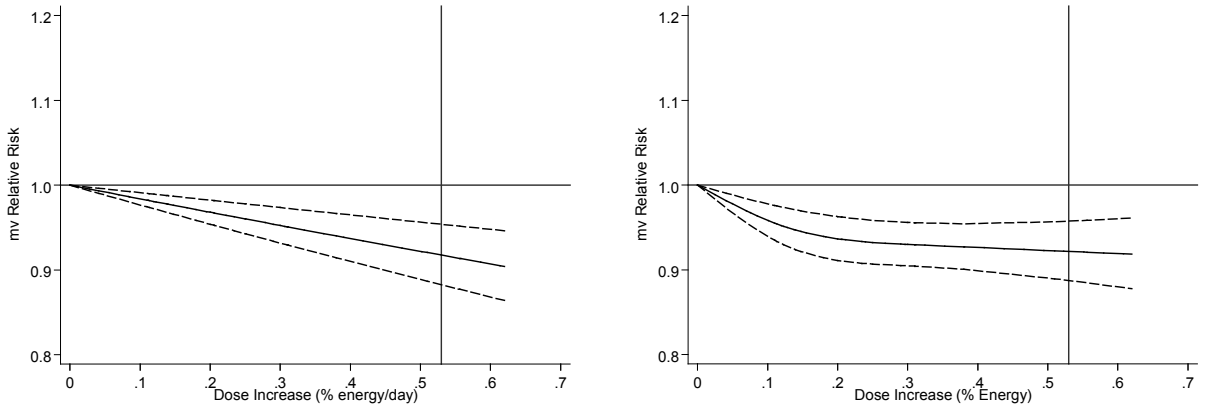
Fig. 173. Dose–response association between ALA (g/day) and most-adjusted RR of cardiovascular mortality in nine studies, assuming linearity (*P*=0.41 for goodness-of-fit) (left), and using non-linear, cubic spline approach (right), with knots at 0, 0.28 and 0.99 g/day



Assuming linearity, a 0.5-g/day increase in ALA was associated with a 4% decrease in risk of cardiovascular mortality (mvRR: 0.96; 95% CI: 0.94 to 0.98). *Horizontal line represents a RR=1.0; vertical line represents the median ALA intake in the studied populations (1.15 g/day).*

ALA: alpha-linolenic acid; CI: confidence interval; mv: multivariable; mvRR: multivariable risk ratio; RR: risk ratio.

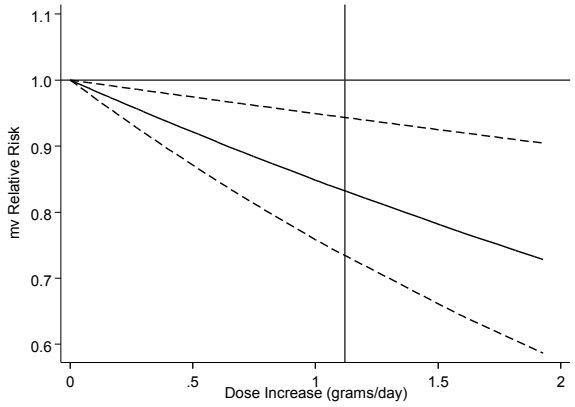
Fig. 174. Dose–response association between ALA (%E) and most-adjusted RR of cardiovascular mortality in nine studies, assuming linearity (*P*=0.37 for goodness-of-fit) (left), and using non-linear, cubic spline approach (right), with knots at 0, 0.12 and 0.31% energy



Assuming linearity, a 0.5% increase in energy from ALA was associated with an 8% decrease in risk of cardiovascular mortality (mvRR: 0.92; 95% CI: 0.89 to 0.96). *Horizontal line represents a RR=1.0; vertical line represents the median ALA intake in the studied populations (0.53%E).*

ALA: alpha-linolenic acid; CI: confidence interval; E: energy; mv: multivariable; mvRR: multivariable risk ratio; RR: risk ratio.

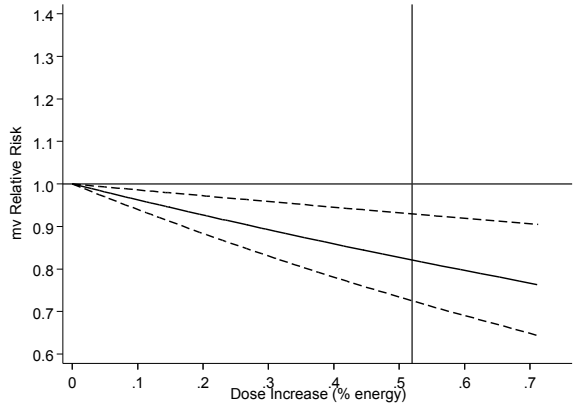
Fig. 175. Dose–response association between ALA (g/day) and most-adjusted RR of CHD mortality in nine studies, assuming linearity (*P*=0.27 for linearity)



Assuming linearity, a 0.5 g/day increase in ALA was associated with an 8% decrease in risk of CHD mortality (mvRR: 0.92; 95% CI: 0.87 to 0.97). *Horizontal line represents a RR=1.0; vertical line represents the median ALA intake in the studied populations (1.12 g/day).*

ALA: alpha-linolenic acid; CHD: coronary heart disease; CI: confidence interval; mv: multivariable; mvRR: multivariable risk ratio; RR: risk ratio.

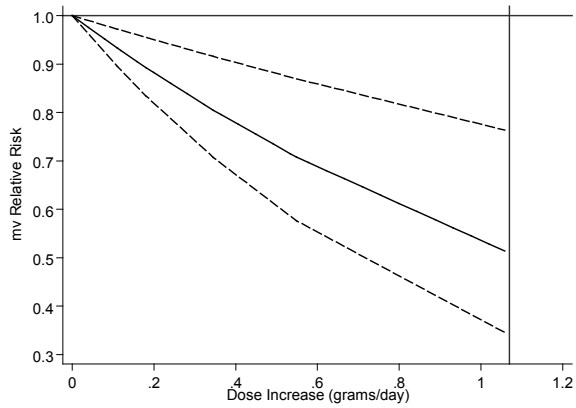
Fig. 176. Dose–response association between ALA (%E) and most-adjusted RR of CHD mortality in eight studies, assuming linearity (*P*=0.27 for linearity)



Assuming linearity, a 0.5% increase in energy from ALA was associated with a 17% decrease in risk of CHD mortality (mvRR: 0.83; 95% CI: 0.73 to 0.93). *Horizontal line represents a RR=1.0; vertical line represents the median ALA intake in the studied populations (0.52%E).*

ALA: alpha-linolenic acid; CHD: coronary heart disease; CI: confidence interval; E: energy; mv: multivariable; mvRR: multivariable risk ratio; RR: risk ratio.

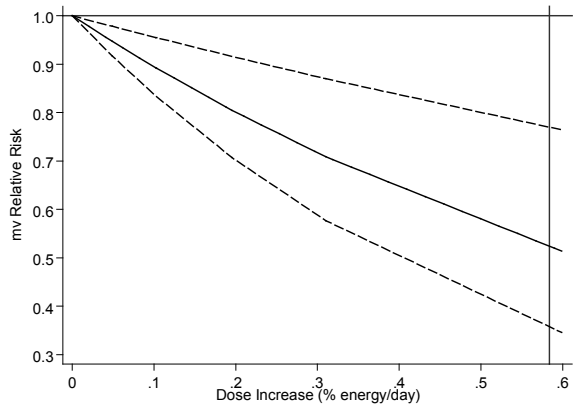
Fig. 177. Dose–response association between ALA (g/day) and sudden cardiac death in two studies, assuming linearity (*P*=0.90 for goodness-of-fit)



Assuming linearity, a 0.5 g/day increase in ALA was associated with a 27% decrease in risk of sudden cardiac death (mvRR: 0.73; 95% CI: 0.61 to 0.88). *Horizontal line represents a RR=1.0; vertical line represents the median ALA intake in the studied populations (1.07 g/day).*

ALA: alpha-linolenic acid; CI: confidence interval; mv: multivariable; mvRR: multivariable risk ratio; RR: risk ratio.

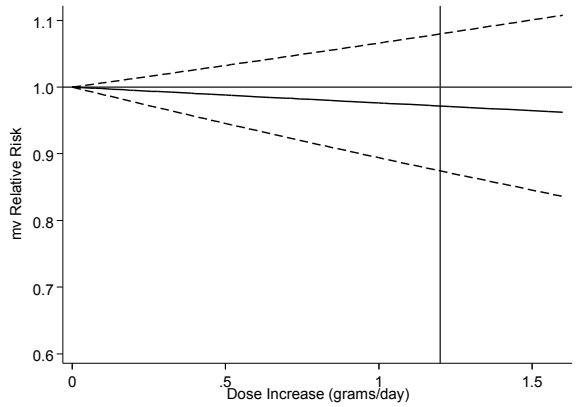
Fig. 178. Dose–response association between ALA (%E) and sudden cardiac death in two studies, assuming linearity (*P*=0.91 for goodness-of-fit)



Assuming linearity, a 0.2% increase in energy from ALA was associated with a 20% decrease in risk of sudden cardiac death (mvRR: 0.80; 95% CI: 0.70 to 0.91). *Horizontal line represents a RR=1.0; vertical line represents the median ALA intake in the studied populations (0.58%E). For Sala-Villa, because the increase in total energy from the low to the high ALA group was not proportional to the increase in ALA, we estimated % energy in the higher group using the ratio of g/day (1.43/1.32), and applied this to the low group's % intake (0.58%) to estimate the % energy intake from ALA in the high-ALA group (set at 0.63%E).*

ALA: alpha-linolenic acid; CI: confidence interval; E: energy; mv: multivariable; mvRR: multivariable risk ratio; RR: risk ratio.

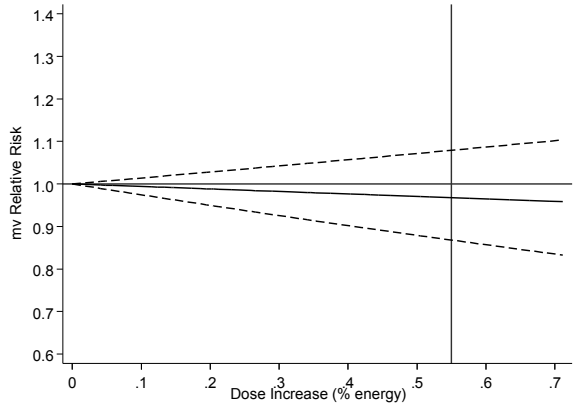
Fig. 179. Dose–response association between ALA (g/day) and most-adjusted RR of total CHD in seven studies, assuming linearity (*P*=0.69 for goodness-of-fit)



There was no evidence of a dose–response association between ALA and risk of CHD (mvRR: 0.99; 95% CI: 0.96 to 1.03 per 0.5 g). *Horizontal line represents a RR=1.0; vertical line represents the median ALA intake in the studied populations (1.12 g/day).*

ALA: alpha-linolenic acid; CHD: coronary heart disease; CI: confidence interval; mv: multivariable; mvRR: multivariable risk ratio; RR: risk ratio.

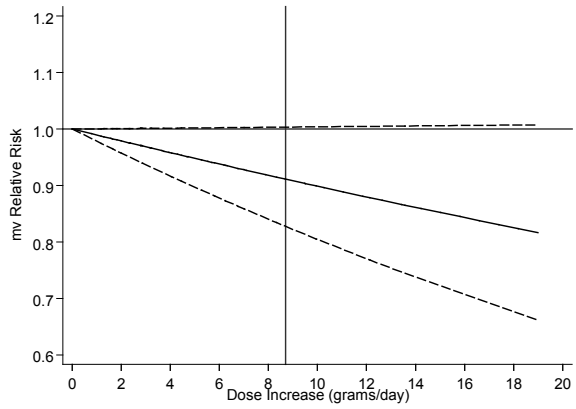
Fig. 180. Dose–response association between ALA (%E) and most-adjusted RR of CHD in seven studies, assuming linearity (*P*=0.70 goodness-of-fit)



There was no evidence of a dose–response association between ALA and risk of CHD (mvRR: 0.99; 95% CI: 0.95 to 1.03 per 0.2%). *Horizontal line represents a RR=1.0; vertical line represents the median ALA intake in the studied populations (0.55%E).*

ALA: alpha-linolenic acid; CHD: coronary heart disease; CI: confidence interval; E: energy; mv: multivariable; mvRR: multivariable risk ratio; RR: risk ratio.

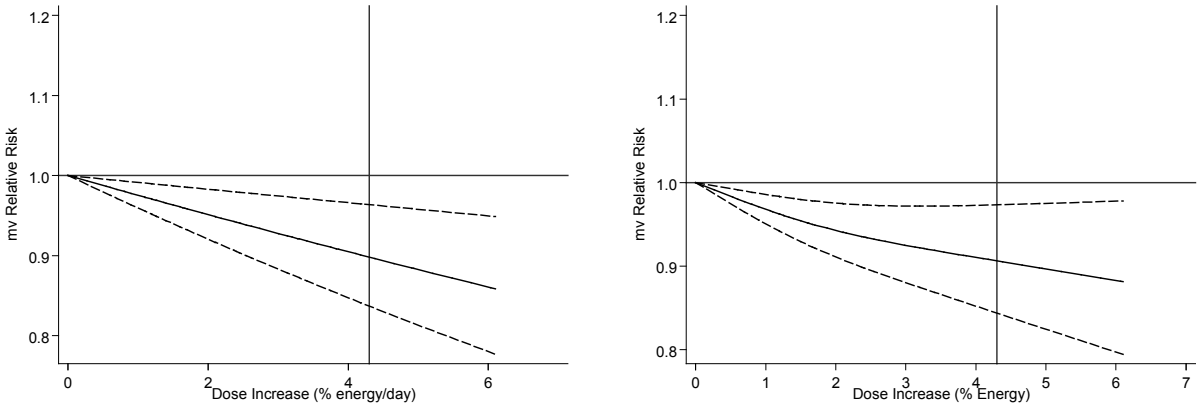
Fig. 181. Dose–response association between total n-6 fatty acids (g/day) and most-adjusted RR of all-cause mortality in nine studies, assuming linearity (*P*=0.08 for goodness-of-fit)



Assuming linearity, a 5 g/day increase in total n-6 fatty acids was associated with a 5% decrease in risk of all-cause mortality (mvRR: 0.95; 95% CI: 0.90 to 1.001). *Horizontal line represents a RR=1.0; vertical line represents the median n-6 fatty acid intake in the studied populations (8.7 g/day).*

CI: confidence interval; mv: multivariable; mvRR: multivariable risk ratio; RR: risk ratio.

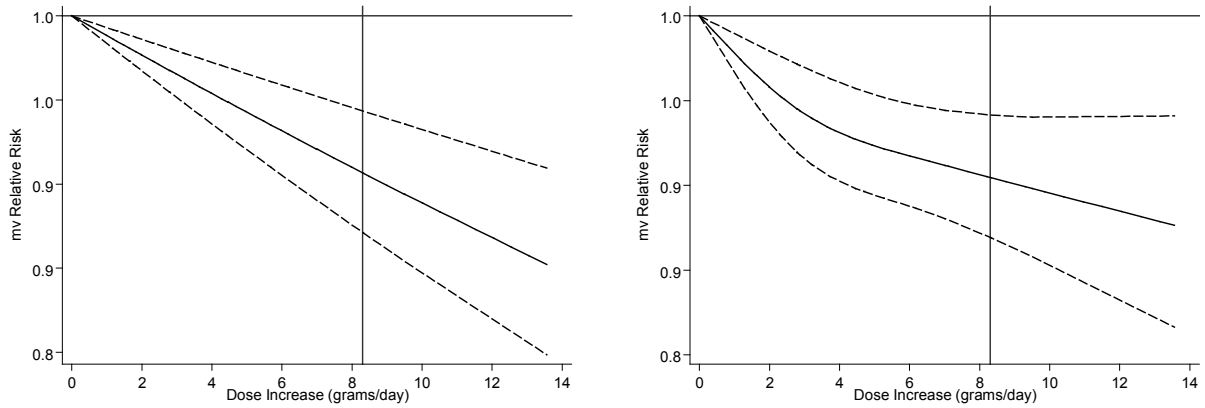
Fig. 182. Dose–response association between total n-6 fatty acids (%E) and most-adjusted RR of all-cause mortality in nine studies, assuming linearity (*P*=0.015 for goodness-of-fit) (left), and using non-linear, cubic spline approach (right), with knots at 0, 1.6 and 3.2% energy



Assuming linearity, a 5% increase in energy from total n-6 fatty acids was associated with a 12% decrease in risk of all-cause mortality (mvRR: 0.88; 95% CI: 0.81 to 0.96).). *Ho*rizontal line represents a RR=1.0; vertical line represents the median n-6 intake in the studied populations (4.3%E).

CI: confidence interval; E: energy; mv: multivariable; mvRR: multivariable risk ratio; RR: risk ratio.

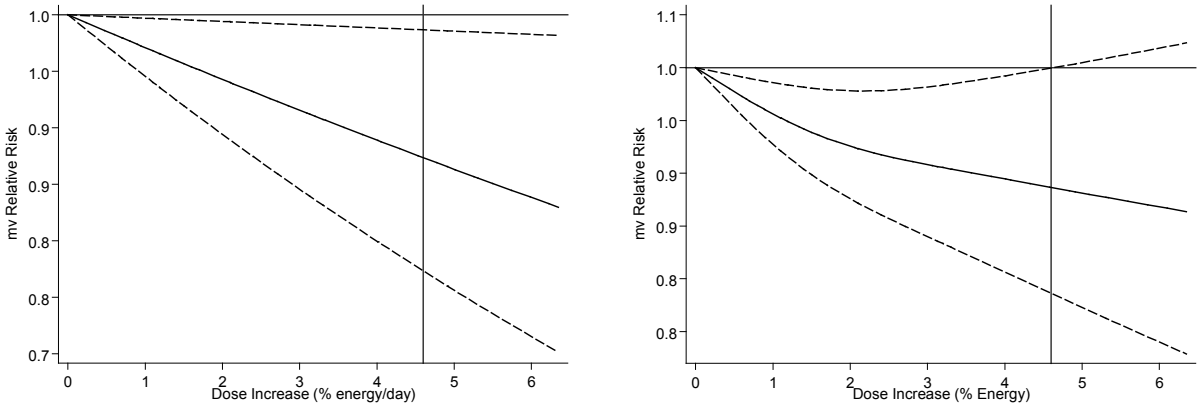
Fig. 183. Dose–response association between total n-6 fatty acids (g/day) and cardiovascular mortality in six studies, assuming linearity (*P*=0.0059 for goodness-of-fit) (left), and using non-linear, cubic spline approach (right), with knots at 0, 2.8 and 6.2 g/day



Assuming linearity, a 5 g/day increase in n-6 fatty acids was associated with a 6% decrease in risk of cardiovascular mortality (mvRR: 0.94; 95% CI: 0.92 to 0.97). *Horizontal line represents a RR=1.0; vertical line represents the median n-6 fatty acids intake in the studied populations (8.3 g/day).*

CI: confidence interval; mv: multivariable; mvRR: multivariable risk ratio; RR: risk ratio.

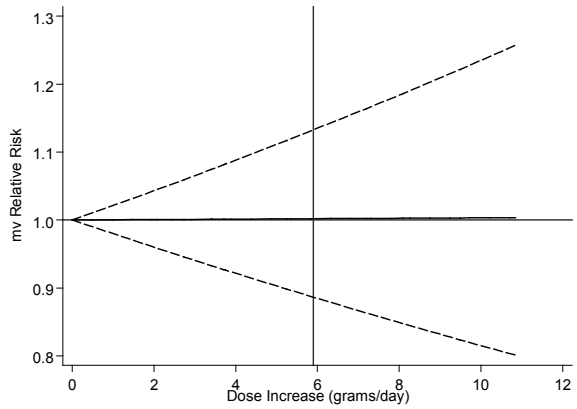
Fig. 184. Dose–response association between total n-6 fatty acids (%E) and cardiovascular mortality in six studies, assuming linearity (*P*=0.09 for goodness-of-fit) (left), and using non-linear, cubic spline approach (right), with knots at 0, 2.8 and 6.2 g/day



Assuming linearity, a 2% increase in energy from n-6 fatty acids was associated with a 6% decrease in risk of cardiovascular mortality (mvRR: 0.94; 95% CI: 0.89 to 0.99). *Horizontal line represents a RR=1.0; vertical line represents the median n-6 fatty acids intake in the studied populations (4.6%E).*

CI: confidence interval; E: energy; mv: multivariable; mvRR: multivariable risk ratio; RR: risk ratio.

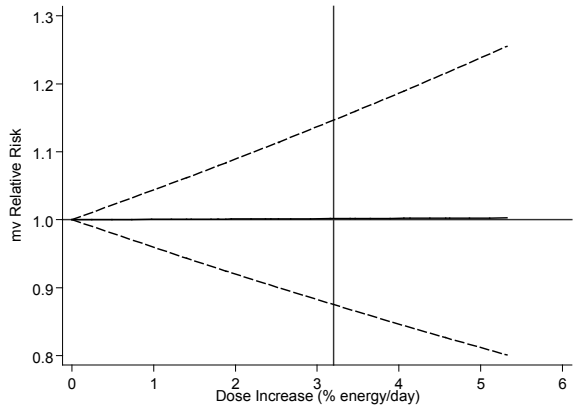
Fig. 185. Dose–response association between total n-6 fatty acids (g/day) and most-adjusted RR of breast cancer in three studies, assuming linearity (*P*=0.80 for goodness-of-fit)



Assuming linearity, a 5-g increase in total n-6 fatty acids was associated with a 0% increased risk of breast cancer (mvRR: 1.00; 95% CI: 0.90 to 1.11). *Horizontal line represents a RR=1.0; vertical line represents the median n-6 intake in the studied populations (5.9 g/day).*

CI: confidence interval; mv: multivariable; mvRR: multivariable risk ratio; RR: risk ratio.

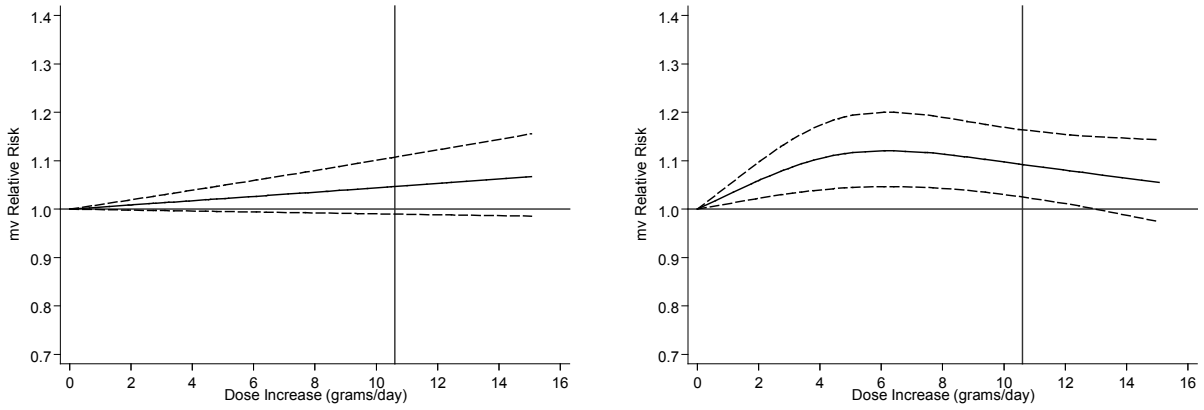
Fig. 186. Dose–response association between total n-6 fatty acids (%E) and most-adjusted RR of breast cancer in three studies, assuming linearity (*P*=0.84 for goodness-of-fit)



Assuming linearity, a 2% increase in energy from total n-6 fatty acids was associated with a 0% increased risk of breast cancer (mvRR: 1.00; 95% CI: 0.92 to 1.09). *Horizontal line represents a RR=1.0; vertical line represents the median ALA intake in the studied populations (3.2%E).*

CI: confidence interval; E: energy; mv: multivariable; mvRR: multivariable risk ratio; RR: risk ratio.

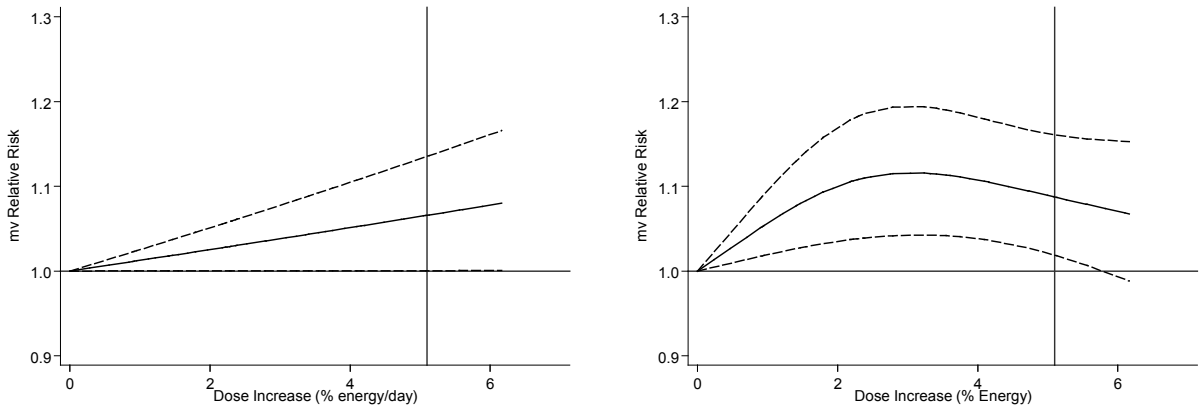
Fig. 187. Dose–response association between total n-6 fatty acids (g/day) and most-adjusted RR of post-menopausal breast cancer in six studies, assuming linearity (*P*=0.0047 for goodness-of-fit) (left), and using non-linear, cubic spline approach (right), with knots at 0, 4.1 and 9.4 g/day



Assuming linearity, a 5 g/day increase in total n-6 fatty acids was associated with a 2% increased risk of post-menopausal breast cancer (mvRR: 1.02; 95% CI: 0.99 to 1.05). *Horizontal line represents a RR=1.0; vertical line represents the median n-6 fatty acids intake in the studied populations (10.6 g/day).*

CI: confidence interval; mv: multivariable; mvRR: multivariable risk ratio; RR: risk ratio.

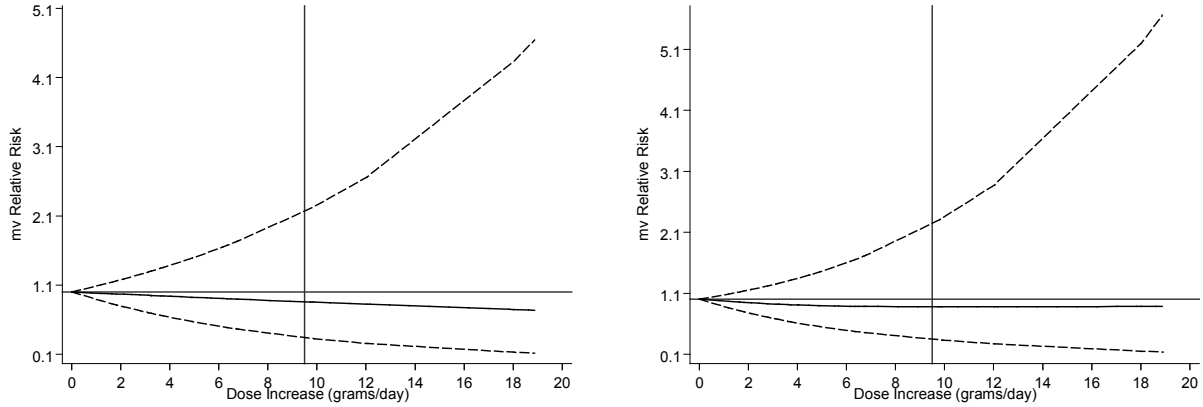
Fig. 188. Dose–response association between total n-6 fatty acids (%E) and most-adjusted RR of post-menopausal breast cancer in six studies, assuming linearity (*P*=0.0067 for goodness-of-fit) (left), and using non-linear, cubic spline approach (right), with knots at 0, 2.2 and 4.7% energy



Assuming linearity, a 2% increase in energy from total n-6 fatty acids was associated with a 3% increased risk of post-menopausal breast cancer (mvRR: 1.03; 95% CI: 1.00 to 1.05). *Horizontal line represents a RR=1.0; vertical line represents the median n-6 fatty acid intake in the studied populations (5.1%E).*

CI: confidence interval; E: energy; mv: multivariable; mvRR: multivariable risk ratio; RR: risk ratio.

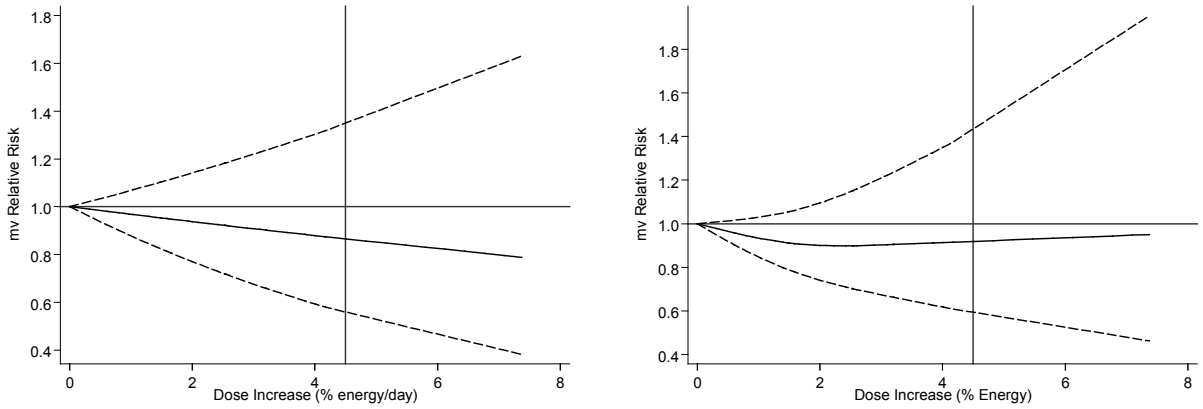
Fig. 189. Dose–response association between LA (g/day) and most-adjusted RR of all-cause mortality in six studies, assuming linearity (*P*<0.0001 for goodness-of-fit) (left), and using non-linear, cubic spline approach (right), with knots at 0, 3.7 and 9.0 g/day



Assuming linearity, a 5 g/day increase in LA was associated with an 8% decrease in risk of all-cause mortality (mvRR: 0.92; 95% CI: 0.56 to 1.50). *Horizontal line represents a RR=1.0; vertical line represents the median LA intake in the studied populations (9.5 g/day).*

CI: confidence interval; LA: linoleic acid; mv: multivariable; mvRR: multivariable risk ratio; RR: risk ratio.

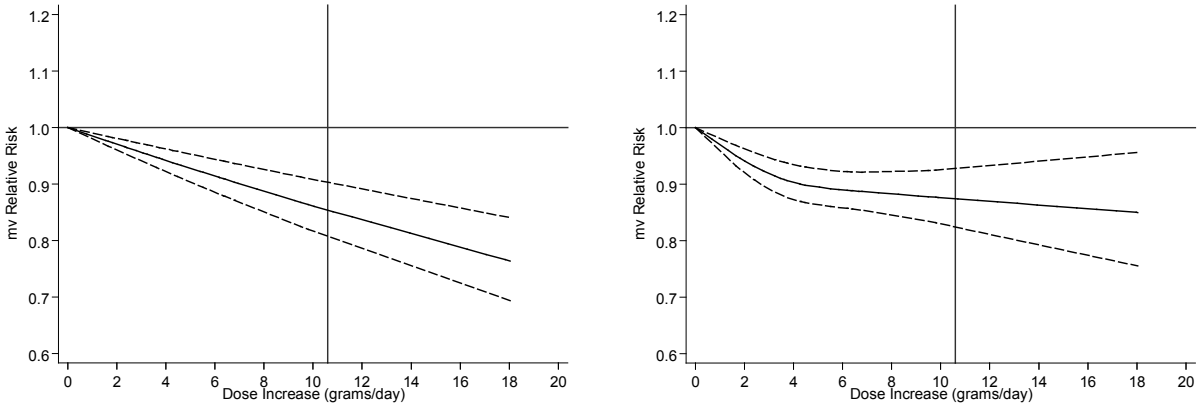
Fig. 190. Dose–response association between LA (%E) and most-adjusted RR of all-cause mortality in six studies, assuming linearity (*P*<0.0001 for goodness-of-fit) (left), and using non-linear, cubic spline approach (right), with knots at 0, 1.6 and 3.2% energy



Assuming linearity, a 2% increase in energy from LA was associated with a 6% decrease in risk of all-cause mortality (mvRR: 0.94; 95% CI: 0.77 to 1.14). *Horizontal line represents a RR=1.0; vertical line represents the median LA intake in the studied populations (4.5%E).*

CI: confidence interval; E: energy; LA: linoleic acid; mv: multivariable; mvRR: multivariable risk ratio; RR: risk ratio.

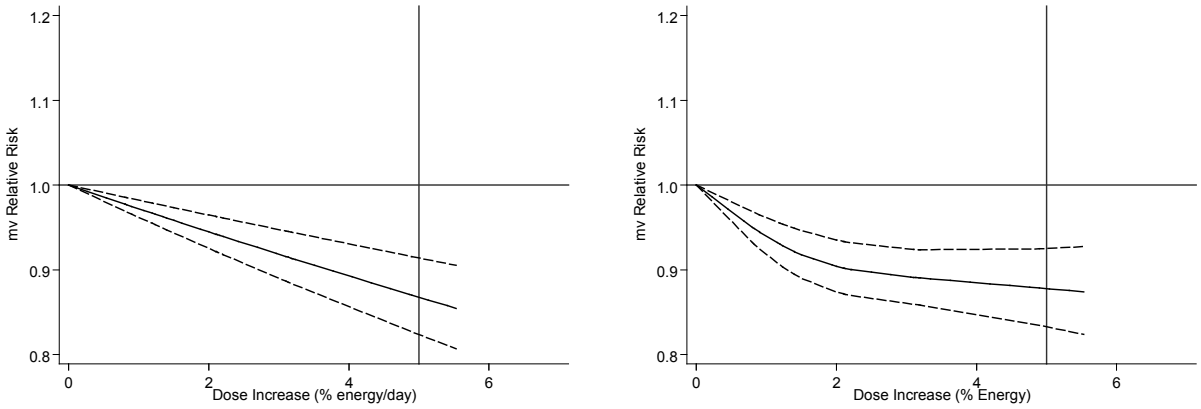
Fig. 191. Dose–response association between LA (g/day) and most-adjusted RR of CVD mortality in five studies, assuming linearity (*P*=0.024 for goodness-of-fit) (left), and using non-linear, cubic spline approach (right), with knots at 0, 3.0 and 6.4 g/day



Assuming linearity, a 5 g/day increase in LA was associated with a 7% decrease in risk of CVD mortality (mvRR: 0.93; 95% CI: 0.90 to 0.95). *Horizontal line represents a RR=1.0; vertical line represents the median LA intake in the studied populations (10.6 g/day).*

CI: confidence interval; CVD: cardiovascular disease; LA: linoleic acid; mv: multivariable; mvRR: multivariable risk ratio; RR: risk ratio.

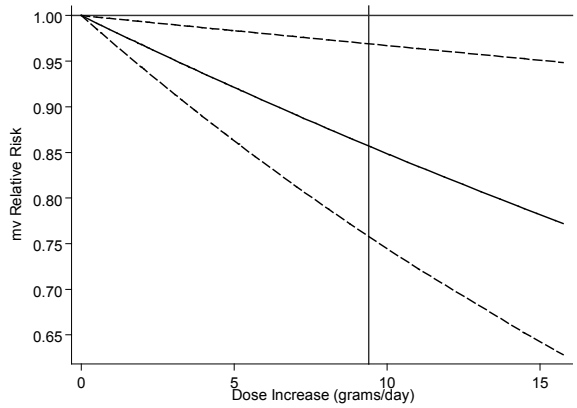
Fig. 192. Dose–response association between LA (%E) and most-adjusted RR of CVD mortality in five studies, assuming linearity (*P*=0.0149 for goodness-of-fit) (left), and using non-linear, cubic spline approach (right), with knots at 0, 1.5 and 3.1% energy



Assuming linearity, a 2% increase in energy from LA was associated with a 6% decrease in risk of CVD mortality (mvRR: 0.94; 95% CI: 0.93 to 0.94). *Horizontal line represents a RR=1.0; vertical line represents the median LA intake in the studied populations (5.0%E).*

CI: confidence interval; CVD: cardiovascular disease; E: energy; LA: linoleic acid; mv: multivariable; mvRR: multivariable risk ratio; RR: risk ratio.

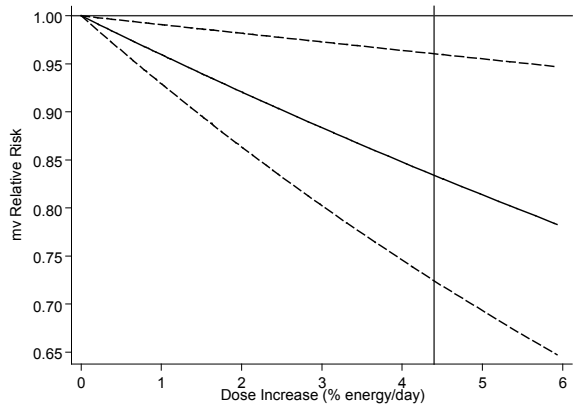
Fig. 193. Dose–response association between total LA (g/day) and ischaemic heart disease mortality in 11 studies, assuming linearity (*P*=0.62 for goodness-of-fit)



Assuming linearity, a 5 g/day increase in LA was associated with an 8% decrease in risk of ischaemic heart disease mortality (mvRR: 0.92; 95% CI: 0.86 to 0.98). *Horizontal line represents a RR=1.0; vertical line represents the median LA intake in the studied populations (9.4 g/day).*

CI: confidence interval; LA: linoleic acid; mv: multivariable; mvRR: multivariable risk ratio; RR: risk ratio.

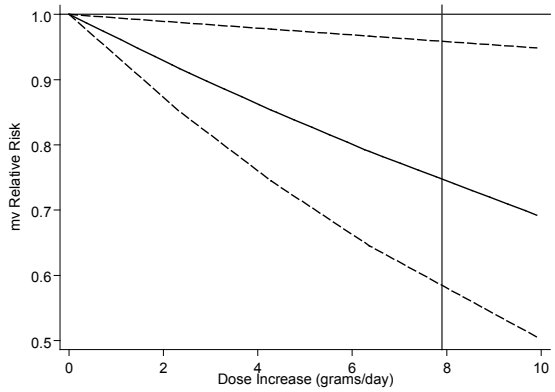
Fig. 194. Dose–response association between total LA (%E) and ischaemic heart disease mortality in 11 studies, assuming linearity (*P*=0.63 for goodness-of-fit)



Assuming linearity, a 2% increase in energy from LA was associated with an 8% decrease in risk of ischaemic heart disease mortality (mvRR: 0.92; 95% CI: 0.86 to 0.98). *Horizontal line represents a RR=1.0; vertical line represents the median LA intake in the studied populations (4.4%E).*

CI: confidence interval; E: energy; LA: linoleic acid; mv: multivariable; mvRR: multivariable risk ratio; RR: risk ratio.

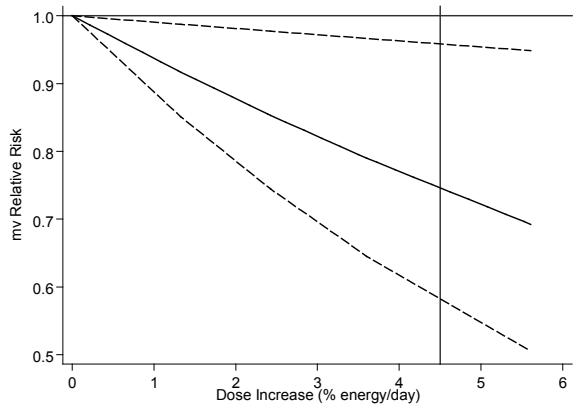
Fig. 195. Dose–response association between total LA (g/day) and sudden cardiac death in one study, assuming linearity (*P*=0.96 for goodness-of-fit)



Assuming linearity, a 5 g/day increase in LA was associated with a 17% decrease in risk of sudden cardiac death (mvRR: 0.83; 95% CI: 0.71 to 0.97). *Horizontal line represents a RR=1.0; vertical line represents the median n-6 fatty acids intake in the studied populations (7.9 g/day).*

CI: confidence interval; LA: linoleic acid; mv: multivariable; mvRR: multivariable risk ratio; RR: risk ratio.

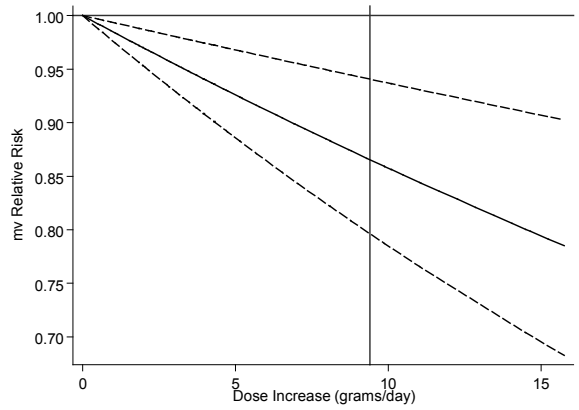
Fig. 196. Dose–response association between total LA (%E) and sudden cardiac death in one study, assuming linearity (*P*=0.96 for goodness-of-fit)



Assuming linearity, a 2% increase in energy from LA was associated with a 12% decrease in risk of sudden cardiac death (mvRR: 0.88; 95% CI: 0.78 to 0.98). *Horizontal line represents a RR=1.0; vertical line represents the median LA in the studied populations (4.5%E).*

CI: confidence interval; E: energy; LA: linoleic acid; mv: multivariable; mvRR: multivariable risk ratio; RR: risk ratio.

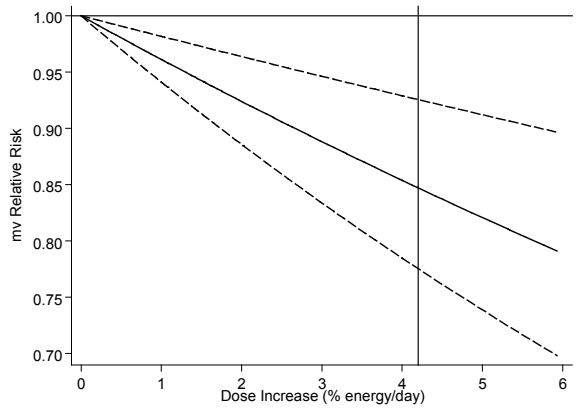
Fig. 197. Dose–response association between total LA (g/day) and total ischaemic heart disease in 16 studies, assuming linearity (*P*=0.15 for goodness-of-fit)



Assuming linearity, a 5 g/day increase in LA was associated with a 7% decrease in risk of total ischaemic heart disease (mvRR: 0.93; 95% CI: 0.89 to 0.97). *Horizontal line represents a RR=1.0; vertical line represents the median LA intake in the studied populations (9.4 g/day).*

CI: confidence interval; LA: linoleic acid; mv: multivariable; mvRR: multivariable risk ratio; RR: risk ratio.

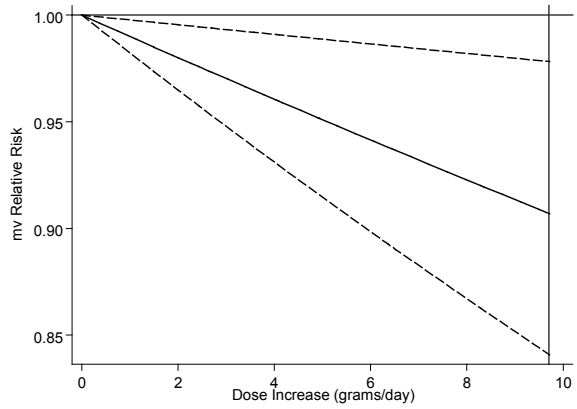
Fig. 198. Dose–response association between total LA (%E) and total ischaemic heart disease in 16 studies, assuming linearity (*P*=0.19 for goodness-of-fit)



Assuming linearity, a 2% increase in energy from LA was associated with a 4% decrease in risk of total ischaemic heart disease (mvRR: 0.96; 95% CI: 0.94 to 0.98). *Horizontal line represents a RR=1.0; vertical line represents the median LA intake in the studied populations (4.2%E).*

CI: confidence interval; E: energy; LA: linoleic acid; mv: multivariable; mvRR: multivariable risk ratio; RR: risk ratio.

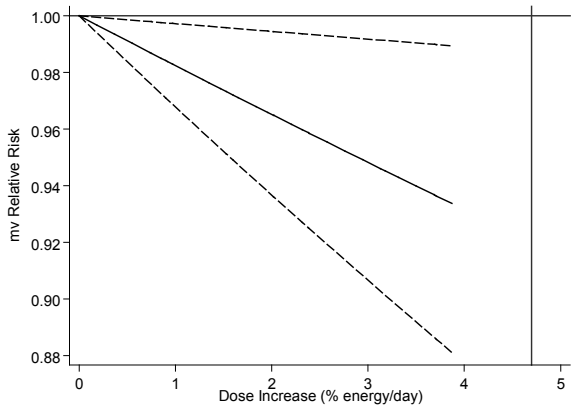
Fig. 199. Dose–response association between total LA (g/day) and type 2 diabetes in four studies, assuming linearity (*P*=0.12 for goodness-of-fit)



Assuming linearity, a 5 g/day increase in LA was associated with a 5% decrease in risk of type 2 diabetes (mvRR: 0.95; 95% CI: 0.91 to 0.99). *Horizontal line represents a RR=1.0; vertical line represents the median LA intake in the studied populations (9.7 g/day).*

CI: confidence interval; LA: linoleic acid; mv: multivariable; mvRR: multivariable risk ratio; RR: risk ratio.

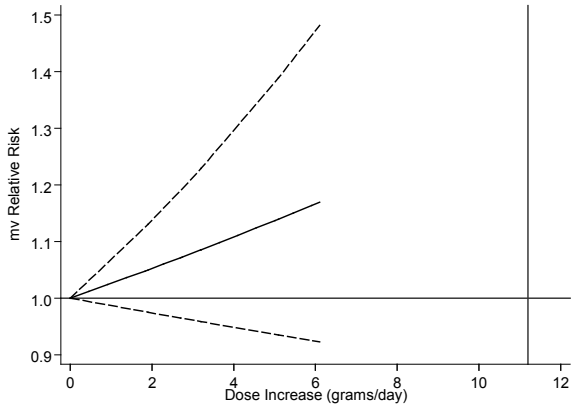
Fig. 200. Dose–response association between total LA (%E) and type 2 diabetes in four studies, assuming linearity (*P*=0.10 for goodness-of-fit)



Assuming linearity, a 2% increase in energy from LA was associated with a 3% decrease in risk of type 2 diabetes (mvRR: 0.97; 95% CI: 0.94 to 0.99). *Horizontal line represents a RR=1.0; vertical line represents the median LA intake in the studied populations (4.7%E).*

CI: confidence interval; E: energy; LA: linoleic acid; mv: multivariable; mvRR: multivariable risk ratio; RR: risk ratio.

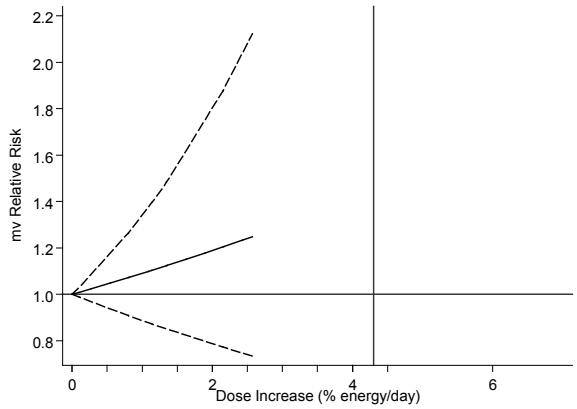
Fig. 201. Dose–response association between total LA (g/day) and depression in two studies, assuming linearity (*P*=0.99 for goodness-of-fit)



Assuming linearity, a 5 g/day increase in LA was associated with a 14% increase in risk of depression (mvRR: 1.14; 95% CI: 0.94 to 1.38). *Horizontal line represents a RR=1.0; vertical line represents the median LA intake in the studied populations (11.2 g/day). Not including data from Lucas et al., because g data not reliably estimable.*

CI: confidence interval; LA: linoleic acid; mv: multivariable; mvRR: multivariable risk ratio; RR: risk ratio.

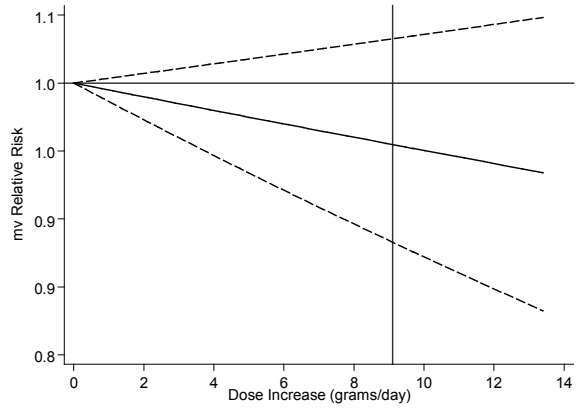
Fig. 202. Dose–response association between total LA (%E) and depression in three studies, assuming linearity (*P*=0.12 for goodness-of-fit)



Assuming linearity, a 2% increase in energy from LA was associated with a 19% increase in risk of depression (mvRR: 1.19; 95% CI: 0.79 to 1.80). *Horizontal line represents a RR=1.0; vertical line represents the median LA intake in the studied populations (4.3%E).*

CI: confidence interval; E: energy; LA: linoleic acid; mv: multivariable; mvRR: multivariable risk ratio; RR: risk ratio.

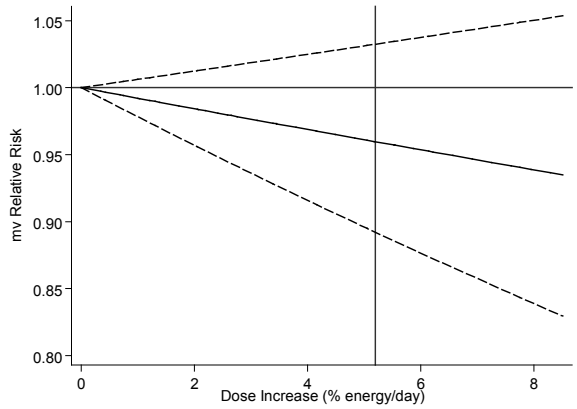
Fig. 203. Dose–response association between total LA (g/day) and breast cancer in four studies, assuming linearity (*P*=0.41 for goodness-of-fit)



Assuming linearity, a 5 g/day increase in LA was associated with a 3% decrease in risk of breast cancer (mvRR: 0.97; 95% CI: 0.93 to 1.02). *Horizontal line represents a RR=1.0; vertical line represents the median LA intake in the studied populations (9.1 g/day).*

CI: confidence interval; LA: linoleic acid; mv: multivariable; mvRR: multivariable risk ratio; RR: risk ratio.

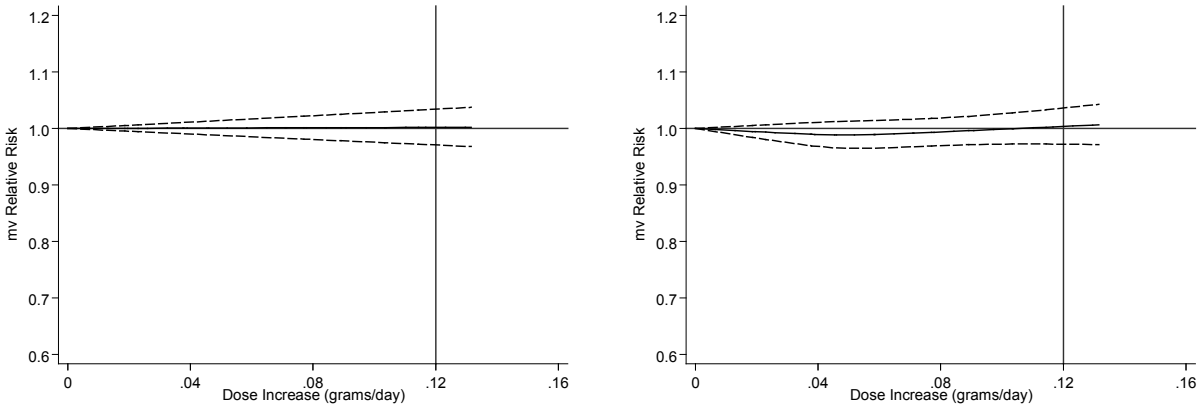
Fig. 204. Dose–response association between total LA (%E) and breast cancer in four studies, assuming linearity (*P*=0.40 for goodness-of-fit)



Assuming linearity, a 2% increase in energy from LA was associated with a 2% decrease in risk of breast cancer (mvRR: 0.98; 95% CI: 0.96 to 1.01). *Horizontal line represents a RR=1.0; vertical line represents the median LA intake in the studied populations (5.2%E).*

CI: confidence interval; E: energy; LA: linoleic acid; mv: multivariable; mvRR: multivariable risk ratio; RR: risk ratio.

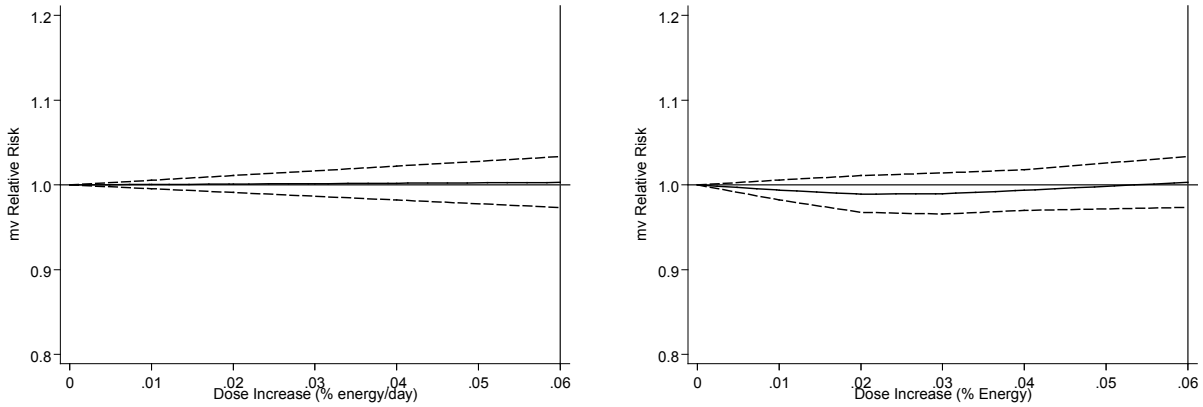
Fig. 205. Dose–response association between ARA (g/day) and most-adjusted RR of all-cause mortality in three studies, assuming linearity (*P*<0.0001 for goodness-of-fit) (left), and using non-linear, cubic spline approach (right), with knots at 0.02, 0.05 and 0.08 g/day



Assuming linearity, a 0.1 g/day increase in ARA was associated with a 0.2% increased risk of all-cause mortality (mvRR: 1.002; 95% CI: 0.98 to 1.03). *Horizontal line represents a RR=1.0; vertical line represents the median ARA intake in the studied populations (0.12 g/day).*

ARA: arachidonic acid; CI: confidence interval; mv: multivariable; mvRR: multivariable risk ratio; RR: risk ratio.

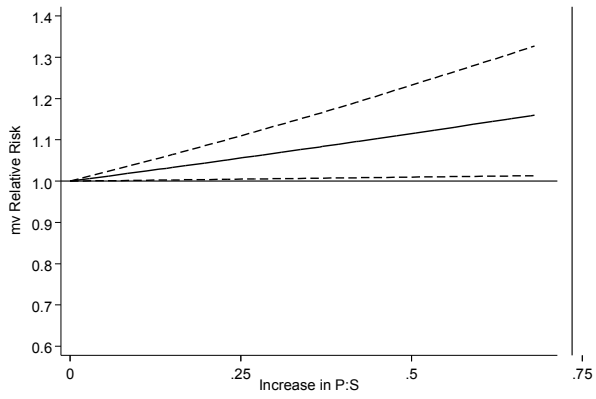
Fig. 206. Dose–response association between ARA (%E) and most-adjusted RR of all-cause mortality in three studies, assuming linearity (*P*<0.0001 for goodness-of-fit) (left), and using non-linear, cubic spline approach (right), with knots at 0.01, 0.02, and 0.04% energy



Assuming linearity, a 0.3% increase in energy from ARA was associated with a 1% increased risk of all-cause mortality (mvRR: 1.01; 95% CI: 0.87 to 1.18). *Horizontal line represents a RR=1.0; vertical line represents the median ARA intake in the studied populations (0.06%E).*

ARA: arachidonic acid; CI: confidence interval; E: energy; LA: linoleic acid; mv: multivariable; mvRR: multivariable risk ratio; RR: risk ratio.

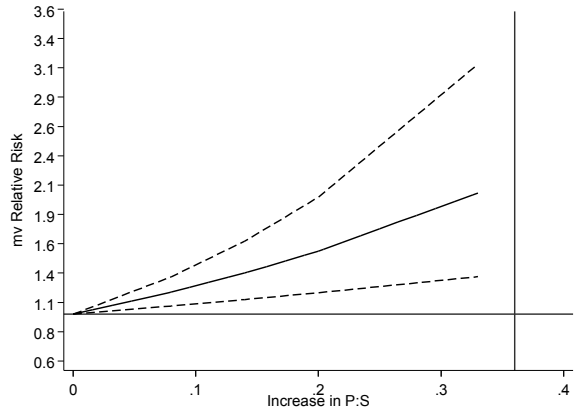
Fig. 207. Dose–response association between P:S and most-adjusted RR of CVD mortality in two studies, assuming linearity (*P*=0.14 for goodness-of-fit).



Assuming linearity, a 0.25 increase in P:S was associated with a 5% increased risk of CVD mortality (mvRR: 1.05; 95% CI: 1.02 to 1.07). *Horizontal line represents a RR=1.0; vertical line represents the median P:S in the studied populations (0.735).*

CI: confidence interval; CVD: cardiovascular disease; mv: multivariable; mvRR: multivariable risk ratio; P:S: polyunsaturated:saturated fat ratio; RR: risk ratio.

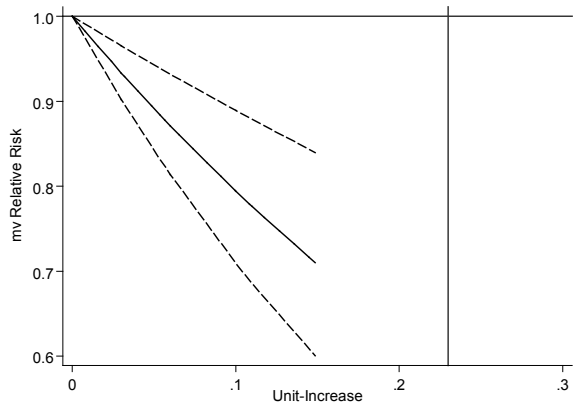
Fig. 208. Dose–response association between P:S and most-adjusted RR of post-menopausal breast cancer in one study, assuming linearity (*P*=0.53 for goodness-of-fit)



Assuming linearity, a 0.25 increase in P:S was associated with a 71% increased risk of post-menopausal breast cancer (mvRR: 1.71; 95% CI: 1.23 to 2.37). *Horizontal line represents a RR=1.0; vertical line represents the median P:S in the studied populations (0.36).*

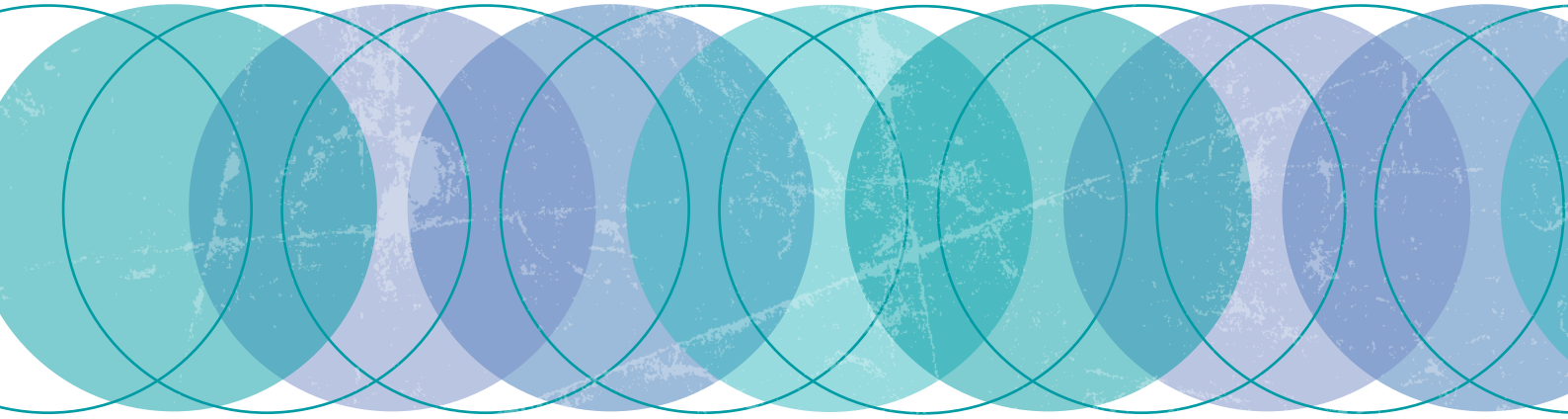
CI: confidence interval; mv: multivariable; mvRR: multivariable risk ratio; P:S: polyunsaturated:saturated fat ratio; RR: risk ratio.

Fig. 209. Dose–response association between n-3:n-6 ratio and depression in three studies, assuming linearity (*P*=0.83 for goodness-of-fit)



Assuming linearity, a 0.1-unit increase in n-3:n-6 ratio was associated with a 21% lower risk of depression (mvRR: 0.79; 95% CI: 0.71 to 0.89). *Horizontal line represents a RR=1.0; vertical line represents the median n-3:n-6 ratio in the studied populations (0.23).*

CI: confidence interval; mv: multivariable; mvRR: multivariable risk ratio; RR: risk ratio.



For more information, please contact:

Department of Nutrition and Food Safety
World Health Organization
Avenue Appia 20, CH-1211 Geneva 27, Switzerland

Email: nutrition@who.int
https://www.who.int/teams/nutrition-and-food-safety

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