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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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.

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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

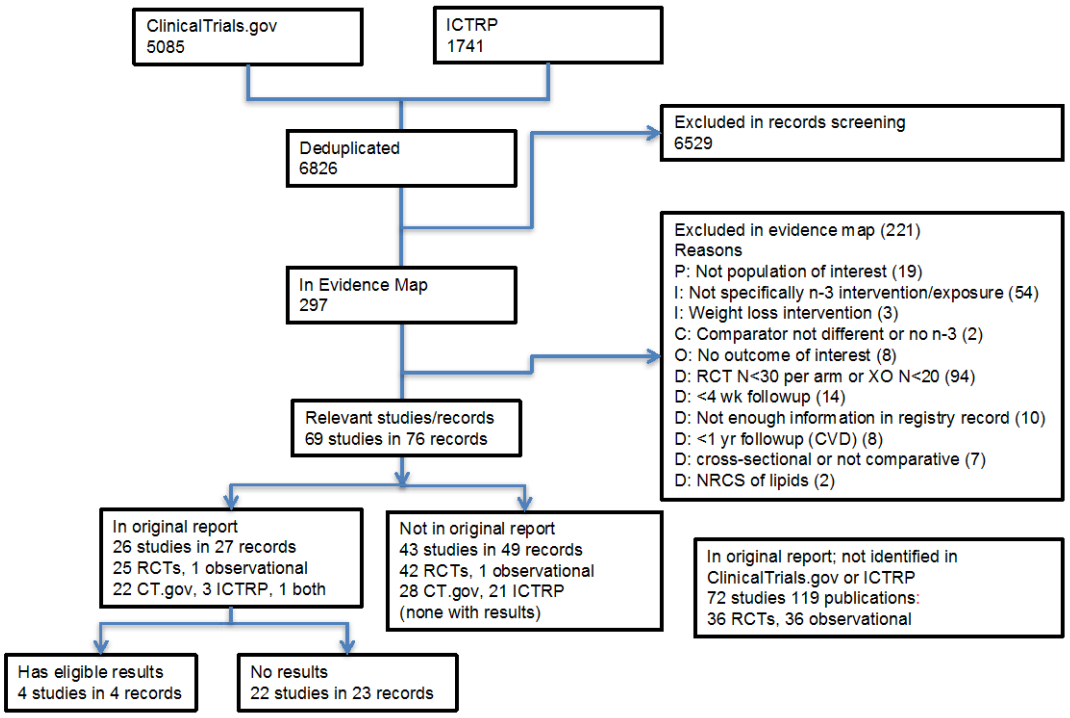
unlikely to directly impact the strength of evidence or the assessment of risk of bias for the evidence-base. All potential revisions to risk of bias and strength of evidence were discussed with the project lead of the original review. We describe and explain any changes to strength of evidence for any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

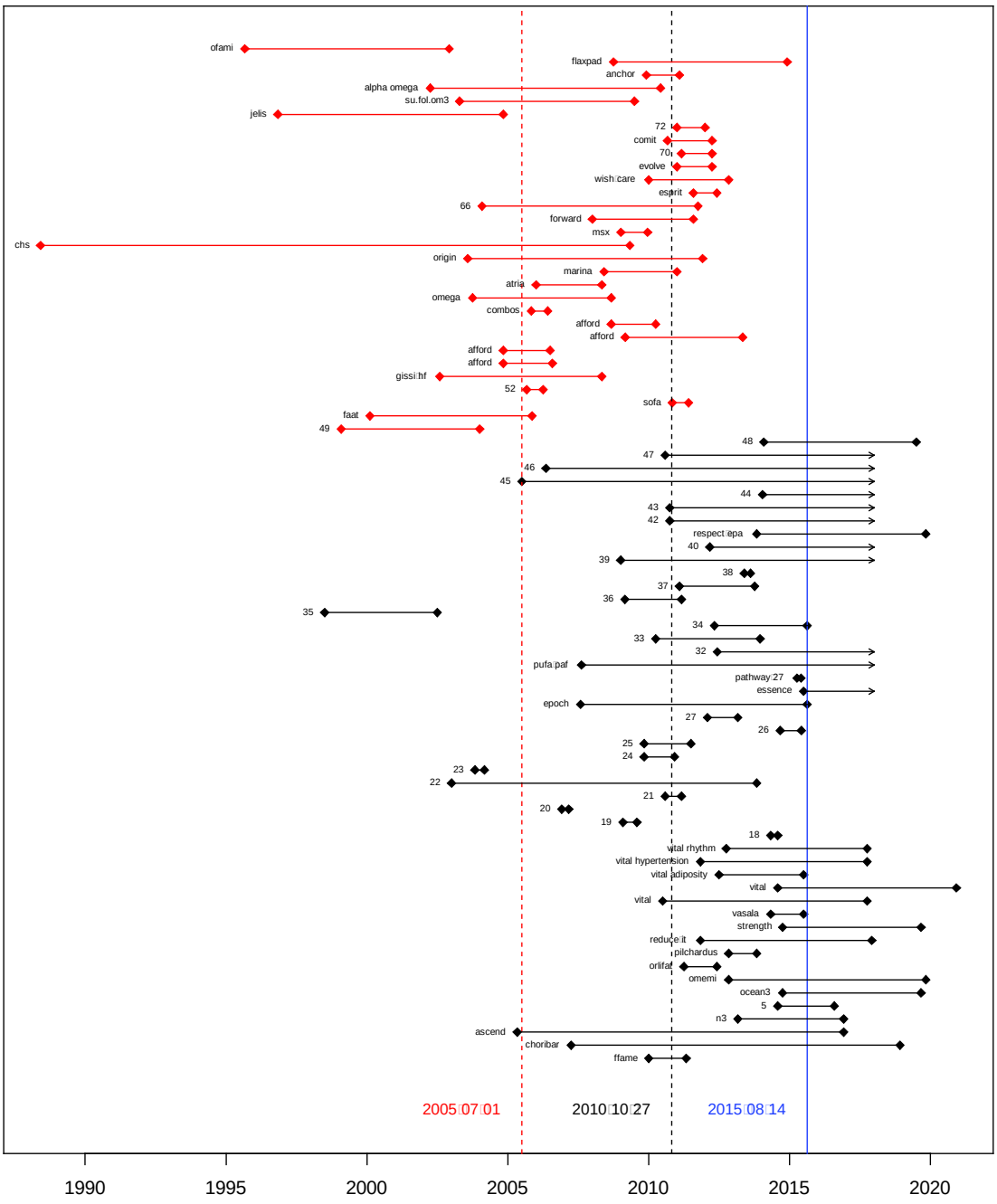
Study Identifier Country/ies Study Name	Registry	Population	Date (start/end)	N total*	Study design: Intervention	Intermediate Outcomes	Clinical Outcomes
NCT01653678, US	CT.gov	HTN	2011-2017	25875	RCT: Vitamin D3 2000 IU/day + Omacor, 1 capsule/day vs. Vitamin D3 2000 IU/day + placebo vs. placebo + Omacor, 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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