Evidence-based Practice Center Methodology Report Protocol

Project Title: Transparency of Reporting Requirements
Report Topic: Omega-3 Fatty Acids and Cardiovascular Disease

I. Background

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: 1) detecting (and correcting results for) information bias using only the identified studies (e.g., using funnel-plot based methods[1-4] or various selection models[5-7]) and 2) examining trial registries, surveying researchers, and perusing the grey literature to identify unpublished study results or ongoing studies.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 prospective clinical trial registries that include prospective registration of full 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]). Empirical analyses of prospective registry data can inform on the time between study completion and publication, the number of unpublished studies, the fidelity of studies to registered protocols, and the congruence of study results between result registries and publications.[8-11]

The existing empirical research on information bias pertains almost exclusively to industry-sponsored drug, device, and biologic trials,[12-14] despite the fact that 41% (n=78,579) of all studies registered in ClinicalTrials.gov are indexed as "observational" or "behavioral/other intervention studies". 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. Drug studies are twice as likely to have results posted in ClinicalTrials.gov as nondrug studies, and industry sponsored studies are more compliant in ClinicalTrials.gov reporting compared to academic sponsored studies.[12] Studies conducted outside the United States may not be registered ClinicalTrials.gov but may be found in a local registry (e.g., accessible through ICTRP).

II. Objectives

The objective of this methodology report is to examine the feasibility and additional 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

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(EPC).[16-18] Our findings will support the development of search methods, data collection, and evaluation techniques to optimize the use of trial registries in the context of systematic reviews.

IV. Methods

Overview

We will use a completed systematic review conducted by our EPC on the relationship between n-3 FA intake and CVD outcomes. This systematic review (hereafter referred to as "original review") was conducted in accordance to IOM standards and AHRQ guidance but did not include ClinicalTrials.gov to identify ongoing studies.

While the original report was being finalized based on peer and public review comments, we will search two clinical trial registries, ClinicalTrials.gov and ICTRP, up to the last search date of the original report (6/8/2015) to identify additional eligible data, comprising 1) additional studies that were not identified in the original review and 2) additional information on the design or results of studies included in the original review. For newly found studies, we will record additional data and assess their risk of bias. For studies identified in the original review, we will also assess the congruence of any additional information on design or results with that in publications included in the original review, and whether the additional information would change study-level risk of bias assessments. At the level of the evidence-base, and for each pertinent exposure-outcome relationship, we will assess whether the additional information changes our overall risk of bias and strength of evidence assessments, or our conclusions.

Terminology

We use the term study to refer to the conducted research. Information about the design or results of studies may be reported in publications or in registry records. It is possible that studies identified through the registry search have no associated publications; and that studies identified in the original review have no records in ClinicalTrials.gov or ICTRP.

Registry searches

Because the registry databases are not indexed, queries can only include text words. Thus, it is 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 ClinicalTrials.gov and ICTRP interfaces. 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.[19, 20] Glanville et al. recommend searching for intervention terms only.[19] We will therefore issue four queries whose union corresponds to the scope of the intended search. We will use a similar search process in ICTRP. **Appendix A** includes the literature searches from the original report and the specific search strategies to be used in ClinicalTrials.gov and ICTRP.

Screening Criteria and Evidence Map

The same eligibility criteria established for the original report will be employed to screen registry records for inclusion (**Appendix B** contains the original report's eligibility criteria). Initial screening will be performed by a single investigator who will peruse the title, intervention(s), and outcome(s) within each record. Records screened in during the initial phase will be included in an evidence map, which will parallel the evidence map created for the original report. This spreadsheet will capture basic intervention, outcome, study design, sample size, and whether results have been reported (but not the actual results data or risk of bias assessment). A researcher other than the one who initially screened the record in will reassess study eligibility and will extract the basic information for the evidence map.

When the evidence map is completed, the still-eligible records will be assessed to determine whether they meet additional operational eligibility criteria used in the original review (based on minimum sample size, minimum duration of followup, and reporting of subgroup analyses or interactions). For comparative studies (comparing different n-3 FA or different intake amounts of n-3 FA), we expect that the primary reason for exclusion will be based on small sample size for studies of lipoprotein, triglyceride, or blood pressure outcomes. For observational studies (that evaluated associations between baseline intake or measures of n-3 FA and followup outcome events), again the primary reason for rejection will likely be small sample size (for all outcomes).

The evidence map will thus provide information on two sets of studies, those that were potentially eligible (based on population, intervention, outcomes, and study design) but would not have been included in the original report (primarily due to small sample size) and studies that would have met full criteria for inclusion in the original report.

Data Extraction and Management

Data extraction has been completed for the original report. As noted above, all potentially relevant study records identified in registry searches will be incorporated into the original report's evidence map to include data on study design, intervention type and duration, population, outcomes, and sample size.

For relevant ClinicalTrials.gov/ICTRP citations that include results and that meet full eligibility criteria for inclusion in the original report, limited data will be extracted into the same customized forms developed and utilized in the original report in the Systematic Review Data Repository (SRDR) online system (http://srdr.ahrq.gov). Specifically, we will capture basic information about the study design, study population, intervention details (i.e., n-3 FA type, dose, and duration), reported outcomes, and results (that were not captured by articles included in the original report). Results data for only the longest-reported followup time in the registry record will be extracted. We will also assess each new study for the same risk of bias questions addressed by the original report.

Analysis

We will provide descriptive statistics on the registry search yield and identify records/publications found exclusively in the original report, in a registry database, or in both. We will characterize registry records and associated publications that have been

discontinued or are in progress/ongoing at the time of this study by detailing study initiation date and rationale for discontinuation or delay. We will, thus, categorize studies as 1) included in the original review but not found in the registry, 2) included in the original review and found in a registry but with no new results data, 3) included in the original review and found in a registry with new data, and 4) identified via the registry but not found in the original review. We will focus on the value of results data identified via registry searches, and thus 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.

Analyses of studies included in the original review that also have a registry record

For these studies, the additional information in the registry records pertains to their design (if the registry record includes protocol information) or their findings (if the record includes results).

Information found in protocols can be examined against information obtained from publications to judge whether important changes in the analysis plan occurred. We will make such comparisons only 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 will assess whether the additional information in the registry records changes the risk of bias assessments in the original review. In the assessment for changes in the analysis plan, we will look for changes in the *estimand* (determined by the population to which the analysis refers [e.g., all assigned to an interventions, all receiving the intervention], the effect measure [e.g., difference in means, odds ratios for specific categorizations of continuous outcomes], and follow-up [the maximum follow up recorded]); the *estimation procedure* (the prescribed statistical learning procedure [e.g., taking unadjusted differences of means, adjusting in regressions and for which factors, or via stratified analysis]); and the plan for *handling missing values*. Deviations from the protocol's analysis plan may be suggestive of selective analysis reporting.

When results are reported in registry records, we will describe whether registry records and publications describe the same outcome concepts, and if yes, whether the results agree qualitatively (are in the same direction). We will also describe which outcome-instantiations are reported in the registry record, the publication, or both. For outcome instantiations that are reported in both, we will record whether the quantitative results are the same (within rounding error) or not.

Analyses of studies that were not included in the original review

Registry records of newly identified studies will be summarized in narrative form and added to the original report's evidence map. We will apply 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 will reassess the risk of bias of the evidence base and the strength of evidence using the same methodology used for the original report. We will evaluate if any additional data are likely to impact the findings of the study included in the original report. We quantify such 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; by meta-analysis), or a change in statistical significance (by meta-analysis). If meta-analyses are not conducted, we will assess whether the new studies fall within the range of the similar studies from the original report. If none of these conditions are met, the additional data are unlikely to directly impact the strength of evidence or the assessment of risk of bias for the evidence-base. We will describe and explain any changes to strength of evidence for any n-3 FA and outcome relationship.

V. References

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VI. Definition of Terms

Not applicable.

VII. Summary of Protocol Amendments

No protocol amendments have been made.

VIII. EPC Team Disclosures

Our research team has no disclosures of potential conflicts of interest.

VIII. Role of the Funder

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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]	
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]	

#	Search	
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$.mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, tx, kw, ct, sh, bt, id, cc]	
29.	Coronary.mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, tx, kw, ct, sh, bt, id, cc]	
30.	heart disease$.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/	

#	Search	
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$).mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, tx, kw, ct, sh, bt, id, cc]	Study designs
59.	exp randomized controlled trials/	
60.	exp Randomized Controlled Trials as Topic/	
61.	exp random allocation/	
62.	exp double-blind method/	
63.	exp single-blind method/	
64.	randomized controlled trial.pt.	
65.	clinical trial.mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, tx, kw, ct, sh, bt, id, cc]	
66.	(clin$ 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]	

#	Search	
86.	food frequency questionnaire$.mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, tx, kw, ct, sh, bt, id, cc]	
87.	or/58-86	
88.	57 and 87	n-3, CVD, Designs
89.	limit 88 to (addresses or autobiography or bibliography or biography or case reports or comment or congresses or dictionary or directory or editorial or festschrift or government publications or historical article or interview or lectures or legal cases or legislation or letter or news or newspaper article or patient education handout or periodical index)	Not non-studies
90.	88 not 89	
91.	limit 90 to english language	Limits
92.	limit 91 to humans	
93.	(guidelines or practice guideline or meta analysis or systematic review).pt.	SRs, GLs
94.	(systematic$ 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)
	  ○ Include: Diabetes, Metabolic Syndrome, Hypertension, Dyslipidemia, existing CVD or symptoms
	  ○ 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)
	  ○ Supplement, diet, or fortified foods (intervention or observational)
	  ○ Minimum duration of intake: 1 year (clinical outcomes), 4 wk (BP, Lipids)
	  ○ Exclude: Dose ≥6 g omega 3 (not total fish/plant oil)
	  ○ Exclude: Adherence to Med diet or Med diet score (**unless omega-3 quantified** [in abstract])
	  ○ Exclude: Soy (or other) protein, soy isoflavones, other non-oil components
	  ○ Exclude: Weight loss diet (eg, fish/fish oil being used in a weight loss diet plan)
	  ○ 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)
	  ○ 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:
	  ○ CVD-related (myocardial infarction, stroke) mortality
	  ○ non-fatal CVD events
	  ▪ myocardial infarction, acute coronary syndrome, stroke/CVA, TIA, unstable angina, amputation 2° PVD, others
	  ○ coronary/cardiac disease
	  ○ peripheral vascular disease (PVD)
	  ○ congestive heart failure (CHF)
	  ○ pulmonary edema
	  ○ ventricular arrhythmia
	  ▪ tachycardia, tachyarrhythmia, fibrillation, bradycardia, sudden death
	  ○ atrial fibrillation, supraventricular tachycardia
	  ○ 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):
	  ○ blood pressure (new-onset hypertension, SBP, DBP, MAP)
	  ○ 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
	  ○ Clinical outcomes, including new-onset hypertension: ≥1 year follow-up
	  ○ Intermediate outcomes (blood pressure and lipids): ≥1 month follow-up

- Adverse events: no minimum follow-up
- Minimum sample sizes (per 2004 protocols*)
  - Clinical outcomes: **RCT/nRCS**: no minimum; **Longitudinal single group** N≥100
  - BP/Lipids (RCT): N≥x (no minimum for now)
  - Adverse events: N≥100
- Tag and REJECT trial **protocols**/designs

* Omega 3 intake:
- Fish oil (incl. menhaden oil, sea mammals, marine, seaweed)
- ALA oils
  - flax seed
  - linseed
  - walnut
  - butternut
  - pumpkin seed
  - canola/rapeseed
  - soy
  - wheatgerm
  - mustard seed
- Fish diet (if omega 3 quantified)
- Mediterranean diet (if omega 3 quantified)
- Food frequency questionnaire (FFQ) etc.: omega 3 quantified [NB. Capture data on daily frequency/dosing pattern]
- n-3 components
  - EPA eicosapentaenoic acid
  - DHA docosahexaenoic acid
  - ALA alpha-linolenic acid
  - DPA docosapentaenoic acid
  - SDA stearidonic acid

† Biomarkers
- Omega-3 (n-3) concentrations
  - Phospholipids (plasma or serum)
  - Adipose tissue FA profile
  - Triaglycerol
  - Cholesteryl ester
  - LDL
  - HDL
  - Cell membrane phospholipids (platelets, red blood cell [RBC, erythrocyte], granulocyte, monocyte [mononuclear], neutrophil, ghost)
    - ALA, SDA, EPA, DHA

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	

Dimension	Instructions
years), choose HIGH risk of bias and describe in Notes	
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.

Dimension	Instructions
Incomplete outcome data (attrition bias) due to amount, nature or handling of incomplete outcome data (ALL STUDIES)	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.
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.	