Methods Research Report

Supplemental Project To Assess the Transparency of Reporting Requirements: Omega-3 Fatty Acids and Cardiovascular Disease

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None of the investigators have any affiliations or financial involvement that conflicts with the material presented in this report.

The information in this report is intended to help health care decisionmakers—patients and clinicians, health system leaders, and policymakers, among others—make well-informed decisions and thereby improve the quality of health care services. This report is not intended to be a substitute for the application of clinical judgment. Anyone who makes decisions concerning the provision of clinical care should consider this report in the same way as any medical reference and in conjunction with all other pertinent information, i.e., in the context of available resources and circumstances presented by individual patients.

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Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of evidence reports and technology assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. The reports and assessments provide organizations with comprehensive, science-based information on common, costly medical conditions and new health care technologies and strategies. The EPCs systematically review the relevant scientific literature on topics assigned to them by AHRQ and conduct additional analyses when appropriate prior to developing their reports and assessments.

To improve the scientific rigor of these evidence reports, AHRQ supports empiric research by the EPCs to help understand or improve complex methodologic issues in systematic reviews. These methods research projects are intended to contribute to the research base in and be used to improve the science of systematic reviews. They are not intended to be guidance to the EPC program, although may be considered by EPCs along with other scientific research when determining EPC program methods guidance.

AHRQ expects that the EPC evidence reports and technology assessments will inform individual health plans, providers, and purchasers as well as the health care system as a whole by providing important information to help improve health care quality. The reports undergo peer review prior to their release as a final report.

We welcome comments on this Methods Research Project. They may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 5600 Fishers Lane, Rockville, MD 20857, or by e-mail to epc@ahrq.hhs.gov.

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Supplemental Project to Assess the Transparency of Reporting Requirements: Omega-3 Fatty Acids and Cardiovascular Disease

Structured Abstract

Introduction. Clinical trial registries that include prospective registration of study protocols and summarized results can inform the prevalence and impact of information bias. This methods report examines the feasibility and added utility of comprehensive searches of registries to supplement the evidence identified in an ongoing systematic review update on omega-3 fatty acids (n-3 FA) and CVD outcomes.

Data sources. We conducted searches in ClinicalTrials.gov and the International Clinical Trials Registry Platform, using terms that matched those used in the original review database searches.

Results. The original report included 98 studies (61 randomized controlled trials in 82 articles, and 37 longitudinal observational studies in 65 articles). We compared our registry search yield with our original report to identify studies: (1) registry record present, included in original review (26 studies, 4 with eligible results); we found that, in general, the agreement between the registry record and the published paper was good when the information was given in both**.** (2) Registry record present, not included in original review (43 studies); of these 23 were completed, 10 were ongoing, and 13 had unknown status. A single record yielded a new publication emanating from a study included in the original report. (3) No registry record, included in original review (72 studies); we posit that this is, in part, because many of the studies in the report predate the requirement to register trials.

Conclusions. While we found that for this project, searching registry data added little to the evidence, one way in which conducting a registry search is of value to a systematic review project is in identifying ongoing research and gaps in knowledge. Several of the studies not found in the original review but identified through registry searches were unfinished or in progress at the time of the search. These studies should be taken in to account when evaluating the state of the literature and calling for future research.

Contents

Background and Objectives

Information biases, including publication bias, time-lag bias, selective outcome reporting bias, selective analysis bias, and fraud are major threats to the validity of systematic reviews. Systematic reviewers have pursued two methods approaches for dealing with information bias, namely, detecting (and possibly correcting results for) information bias based only on the identified studies (e.g., using funnel-plot based methods[1-4] or various selection models[5-7]), and examining trial registries, surveying researchers, and perusing the grey literature to identify unpublished study results or ongoing studies. Arguably the best way to obtain empirical data on the prevalence and impact of information bias and perhaps to mitigate its impact is through clinical trial registries that include prospective registration of study protocols, as well as summarized results (e.g., the National Library of Medicine ClinicalTrials.gov registry and registry networks, such as International Clinical Trials Registry Platform [ICTRP]). Advocates of clinical trial registration emphasize the role of registry platforms to disseminate aggregated results to researchers, clinicians, and study participants. Registries enhance transparency by providing an inventory of studies that are in progress or have been completed.[8-10]

Empirical analyses of prospective registration of studies (defined here as registration of investigational studies prior to enrollment of the first patient or, for observational studies, prior to initial analyses) can inform on the time between study completion and publication, the number of unpublished studies, the fidelity of studies to registered protocols, and the congruence of study results between registry records and publications.[11-14]

This methods report assesses the value of searching ClinicalTrials.gov and ICTRP registry records in a systematic review of dietary supplements. Obtaining empirical data on studies of dietary supplements (e.g., fish oil) and interventions (e.g., increase of fish servings per week) in the context of a major clinical condition (e.g., cardiovascular disease [CVD]) adds to existing knowledge because the mechanisms through which information bias operates in this case may differ from studies of medications. The existing empirical research on information bias pertains almost exclusively to industry-sponsored drug, device, and biologic trials,[15-17] despite the fact that 42 percent (88023) of all studies registered in ClinicalTrials.gov are indexed as "observational" or "behavioral/other intervention studies". [18] Omega-3 fatty acids derive from both dietary supplements and consumption through a variety of plants and animal sources and these studies typically fall under these observational and other intervention studies. The inclusion of registry searches in our omega-3 review, will add to our understanding of the role of registry searching in non-industry, non-drug studies.

Objectives

We examine the feasibility and added utility—in terms of impact on risk of bias and strength of evidence assessments—of comprehensive searches of the ClinicalTrials.gov and ICTRP registries to supplement the evidence identified in an ongoing systematic review update on omega-3 fatty acids (n-3 FA) and CVD outcomes conducted by the Brown Evidence-based Practice Center (EPC).[19-21]

Methods

Overview

The Brown EPC conducted a review of the relationship between n-3 FA intake and CVD outcomes, following Institute of Medicine standards and Agency for Healthcare Research and Quality (AHRQ) guidance. This review (hereafter, "original review") did not include registry searches as part of the strategy to identify ongoing studies.

We searched ClinicalTrials.gov and ICTRP up to the last search date of the original review (6/8/2015) to identify additional studies not identified in the original review, or additional information on the design or results of studies included in the original review.

Terminology

We use the term *study* to refer to the conducted research; a study may have one or more corresponding *registry records* in ClinicalTrials.gov or ICTRP *registries*, and these study results may be reported in the peer-reviewed literature as *publications*. A registry record provides basic information about a study's design, and may include optional information on its results or publications associated with it. Studies identified through the registry search may have no associated publications; studies identified by the original report may have no records in a registry. A study was deemed to have been registered *prospectively* registration of data (defined here as registration of investigational studies prior to enrollment of the first patient or, for observational studies, prior to initial analyses.

Registry Searches

Because the registry databases are not indexed, queries can include only text words. Thus, it was necessary to translate the search of the original review, which includes text words, as well as controlled-vocabulary (MeSH) terms, to a semantically equivalent query using the registry interfaces. In addition, the ClinicalTrials.gov search interface allows only for queries with a limited number of characters, and documentation on advanced searching options, such as truncation and adjacency searching, is sparse.[22, 23] It is therefore better to search for "intervention" terms only.[22] We conducted four queries in ClinicalTrials.gov whose union corresponded to the scope of the original search; we used an analogous search process in ICTRP. Appendix A includes the literature searches from the original report and the specific search strategies used in ClinicalTrials.gov and ICTRP.

Screening, Data Extraction, and Data Management

Registry records were screened using the same approach employed in the original review (Appendix B). An evidence map comprised of registry records for eligible comparative and non-comparative studies was compiled, without minimum sample size or minimum follow up requirements. Basic study information (intervention, outcome, study design, sample size, and follow up duration) was recorded, noting if results were reported in the registry. Additional data was extracted from records that (1) included results and (2) met full eligibility criteria for the original report. These data include detailed study population data, the intervention details (i.e., n-3 FA type, dose, and duration), the reported outcomes, the numerical results, and on methodological items to assess the study risk of bias.

Data were extracted into the same customized forms developed and utilized for the original review in the Systematic Review Data Repository (SRDR) online system (http://srdr.ahrq.gov). Disagreements were resolved by discussion, with adjudication, when necessary, by the original report's project lead.

Analysis

Our study yield was categorized as follows: 1) registry record present, included in original review; 2) registry record present, not included in original review; and 3) no registry record, included in original review. Characteristics of studies found exclusively in the original review, in a registry database, or in both sources, were documented.

Study initiation date, study status (e.g., discontinued, in progress/ongoing) and, when available, rationale for discontinuation or delay were also documented.

We quantified the number of studies and publications included in the original review but not found to have a registry record. We focused on the value of results data identified via registry searches, and thus in our analyses, we highlight the congruence, or lack thereof, among data identified via the registry and found in the original report in light of additional study data identified via registry searches.

Studies included in the original review and found to have a registry record were reviewed for additional information pertinent to study design (if the registry record includes protocol information) or study findings (if the record includes results). Study design information extracted from the registry record was compared to that extracted from corresponding publications to assess if changes in the outcomes or analysis plan occurred.

Comparisons between registry records and publications were made with respect to 1) general design items used to inform risk of bias assessments and 2) the analysis plan of the eligible exposure-outcome relationships. The risk of bias of each study result in the original review was evaluated based on predefined questions (Appendix C). We assessed whether additional information identified in registry records changed the risk of bias assessments of the original review.

When study results were identified in registry records and in corresponding publications, we determined if the same outcome concepts were employed, and if yes, whether the results agree qualitatively (i.e. same direction). We also describe which outcome measures were reported in the registry record, the publication, or both.

Registry records of newly identified studies (not included in the original review) are summarized in narrative form and added to the original report's evidence map. We applied the same risk of bias assessments as in the original review (Appendix C).

Risk of Bias for the Evidence Base and Strength of Evidence

For outcomes with new data from the registries for specific n-3 FA comparisons, we reassessed the risk of bias of the evidence base and the strength of evidence using the same methodology used for the original report. We evaluated whether the additional data are likely to impact the findings of the study. We quantified this impact as a potential increase in total study population sample size (>20%), a change in the magnitude of outcome measures (20% change in estimate or a change in direction; ideally by meta-analysis), or a change in statistical significance (ideally by meta-analysis). Because meta-analyses were not conducted for most outcomes, we assessed whether the results from the new studies fall within the range of similar studies from the original report. If none of these conditions were met, the additional data were considered

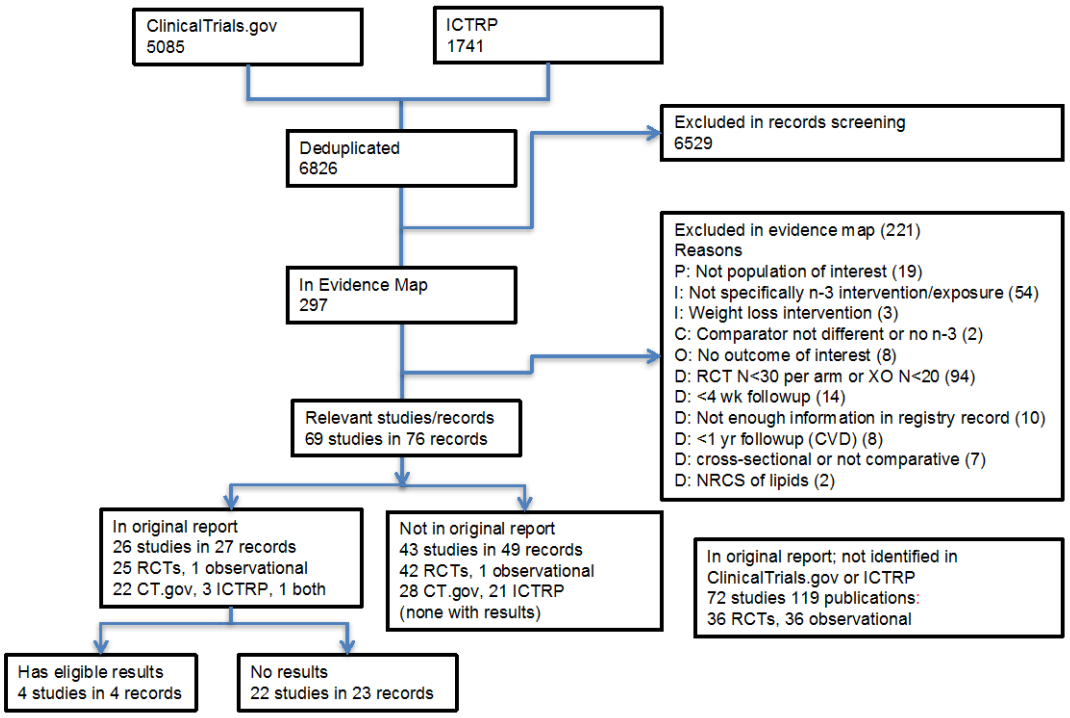
unlikely to directly impact the strength of evidence or the assessment of risk of bias for the evidence-base. All potential revisions to risk of bias and strength of evidence were discussed with the project lead of the original review. We describe and explain any changes to strength of evidence for any n-3 FA and outcome relationship.

Results

Registry Search Yield

Our initial search yield identified 6826 unique records (5085 in ClinicalTrials.gov, 1741 in ICTRP), (See Figure 1). After initial exclusion criteria were applied, 297 unique records were added to the evidence map and further assessed based on evaluation of basic population, intervention, outcome, study design, sample size criteria, and whether results were reported. At this juncture, 221 studies were excluded in the second round of screening, based on outcome-specific criteria defined in the report, most frequently because the study size was too small (43%; n=94) for the design (<30/arm in randomized controlled trials [RCTs] or <20 in crossover studies [XO]), the intervention/exposure was not specifically an n-3 FA (25%; n=54), or because the study did not evaluate a population of interest (9%; n=19). A full list of the excluded records and the reasons for exclusion is in Appendix D. A few studies had multiple registry records; one in ClinicalTrials.gov and a second in a national registry of another country listed in the ICTRP.

Figure 1. Literature flow



RCT: randomized controlled trial; XO crossover study; CT.gov: ClinicalTrials.gov; ICTRP: International Clinical Trials Registry Platform; CVD: cardiovascular disease; NRCS: non-randomized comparative study.

Comparison of Registry Searches with Original Review

The original report included 98 studies (61 randomized controlled trials in 82 articles, and 37 longitudinal observational studies in 65 articles). We compared our registry search yield with our original report to identify studies (1) registry record present, included in original review; (2) registry record present, not included in original review; and (3) no registry record, included in original review. See Figure 1.

Studies Identified via Registry Searches and Found in Original Review

Overall, 69 studies in 76 records identified through registry searches met full criteria for inclusion in the original report. Of these, 26 studies (in 27 registry records) were included in the original report (25 RCTs, 1 observational Study); 22 of these were found in ClinicalTrials.gov, 3 were found in ICTRP, and 1 was identified in both registries (see Table 1 for the overall description of studies; the subsequent tables highlight differences between registry records and articles). Of the 26 studies in both sources, only 4 studies (in 4 records) included eligible results in the registry records. In general, the agreement between the registry record and the published paper was good when the information was given in both. A fifth record of a factorial study reported results, but no comparison between the n-3 FA and no n-3 FAs was reported in the record. Full information on the comparison of results for the four studies that have them is in the Results section and Table 3 below.

Study Design

For all 26 studies found in both the report and registries, we were able to extract some study design information via registry records. When possible, study design information extracted from the registry record was compared to corresponding publications to assess if changes in analysis plan occurred. In general, agreement was very good between the registry record and the report, particularly in terms of population and eligibility criteria. There were some small disagreements in study start date, duration of intervention, and reporting of industry relationship when the only role of the sponsor was solely to provide materials. See Appendix E, Tables 1 and 2 for full details.

Table 1. Overall description of studies in both the report and registry from the registry records

Study Identifier Country/ies Study Name	Registry	Population	Dates	N total	Study design: Intervention	Intermediate Outcomes	Clinical Outcomes
Registry record reported results							
NCT01242527 US, Denmark, Netherlands, Hungary, India, Russia, Ukraine EVOLVE	CT.gov	At risk	2011-2012	399	RCT: Fish oil (EPA+DHA) 2, 3, or 4 g/d vs. Placebo	Lipids	
NCT01408303 US ESPRIT	CT.gov	At risk	2011-2012	646	RCT: Fish oil (EPA+DHA) 2 or 4 g/d vs. Placebo	Lipids	
NCT01198275 Italy ATRIA	CT.gov	CVD, existing	2006-2008	199	RCT: Fish oil (EPA+DHA) 0.850-0.882 g/d vs. Placebo		Arrhythmia event

Study Identifier Country/ies Study Name	Registry	Population	Dates	N total	Study design: Intervention	Intermediate Outcomes	Clinical Outcomes
NCT00781950 Canada FLAXPAD	CT.gov	CVD, existing	2008-2014	110	RCT: ALA 30 g/d vs. Placebo	BP, Lipids	Cardiac event, Stroke/TIA, Death
Registry record did not report results							
NCT00005133 US CHS	CT.gov	Healthy	1988-2009	nd	Observational - Quantile: unclear n-3		Cardiac event, Stroke/TIA
NCT01313988 Sweden	CT.gov	Healthy	2011-2012	332	RCT: All n-3 PUFA vs. Placebo	Lipids	
NCT00110838 Germany, Netherlands, UK, Austria, Belgium, Czech Republic, Poland, Switzerland SOFA	CT.gov	Healthy	2010-2011	256	RCT: Fish oil (EPA+DHA) 2 g/d vs. Placebo	Lipids	
NCT00266292 Denmark	CT.gov	Healthy	2005-2006	60	RCT: Fish oil (EPA+DHA) vs. Placebo	BP, Lipids	
NCT01856179 Germany	CT.gov	Healthy	2011-2012	78	RCT: SDA 15-18 g/d vs. nd	Lipids	
NCT00317707 Italy	CT.gov	At risk	2004-2011	12513	RCT: All n-3 PUFA vs. Placebo		Cardiac event, Death
NCT00141232/ISRCTN76737502 UK AFFORD	ICTRP/	At risk	2004-2006	810	RCT: Fish oil (EPA+DHA) vs. Placebo	Lipids	
NCT00246701 US COMBOS	CT.gov	At risk	2005-2006	256	RCT: Fish oil (EPA+DHA) vs. Placebo	Lipids	
NCT00069784 Canada ORIGIN	CT.gov	At risk	2003-2011	12537	RCT: Fish oil (EPA+DHA) 0.84 g/d vs. Placebo		Cardiac event, Stroke/TIA, Death
NCT01758601 Spain WISH-CARE	CT.gov	At risk	2010-2012	273	RCT - XO: Fish oil (EPA+DHA) 1 serving of hake/day vs. no intervention	Lipids	
NCT00231738 Japan JELIS	CT.gov	At risk	1996-2004	18000	RCT: EPA 1.8 g/d vs. nd		Cardiac event, Stroke/TIA, Death
NCT01047501 US ANCHOR	CT.gov	At risk	2009-2011	702	RCT: EPA 2 or 4 g/d vs. Placebo	Lipids	
NCT01351012 Canada COMIT	CT.gov	At risk	2010-2012	140	RCT - XO: ALA, DHA + ALA DHA 7.2, ALA 4.2-13.8 vs. ALA 4.2-13.8 g/d	Lipids	
DRKS00006232 Germany MSX	CT.gov	At risk	2009-2009	81	RCT: ALA 3.5 g/d vs. ALA 0.9 g/d	BP, Lipids	
NCT00004558 US	ICTRP	CVD, existing	1999-2004	200	RCT: Omega-3 (Unspecified) vs. Placebo		Arrhythmia event
NCT00127452 Netherlands Alpha Omega	CT.gov	CVD, existing	2002-2010	4837	RCT: All n-3 PUFA Fish oil 0.4 g/d, ALA 2 g/d vs. Placebo		Cardiac event, Stroke/TIA, Arrhythmia event, PVD event, Death

Study Identifier Country/ies Study Name	Registry	Population	Dates	N total	Study design: Intervention	Intermediate Outcomes	Clinical Outcomes
NCT00251134 Germany OMEGA	CT.gov	CVD, existing	2003-2008	3800	RCT: All n-3 PUFA 1 g/d vs. Placebo		Cardiac event, Arrhythmia event, Death
NCT00336336 Italy GISSI-HF	CT.gov	CVD, existing	2002-2008	6975	RCT: All n-3 PUFA 1 g/d vs. Placebo		Cardiac event, Stroke/TIA, Arrhythmia event, Death
ISRCTN41926726 France SU.FOL.OM3	CT.gov	CVD, existing	2003-2009	2400	RCT: Fish oil (EPA+DHA) 0.6 g/d vs. Placebo		Cardiac event, Stroke/TIA, Death
ISRCTN66664610 UK MARINA	ICTRP	CVD, existing	2008-2010	360	RCT: Fish oil (EPA+DHA) 0.45, 0.9, or 1.8 g/d vs. Placebo	BP, Lipids	
NCT00004559 US FAAT	ICTRP	CVD, existing	2000-2005	nd	RCT: Fish oil (EPA+DHA) 4 g/d vs. Placebo		Arrhythmia event
NCT00597220 Argentinia FORWARD	CT.gov	CVD, existing	2008-2011	1600	RCT: Fish oil (EPA+DHA) 1 g/d vs. Placebo		Stroke/TIA, Arrhythmia event

RCT: randomized controlled trial; XO: crossover tiral; CT.gov: ClinicalTrials.gov; ICTRP: International Clinical Trials Registry Platform; CVD: cardiovascular disease; NRCS: non-randomized comparative study; TIA: transient ischemic attack; PVD: peripheral vascular disease; BP: blood pressure; EPA: eicosapentaenoic acid; DHA: docosahexaenoic acid; ALA: alphalinolenic acid; PUFA: polyunsaturated fatty acids; SDA: stearidonic acid

Outcomes

Outcomes of interest described in the original review (see Appendix B), were identified in registry records and in publications and compared. Registry records include data entry fields for primary and secondary outcomes and these measures were extracted and characterized as such. Disposition of primary outcomes found in publications were determined if they were 1) explicitly stated as such, 2) the outcome used in reported power calculations, or 3) where implied by focus of the original article.

We identified several discrepancies between outcomes reported in registry records and resulting publications (Table 2). The overwhelming number discrepancies (24 outcomes in 12 papers) had to do with more outcomes being reported in the paper than were prespecified in the record. In general, these were intermediate outcomes (e.g., lipids and blood pressure), though in three papers they were clinical outcomes, including nonfatal stroke, myocardial infarction, and revascularization, among others). All of the added clinical and blood pressure outcomes were reported as not having a significant difference between groups. As would be expected, triglycerides were consistently reported as significantly favoring the Omega-3 group, but cholesterol overall showed a nonsignificant difference.

In three cases, a record prespecified a clinical outcome as primary, and it was either reported as secondary or not at all in the paper. In the study by Bosch, the prespecified outcome was a composite of "the First Occurrence of Cardiovascular (CV) Death, Nonfatal Myocardial Infarction, Nonfatal Stroke, Revascularization Procedure or Hospitalization for Heart Failure." All of these outcomes were reported in the paper as secondary outcomes, except Cardiovascular (CV) Death, which was reported as primary. None of these results was significantly different between groups.[24] The paper by Damsgaard reported the prespecified lipid outcomes, which were not significant, but not the prespecified blood pressure outcomes.[25] For the study by Rodriguez-Leyva, we went to their published protocol,[26] which differed from the record in two

outcomes (total and CVD mortality), which were reported as not significantly different between groups in the paper. Both of these outcomes were specified as primary in the record and secondary in the published protocol. It is worth noting that the paper also reported nonsignificant differences for the other two primary outcomes (stroke and MI). In general, this suggests that there is probably not major problem with selective outcome reporting in this body of literature.[27]

Table 2. Outcome discrepancies

Study name, Date, PMID, Registry number	N record/N publication	Current prespecified outcome (from registry)	In papers (as primary/ secondary) (time point)	In Registry Record (as primary/secondary) (time point)	Outcome (favors n-3, favors other, not significant (NS), results not reported (ND))
Baxheinrich, 2012, 22894911, DRKS00006232	81/81	Blood pressure	Secondary (3 and 6 months)	Secondary (3 and 6 months)	Favors n-3
		Lipids	Secondary (3 and 6 months)	Secondary (3 and 6 months)	Favors n-3 for TG; NS for others
Bosch, 2012, 22686415, NCT00069784	12537/ 12536	MACE: Composite of the First Occurrence of Cardiovascular (CV) Death, Nonfatal Myocardial Infarction, Nonfatal Stroke, Revascularization Procedure or Hospitalization for Heart Failure	Secondary (6+ years), except for "death from cardiovascular causes'" which is also primary in the paper	Primary (mean 6.2 years)	NS
		Death from cardiovascular causes	Primary (6+ years)	Primary (mean 6.2 years)	NS
		Total mortality (all causes)	Secondary (6+ years)	Secondary (mean 6.2 years)	NS
		Lipids	Secondary (6+ years)		NS
		Blood pressure	Secondary (6+ years)		NS
Brinton, 2013, 23835245, NCT01047501	702/687	Lipids (Tg)	Primary (3 months)	Primary (12 weeks)	Favors n-3
		Lipids (other)	Secondary (3 months)	Secondary (12 weeks)	Favors n-3
Brouwer, 2006, 16772624, NCT00110838	546/546	ICD intervention/device insertion	Primary (1 year)	Primary (1 year)	NS
		Total mortality (all causes)	Secondary (1 year)	Secondary (1 year)	NS
		Myocardial infarction	Secondary (1 year)	Secondary (1 year)	NS
		Cardiac mortality	Secondary (1 year)	Secondary (1 year)	NS
		Arrythmic events (VF/VT)	Secondary (1 year)	Secondary (1 year)	NS
Damsgaard, 2008, 18492834, NCT00266292	60/64	Lipids	Primary (8 weeks)	Primary (2 months)	NS
		Blood pressure		Primary (2 months)	ND
Galan, 2010, 21115589, ISRCTN41926726	2400/2501	MACE: Combination of myocardial infarction, cerebral vascular	Primary (median 4.7 years)	Primary (nd)	NS

Study name, Date, PMID, Registry number	N record/N publication	Current prespecified outcome (from registry)	In papers (as primary/ secondary) (time point)	In Registry Record (as primary/secondary) (time point)	Outcome (favors n-3, favors other, not significant (NS), results not reported (ND))
		ischemic accident or cardiovascular deaths			
		Total mortality (all causes)	Secondary (median 4.7 years)	Secondary (nd)	Favors other
		CVD mortality	Secondary (median 4.7 years)	Secondary (nd)	NS
		Myocardial infarction	Secondary (median 4.7 years)	Secondary (nd)	NS
		Acute Coronary Syndrome	Secondary (median 4.7 years); as part of a composite outcome	Secondary (nd)	NS
		Ischemic cerebral vascular accidents (stroke)	Secondary (median 4.7 years)	Secondary (nd)	NS
		Revascularization	Secondary (median 4.7 years)	Secondary (nd)	NS
Holman, 2009, 19002433, NCT00141232 and ISRCTN76737502	810/658	Lipids (Tg)	Primary (4 months)	Primary (4 months)	Favors n-3
		Blood pressure	Secondary (4 months)		NS
Jones, 2014, 24829493, NCT01351012	140/130	Lipids	Secondary (4 weeks)	Secondary (4 weeks)	Favors n-3
		Blood pressure	Secondary (4 weeks)	Secondary (4 weeks)	Favors n-3
Kastelein, 2014, 24528690, NCT01242527	399/393	Lipids (Tg)	Primary (12 weeks)	Primary (12 weeks)	Favors n-3
		Lipids (other)	Secondary (12 weeks)		Favors n-3
Kromhout, 2010, 20929341, NCT00127452	4837/4837	Major cardiovascular events, which comprises fatal cardiovascular diseases (CVD), non-fatal myocardial infarction, non-fatal cardiac arrest, non-fatal stroke and cardiac interventions (PCI and CABG)	Primary (40 months)	Primary (40 months)	NS
		cardiovascular diseases (CVD	Secondary (40 months)	Secondary (40 months)	NS
		Cardiac mortality	Secondary (40 months)	Secondary (40 months)	NS
		Arrythmia	Secondary (40 months)		NS
		Total mortality (all causes)	Secondary (40 months)	Secondary (40 months)	NS
		Lipids (in appendix)	Secondary (40 months)		NS
		Blood pressure (in	Secondary (40		NS

Study name, Date, PMID, Registry number	N record/N publication	Current prespecified outcome (from registry)	In papers (as primary/ secondary) (time point)	In Registry Record (as primary/secondary) (time point)	Outcome (favors n-3, favors other, not significant (NS), results not reported (ND))
		appendix)	months)		
Kuhnt 2014, 24553695, NCT01856179	78/59	EPA concentrations	Primary (56 days)	Primary (2 months)	N/A (not an outcome of interest for the report)
		Lipids	Secondary (2 months)		Favors n-3
		Blood pressure	Secondary (2 months)		Favors n-3
Leaf, 2005, 16267249, NCT00004559	Nd/402	VT or VF event	Primary (12 months)	Primary (nd)	NS
		Total mortality (all causes)	Secondary (1 year)		NS
		Cardiac mortality	Secondary (1 year)		NS
		Sudden cardiac death	Secondary (1 year)		NS
Macchia, 2013, 23265344, NCT00597220	1600/586	Atrial fibrillation	Primary (12 months)	Primary (12 months)	NS
		Total mortality (all causes)	Secondary (12 months)	Secondary (12 months)	NS
		MACE: all-cause mortality, nonfatal stroke, nonfatal acute myocardial infarction (AMI), systemic embolism, heart failure development, or severe bleeding	Secondary (12 months)		NS
		hospitalizations for CV reasons	Secondary (12 months)	Secondary (12 months)	NS
		Thromboembolism	Secondary (12 months)	Secondary (12 months)	NS
Maki, 2010, 20451686, NCT00246701	256/254	Lipids	Primary (8 weeks)	Primary (8 weeks)	Favors n-3
Maki, 2013, 23998969, NCT01408303	646/627	Lipids	Primary (1.5 months)	Primary (6 weeks)	Favors n-3
Nodari, 2011, 21844082, NCT01198275	199/133	Atrial fibrillation (maintenance of sinus rhythm)	Primary (1 year)	Primary (1 year)	Favors n-3
		Time to a First Recurrence of Atrial fibrillation	Secondary (median 718 days)	Secondary (12 months)	Favors n-3
Raitt, 2005, 15956633, NCT00004558	200/200	VT or VF	Primary (median of 718 days)	Primary (nd)	NS
		Total mortality (all causes)	Secondary (2 years)	Secondary (nd)	NS
		Hospitalization rates	Secondary (2 years)	Secondary (nd)	NS
		Cardiac mortality	Secondary (2 years)		NS
		Sudden Cardiac Death	Secondary (2 years)		NS
		Revascularization	Secondary (2 years)		NS

Study name, Date, PMID, Registry number	N record/N publication	Current prespecified outcome (from registry)	In papers (as primary/ secondary) (time point)	In Registry Record (as primary/secondary) (time point)	Outcome (favors n-3, favors other, not significant (NS), results not reported (ND))
		Myocardial infarction	Secondary (2 years)		NS
Ras, 2014, 25122648, NCT01313988	332/314	Lipids (Tg)	Primary (1 month)	Primary (4 weeks)	Favors n-3
Rauch, 2010, 21060071, NCT00251134	3800/3804	Sudden cardiac death	Primary (1 year)	Primary (12 months)	NS
		Total mortality (all causes)	Secondary (1 year)	Secondary (12 months)	NS
		MACCE: Total mortality, re-infarction or stroke	Secondary (1 year)	Secondary (12 months)	NS
		Total rehospitalisation	Secondary (1 year)	Secondary (12 months)	NS
		VT or VF	Secondary (1 year)	Secondary (12 months)	NS
		Arrhythmia device insertion	Secondary (1 year)	Secondary (12 months)	Favors other
		Revascularization	Secondary (1 year)	Secondary (12 months)	NS
Rodriguez-Leyva, 2013, 24126178, NCT00781950 (outcome information from published protocol, PMID 21616170)	110/87	Total mortality (all causes)	Secondary (1 year)	Primary (1 year)	NS
		CVD mortality	Secondary (1 year)	Primary (1 year)	NS
		Stroke	Primary (1 year)	Primary (1 year)	NS
		Myocardial infarction	Primary (1 year)	Primary (1 year)	NS
		Blood pressure	Secondary (1, 6, and 12 months)	Secondary (1 year)	Favors n-3
		Lipids	Secondary (1, 6, and 12 months)	Secondary (1 year)	ND
Roncaglioni, 2013, 23656645, NCT00317707	12513/ 12513	MACE: death from cardiovascular causes or hospital admission from cardiovascular causes	Primary (5 years)	Primary (5 years)	NS
		Lipids (in appendix)	Secondary (5 years)		Favors n-3
		Blood pressure (in appendix)	Secondary (5 years)		NS
Sanders, 2011, 21865334, ISRCTN66664610	360/310	Lipids	Secondary (1 year)	Secondary (6 months, 12 months)	Favors n-3
		Blood pressure	Secondary (1 year)		NS
Tavazzi, 2008, 18757090, NCT00336336	6975/6975	Total mortality (all causes)	Primary (stated) (3.9 years)	Primary (from enrollment to 1252 deaths in R2 arm)	NS
		Total mortality (all causes) or hospitalization for any reason		Primary (from enrollment to 1252 deaths in R2 arm)	Favors n-3 (when adjusted)
		CVD mortality	Secondary (3.9 years)	Secondary (from enrollment to 1252 deaths in R2 arm)	Favors n-3 (when adjusted)
		Hospitalization for any reason	Secondary (3.9 years)	Secondary (from enrollment to 1252 deaths	Favors n-3 (when adjusted)

Study name, Date, PMID, Registry number	N record/N publication	Current prespecified outcome (from registry)	In papers (as primary/ secondary) (time point)	In Registry Record (as primary/secondary) (time point)	Outcome (favors n-3, favors other, not significant (NS), results not reported (ND))
				in R2 arm)	
		Heart failure	Secondary (3.9 years)	Secondary (from enrollment to 1252 deaths in R2 arm)	NS
		Sudden cardiac death	Secondary (3.9 years)	Secondary (from enrollment to 1252 deaths in R2 arm)	NS
		Congestive heart failure	Secondary (3.9 years)	Secondary (from enrollment to 1252 deaths in R2 arm)	NS
		Myocardial infarction	Secondary (3.9 years)	Secondary (from enrollment to 1252 deaths in R2 arm)	NS
		Stroke death	Secondary (3.9 years)	Secondary (from enrollment to 1252 deaths in R2 arm)	NS
		Stroke	Secondary (3.9 years)	Secondary (from enrollment to 1252 deaths in R2 arm)	NS
		Lipids	Secondary (3.9 years)		Favors n-3
		Blood pressure	Secondary (3.9 years)		NS
Vazquez, 2014, 24462043, NCT01758601	273/273	Lipids	Primary (2 months)	Primary (8 weeks)	Favors n-3
		Blood pressure	Secondary (2 months)	Secondary (8 weeks)	Favors n-3
Yokoyama, 2007, 17398308, NCT00231738	18000/9319	Major coronary events (sudden cardiac death, fatal and nonfatal myocardial infarction, unstable angina pectoris including hospitalization for ischemic episodes,events of angioplasty/ stenting or coronary artery bypass grafting)	Primary (4.6 years)	Primary (nd)	Favors n-3
		Total mortality (all causes)	Secondary (4.6 years)	Secondary (nd)	NS
		Stroke	Secondary (4.6 years)	Secondary (nd)	NS
		Peripheral artery disease	Secondary (4.6 years)	Secondary (nd)	ND
		Lipids	Secondary (4.6 years)		Favors n-3
		Blood pressure	Secondary (4.6 years)		NS

Baselines

For the four studies that had results data in both the registry record and publications,[27-30] baseline data, results, and adverse events were compared. The baseline data provided in registry records were limited to age, gender, and in one record[29] race. All of the baselines provided matched the corresponding publications exactly (for further details, see Appendix E, Table E-5).

Results

The results, as reported in both the records and the publications, are given in Table 3. In one paper there was a discrepancy in how the results were reported, which lead to a difference in significance.[30] However, the significant results were reported in the registry record, while the non-significant findings were reported in the paper, so there is little indication of reporting bias. In addition, the odds ratio reported in the record falls within the confidence intervals of that in the report, and so is unlikely to differ in either direction or magnitude.

In a second study, the record and the paper do not agree in terms of outcomes reported or results given.[27] This is a recent study so it is possible that the paper for the clinical outcomes is still in process. One outcome, all-cause mortality, was given in the record but not in either paper. This outcome was not found to be significant. A second outcome, stroke, was reported in both the paper and the record, but the results differed in both direction and magnitude. A third outcome, myocardial infarction, was reported slightly differently, but neither odds ratio was found to be statistically significant.

Otherwise, the discrepancies were small, mostly involved the number analyzed, and did not affect the results. Full details are given in Table 3; discrepancies are indicated by bold/italic text.

Table 3. Results

Study Year PMID Region**	Outcome	Int (n-3 FA)	Control	F/up Time	Int n/N, % or N per arm for continuous outcomes	Ctrl n/N,% or N per arm for continuous outcomes	Effect Size	Reported P value
Marine oil vs. Placebo								
Nodari 2011 21844082 Italy	arrhythmia_A Fib (recurrence of AFib)	EPA+DHA (0.850−0.88 2 g/d (marine oil))	Placebo	1 y	15 / 100, 15%	25 / 99, 25%	OR 0.52 (0.26, 1.06)[a]	NR
NCT011982 75 (Nodari 2011 21844082)	arrhythmia_A Fib *(no Atrial Fibrillation recurrence at 1-year followup)**	EPA+DHA (0.850-0.882 2 g/d (Omacor))	Placebo	1 y	*61/100, 61%*	*34/99 34%*	*OR 0.441 (0.292, 0.666) These results are not in the paper*	*p<0.05*
Maki 2013 23998969 US	lipid_LDL cholesterol	EPA+DHA (4 g/d total oil -free fatty acid oil)	Placebo	1.5 mo	207	211	−0.5 (−4.1, 3.1) (-6%)	p<0.0001
NCT014083 03 (Maki 2013 23998969 US)	lipid_LDL cholesterol	EPA+DHA (4 g/d Epanova)	Placebo	1.5 mo	*204*	*210*	-6%	p<0.0001

Study Year PMID Region**	Outcome	Int (n-3 FA)	Control	F/up Time	Int n/N, % or N per arm for continuous outcomes	Ctrl n/N,% or N per arm for continuous outcomes	Effect Size	Reported P value
Maki 2013 23998969 US	lipid_LDL cholesterol	EPA+DHA (4 g/d total oil -free fatty acid oil)	2 g/d total oil (free fatty acid oil) [nd]	1.5 mo	207	209	−3.7 (−7.3, −0.1) (3%)	
NCT01408303 (Maki 2013 23998969 US)	lipid_LDL cholesterol	EPA+DHA (4 g/d Epanova)	EPA/DHA((2 g/d total oil (Epanova)	1.5 mo	*204*	209	-3.05%	
Maki 2013 23998969 US	lipid_LDL cholesterol	EPA+DHA 2 g/d free fatty acid oil)	Placebo	1.5 mo	209	211	-3%	p<0.05
NCT01408303 (Maki 2013 23998969 US)	lipid_LDL	EPA+DHA (4 g/d Epanova)	Placebo	1.5 mo	209	*210*	-2.95%	p<0.05
Kastelein 2014 24528690 Europe	lipid_Tg	EPA+DHA (EPA: 2.20 g/d, DHA: 0.80 g/d)	Placebo	12 wk	99	98	−173.1 (−250.3, −95.8)	p<0.001
NCT01242527 (Kastelein 2014 24528690)	lipid_Tg	EPA+DHA (Epanova 4g/d)	Placebo	12 wk	*95*	98	-26.6% (Matches % change in paper)	p<0.001
Kastelein 2014 24528690 Europe	lipid_Tg	EPA+DHA (EPA: 1.65 g/d, DHA: 0.60 g/d)	Placebo	12 wk	97	98	−156.3 (−238.8, −73.8)	p<0.01
NCT01242527 (Kastelein 2014 24528690)	lipid_Tg	EPA+DHA (Epanova 3g)	Placebo	12 wk	*94*	98	-21.2% (Matches % change in paper)	p<0.01
Kastelein 2014 24528690 Europe	lipid_Tg	EPA+DHA (EPA: 1.10 g/d, DHA: 0.40 g/d)	Placebo	12 wk	99	98	−156.4 (−238.1, −74.6)	p<0.01
NCT01242527 (Kastelein 2014 24528690)	lipid_Tg	EPA+DHA (Epanova 2g)	Placebo	12 wk	*95*	98	-21.68% (Matches % change in paper)	p<0.01
NCT00781950 (Rodriguez-Leyva 2013 24126178)	MACE (All-cause Mortality, Cardiovascular Mortality, Stroke, and Myocardial Infarctions)	ALA (flaxseed)	Placebo (wheat and wheat bran)	1 y	5/58 (8.6%)	4/52 (7.7%)	OR 1.13 (0.29, 4.46) *This outcome is not in the paper*	NS

Study Year PMID Region**	Outcome	Int (n-3 FA)	Control	F/up Time	Int n/N, % or N per arm for continuous outcomes	Ctrl n/N,% or N per arm for continuous outcomes	Effect Size	Reported P value
NCT00781950 (Rodriguez-Leyva 2013 24126178)	death_all cause	ALA (flaxseed)	Placebo (wheat and wheat bran)	1 y	1/58 1.7%	0/52, 0%	OR 2.73 (0.11, 68.64) *This outcome is not in the paper*	NS
Rodriguez-Leyva 2013 24126178	cardiac_MI	ALA (5.9 g/d flaxseed)	Placebo	1y	2/58 3.4%	4/52 7.7%	OR 0.43 (0.08, 2.44) *Slight difference*	NS
NCT00781950 (Rodriguez-Leyva 2013 24126178)	cardiac_MI	ALA (flaxseed)	Placebo (wheat and wheat bran)	1 y	1/58 1.7%	3/52 5.8%	OR 0.29 (0.03, 2.84) *Slight difference*	NS
Rodriguez-Leyva 2013 24126178	cerebro_Stroke	ALA (5.9 g/d flaxseed)	Placebo	1y	1/58 1.7%	2/52 3.8%	OR 0.44 (0.04, 4.98) *Different in direction and magnitude*	NS
NCT00781950 (Rodriguez-Leyva 2013 24126178)	cerebro_Stroke	ALA (flaxseed)	Placebo (wheat and wheat bran)	1 y	3/58 5.2%	1/52 1.9%	OR 2.78 (0.28, 27.61) *Different in direction and magnitude*	NS
Rodriguez-Leyva 2013 24126178	bp_DBP	ALA (5.9 g/d flaxseed)	Placebo	1y	45	41	−2.1 (−7.2, 3.0)	
NCT00781950 (Rodriguez-Leyva 2013 24126178)	bp_DBP	ALA (flaxseed)	Placebo (wheat and wheat bran)	1 y	45	41	71.8 (1.7) vs. 78.5 (1.5) Final values; no baselines given. Matches paper.	
Rodriguez-Leyva 2013 24126178	bp_SBP	ALA (5.9 g/d flaxseed)	Placebo	1y	45	41	−7.3 (−15.4, 0.80)	
NCT00781950 (Rodriguez-Leyva 2013 24126178)	bp_SBP	ALA (flaxseed)	Placebo (wheat and wheat bran)	1 y	45	41	136.2 (3.8) vs.145.6 (3.4) Final values; no baselines given. Matches paper.	

* discrepancies are indicated by bold italic text; **for each shading the first row (with no NCT number) is the published study from the original report, the second row is the corresponding registry record; AFib = atrial fibrillation, LDL = low-density lipoprotein, HDL = high-density lipoprotein, MI = myocardial infarction, DBP = diastolic blood pressure, SBP = systolic blood pressure.

Adverse Events

Both the papers and the records with results mentioned adverse events. The reported adverse events matched the paper in all but one study. Nausea, which is thought to be an adverse effect of Omega-3 supplementation, was reported in the record for the Rodriguez-Leyva study but was not reported in the paper.[27] Full details are given in Appendix E, Table E-6.

Risk of Bias

We evaluated the risk of bias for all studies identified in both the report and the records. In general, there was insufficient evidence to make judgements on specific risk of bias items. Where the evidence was sufficient, the records and reports agreed most of the time. Details are in Appendix E, Tables E-7 and E88. We did not find any new information that would change our initial risk of bias or strength or evidence assessments.

Relevant Studies Identified via Registry Searches and Not Found in Original Review

Of the 69 studies in 76 records identified through registry searches that met full criteria for inclusion in the original report, 43 studies (in 49 records) were not found in the original review (42 randomized controlled trials and 1 Observational Study); 28 (57%) records in ClinicalTrials.gov and 21 records in ICTRP (43%). The completion status of studies described in the 49 records are as follows; completed n = 23, ongoing n= 10 and unknown status n=13. The study enrollment estimates for studies completed as of December 31, 2016 account for a projected 20088 participants. An additional 145275 participants were estimated to enroll in the remaining studies (ongoing and unknown status). The mean start date of the studies included in the report was about 5 years earlier than the mean start date of the studies not in the report (Figure 2). In addition, many of the studies not in the report were not completed at the time of the search, which explains why they did not have publications or results.

Reviewing the evidence map for the original report, we identified publications for seven of these studies, which did not meet inclusion/exclusion criteria for the original report. Details about these studies are in Table 4. A single record yielded a new publication emanating from a study included in our original report. This new manuscript was published in the intervening time since the last update of the report search. Relevant results from this study were already identified in another publication and included in the report, the results in this newly identified manuscript were added to the report, but did not change the direction or magnitude of the results for those outcomes.

Table 4. Overall description of studies in the registry but not the report

Study Identifier Country/ies Study Name	Registry	Population	Date (start/end)	N total*	Study design: Intervention	Intermediate Outcomes	Clinical Outcomes
CTRI/2012/08/002856, India	ICTRP (Clinical Trial Registry of India)	Healthy/obese	2012-?	60	RCT: EPA 180 mg + DHA 120 mg capsules vs. EPA 180 mg + DHA 120 mg capsules capsules + probiotic capsules vs. probiotic capsules vs. placebo	BP/Lipids	Cardiac event/arrhythmia
NCT00232219, Australia	CT.gov	CVD, existing	2003-2013	200	RCT: Fish oil capsules (1.8g/d of EPA+DHA)		Arrhythmia event

Study Identifier Country/ies Study Name	Registry	Population	Date (start/end)	N total*	Study design: Intervention	Intermediate Outcomes	Clinical Outcomes
NCT02183285, no location listed	CT.gov	Healthy	2003-2004	203	RCT: Multivitamin, Multimineral + Omega-3 Fatty Acids vs Multivitamin, Multimineral without Omega-3 Fatty Acids vs placebo	BP/Lipids	AEs
NCT01350973, no location listed	CT.gov	Dyslipidemia	2009-2010	611	RCT: Omacor 2 g, capsules, orally, once daily for up to 12 weeks vs. Omacor 2 g, capsules, orally, twice daily for up to 12 weeks vs. EPA-E, 0.6 g, orally, three-times daily for up to 12 weeks.	BP/Lipids	AEs
NCT01350999, no location listed	CT.gov	Dyslipidemia	2009-2011	503	RCT: Omacor 2 g, capsules, orally, once daily for up to 52 weeks vs. Omacor 2 g, capsules, orally, twice daily for up to 52 weeks vs. EPA-E, 0.6 g, orally, three-times daily for up to 52 weeks.	BP/Lipids, HTN	
NCT01048502, US	CT.gov	CVD, existing	2010-2011	100	RCT: Tricor 145 mg/day vs. Lovaza 900 mg/day vs. Lovaza 3600 mg/day vs placebo	BP/Lipids	
NCT02239198, US	CT.gov	Healthy	2007-2008	150	RCT: Complete nutrition bar with omega-3 fatty acids vs. Nutrition bar without omega-3 fatty acids vs. Nutrition bar without added minerals and vitamins	BP/Lipids	
NCT00135226, UK	CT.gov	DM	2005-2016	15480	RCT: Aspirin 100 mg/day + Omega-3-Ethyl Esters 1g/day vs. Aspirin 100 mg/day + Placebo vs. Placebo + Omega-3-Ethyl Esters 1g/day vs. Placebo		Cardiac events, stroke/TIA
NCT01810003, Canada	CT.gov	CVD, existing	2013-2016	170	RCT: DHA 3g/day (10 wks) vs. EPA 3g/day (10 wks) vs. placebo	BP/Lipids	
NCT02210767, US	CT.gov	Healthy	2014-2016	50	RCT: 2 oz walnuts/day (ALA) vs. fatty acids not from walnuts vs. low ALA diet	BP/Lipids	
NCT02285166, Japan	CT.gov	Dyslipidemia	2014-2019	14000	RCT: Lotriga 2-4g/day vs. standard antihyperlipidemic therapy	BP/Lipids, HTN	Cardiac events, stroke/TIA, arrhythmia, PDV, death
NCT01841944, Norway	CT.gov	CVD, existing	2012-2019	1400	RCT: Pikasol (1.8 g EPA+DHA)/day vs. placebo		Cardiac events, stroke/TIA, arrhythmia, death

Study Identifier Country/ies Study Name	Registry	Population	Date (start/end)	N total*	Study design: Intervention	Intermediate Outcomes	Clinical Outcomes
NCT01320228, Denmark	CT.gov	Healthy	2011-2012	69	RCT: Alli (60 mg t.i.d) + 5 g flaxseed fibers and 1200 mg Ca from Capolac vs. Alli (60 mg t.i.d) + 5 g flaxseed fibers vs. Alli (60 mg t.i.d) + 1200 mg Ca from Capolac vs. Alli (60 mg t.i.d) + placebo	BP/Lipids	
NCT02294526, no location listed	CT.gov	DM	2012-2013	35	RCT: Sardine (100g per day, 5 days a week) diet vs no sardine diet	BP/Lipids	
NCT01492361, US, Australia, Canada, India, Netherlands, New Zealand, Poland, Romania, Russian Federation, South Africa, Ukraine	CT.gov	CVD, existing	2011-2017	8000	RCT: VASCEPA (icosapent ethyl) vs. placebo	BP/Lipids	Cardiac events, stroke/TIA, arrhythmia, death
NCT02104817, US, Argentina, Australia, Brazil, Canada, Czech Republic, Denmark, Estonia, Hungary, Italy, Japan, Korea, Latvia, Lithuania, Mexico, Netherlands, New Zealand, Poland, Romania, Russian Federation, South Africa, Taiwan, Ukraine, United Kingdom	CT.gov	Other (mixed) CVD high risk	2014-2019	13000	RCT: Epanova + statin daily vs. placebo + statin daily		Cardiac events, stroke/TIA, arrhythmia, death
NCT02243969, Netherlands	CT.gov	Mixed	2014-2015	72	RCT: Flaxseed oil (ALA) 10g/day (12 wks) vs. placebo	BP/Lipids	
NCT01169259, US	CT.gov	Mixed	2010-2017	25874	RCT: Vitamin D3 2000 IU/day + Omacor, 1 capsule/day vs. Vitamin D3 2000 IU/day + placebo vs. placebo + Omacor, 1 capsule/day vs. placebo		Cardiac events
NCT02271230, US	CT.gov	CVD, existing	2014-2020	25875	RCT: Vitamin D 2000 IU/day vs. EPA/DHA 1g/day vs. placebo		Cardiac events
NCT01785004, US	CT.gov	Healthy	2012-2015	600	RCT: Vitamin D3 2000 IU/day + Omacor, 1 capsule/day vs. Vitamin D3 2000 IU/day + placebo vs. placebo + Omacor, 1 capsule/day vs. placebo	BP/Lipids	

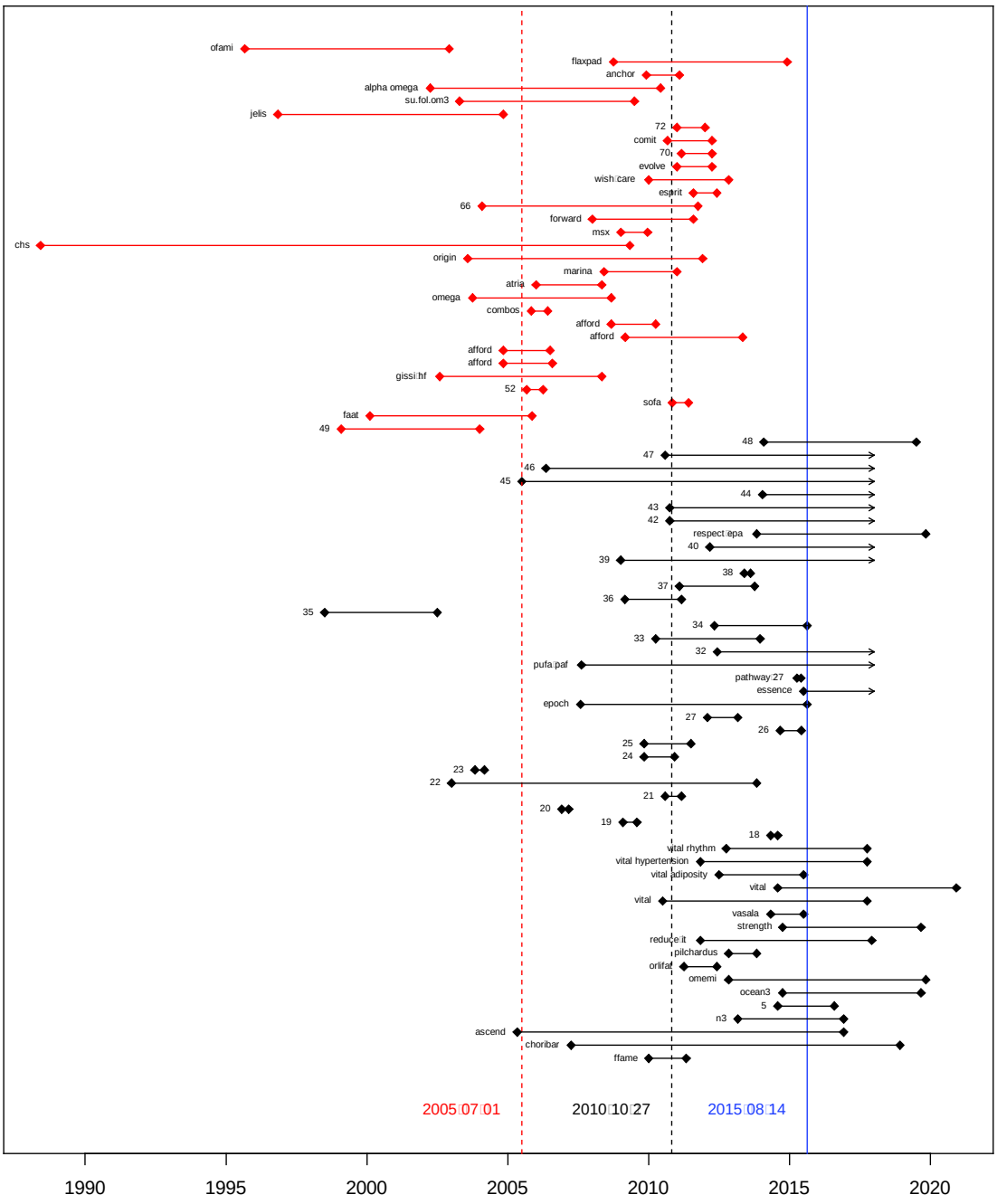
Study Identifier Country/ies Study Name	Registry	Population	Date (start/end)	N total*	Study design: Intervention	Intermediate Outcomes	Clinical Outcomes
NCT01653678, US	CT.gov	HTN	2011-2017	25875	RCT: Vitamin D3 2000 IU/day + Omacor, 1 capsule/day vs. Vitamin D3 2000 IU/day + placebo vs. placebo + Omacor, 1 capsule/day vs. placebo	BP/Lipids, HTN	
NCT02178410, US	CT.gov	CVD, existing	2012-2017	25875	RCT: Vitamin D3 2000 IU/day + Omacor, 1 capsule/day vs. Vitamin D3 2000 IU/day + placebo vs. placebo + Omacor, 1 capsule/day vs. placebo		Cardiac events, arrhythmia, death
NCT02155816, US	CT.gov	Healthy	2014-2014	68	RCT: Omega 3 (1000mg/day) for 8 wks vs. Omega 7 (210mg/day) and Omega 3 (1000mg/day) for 8 wks vs. placebo	BP/Lipids	
NCT00967733, no location listed	CT.gov	CVD, existing	2009-2009	130	RCT: Flaxseed oil (ALA) 2-4 g/day + olive oil cooking vs. Olive oil pill 1g/day + olive oil cooking vs. Flaxseed oil (ALA) 2-4 g/day + sunflower oil cooking vs. Olive oil pill 1g/day + sunflower oil cooking	BP/Lipids	
NCT00422266, India	CT.gov	Dyslipidemia	2006-2007	178	RCT: Not explicitly described	BP/Lipids	
NCT01224249, Denmark	CT.gov	Healthy	2010-2011	102	Obs: Fish and shellfish 1000 g/week for six months vs. no comparator	BP/Lipids	
ACTRN12607000278437, Australia	ICTRP	Healthy	2007-?	400	RCT: DHA 430 mg/EPA 150 mg QID vs. olive oil	BP	
DRKS00006742, Germany	ICTRP	HTN	2015-2015	100	RCT: Milk with DHA 250 mg/day (4 weeks) vs. Milk with beta-glucans 3g/day (4 weeks) vs. Milk with anthocyanins 320mg/day (4 weeks) vs. Milk with DHA 250mg + beta-glucans 3g/day (4 weeks) vs. Milk with DHA 250mg + anthocyanins 320mg/day (4 weeks)	BP/Lipids	
JPRN-UMIN000011934, Japan	ICTRP	CVD, existing	2010-2013	80	RCT: EPA 1800mg + statin therapy/day (2 yrs) vs. Ezetimibe 10 mg + statin therapy/day (2yrs) vs. statin therapy (2yrs)		Cardiac events, PVD, death

Study Identifier Country/ies Study Name	Registry	Population	Date (start/end)	N total*	Study design: Intervention	Intermediate Outcomes	Clinical Outcomes
JPRN-UMIN000007956, Japan	ICTRP	CVD, existing	2012-?	80	RCT: EPA 1800 mg/day + statin therapy vs. statin therapy	BP/Lipids	
ISRCTN16448451, UK	ICTRP	CVD, existing	1998-2002	nd	RCT: fish oil + normal diet vs. normal diet		Arrhythmia
ISRCTN24439243, Spain	ICTRP	Other (mixed) CVD high risk	2009-2011	250	RCT: increased fish consumption + normal diet vs. normal diet	BP/Lipids	
RBR-5668v4, Brazil	ICTRP	Other (mixed) CVD high risk	2011-2013	87	RCT: Omega-3 900my/day + dietary guidance vs. dietary guidance	BP/Lipids	
IRCT2013080514273N1, no location listed	ICTRP	CVD, existing	2013-2013	60	RCT:	BP/Lipids	
JPRN-UMIN000006416, Japan	ICTRP	CVD, existing	2009-?	100	RCT: Aspirin100 mg/day vs. EPA ethyl ester 1800mg/day + Aspirin100mg/day	BP/Lipids	
JPRN-UMIN000007266, Japan	ICTRP	CVD, existing	2012-?	200	RCT: EPA vs. antiplatelet + statins		Cardiac events, stroke/TIA, PVD, death
JPRN-UMIN000012069, Japan	ICTRP	CVD, existing	2013-2019	3200	RCT: EPA 1800 mg/day + statin therapy vs. statin therapy		Cardiac events, stroke/TIA, PVD, death
JPRN-UMIN000016723, Japan	ICTRP	CVD, existing	2010-?	200	RCT: pitavastatin 2 mg/day + EPA 1800 mg/day vs. pitavastatin 2 mg/day		Cardiac events, stroke/TIA
JPRN-UMIN000018056, Japan	ICTRP	Dyslipidemia	2015-?	40	RCT: DHA+EPA 2g/day (4 wks) at 4 wks, triglycerides >150 mg/dl, dose increased to 4mg/day (8 weeks); triglycerides <150mg/dl, does maintained at 2mg/day vs. observation	BP/Lipids	Cardiac events
JPRN-UMIN000004024, Japan	ICTRP	Dyslipidemia	2010-?	100	RCT: EPA (no other details reported)	BP/Lipids	
JPRN-UMIN000012852, Japan	ICTRP	CVD, existing	2014-?	100	RCT: EPA 1800 mg/day + statin therapy vs. statin therapy		Cardiac events, stroke/TIA, PVD, death
EUCTR2006-006863-22-GB, UK	ICTRP	CVD, existing	2007-?	100	RCT: Cardiozen 500 mg vs. placebo (no other information)		arrhythmia
EUCTR2005-001354-25-GB, UK	ICTRP	CVD, existing	2005-?	150	RCT: Omacor vs. placebo (no other information)		Arrhythmia
EUCTR2005-004969-41-IT, Italy	ICTRP	CVD, existing	2006-?	266	RCT: SEACOR 1000MG vs. placebo (no other information)		Arrhythmia
NCT02103517, China	CT.gov	Healthy	2014-2015	400	RCT: Omega-3 FA 4gm/day (3 mos) vs. placebo	BP/Lipids	
JPRN-UMIN000003947, Japan	ICTRP	CVD, existing	2010-?	200	RCT: EPA 1800 mg/day + statin therapy vs. statin therapy		Cardiac events, PVD, Death

Study Identifier Country/ies Study Name	Registry	Population	Date (start/end)	N total*	Study design: Intervention	Intermediate Outcomes	Clinical Outcomes
JPRN-UMIN000012825, Japan	ICTRP	CVD, existing	2014-2019	180	RCT: Statin vs. Statin + EPA vs. Statin + EPA + DHA	BP/Lipids	
NCT01723345, Iran	CT.gov	CVD, existing	2012-2013	90	RCT: EPA 400 mg + DHA 200 mg 12 h prior to PCI vs standard treatment		Cardiac events
NCT01422317 Norway OFAMI	CT.gov	CVD, existing	1995-2002	300	RCT: Fish oil (EPA+DHA) 3.464 g/d vs. Placebo	Lipids	Cardiac event

RCT: randomized controlled trial; XO: crossover tiral; CT.gov: ClinicalTrials.gov; ICTRP: International Clinical Trials Registry Platform; CVD: cardiovascular disease; NRCS: non-randomized comparative study; TIA: transient ischemic attack; PVD: peripheral vascular disease; BP: blood pressure; EPA: eicosapentaenoic acid; DHA: docosahexaenoic acid; ALA: alphalinolenic acid; PUFA: polyunsaturated fatty acids; SDA: stearidonic acid

Figure 2. Timing of studies



Red lines indicate studies in the review; black lines indicate studies not in the review. The red dashed line is the mean start date for studies in the review. The black dashed line is the mean start date for studies not in the review. The blue solid line is the date of the search. Lines with arrows indicate records that did not give an estimated completion date. In two cases, no start date was given, so we used the date of entry into the registry.

Studies Included in the Original Review, with No Registry Record

The original report's 98 studies included 61 randomized controlled trials in 82 articles and 37 longitudinal observational studies in 65 articles. Of these, we were unable to find a registry record for 72 studies (73%), including 36 randomized controlled trials (59%) and 36 longitudinal observational studies (97%). This may be due to the fact that many of the studies in the report were completed before the requirement to register in ClinicalTrials.gov.

Discussion

Summary of Findings

Studies Identified via Registry Searches and Found in Original Review

Overall, 69 studies in 76 records identified through registry searches met full criteria for inclusion in the original report. Of these, 26 studies (in 27 registry records) were included in the original report (25 RCTs, 1 observational Study); 22 of these were found in ClinicalTrials.gov, 3 were found in ICTRP, and 1 was identified in both registries. Of the 26 studies in both sources, only 4 studies (in 4 records) included eligible results in the registry records. In general, the agreement between the registry record and the published paper was good when the information was given in both. A fifth record of a factorial study reported results, but no comparison between the n-3 FA and no n-3 FAs was reported in the record.

Relevant Studies Identified via Registry Searches and Not Found in Original Review

Of the 69 studies in 76 records identified through registry searches that met full criteria for inclusion in the original report, 43 studies (in 49 records) were not found in the original review (42 randomized controlled trials and 1 Observational Study); 28 (57%) records in ClinicalTrials.gov and 21 records in ICTRP (43%). The completion status of studies described in the 49 records are as follows; completed n = 23, ongoing n= 10 and unknown status n=13. The study enrollment estimates for studies completed as of December 31, 2016 account for a projected 20,088 participants. An additional 145,275 participants were estimated to enroll in the remaining studies (ongoing and unknown status).

Reviewing the evidence map for the original report, we identified publications for seven of these studies, which did not meet inclusion/exclusion criteria for the original report. A single record yielded a new publication emanating from a study included in our original report. This new manuscript was published in the intervening time since the last update of the report search. Relevant results from this study were already identified in another publication and included in the report, the results in this newly identified manuscript were added to the report, but did not change the direction or magnitude of the results for those outcomes.

Studies Included in the Original Review, with No Registry Record

The original report's 98 studies included 61 randomized controlled trials in 82 articles and 37 longitudinal observational studies in 65 articles. Of these, we were unable to find a registry record for 72 studies (73%), including 36 randomized controlled trials (59%) and 36 longitudinal observational studies (97%).

Process Limitations

Our study demonstrated that the EPC systematic review process was amenable to adaptions required for searching, abstracting, and analyzing registry search yields. We used a very broad search and screened out a large number of records, requiring more staff time than is spent on registry searching for typical EPC systematic reviews. More precise searching may reduce associated study costs and sensitivity of the search. In general, we found that registry records were easy to screen and extract – often easier than the resulting publications. Study design and interventions information was readily identifiable and in almost all cases matched that of the papers. However, the patient-level information (baselines and outcomes) was limited in scope and detail. The addition of individual patient data to these records could be very valuable.

Despite the relative ease of conducting registry searches in our study, the searches yielded no new information that would change our initial risk of bias or strength or evidence assessments. When available, study design, baselines, adverse events reporting, and results reported in the registry and publication typically aligned. Data identified via registry searches generally provided insufficient evidence to make judgments on specific risk of bias items. It was also difficult to draw any conclusions about publication bias based on our analyses.

Study outcomes information had highest number of discrepancies, potentially indication selective reporting bias. However, because many of these studies are relatively recent, it is also possible that information on these outcomes has not been published yet, but will be, indicating time lag, but not publication, bias

Challenges to Incorporating Clinical Trial Registry Records into the Systematic Review Process

Statistical Plans

We found no reporting of statistical design for any of the studies in our report. We reviewed Clinicaltrials.gov guidance to better understand this consistent pattern of non-reporting. Based on ClinicalTrials.gov guidance,[31] statistical analysis plans (i.e., describing the analytical principles and statistical techniques to be employed in order to address the primary and secondary objectives, as specified in the study protocol or plan) and plans for missing data (i.e., to address situations where variables are reported as missing, unavailable, "non-reported," uninterpretable, or considered missing because of data inconsistency or out-of-range results) are requested only for observational studies registered as patient registries.[31] Our report included very few observational studies, and thus, statistical design reporting could not be assessed.

Results

In September 2008, ClinicalTrials.gov added a results database to the registry record. Nevertheless, submission of results to a trial registry is not always required of investigators/authors. The Food and Drug Administration Amendments Act of 2007 (FDAAA; U.S. Public Law 110-85, Title VIII), mandates the posting of summary results data for certain trials in ClinicalTrials.gov.[32] Of import, ICJME has stated that more detailed descriptions of trial

results “beyond those included in ClinicalTrials.gov” may be considered prior publication, at the discretion of journal editors. Further, ICMJE does not require reporting of results for interventional clinical studies trials.[32]

Thus, a lack of results in a trial registry can be attributed to changes in the reporting requirements over time or a function of why investigators chose to register their study in the first place. Utilizing registry records to assess information bias pivot on both sponsor/investigator compliance with registration and sponsor/investigators perception of registry purpose, thus interpreting these omissions may unintentionally aggregate bias with inconsistent interpretation of the purpose, role and scope of ClinicalTrials.gov.

Next Steps

One way in which conducting a registry search is of value to a systematic review project is in identifying ongoing research, as well as gaps in knowledge, and facilitating prioritization of future research to reduce redundancy. Several of the studies not found in the original review but identified through registry searches were unfinished or in progress at the time of the search, these studies should be taken in to account when evaluating the state of the literature and calling for future research.

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Appendix A. Search Strategies

Registry Searches

Databases: ClinicalTrials.gov 8/14/2015 (5084 unique citations)

Search 1: Omega 3 OR Omega3 OR Omega-3 OR Fish OR n-3 OR Docosahexaenoic OR DHA OR Eicosapentaenoic OR EPA OR ALA OR alpha linolenic OR alphalinolenic OR alpha-linolenic OR fatty acids OR fatty acid OR PUFA OR SDA OR stearidonic

Search 2: Ropufa OR MaxEPA OR Omacor OR Efamed OR ResQ OR Epagis OR Almarin OR Coromega OR Lovaza OR Vascepa OR icosapent ethyl OR mediterranean diet

Search 3: salmon OR mackerel OR herring OR tuna OR halibut OR seaweed OR anchovy OR anchovies OR sardine OR sardines OR cod liver oil OR codliver oil OR marine oil

Search 4: walnut OR walnuts OR butternut OR butternuts OR soybean OR soybeans OR pumpkin seed OR pumpkin seeds OR flax OR flaxseed OR flax seed OR linseed OR rape seed OR rapeseed OR canola OR soy OR soybean OR walnut OR mustard seed OR perilla OR shiso

Databases: ICTRP 8/14/2015 (3468 unique citations)

Omega 3 OR Omega3 OR Omega-3 OR Fish OR n-3 OR Docosahexaenoic OR DHA OR Eicosapentaenoic OR EPA OR ALA OR alpha linolenic OR alphalinolenic OR alpha-linolenic OR fatty acids OR fatty acid OR PUFA OR SDA OR stearidonic OR Ropufa OR MaxEPA OR Omacor OR Efamed OR ResQ OR Epagis OR Almarin OR Coromega OR Lovaza OR Vascepa OR icosapent ethyl OR mediterranean diet OR salmon OR mackerel OR herring OR tuna OR halibut OR seaweed OR anchovy OR anchovies OR sardine OR sardines OR cod liver oil OR codliver oil OR marine oil OR walnut OR walnuts OR butternut OR butternuts OR soybean OR soybeans OR pumpkin seed OR pumpkin seeds OR flax OR flaxseed OR flax seed OR linseed OR rape seed OR rapeseed OR canola OR soy OR soybean OR walnut OR mustard seed OR perilla OR shiso

Original Report

Omega 3 CVD update 2015-update search (Search 1 for updated outcomes, limited to 2002-2015)

Databases: MEDLINE, CAB Abstracts, Cochrane through Ovid 6/8/2015

#	Search	
1.	exp fatty acids, omega-3/	Omega 3 terms
2.	((omega-3 or omega 3 or omega3) and fatty acid$).mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, tx, kw, ct, sh, bt, id, cc]	
3.	fatty acids, essential/	
4.	linolenic acids/	
5.	exp fish oils/	
6.	((n 3 or n3 or n-3) and (oil$ or pufa or fatty acid$ or omega 3)).mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, tx, kw, ct, sh, bt, id, cc]	

#	Search	
7.	Docosahexaenoic Acids/	
8.	docosahexa?noic.mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, tx, kw, ct, sh, bt, id, cc] or docosapenta?noic.mp.	
9.	Eicosapentaenoic Acid/	
10.	eicosapenta?noic.mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, tx, kw, ct, sh, bt, id, cc]	
11.	icosapent?enoic.mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, tx, kw, ct, sh, bt, id, cc]	
12.	(alpha linolenic or alphalinolenic or alpha-linolenic).mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, tx, kw, ct, sh, bt, id, cc]	
13.	(linolenate or cervonic or timnodonic or stearidonic).mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, tx, kw, ct, sh, bt, id, cc]	
14.	menhaden oil$.mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, tx, kw, ct, sh, bt, id, cc]	
15.	((flax or flaxseed or flax seed or linseed or rape seed or rapeseed or canola or soy or soybean or walnut or mustard seed or perilla or shiso) adj2 oil$).mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, tx, kw, ct, sh, bt, id, cc]	
16.	(walnut$ or butternut$ or soybean$ or pumpkin seed$).mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, tx, kw, ct, sh, bt, id, cc]	
17.	(fish adj2 oil$).mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, tx, kw, ct, sh, bt, id, cc]	
18.	(cod liver oil$ or codliver oil$ or marine oil$ or marine fat$).mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, tx, kw, ct, sh, bt, id, cc]	
19.	(salmon or mackerel or herring or tuna or halibut or seaweed or anchov$ or sardine$).mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, tx, kw, ct, sh, bt, id, cc]	
20.	(Ropufa or MaxEPA or Omacor or Efamed or ResQ or Epagis or Almarin or Coromega or Lovaza or Vascepa or icosapent ethyl).mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, tx, kw, ct, sh, bt, id, cc]	
21.	(fish consumption or fish intake or (fish adj2 diet$)).mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, tx, kw, ct, sh, bt, id, cc]	
22.	(mediterranean adj diet$).mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, tx, kw, ct, sh, bt, id, cc]	
23.	((red blood cell or phospholipid or plasma fatty acid or plasma or phospholipid or triacylglycerol or cholesteryl or ester or adipos$ or fatty acid or erythrocyte or ghost or platelet or granulocyte or neutrophil or mononuclear or LDL or HDL) and (DHA or docosahexa?noic or docosapenta?noic or EPA or eicosapenta?noic or SDA or linolenic or stearidonic or omega)).mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, tx, kw, ct, sh, bt, id, cc]	n-3 Biomarkers
24.	or/1-23	n-3
25.	exp cardiovascular diseases/	Cardiovascular diseases, risk factors, adverse events
26.	atherosclero$.mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, tx, kw, ct, sh, bt, id, cc]	
27.	Arteriosclero$.mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, tx, kw, ct, sh, bt, id, cc]	
28.	cardioprotect$.mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, tx, kw, ct, sh, bt, id, cc]	

#	Search	
29.	Coronary.mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, tx, kw, ct, sh, bt, id, cc]	
30.	heart disease$.mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, tx, kw, ct, sh, bt, id, cc]	
31.	Myocardial infarct$.mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, tx, kw, ct, sh, bt, id, cc]	
32.	exp Cerebrovascular Accident/	
33.	stroke.mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, tx, kw, ct, sh, bt, id, cc]	
34.	(Transient Ischemic Attack or TIA).mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, tx, kw, ct, sh, bt, id, cc]	
35.	exp lipids/	
36.	lipid$.mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, tx, kw, ct, sh, bt, id, cc]	
37.	exp cholesterol/	
38.	cholesterol.mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, tx, kw, ct, sh, bt, id, cc]	
39.	exp Lipoproteins, LDL/	
40.	exp Lipoproteins, HDL/	
41.	exp triglycerides/	
42.	triglycerides.mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, tx, kw, ct, sh, bt, id, cc]	
43.	exp Hyperlipidemias/	
44.	hypertriglyceridem$.mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, tx, kw, ct, sh, bt, id, cc]	
45.	hyperlipidemia$.mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, tx, kw, ct, sh, bt, id, cc]	
46.	exp dyslipidemias/	
47.	dyslipidemia$.mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, tx, kw, ct, sh, bt, id, cc]	
48.	exp blood pressure/	
49.	blood pressure.mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, tx, kw, ct, sh, bt, id, cc]	
50.	(diastol$ or systol$ or mean arterial).mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, tx, kw, ct, sh, bt, id, cc]	
51.	exp hypertension/	
52.	hypertension.mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, tx, kw, ct, sh, bt, id, cc]	
53.	exp Hemorrhage/	
54.	hemorrhag$.mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, tx, kw, ct, sh, bt, id, cc]	
55.	bleeding.mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, tx, kw, ct, sh, bt, id, cc]	
56.	or/25-55	
57.	24 and 56	n-3 & CVD
58.	(random$ or rct$).mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, tx, kw, ct, sh, bt, id, cc]	Study designs
59.	exp randomized controlled trials/	
60.	exp Randomized Controlled Trials as Topic/	
61.	exp random allocation/	
62.	exp double-blind method/	

#	Search	
63.	exp single-blind method/	
64.	randomized controlled trial.pt.	
65.	clinical trial.mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, tx, kw, ct, sh, bt, id, cc]	
66.	(clin$ adj trial$).mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, tx, kw, ct, sh, bt, id, cc]	
67.	((singl$ or doubl$ or trebl$ or tripl$) adj (blind$ or mask$)).mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, tx, kw, ct, sh, bt, id, cc]	
68.	exp placebos/	
69.	placebo$.mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, tx, kw, ct, sh, bt, id, cc]	
70.	randomly allocated.mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, tx, kw, ct, sh, bt, id, cc]	
71.	(allocated adj2 random$).mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, tx, kw, ct, sh, bt, id, cc]	
72.	comparative study.mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, tx, kw, ct, sh, bt, id, cc]	
73.	follow-up studies/	
74.	(follow up or followup).mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, tx, kw, ct, sh, bt, id, cc]	
75.	exp case-control studies/	
76.	(case adj20 control).mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, tx, kw, ct, sh, bt, id, cc]	
77.	exp longitudinal studies/	
78.	longitudinal.mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, tx, kw, ct, sh, bt, id, cc]	
79.	exp cohort studies/	
80.	cohort.mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, tx, kw, ct, sh, bt, id, cc]	
81.	exp prospective studies/	
82.	exp evaluation studies/	
83.	(observational adj (study or studies)).mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, tx, kw, ct, sh, bt, id, cc]	
84.	Cross-Sectional Studies/	
85.	(cross section$ or cross-section$).mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, tx, kw, ct, sh, bt, id, cc]	
86.	food frequency questionnaire$.mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, tx, kw, ct, sh, bt, id, cc]	
87.	or/58-86	
88.	57 and 87	n-3, CVD, Designs
89.	limit 88 to (addresses or autobiography or bibliography or biography or case reports or comment or congresses or dictionary or directory or editorial or festschrift or government publications or historical article or interview or lectures or legal cases or legislation or letter or news or newspaper article or patient education handout or periodical index)	Not non-studies
90.	88 not 89	

#	Search	
91.	limit 90 to english language	Limits
92.	limit 91 to humans	
93.	(guidelines or practice guideline or meta analysis or systematic review).pt.	SRs, GLs
94.	(systematic$ adj3 review$).tw.	
95.	93 or 94	
96.	57 and 95	
97.	limit 96 to yr="2002 - 2015"	Non-SRs
98.	92 not 96	SRs
99.	limit 98 to yr="2002 - 2015"	

Omega 3 CVD update 2015-new outcomes 6/8/2015 (Only difference is new outcomes and publication dates)

#	Search	
1.	exp fatty acids, omega-3/	
2.	((omega-3 or omega 3 or omega3) and fatty acid$).mp. [mp=ti, ot, ab, nm, hw, kw, kf, px, rx, ui, an, tx, sh, ct, bt, id, cc]	
3.	fatty acids, essential/	
4.	linolenic acids/	
5.	exp fish oils/	
6.	((n 3 or n3 or n-3) and (oil$ or pufa or fatty acid$ or omega 3)).mp. [mp=ti, ot, ab, nm, hw, kw, kf, px, rx, ui, an, tx, sh, ct, bt, id, cc]	
7.	Docosahexaenoic Acids/	
8.	docosahexa?noic.mp. [mp=ti, ot, ab, nm, hw, kw, kf, px, rx, ui, an, tx, sh, ct, bt, id, cc] or docosapenta?noic.mp.	
9.	Eicosapentaenoic Acid/	
10.	eicosapenta?noic.mp. [mp=ti, ot, ab, nm, hw, kw, kf, px, rx, ui, an, tx, sh, ct, bt, id, cc]	
11.	icosapent?enoic.mp. [mp=ti, ot, ab, nm, hw, kw, kf, px, rx, ui, an, tx, sh, ct, bt, id, cc]	
12.	(alpha linolenic or alphalinolenic or alpha-linolenic).mp. [mp=ti, ot, ab, nm, hw, kw, kf, px, rx, ui, an, tx, sh, ct, bt, id, cc]	
13.	(linolenate or cervonic or timnodonic or stearidonic).mp. [mp=ti, ot, ab, nm, hw, kw, kf, px, rx, ui, an, tx, sh, ct, bt, id, cc]	
14.	menhaden oil$.mp. [mp=ti, ot, ab, nm, hw, kw, kf, px, rx, ui, an, tx, sh, ct, bt, id, cc]	
15.	((flax or flaxseed or flax seed or linseed or rape seed or rapeseed or canola or soy or soybean or walnut or mustard seed or perilla or shiso) adj2 oil$).mp. [mp=ti, ot, ab, nm, hw, kw, kf, px, rx, ui, an, tx, sh, ct, bt, id, cc]	
16.	(walnut$ or butternut$ or soybean$ or pumpkin seed$).mp. [mp=ti, ot, ab, nm, hw, kw, kf, px, rx, ui, an, tx, sh, ct, bt, id, cc]	
17.	(fish adj2 oil$).mp. [mp=ti, ot, ab, nm, hw, kw, kf, px, rx, ui, an, tx, sh, ct, bt, id, cc]	
18.	(cod liver oil$ or codliver oil$ or marine oil$ or marine fat$).mp. [mp=ti, ot, ab, nm, hw, kw, kf, px, rx, ui, an, tx, sh, ct, bt, id, cc]	
19.	(salmon or mackerel or herring or tuna or halibut or seaweed or anchov$ or sardine$).mp. [mp=ti, ot, ab, nm, hw, kw, kf, px, rx, ui, an, tx, sh, ct, bt, id, cc]	
20.	(Ropufa or MaxEPA or Omacor or Efamed or ResQ or Epagis or Almarin or Coromega or Lovaza or Vascepa or icosapent ethyl).mp. [mp=ti, ot, ab, nm, hw, kw, kf, px, rx, ui, an, tx, sh, ct, bt, id, cc]	
21.	(fish consumption or fish intake or (fish adj2 diet$)).mp. [mp=ti, ot, ab, nm, hw, kw, kf, px, rx, ui, an, tx, sh, ct, bt, id, cc]	
22.	(mediterranean adj diet$).mp. [mp=ti, ot, ab, nm, hw, kw, kf, px, rx, ui, an, tx, sh, ct, bt, id, cc]	
23.	((red blood cell or phospholipid or plasma fatty acid or plasma or phospholipid or triacylglycerol or cholesteryl or ester or adipos$ or fatty acid or erythrocyte or ghost or platelet or granulocyte or neutrophil or mononuclear or LDL or HDL) and (DHA or docosahexa?noic or Docosapenta?noic or EPA or eicosapenta?noic or SDA or linolenic or stearidonic or omega)).mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, tx, kw, ct, sh, bt, id, cc]	
24.	or/1-23	

25.	(random$ or rct$).mp. [mp=ti, ot, ab, nm, hw, kw, kf, px, rx, ui, an, tx, sh, ct, bt, id, cc]	
26.	exp randomized controlled trials/	
27.	exp Randomized Controlled Trials as Topic/	
28.	exp random allocation/	
29.	exp double-blind method/	
30.	exp single-blind method/	
31.	randomized controlled trial.pt.	
32.	clinical trial.mp. [mp=ti, ot, ab, nm, hw, kw, kf, px, rx, ui, an, tx, sh, ct, bt, id, cc]	
33.	(clin$ adj trial$).mp. [mp=ti, ot, ab, nm, hw, kw, kf, px, rx, ui, an, tx, sh, ct, bt, id, cc]	
34.	((singl$ or doubl$ or trebl$ or tripl$) adj (blind$ or mask$)).mp. [mp=ti, ot, ab, nm, hw, kw, kf, px, rx, ui, an, tx, sh, ct, bt, id, cc]	
35.	exp placebos/	
36.	placebo$.mp. [mp=ti, ot, ab, nm, hw, kw, kf, px, rx, ui, an, tx, sh, ct, bt, id, cc]	
37.	randomly allocated.mp. [mp=ti, ot, ab, nm, hw, kw, kf, px, rx, ui, an, tx, sh, ct, bt, id, cc]	
38.	(allocated adj2 random$).mp. [mp=ti, ot, ab, nm, hw, kw, kf, px, rx, ui, an, tx, sh, ct, bt, id, cc]	
39.	comparative study.mp. [mp=ti, ot, ab, nm, hw, kw, kf, px, rx, ui, an, tx, sh, ct, bt, id, cc]	
40.	follow-up studies/	
41.	(follow up or followup).mp. [mp=ti, ot, ab, nm, hw, kw, kf, px, rx, ui, an, tx, sh, ct, bt, id, cc]	
42.	exp case-control studies/	
43.	(case adj20 control).mp. [mp=ti, ot, ab, nm, hw, kw, kf, px, rx, ui, an, tx, sh, ct, bt, id, cc]	
44.	exp longitudinal studies/	
45.	longitudinal.mp. [mp=ti, ot, ab, nm, hw, kw, kf, px, rx, ui, an, tx, sh, ct, bt, id, cc]	
46.	exp cohort studies/	
47.	cohort.mp. [mp=ti, ot, ab, nm, hw, kw, kf, px, rx, ui, an, tx, sh, ct, bt, id, cc]	
48.	exp prospective studies/	
49.	exp evaluation studies/	
50.	(observational adj (study or studies)).mp. [mp=ti, ot, ab, nm, hw, kw, kf, px, rx, ui, an, tx, sh, ct, bt, id, cc]	
51.	Cross-Sectional Studies/	
52.	(cross section$ or cross-section$).mp. [mp=ti, ot, ab, nm, hw, kw, kf, px, rx, ui, an, tx, sh, ct, bt, id, cc]	
53.	food frequency questionnaire$.mp. [mp=ti, ot, ab, nm, hw, kw, kf, px, rx, ui, an, tx, sh, ct, bt, id, cc]	
54.	or/25-53	
55.	24 and 54	
56.	exp heart failure/	
57.	Heart failure$.mp. [mp=ti, ot, ab, nm, hw, kw, kf, px, rx, ui, an, tx, sh, ct, bt, id, cc]	
58.	exp pulmonary edema/	
59.	pulmonary edema.mp. [mp=ti, ot, ab, nm, hw, kw, kf, px, rx, ui, an, tx, sh, ct, bt, id, cc]	
60.	pulmonary oedema.mp. [mp=ti, ot, ab, nm, hw, kw, kf, px, rx, ui, an, tx, sh, ct, bt, id, cc]	
61.	(ejection adj2 fraction).mp. [mp=ti, ot, ab, nm, hw, kw, kf, px, rx, ui, an, tx, sh, ct, bt, id, cc]	
62.	exp peripheral vascular diseases/	

63.	(peripheral and vascular and disease$).mp. [mp=ti, ot, ab, nm, hw, kw, kf, px, rx, ui, an, tx, sh, ct, bt, id, cc]	
64.	claudication.mp. [mp=ti, ot, ab, nm, hw, kw, kf, px, rx, ui, an, tx, sh, ct, bt, id, cc]	
65.	exp arrhythmias, cardiac/	
66.	(arrhythmi$ or Antiarrhythmi$).mp. [mp=ti, ot, ab, nm, hw, kw, kf, px, rx, ui, an, tx, sh, ct, bt, id, cc]	
67.	Fibrillation.mp. [mp=ti, ot, ab, nm, hw, kw, kf, px, rx, ui, an, tx, sh, ct, bt, id, cc]	
68.	Flutter.mp. [mp=ti, ot, ab, nm, hw, kw, kf, px, rx, ui, an, tx, sh, ct, bt, id, cc]	
69.	exp tachycardia/	
70.	tachycardia.mp. [mp=ti, ot, ab, nm, hw, kw, kf, px, rx, ui, an, tx, sh, ct, bt, id, cc]	
71.	tachyarrhythmia.mp. [mp=ti, ot, ab, nm, hw, kw, kf, px, rx, ui, an, tx, sh, ct, bt, id, cc]	
72.	exp bradycardia/	
73.	bradycardia.mp. [mp=ti, ot, ab, nm, hw, kw, kf, px, rx, ui, an, tx, sh, ct, bt, id, cc]	
74.	exp death, sudden/	
75.	(sudden adj death).mp. [mp=ti, ot, ab, nm, hw, kw, kf, px, rx, ui, an, tx, sh, ct, bt, id, cc]	
76.	or/56-75	
77.	24 and 54 and 76	
78.	limit 77 to (addresses or autobiography or bibliography or biography or case reports or comment or congresses or dictionary or directory or editorial or festschrift or government publications or historical article or interview or lectures or legal cases or legislation or letter or news or newspaper article or patient education handout or periodical index)	
79.	77 not 78	
80.	limit 79 to english language	
81.	limit 80 to humans	
82.	(guidelines or practice guideline or meta analysis or systematic review).pt.	
83.	(systematic$ adj3 review$).tw.	
84.	82 or 83	
85.	24 and 76 and 84	
86.	81 not 85	

EMBASE searches run on 6/8/2015

Search 1

fatty AND acids, AND essential OR essential AND fatty AND ('acids'/exp OR acids) OR (n AND 3 OR n3 OR 'n 3' AND (oil* OR pufa OR fatty AND acid* OR omega AND 3 OR omega3 OR 'omega 3')) OR docosahexa*noic OR docosapenta*noic OR eicosapenta*noic OR icosapent*enoic OR (alpha AND linolenic OR alphalinolenic OR 'alpha linolenic' OR linolenic AND acids) OR (linoleic AND acid) OR cervonic OR timnodonic OR stearidonic OR (flaxseed OR flax AND seed OR linseed OR rape AND seed OR rapeseed OR canola OR soy OR soybean OR walnut OR mustard AND seed OR perilla OR shiso OR menhaden OR fish AND oil*) OR (walnut* OR butternut* OR soybean* OR pumpkin AND seed*) OR (cod AND liver AND oil* OR codliver AND oil* OR marine AND oil* OR marine AND fat*) OR salmon OR mackerel OR herring OR tuna OR halibut OR seaweed OR anchov* OR sardine* OR (ropufa OR maxepa OR omacor OR efamed OR resq OR epagis OR almarin OR coromega OR lovaza OR vascepa OR icosapent AND ethyl) OR (fish AND consumption OR fish AND intake) OR fish NEAR/2 diet* OR Mediterranean NEAR/2 diet* OR (red AND blood AND cell OR phospholipid OR plasma AND fatty AND acid OR plasma OR phospholipid OR triacylglycerol OR cholesteryl

OR ester OR adipos* OR fatty AND acid OR erythrocyte OR ghost OR platelet OR granulocyte OR neutrophil OR mononuclear OR ldl OR hdl AND (dha OR docosahexa?noic OR docosapenta?noic OR epa OR eicosapenta?noic OR sda OR linolenic OR stearidonic OR omega))
AND ('cardiovascular disease' OR atherosclero* OR arteriosclero* OR cardioprotect* OR (coronary OR heart AND disease* OR myocardial AND infarct*) OR (cerebrovascular AND accident) OR stroke.mp OR (transient AND ischemic AND attack) OR tia OR lipid* OR cholesterol OR 'low density lipoprotein' OR 'high density lipoprotein' OR hyperlipidemia* OR hypertriglyceridem* OR dyslipidemia* OR (blood AND pressure) OR (diastol* OR systol* OR mean AND arterial) OR hypertension OR hemorrhag* OR 'bleeding')
AND (randomized AND controlled AND trial OR 'randomization' OR 'single blind procedure' OR 'double blind procedure' OR 'crossover procedure' OR 'placebo' OR rct OR (random* AND allocat*) OR (single AND blind*) OR (double AND blind*) OR (treble OR triple) NEAR/2 blind* OR (prospective AND study) OR 'clinical study' OR 'case control study' OR 'longitudinal study' OR 'retrospective study' OR 'prospective study' OR 'cohort analysis' OR cohort NEAR/2 (study OR studies) OR (case AND control NEAR/2 (study OR studies)) OR (follow AND up NEAR/2 (study OR studies)) OR observational NEAR/2 (study OR studies) OR (food AND frequency AND questionnaire*)) NOT ('abstract report' OR 'case study' OR 'case report') AND [humans]/lim AND [english]/lim AND [2000-2014]/py

Search2
fatty AND acids, AND essential OR essential AND fatty AND ('acids'/exp OR acids) OR (n AND 3 OR n3 OR 'n 3' AND (oil* OR pufa OR fatty AND acid* OR omega AND 3 OR omega3 OR 'omega 3')) OR docosahexa*noic OR docosapenta*noic OR eicosapenta*noic OR icosapent*enoic OR (alpha AND linolenic OR alphalinolenic OR 'alpha linolenic' OR linolenic AND acids) OR (linoleic AND acid) OR cervonic OR timnodonic OR stearidonic OR (flaxseed OR flax AND seed OR linseed OR rape AND seed OR rapeseed OR canola OR soy OR soybean OR walnut OR mustard AND seed OR perilla OR shiso OR menhaden OR fish AND oil*) OR (walnut* OR butternut* OR soybean* OR pumpkin AND seed*) OR (cod AND liver AND oil* OR codliver AND oil* OR marine AND oil* OR marine AND fat*) OR salmon OR mackerel OR herring OR tuna OR halibut OR seaweed OR anchov* OR sardine* OR (ropufa OR maxepa OR omacor OR efamed OR resq OR epagis OR almarin OR coromega OR lovaza OR vascepa OR icosapent AND ethyl) OR (fish AND consumption OR fish AND intake) OR fish NEAR/2 diet* OR mediterranean NEAR/2 diet* OR (red AND blood AND cell OR phospholipid OR plasma AND fatty AND acid OR plasma OR phospholipid OR triacylglycerol OR cholesteryl OR ester OR adipos* OR fatty AND acid OR erythrocyte OR ghost OR platelet OR granulocyte OR neutrophil OR mononuclear OR ldl OR hdl AND (dha OR docosahexa?noic OR docosapenta?noic OR epa OR eicosapenta?noic OR sda OR linolenic OR stearidonic OR omega))
AND ('cardiovascular disease' OR atherosclero* OR arteriosclero* OR cardioprotect* OR (coronary OR heart AND disease* OR myocardial AND infarct*) OR (cerebrovascular AND accident) OR stroke.mp OR (transient AND ischemic AND attack) OR tia OR lipid* OR cholesterol OR 'low density lipoprotein' OR 'high density lipoprotein' OR hyperlipidemia* OR hypertriglyceridem* OR dyslipidemia* OR (blood AND pressure) OR (diastol* OR systol* OR mean AND arterial) OR hypertension OR hemorrhag* OR 'bleeding')

AND (randomized AND controlled AND trial OR 'randomization' OR 'single blind procedure' OR 'double blind procedure' OR 'crossover procedure' OR 'placebo' OR rct OR (random* AND allocat*) OR (single AND blind*) OR (double AND blind*) OR (treble OR triple) NEAR/2 blind* OR (prospective AND study) OR 'clinical study' OR 'case control study' OR 'longitudinal study' OR 'retrospective study' OR 'prospective study' OR 'cohort analysis' OR cohort NEAR/2 (study OR studies) OR (case AND control NEAR/2 (study OR studies)) OR (follow AND up NEAR/2 (study OR studies)) OR observational NEAR/2 (study OR studies) OR (food AND frequency AND questionnaire*)) NOT ('abstract report' OR 'case study' OR 'case report') AND [humans]/lim AND [english]/lim

Appendix B.
Inclusion criteria: Effects of Omega-3 Fatty Acids on Cardiovascular Disease

P	• Healthy population without CVD or with low to intermediate CVD risk • Adults without CVD but with high risk (e.g., diabetes, metabolic syndrome, hypertension, dyslipidemia, older age) • Adults with clinical CVD (e.g., MI, stroke, angina with confirming clinical tests) • Adults (≥18 y) o Include: Diabetes, Metabolic Syndrome, Hypertension, Dyslipidemia, existing CVD or symptoms o Exclude: Selected for having non-CVD, non-DM related disease (eg, cancer, gastrointestinal disease, dialysis, chronic renal failure, rheumatic disease) or condition (eg, pregnancy)
I/C	• Intake:* EPA, DHA, EPA+DHA, SDA, and/or ALA **quantified (does not need to be quantified in abstract, except Med diet)** • Abstract needs to quantify the food or supplement (at a minimum) o Supplement, diet, or fortified foods (intervention or observational) o Minimum duration of intake: 1 year (clinical outcomes), 4 wk (BP, Lipids) o Exclude: Dose ≥6 g omega 3 (not total fish/plant oil) o Exclude: Adherence to Med diet or Med diet score (**unless omega-3 quantified** [in abstract]) o Exclude: Soy (or other) protein, soy isoflavones, other non-oil components o Exclude: Weight loss diet (eg, fish/fish oil being used in a weight loss diet plan) o Exclude: Combination interventions of omega-3 & something else (eg, vitamin , E), but include if all participants have the same other intervention (eg, vit E vs vit E + n-3) o Exclude: Comparator is an active intervention (eg, pravastatin) • Biomarker:† Level measured (quantified) • **Comparator must be lower dose/exposure omega-3 or no supplement etc. (eg, not vs. statin)**
O	• **Must mention CVD (or BP or lipids) in abstract** • All-cause mortality • Cerebro/cardio-vascular disease (CVD) events: o CVD-related (myocardial infarction, stroke) mortality o non-fatal CVD events ▪ myocardial infarction, acute coronary syndrome, stroke/CVA, TIA, unstable angina, amputation 2° PVD, others o coronary/cardiac disease o peripheral vascular disease (PVD) o congestive heart failure (CHF) o pulmonary edema o ventricular arrhythmia ▪ tachycardia, tachyarrhythmia, fibrillation, bradycardia, sudden death o atrial fibrillation, supraventricular tachycardia o cardiovascular invasive interventions (revascularization) ▪ CABG (bypass), PCI (coronary angioplasty), vascular (arterial) surgery (carotid, peripheral) ▪ Thrombolysis (eg, tPA to dissolve clot) • Major CVD risk factors (intermediate outcomes): o blood pressure (new-onset hypertension, SBP, DBP, MAP) o key lipid values (HDL-cholesterol, LDL-cholesterol, triglycerides, LDL:HDL, TC:HDL) ▪ Accept abstracts of LDL (or other lipid) particle size • Adverse events (eg, bleeding, gastrointestinal), only from intervention studies of supplements
D	• RCTs (all outcomes) • Randomized cross-over (XO) studies (blood pressure and lipids, adverse events) • Nonrandomized comparative studies, prospective or retrospective **longitudinal** (clinical outcomes, adverse events): **measure of n-3 intake/exposure must have occurred ≥1 year prior to measurement of events** • Prospective or retrospective cohort (single group) studies, where groups are compared based on n-3 FA

	intake or intake biomarker values (clinical outcomes) : **measure of n-3 intake/exposure ≥1 year prior to events** • Nested case-control studies (clinical outcomes) (case control study done within a prospective study): **measure of n-3 intake/exposure must have occurred ≥1 year prior to measurement of events** • Exclude: cross-sectional (exposure and outcome measured at same time), case control (retrospective) • **UNCLEAR: observational studies for blood pressure and lipids [tag as maybe]** • Timing o Clinical outcomes, including new-onset hypertension: ≥1 year follow-up o Intermediate outcomes (blood pressure and lipids): ≥1 month follow-up o Adverse events: no minimum follow-up • Minimum sample sizes (per 2004 protocols*) o Clinical outcomes: **RCT/nRCS**: no minimum; **Longitudinal single group** N≥100 o BP/Lipids (RCT): N≥x (no minimum for now) o Adverse events: N≥100 • Tag and REJECT trial **protocols**/designs

Appendix C.
Risk of Bias Criteria from the Original Report

Comparative Studies

Dimension	Instructions
Was the allocation sequence (RANDOMIZATION METHOD) adequately generated?	There is a LOW RISK OF BIAS if the investigators describe a random component in the sequence generation process such as: referring to a random number table, using a computer random number generator, coin tossing, shuffling cards or envelopes, throwing dice, drawing of lots. There is a HIGH RISK OF BIAS if the investigators describe a non-random component in the sequence generation process, such as: sequence generated by odd or even date of birth, date (or day) of admission, hospital or clinic record number; or allocation by judgement of the clinician, preference of the participant, results of a laboratory test or a series of tests, or availability of the intervention. IF HIGH RISK OF BIAS, EXPLAIN IN NOTES.
Was ALLOCATION adequately concealed (prior to assignment)?	There is a LOW RISK OF BIAS if the participants and investigators enrolling participants could not foresee assignment because one of the following, or an equivalent method, was used to conceal allocation: central allocation (including telephone, web-based and pharmacy-controlled randomization); sequentially numbered drug containers of identical appearance; or sequentially numbered, opaque, sealed envelopes. There is a HIGH RISK OF BIAS if participants or investigators enrolling participants could possibly foresee assignments and thus introduce selection bias, such as allocation based on: using an open random allocation schedule (e.g. a list of random numbers); assignment envelopes were used without appropriate safeguards (e.g. if envelopes were unsealed or non-opaque or not sequentially numbered); alternation or rotation; date of birth; case record number; or other explicitly unconcealed procedures. IF HIGH RISK OF BIAS, EXPLAIN IN NOTES.
Were PARTICIPANTS adequately BLINDED?	There is a LOW RISK OF BIAS if blinding of participants was ensured and it was unlikely that the blinding could have been broken; or if there was no blinding or incomplete blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding.
Were OUTCOME ASSESSORS adequately BLINDED?	There is LOW RISK OF BIAS if the blinding of the outcome assessment was ensured and it was unlikely that the blinding could have been broken; or if there was no or incomplete blinding, but the outcome is unlikely to be influenced by lack of blinding (ie, lab tests--lipids--inherently low risk of bias, but not blood pressure).
If outcome assessor blinding risk of bias is different for different outcomes (eg, lipids vs. MI), choose HIGH risk of bias and describe in Notes	
Incomplete outcome data (ATTRITION BIAS) due to amount, nature or handling of incomplete outcome data	There is a LOW RISK OF BIAS if there were no missing outcome data; reasons for missing outcome data were unlikely to be related to the true outcome; missing outcome data were balanced in numbers, with similar reasons for missing data across groups (****The percentage of withdrawals and drop-outs should not exceed 20% for short-term follow-up [<=1 year] and 30% for long-term follow-up [>1 year]****). IF HIGH RISK OF BIAS, EXPLAIN IN NOTES.
If attrition risk of bias is different for different outcomes (eg, lipids vs. MI) or different time points (eg, 1 year vs. 5 years), choose HIGH risk of bias and describe in Notes	

Dimension	Instructions
Is there evidence of SELECTIVE OUTCOME REPORTING bias (Yes/No)?	For LIPIDS, are only selected lipids/lipoproteins reported, were lipids measured at baseline and was a blood sample taken at follow-up but follow-up lipids were not reported, were subgroup lipid outcomes omitted? For BLOOD PRESSURE, was BP measured at baseline and was there a follow-up clinical encounter (where follow-up BP would have been measured), but BP is not reported, were subgroup BP outcomes omitted? For CLINICAL OUTCOMES, are all outcomes in the Methods section (all pre-specified outcomes) reported, were all components of composite outcomes reported? DESCRIBE ISSUES IN NOTES.
INTENTION-TO-TREAT analysis? (Yes/No)	YES if they state ITT and methods used were actually ITT, or **all** participants were analyzed in the group to which they were allocated by randomization (no cross-over). IF NO ITT, EXPLAIN IN NOTES.
Group SIMILARITY AT BASELINE (**GENERAL**)	There is LOW RISK OF BIAS if groups are similar at baseline for demographic and other factors ("Table 1"). Also LOW risk of bias if any baseline differences were adjusted for in all relevant analyses. IF HIGH RISK OF BIAS, EXPLAIN IN NOTES.
Group SIMILARITY AT BASELINE (**OMEGA-3**)	There is LOW RISK OF BIAS if groups were similar (or statistical adjustments were made to account for differences) in omega-3 intake or status (biomarkers) at baseline. There is HIGH RISK OF BIAS if groups had different omega-3 intake/status at baseline that was not accounted for. There is UNCLEAR RISK OF BIAS if baseline omega-3 status was not reported.
Was there incomplete COMPLIANCE with interventions across groups?	There is LOW RISK OF BIAS if compliance with the interventions was acceptable (>=80% across intervention duration), based on the reported actual compliance compared to protocol or increased biomarker levels were reported during or at the end of the intervention. There is HIGH RISK OF BIAS if compliance was low (<80%) or no change in biomarker levels were found during or at the end of the intervention. There is UNCLEAR RISK OF BIAS if these data were not reported.
Additional Bias: Bias due to problems not covered elsewhere in the table.	IF YES, EXPLAIN IN NOTES.

Observational Studies

Dimension	Instructions
Selection bias (NOT NESTED CASE CONTROL): Is there clear demonstration that the outcome of interest was not present at the start of the study (baseline)?	If the answer is no, the study will need to be reassessed for eligibility.
Comparability/Adjustment (ALL OBSERVATIONAL STUDIES): Were the analyses adjusted for confounders (or other factors)?	If YES, add to the Notes one of the following: ** Including diet and CVD risk factors (eg, lipids, BP, DM) ** Including diet but not CVD risk factors ** Including CVD risk factors, but not diet ** Neither diet nor CVD risk factors ** If UNCLEAR, answer No.
Outcome assessment (ALL STUDIES): Were OUTCOME ASSESSORS adequately BLINDED?	There is LOW RISK OF BIAS if the blinding of the outcome assessment was ensured and it was unlikely that the blinding could have been broken (independent blind assessment or record linkage). UNCLEAR RISK OF BIAS if not or poorly reported. HIGH RISK OF BIAS if self-report or other unblinded assessment. IF HIGH RISK OF BIAS, EXPLAIN IN NOTES.
Incomplete outcome data (attrition bias) due to amount, nature or handling of incomplete	There is a LOW RISK OF BIAS if there were no missing outcome data; reasons for missing outcome data were unlikely to be related to

Dimension	Instructions
outcome data (ALL STUDIES)	the true outcome; missing outcome data were balanced in numbers, with similar reasons for missing data across groups (****The percentage of withdrawals and drop-outs should not exceed 20% for short-term follow-up (1 year) and 30% for long-term follow-up (>1 year)****). IF HIGH RISK OF BIAS, EXPLAIN IN NOTES.
Nutrition, FFQ Baseline intake: Was the dietary assessment instrument (eg, FFQ) described to have measured n-3 FA (ALL STUDIES WITH FFQ)?	If YES, answer Yes and add to the Notes one of the following: ** Measured n-3 FA from BOTH diet and supplements ** Measured n-3 FA from ONLY diet or ONLY supplements ** If NO (or UNCLEAR), answer No and add to the Notes one of the following: ** Instrument reported but no adequate description regarding n-3 FA intake measurement ** No data on instrument or method used to measure n-3 FA intake
Nutrition, Baseline data: Were the ranges or distributions of the nutrient exposures adequately reported (ie, quantile means/medians SD and/or ranges) (ALL OBSERVATIONAL STUDIES)?	If analyzed in quantiles, we need the quantile thresholds AND the mean or median within each quantile. If analyzed as a continuous variable, we need overall mean or median and SD (or equivalent) or range.
Additional Bias: Bias due to problems not covered elsewhere in the table.	IF YES, EXPLAIN IN NOTES.
Do any specific outcomes have a high risk of bias (different than others)? If so, describe in Notes.	

Appendix D. Excluded Studies

NCT Number	Title	Acronym	URL	Rejection Reason
NCT00947635	Cholesterol and Fatty Acid Synthesis in Islet and Liver Transplant Patients and Effect of Dietary Intervention	null	https://ClinicalTrials.gov/show/NCT00947635	P: not population of interest (transplant)
NCT00008801	hOKT3gamma1 (Ala-Ala) for the Prevention of Human Islet Allograft Failure	null	https://ClinicalTrials.gov/show/NCT00008801	P: not population of interest (transplant)
NCT00004827	Study of Docosahexaenoic Acid (DHA) Supplementation in Patients With X-Linked Retinitis Pigmentosa	null	https://ClinicalTrials.gov/show/NCT00004827	P: not population of interest (retinitis pigmentosa)
NCT00620529	The Effects of Fish Oils on Blood Pressure, Heart Rate Variability and Liver Fat in the Polycystic Ovary Syndrome	fops	https://ClinicalTrials.gov/show/NCT00620529	P: not population of interest (PCOS)
NCT00010842	Natural Antioxidants in the Treatment of Multiple Sclerosis	null	https://ClinicalTrials.gov/show/NCT00010842	P: not population of interest (MS)
NCT00598910	Effect of Omacor on Triglycerides in HIV Infected Subjects	null	https://ClinicalTrials.gov/show/NCT00598910	P: not population of interest (HIV)
NCT00691288	Effect of Omega-3 Fatty Acid Supplementation on Hypertriglyceridemia in HIV-infected Children	null	https://ClinicalTrials.gov/show/NCT00691288	P: not population of interest (HIV)
NCT00296153	Omacor and Cardiovascular Risk Factors in HIV Patients on HAART Treatment	null	https://ClinicalTrials.gov/show/NCT00296153	P: not population of interest (HIV)
EUCTR2007-001921-86-DE	A double-blind, placebo-controlled, parallel-group, multi-center study to investigate the effect of Omacor? (n-3 PUFA) on lipid parameters in HIV infected patients treated with HAART	null	https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2007-001921-86	P: not population of interest (HIV)
NCT00678067	Effects of Docosahexaenoic and Eicosapentaenoic Acids in Hypercholesterolemic Children Plus Diet on Docosahexaenoic Acid (DHA) Status	DHA-RICHOIL	https://ClinicalTrials.gov/show/NCT00678067	P: not population of interest (children)

NCT00379171	Milk Types and Fish Oil in 9- to 12-Month-Old Infants	null	https://ClinicalTrials.gov/show/NCT00379171	P: not population of interest (children)
NCT01457794	OPUS School Meal Study	null	https://ClinicalTrials.gov/show/NCT01457794	P: not population of interest (children)
NCT01665742	Anti-inflammatory Dietary Intervention in Overweight and Obese Adolescents	null	https://ClinicalTrials.gov/show/NCT01665742	P: not population of interest (children)
NCT00924274	Effect of Rapeseed Oil and Sunflower Oil	null	https://ClinicalTrials.gov/show/NCT00924274	P: not population of interest (children)
NCT00924339	Soy Food Intervention Trial	SOYFIT	https://ClinicalTrials.gov/show/NCT00924339	P: not population of interest (children)
NCT00929552	Effect of Fish Oil on Markers of the Metabolic Syndrome in Overweight Adolescent Boys	TeenFisk	https://ClinicalTrials.gov/show/NCT00929552	P: not population of interest (children)
NCT00586950	123I-BMIPP SPECT Analysis for Decreasing Cardiac Events in Hemodialysis Patients	B-SAFE	https://ClinicalTrials.gov/show/NCT00586950	P: not population of interest (acute lung injury)
NCT01814956	Different Lipid Emulsions in Acute Lung Injury Patients	null	https://ClinicalTrials.gov/show/NCT01814956	P: not population of interest (acute lung injury)
NCT02410668	The Effects of Flaxseed Supplement on Weight and Biochemical Factors in Overweight and Obese Subject	null	https://ClinicalTrials.gov/show/NCT02410668	I: Weight loss intervention
ACTRN12610000750088	The Effect of Fish Oil Oral Supplementation on Fat Metabolism in Obese Subjects on a Weight Loss Diet.	WIFA	http://www.anzctr.org.au/ACTRN12610000750088.aspx	I: Weight loss intervention
NCT01799720	Oxidized Omega-3 Supplements With Different Oxidation	GPTPASPAD	https://ClinicalTrials.gov/show/NCT01799720	I: Weight loss intervention
NCT00729430	Evaluating a Heart Magnetic Resonance Imaging (MRI) Procedure and the Effect of Fish Oil Supplementation in People Who Have Recently Had a Heart Attack (The PROSPECT-CMR Study)	Omega-REMODEL	https://ClinicalTrials.gov/show/NCT00729430	I: Not specifically n-3 intervention/exposure
NCT01343342	Genes, Omega-3 Fatty Acids and Cardiovascular Disease Risk Factors	FAS	https://ClinicalTrials.gov/show/NCT01343342	I: Not specifically n-3 intervention/exposure
NCT00410839	Studies of the Prevention of Atrial Fibrillation by ALA	none	https://ClinicalTrials.gov/show/NCT00410839	I: Not specifically n-3 intervention/exposure
NCT01089231	Effects of Omega-3 Fatty Acids on the Human Gene Expression	null	https://ClinicalTrials.gov/show/NCT01089231	I: Not specifically n-3 intervention/exposure
NCT00410020	Arrhythmia Prevention With an	null	https://ClinicalTrials.gov/show/NCT00410020	I: Not specifically n-3

	Alpha-Linolenic Enriched Diet			intervention/exposure
NCT00487591	An Evaluation of Simvastatin Plus Omacor Compared to Simvastatin Plus Placebo in Subjects With Mixed Dyslipidemia	null	https://ClinicalTrials.gov/show/NCT00487591	I: Not specifically n-3 intervention/exposure
NCT01384032	Study Into Genetic Influence on Cholesterol Response to Dietary Fat	Satgene	https://ClinicalTrials.gov/show/NCT01384032	I: Not specifically n-3 intervention/exposure
NCT01000194	Acute Fatty Acid Intervention Study (AFAST)	AFAST	https://ClinicalTrials.gov/show/NCT01000194	I: Not specifically n-3 intervention/exposure
NCT01561846	Cheese Intake,CLA and Hypercholesterolemia	CASU	https://ClinicalTrials.gov/show/NCT01561846	I: Not specifically n-3 intervention/exposure
NCT00655902	Copenhagen Obesity Risk Assessment Study	COBRA	https://ClinicalTrials.gov/show/NCT00655902	I: Not specifically n-3 intervention/exposure
NCT00924937	CORonary Diet Intervention With Olive Oil and Cardiovascular PREVention	CORDIOPREV	https://ClinicalTrials.gov/show/NCT00924937	I: Not specifically n-3 intervention/exposure
ISRCTN35739639	Effects of Mediterranean diet on the primary prevention of cardiovascular disease	Death of any cause and incidence of angina leading to a revascularisation procedure, heart failure, diabetes mellitus, dementia, and cancer. Other outcomes: 1. Changes in blood pressure 2. Body weight 3. Adiposity measures 4. Blood sugar 5. Lipid profile 6. Markers of inflammation 7. Other intermediate markers of cardiovascular risk Added 07/05/2009: All participants are evaluated yearly for primary and	http://isrctn.com/ISRCTN35739639	I: Not specifically n-3 intervention/exposure

		secondary endpoints.		
NCT00520182	Dietary Interventions in Type 2 Obese Diabetic Patients in the Community	DIPAC	https://ClinicalTrials.gov/show/NCT00520182	I: Not specifically n-3 intervention/exposure
NCT00937963	Healthy Fatty Acids in Transition	FAT	https://ClinicalTrials.gov/show/NCT00937963	I: Not specifically n-3 intervention/exposure
NCT02106208	Study of the Impact of Dairy Fat on Cardiovascular Health.	HDL	https://ClinicalTrials.gov/show/NCT02106208	I: Not specifically n-3 intervention/exposure
NCT01314586	Flax Lignans and Heart Health	ISULignan	https://ClinicalTrials.gov/show/NCT01314586	I: Not specifically n-3 intervention/exposure
NCT02027285	Nutrition, Health and Quality of Life: Development of New Formulations of Traditional Products of the "Made in Italy" Diet Optimized for Consumers With an Age Over 50 Years (MIAO 50)	MIAO50	https://ClinicalTrials.gov/show/NCT02027285	I: Not specifically n-3 intervention/exposure
NCT01679496	Fat Quality on Blood Lipids and Immune Response	NoMa	https://ClinicalTrials.gov/show/NCT01679496	I: Not specifically n-3 intervention/exposure
NCT00445614	The Effects of Trout Fed With a Vegetable Based Feed on Cardiovascular Risk Markers and Plasma Proteome	null	https://ClinicalTrials.gov/show/NCT00445614	I: Not specifically n-3 intervention/exposure
NCT00269425	The Heart Institute of Spokane Diet Study	null	https://ClinicalTrials.gov/show/NCT00269425	I: Not specifically n-3 intervention/exposure
NCT00059254	Differential Metabolism of Dietary Fatty Acids	null	https://ClinicalTrials.gov/show/NCT00059254	I: Not specifically n-3 intervention/exposure
NCT00535886	The Effects of Natural Versus Man-Made Trans Fatty Acids on Lipoprotein Profiles: A Pilot Study	null	https://ClinicalTrials.gov/show/NCT00535886	I: Not specifically n-3 intervention/exposure
NCT00274729	Mono Unsaturated Fatty Acids in Obesity - Weight Maintenance and Prevention of Lifestyle Diseases in Obese Subjects.	null	https://ClinicalTrials.gov/show/NCT00274729	I: Not specifically n-3 intervention/exposure
NCT00074945	Obesity and Fatty Acid Flux Comparison Trials	null	https://ClinicalTrials.gov/show/NCT00074945	I: Not specifically n-3 intervention/exposure
NCT01235832	The Effect of Avocado on Cardiovascular Disease (CVD) Risk Factors	null	https://ClinicalTrials.gov/show/NCT01235832	I: Not specifically n-3 intervention/exposure
NCT01023646	Glycemic Index - Variability Among Individuals	null	https://ClinicalTrials.gov/show/NCT01023646	I: Not specifically n-3 intervention/exposure
NCT00429195	The Effect of Dietary Fat Modification on Risk Factors Associated With the Metabolic Syndrome	null	https://ClinicalTrials.gov/show/NCT00429195	I: Not specifically n-3 intervention/exposure

NCT01621087	Dietary Linoleic Acid for Secondary Prevention of Coronary Heart Disease and Death in the Sydney Heart Study: an RCT	null	https://ClinicalTrials.gov/show/NCT01621087	I: Not specifically n-3 intervention/exposure
NCT02506920	Gender Dependent Difference in Lipemia After 6 x OFTT in Young Healthy Subjects	null	https://ClinicalTrials.gov/show/NCT02506920	I: Not specifically n-3 intervention/exposure
NCT00400036	Dietary Fish Protein in Subjects With Insulin Resistance	null	https://ClinicalTrials.gov/show/NCT00400036	I: Not specifically n-3 intervention/exposure
NCT00405197	MARIS Study; Mediterranean Approach to Reduce Insulin-Resistance Study	null	https://ClinicalTrials.gov/show/NCT00405197	I: Not specifically n-3 intervention/exposure
NCT00005513	Framingham Nutrition Studies	null	https://ClinicalTrials.gov/show/NCT00005513	I: Not specifically n-3 intervention/exposure
NCT01710280	Palmitic Acid in the Sn-2 Position of Triacylglycerols and Postprandial Lipemia	null	https://ClinicalTrials.gov/show/NCT01710280	I: Not specifically n-3 intervention/exposure
NCT02145936	Effect of Dietary Fatty Acids on Cardiovascular Disease Risk Indicators and Inflammation	null	https://ClinicalTrials.gov/show/NCT02145936	I: Not specifically n-3 intervention/exposure
NCT01412346	Health Effects of a Nordic Diet Rich in Plant-based Foods and Fish	null	https://ClinicalTrials.gov/show/NCT01412346	I: Not specifically n-3 intervention/exposure
NCT01399216	Effects of a Supplement Containing Fucoidan on Basal Body Temperature	null	https://ClinicalTrials.gov/show/NCT01399216	I: Not specifically n-3 intervention/exposure
NCT02311790	Palmitoleic Isomer Study	null	https://ClinicalTrials.gov/show/NCT02311790	I: Not specifically n-3 intervention/exposure
NCT00223574	Canadian Trial of Dietary Carbohydrates in Diabetes	null	https://ClinicalTrials.gov/show/NCT00223574	I: Not specifically n-3 intervention/exposure
NCT01066091	Postprandial Inflammatory Response in Healthy Men: Effect of Dietary Fat Source, Obesity and Age	null	https://ClinicalTrials.gov/show/NCT01066091	I: Not specifically n-3 intervention/exposure
NCT01241695	Safety, Acceptability and Efficacy of a Long-term Intervention With a Diabetes-specific Low-carbohydrate, High-mono-unsaturated Fatty Acid Containing Oral Nutritional Supplement on Glycaemic Control in Type 2 Diabetic Patients	null	https://ClinicalTrials.gov/show/NCT01241695	I: Not specifically n-3 intervention/exposure
NCT00994513	Effect of Alpha Lipoic Acid on Obesity Related Comorbidities	null	https://ClinicalTrials.gov/show/NCT00994513	I: Not specifically n-3 intervention/exposure

NCT01570270	Cheese Intake and Hypercholesterolemia	null	https://ClinicalTrials.gov/show/NCT01570270	I: Not specifically n-3 intervention/exposure
NCT02086396	Effect of Weight Loss Diet and Pumpkin Seed Flour Consumption on Obese Women	null	https://ClinicalTrials.gov/show/NCT02086396	I: Not specifically n-3 intervention/exposure
NCT02391779	Flaxseed Lignan Supplementation in Elderly Participants With Stage I Hypertension	null	https://ClinicalTrials.gov/show/NCT02391779	I: Not specifically n-3 intervention/exposure
NCT00363233	The Potential Effects and Mechanisms of Flax Lignans on Type 2 Diabetes Mellitus	null	https://ClinicalTrials.gov/show/NCT00363233	I: Not specifically n-3 intervention/exposure
NCT01188902	The Metabolic Effect of Walnut Consumption in Healthy Men and Healthy Postmenopausal Women	null	https://ClinicalTrials.gov/show/NCT01188902	I: Not specifically n-3 intervention/exposure
NCT00204412	Exercise and Flax-Based Nutritional Supplementation for Lowering Cholesterol	null	https://ClinicalTrials.gov/show/NCT00204412	I: Not specifically n-3 intervention/exposure
CTRI/2009/091/001012	Effects of the walnut consumption in the young male patients of Essential Hypertension on sleep, stress,blood pressure and various parameters of Anthropometry.	null	http://www.ctri.nic.in/Clinicaltrials/pmaindet2.php?trialid=1148	I: Not specifically n-3 intervention/exposure
NCT00153764	Effectiveness of a Vitamin Mineral Supplement	Omega-3	https://ClinicalTrials.gov/show/NCT00153764	I: Not specifically n-3 intervention/exposure
NCT01696097	The Effects of Pork vs. Chicken/Fish in a DASH Diet on Blood Pressure Regulation in Middle Aged and Older Adults	S31	https://ClinicalTrials.gov/show/NCT01696097	I: Not specifically n-3 intervention/exposure
NCT02379169	Effects of Sea Buckthorn Oil and Lutein on Eye Health	SBEYE	https://ClinicalTrials.gov/show/NCT02379169	I: Not specifically n-3 intervention/exposure
NCT00685581	Impact of Vaccenic Acid Consumption on the Metabolism of Saturated Fatty Acids: Relationship With Cardiovascular Risk Factors	TRANSQUAL WPC	https://ClinicalTrials.gov/show/NCT00685581	I: Not specifically n-3 intervention/exposure
NCT00901043	Effects of Walnut Consumption on Endothelial Function in Type 2 Diabetes	WALNUT	https://ClinicalTrials.gov/show/NCT00901043	I: Not specifically n-3 intervention/exposure
NCT01413646	Effects of Walnuts on Endothelial Function in Overweight Adults With at Least One Factor of Metabolic Syndrome	Walnut2	https://ClinicalTrials.gov/show/NCT01413646	I: Not specifically n-3 intervention/exposure
NCT02330848	Walnut Ingestion in Adults at Risk for Diabetes: Effects on Body	Walnut3	https://ClinicalTrials.gov/show/NCT02330848	I: Not specifically n-3 intervention/exposure

	Composition, Diet Quality, and Cardiac Risk Measures			
NCT01471366	Method of Fish Oil Administration on Patient Compliance	null	https://ClinicalTrials.gov/show/NCT01471366	C: Comparator not different or no n-3
NCT01671254	Effect of Citrus Bioflavonoids/Vitamin E in Conjunction With Fish Oil Supplementation	null	https://ClinicalTrials.gov/show/NCT01671254	C: Comparator not different or no n-3
NCT02422446	Effects of Eicosapentaenoic Acid on Endothelial Function in Diabetic Subjects	null	https://ClinicalTrials.gov/show/NCT02422446	O: No outcome of interest (in primary or secondary list)
NCT02153073	Evaluation of the Safety and Efficacy of Long-term Use of Lotriga	null	https://ClinicalTrials.gov/show/NCT02153073	O: No outcome of interest (in primary or secondary list)
NCT00392717	Regulation of Lipoprotein Metabolism in Obese Men	null	https://ClinicalTrials.gov/show/NCT00392717	O: No outcome of interest
JPRN-UMIN000017867	Consideration of cardiac function improvement effect of Omega-3 fatty acids(EPA +DHA)	null	http://www.umin.ac.jp/ctr/index.htm	O: No outcome of interest
NCT00435045	Evaluation of Efficacy and Safety of Omacor, Co-Administered With Atorvastatin, in Subjects With Hypertriglyceridemia	null	https://ClinicalTrials.gov/show/NCT00435045	O: No outcome of interest
NCT00728338	Docosahexenoic Acid (DHA) Supplementation and Cardiovascular Disease in Men With High Triglycerides	null	https://ClinicalTrials.gov/show/NCT00728338	O: No outcome of interest
NCT01734538	Effect of 12 wk of Omega-3 FA Supplementation on Metabolic and Physical Health Parameters in Older Adults	null	https://ClinicalTrials.gov/show/NCT01734538	O: No outcome of interest
NCT00149409	Omega-3-Polyunsaturated Fatty-Acids (N3-Pufa) In Patients With Severe Chronic Heart Failure	null	https://ClinicalTrials.gov/show/NCT00149409	O: No outcome of interest
NCT02132728	Impact of Flaxseed on the Syndrome Metabolic Inflammation	null	https://ClinicalTrials.gov/show/NCT02132728	D: RCT N<30 per arm or XO N<20
NCT01505803	The Effect of a Nutritional Supplement in Individuals With Type 2 Diabetes Mellitus: a Pilot Study	null	https://ClinicalTrials.gov/show/NCT01505803	D: RCT N<30 per arm or XO N<20
NCT00560014	Nutrient Levels Alter Transplant Outcome	null	https://ClinicalTrials.gov/show/NCT00560014	D: RCT N<30 per arm or XO N<20
NCT02410161	Effect of an Alpha-linolenic Acid-rich Supplement on Ketogenesis	null	https://ClinicalTrials.gov/show/NCT02410161	D: RCT N<30 per arm or XO N<20

	and Plasma Fatty Acids			
NCT01896414	Metabolic Actions of Omega-3 Fatty Acids	null	https://ClinicalTrials.gov/show/NCT01896414	D: RCT N<30 per arm or XO N<20
NCT02011906	The Effects of Omega 3 and Vitamin E Supplementation on the Serum Antioxidant Enzymes and Gene Expressions of PGC-1a, h TERT, FOXOs and SIRTs in CAD Patients	null	https://ClinicalTrials.gov/show/NCT02011906	D: RCT N<30 per arm or XO N<20
NCT00935922	CCRC: Understanding the Effects of Omega-3 Fatty Acids Versus Lignans in Flaxseed on Metabolic and Inflammatory Markers Leading to Diabetes and Cardiovascular Disease	null	https://ClinicalTrials.gov/show/NCT00935922	D: RCT N<30 per arm or XO N<20
NCT01788917	Effects of Supplementation With Linseed Oil on Blood Lipids in Vegetarians	null	https://ClinicalTrials.gov/show/NCT01788917	D: RCT N<30 per arm or XO N<20
NCT00694746	Study of Fish Oil to Reduce ALT Levels in Adolescents	null	https://ClinicalTrials.gov/show/NCT00694746	D: RCT N<30 per arm or XO N<20
NCT01180764	Effects of Lovaza on High Density Lipoprotein (HDL) Composition and Function in Hypertriglyceridemia	null	https://ClinicalTrials.gov/show/NCT01180764	D: RCT N<30 per arm or XO N<20
NCT01594983	A Pilot Study to Assess the Efficacy and Safety of LCQ908 Alone and in Combination With Fenofibrate or LovazaÂ® in Patients With Severe Hypertriglyceridemia	null	https://ClinicalTrials.gov/show/NCT01594983	D: RCT N<30 per arm or XO N<20
NCT00715312	Effect of Oleic Acid on Inflammation Markers and Blood Lipid Metabolites: A Randomised, Double-Blind, Crossover Study	null	https://ClinicalTrials.gov/show/NCT00715312	D: RCT N<30 per arm or XO N<20
JPRN-UMIN000002336	A fish-based diet intervention and serum adiponectin concentration	null	http://www.umin.ac.jp/ctr/index.htm	D: RCT N<30 per arm or XO N<20
JPRN-UMIN000013776	Effect of EPA/DHA combination therapy on LDL particle size in patients with hyperlipidemia and type 2 diabetes taking HMG-CoA reductive enzyme inhibitors and DPP-4 inhibitors.	null	http://www.umin.ac.jp/ctr/index.htm	D: RCT N<30 per arm or XO N<20
JPRN-UMIN000016714	Effect of ingestion of eicosapentaenoic acid-rich fish oil	null	http://www.umin.ac.jp/ctr/index.htm	D: RCT N<30 per arm or XO N<20

	on exercise performance in swimming			
JPRN-UMIN000017072	Double-Blind, Placebo-Controlled Study for the Effect of Lyophilized Herring-Roe Powder on Lipid Metabolism Improvement	null	http://www.umin.ac.jp/ctr/index.htm	D: RCT N<30 per arm or XO N<20
ChiCTR-IOR-15006329	Effect of long term small doses of EPA/DHA supplement on cardiovascular risk factors among people with metabolic syndrome	null	http://www.chictr.org.cn/showproj.aspx?proj=10889	D: RCT N<30 per arm or XO N<20
ISRCTN22073289	The effect of dietary rapeseed (canola) versus olive oil supplementation on serum lipids, liver enzymes and postprandial inflammatory responses in adipose tissue in obese men.	null	http://isrctn.com/ISRCTN22073289	D: RCT N<30 per arm or XO N<20
DRKS00006765	Influence of omega-3 fatty acids on levels of oxylipins in blood and urine	null	http://www.drks.de/DRKS00006765	D: RCT N<30 per arm or XO N<20
NCT00720655	Effects of Fatty and Lean Fish Intake on Cardiovascular Risk Factors in Subjects With Coronary Heart Disease	null	https://ClinicalTrials.gov/show/NCT00720655	D: RCT N<30 per arm or XO N<20
NCT01244048	Intervention With n3 LC-PUFA-supplemented Yogurt	null	https://ClinicalTrials.gov/show/NCT01244048	D: RCT N<30 per arm or XO N<20
NCT01705678	Investigation Into the Effects of Krill Oil vs. Fish Oil on Markers of Cardiovascular Disease	null	https://ClinicalTrials.gov/show/NCT01705678	D: RCT N<30 per arm or XO N<20
ACTRN12610000718044	Is fish intake or fish oil supplementation better for people with coronary heart disease? An Australian secondary prevention trial.	null	http://www.anzctr.org.au/ACTRN12610000718044.aspx	D: RCT N<30 per arm or XO N<20
NCT00536185	Heart & Health Study	none	https://ClinicalTrials.gov/show/NCT00536185	D: RCT N<30 per arm or XO N<20
NCT01377402	ARgentinean Risk Assessment Registry in ACS; the ARRA-RACS Study	ARRA-RACS	https://ClinicalTrials.gov/show/NCT01377402	D: RCT N<30 per arm or XO N<20
NCT01047683	Efficacy and Safety of AMR101 (Ethyl Icosapentate) in Patients With Fasting Triglyceride (Tg) Levels â‰¥ 500 and â‰¤ 2000 mg/dL	MARINE	https://ClinicalTrials.gov/show/NCT01047683	D: RCT N<30 per arm or XO N<20
EUCTR2009-010520-25-	A Phase 3, Multi-Center, Placebo-	MARINE	https://www.clinicaltrialsregister.eu/ctr-	D: RCT N<30 per arm or XO

NL	Controlled, Randomized, Double-Blind, 12-Week Study With an Open-Label Extension to Evaluate the Efficacy and Safety of AMR101 in Patients With Fasting Triglyceride Levels =>500 mg/dL and <=2000 mg/dL: The AMR101 MARINE Study - The Marine Study		search/search?query=eudract_number:2009-010520-25	N<20
ACTRN12605000207617	Fish Oils (Omega 3) in ischaemic stroke	FOILS	http://www.anzctr.org.au/ACTRN12605000207617.aspx	D: RCT N<30 per arm or XO N<20
NCT01437930	Intervention With n-3 Polyunsaturated Fatty Acids (PUFA)-Supplemented Products in Moderate Hypertriglyceridemic Patients	ZZ none	https://ClinicalTrials.gov/show/NCT01437930	D: RCT N<30 per arm or XO N<20
ISRCTN76272133	Effects of fish oil on blood vessel function	Blood lipids, glucose, insulin, inflammatory markers, nitric oxide, dietary intake. All outcome measures to be assessed at baseline and after 8 weeks intervention on each arm of the crossover study (i.e. Week 0, week 8, week 16 and week 24.	http://isrctn.com/ISRCTN76272133	D: RCT N<30 per arm or XO N<20
NCT01737099	Efficacy and Safety Study of DHA-O in Adults With Hypertriglyceridemia	DHA-O	https://ClinicalTrials.gov/show/NCT01737099	D: RCT N<30 per arm or XO N<20
NCT02009865	EpanovaÂ® for Lowering Very High Triglycerides II (EVOLVE II)	EVOLVEII	https://ClinicalTrials.gov/show/NCT02009865	D: RCT N<30 per arm or XO N<20
EUCTR2012-003029-11-DK	A double-blind, placebo-controlled, intervention trial comparing the triglyceride-lowering effect of omega-3 polyunsaturated fatty acids, as either ethyl ester or triglycerides in patients with moderately elevated triglyceride levels in the blood in non fasting state.	EVT	https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2012-003029-11	D: RCT N<30 per arm or XO N<20

NCT01577056	Postprandial Lipid Metabolism in Familial Hypercholesterolaemia:Effects of Fish Oils	FIFH	https://ClinicalTrials.gov/show/NCT01577056	D: RCT N<30 per arm or XO N<20
NCT00733772	Flaxseed Intervention on Metabolic Syndrome	FIMS	https://ClinicalTrials.gov/show/NCT00733772	D: RCT N<30 per arm or XO N<20
NCT01916434	Farmed Fish Human Intervention Study	FISHDISH	https://ClinicalTrials.gov/show/NCT01916434	D: RCT N<30 per arm or XO N<20
EUCTR2013-004342-42-NL	The effect of fish oil on red blood cell function and walking distance in patients with arterial occlusion in the legs	FISHTIC	https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2013-004342-42	D: RCT N<30 per arm or XO N<20
NCT02042274	Efficacy Study Regarding the Beneficial Effects of Omega-3 Fatty Acids on Cardiometabolic Health	FOHS	https://ClinicalTrials.gov/show/NCT02042274	D: RCT N<30 per arm or XO N<20
NCT02400203	FREE Living Hulled HEMP Seed and Oil Trial	FREEHEMP	https://ClinicalTrials.gov/show/NCT02400203	D: RCT N<30 per arm or XO N<20
NCT02211612	Overeating Different Fats and Influence on Muscle Mass and Body Fat Accumulation	LIPOGAIN-2	https://ClinicalTrials.gov/show/NCT02211612	D: RCT N<30 per arm or XO N<20
NCT00286234	Niacin, N-3 Fatty Acids and Insulin Resistance	null	https://ClinicalTrials.gov/show/NCT00286234	D: RCT N<30 per arm or XO N<20
NCT01129050	Effects of Omega-3 Fatty Acids on Markers of Inflammation	null	https://ClinicalTrials.gov/show/NCT01129050	D: RCT N<30 per arm or XO N<20
NCT00246636	Evaluation of Efficacy and Safety of Omacor (Omega-3-acid Ethyl Esters) as Add-on Therapy in Hypertriglyceridemic Subjects Treated With Antara (Fenofibrate) Followed by an 8-week Extension	null	https://ClinicalTrials.gov/show/NCT00246636	D: RCT N<30 per arm or XO N<20
NCT00927199	Efficacy of High-oleic Canola and Flaxseed Oils for Hypercholesterolemia and Cardiovascular Disease Risk Factors	null	https://ClinicalTrials.gov/show/NCT00927199	D: RCT N<30 per arm or XO N<20
NCT01145066	Botanical Oil Supplementation in Diabetic and Metabolic Syndrome Subjects	null	https://ClinicalTrials.gov/show/NCT01145066	D: RCT N<30 per arm or XO N<20
NCT01725646	An Efficacy and Safety Study of OmacorÂ® in Taiwanese Hypertriglyceridemic Patients	null	https://ClinicalTrials.gov/show/NCT01725646	D: RCT N<30 per arm or XO N<20
NCT00315770	Health of Young European Families and Fish Consumption	null	https://ClinicalTrials.gov/show/NCT00315770	D: RCT N<30 per arm or XO N<20

NCT01768429	The Effect of n-3 Fatty Acids and Fish on Glucose and Lipid Metabolism in Subjects With Impaired Glucose Metabolism	null	https://ClinicalTrials.gov/show/NCT01768429	D: RCT N<30 per arm or XO N<20
NCT00350194	The Effects of Omega-3 Fatty Acids on Metabolic Syndrome	null	https://ClinicalTrials.gov/show/NCT00350194	D: RCT N<30 per arm or XO N<20
NCT01749202	Effects of Stearidonic Acid-Containing Foods on Eicosapentaenoic Acid Levels in Red Blood Cells and Omega-3 Index	null	https://ClinicalTrials.gov/show/NCT01749202	D: RCT N<30 per arm or XO N<20
NCT00976872	Omega 3 Action on Cardiovascular Risk Factors in Patients Treated With Statins	null	https://ClinicalTrials.gov/show/NCT00976872	D: RCT N<30 per arm or XO N<20
NCT02092584	Effect of Omega-3 Supplementation on Serum Level and Gene Expression of IGF-1and IGFBP-3 in Men With CVD.	null	https://ClinicalTrials.gov/show/NCT02092584	D: RCT N<30 per arm or XO N<20
NCT01478776	The Impact of Omega-3 Supplementation on Gene Expression in Type 2 Diabetics	null	https://ClinicalTrials.gov/show/NCT01478776	D: RCT N<30 per arm or XO N<20
NCT01365078	Stearidonic Acid and Lipid Metabolism	null	https://ClinicalTrials.gov/show/NCT01365078	D: RCT N<30 per arm or XO N<20
NCT00360217	The Triglyceride Lowering Effect of an Omega-3 Fat (DHA) in Addition to Statin Therapy for Patients With CAD or Diabetes	null	https://ClinicalTrials.gov/show/NCT00360217	D: RCT N<30 per arm or XO N<20
NCT01712867	The Effect of Phytosterol Esters of Omega-3 (Vayarol) Versus Omega-3 Acids Ethyl Esters in Reducing Triglyceride Levels	null	https://ClinicalTrials.gov/show/NCT01712867	D: RCT N<30 per arm or XO N<20
NCT01690312	Clinical Study to Assess High-DHA Fish Oil on Biomarkers of Cardiovascular Disease Risk in Adults on Statin Therapy	null	https://ClinicalTrials.gov/show/NCT01690312	D: RCT N<30 per arm or XO N<20
NCT02035215	Phase 3 Study to Evaluate the Efficacy and Safety of Omega-3-acids Ethylesters 90 in Type â…¡b Hyperlipidemia	null	https://ClinicalTrials.gov/show/NCT02035215	D: RCT N<30 per arm or XO N<20
NCT02305355	Efficacy and Safety of Prescription Omega-3 Fatty Acid Added to Stable Statin Therapy in Patients With Type 2 Diabetes and Hypertriglyceridemia	null	https://ClinicalTrials.gov/show/NCT02305355	D: RCT N<30 per arm or XO N<20

NCT01526824	Lovaza's Effect on Clopidogrel in a Neuro Population	null	https://ClinicalTrials.gov/show/NCT01526824	D: RCT N<30 per arm or XO N<20
NCT01997268	The Efficacy of EPA+DHA (SC401B) for Lowering Triglyceride Levels (â‰¥ 500 mg/dL)	null	https://ClinicalTrials.gov/show/NCT01997268	D: RCT N<30 per arm or XO N<20
NCT02091583	Canola Oil, Fibre and DHA Enhanced Clinical Trial	null	https://ClinicalTrials.gov/show/NCT02091583	D: RCT N<30 per arm or XO N<20
NCT00758927	The Effects of Omega-3 Fatty Acid (OMACOR) on the Low-density Lipoprotein (LDL) Sub-fraction in Type 2 Diabetic Patients	null	https://ClinicalTrials.gov/show/NCT00758927	D: RCT N<30 per arm or XO N<20
NCT01858948	SGA-induced Metabolic Syndrome in Bipolar Youth	null	https://ClinicalTrials.gov/show/NCT01858948	D: RCT N<30 per arm or XO N<20
NCT00804427	Effect of Fish Oil on Plasma Triglycerides in Adults	null	https://ClinicalTrials.gov/show/NCT00804427	D: RCT N<30 per arm or XO N<20
NCT01028274	Safety and Efficacy of a Natural Health Product in Reducing Cholesterol and Triglyceride Levels.	null	https://ClinicalTrials.gov/show/NCT01028274	D: RCT N<30 per arm or XO N<20
NCT02183922	Microencapsulated Fish Oil or Conjugated Linoleic Acid in Metabolic Syndrome	null	https://ClinicalTrials.gov/show/NCT02183922	D: RCT N<30 per arm or XO N<20
NCT01415388	Study to Investigate the Effects of Krill Oil on Fasting Serum Triglycerides	null	https://ClinicalTrials.gov/show/NCT01415388	D: RCT N<30 per arm or XO N<20
NCT02436369	The Effect of Yogurt Enriched With Flaxseed on Cardiovascular Risk Factors in Type 2 Diabetic Patients	null	https://ClinicalTrials.gov/show/NCT02436369	D: RCT N<30 per arm or XO N<20
NCT00746811	Trial to Assess the Effects of P-OM3 on LDL-C in Subjects With Primary Hypercholesterolemia	null	https://ClinicalTrials.gov/show/NCT00746811	D: RCT N<30 per arm or XO N<20
NCT00365742	Statin Therapy Vs. Therapeutic Lifestyle Changes and Supplements	null	https://ClinicalTrials.gov/show/NCT00365742	D: RCT N<30 per arm or XO N<20
NCT01604681	Supplementation With Flaxseed Oil in the State of Rio de Janeiro	null	https://ClinicalTrials.gov/show/NCT01604681	D: RCT N<30 per arm or XO N<20
NCT00051415	Safety and Effectiveness of Flaxseed for Reducing High Cholesterol	null	https://ClinicalTrials.gov/show/NCT00051415	D: RCT N<30 per arm or XO N<20
NCT00852735	Effect of the Antioxidant Micronutrients of Rapeseed Oil on the Prevention of Cardiovascular Diseases (Optim'Oils)	null	https://ClinicalTrials.gov/show/NCT00852735	D: RCT N<30 per arm or XO N<20

NCT02119429	Pumpkin Seed Oil Supplementation in Premenopausal Women	null	https://ClinicalTrials.gov/show/NCT02119429	D: RCT N<30 per arm or XO N<20
EUCTR2006-003544-27-NL	An Evaluation of Simvastatin 20 mg Plus Omacor 4 g Compared to Simvastatin 20 mg Plus Placebo in Subjects with Mixed Dyslipidemia	null	https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2006-003544-27	D: RCT N<30 per arm or XO N<20
ACTRN12605000641695	Effectiveness of DPA in comparison to DHA in lowering plasma triglyceride levels and other cardiovascular risk factors	null	http://www.anzctr.org.au/ACTRN12605000641695.aspx	D: RCT N<30 per arm or XO N<20
ACTRN12607000566437	Long Chain Omega-3 Polyunsaturated Fatty Acids and Heart Health in Humans	null	http://www.anzctr.org.au/ACTRN12607000566437.aspx	D: RCT N<30 per arm or XO N<20
ChiCTR-TRC-12002014	Influence of different source of n-3 fatty acid on plasma lipid in moderately hypercholesterolemia subject and the valid dosage	null	http://www.chictr.org/en/proj/show.aspx?proj=2638	D: RCT N<30 per arm or XO N<20
ACTRN12614000732684	The Aboriginal Cardiovascular Omega-3 Randomised Controlled Trial	null	http://www.anzctr.org.au/ACTRN12614000732684.aspx	D: RCT N<30 per arm or XO N<20
ChiCTR-TRC-14005084	Effect of deep sea fish oil on blood biochemical indicators in elderly patients with type 2 diabetes mellitus: an intervention study	null	http://www.chictr.org.cn/showproj.aspx?proj=4491	D: RCT N<30 per arm or XO N<20
ACTRN12615000472572	The effect of 30 day krill oil supplementation on cardiovascular risk factors	null	http://www.anzctr.org.au/ACTRN12615000472572.aspx	D: RCT N<30 per arm or XO N<20
IRCT201411141525N5	Comparison of the effect of Omega 3 capsules and fish Consumption on Lipid Profile in Patients with Dyslipidemia	null	http://www.irct.ir/searchresult.php?id=1525&number=5	D: RCT N<30 per arm or XO N<20
IRCT201309303387N4	The effect of of aerobic training plus Flax seed supplementation on serum lipids and lipoprotein profile and C-reactive protein in sedentary obese women.	null	http://www.irct.ir/searchresult.php?id=3387&number=4	D: RCT N<30 per arm or XO N<20
IRCT201207108559N3	Effect of omega-3 supplementation and aerobic training on cardiac risk factors	null	http://www.irct.ir/searchresult.php?id=8559&number=3	D: RCT N<30 per arm or XO N<20
IRCT2013011312122N1	Effect of omega-3 fatty acid supplementation on diabetes mellitus patients	null	http://www.irct.ir/searchresult.php?id=12122&number=1	D: RCT N<30 per arm or XO N<20
IRCT2012110411362N1	Effect of fish oil supplement on	null	http://www.irct.ir/searchresult.php?id=11362&number=1	D: RCT N<30 per arm or XO

	chronic atrial fibrillation			N<20
NCT00504309	Vascular and Lipid Effects of Omega-3 Fatty Acids in People With Moderately Elevated Triglycerides	OMEGA	https://ClinicalTrials.gov/show/NCT00504309	D: RCT N<30 per arm or XO N<20
NCT02195609	Evaluate the Effect of Omega-3 vs Soy Isoflavones in Postmenopausal Women With Moderate to Severe Vasomotor Symptoms	OMEGASI	https://ClinicalTrials.gov/show/NCT02195609	D: RCT N<30 per arm or XO N<20
NCT01928966	Effect of Pumpkin Seeds on the Dietary Fatty Acid Intake and Blood Pressure in Women	PSS1	https://ClinicalTrials.gov/show/NCT01928966	D: RCT N<30 per arm or XO N<20
NCT02089035	Replacement of Saturated Fat in Dairy on Total Cholesterol	RESET	https://ClinicalTrials.gov/show/NCT02089035	D: RCT N<30 per arm or XO N<20
EUCTR2009-014730-22-IT	SO03-01 - EVALUATION OF THE EFFECT OF N-3 SUPPLEMENTATION ON FUNCTIONAL IMPROVEMENT IN POSTSTROKE PATIENTS - SO3-01	SO3-01	https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2009-014730-22	D: RCT N<30 per arm or XO N<20
NCT02036307	Supplementation With Omega-3: Mechanism of Action	SOMA	https://ClinicalTrials.gov/show/NCT02036307	D: RCT N<30 per arm or XO N<20
NCT00934219	Triglyceride Lowering Study	TGLL	https://ClinicalTrials.gov/show/NCT00934219	D: RCT N<30 per arm or XO N<20
NCT00441480	Effect of Plant Sterols Esterified to Fish Oil Fatty Acids on Plasma Lipid Levels	null	https://ClinicalTrials.gov/show/NCT00441480	D: RCT N<30 per arm or XO N<20
NCT00891293	A Second Open-Label Extension of a Double-Blind, Parallel, Phase IV Study to Assess the Efficacy and Safety of Adjunctive LovazaÂ® (Formerly Known as OmacorÂ®) Therapy in Hypertriglyceridemic Subjects Treated With Antaraâ„¢	null	https://ClinicalTrials.gov/show/NCT00891293	D: RCT N<30 per arm or XO N<20
NCT02025920	Project Healthy Eating in Adults. A Study on the Health Effects of Fish Intake in Overweight Adults (FINS)	null	https://ClinicalTrials.gov/show/NCT02025920	D: nRCS Lipids
JPRN-UMIN000010397	Effect of combination therapy with DPP-4 inhibitor and omega 3-fatty acid on glycemic control in type2 diabetes with dyslipidemia	null	http://www.umin.ac.jp/ctr/index.htm	D: nRCS Lipids

NCT00527436	Fish Oil and Biomarkers of Cardiovascular Risk	null	https://ClinicalTrials.gov/show/NCT00527436	D: Not enough information in trial record
NCT02130908	A Study on the Possible Health Effects of Lean Fish, Fatty Fish and Lean Meat Intake in Non-obese Adults	FISK1	https://ClinicalTrials.gov/show/NCT02130908	D: Not enough information in trial record
NCT02350595	A Study on the Possible Health Effects of Lean Fish and Fatty Fish Intake in Overweight or Obese Adults	FISK2	https://ClinicalTrials.gov/show/NCT02350595	D: Not enough information in trial record
NCT01119690	HÃ¤meenlinna Metabolic Syndrome Research Program: Effects of Rapeseed Oil on Serum Lipids and Platelet Function	HMS-03	https://ClinicalTrials.gov/show/NCT01119690	D: Not enough information in trial record
NCT00000461	Harvard Atherosclerosis Reversibility Project (HARP)	null	https://ClinicalTrials.gov/show/NCT00000461	D: Not enough information in trial record
NCT01821131	Flax Muffins and Cholesterol Lowering	null	https://ClinicalTrials.gov/show/NCT01821131	D: Not enough information in trial record
NCT01952340	The Efficacy of Dietary Flaxseed for the Reduction of Blood Pressure in Newly Diagnosed Hypertensive Individuals	null	https://ClinicalTrials.gov/show/NCT01952340	D: Not enough information in trial record
NCT00000511	Polyunsaturates and KCL to Control Mild Hypertension	null	https://ClinicalTrials.gov/show/NCT00000511	D: Not enough information in trial record
NCT02069106	Efficacy Study of Daily Pro-Omega LDL for Low-Density Lipoprotein Cholesterol and Triglyceride Reduction	PrOteCT	https://ClinicalTrials.gov/show/NCT02069106	D: Not enough information in trial record
NCT00841451	Pulmonary Vein Isolation Outcomes With Fish Oils	PUFA	https://ClinicalTrials.gov/show/NCT00841451	D: Not enough information in trial record
NCT00005236	Atherosclerosis and Omega-3 Fatty Acids in Alaskan Natives	null	https://ClinicalTrials.gov/show/NCT00005236	D: Non-comparative
NCT02349555	Nutritional Supplement Impact on Metabolic Parameters	null	https://ClinicalTrials.gov/show/NCT02349555	D: Non-comparative
NCT00903409	Open-Label Extension of a Randomized, Double-Blind, Placebo-Controlled Study to Assess the Efficacy and Safety of LovazaÂ® and Simvastatin Therapy in Hypertriglyceridemic Subjects	COMBOS	https://ClinicalTrials.gov/show/NCT00903409	D: non-comparative
NCT00404872	Evaluating the Relationship Between Fatty Acids and Heart Disease	null	https://ClinicalTrials.gov/show/NCT00404872	D: non-comparative

NCT02296385	Genotype-related Effects of PUFA	null	https://ClinicalTrials.gov/show/NCT02296385	D: non-comparative
JPRN-UMIN000011169	Effect of EPA/DHA supplementation added on DPP4 inhibitors on lipid and glucose metabolism in patients with type 2 diabetes	null	http://www.umin.ac.jp/ctr/index.htm	D: non-comparative
JPRN-JapicCTI-142680	Specified drug-use survey of Lotriga Granular Capsules: Outcome prevention on Cardiovascular Events by Antihyperlipidemic therapy with N3-fatty acid in Japan (OCEAN3)	OCEAN3	http://www.clinicaltrials.jp/user/showCteDetailE.jsp?japicId=JapicCTI-142680	D: non-comparative
NCT01803594	Feeding Trial to Determine How Combinations of Different Dietary Bioactive Ingredients Influence High Density Lipoprotein (HDL) Metabolism	HDL	https://ClinicalTrials.gov/show/NCT01803594	D: <4 wk followup
NCT01175330	Omega 3 Fatty Acid Efficiency for Prevention of Atrial Fibrillation After Coronary Artery Bypass Grafting	none	https://ClinicalTrials.gov/show/NCT01175330	D: <4 wk followup
NCT01908374	Bioavailability of EPA and DHA From Two Dietary Supplements	null	https://ClinicalTrials.gov/show/NCT01908374	D: <4 wk followup
NCT02521779	The Role of Dietary Fat on Postprandial Endotoxemia in Healthy Adults	null	https://ClinicalTrials.gov/show/NCT02521779	D: <4 wk followup
NCT02246933	Effects of a PUFA-rich Diet on Acute Metabolic and Inflammatory High-Fat Meal Responses	null	https://ClinicalTrials.gov/show/NCT02246933	D: <4 wk followup
NCT01067911	Optimizing Dietary Fatty Acids to Lower Metabolic Risk Factors Among Canadians	null	https://ClinicalTrials.gov/show/NCT01067911	D: <4 wk followup
NCT02209766	A Ph1 Study in Healthy Male Japanese and Caucasian After Single and Multiple Doses of D5884(Omega-3-carboxylic Acids)	null	https://ClinicalTrials.gov/show/NCT02209766	D: <4 wk followup
NCT00179400	Insulin Action in Individuals With Type 2 Diabetes by Natural Fatty Acids or the Medication Pioglitazone	null	https://ClinicalTrials.gov/show/NCT00179400	D: <4 wk followup
NCT00475774	Body Fat Distribution and Fat Metabolism	null	https://ClinicalTrials.gov/show/NCT00475774	D: <4 wk followup
NCT01579656	Effect of Flax, Poppy, Sesame & Salba on Postprandial Blood	null	https://ClinicalTrials.gov/show/NCT01579656	D: <4 wk followup

	Glucose Response, Vascular, Appetite & Sensory Parameters			
NCT01428960	Study of Acute Effects of Sn-1 and Sn-3 Palmitic Acid-rich or Stearic Acid-rich Fats on Metabolic Markers	null	https://ClinicalTrials.gov/show/NCT01428960	D: <4 wk followup
NCT00465036	Effect of Flaxseed on Lipid Uptake and Appetite	null	https://ClinicalTrials.gov/show/NCT00465036	D: <4 wk followup
NCT01124487	The Acute Effects of Oleic Acid Enriched-diets on Lipids, Insulin Sensitivity and Serum Inflammatory Markers	null	https://ClinicalTrials.gov/show/NCT01124487	D: <4 wk followup
NCT00846937	Plant Stanol Ester Beverage and Ileostoma Patients	STOMA	https://ClinicalTrials.gov/show/NCT00846937	D: <4 wk followup
NCT00552084	Evaluating the Effectiveness of Fish Oil Supplements at Reducing the Recurrence of Atrial Fibrillation	null	https://ClinicalTrials.gov/show/NCT00552084	D: <1 yr CVD
NCT01521845	Study of the Effect of omega3 on Biomarkers of Cardiac Necrosis (CKMB and Troponin I) and Inflammation Marker (CRP) After Elective Percutaneous Coronary Intervention (PCI)	null	https://ClinicalTrials.gov/show/NCT01521845	D: <1 yr CVD
NCT00402363	Evaluation of Efficacy and Safety of Lovaza (Omega-3-Acid Ethyl Esters) in Recurrent, Symptomatic Atrial Fibrillation	null	https://ClinicalTrials.gov/show/NCT00402363	D: <1 yr CVD
NCT00232245	Use of Fish Oils to Reduce the Frequency and Duration of Episodes of Atrial Fibrillation in Patients With Paroxysmal Atrial Fibrillation.	null	https://ClinicalTrials.gov/show/NCT00232245	D: <1 yr CVD
JPRN-UMIN000011869	Relationship Between Arteriosclerosis Obliterans and Serum Level of Eicosapentaenoic Acid as Prospective Interventional Study	null	http://www.umin.ac.jp/ctr/index.htm	D: <1 yr CVD
JPRN-UMIN000013472	Clinical effect of early loading of eicosepentanoic acid for acute myocardial infarction: a prospective, open-labeled, randomized controlled clinical trial	null	http://www.umin.ac.jp/ctr/index.htm	D: <1 yr CVD
NCT01235130	Multi-center Study to Evaluate the Effect of N-3 Fatty Acids (OMEGA-	AFFORD	https://ClinicalTrials.gov/show/NCT01235130	D: <1 yr CVD

	3) on Arrhythmia Recurrence in Atrial Fibrillation			
ISRCTN52203885	N-3 fatty acid supplementation on arrhythmia recurrence in atrial fibrillation	AFFORD	http://isrctn.com/ISRCTN52203885	D: <1 yr CVD

Appendix E. Studies in Both the Report and Registry

Table E-1a. Studies in both the report and registry

Study	Registry	Population	Dates	N total*	Study design: Intervention	Intermediate Outcomes	Clinical Outcomes
Has Results							
NCT01242527, US, Denmark, Netherlands, Hungary, India, Russian Federation, Ukraine, EVOLVE	CT.gov	At risk	2011-2012	399	RCT: Fish oil (EPA+DHA) 2, 3, or 4 g/d vs. Placebo	Lipids	
NCT01408303, US, ESPRIT	CT.gov	At risk	2011-2012	646	RCT: Fish oil (EPA+DHA) 2 or 4 g/d vs. Placebo	Lipids	
NCT01198275, Italy, ATRIA	CT.gov	CVD, existing	2006-2008	199	RCT: Fish oil (EPA+DHA) 0.850-0.882 g/d vs. Placebo		Arrhythmia event
NCT00781950, Canada, FLAXPAD	CT.gov	CVD, existing	2008-2014	110	RCT: ALA 30 g/d vs. Placebo	BP/Lipids	Cardiac event, Stroke/TIA, Death
No Results							
NCT00005133, US, CHS	CT.gov	Healthy	1988-2009	nd	Observational – Quantile		Cardiac event, Stroke/TIA
NCT01313988, Sweden, none	CT.gov	Healthy	2011-2012	332	RCT: All n-3 PUFA vs. Placebo	Lipids	
NCT00110838, Germany, Netherlands, UK, Austria, Belgium, Czech Republic, Poland, Switzerland, SOFA	CT.gov	Healthy	2010-2011	256	RCT: Fish oil (EPA+DHA) 2 g/d vs. Placebo	Lipids	
NCT00266292, Denmark, none	CT.gov	Healthy	2005-2006	60	RCT: Fish oil (EPA+DHA) vs. Placebo	BP/Lipids	
NCT01856179, Germany, none	CT.gov	Healthy	2011-2012	78	RCT: SDA 15-18 g/d vs. nd	Lipids	
NCT00317707, Italy, none	CT.gov	At risk	2004-2011	12513	RCT: All n-3 PUFA vs. Placebo		Cardiac event, Death
NCT00141232/ISRCTN76737502, UK, AFFORD	ICTRP/ CT.gov	At risk	2004-2006	810	RCT: Fish oil (EPA+DHA) vs. Placebo	Lipids	
NCT00246701, US, COMBOS	CT.gov	At risk	2005-2006	256	RCT: Fish oil (EPA+DHA) vs. Placebo	Lipids	
NCT00069784, Canada, ORIGIN	CT.gov	At risk	2003-2011	12537	RCT: Fish oil (EPA+DHA) 0.84 g/d vs. Placebo		Cardiac event, Stroke/TIA, Death
NCT01758601, Spain, WISH-CARE	CT.gov	At risk	2010-2012	273	RCT - XO: Fish oil (EPA+DHA) 1 serving of hake/day vs. no intervention	Lipids	
NCT00231738, Japan, JELIS	CT.gov	At risk	1996-2004	18000	RCT: EPA 1.8 g/d vs. nd		Cardiac event, Stroke/TIA, Death

NCT01047501, US, ANCHOR	CT.gov	At risk	2009-2011	702	RCT: EPA 2 or 4 g/d vs. Placebo	Lipids	
NCT01351012, Canada, COMIT	CT.gov	At risk	2010-2012	140	RCT - XO: ALA, DHA + ALA DHA 7.2, ALA 4.2-13.8 vs. ALA 4.2-13.8 g/d	Lipids	
DRKS00006232, Germany, MSX	ICTRP	At risk	2009-2009	81	RCT: ALA 3.5 g/d vs. ALA 0.9 g/d	BP/Lipids	
NCT00004558, US, none	CT.gov	CVD, existing	1999-2004	200	RCT: Omega-3 (Unspecified) vs. Placebo		Arrhythmia event
NCT00127452, Netherlands, Alpha Omega	CT.gov	CVD, existing	2002-2010	4837	RCT: All n-3 PUFA Fish oil 0.4 g/d, ALA 2 g/d vs. Placebo		Cardiac event, Stroke/TIA, Arrhythmia event, PVD event, Death
NCT00251134, Germany, OMEGA	CT.gov	CVD, existing	2003-2008	3800	RCT: All n-3 PUFA 1 g/d vs. Placebo		Cardiac event, Arrhythmia event, Death
NCT00336336, Italy, GISSI-HF	CT.gov	CVD, existing	2002-2008	6975	RCT: All n-3 PUFA 1 g/d vs. Placebo		Cardiac event, Stroke/TIA, Arrhythmia event, Death
ISRCTN41926726, France, SU.FOL.OM3	ICTRP	CVD, existing	2003-2009	2400	RCT: Fish oil (EPA+DHA) 0.6 g/d vs. Placebo		Cardiac event, Stroke/TIA, Death
ISRCTN66664610, UK, MARINA	ICTRP	CVD, existing	2008-2010	360	RCT: Fish oil (EPA+DHA) 0.45, 0.9, or 1.8 g/d vs. Placebo	BP/Lipids	
NCT00004559, US, FAAT	CT.gov	CVD, existing	2000-2005	nd	RCT: Fish oil (EPA+DHA) 4 g/d vs. Placebo		Arrhythmia event
NCT00597220, Argentinia, FORWARD	CT.gov	CVD, existing	2008-2011	1600	RCT: Fish oil (EPA+DHA) 1 g/d vs. Placebo		Stroke/TIA, Arrhythmia event
NCT01422317, Norway, OFAMI	CT.gov	CVD, existing	1995-2002	300	RCT: Fish oil (EPA+DHA) 3.464 g/d vs. Placebo	Lipids	Cardiac event

Table E-1b. Studies in the registry only

Study (Registry ID, Locations, Study Acronym – if available)	Registry	Population	Date (start/end)	N total*	Study design: Intervention	Intermediate Outcomes	Clinical Outcomes
In Not In report							
CTRI/2012/08/002856, India	ICTRP (Clinical Trial Registry of India)	Healthy/obese	2012-?	60	RCT: EPA 180 mg + DHA 120 mg capsules vs. EPA 180 mg + DHA 120 mg capsules capsules + probiotic capsules vs. probiotic capsules vs. placebo	BP/Lipids	Cardiac event/arrhythmia
NCT00232219, Australia	CT.gov	CVD, existing	2003-2013	200	RCT: Fish oil capsules (1.8g/d of EPA+DHA)		Arrhythmia event
NCT02183285, no location listed	CT.gov	Healthy	2003-2004	203	RCT: Multivitamin, Multimineral + Omega-3 Fatty Acids vs Multivitamin, Multimineral without Omega-3 Fatty Acids vs placebo	BP/Lipids	AEs
NCT01350973, no location listed	CT.gov	Dyslipidemia	2009-2010	611	RCT: Omacor 2 g, capsules, orally, once daily for up to 12 weeks vs. Omacor 2 g, capsules, orally, twice daily for up to 12	BP/Lipids	AEs

					weeks vs. EPA-E, 0.6 g, orally, three-times daily for up to 12 weeks.		
NCT01350999, no location listed	CT.gov	Dyslipidemia	2009-2011	503	RCT: Omacor 2 g, capsules, orally, once daily for up to 52 weeks vs. Omacor 2 g, capsules, orally, twice daily for up to 52 weeks vs. EPA-E, 0.6 g, orally, three-times daily for up to 52 weeks.	BP/Lipids, HTN	
NCT01048502, US	CT.gov	CVD, existing	2010-2011	100	RCT: Tricor 145 mg/day vs. Lovaza 900 mg/day vs. Lovaza 3600 mg/day vs placebo	BP/Lipids	
NCT02239198, US	CT.gov	Healthy	2007-2008	150	RCT: Complete nutrition bar with omega-3 fatty acids vs. Nutrition bar without omega-3 fatty acids vs. Nutrition bar without added minerals and vitamins	BP/Lipids	
NCT00135226, UK	CT.gov	DM	2005-2016	15480	RCT: Aspirin 100 mg/day + Omega-3-Ethyl Esters 1g/day vs. Aspirin 100 mg/day + Placebo vs. Placebo + Omega-3-Ethyl Esters 1g/day vs. Placebo		Cardiac events, stroke/TIA
NCT01810003, Canada	CT.gov	CVD, existing	2013-2016	170	RCT: DHA 3g/day (10 wks) vs. EPA 3g/day (10 wks) vs. placebo	BP/Lipids	
NCT02210767, US	CT.gov	Healthy	2014-2016	50	RCT: 2 oz walnuts/day (ALA) vs. fatty acids not from walnuts vs. low ALA diet	BP/Lipids	
NCT02285166, Japan	CT.gov	Dyslipidemia	2014-2019	14000	RCT: Lotriga 2-4g/day vs. standard antihyperlipidemic therapy	BP/Lipids, HTN	Cardiac events, stroke/TIA, arrhythmia, PDV, death
NCT01841944, Norway	CT.gov	CVD, existing	2012-2019	1400	RCT: Pikasol (1.8 g EPA+DHA)/day vs. placebo		Cardiac events, stroke/TIA, arrhythmia, death
NCT01320228, Denmark	CT.gov	Healthy	2011-2012	69	RCT: Alli (60 mg t.i.d) + 5 g flaxseed fibers and 1200 mg Ca from Capolac vs. Alli (60 mg t.i.d) + 5 g flaxseed fibers vs. Alli (60 mg t.i.d) + 1200 mg Ca from Capolac vs. Alli (60 mg t.i.d) + placebo	BP/Lipids	
NCT02294526, no location listed	CT.gov	DM	2012-2013	35	RCT: Sardine (100g per day, 5 days a week) diet vs no sardine diet	BP/Lipids	
NCT01492361, US, Australia, Canada, India, Netherlands, New Zealand, Poland, Romania, Russian Federation, South Africa, Ukraine	CT.gov	CVD, existing	2011-2017	8000	RCT: VASCEPA (icosapent ethyl) vs. placebo	BP/Lipids	Cardiac events, stroke/TIA, arrhythmia, death
NCT02104817, US, Argentina, Australia, Brazil, Canada, Czech Republic, Denmark, Estonia, Hungary, Italy, Japan, Korea,	CT.gov	Other (mixed) CVD high risk	2014-2019	13000	RCT: Epanova + statin daily vs. placebo + statin daily		Cardiac events, stroke/TIA, arrhythmia, death

Latvia, Lithuania, Mexico, Netherlands, New Zealand, Poland, Romania, Russian Federation, South Africa, Taiwan, Ukraine, United Kingdom							
NCT02243969, Netherlands	CT.gov	Mixed	2014-2015	72	RCT: Flaxseed oil (ALA) 10g/day (12 wks) vs. placebo	BP/Lipids	
NCT01169259, US	CT.gov	Mixed	2010-2017	25874	RCT: Vitamin D3 2000 IU/day + Omacor, 1 capsule/day vs. Vitamin D3 2000 IU/day + placebo vs. placebo + Omacor, 1 capsule/day vs. placebo		Cardiac events
NCT02271230, US	CT.gov	CVD, existing	2014-2020	25875	RCT: Vitamin D 2000 IU/day vs. EPA/DHA 1g/day vs. placebo		Cardiac events
NCT01785004, US	CT.gov	Healthy	2012-2015	600	RCT: Vitamin D3 2000 IU/day + Omacor, 1 capsule/day vs. Vitamin D3 2000 IU/day + placebo vs. placebo + Omacor, 1 capsule/day vs. placebo	BP/Lipids	
NCT01653678, US	CT.gov	HTN	2011-2017	25875	RCT: Vitamin D3 2000 IU/day + Omacor, 1 capsule/day vs. Vitamin D3 2000 IU/day + placebo vs. placebo + Omacor, 1 capsule/day vs. placebo	BP/Lipids, HTN	
NCT02178410, US	CT.gov	CVD, existing	2012-2017	25875	RCT: Vitamin D3 2000 IU/day + Omacor, 1 capsule/day vs. Vitamin D3 2000 IU/day + placebo vs. placebo + Omacor, 1 capsule/day vs. placebo		Cardiac events, arrhythmia, death
NCT02155816, US	CT.gov	Healthy	2014-2014	68	RCT: Omega 3 (1000mg/day) for 8 wks vs. Omega 7 (210mg/day) and Omega 3 (1000mg/day) for 8 wks vs. placebo	BP/Lipids	
NCT00967733, no location listed	CT.gov	CVD, existing	2009-2009	130	RCT: Flaxseed oil (ALA) 2-4 g/day + olive oil cooking vs. Olive oil pill 1g/day + olive oil cooking vs. Flaxseed oil (ALA) 2-4 g/day + sunflower oil cooking vs. Olive oil pill 1g/day + sunflower oil cooking	BP/Lipids	
NCT00422266, India	CT.gov	Dyslipidemia	2006-2007	178	RCT: Not explicitly described	BP/Lipids	
NCT01224249, Denmark	CT.gov	Healthy	2010-2011	102	Obs: Fish and shellfish 1000 g/week for six months vs. no comparator	BP/Lipids	
ACTRN12607000278437, Australia	ICTRP	Healthy	2007-?	400	RCT: DHA 430 mg/EPA 150 mg QID vs. olive oil	BP	
DRKS00006742, Germany	ICTRP	HTN	2015-2015	100	RCT: Milk with DHA 250 mg/day (4 weeks) vs. Milk with beta-glucans 3g/day (4 weeks) vs. Milk with anthocyanins 320mg/day (4 weeks) vs. Milk with DHA 250mg + beta-glucans 3g/day (4 weeks) vs. Milk with DHA 250mg + anthocyanins 320mg/day (4 weeks)	BP/Lipids	

JPRN-UMIN000011934, Japan	ICTRP	CVD, existing	2010-2013	80	RCT: EPA 1800mg + statin therapy/day (2 yrs) vs. Ezetimibe 10 mg + statin therapy/day (2yrs) vs. statin therapy (2yrs)		Cardiac events, PVD, death
JPRN-UMIN000007956, Japan	ICTRP	CVD, existing	2012-?	80	RCT: EPA 1800 mg/day + statin therapy vs. statin therapy	BP/Lipids	
ISRCTN16448451, UK	ICTRP	CVD, existing	1998-2002	nd	RCT: fish oil + normal diet vs. normal diet		Arrhythmia
ISRCTN24439243, Spain	ICTRP	Other (mixed) CVD high risk	2009-2011	250	RCT: increased fish consumption + normal diet vs. normal diet	BP/Lipids	
RBR-5668v4, Brazil	ICTRP	Other (mixed) CVD high risk	2011-2013	87	RCT: Omega-3 900my/day + dietary guidance vs. dietary guidance	BP/Lipids	
IRCT2013080514273N1, no location listed	ICTRP	CVD, existing	2013-2013	60	RCT:	BP/Lipids	
JPRN-UMIN000006416, Japan	ICTRP	CVD, existing	2009-?	100	RCT: Aspirin100 mg/day vs. EPA ethyl ester 1800mg/day + Aspirin100mg/day	BP/Lipids	
JPRN-UMIN000007266, Japan	ICTRP	CVD, existing	2012-?	200	RCT: EPA vs. antiplatelet + statins		Cardiac events, stroke/TIA, PVD, death
JPRN-UMIN000012069, Japan	ICTRP	CVD, existing	2013-2019	3200	RCT: EPA 1800 mg/day + statin therapy vs. statin therapy		Cardiac events, stroke/TIA, PVD, death
JPRN-UMIN000016723, Japan	ICTRP	CVD, existing	2010-?	200	RCT: pitavastatin 2 mg/day + EPA 1800 mg/day vs. pitavastatin 2 mg/day		Cardiac events, stroke/TIA
JPRN-UMIN000018056, Japan	ICTRP	Dyslipidemia	2015-?	40	RCT: DHA+EPA 2g/day (4 wks) at 4 wks, triglycerides >150 mg/dl, dose increased to 4mg/day (8 weeks); triglycerides <150mg/dl, does maintained at 2mg/day vs. observation	BP/Lipids	Cardiac events
JPRN-UMIN000004024, Japan	ICTRP	Dyslipidemia	2010-?	100	RCT: EPA (no other details reported)	BP/Lipids	
JPRN-UMIN000012852, Japan	ICTRP	CVD, existing	2014-?	100	RCT: EPA 1800 mg/day + statin therapy vs. statin therapy		Cardiac events, stroke/TIA, PVD, death
EUCTR2006-006863-22-GB, UK	ICTRP	CVD, existing	2007-?	100	RCT: Cardiozen 500 mg vs. placebo (no other information)		Arrhythmia
EUCTR2005-001354-25-GB, UK	ICTRP	CVD, existing	2005-?	150	RCT: Omacor vs. placebo (no other information)		Arrhythmia
EUCTR2005-004969-41-IT, Italy	ICTRP	CVD, existing	2006-?	266	RCT: SEACOR 1000MG vs. placebo (no other information)		Arrhythmia
NCT02103517, China	CT.gov	Healthy	2014-2015	400	RCT: Omega-3 FA 4gm/day (3 mos) vs. placebo	BP/Lipids	
JPRN-UMIN000003947, Japan	ICTRP	CVD, existing	2010-?	200	RCT: EPA 1800 mg/day + statin therapy vs. statin therapy		Cardiac events, PVD, Death
JPRN-UMIN000012825, Japan	ICTRP	CVD, existing	2014-2019	180	RCT: Statin vs. Statin + EPA vs. Statin + EPA + DHA	BP/Lipids	

NCT01723345, Iran	CT.gov	CVD, existing	2012-2013	90	RCT: EPA 400 mg + DHA 200 mg 12 h prior to PCI vs standard treatment		Cardiac events

Table E-2. Design Details Comparative Studies

Author, year, PMID, country, trial name	Study Design, study start date	Funding source/Conflict of interest	Duration of Intervention/ duration of washout period	Eligibility Criteria	Study Population	Registration (prospective/ retrospective)*
Baxheinrich, 2012, 22894911, Germany	Trial: Randomized Parallel, 2010 (approx.)	Industry funded/No conflict of interest (explicitly stated)	6 months	To be enrolled in the study, subjects had to meet the diagnosis criteria of the metabolic syndrome according to the definition of the International Diabetes Federation (Table 1). Exclusion criteria were CVD, severe illnesses such as renal failure or liver disease, food allergy or intolerance, pregnancy or lactation, smoking, alcohol abuse and insulin therapy or severe diabetic complications in case of diagnosed type 2 diabetes mellitus.	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease): Diabetes and/or metabolic syndrome*	

Author, year, PMID, country, trial name	Study Design, study start date	Funding source/Conflict of interest	Duration of Intervention/ duration of washout period	Eligibility Criteria	Study Population	Registration (prospective/ retrospective)*
DRKS00006232 (Baxheinrich, 2012, 22894911)	Trial: Randomized Parallel, 2008	Industry funded/ Conflict of interest stated	6 months	Inclusion Criteria: 18-70 years old, male and female. Participants who had the following traits of metabolic syndrome were included: central obesity (waist circumference ≥94 cm for men and ≥80 cm for women) plus two of the following criteria (i) fasting serum concentrations of triacylglycerols ≥1.7 mmol/L, (ii) reduced serum HDL cholesterol (<1.03 mmol/L in men; <1.29 mmol/L in women), (iii) elevated blood pressure (systolic ≥130 mmHg; diastolic ≥85 mmHg), (iv) fasting plasma glucose ≥6.5 mmol/L Exclusion Criteria: smoking; insulin-dependent diabetes mellitus; liver, gastrointestinal, or inflammatory diseases; a history of cardiovascular events; use of anti-obesity medications or antiinflammatory drugs; cancer; pregnancy or breast-feeding; alcohol abuse	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease): elevated blood pressure (systolic ≥130 mmHg; diastolic ≥85 mmHg), triacylglycerols ≥1.7 mmol/L; reduced serum HDL cholesterol (<1.03 mmol/L in men; <1.29 mmol/L in women),	Retrospective

Author, year, PMID, country, trial name	Study Design, study start date	Funding source/Conflict of interest	Duration of Intervention/ duration of washout period	Eligibility Criteria	Study Population	Registration (prospective/ retrospective)*
Bosch, 2012, 22686415, Canada, ORIGIN	Trial: Randomized Factorial Design, 2003	Industry funded	2 years	At least 50 years old; a diagnosis of diabetes with receipt of no more than one oral glucose-lowering drug, impaired glucose tolerance (plasma glucose level at 2 hours, =7.8 mM [140 mg per deciliter] and <11.1 mM [200 mg per deciliter] after a 75-g oral glucose load), or impaired fasting glucose (range, =6.1 mM [110 mg per deciliter] to <7.0 mM [126 mg per deciliter]); a history of myocardial infarction, stroke, or revascularization; angina with documented ischemia; a ratio of urinary albumin to creatinine of more than 30 mg per gram; left ventricular hypertrophy; 50% or more stenosis of a coronary, carotid, or lower-limb artery on angiography; or an ankle brachial index of less than 0.9. Participants were excluded if they were unwilling to discontinue use of a nonstudy preparation of n 3 fatty acids, had a locally measured glycated hemoglobin level of 9% or more, had undergone coronary-artery bypass grafting within the previous 4 years with no intervening cardiovascular event, had severe heart failure, or had a cancer that might affect survival.	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease): Diabetes and/or metabolic syndrome*; Hypertension; Cardiac disease; Cerebrovascular disease; Peripheral vascular disease; Arrhythmia	

Author, year, PMID, country, trial name	Study Design, study start date	Funding source/Conflict of interest	Duration of Intervention/ duration of washout period	Eligibility Criteria	Study Population	Registration (prospective/ retrospective)*
NCT00069784 (Bosch, 2012, 22686415)	Trial: Randomized Factorial Design, 2003	Industry funded/Conflict of interest stated (principal Investigators are NOT employed by the organization sponsoring the study.	6.2 years	Ages Eligible for Study: 50 Years and older. Genders Eligible for Study: Both. Inclusion criteria: Individuals with IFG and/or IGT, or early diabetes, as defined below. Glucose tolerance status was determined by a 75 g oral glucose tolerance test (OGTT) that was performed fasting (ie, no consumption of food or beverage other than water for at least 8 hours) at the time of screening for all candidates who were not known to have diabetes. The qualifying OGTT could be obtained up to 4 weeks prior to screening provided that anti-diabetic therapy (if any) remained unchanged between the qualifying OGTT and the screening visit. Two plasma glucose values were drawn during the OGTT - a fasting value (FPG) and a value drawn two hours after the 75 g oral glucose load was administered (postprandial plasma glucose [PPG]). Impaired glucose tolerance (IGT), defined as a PPG value ≥140 and <200 mg/dL (ie, ≥7.8 and <11.1 mmol/L), with a FPG <126 mg/dL (7.0 mmol/L). OR - Impaired fasting glucose (IFG), defined as an FPG ≥110 and <126 mg/dL (≥6.1 and <7 mmol/L), without diabetes mellitus (PPG must be <200 mg/dL [11.1 mmol/L]). OR Early type 2 diabetes, defined as a FPG ≥126 mg/dL (7.0 mmol/L) or a PPG of ≥200 mg/dL (11.1 mmol/L), or a previous diagnosis of diabetes, and either: on no pharmacological treatment (while ambulatory) for at least 10 weeks prior to screening, with screening glycated hemoglobin <150% of the upper limit of normal (ULN) for the laboratory (eg, <9% if the ULN is 6%) or taking one oral antidiabetic drug (OAD) from among sulfonylureas	Primary Prevention, Increased CVD Risk: Diabetes and/or metabolic syndrome, Hypertension; Cardiac disease; Cerebrovascular disease; Peripheral vascular disease; Arrhythmia	Retrospective

Author, year, PMID, country, trial name	Study Design, study start date	Funding source/Conflict of interest	Duration of Intervention/ duration of washout period	Eligibility Criteria	Study Population	Registration (prospective/ retrospective)*
Brinton, 2013, 23835245, US, ANCHOR	Trial: Randomized Parallel	Industry funded	12 weeks	>18 years of age at high risk for CVD (patients with clinical coronary heart disease [CHD] or CHD risk equivalents [10-year risk 20%]) as defined by the National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III) guidelines. On stable statin therapy (atorvastatin, rosuvastatin, or simvastatin with or without ezetimibe) for 4 weeks at doses expected to produce "optimal" LDLC levels for high-risk patients (40 and <100 mg/dL). Patients who had A1c >9.5% or were being treated with antidiabetes medication that had not been stable for 4 weeks at screening were excluded from the ANCHOR study.	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)	

Author, year, PMID, country, trial name	Study Design, study start date	Funding source/Conflict of interest	Duration of Intervention/ duration of washout period	Eligibility Criteria	Study Population	Registration (prospective/ retrospective)*
NCT01047501 (Brinton, 2013, 23835245)	Trial: Randomized Parallel, 2009	Industry funded/No Data regarding conflict of interest	12 weeks	Inclusion Criteria: Men and women, ages >18; Fasting triglyceride ≥200 mg/dL and <500 mg/dL; LDL-C (low density lipoprotein - cholesterol) ≥40 mg/dL and <100mg/dL; High risk for Coronary heart disease; On stable dose of statin (atorvastatin, rosuvastatin or simvastatin); Provide written informed consent and authorization for protected health information disclosure. Exclusion Criteria: Women who are pregnant or lactating, or planning to become pregnant; Use of non-statin lipid-altering drugs which cannot be stopped including fibrates, niacin, fish oil and other products containing omega-3 fatty acids or other dietary supplements with potential lipid-altering effects; History of bariatric surgery or currently on weight loss drugs; Uncontrolled hypertension (BP > 160/100); HIV infection or on treatment with HIV-protease inhibitors, cyclophosphamide,or isotretinoin; Consumption of more than 2 alcoholic beverages per day; History of cancers (except if been disease free for >5 years OR history was basal or squamous cell skin cancer); Participation in another clinical trial involving an investigational agent in the last 30 days; Other parameters will be assessed at the study center to ensure eligibility for this study.	Primary Prevention, Increased CVD Risk:	Retrospective

Author, year, PMID, country, trial name	Study Design, study start date	Funding source/Conflict of interest	Duration of Intervention/ duration of washout period	Eligibility Criteria	Study Population	Registration (prospective/ retrospective)*
Brouwer, 2006, 16772624, Germany, Netherlands, Sweden, UK, Poland, Czech Republic, Belgium, Austria, SOFA trial	Trial: Randomized Parallel, 2001	No industry relationship reported (funding or affiliations reported)/No Data regarding conflict of interest	12 months	Men and women >=18 years old, experienced at least 1 true, confirmed, spontaneous VT or VF in the preceding year, and either had and ICD or were about to receive one. Exclusion: receipt of an ICD for prophylactic reasons; ICD as a "bridge" to heart transplantation; refractory supraventricular arrhythmia with rapid ventricular rates despite antiarrhythmic therapy; a projected life span of <1 year; use of supplemental omega-3 PUFA during the past 3 months or consumption >8g of omega-3 PUFAs from fish or seafood per month (267 mg/d) as judged by a seafood FFQ; pregnant women; women of childbearing age who did not use adequate contraception, and patients with a known history of recent drug or alcohol abuse.. excluded patients with high baseline omega-3 intake from supplements and/or foods	Secondary Prevention (history of CVD event): Arrhythmia (at least 1 true, confirmed, spontaneous VT or VF in the preceding year, and either had and ICD or were about to receive one.)	

Author, year, PMID, country, trial name	Study Design, study start date	Funding source/Conflict of interest	Duration of Intervention/ duration of washout period	Eligibility Criteria	Study Population	Registration (prospective/ retrospective)*
NCT00110838 (Brouwer, 2006, 16772624)	Trial: Randomized Parallel, 2001	No industry relationship reported/No Data regarding conflict of interest	12 months	Inclusion Criteria: ICD is capable of recording ECG strips for at least 10 of its (attempted) therapeutic interventions; 18 years or older; written informed consent. Exclusion Criteria: Primary prophylactic indication; ICD implantation as a 'bridge' to heart transplantation; Refractory supraventricular arrhythmias with rapid ventricular rates despite antiarrhythmic therapy; a projected lifespan of less than 1 year; participation in another trial (during or within 30 days before SOFA); use of any supplemental n-3 fatty acid during the last 3 months; intake of more than 8g of n-3 fatty acids from fish per month as judged by a fish frequency questionnaire; pregnant women and women of childbearing potential who do not use adequate contraception; patients known to have a history of recent drug or alcohol abuse	Primary Prevention, Increased CVD Risk: Arrhythmia	Prospective
Damsgaard, 2008, 18492834, Denmark	Trial: Randomized Factorial Design, 2005	Industry only donated materials (eg, supplements)/No conflict of interest (explicitly stated)	8 weeks	Healthy males, aged 18-40 y, with no chronic diseases, no regular medication, and no strong allergies who were smoking <5 cigarettes/week, exercising strenuously <7 h/wk, eating homemade meals >5 d/wk, and consumed butter/margarine/or oil daily.	Primary Prevention, Healthy	

Author, year, PMID, country, trial name	Study Design, study start date	Funding source/Conflict of interest	Duration of Intervention/ duration of washout period	Eligibility Criteria	Study Population	Registration (prospective/ retrospective)*
NCT00266292 (Damsgaard, 2008, 18492834)	Trial: Randomized Factorial Design, 2005	No industry relationship reported/No Data regarding conflict of interest	2 months	Ages Eligible for Study: 18 Years to 40 Years ;Genders Eligible for Study: Male; Accepts Healthy Volunteers: Yes; Healthy (no chronic diseases and no regular medications); BMI >18.5 and <27.5 kg/m2; Daily use of fats and home cooking >5 d/wk; Heavy exercise <7 h/wk; Not daily smokers (<5 cigarets/wk)	Primary Prevention, Healthy	Retrospective
Galan, 2010, 21115589, France, SU.FOL.OM3	Trial: Randomized Parallel, 2003	Industry funded	Median 4.7 years (mean 4.2, SD 1.0)	History of CVD (acute coronary event, including ACS, or cerebral ischemic event, excluding TIA, within 12 mo), 45-80 y. Exclude disease or treatment that might interfere with metabolism of homocysteine or n-3 FA (eg, methotrexate), SCr >200 mcmol/L, CrCl <40 ml/min.	Secondary Prevention (history of CVD event): Cardiac disease (Coronary event w/in 12 mo, including MI, ACS or suspected ACS); Cerebrovascular disease (CVA (not TIA))	

Author, year, PMID, country, trial name	Study Design, study start date	Funding source/Conflict of interest	Duration of Intervention/ duration of washout period	Eligibility Criteria	Study Population	Registration (prospective/ retrospective)*
ISRCTN41926726 (Galan, 2010, 21115589)	Trial: Randomized Factorial Design 2003	Industry funded/ Conflict of interest stated	nd	Participant inclusion criteria 1. Participants should have experienced a coronary or cerebral event during 1 to 12 months before baseline. A coronary or cerebral event is defined as: a. Myocardial infarction (validated and documented by a combination of clinical, enzymatic, or electrocardiogram [ECG] parameters) b. Acute coronary syndrome without necrosis (validated and documented by a combination of clinical, enzymatic or ECG parameters) c. A cerebral vascular ischemic accident (defined by criteria validated in epidemiological studies) 2. The participants should be 45-80 years at baseline Exclusion criteria 1. Age <45 years or >80 years 2. Cardiovascular pathology not well defined 3. Patients that are incapable of understanding the study protocol 4. Patients with a pathology that might interfere with homocysteine or omega-3 fatty acid metabolism, in particular those that use methotrexate for the treatment of a cancer or rheumatoid arthritis and chronic renal failure (plasma level of creatinine >200 μmol/l or creatinine clearance <40 ml/min) 5. Patients with a non-cardiovascular pathology with a suspected survival time less than the 5 years period of the study (solid cancer, evolved dementia, leukemia etc.)	Secondary Prevention (history of CVD event): MI, ACS, stroke within a year	Retrospective

Author, year, PMID, country, trial name	Study Design, study start date	Funding source/Conflict of interest	Duration of Intervention/ duration of washout period	Eligibility Criteria	Study Population	Registration (prospective/ retrospective)*
Holman, 2009, 19002433, UK, AFORRD	Trial: Randomized Factorial Design, 2004	Industry funded	4 months	Patients with type 2 diabetes for at least 3 months, aged 18 years, with no known CVD events, and not thought by their general practitioner to be at high enough CVD risk to require immediate lipid-lowering therapy.	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease): Diabetes and/or metabolic syndrome*	
NCT00141232 and ISRCTN76737502 (Holman, 2009, 19002433)	Trial: Randomized Factorial Design, 2004	Industry funded/No Data regarding conflict of interest	1 year	Aged 18 years or above; have had Type 2 Diabetes for at least 3 months; not known to have had a cardiovascular event; have provided written informed consent; in UK general practice.	Primary Prevention, Increased CVD Risk: Diabetes and/or metabolic syndrome	Retrospective

Author, year, PMID, country, trial name	Study Design, study start date	Funding source/Conflict of interest	Duration of Intervention/ duration of washout period	Eligibility Criteria	Study Population	Registration (prospective/ retrospective)*
Jones, 2014, 24829493, Canada, COMIT	Trial: Randomized Cross-over, 2010	Industry funded/Conflict of interest stated (All authors report having received grants and funding from food companies)	4 weeks/4 weeks	Inclusion: any of the following: triglyceride level (TG) 1.7 mmol/L, high density lipoprotein cholesterol level (HDL) <1 mmol/L (males) or <1.3 mmol/L (females), blood pressure 130 mmHg (systolic) and/or 85 mmHg (diastolic) and glucose level 5.5 mmol/L, waist circumference 94 cm for men and 80 cm for women. Exclusion: thyroid disease (unless controlled by medication), diabetes mellitus, kidney disease, liver disease, current smokers, or those consuming more than two alcoholic drinks per week, or medications known to affect lipid metabolism or endothelial function (including aspirin or other non-steroidal anti-inflammatory drugs), cholestyramine, colestipol, niacin, clofibrate, gemfibrozil, probucol, or 3-hydroxy-3-methyl-glutaryl-CoA (HMG-CoA) reductase inhibitors.. At the beginning of the study, the Adult Treatment Panel III (ATP III) metabolic syndrome criteria for waist circumference (>102 cm for men and >88 cm for women) were followed [28]. As the trial progressed, the International Diabetes Federation (IDF) metabolic syndrome criteria for waist circumference (94 cm for men and 80 cm for women) were adopted to identify individuals in the initial stages of abdominal obesity who might benefit from dietary intervention.	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease): Hypertension (blood pressure 130 mmHg (systolic) and/or 85 mmHg (diastolic)); Dyslipidemia (TG 1.7 mmol/L, HDL <1 mmol/L (males) or <1.3 mmol/L (females)); Obesity/Overweight (waist circumference 94 cm for men and 80 cm for women); Other (glucose level 5.5 mmol/L)	

Author, year, PMID, country, trial name	Study Design, study start date	Funding source/Conflict of interest	Duration of Intervention/ duration of washout period	Eligibility Criteria	Study Population	Registration (prospective/ retrospective)*
NCT01351012 (Jones, 2014, 24829493)	Trial: Randomized Cross-over, 2010	No industry relationship reported/No Data regarding conflict of interest	4 weeks/4 weeks	Inclusion Criteria: Waist circumference ≥94 cm (males) or ≥80 cm (females); age 18-65 years; plus at least one of the following: Triglycerides ≥1.7 mmol/L; High density lipoprotein (HDL) cholesterol <1 mmol/L (males) or <1.3 mmol/L (females); Low density lipoprotein (LDL) cholesterol ≥3.5 mmol/L; Blood pressure ≥130 mmHg (systolic) and/or ≥85 mmHg (diastolic); Glucose ≥5.5 mmol/L. Exclusion Criteria: Thyroid disease; Diabetes mellitus; Kidney disease; Liver disease; Smoking; Heavy drinking; Use of medication known to affect lipid metabolism during the last 3 months(cholestyramine, colestipol, niacin, clofibrate, gemfibrozil, probucol, HMG CoA reductase inhibitors).	Primary Prevention, Increased CVD Risk: Hypertension; Dyslipidemia; Obesity/Overweight	Retrospective

Author, year, PMID, country, trial name	Study Design, study start date	Funding source/Conflict of interest	Duration of Intervention/ duration of washout period	Eligibility Criteria	Study Population	Registration (prospective/ retrospective)*
Kastelein, 2014, 24528690, US, Denmark, Netherlands, India, Hungary, Ukraine, Russia, EVOLVE	Trial: Randomized Parallel, 2011	Industry funded/Conflict of interest stated (The authors acknowledge that they have either received research grant funding from, or are employees of, or have ownership in Omthera Pharmaceuticals, Inc, the manufacturer of the product studied. The relationship of authors Dr Kastelein, Mr Machielse, Mr Kling, and Dr Davidson to Omthera are considered significant according to the definitions used by the Food and Drug Administration. The following authors further disclose that they have other modest relationships with industry that might pose a potential conflict of interest(s): Dr Kastelein (Amarin), Dr Maki (Abbott, Amarin, DSM, GSK, Pharmavite, Trygg Pharma), Dr Susekov (Abbott, Actavis, Amarin, Amgen, AstraZeneca, Gedeon-Richter, Genzyme, KRKA,	12 weeks	Participants included men and women (nonpregnant, nonlactating) >=18 years of age with average serum TG concentrations >=500 mg/dL but <2000 mg/dL at screening (1 and 2 weeks before random assignment) who were either untreated for dyslipidemia or were using a stable (for at least 6 weeks before the first qualifying lipid measurement) dosage of a statin, CAI, or their combination. Subjects were also required to have a body mass index (calculated as weight divided by height squared; kg/m2) >=20 and be willing to maintain their customary activity level, follow the TLC diet with weight maintenance, and restrict their consumption of fish to no more than twice per week throughout the study. Persons with known lipoprotein lipase impairment or deficiency, apolipoprotein (Apo) CII deficiency, or familial dysbetalipoproteinemia were excluded from the study, as were persons with a history of pancreatitis, symptomatic gallstone disease (unless treated with cholecystectomy), uncontrolled diabetes (glycosylated hemoglobin $9%), or cancer in the past 2 years (basal cell carcinoma was not exclusionary). Persons with a recent history (past 6 months) of a cardiovascular event (ie, myocardial infarction, acute coronary syndrome, new onset angina, stroke, transient ischemic attack, or unstable congestive heart failure that required a change in treatment); revascularization procedure; aortic aneurysm; nephrotic syndrome; or pulmonary, hepatic, biliary, gastrointestinal, or immunologic disease were also excluded. Persons with uncontrolled hypothyroidism, thyroid-stimulating hormone >5 mIU/L, or poorly controlled	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease): Dyslipidemia (average serum TG concentrations 500-2000 mg/dL); Obesity/Overweight (body mass index >=20)	

Author, year, PMID, country, trial name	Study Design, study start date	Funding source/Conflict of interest	Duration of Intervention/ duration of washout period	Eligibility Criteria	Study Population	Registration (prospective/ retrospective)*
NCT01242527 (Kastelein, 2014, 24528690)	Trial: Randomized Parallel, 2011	Industry funded/ Conflict of interest stated	12 weeks	Inclusion Criteria: Men or women, >=18 years of age. Very high serum TG values in the range >=500 mg/dL and <2000 mg/dL (>=5.65 mmol/L and <22.60 mmol/L) Exclusion Criteria: Allergy or intolerance to omega-3 fatty acids, omega-3-acid ethyl esters, or fish. Known lipoprotein lipase impairment or deficiency or apolipoprotein C-II deficiency or familial dysbetalipoproteinemia. Unable to discontinue use of omega-3 drugs/supplements. Unable to discontinue use of bile acid sequestrants, fibrates or niacin (other than niacin-containing vitamins <200 mg), or any supplement used to alter lipid metabolism. Women who are pregnant, lactating, or planning to become pregnant. Women of childbearing potential who are not using acceptable contraceptive methods. Use of tamoxifen, estrogens or progestins that has not been stable for >4 weeks prior to Visit 1. Use of oral or injected corticosteroids or anabolic steroids. History of pancreatitis. History of symptomatic gallstone disease, unless treated with cholecystectomy. Uncontrolled diabetes. Uncontrolled hypothyroidism or thyroid stimulating hormone (TSH). History of cancer (other than basal cell carcinoma) in the past 2 years. Cardiovascular event (i.e., myocardial infarction, acute coronary syndrome, new onset angina, stroke, transient ischemic attack, unstable congestive heart failure requiring a change in treatment) or revascularization procedure within six months prior to Visit 1. Use of anticoagulants (e.g. warfarin	Primary Prevention, Increased CVD Risk: Dyslipidemia: serum TG values in the range >=500 mg/dL and <2000 mg/dL (>=5.65 mmol/L and <22.60 mmol/L)	Retrospective

Author, year, PMID, country, trial name	Study Design, study start date	Funding source/Conflict of interest	Duration of Intervention/ duration of washout period	Eligibility Criteria	Study Population	Registration (prospective/ retrospective)*
Kromhout, 2010, 20929341, Netherlands, DART	Trial: Randomized Factorial Design, 2002	Industry only donated materials (eg, supplements)/No conflict of interest (explicitly stated)	40 months	Men and women 60 to 80 years of age, who had had a clinical diagnosed MI up to 10 years before randomization. Exclusion criteria: daily consumption of <10 10 g of margarine, use of n-3 fatty-acid supplements, unintended weight loss of >5 kg in the previous year, and a diagnosis of cancer with an estimated life expectancy of <1 year.	Secondary Prevention (history of CVD event): Cardiac disease (myocardial infarction)	
NCT00127452 (Kromhout, 2010, 20929341) Alpha Omega	Trial: Randomized Parallel, 2002	No industry relationship reported/No Data regarding conflict of interest	40 months	Inclusion criteria: Men and women; Aged 60 through 80 y; Verified clinically diagnosed myocardial infarction up to 10 y before randomization; Written informed consent. Exclusion criteria: Living in a nursing home or other institution; Participation in another scientific study; Habitual margarine intake < 10 g per day; Habitual fish intake > 150 g per day; Habitual alcohol intake > 6 drinks per day; Use of fish oil capsules or other supplements containing omega-3 fatty acids; Presence of cancer with < 1 y of life expectancy; Cognitive impairment, as indicated by the Mini Mental State Examination (score <= 21); Unintended weight loss > 5 kg in the past year; Lack of facilities for cooled margarine storage at home; Inability or unwillingness to comply with study procedures	Secondary Prevention (history of CVD event): Cardiac disease (verified clinically diagnosed myocardial infarction up to 10 y before randomization)	Retrospective

Author, year, PMID, country, trial name	Study Design, study start date	Funding source/Conflict of interest	Duration of Intervention/ duration of washout period	Eligibility Criteria	Study Population	Registration (prospective/ retrospective)*
Kuhnt 2014, 24553695, Germany	Trial: Randomized Parallel, 2011	No conflict of interest (explicitly stated)	8 weeks	Normolipidemic and normal-weight (BMI 18-25) individuals were recruited for 2 age groups: group I, 20-35 y; and group II 49-69 y. Older overweight individuals were recruited for echium oil (EO) intervention only (49-69 y; BMI >25 with markers of metabolic syndrome or BMI >= 30). Patients with markers of metabolic syndrome were mainly enlisted from the diabetes research center. This subgroup - EO III (older overweight individuals who were recruited for echium oil intervention only; 49-69 y; BMI >25 with markers of metabolic syndrome) was not included in this systematic review.	Primary Prevention, Healthy	
NCT01856179 (Kuhnt, 2014, 24553695)	Trial: Randomized Parallel, 2011	No industry relationship reported	56 days	Inclusion Criteria: healthy subjects, 20-70 years. Exclusion Criteria: cholesterol lowering drugs; chronic diseases; pregnancy, lactation; intake of nutritional supplements.	Primary Prevention, Healthy	Retrospective
Leaf, 2005, 16267249, US, FAAT	Trial: Randomized Parallel, 1999	Industry only donated materials (eg, supplements)/No Data regarding conflict of interest	1 year	Subjects were included who had an ICD implanted because of a history of cardiac arrest, sustained ventricular tachycardia (VT), or syncope with inducible, sustained VT or ventricular fibrillation (VF) during electrophysiologic studies. The qualifying ICD implantation was required to have occurred within 12 months before entry into the study or if the patient had experienced at least 1 spontaneous ICD event for VT/VF in the preceding 12 months.. -	Secondary Prevention (history of CVD event): Arrhythmia (ICD implanted)	
NCT00004559 (Leaf, 2005, 16267249)	Trial: Randomized Parallel, 1999	No industry relationship reported/No Data regarding conflict of interest	nd	Ages Eligible for Study: 18 Years to 75 Years; Genders Eligible for Study: Both; Accepts Healthy Volunteers: No	Secondary Prevention (history of CVD event): Cardiac disease, Arrhythmia	Prospective

Author, year, PMID, country, trial name	Study Design, study start date	Funding source/Conflict of interest	Duration of Intervention/ duration of washout period	Eligibility Criteria	Study Population	Registration (prospective/ retrospective)*
Macchia, 2013, 23265344, Italy, Argentina, FORWARD	Trial: Randomized Parallel, 2008	Industry funded/No conflict of interest (explicitly stated)	12 months	Patients with previous persistent AF (>=2 symptomatic episodes of documented AF in the 6 months before randomization, with last episode occurring within 3 to 90 days before randomization (paroxysmal AF); or successful electrical or pharmacological cardioversion for persistent AF performed within 3 to 28 days before randomization.	Secondary Prevention (history of CVD event): Arrhythmia	
NCT00597220 (Macchia, 2013, 23265344)	Trial: Randomized Parallel, 2008	Industry funded/ No Data regarding conflict of interest	12 months	Inclusion Criteria: Persistent atrial fibrillation; Age 21+ Exclusion Criteria: Contraindications or known hypersensitivity to n-3 PUFA; Current treatment with n-3 PUFA for any reason; Heart failure NYHA class IV; Coronary artery bypass surgery or valve replacement within the past 3 months; Planned cardiac procedures; Known sick-sinus syndrome; Diagnosis of Wolff-Parkinson-White; Clinical significant valvular etiologies; Presence of arrhythmia associated with an acute reversible condition; Advanced chronic lung disease; Contraindications for anticoagulation therapy; Pregnancy or lactation; Any non cardiac illness associated with a life expectancy of < 2 years; Treatment with any investigational agent within 3 month before randomization; Any condition that in the opinion of the investigator would jeopardize the evaluation of efficacy or safety or be associated with poor adherence to the protocol	Secondary Prevention (history of CVD event): Arrhythmia	Prospective

Author, year, PMID, country, trial name	Study Design, study start date	Funding source/Conflict of interest	Duration of Intervention/ duration of washout period	Eligibility Criteria	Study Population	Registration (prospective/ retrospective)*
Maki, 2010, 20451686, US, COMBOS	Trial: Randomized Parallel, 2005	Industry funded	8 weeks	Eligible patients were men or women between the ages of 18 and 79 years who had been receiving a stable dose of a statin for the control of LDL-C levels for =>8 weeks before screening and were judged to be in good health on the basis of a medical history, physical examination, electrocardiogram, and laboratory tests, including serum chemistry, hematology, and urinalysis. Major inclusion criteria included a mean fasting TG level >=200 and <500 mg/dL, and a mean LDL-C level below or within 10% of the patient's NCEP ATPIII goal. Major exclusion criteria included poorly controlled diabetes mellitus (glycosylated hemoglobin [HbAlc] >8.0% at screening); history of a cardiovascular event, a revascularization procedure, or an aortic aneurysm or resection within 6 months of screening; history of pancreatitis; sensitivity to statins or omega-3 fatty acids; poorly controlled hypertension (resting blood pressure =>160 mm Hg systolic and/or =>100 mm Hg diastolic at 2 consecutive visits); serum creatinine level =>2.0 mg/dL; serum transaminase (aspartate aminotransferase lAST] or alanine aminotransferase [ALT]) >1.5 times the upper limit of normal (ULN) (45 U/L for ALT, 31 U/L for AST); or creatine kinase (CK) level >2 times the ULN.	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease): Dyslipidemia (mean fasting TG level _>200 and <500 mg/dL, and a mean LDL-C level below or within 10% of the patient's NCEP ATP III goal.)	

Author, year, PMID, country, trial name	Study Design, study start date	Funding source/Conflict of interest	Duration of Intervention/ duration of washout period	Eligibility Criteria	Study Population	Registration (prospective/ retrospective)*
NCT00246701 (Maki, 2010, 20451686)	Trial: Randomized Parallel, 2005	Industry funded/ No Data regarding conflict of interest	8 weeks	Inclusion Criteria: Men and women ages 18-79 years, inclusive; Current therapy with a statin drug; Triglyceride levels between 200 and 499 mg/dL; Normally active and in good health on the basis of medical history, brief physical examination, electrocardiogram, and routine laboratory tests; Provide written informed consent and authorization for protected health information disclosure Exclusion Criteria: Sensitivity to statin drugs or omega-3 fatty acids; Lipoprotein lipase impairment or apo C-2 deficiency or type III hyperlipidemia; Unexplained muscle pain or weakness; History of pancreatitis; Recent history of certain heart, kidney, liver, lung, or gastrointestinal diseases, or cancer (except non-melanoma skin cancer); Poorly controlled diabetes, or receiving insulin therapy; Pregnant or lactating females; Women of childbearing potential who are not using a medically approved method of contraception; Use of certain types of hormones, anticonvulsant drugs, immunologic drugs, antibiotic, antifungal and antiviral drugs, and cardiac drugs; Use of warfarin (Coumadin)	Primary Prevention, Increased CVD Risk: Dyslipidemia	Prospective

Author, year, PMID, country, trial name	Study Design, study start date	Funding source/Conflict of interest	Duration of Intervention/ duration of washout period	Eligibility Criteria	Study Population	Registration (prospective/ retrospective)*
Maki, 2013, 23998969, US, ESPRIT TRIAL	Trial: Randomized Parallel, 2011	Industry funded	6 weeks	Participants included men and non pregnant, nonlactating women 18 years of age with fasting triglyceride (TG) levels 200 mg/dL and <500 mg/dL(after 4 weeks of the statin/diet lead-in) and at high risk for a future cardiovascular event.	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease): Dyslipidemia ((TG) levels 200 mg/dL and <500 mg/dL)	

Author, year, PMID, country, trial name	Study Design, study start date	Funding source/Conflict of interest	Duration of Intervention/ duration of washout period	Eligibility Criteria	Study Population	Registration (prospective/ retrospective)*
NCT01408303 (Maki, 2013, 23998969)	Trial: Randomized Parallel, 2011	Industry funded	6 weeks	Inclusion Criteria: Men or women, ≥18 years of age. Fasting triglyceride (TG) level ≥200 mg/dL and <500 mg/dL. The subject is a high risk for a future cardiovascular event. The subject is treated with a statin and at or near LDL-C goal. Exclusion Criteria: Allergy or intolerance to omega-3 fatty acids and omega-3-acid ethyl esters. Use of fibrates, bile acid sequestrants, or niacin or its analogues (greater than 200 mg/d) during screening. Use of simvastatin 80 mg or Vytorin10/80 mg during screening. Use of any eicosapentaenoic acid (EPA) or docosahexaenoic acid (DHA) products. Use of any supplement for the purpose of lowering plasma cholesterol during screening. Use of weight loss drugs or programs during screening. Use of erythromycin, telithromycin, clarithromycin, cyclosporine, itraconazole, ketoconazole, protease inhibitors, or nefazodone during screening. Use of anticoagulants during screening. Use of oral or injected corticosteroids during screening.Use of tamoxifen, estrogens, progestins, or testosterone, that has not been stable for >4 weeks at Visit 1, or is unstable during screening. Use of >750 mL/d grapefruit juice during screening. Known lipoprotein lipase impairment or deficiency, or apolipoprotein C-II deficiency or familial dysbetalipoproteinemia. History of pancreatitis. Type I diabetes mellitus, use of insulin, or HbA1c >10% at Visit 1. Poorly controlled hypertension Uncontrolled hypothyroidism, or thyroid stimulating hormone (TSH) >1.5xULN at Visit 2. Recent history or current significant nephrotic	Primary Prevention, Increased CVD Risk: Dyslipidemia (Fasting triglyceride (TG) level ≥200 mg/dL and <500 mg/dL.)	Prospective

Author, year, PMID, country, trial name	Study Design, study start date	Funding source/Conflict of interest	Duration of Intervention/ duration of washout period	Eligibility Criteria	Study Population	Registration (prospective/ retrospective)*
Nodari, 2011, 21844082, Italy	Trial: Randomized Parallel, 2006	No industry relationship reported (funding or affiliations reported)	1 year	Eligibility was determined at a screening visit that included medical history, physical examination, 12-lead ECG, chest x-ray, and 2-dimensional Doppler echocardiography, plus complete blood count, routine chemistry, thyroid function tests, and pregnancy test in fertile women.	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease): Arrhythmia	
NCT01198275 (Nodari, 2011, 21844082) ATRIA	Trial: Randomized Parallel, 2006	No industry relationship reported/ No Data regarding conflict of interest	12 months	Inclusion Criteria: persistent Atrial Fibrillation (AF) lasting > one month history of at least one AF relapse after previous electrical or Pharmacological cardioversion Exclusion Criteria: left atrium size > 6 cm severe valvulopathy myocardial infarction during the previous 6 months unstable angina NYHA heart failure class IV or hemodynamic instability cardiac surgery during the previous 3 months significant pulmonary thyroid and hepatic disease contraindications to treatment with amiodarone or RASS inhibitors chronic renal dysfunction QT > 480 msec in the absence of bundle-branch block bradycardia < 50 b/min diagnosis of paroxysmal AF hyperkalemia pregnancy any disease or other medical treatment that, in the opinion of the investigators, could interfere with the study.	Secondary Prevention (history of CVD event): Arrhythmia	Retrospective

Author, year, PMID, country, trial name	Study Design, study start date	Funding source/Conflict of interest	Duration of Intervention/ duration of washout period	Eligibility Criteria	Study Population	Registration (prospective/ retrospective)*
Raitt, 2005, 15956633, US	Trial: Randomized Parallel, 2001	No industry relationship reported (funding or affiliations reported)	718 days (median)	Patients were eligible for entry if they were receiving an implantable cardioverter defibrillator (ICD) for an electrocardiogram-documented episode of sustained ventricular tachycardia (VT) or ventricular fibrillation (VF) that was not the result of acute myocardial infarction or a reversible cause or who had a preexisting ICD and had received ICD therapy for an episode of electrogramdocumented VT/VF within the previous 3 months.	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease): Arrhythmia	
NCT00004558 (Raitt, 2005, 15956633)	Trial: Randomized Parallel, 2000	No data/no data	nd	Survivors of VT and VF with an implantable defibrillator. 18 Years to 75 Years	Secondary Prevention (history of CVD event): Arrhythmia	Retrospective
Ras, 2014, 25122648, Sweden	Trial: Randomized Parallel, 2011	Industry funded/conflict of interest: Ras, Demonty, Zebregs, and Trautwein were employed by Unilever Research and Development at the time of study conduct. Unilever markets food products enriched with plant sterols.	4 weeks	Apparently healthy; aged 25–75 y; fasting TC concentration between 5 and 8 mmol/L; BMI between 18 and 30 kg/m2; systolic blood pressure >=160 mm Hg, diastolic blood pressure >=90 mm Hg and heart rate between 50 and 100 beats/min; no use of medication that could influence the study outcomes; no use of nicotine-containing products; 10-y cardiovascular disease risk >=10 according to the Systematic Coronary Risk Evaluation (SCORE); willing to comply with the study protocol; and having signed the informed and biobank consents	Primary Prevention, Healthy	

Author, year, PMID, country, trial name	Study Design, study start date	Funding source/Conflict of interest	Duration of Intervention/ duration of washout period	Eligibility Criteria	Study Population	Registration (prospective/ retrospective)*
NCT01313988 (Ras, 2015, 25122648)	Trial: Randomized Parallel, 2011	Authors report industry affiliation	4 weeks	Inclusion Criteria: Apparently healthy men and women; Age ≥ 25 and ≤ 75 years old; Body mass index (BMI) ≥ 18 and ≤ 30 kg/m2; Total cholesterol levels at screening ≥ 5.0 and ≤ 8.0 mmol/L; 10-year CVD risk equal or lower than 10% according to "SCORE"; Blood pressure, heart rate, hematological parameters, clinical chemical parameters within normal reference ranges; Informed consent and biobank consent signed; Willing to comply to study protocol during study; Agreeing to be informed about medically relevant personal test-results by a physician; Not smoking; Accessible veins on the forearm; Habitually consuming spreads. Exclusion Criteria: Pregnant or having the wish to become pregnant, or lactating; Use of prescribed medication which may interfere with study measurements; Use of antibiotics in the 3 months before screening or during the study; Use of any medically- or self-prescribed diet with the purpose to reduce weight; Intolerance for gluten or lactose; Reported food allergy; Having bleeding disorders; Recent blood donation; Excessive alcohol consumption; Strenuous exercise; Reported weight change ≥ 10 % of body weight or use of prescribed weight reduction drugs; Recent participation in another nutritional or medical trial; Participation in night shift work.	Primary Prevention, Healthy	Retrospective

Author, year, PMID, country, trial name	Study Design, study start date	Funding source/Conflict of interest	Duration of Intervention/ duration of washout period	Eligibility Criteria	Study Population	Registration (prospective/ retrospective)*
Rauch, 2010, 21060071, Germany, OMEGA	Trial: Randomized Parallel, 2003	Industry funded	1 year	Minimum age of 18 who were admitted to hospital for acute STEMI or non-STEMI and gave written informed consent to participate in the study.	Secondary Prevention (history of CVD event): Cardiac disease (Myocardial infarction)	
NCT00251134 (Rauch, 2010, 21060071)	Trial: Randomized Parallel, 2003	Industry funded/No Data regarding conflict of interest	12 months	Inclusion Criteria: Myocardial infarction 3-14 days before randomisation (STEMI and NSTEMI), Ability to take Ω-3-FAE or olive oil without risk, Informed consent Exclusion Criteria: Premenopausal women who are not surgically sterile, who are pregnant or nursing, who are of child-bearing potential and are not practising acceptable means of birth control (pregnancy testing required before randomisation), Known hypersensitivity to study medication, Dislike of fish oil, Haemorrhagic diathesis, Unwillingness to discontinue other medications containing fish oil, Legal incapacity, History of drug or alcohol abuse within 6 months, Any investigational therapy within one month of signing informed consent form	Secondary Prevention (history of CVD event): Cardiac disease (Myocardial infarction)	Retrospective
Rodriguez-Leyva, 2013, 24126178, Canada, FlaxPAD	Trial: Randomized Parallel, 2008	Industry funded	6 months	Patients must be >40 years old, had PAD (peripheral artery disease) for > 6 months with ankle brachial index <0.9.. exclusion criteria: inability to walk, bowel disease, moderate to severe renal failure, life expectancy <2 years with high baseline cardiac risk, allergies to any ingredient in the study product, patients who plan to undergo surgery during the course of the trial, and no more than 2 fish meals per week	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease): Peripheral vascular disease (nd)	

Author, year, PMID, country, trial name	Study Design, study start date	Funding source/Conflict of interest	Duration of Intervention/ duration of washout period	Eligibility Criteria	Study Population	Registration (prospective/ retrospective)*
NCT00781950 (Rodriguez-Leyva, 2013, 24126178)	Trial: Randomized Parallel, 2008	nd	1 year (originally 2 years)	Inclusion Criteria: Subjects with peripheral arterial disease for more than 6 months. Male or female with claudication secondary to lower extremity atherosclerotic arterial disease. (with limited IC but not incapacitated for walking on the level) confirmed with ankle/brachial pressures< or = to 0.9 in one or both legs) or who have had a previous intervention for peripheral arterial disease.Over 40 years old Able to comply with protocol requirementsAble to provide informed consent Subjects taking anti-platelet therapy medication must be on a stable dose for 3 months prior to as well as during the study.Subjects taking lipid lowering medication must be on a stable dose for 3 months prior to as well as during the study. Exclusion Criteria: Patients with ischemic rest pain in limbs, ulceration, or gangrene. At baseline, any condition that prevents walking on a treadmill. History of major bleeding. Patients with bowel disease (including Crohn's disease, celiac disease, peptic ulcer disease, irritable bowel syndrome and diverticulosis). Patients with an estimated life expectancy less than 2 years and with high baseline cardiac risk (post ischemic or diabetic cardiomyopathy with EF<40%, Canadian Cardiovascular Society Class 3 or 4 angina or need for coronary revascularization procedures). Moderate to severe renal failure. Subjects that are on supplements other that those prescribed by their clinician for the entire duration of the study. Fish limitations (no more than 2 fish meals per week) Gluten allergy Subjects with allergies to any ingredient in the study product or placebo. Patients	Secondary Prevention (history of CVD event): peripheral arterial disease for more than 6 months	Prospective

Author, year, PMID, country, trial name	Study Design, study start date	Funding source/Conflict of interest	Duration of Intervention/ duration of washout period	Eligibility Criteria	Study Population	Registration (prospective/ retrospective)*
Roncaglioni, 2013, 23656645, Italy	Trial: Randomized Parallel, 2004	No Data on funding or affiliations/No Data regarding conflict of interest	median 5 years	Participants with at least one of the following: multiple cardiovascular risk factors, clinical evidence of atherosclerotic vascular disease, or any other condition putting the patient at high cardiovascular risk in opinion of patient's general practitioner. multiple cardiovascular risk factors defined as at least four of the following(or for diabetic patients, one of the following): age >65 years, male sex, hypertension, hypercholesterolemia, current smoker, obesity, family history cardiovascular disease	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease)	
NCT00317707 (Roncaglioni, 2013, 23656645)	Trial: Randomized Parallel, 2004	No Data on funding or affiliations/No Data regarding conflict of interest	5 years	Inclusion Criteria: Multiple risk factors: diabetes, age => 65 years, male sex, hypertension, hypercholesterolemia, smoking, obesity, family history of premature cardiovascular disease; Previous manifestations of atherosclerotic disease ischemic stoke, transient ischemic attack [TIA], peripheral artery disease, previous arterial revascularisation procedures, angina pectoris) Exclusion Criteria: Contraindications (known allergies to n-3 PUFA) or indications (previous myocardial infarction) for the treatment with n-3 PUFA; Serious comorbidity with an unfavourable prognosis over the short term; Expected non compliance over a long period of time; Pregnancy	Primary Prevention, Increased CVD Risk: diabetes, hypertension, dyslipidemia, obesity	Retrospective

Author, year, PMID, country, trial name	Study Design, study start date	Funding source/Conflict of interest	Duration of Intervention/ duration of washout period	Eligibility Criteria	Study Population	Registration (prospective/ retrospective)*
Sanders, 2011, 21865334, UK, MARINA trial	Trial: Randomized Parallel, 2008	Industry only donated materials (eg, supplements)/No conflict of interest (explicitly stated)	12 months	Nonsmokers (confirmed by cotinine testing) men and women aged 45 70 y. Exclusions: a medical history of CVD; overall risk of cardiovascular disease >20% over the next 10 y; cancer (excluding basal cell carcinoma) in the previous 5 y; type 1 DM; uncontrolled type 2 DM; chronic renal, liver, or inflammatory bowel disease; history of substance abuse or alcoholism; pregnancy; weight change of >3 kg in preceding 2 mo; and BMI <20 and >35.	Primary Prevention, Healthy	

Author, year, PMID, country, trial name	Study Design, study start date	Funding source/Conflict of interest	Duration of Intervention/ duration of washout period	Eligibility Criteria	Study Population	Registration (prospective/ retrospective)*
ISRCTN66664610 (Sanders, 2011, 21865334)	Trial: Randomized Parallel, 2008	No industry relationship reported/No Data regarding conflict of interest	1 year	Men and women, aged 45 - 70 years Participant exclusion criteria: 1. A reported history of angina, myocardial infarction or stroke 2. Clinical history of cancer (excluding basal cell carcinoma) in the past five years 3. Uncontrolled type 2 diabetes mellitus (fasting plasma glucose greater than 7 mmol/L) 4. Type 1 diabetes mellitus 5. Chronic renal, liver or inflammatory bowel disease 6. Current cigarette smoker 7. History of substance abuse or alcoholism (previous weekly alcohol intake greater than 60 units/men or 50 units/women) 8. Current self-reported weekly alcohol intake not exceeding 21 units for women and 28 for men 9. Currently pregnant, planning pregnancy or having had a baby in the last 12 months (there are no hazards from the EPA or DHA with regard to pregnancy outcome) 10. Allergy or intolerance to any component of study capsules 11. Unwilling to follow the protocol and/or give informed consent 12. Unwilling to refrain from use of dietary supplements including other sources of fish oil (e.g. cod liver oil) 13. Unwilling to restrict consumption of oily fish 14. Weight change of greater than 3 kg in preceding 2 months 15. Body mass index less than 20 and greater than 35 kg/m^2 16. Subjects with an overall risk of cardiovascular disease over the next ten years of greater than 20% who have untreated high blood pressure or raised cholesterol (subjects who are on stable medication for blood pressure or serum cholesterol [statins] will be included)	Primary Prevention, Healthy	Retrospective

Author, year, PMID, country, trial name	Study Design, study start date	Funding source/Conflict of interest	Duration of Intervention/ duration of washout period	Eligibility Criteria	Study Population	Registration (prospective/ retrospective)*
Tavazzi, 2008, 18757090, Italy, GISSI-HF	Trial: Randomized Parallel, 2002	Industry funded	3.9 years	Eligible patients were men and women aged 18 years or older, with clinical evidence of heart failure of any cause that was classified according to the European Society of Cardiology (ESC) guidelines as New York Heart Association (NYHA) class II IV, provided that they had had their LVEF measured within 3 months before enrolment. When LVEF was greater than 40%, the patient had to have been admitted at least once to hospital for heart failure in the preceding year to meet the inclusion criteria. Major exclusion criteria included specific indication or contraindication to n-3 PUFA; known hypersensitivity to study treatments; presence of any non-cardiac comorbidity (eg, cancer) that was unlikely to be compatible with a sufficiently long follow-up; treatment with any investigational agent within 1 month before randomisation; acute coronary syndrome or revascularisation procedure within the preceding 1 month; planned cardiac surgery, expected to be done within 3 months after randomisation; significant liver disease; and pregnant or lactating women or women of childbearing potential who were not adequately protected against becoming pregnant..	Secondary Prevention (history of CVD event): Cardiac disease (symptomatic heart failure of any cause and with any level of left ventricular ejection fraction (LVEF).)	

Author, year, PMID, country, trial name	Study Design, study start date	Funding source/Conflict of interest	Duration of Intervention/ duration of washout period	Eligibility Criteria	Study Population	Registration (prospective/ retrospective)*
NCT00336336 (Tavazzi, 2008, 18757090)	Trial: Randomized Parallel, 2002	No industry relationship reported/No Data regarding conflict of interest	Time Frame: from enrollment to 1252 deaths in R2 arm	Clinical evidence of heart failure according to the European Society of Cardiology guidelines (New York Heart Association class II-IV) (32); Any left ventricular Ejection Fraction (EF) measured within 3 months from enrolment (if EF% >40%, at least 1 hospital admission for Congestive Heart Failure(CHF) in the previous year); 18 Years and older; Any etiology; Informed consent (obtained before any study specific procedure). Exclusion Criteria: COMMON EXCLUSION CRITERIA (R1=n-3 PUFA vs placebo and R2=rosuvastatin vs placebo): Acute Myocardial Infarction, unstable angina or revascularization procedure within 1 month; planned cardiac surgery, expected to be performed within 3 months; congenital or primary valvular etiology; known hypersensitivity to study treatments; significant liver disease; pregnant or lactating women or women of childbearing potential who are not protected from pregnancy by an accepted method of contraception; any condition that in the opinion of the investigator would jeopardize the evaluation of efficacy or safety or be associated with poor adherence to the protocol; presence of any non-cardiac disease (e.g. cancer) that is likely to significantly shorten life expectancy; treatment with any investigational agent within 1 month before randomization; patients already on treatment with n-3 PUFA or statin for whom the prescription is confirmed. EXCLUSION CRITERIA FOR R2 (statin hypothesis): current serum creatinine level >2.5 mg/dL; current ALT, AST level >1.5 times the upper normal limit; current CPK upper normal limits.	Secondary Prevention (history of CVD event): Cardiac disease	Retrospective

Author, year, PMID, country, trial name	Study Design, study start date	Funding source/Conflict of interest	Duration of Intervention/ duration of washout period	Eligibility Criteria	Study Population	Registration (prospective/ retrospective)*
Vazquez, 2014, 24462043, Spain	Trial: Randomized Cross-over, 2011	Industry funded/No conflict of interest (explicitly stated)	8 weeks/0 weeks	Exclusion criteria were the following: patients taking n-3 LCFA supplements, fish allergy and positive antibodies to Anisakis spp., presence of a body mass index (BMI) 40 kg/m2, chronic kidney disease, liver failure, chronic psychopathy, neoplasia or refusal to participate in the study.	Primary Prevention, Healthy	
NCT01758601 (Vazquez, 2014, 24462043) WISH-CARE	Trial: Randomized Cross-over, 2010	Industry/No Data regarding conflict of interest	8 weeks/0 weeks	Inclusion Criteria: We included adult patients (18 Years to 65 Years) with the metabolic syndrome as defined by the Third Report of the National Cholesterol Education Program, Adult Treatment Panel III. Exclusion Criteria: Fish allergy and positive antibodies to Anisakis spp. Morbid obesity with BMI ≥40kg/m2. Chronic renal failure. Chronic psychopathy. Neoplasia. Refusal to participate in the study.	Primary Prevention, Increased CVD Risk: Diabetes and/or metabolic syndrome	Retrospective

Author, year, PMID, country, trial name	Study Design, study start date	Funding source/Conflict of interest	Duration of Intervention/ duration of washout period	Eligibility Criteria	Study Population	Registration (prospective/ retrospective)*
Yokoyama, 2007, 17398308, Japan, JELIS	Trial: Randomized Parallel, 1996	Industry funded/Conflict of interest stated ('M Yokoyama received travel costs from Mochida Pharmaceutical Co Ltd, Tokyo, Japan, to participate in the scientific meeting. Other authors have no conflicts of interest.')	5 years	Inclusion criteria: Total cholesterol concentration of 6 5 mmol/L or greater, which corresponded to a LDL cholesterol of 4 4 mmol/L or greater. Exclusion criteria: acute myocardial infarction within the past 6 months, unstable angina pectoris, a history or complication of serious heart disease (such as severe arrhythmia, heart failure, cardiomyopathy, valvular disease, or congenital disease), cardiovascular reconstruction within the past 6 months, cerebrovascular disorders within the past 6 months, complications of serious hepatic or renal disease, malignant disease, uncontrollable diabetes, hyperlipidaemia due to other disorders, hyperlipidaemia caused by drugs such as steroid hormones, haemorrhage (including haemo philia, capillary fragility, gastrointestinal ulcer, urinary tract haemorrhage, haemoptysis, and vitreous haemorrhage), haemorrhagic diathesis, hypersensitivity to the study drug formulation, patients intention to undergo surgery, and judgment by the physician in charge that a patient was inappropriate for the study.	Primary Prevention, Increased CVD Risk (ie, diabetes, metabolic syndrome*, hypertension, dyslipidemia, or chronic kidney disease): Dyslipidemia (total cholesterol concentration of 6 5 mmol/L or greater, which corresponded to a LDL cholesterol of 4 4 mmol/L or greater)	

Author, year, PMID, country, trial name	Study Design, study start date	Funding source/Conflict of interest	Duration of Intervention/ duration of washout period	Eligibility Criteria	Study Population	Registration (prospective/ retrospective)*
NCT00231738 (Yokoyama, 2007, 17398308)	Trial: Randomized Parallel, 1996	Industry funded /Authors report industry affiliation	nd	Inclusion Criteria: Age 40 Years to 75 Years; Eligible participants had a total cholesterol level of >=250mg/dL(6.5mmol/L) at baseline; Hyperlipidemic patients with serum total cholesterol of 250mg/dL or more. (Measurement of serum total cholesterol); Serum total cholesterol should be measured twice at interval of 2-4weeks. A single measurement is acceptable if the cholesterol is measured by blood collection at fasting under strict compliance with dietary advice after withdrawal of the antihyperlipemic drug; (Wash Out) The wash out period of 4weeks (8 weeks for probucol) is necessary in patients under treatment with antihyperlipemic drug. However, if treatment with the antihyperlipemic drug was started within 6 months of the initiation of the study, the patient can participate in the study without the washout period. Exclusion Criteria: Acute myocardial infarction occurring within last 6 months; Unstable angina pectoris; A history or complication of serious heart disease(severe arrhythmia, heart failure, cardiac myopathy, valvular disease, congenital disease, etc.); Receiving cardiovascular reconstruction within last 6 months; Cerebrovascular disorders occurring within last 6 months; Complication of serious hepatic disease or renal disease; Malignant tumor; Uncontrollable diabetes; Hyperlipidemia arising from the following disease: Nephrotic syndrome, hypothyroidism, Cushing's syndrome, secondary hyperlipidemia due to other disease; Hyperlipidemia due to some drugs such as steroid hormone; Hemorrhage(hemophilia, capillary fragility, gastrointestinal ulcer, urinary tract hemorrhage, hemoptysis, vitreous hemorrhage, etc.); Hemorrhagic diathesis;	Primary Prevention, Increased CVD Risk: Dyslipidemia	Retrospective

Table E-3. Design Details: Observational studies

Author, year, PMID, country	Study name	Study Design	Funding source/Conflict of interest	Study start date(s)	Eligibility Criteria	Study Population	Registration (prospective/ retrospective)*
Lemaitre, 2012, 22743310, US	Cardiovascular Health Study	Prospective, longitudinal study of intake (eg, FFQ, biomarker)	Authors report industry affiliation	1989	The cohort consisted of 5201 noninstitutionalized men and women aged >=65 y, recruited in 1989 1990, plus an additional 687 black participants recruited in 1992 and 1993. Each paper excluded participants with their outcome of interest at baseline.	Primary Prevention, Healthy	
NCT00005133 (Lemaitre, 2012, 22743310, US)	Cardiovascular Health Study	Prospective, longitudinal study of intake (eg, FFQ, biomarker)	nd	1988	men and women 65 years and older	Primary Prevention, Healthy	Retrospective

* Prospective = First received date within 30 days of start date.

Table E-4: Outcomes Observational Studies

Study name, Date, PMID, Registry number	N record/N publication	Outcome	In papers (timepoint)	In Registry Record (timepoint)
Lemaitre, 2012, 22743310 NCT00005133	nd/3941	Atrial fibrillation	16 years	
		Sudden cardiac death	16 years	
		Total CHD	16 years	11 years
		Congestive heart failure	16 years	
		Myocardial infarction		11 years
		Stroke (total)	16 years	11 years
		Stroke, hemorrhagic	16 years	
		Stroke, ischemic	16 years	
		Total mortality (all causes)	16 years	
		CHD mortality	16 years	
		CVD mortality	16 years	

Table E-5: Baselines, Comparative Studies

Author, year, PMID	Arm (N)	Male %	Race %	Age mean years	SBP mean (SD) mmHg	DBP mean (SD) mmHg	MAP mean (SD) mmHg	Total Cholesterol mean (SD) mg/dL [mmol/L]	LDL mean (SD) mg/dL [mmol/L]	HDL mean (SD) mg/dL [mmol/L]	Triglycerides mean (SD) mg/dL [mmol/L]	BMI mean (SD) Kg/m2	Do they match where there is data
Kastelein 2014 24528690	Placebo [olive oil] (98)	77.8	96 white, 4 Asian, 6.1 Hispanic	50.8 (10.6)	130.4 (12.1)	80.5 (6.2)		median 246 (range 135, 409)	median 78.2 (range 22.7, 161)	median 28.7 (range 14, 60)	median 682 (range 418, 2007)	30.4 (4.3)	
	"Fish oil" (DHA+EPA) [Omega3 2 g/d; olive oil 2 g/d] (99)	80.0	93 white, 5 Asian, 8 Hispanic, 2 other	51.1 (9.8)	130.1 (12.4)	80.9 (7.7)		Median 241 (range 131, 542)	median 77.3 (range 19.7, 182)	median 27.3 (range 13.3, 47.3)	median 717 (range 415, 1578)	31.4 (4.8)	
	"Fish oil" (DHA+EPA) [Omega3 3 g/d, olive oil 1 g/d] (97)	78.2	91.1 white, 1 black, 5.9 Asian, 4 Hispanic, 2 other	51.2 (8.8)	129.2 (11.1)	81.1 (7.5)		median 244 (range 151, 641)	median 81.0 (range 19.7, 213)	median 28.0 (range 15.3, 58.7)	median 728 (range 439, 2158)	31.8 (4.1)	
	"Fish oil" (DHA+EPA) [Omega3 4 g/d] (99)	71.7	88.9 white, 2 black, 8.1 Asian, 7.1 Hispanic, 1 other	52.9 (10.9)	129.6 (12.1)	80.7 (7.6)		median 254 (range 119, 564)	median 90.3 (range 11.7, 223)	median 28.7 (range 12.7. 69.3)	median 655 (range 435, 2095)	31.0 (5.1)	
NCT01242527 (Kastelein 2014 24528690)	Placebo [olive oil] (99)	77.8	6 Hispanic or Latino; 94 not Hispanic or Latino	50.8 (10.6)									Yes – exact match
	"Fish oil" (DHA+EPA) [Omega3 2 g/d; olive oil 2 g/d] (100)	80	8 Hispanic or Latino; 92 not Hispanic or Latino	51.1 (9.8)									Yes – exact match

Author, year, PMID	Arm (N)	Male %	Race %	Age mean years	SBP mean (SD) mmHg	DBP mean (SD) mmHg	MAP mean (SD) mmHg	Total Cholesterol mean (SD) mg/dL [mmol/L]	LDL mean (SD) mg/dL [mmol/L]	HDL mean (SD) mg/dL [mmol/L]	Triglycerides mean (SD) mg/dL [mmol/L]	BMI mean (SD) Kg/m2	Do they match where there is data
	"Fish oil" (DHA+EPA) [Omega3 3 g/d, olive oil 1 g/d] (101)	78	4 Hispanic or Latino; 96 not Hispanic or Latino	51.2 (8.8)									Yes – exact match
	"Fish oil" (DHA+EPA) [Omega3 4 g/d]) (99)	71.7	7 Hispanic or Latino; 93 not Hispanic or Latino	52.9 (10.9)									Yes – exact match
Maki, 2013, 23998969	Placebo (211)	56.7	91.6 white, 4.7 black, 1.4 Asian, 2.3 American Indian or Alaska native, native Hawaiian, or Pacific Islander, multiple, other	61.5 (9.6)	128.9 (14.3)	76.1 (7.7)		174 (29.5)	91.7 (27.3)	38.3 (9.0)	280 (70.7)	32.7 (5.3)	
	All n3 PUFAs (ALA+DHA+EPA) [2 g] (209)	57.2	96.3 white, 3.3 black, 1 other	60.9 (10)	128.3 (15)	75.7 (8.9)		179 (29.1)	92.3 (26.0)	38.7 (9.9)	284 (76.7)	33.3 (6.2)	
	All n3 PUFAs (ALA+DHA+EPA) [4 g] (207)	63.4	94.4 white, 2.3 black, 1.9 Asian, 1.4 other	60.1 (9.2)	129.7 (13.3)	77.1 (9.0)		178 (29.1)	93.6 (27.6)	38.8 (10.9)	287 (82.8)	33.3 (6.6)	

Author, year, PMID	Arm (N)	Male %	Race %	Age mean years	SBP mean (SD) mmHg	DBP mean (SD) mmHg	MAP mean (SD) mmHg	Total Cholesterol mean (SD) mg/dL [mmol/L]	LDL mean (SD) mg/dL [mmol/L]	HDL mean (SD) mg/dL [mmol/L]	Triglycerides mean (SD) mg/dL [mmol/L]	BMI mean (SD) Kg/m2	Do they match where there is data
NCT01408303 (Maki, 2013, 23998969)	Placebo (216)	57		61.5 (9.6)									Yes – exact match
	All n3 PUFAs (ALA+DHA+EPA) [2 g] (215)	57		60.9 (10)									Yes – exact match
	All n3 PUFAs (ALA+DHA+EPA) [4 g] (216)	63		60.1 (9.2)									Yes – exact match
Nodari, 2011, 21844082	Placebo (99)	63.6		69 (9)	136 (16)	82 (9)						23.6 (5.3)	
	All n3 PUFAs (ALA+DHA+EPA) (100)	70		70 (6)	134 (20)	82 (10)						23.8 (5.2)	
	Placebo (66)	84.9		64 (9)	120.5 (12.2)	76.2 (5.1)		187 (28)			154 (76)	25.7 (2.22)	
	"Fish oil" (DHA+EPA) (67)	95.5		61 (11)	119.5 (9.2)	76.0 (5.2)		187 (26)			149 (62)	25.9 (2.3)	No match in record for this arm
NCT01198275 (Nodari, 2011, 21844082)	Placebo (Olive oil) (99)	63		69 (9)									Yes – exact match
	DHA+EPA (2g) (100)	70		70 (6)									Yes – exact match to All n-3 PUFA arm of paper
Rodriguez-Leyva, 2013, 24126178	Placebo (52)			65.3 (9.4)	142.4 (17.5)	79.0 (15.7)		[4.5 (1.3)]	[2.6 (1.0)]	[1.2 (0.3)]	[1.7 (0.8)]	28.1 (4.4)	

Author, year, PMID	Arm (N)	Male %	Race %	Age mean years	SBP mean (SD) mmHg	DBP mean (SD) mmHg	MAP mean (SD) mmHg	Total Cholesterol mean (SD) mg/dL [mmol/L]	LDL mean (SD) mg/dL [mmol/L]	HDL mean (SD) mg/dL [mmol/L]	Triglycerides mean (SD) mg/dL [mmol/L]	BMI mean (SD) Kg/m2	Do they match where there is data
	All n3 PUFAs (ALA+DHA+EPA) [flaxseed group] (58)			67.4 (8.06)	143.3 (22.2)	77.0 (9.5)		[4.4 (1.1)]	[2.5 (1.0)]	[1.2 (0.3)]	[1.6 (0.7)]	27.4 (4.4)	
NCT00781950 (Rodriguez-Leyva, 2013, 24126178)	Placebo (52)	73		65.3 (9.4)									Yes – exact match
	ALA (flaxseed) (58)	74		67.4 (8.1)									Yes – exact match

Table E-6: Adverse effects/events

Study Year PMID Region (Population)	F/up Time	n-3 FA (N)	Dose	AE n-3 FA	Control (N)	AE Control	Match
Maki 2013 23998969 US	1.5 mo	EPA+DHA (216)	4 g/d	Total: 41.7% Serious AEs: 0.5% (coronary artery disease) AEs related to treatment: 20.4% (nausea, diarrhea, or epigastric discomfort) AEs leading to discontinuation: 3.2%	Placebo (216)	Total: 27.9% Serious AEs: 1.4% (intestinal obstruction, bronchitis, and hyperglycemia) AEs related to treatment: 6.0% (nausea, diarrhea, or epigastric discomfort) AEs leading to discontinuation: 0.9%	
NCT01408303 (Maki, 2013 23998969)		EPA+DHA (216)	4 g/d	Serious AEs: 1 coronary artery disease (0.5%) AEs related to treatment: 36 diarrhea, 13 nausea	Placebo (215)	Serious AEs: 1 intestinal obstruction, 1 bronchitis, and 1 hyperglycemia (1.4%) AEs related to treatment: 5 diarrhea; 3 nausea	Serious AEs match paper; other AEs match paper
Maki 2013 23998969 US		EPA+DHA (215)	2 g/d	Total: 33.0% Serious AEs: 1.4% (diverticular perforation, musculoskeletal chest pain, and osteoarthritis) AEs related to treatment: 9.8% (nausea, diarrhea, or epigastric discomfort) AEs leading to discontinuation: 1.4%			
NCT01408303 (Maki, 2013 23998969)		EPA+DHA (215)	2 g/d	Serious AEs: 1 diverticular perforation, 1 musculoskeletal chest pain, and 1 osteoarthritis (1.4%) AEs related to treatment: 13 diarrhea; 6 nausea			Serious AEs match paper; other AEs match paper

Nodari 2011 21844082 Italy (CVD)	1 y	EPA+DHA (94)	0.850−0.882 g/d	Total: 2.1%	Placebo (94)	Total: 3.2%	
NCT01198275 (Nodari, 2011 21844082)		EPA+DHA (100)	0.850−0.882 g/d	Record reported no serious or other adverse events in the population. No details as to what was specified as an adverse event.	Placebo (99)	Record reported no serious or other adverse events in the population. No details as to what was specified as an adverse event.	Matches paper (withdrawal information not given in registry record)
Kastelein 2014 24528690 Europe (Dyslipidemia)	12 wk	EPA+DHA (99) (4 g/d)	3.0 g/d	Total: 44.4% AEs related to treatment: 25.3% Severe AEs‡‡: 1.0% Diarrhea: 10.1% Nausea: 5.1% Vomiting: 0% Abdominal pain: 1.0%	Placebo (99)	Total: 26.3% AEs related to treatment: 3.0% Severe AEs§§: 5.1% Diarrhea: 2.0% Nausea: 1.0% Vomiting: 1.0% Abdominal pain: 1.0%	
NCT01242527 (Kastelein 2014 24528690		EPA+DHA (100)	4 g/d	10 diarrhea 5 nausea 1 nasopharyngitis	Placebo (99)	1 abdominal pain 2 diarrhea 1 nausea 1 nasopharyngitis	Fewer AEs reported in record than in paper, but the ones that were reported match
Kastelein 2014 24528690 Europe		EPA+DHA (101) (3 g/d)	EPA: 2.25 g/d	Total: 42.6% AEs related to treatment: 16.8% Severe AEs: 3.0% Diarrhea: 5.9% Nausea: 8.9% Vomiting: 4.0% Abdominal pain: 1.0%			
NCT01242527 (Kastelein 2014 24528690		EPA+DHA (101)	3 g/d	6 diarrhea 9 nausea 3 nasopharyngitis			Fewer AEs reported in record than in paper, but the ones that were reported match
Kastelein 2014 24528690 Europe		EPA+DHA (100) (2 g/d)	EPA: 1.50 g/d	Total: 40.0% AEs related to treatment: 18.0% Severe AEs: 2.0% Diarrhea: 10.0% Nausea: 6.0% Vomiting: 2.0% Abdominal pain: 4.0%			
NCT01242527 (Kastelein 2014 24528690)		EPA+DHA (99)	2 g/d	10 diarrhea 6 nausea 7 nasopharyngitis			Fewer AEs reported in record than in paper, but the ones that were reported match

Rodriguez-Leyeza, 2013 24126178	1 y	ALA (59)	5.9 g/d	No AEs reported	Placebo (52)	No AEs reported	
NCT00781950 (Rodriguez-Leyeza, 2013 24126178)		ALA (59)	5.9 g/d	3 nausea		O nausea	Nausea was an AE in the record, but not mentioned in the papers

Table E-7: Risk of Bias, Comparative Studies

Author, Year PMIDS*	Randomization: allocation sequence adequately generated	Allocation adequately concealed	Participants adequately blinded	Outcome assessors adequately blinded	Attrition bias: Incomplete outcome data	Selective outcome reporting bias (Yes/No)	Intention-to-treat analysis? (Yes/No)	Group similarity at baseline (general)	Group similarity at baseline (Omega-3)	Similar compliance across groups	Additional bias
Baxheinrich, 2012, 22894911	Unclear	Unclear	High	Low	Low	No	No	Low	Unclear	High	
DRKS00006232 (Baxheinrich, 2012, 22894911)	Unclear	Unclear	Low	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	
Bosch, 2012, 22686415	Unclear	Low	Low	Low	Low	No	No	Low	Low	Unclear	
NCT00069784 (Bosch, 2012, 22686415)	Unclear	Unclear	Low	Unclear	Unclear (numbers lost to followup given for the wrong arms)	Unclear	Yes	Unclear (baselines given for wrong arms)	Unclear (baselines given for wrong arms)	Unclear (baselines given for wrong arms)	
Brinton, 2013, 22819432 23835245	Unclear	Low	Low	Low	Low	No	Yes	Low	Unclear	Unclear	
NCT01047501 (Brinton, 2013, 23835245)	Unclear	Low	Low	Low	Unclear	No	Yes	Unclear	Unclear	Unclear	No
Brouwer, 2006, 16772624	Low	Low	Low	Low	Low	No	Yes	Low	Low	Low	
NCT00110838 (Brouwer, 2006, 16772624)	Unclear	Low	Low	Low	Unclear	No	Unclear	Low	Unclear	Unclear	No
Damsgaard, 2008, 18492834	Low	Low	Low	Low	Low	No	Yes	Low	Low	Low	

Author, Year PMIDS*	Randomization: allocation sequence adequately generated	Allocation adequately concealed	Participants adequately blinded	Outcome assessors adequately blinded	Attrition bias: Incomplete outcome data	Selective outcome reporting bias (Yes/No)	Intention-to-treat analysis? (Yes/No)	Group similarity at baseline (general)	Group similarity at baseline (Omega-3)	Similar compliance across groups	Additional bias
NCT00266292 (Damsgaard, 2008, 18492834)	Unclear	Low	Low	Low	Unclear	No	Yes	Low	Unclear	Unclear	No
Galan, 2010, 18544171 21115589 21801476 22365647	Low	Low	Low	Unclear	Low	No	Yes	Low	Low	Low	
ISRCTN41926726 (Galan, 2010, 1 21115589)	Unclear	Unclear	Low	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	
Holman, 2009, 19002433 21036355	Low	Low	Low	Low	Low	Yes	No	Low	Low	Low	
NCT00141232 and ISRCTN76737502 (Holman, 2009, 19002433)	Unclear	Unclear	Low	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	
Jones, 2014, 24829493	Low	Low	Low	Low	High	No	Unclear	Low	Low	Low	
NCT01351012 (Jones, 2014, 24829493)	Unclear	Low	Low	Low	Unclear	No	Yes	Unclear	Unclear	Unclear	No
Kastelein, 2014, 24528690	Unclear	Unclear	Low	Unclear	Low	No	Yes	Low	Low	High	
NCT01242527 (Kastelein, 2014, 24528690)	Unclear	Unclear	Low	Low	Low	Unclear	Yes	Unclear (only demographic information given)	Unclear	Unclear	
Kromhout, 2010, 20362710 20929341 22110169 22301766	Low	Low	Low	Low	Low	No	Yes	Low	Low	High	
NCT00127452 (Kromhout, 2010, 20929341)	Unclear	Low	Low	Low	Unclear	No	Yes	Unclear	Unclear	Unclear	No

Author, Year PMIDS*	Randomization: allocation sequence adequately generated	Allocation adequately concealed	Participants adequately blinded	Outcome assessors adequately blinded	Attrition bias: Incomplete outcome data	Selective outcome reporting bias (Yes/No)	Intention-to-treat analysis? (Yes/No)	Group similarity at baseline (general)	Group similarity at baseline (Omega-3)	Similar compliance across groups	Additional bias
Kuhnt, 2014, 24553695	Low	Low	Low	Low	Low	No	No	Low	Low	Unclear	
NCT01856179 (Kuhnt, 2014, 24553695)	Low	Unclear	Low	Low	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	
Leaf, 2005, 16267249	Low	Unclear	Low	Low	Low	No	Yes	Low	Low	Low	
NCT00004559 (Leaf, 2005, 16267249)	Unclear	Low	Low	Low	Unclear	No	Yes	Unclear	Unclear	Unclear	No
Macchia, 2013, 23265344	Unclear	Low	Low	Low	Unclear	No	No	Low	Unclear	Unclear	
NCT00597220 (Macchia, 2013, 23265344)	Low	Unclear	Low	Low	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	
Maki, 2010, 17825687 20451686	Low	Low	Low	Low	Low	No	Yes	High	Unclear	Low	
NCT00246701 (Maki, 2010, 20451686)	Low	Unclear	Low	Low	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	
Maki, 2013, 23998969	Unclear	Unclear	Low	Low	High	No	Yes	Low	Low	Low	
NCT01408303 (Maki, 2013, 23998969)	Unclear	Unclear	Low	Unclear	Low	No	Yes	Unclear (only age and gender baselines given)	Unclear	Low	
Nodari, 2011, 21844082	Low	Low	Low	Low	Unclear	No	No	Low	Unclear	Unclear	
NCT01198275 (Nodari, 2011, 21844082)	Unclear	Unclear	Low	Unclear	Low	Unclear	Unclear	Unclear	Unclear	Unclear	
Raitt, 2005, 15956633	Unclear	Low	Low	Low	Low	No	No	Low	Unclear	Unclear	
NCT00004558 (Raitt, 2005, 15956633)	Unclear	Unclear	Low	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	

Author, Year PMIDS*	Randomization: allocation sequence adequately generated	Allocation adequately concealed	Participants adequately blinded	Outcome assessors adequately blinded	Attrition bias: Incomplete outcome data	Selective outcome reporting bias (Yes/No)	Intention-to-treat analysis? (Yes/No)	Group similarity at baseline (general)	Group similarity at baseline (Omega-3)	Similar compliance across groups	Additional bias
Ras, 2015, 25122648	Low	Low	Low	Low	Low	Yes	Yes	Low	Unclear	Low	
NCT01313988 (Ras, 2015, 25122648)	Unclear	Low	Low	Low	Unclear	No	Yes	Unclear	Unclear	Unclear	No
Rauch, 2010, 21060071	Low	Low	Low	Low	Low	No	Yes	Low	Unclear	Low	Unclear (High underlying levels of fish consumption during the study could have influenced the clinical event rate during followup.)
NCT00251134 (Rauch, 2010, 21060071)	Low	Unclear	Low	Low	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	
Rodriguez-Leyva, 2013, 24126178 25694068	Low	Low	High	Low	Low	No	Yes	Low	Low	Low	
NCT00781950 (Rodriguez-Leyva, 2013, 24126178)	Unclear	Unclear	Low	Unclear	High (greater than 20% not completed in both arms (22% ALA; 21% placebo))	Unclear	Unclear	Unclear (only demographic baselines given)	Unclear	Unclear (no compliance data given)	
Roncaglioni, 2013, 23656645	Low	Low	Low	Low	Low	No	Yes	Low	Low	Low	
NCT00317707 (Roncaglioni, 2013, 23656645)	Low	High	Low	Low	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	

Author, Year PMIDS*	Randomization: allocation sequence adequately generated	Allocation adequately concealed	Participants adequately blinded	Outcome assessors adequately blinded	Attrition bias: Incomplete outcome data	Selective outcome reporting bias (Yes/No)	Intention-to-treat analysis? (Yes/No)	Group similarity at baseline (general)	Group similarity at baseline (Omega-3)	Similar compliance across groups	Additional bias
Sanders, 2011, 21865334	Low	Low	Low	Low	Low	No	No	Low	Low	Low	
ISRCTN66664610 (Sanders, 2011, 21865334)	Unclear	Unclear	Low	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	
Tavazzi, 2008, 18757090 19589110 21315217 23351824 23839902	Low	Low	Low	Low	Low	Yes	Yes	Low	Low	Low	
NCT00336336 (Tavazzi, 2008, 18757090)	Unclear	Low	Low	Low	Unclear	No	Yes	Unclear	Unclear	Unclear	No
Vazquez, 2014, 24462043	Low	Low	Low	Low	Low	No	Yes	Low	Unclear	Low	
NCT01758601 (Vazquez, 2014, 24462043)	Unclear	Low	Low	Low	Unclear	No	Yes	Unclear	Unclear	Unclear	No
Yokoyama, 2007, 17398308 18451347 18667204 19423946 20484828 22186099 22653220	Low	Low	High	Low	Low	No	Yes	Low	Unclear	Unclear	
NCT00231738 (Yokoyama, 2007, 17398308)	Unclear	High	High	High	Unclear	No	Yes	Unclear	Unclear	Unclear	No

* Author, year of primary study. PMIDs of all included articles.

Table E-8: Risk of Bias, Observational Studies

Study PMIDs	Selection bias (outcome of interest not present at baseline)	Comparability/ Adjustment (adjusted for confounders or other factors)	Outcome assessors adequately blinded	Incomplete outcome data (attrition bias)	Dietary assessment instrument described (studies with FFQ)?	Nutrient exposures adequately reported
Cardiovascular Health Study 21810709 22282329 22743310 23525429 23546563 25159901	Low	Yes (Diet and CVD risk factors)	Low	Low	Not Applicable (biomarker)	Yes
NCT00005133 (Cardiovascular Health Study)	Low	Unclear	Unclear	Unclear	Unclear	Unclear