GLOBAL ORGANIZATION FOR EPA AND DHA OMEGA-3S

19 December 2024

Center for Evidence and Practice Improvement
Agency for Healthcare Research and Quality
ATTN: EPC SEADs Coordinator
5600 Fishers Lane, Mail Stop 06E53A
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RE: Request for Supplemental Evidence and Data (SEAD) Submission for *Dietary Intake of Polyunsaturated Fatty Acids and Plasma Lipid and Cardiovascular Events*

Dear EPC SEADs Coordinator:

GOED, the Global Organization for EPA and DHA Omega-3s, represents the worldwide EPA and DHA omega-3 industry, with a membership built on a quality standard unparalleled in the market. Members must comply with quality and ethics guidelines that ensure they produce quality products that consumers can trust. Our 200+ members and partners represent the entire supply chain of EPA and DHA omega-3s, from fisheries and crude oil suppliers to refiners, concentrators and finished product brands. Our mission is to use science-based information to promote consumption of and enable access to quality EPA & DHA from all sources for a positive impact on public health.

Given our mission, we appreciate the opportunity to provide comments (i.e. supplemental evidence and data (SEAD)) on the research protocol for *Dietary Intake of Polyunsaturated Fatty Acids and Plasma Lipid and Cardiovascular Events*.[1] We will focus on EPA and DHA as it relates to the two key questions (see below). In addition, while your request is specific to providing supplemental evidence and data on the research protocol, we have provided some commentary to put the evidence into context.

1. What are the effects of different dietary **polyunsaturated fatty acid intake** on plasma lipid concentrations in the general population?

2. What are the effects of different dietary **polyunsaturated fatty acid intake** on cardiovascular events in the general population?

[1] https://effectivehealthcare.ahrq.gov/products/polyunsaturated-fatty/protocol

Meta-analyses of interventional trials as a starting point to establish a list of relevant articles for this AHRQ review

Two recent meta-analyses are useful to establish a list of articles on relevant interventional trials, and to support some of our observations. The first, by Abdelhamid *et al*, includes a literature review that identified all articles >12 months whose intervention included EPA, DHA, ALA or the recommendation to increase their intake. This study observed that, for many outcomes, the results of clinical trials are heterogeneous.

The second, by Bernasconi[2] *et al*, focused on the reasons for this heterogeneity. It covered the 40 studies identified by Abdelhamid *et al* for which the intervention consisted of providing participants a known dosage of EPA/DHA (therefore excluding studies where the intervention was dietary advice). This meta-analysis focused on five outcomes: CVD events, Myocardial Infarction (MI), Coronary Heart Disease (CHD) events, Fatal MI and CHD mortality; finding significant risk reduction in all, except for CVD. The benefit was found to increase with dosage for CVD events and MI, at least for the range of dosages that match the habitual intakes commonly obtained through diet and the intake of over-the-counter (OTC) dietary supplements.

Bernasconi *et al* examined other plausible, previously proposed explanations for the trial heterogeneity, and found that the magnitude of the protective effect was independent of year of publication (a proxy for changing standards in cardiovascular prevention and care, or for evolving standards of trial design), baseline risk, and whether the intervention consisted of only EPA or a combination of EPA and DHA.

The GOED Clinical Study Database (CSD) as a tool for compiling lists of potentially relevant studies

In order to provide a reference list for the AHRQ, GOED used an internal resource to support this research effort. The GOED Clinical Study Database (CSD) (see Bernasconi, Wilkin *et al*,) is a novel tool developed to catalog published research on EPA/DHA. Briefly, the CSD uses a wide search to retrieve lists of articles from PubMed that could potentially address the health effects of EPA/DHA. These articles are reviewed by scientists who answer the following questions:

1. What type of study is covered in the article?
2. Is the article about EPA/DHA?

[2] In the interest of full disclosure, we consider it necessary to mention that the first author is a GOED employee and a co-signer of the current letter.

Each article is independently reviewed by two scientists, and a third in case of disagreement. The results of this review (99% finished as of Nov, 2024 – a lag time in PubMed assigning and reviewing MeSH terms makes it impossible to surpass that level of completeness) can be used to create carefully curated lists of studies, with reasonable certainty they will be about EPA/DHA, and they are of the required study type. In particular, the CSD makes it possible to identify all clinical interventional articles for which the intervention includes EPA/DHA. A second step in populating the CSD consists of extracting, from each of these articles, more detailed information, including:

1. Dosage, duration, treatment and placebo
2. Number of participants and their baseline characteristics
3. Outcomes measured

This stage of data extraction has been focused on articles that have associated a MeSH term that describes a disease or mental condition and is 94.4% finished – data has been extracted for articles published up to and including the year 2020, and most articles published in 2021.

During this data extraction, measured outcomes were matched, whenever possible, with the controlled vocabulary defined by the MeSH ontology. If the outcome was not included in MeSH, the controlled vocabulary was extended. This makes it possible to query the database for articles that have actually measured a desired outcome – not just the studies that mention that outcome in their title, abstract or associated MeSH term.

As an example, a PubMed search for clinical trials or RCTs about blood pressure and EPA/DHA, using the query string below, identifies 374 articles, not all of which are interventional, or include EPA/DHA as part of their intervention, and with no possibility to filter articles by study length.

Search terms:
(omega-3 OR fish oil of docosahexa* of eicosapenta*) AND
("blood pressure" or hypertension)

A CSD search for articles that measured blood pressure as an outcome finds 501 articles, of which 470 were longer than 4 weeks. Because of all the levels of manual review, all these articles are interventional and include EPA/DHA as part of their intervention.

The capabilities of the CSD will be used extensively throughout this document to identify potentially relevant articles. All PubMed and CSD searches were conducted during the week of December 16, 2024.

Trial length (recommendation to extend from minimum 4 weeks to 1 year or longer).

We are concerned about your inclusion criteria of a "minimum intervention length of 4 weeks," particularly for Key Question 2. Abdelhamid *et al* provides a complete list of trials of length of at least one year, until 2019. It also provides a compelling rationale (In the "Types of Studies" section of the Methods) why shorter studies would likely not have time to make a difference in the number of cardiovascular events: a shorter intervention wouldn't even be long enough to allow EPA/DHA to reach a new equilibrium in most body compartments.

This is not a purely theoretical consideration. A recent pharmaceutical study, REDUCE-IT (Bhatt *et al*), conducted using a high EPA dosage on patients at very high cardiovascular risk, found large protective effects but observed that even in these conditions, which are particularly favorable to detect an effect, survival curves for the placebo and treated groups did not start to separate until after at least a year post-randomization.

In the largest primary prevention trial to date, VITAL (Manson *et al*), which was conducted with a much smaller mixed EPA/DHA dosage on participants at low risk of cardiovascular events, survival curves for the placebo and treated arms only started separating after more than two years. It may be advisable to consider a minimum trial length as an exclusion criterion, since including shorter trials where the treatment is not given a sufficient time to have an effect may bias effect estimates.

If our proposal is accepted to restrict the analysis to trials longer than a year instead of the four weeks in the protocol, then Abdelhamid *et al*'s can be used for a complete list of interventional studies published until 2019.

GOED regularly monitors PubMed for clinical trials reporting cardiovascular events and involving EPA/DHA as part of their intervention and we are aware of only two such trials longer than one year published since 2019: STRENGTH (Nicholls *et al*) and OMEMI (Kalstad *et al*). It is important to mention that the results of these trials changed some of the estimates in the meta-analysis of Bernasconi *et al*, but little of the conclusions (Bernasconi, Lavie & Milani).

For possible additional trials published during or after 2019, we conducted a PubMed query for articles that have associated any MeSH term corresponding to a cardiovascular disease and a publication date between 2019 and 2024 (see below) and its results were searched in the CSD to isolate interventional articles whose intervention involves EPA/DHA.

Search terms:
"cardiovascular diseases" [MH] AND 2019:2024[DP]

The resulting 101 articles are listed in section A1 of the Appendix. These articles require further review to determine whether they fit the Population inclusion criteria of the AHRQ request..

Of these articles, only 6 mention the word “Healthy” in their abstract or title – see section A2 of the appendix.

Primary prevention trials are limited, but results from secondary prevention trials can be generalized

A majority of supplementation trials has been conducted on populations with established CVD, or at high risk of cardiovascular events (see section A3 of the appendix). The reason is not an expectation of a lack of effect in primary prevention, but rather a matter of statistical power (Rice *et al*) – a low occurrence of events makes it necessary to design large-scale, expensive trials to achieve sufficient power.

To our knowledge, the only long-term (≥ 1 yr) clinical trials including at least some participants without established cardiovascular diseases are listed in section A4 of the appendix (for references, see section A3). It is important to observe that, in many cases these are small trials, or studies conducted in populations at high risk.

The only large-scale trials (n >1000) with at least some primary prevention participants to date are:

1. AREDS2 (n = 4,203): patients were at high risk of macular degeneration, but not cardiovascular diseases.
2. JELIS (n = 18,645): patients with hypertriglyceridemia and on statins, of whom 14,981 (the primary prevention cohort), had no evidence of coronary heart disease.
3. ORIGIN (n = 12,536): patients at high risk, of whom 59% had a previous CVD event.
4. MAPT (n = 1,652): elderly patients with memory complaints.
5. ASCEND (15,480): patients with diabetes, but no evidence of atherosclerotic cardiovascular disease.
6. REDUCE-IT (n = 8,179): high risk patients, of whom 70.7% had a previous CVD event.
7. VITAL (n = 25,871): Participants without a prior history of heart disease or stroke.
8. STRENGTH (n = 13,078): Participants at high risk, of whom 55.9% had established CVD at baseline.

In VITAL, the largest primary prevention trial to date, which used a dosage of 860 mg/day EPA/DHA, the event rates for major cardiovascular events (the primary outcome) were 2.98% and 3.24% for the treated and placebo groups, respectively. This corresponds to a (non-statistically significant) relative risk reduction of 8%, in line with the dose-effect curves of Bernasconi *et al*, which estimates that each additional 1,000 mg/day results in risk reductions of 5.8% (95%-CI: 1.6% - 9.9%).

A power calculation for a two-sided two-sample test for proportions shows that if the results of VITAL are representative of the effect of 860 mg/day EPA/DHA in primary prevention, then a clinical trial with 80% power to detect such a difference at a p-value cutoff of 0.05 would require 146,810 participants. These eight trials combined include approximately 75,000 participants in their primary prevention cohorts, and it is likely that a meta-analysis of primary prevention trials may be underpowered.

Bernasconi *et al* analyzed the relationship between baseline risk (using the absolute risk in the placebo group) and cardiovascular risk reduction. A statistically significant ($p<.05$) result was found for MI, after correcting for the effect of dosage. The estimated slope for this relationship is positive, suggesting that for equal dosages, EPA/DHA supplementation is more effective for MI prevention in lower risk populations. No such relationship was found for cardiovascular events (whether correcting for the effect of dosage or not), suggesting that in terms of relative risk reduction, equal dosages of EPA+DHA are equally effective for primary and secondary prevention.

The dearth of primary prevention research may be offset by the fact that it is possible to generalize the results of the totality of existing research (primary, secondary and mixed) to the primary research situation.

Articles that report relevant measurements of blood lipid concentrations as outcomes (Key Question 1)

The CSD allows searches of interventional studies with EPA/DHA as part of their intervention, with a length > 4 weeks, and that reported specific outcomes or their descendants in the extended MeSH ontology used by the CSD (see Bernasconi, Wilkin *et al* for details).

The following subsection describes the search strategy used for each blood lipid concentration outcome and provides necessary background information, if relevant. In all cases, the results of each search is included as a separate tab in the attached workbook, and studies that include the word healthy in either the title or abstract are flagged.

Not all studies included in these lists meet all criteria in the PICOTS typology included in the AHRQ protocol; however, the CSD design ensures that all articles are on interventional trials that meet the Intervention, Outcomes and Timing inclusion criteria described in the protocol. Given the large number of articles that measured certain outcomes (particularly for Key Question 1) and the tight deadline in the consultation period, it was impossible to conduct a manual review to identify which of these studies meet the Population criteria.

LDL cholesterol (LDL-c)

Search was conducted using the MeSH term [Cholesterol, LDL], or any of its descendants. Results are included in the LDL-C sheet in the attached workbook (811 articles).

HDL cholesterol

Search was conducted using the MeSH term [Cholesterol, HDL], or any of its descendants. Results are included in the HDL-C sheet in the attached workbook (871 articles).

Non-HDL-cholesterol

The search was conducted using the term [Cholesterol, Non-HDL], which is part of the MeSH vocabulary, but part of the extended vocabulary used by the CSD, or by searching all articles that measured both [Cholesterol] and [Cholesterol, HDL]. Results are included in the Non-HDL-C sheet in the attached workbook (931 articles).

Triglycerides (triacylglycerol) (Tg)

Search was conducted using the MeSH term [Triglycerides], or any of its descendants. Results are included in the HDL-C sheet in the attached workbook (1065).

Lipoprotein(a)

Search was conducted using the MeSH term [Lipoprotein(a)], or any of its descendants. Results are included in the Lp(a) sheet in the attached workbook (54 articles).

Apolipoprotein B (ApoB)

Search was conducted using the MeSH term [Apolipoproteins B], or any of its descendants. Results are included in the Apo B sheet in the attached workbook (225 articles).

Articles that report relevant cardiovascular events as outcomes (Key Question 2)

The following subsection describes the search strategy used for each outcome and provides necessary background information, if relevant. In all cases the results of the searches are included in the attached workbook and studies that include the word healthy in either the title or abstract are flagged.

Myocardial Infarction

Search was conducted using the MeSH term [Myocardial Infarction], or any of its descendants. Results are included in the Myocardial Infarction sheet in the attached workbook (38 articles).

Coronary Heart Artery Disease

Search was conducted using the MeSH term [Coronary Disease], or any of its descendants. Results are included in the Coronary Disease sheet in the attached workbook (43 articles).

Revascularization

Search was conducted using the MeSH term [Myocardial Revascularization], or any of its descendants. Results are included in the Revascularization sheet in the attached workbook (33 articles).

Cardiovascular Disease-Related Mortality

Search was conducted using the following terms, or any of their descendants: [Cause of Death, Vascular], [Cause of Death, Other Vascular], [Cause of Death, Stroke], [Cause of Death, Coronary], [Death, Sudden, Cardiac], [Risk of Cardiovascular Death]. These terms are not part of the MeSH controlled vocabulary, but of the extended terminology used by the CSD (Bernasconi, Wilkin *et al*). Results are included in the Cardiovascular Mortality sheet in the attached workbook (37 articles).

Stroke

Search was conducted using the MeSH term [Stroke], or any of its descendants. Results are included in the Revascularization sheet in the attached workbook (32 articles).

Atrial Fibrillation

Significant concerns have recently been raised (Bae *et al*, for example) about the possibility of omega-3 fatty acid intake increasing the risk of atrial fibrillation (AF), but little or no increase has been seen with the lower dosages (≤1 g/d) that are typical of habitual dietary intake, including the use of OTC dietary supplements. In the much larger dosages used in pharmaceutical trials, where a more significant increase is reported, the clinical implications of

the reported increase are unclear. In REDUCE-IT, for example, which used 4 g/day of EPA, an absolute increase of 1% in AF risk was more than offset by an absolute 5% reduction in the risk of major cardiovascular events. Surprisingly, in that study the risk of stroke, the more serious consequence of AF, decreased with the use of omega-3s.

Whereas the presence of a dose-effect relationship reported by Bae *et al* indicates the effect is possibly real, there is considerable uncertainty about its magnitude. Of 91 interventional trials with CVD outcomes with length of more than one year identified in the literature search of Abdelhamid *et al*, Bae *et al* found just eight studies that included AF as an outcome. It is possible that studies with a small or null observed effect may have been omitted from the meta-analysis because of a selective reporting bias that would tend to exaggerate the magnitude of the risk. In addition, Samuel and Nattel observed the presence of an informative censoring bias because EPA and DHA reduce the risk of multiple CVD and mortality risks: patients in the treated groups of EPA/DHA trials would thus have more time and opportunity to develop AF than controls.

A CSD search was conducted using the MeSH term [atrial fibrillation] or any of its descendants. Results are included in the Atrial Fibrillation sheet in the attached workbook (26 articles).

Articles that report other relevant cardiovascular outcomes not included in either Key Question

Blood Pressure and Hypertension

Blood pressure (BP) is one of the most commonly used biomarkers of cardiovascular risk, and a significant body of research has been devoted to the relationship between omega-3 intake and BP. The meta-analysis of Miller *et al*,[3] based on 70 interventional studies, found statistically significant and clinically relevant reductions in both systolic and diastolic pressure, including in normotensive subjects.

While blood pressure (as a marker of risk) and hypertension (as an outcome event) are not included in the protocol, we strongly believe that they are too important to be omitted, and suggest that their inclusion be reconsidered.

[3] In the interest of full disclosure, this meta-analysis was commissioned by GOED, who had no role in the study design or conduct; the acquisition, extraction, management, or analysis of data; the interpretation of research findings; or the writing of the manuscript. This meta-analysis served as the basis for GOED's Successful Petition for a Qualified Health Claim for Eicosapentaenoic Acid and Docosahexaenoic Acid and Reduction of Blood Pressure in the General Population (Docket No. FDA-2014-Q-1146).

A CSD search was conducted using the MeSH terms [blood pressure] and [hypertension] or any of their descendants. Results are included in the Blood Pressure sheet in the attached workbook (470 articles).

References

Abdelhamid AS, Brown TJ, Brainard JS, et al. Omega-3 fatty acids for the primary and secondary prevention of cardiovascular disease. *Cochrane Database Syst Rev*. 2018;7(7):CD003177. Published 2018 Jul 18. doi:10.1002/14651858.CD003177.pub3

Bernasconi AA, Wiest MM, Lavie CJ, Milani RV, Laukkanen JA. Effect of Omega-3 Dosage on Cardiovascular Outcomes: An Updated Meta-Analysis and Meta-Regression of Interventional Trials. *Mayo Clin Proc*. 2021;96(2):304-313.

Bernasconi AA, Wilkin AM, Roke K, Ismail A. Development of a novel database to review and assess the clinical effects of EPA and DHA omega-3 fatty acids. *Prostaglandins Leukot Essent Fatty Acids*. 2022;183:102458. doi:10.1016/j.plefa.2022.102458

Rice HB, Bernasconi A, Maki KC, Harris WS, von Schacky C, Calder PC. Conducting omega-3 clinical trials with cardiovascular outcomes: Proceedings of a workshop held at ISSFAL 2014. *Prostaglandins Leukot Essent Fatty Acids*. 2016;107:30-42. doi:10.1016/j.plefa.2016.01.003

Nicholls SJ, Lincoff AM, Garcia M, et al. Effect of High-Dose Omega-3 Fatty Acids vs Corn Oil on Major Adverse Cardiovascular Events in Patients at High Cardiovascular Risk: The STRENGTH Randomized Clinical Trial. *JAMA*. 2020;324(22):2268-2280. doi:10.1001/jama.2020.22258

Kalstad AA, Myhre PL, Laake K, et al. Effects of n-3 Fatty Acid Supplements in Elderly Patients after Myocardial Infarction: A Randomized Controlled Trial [published online ahead of print, 2020 Nov 15]. *Circulation*. 2020;10.1161/CIRCULATIONAHA.120.052209. doi:10.1161/CIRCULATIONAHA.120.052209

Bernasconi AA, Lavie CJ, Milani RV, Laukkanen JA. Omega-3 Benefits Remain Strong Post-STRENGTH. *Mayo Clin Proc*. 2021;96(5):1371-1372. doi:10.1016/j.mayocp.2021.03.004

Bae JH, Lim H, Lim S. The Potential Cardiometabolic Effects of Long-Chain ω-3 Polyunsaturated Fatty Acids: Recent Updates and Controversies [published correction appears in Adv Nutr. 2024 Jan;15(1):100134. doi: 10.1016/j.advnut.2023.10.006]. *Adv Nutr*. 2023;14(4):612-628. doi:10.1016/j.advnut.2023.03.014

Samuel M, Nattel S. Fish Oil Supplements May Increase the Risk for Atrial Fibrillation: What Does This Mean?. *Circulation*. 2021;144(25):1991-1994. doi:10.1161/CIRCULATIONAHA.121.057464

Miller PE, Van Elswyk M, Alexander DD. Long-chain omega-3 fatty acids eicosapentaenoic acid and docosahexaenoic acid and blood pressure: a meta-analysis of randomized controlled trials. *Am J Hypertens*. 2014;27(7):885-896. doi:10.1093/ajh/hpu024

GOED appreciates the opportunity to provide feedback on this protocol. We remain at your disposal should any questions arise.

Sincerely,

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Appendix

A1 Interventional articles about cardiovascular diseases (2019-2024)

Year	PMID	Title
2024	38732508	Validation of Nutritional Approaches to Modulate Cardiovascular and Diabetic Risk Factors in Patients with Hypertriglyceridemia or Prediabetes-The MoKaRi II Randomized Controlled Study.
2024	38237669	Fish Oil Supplementation Modifies the Proteome, Lipidome, and Function of High-Density Lipoprotein: Findings from a Trial in Young Healthy Adults.
2024	38052385	ASCEND-Eye: Effects of Omega-3 Fatty Acids on Diabetic Retinopathy.
2024	37704431	Effect of Eicosapentaenoic Acid/Docosahexaenoic Acid on Coronary High-Intensity Plaques Detected Using Noncontrast T1-weighted Imaging: The AQUAMARINE EPA/DHA Randomized Study.
2023	38056999	Omega-3 supplementation effects on cardiovascular risk and inflammatory profile in chronic kidney disease patients in hemodialysis treatment: An intervention study.
2023	38018439	Risk Factors for the Development of New-Onset Persistent Atrial Fibrillation: Subanalysis of the VITAL Study.
2023	37960168	Fish Oil Supplementation with Resistance Exercise Training Enhances Physical Function and Cardiometabolic Health in Postmenopausal Women.
2023	37862823	Omega-3 fatty acids supplementation improves early-stage diabetic nephropathy and subclinical atherosclerosis in pediatric patients with type 1 diabetes: A randomized controlled trial.

2023	37839707	Effects of prenatal docosahexaenoic acid supplementation on offspring cardiometabolic health at 11 years differs by maternal single nucleotide polymorphism rs174602: follow-up of a randomized controlled trial in Mexico.
2023	37681568	Regression of Coronary Fatty Plaque and Risk of Cardiac Events According to Blood Pressure Status: Data From a Randomized Trial of Eicosapentaenoic Acid and Docosahexaenoic Acid in Patients With Coronary Artery Disease.
2023	37598001	Improved arterial inflammation with high dose omega-3 fatty acids in patients with elevated lipoprotein(a): Selective effect of eicosapentaenoic acid?
2023	37515843	Omega-3 fatty acid supplements and risk of atrial fibrillation and 'micro-atrial fibrillation': A secondary analysis from the OMEMI trial.
2023	37301235	Omega-3 polyunsaturated fatty acids (n-3 PUFAs), somatic and fatigue symptoms in cardiovascular diseases comorbid major depressive disorder (MDD): A randomized controlled trial.
2023	37202530	Lipid profile after omega-3 supplementation in neonates with intrauterine growth retardation: a randomized controlled trial.
2023	37049437	Consumption of Nutritionally Enriched Hen Eggs Enhances Endothelium-Dependent Vasodilation via Cyclooxygenase Metabolites in Healthy Young People-A Randomized Study.
2023	37023475	Final efficacy and cost analysis of a fish skin graft vs standard of care in the management of chronic diabetic foot ulcers: a prospective, multicenter, randomized controlled clinical trial.
2023	36802845	Cardiovascular Benefits of Icosapent Ethyl in Patients With and Without Atrial Fibrillation in REDUCE-IT.
2023	36579646	Docosahexaenoic Acid Levels and Omega-3 Index, but Not Eicosapentaenoic Acid Levels, Are Associated With Improved

		Cognition in Cognitively Healthy Subjects With Coronary Artery Disease.
2023	35953437	Potential effects of icosapent ethyl on cardiovascular outcomes in cigarette smokers: REDUCE-IT smoking.
2023	35772177	Effect of omega-3 fatty acids on cardiovascular events in high-risk patients with hypertriglyceridemia in Japan: a 3-year post-marketing surveillance study (OCEAN3 survey).
2022	36818927	EFFICACY OF A LIPID-LOWERING DIET ON KEY FATTY ACID RATIOS AND OMEGA-3 INDEX IN HYPERLIPIDEMIC SUBJECTS.
2022	35762321	Effects of Randomized Treatment With Icosapent Ethyl and a Mineral Oil Comparator on Interleukin-1β, Interleukin-6, C-Reactive Protein, Oxidized Low-Density Lipoprotein Cholesterol, Homocysteine, Lipoprotein(a), and Lipoprotein-Associated Phospholipase A2: A REDUCE-IT Biomarker Substudy.
2022	35744059	Omega-3 Fatty Acids Improve Chronic Kidney Disease-Associated Pruritus and Inflammation.
2022	35483753	Prevention of Cardiovascular Events and Mortality With Icosapent Ethyl in Patients With Prior Myocardial Infarction.
2022	35389487	A Randomized Trial of ω-3 Fatty Acid Supplementation and Circulating Lipoprotein Subclasses in Healthy Older Adults.
2022	35377160	Impact of Icosapent Ethyl on Cardiovascular Risk Reduction in Patients With Heart Failure in REDUCE-IT.
2022	35361442	1 Year HIIT and Omega-3 Fatty Acids to Improve Cardiometabolic Risk in Stage-A Heart Failure.
2022	35361440	Diabetes Mellitus, Race, and Effects of Omega-3 Fatty Acids on Incidence of Heart Failure Hospitalization.

2022	35261279	Treatment With Icosapent Ethyl to Reduce Ischemic Events in Patients With Prior Percutaneous Coronary Intervention: Insights From REDUCE-IT PCI.
2022	35027114	Consistency of Benefit of Icosapent Ethyl by Background Statin Type in REDUCE-IT.
2022	34982486	Changes in eicosapentaenoic acid and docosahexaenoic acid and risk of cardiovascular events and atrial fibrillation: A secondary analysis of the OMEMI trial.
2022	34842343	Omega 3 fatty acids can reduce early doxorubicin-induced cardiotoxicity in children with acute lymphoblastic leukemia.
2022	34776470	Effect of Omega-3 Fatty Acids on Coronary Plaque Morphology - A Serial Computed Tomography Angiography Study.
2022	34706839	Effectiveness of hospital lipid-lowering protocol of intensive lipid-lowering therapy for patients with acute coronary syndrome.
2022	33298663	Effects of a Japanese Cuisine-Based Antihypertensive Diet and Fish Oil on Blood Pressure and Its Variability in Participants with Untreated Normal High Blood Pressure or Stage I Hypertension: A Feasibility Randomized Controlled Study.
2021	34706555	Benefits of Icosapent Ethyl Across the Range of Kidney Function in Patients With Established Cardiovascular Disease or Diabetes: REDUCE-IT RENAL.
2021	34620410	Comparative Reductions in Investigator-Reported and Adjudicated Ischemic Events in REDUCE-IT.
2021	34371898	Effects of Mediterranean Diet or Low-Fat Diet on Blood Fatty Acids in Patients with Coronary Heart Disease. A Randomized Intervention Study.
2021	34298398	ω-3 fatty acid alleviates virus-induced myocardial injury by regulating TLR4 and TLR3 expression.

2021	33872197	A Multicenter, Blinded, Randomized Controlled Clinical Trial Evaluating the Effect of Omega-3-Rich Fish Skin in the Treatment of Chronic, Nonresponsive Diabetic Foot Ulcers.
2021	33839465	Pilot assessment of omega-3 fatty acids and potassium thiocyanate in sickle cell anemia patients with conditional peak systolic cerebral artery blood velocity.
2021	33724323	Effect of Marine Omega-3 Fatty Acid and Vitamin D Supplementation on Incident Atrial Fibrillation: A Randomized Clinical Trial.
2021	33684737	Omega-3 fatty acids reduce cardiometabolic risk in first-episode schizophrenia patients treated with antipsychotics: Findings from the OFFER randomized controlled study.
2021	33675344	ω-3 Ethyl ester results in better cognitive function at 12 and 30 months than control in cognitively healthy subjects with coronary artery disease: a secondary analysis of a randomized clinical trial.
2021	33573042	The Effect of Omega-3 Fatty Acid Supplementation on Serum Adipocytokines, Lipid Profile and Biochemical Markers of Inflammation in Recreational Runners.
2021	33413727	No effect of salmon fish protein on 2-h glucose in adults with increased risk of type 2 diabetes: a randomised controlled trial.
2021	33191772	Effects of n-3 Fatty Acid Supplements in Elderly Patients After Myocardial Infarction: A Randomized, Controlled Trial.
2021	33188400	APOE Genotype Disclosure and Lifestyle Advice in a Randomized Intervention Study with Finnish Participants.
2021	33148016	Reduction in Revascularization With Icosapent Ethyl: Insights From REDUCE-IT Revascularization Analyses.
2021	33131164	Effect of vitamin D and/or omega-3 fatty acid supplementation on stroke outcomes: A randomized trial.
2021	33041091	Omega-3 polyunsaturated fatty acid supplementation improves lipid metabolism and endothelial function by providing a beneficial

		eicosanoid-pattern in patients with acute myocardial infarction: A randomized, controlled trial.
2021	32609331	Effect of icosapent ethyl on progression of coronary atherosclerosis in patients with elevated triglycerides on statin therapy: a prospective, placebo-controlled randomized trial (EVAPORATE): interim results.
2020	33396567	Long Chain Omega-3 Polyunsaturated Fatty Acids Improve Vascular Stiffness in Abdominal Aortic Aneurysm: A Randomized Controlled Trial.
2020	33284131	A Remote Nutritional Intervention to Change the Dietary Habits of Patients Undergoing Ablation of Atrial Fibrillation: Randomized Controlled Trial.
2020	33228511	[Influence of Omega-3 PUFA on Non-invasive factors determining the risk of arrhYthmias eXcess and sudden cardiac death in patients with HFpEF with ischemic etiology (ONYX)].
2020	33190147	Effect of High-Dose Omega-3 Fatty Acids vs Corn Oil on Major Adverse Cardiovascular Events in Patients at High Cardiovascular Risk: The STRENGTH Randomized Clinical Trial.
2020	33170239	Effect of Vitamin D Supplementation, Omega-3 Fatty Acid Supplementation, or a Strength-Training Exercise Program on Clinical Outcomes in Older Adults: The DO-HEALTH Randomized Clinical Trial.
2020	32861211	Predictors of endothelial function improvement in patients with mild hypertriglyceridemia without evidence of coronary artery disease treated with purified eicosapentaenoic acid.
2020	32860032	Effect of icosapent ethyl on progression of coronary atherosclerosis in patients with elevated triglycerides on statin therapy: final results of the EVAPORATE trial.

2020	32805184	Effects of Fatty Acid Therapy in Addition to Strong Statin on Coronary Plaques in Acute Coronary Syndrome: An Optical Coherence Tomography Study.
2020	32759543	Concomitant Use of Rosuvastatin and Eicosapentaenoic Acid Significantly Prevents Native Coronary Atherosclerotic Progression in Patients With In-Stent Neoatherosclerosis.
2020	32756661	Effects of plant oils with different fatty acid composition on cardiovascular risk factors in moderately hypercholesteremic Chinese adults: a randomized, double-blinded, parallel-designed trial.
2020	32696697	Treatment With a Marine Oil Supplement Alters Lipid Mediators and Leukocyte Phenotype in Healthy Patients and Those With Peripheral Artery Disease.
2020	32636128	Administration of eicosapentaenoic acid may alter lipoprotein particle heterogeneity in statin-treated patients with stable coronary artery disease: A pilot 6-month randomized study.
2020	32488098	The Effect of Corrected Inflammation, Oxidative Stress and Endothelial Dysfunction on Fmd Levels in Patients with Selected Chronic Diseases: A Quasi-Experimental Study.
2020	32380746	Consumption of Goat Cheese Naturally Rich in Omega-3 and Conjugated Linoleic Acid Improves the Cardiovascular and Inflammatory Biomarkers of Overweight and Obese Subjects: A Randomized Controlled Trial.
2020	32165597	Omega-3 in Patients Undergoing Continuous Ambulatory Peritoneal Dialysis, Effects on Inflammatory Markers and Lipid Profile.
2020	32114641	Diets naturally rich in polyphenols and/or long-chain n-3 polyunsaturated fatty acids differently affect microbiota composition in high-cardiometabolic-risk individuals.
2020	32044905	Lowering effects of fish oil supplementation on proinflammatory markers in hypertension: results from a randomized controlled trial.

2020	32014347	Fish oil reduces subclinical inflammation, insulin resistance, and atherogenic factors in overweight/obese type 2 diabetes mellitus patients: A pre-post pilot study.
2020	31707829	REDUCE-IT USA: Results From the 3146 Patients Randomized in the United States.
2020	31543378	Administration of eicosapentaenoic acid may alter high-density lipoprotein heterogeneity in statin-treated patients with stable coronary artery disease: A 6-month randomized trial.
2020	30902738	Omega-3 polyunsaturated fatty acids in cardiovascular diseases comorbid major depressive disorder - Results from a randomized controlled trial.
2019	31868025	The Effect of Docosahexaenoic Acid and α-Lipoic Acid as Prevention of Bortezomib-Related Neurotoxicity in Patients With Multiple Myeloma.
2019	31757095	The Effect of Marine -3 Polyunsaturated Fatty Acids on Heart Rate Variability in Renal Transplant Recipients: A Randomized Controlled Trial.
2019	31532795	Genetic profiling of fatty acid desaturase polymorphisms identifies patients who may benefit from high-dose omega-3 fatty acids in cardiac remodeling after acute myocardial infarction-Post-hoc analysis from the OMEGA-REMODEL randomized controlled trial.
2019	31439224	Reduction in First and Total Ischemic Events With Icosapent Ethyl Across Baseline Triglyceride Tertiles.
2019	31334703	Effect of rosuvastatin and eicosapentaenoic acid on neoatherosclerosis: the LINK-IT Trial.
2019	31306043	Icosapent ethyl reduces atherogenic markers in high-risk statin-treated patients with stage 3 chronic kidney disease and high triglycerides.
2019	31277790	Effects of Icosapent Ethyl (Eicosapentaenoic Acid Ethyl Ester) on Atherogenic Lipid/Lipoprotein, Apolipoprotein, and Inflammatory

		Parameters in Patients With Elevated High-Sensitivity C-Reactive Protein (from the ANCHOR Study).
2019	31262371	Effects of -3 PUFA on endothelial function in patients with peripheral arterial disease: a randomised, placebo-controlled, double-blind trial.
2019	31190359	A comparison between the effects of flaxseed oil and fish oil supplementation on cardiovascular health in type 2 diabetic patients with coronary heart disease: A randomized, double-blinded, placebo-controlled trial.
2019	31163106	A Randomized Placebo-Controlled Trial of Omega-3 and Sertraline in Depressed Patients With or at Risk for Coronary Heart Disease.
2019	31100620	Effects of dietary intervention and n-3 PUFA supplementation on markers of gut-related inflammation and their association with cardiovascular events in a high-risk population.
2019	31055222	An omega-3 fatty acid plasma index ≥4% prevents progression of coronary artery plaque in patients with coronary artery disease on statin treatment.
2019	31023432	Cardiovascular Benefits of Fish-Oil Supplementation Against Fine Particulate Air Pollution in China.
2019	30993750	Eicosapentaenoic acid therapy is associated with decreased coronary plaque instability assessed using optical frequency domain imaging.
2019	30914500	n-3 PUFAs improve erythrocyte fatty acid profile in patients with small AAA: a randomized controlled trial.
2019	30913208	Fish oil and aspirin effects on arteriovenous fistula function: Secondary outcomes of the randomised omega-3 fatty acids (Fish oils) and Aspirin in Vascular access OUtcomes in REnal Disease (FAVOURED) trial.
2019	30898607	Effects of Icosapent Ethyl on Total Ischemic Events: From REDUCE-IT.

2019	30854986	Comparing the serum TAG response to high-dose supplementation of either DHA or EPA among individuals with increased cardiovascular risk: the ComparED study.
2019	30839013	Effects of n-3 fatty acid supplements on cardiometabolic profiles in hypertensive patients with abdominal obesity in Inner Mongolia: a randomized controlled trial.
2019	30803749	The Effects of OMEGA-3 Fatty Acid Supplementation Upon Interleukin-12 and Interleukin-18 in Chronic Kidney Disease Patients.
2019	30785660	Effects of basal insulin glargine and omega-3 on lower limb arterial disease outcome in patients with dysglycaemia: An analysis of the Outcome Reduction with an Initial Glargine INtervention (ORIGIN) trial.
2019	30584220	Bezafibrate Ameliorates Arterial Stiffness Assessed by Cardio-Ankle Vascular Index in Hypertriglyceridemic Patients with Type 2 Diabetes Mellitus.
2019	30511840	Lowering Effects of n-3 Fatty Acid Supplements on Blood Pressure by Reducing Plasma Angiotensin II in Inner Mongolia Hypertensive Patients: A Double-Blind Randomized Controlled Trial.
2019	30415637	Marine n-3 Fatty Acids and Prevention of Cardiovascular Disease and Cancer.
2019	30415628	Cardiovascular Risk Reduction with Icosapent Ethyl for Hypertriglyceridemia.
2019	30143885	Does administration of eicosapentaenoic acid increase soluble thrombomodulin level in statin-treated patients with stable coronary artery disease?
2019	29752009	Effects of omega-3 polyunsaturated fatty acids on fibrosis, endothelial function and myocardial performance, in ischemic heart failure patients.

2019	29474306	THREE-YEAR OUTCOMES IN A RANDOMIZED SINGLE-BLIND CONTROLLED TRIAL OF INTRAVITREAL RANIBIZUMAB AND ORAL SUPPLEMENTATION WITH DOCOSAHEXAENOIC ACID AND ANTIOXIDANTS FOR DIABETIC MACULAR EDEMA.

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A2 Interventional articles about cardiovascular diseases (2019-2024) that mention the word “Healthy” in their title or abstract

Year	PMID	Title
2024	38237669	Fish Oil Supplementation Modifies the Proteome, Lipidome, and Function of High-Density Lipoprotein: Findings from a Trial in Young Healthy Adults.
2023	36579646	Docosahexaenoic Acid Levels and Omega-3 Index, but Not Eicosapentaenoic Acid Levels, Are Associated With Improved Cognition in Cognitively Healthy Subjects With Coronary Artery Disease.
2022	35389487	A Randomized Trial of ω-3 Fatty Acid Supplementation and Circulating Lipoprotein Subclasses in Healthy Older Adults.
2021	33675344	ω-3 Ethyl ester results in better cognitive function at 12 and 30 months than control in cognitively healthy subjects with coronary artery disease: a secondary analysis of a randomized clinical trial.
2020	32696697	Treatment With a Marine Oil Supplement Alters Lipid Mediators and Leukocyte Phenotype in Healthy Patients and Those With Peripheral Artery Disease.
2019	31023432	Cardiovascular Benefits of Fish-Oil Supplementation Against Fine Particulate Air Pollution in China.

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A3 Interventional trials with supplementation as an intervention (≥ 1 year)

The following table shows all trials included in Bernasconi *et al* and Bernasconi, Lavie & Milani, with a short description of the number and characteristics of their participants.

Trial	Population	n (treated/control)	Dose (mg/day)	Composition	Publication Year	Length (months)
Nye (1)	Patients undergoing percutaneous transluminal coronary angioplasty.	73 (36/37)	3600	EPA+DHA	1990	12
HARP (2)	Patients with angiographically documented coronary heart disease and normal plasma lipid levels.	80 (41/39)	400	EPA+DHA	1995	24
SHOT (3)	Patients undergoing coronary artery bypass grafting.	610 (317/293)	3320	EPA+DHA	1996	12
GISSI-P (4)	Patients surviving a recent (< or = 3 months) myocardial infarction.	11324 (5666/5658)	866	EPA+DHA	1999	42
SCIMO (5)	People with angiographically proven coronary artery disease.	223 (112/111)	2000	EPA+DHA	1999	24
Brox (6)	Subjects with moderate hypercholesterolemia.	120 (80/40)	3000	EPA+DHA	2001	14
OFAMI (7)	Patients with recent myocardial infarction.	300 (150/150)	3360	EPA+DHA	2001	24

AREDS2 (8)	Participants who were at risk for developing late age-related macular degeneration	4203 (2147/2056)	1000	EPA+DHA	2003	60
FAAT (9)	Patients with implanted cardioverter/defibrillators	402 (200/202)	2600	EPA+DHA	2005	12
Puri (10)	Patients with Huntington disease.	121 (60/61)	1900	EPA only	2005	12
Raitt (11)	Patients with an implantable cardioverter defibrillator and a recent episode of sustained ventricular tachycardia or ventricular fibrillation.	200 (100/100)	1300	EPA+DHA	2005	24
Baldassare (12)	Patients with combined hyperlipoproteinemia.	64 (32/32)	1800	EPA+DHA	2006	24
SOFA (13)	Patients with implantable cardioverter defibrillators.	546 (273/273)	799	EPA+DHA	2006	12
JELIS (14)	Hypercholesterolaemic patients on statins.	18645 (9326/9319)	1800	EPA only	2007	60
EPIC-1 (15)	Patients with quiescent Crohn disease.	374 (188/186)	3000	EPA+DHA	2008	52
GISSI-HF (16)	Patients with chronic heart failure.	6975 (3494/3481)	867	EPA+DHA	2008	47
Nutristroke (17)	Stroke patients.	72 (38/34)	500	EPA+DHA	2009	12
OMEGA (18)	Patients with depression, after a myocardial infarction.	3453 (1752/1701)	846	EPA+DHA	2009	12
AlphaOmega (19)	Patients, 60 - 80 years, who had had a myocardial infarction and were receiving state-of-the-art antihypertensive,	4837 (2404/2433)	400	EPA+DHA	2010	40

	antithrombotic, and lipid-modifying therapy.					
DO-IT (20)	Elderly men with hypercholesterolaemia.	563 (282/281)	1320	EPA+DHA	2010	36
SU.FOL. OM3 (21)	Participants with coronary heart disease.	2501 (1253/1248)	600	EPA+DHA	2010	48
Nodari (22)	Patients with dilated cardiomyopathy.	133 (67/66)	1700	EPA+DHA	2011	12
Kumar (23)	Patients with persistent atrial fibrillation.	78 (39/39)	1740	EPA+DHA	2012	12
ORIGIN (24)	Patients with dysglycemia and at a high risk for cardiovascular events.	12536 (6281/6255)	840	EPA+DHA	2012	72
AFFORD (25)	Patients with symptomatic paroxysmal or persistent atrial fibrillation.	316 (153/163)	2400	EPA+DHA	2013	12
FORWARD (26)	Participants with confirmed symptomatic paroxysmal AF that required cardioversion.	586 (289/297)	850	EPA+DHA	2013	12
Risk & Prevention (27)	Patients with multiple cardiovascular risk factors or atherosclerotic vascular disease but not myocardial infarction.	12505 (6239/6266)	870	EPA+DHA	2013	60
Doi (28)	Patients with acute coronary syndromes.	238 (119/119)	1800	EPA only	2014	12
EPE-A (29)	Subjects with NASH and nonalcoholic fatty liver disease (NAFLD) activity scores ≥ 4, with minimum scores of 1 for steatosis and inflammation, along with	243 (168/75)	2700	EPA only	2014	12

	either ballooning or at least stage 1a fibrosis.					
Shinto (30)	Patients 55+ with a diagnosis of probable Alzheimer's disease	26 (13/13)	1650	EPA+DHA	2014	12
Proudman (31)	Patients with recent-onset rheumatoid arthritis.	140 (87/53)	5500	EPA+DHA	2015	12
Derosa (32)	Patients with impaired fasting glucose or impaired glucose tolerance.	258 (128/130)	2550	EPA+DHA	2016	18
FOSTAR (33)	Patients with knee osteoarthritis and regular knee pain.	202 (101/101)	4500	EPA+DHA	2016	24
Sandhu (34)	Healthy postmenopausal women with high breast density as detected on routine screening mammograms.	213 (107/106)	3360	EPA+DHA	2016	24
HEARTS (35)	Subjects with stable coronary artery disease, on statins.	283 (143/142)	3360	EPA+DHA	2017	30
MAPT (36)	Elderly adults with memory complaints	1652 (820/832)	1030	EPA+DHA	2017	36
ASCEND (37)	Patients with diabetes but without evidence of atherosclerotic cardiovascular disease	15480 (7740/7740)	840	EPA+DHA	2018	89
ENRGISE (38)	Patients aged 70+, with self-reported mobility impairment.	289 (148/141)	1800	EPA+DHA	2018	12
REDUCE-IT (39)	Patients with established cardiovascular disease or with diabetes and other risk factors, receiving statin therapy and with a	8179 (4089/4090)	3880	EPA only	2018	59

	fasting triglyceride level of 135 -499 mg/dl.					
VITAL (40)	Participants without a prior history of heart disease, stroke, or cancer.	25871 (12933/12938)	840	EPA+DHA	2018	64
OMEMI (41)	Elderly participants with a recent MI.	1027 (505/509)	1800	EPA+DHA		
STRENGTH (42)	Statin-treated participants at high cardiovascular risk, with hypertriglyceridemia and low HDL-C.	13078(6539/6539)	3000	EPA+DHA		

1. Nye ER, Ablett MB, Robertson MC, Ilsley CD, Sutherland WH. Effect of eicosapentaenoic acid on restenosis rate, clinical course and blood lipids in patients after percutaneous transluminal coronary angioplasty. Aust N Z J Med. 1990;20(4):549-52.
2. Sacks FM, Stone PH, Gibson CM, Silverman DI, Rosner B, Pasternak RC. Controlled trial of fish oil for regression of human coronary atherosclerosis. HARP Research Group. J Am Coll Cardiol. 1995;25(7):1492-8.
3. Eritsland J, Arnesen H, Grønseth K, Fjeld NB, Abdelnoor M. Effect of dietary supplementation with n-3 fatty acids on coronary artery bypass graft patency. Am J Cardiol. 1996;77(1):31-6.
4. Dietary supplementation with n-3 polyunsaturated fatty acids and vitamin E after myocardial infarction: results of the GISSI-Prevenzione trial. Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico. Lancet. 1999;354(9177):447-55.
5. Von schacky C, Baumann K, Angerer P. The effect of n-3 fatty acids on coronary atherosclerosis: results from SCIMO, an angiographic study, background and implications. Lipids. 2001;36 Suppl:S99-102.
6. Brox J, Olaussen K, Osterud B, et al. A long-term seal- and cod-liver-oil supplementation in hypercholesterolemic subjects. Lipids. 2001;36(1):7-13.
7. Nilsen DW, Albrektsen G, Landmark K, Moen S, Aarsland T, Woie L. Effects of a high-dose concentrate of n-3 fatty acids or corn oil introduced early after an acute myocardial infarction on serum triacylglycerol and HDL cholesterol. Am J Clin Nutr. 2001;74(1):50-6.

8. Chew EY, Clemons TE, Agrón E, et al. Effect of Omega-3 Fatty Acids, Lutein/Zeaxanthin, or Other Nutrient Supplementation on Cognitive Function: The AREDS2 Randomized Clinical Trial. JAMA. 2015;314(8):791-801.
9. Leaf A, Albert CM, Josephson M, et al. Prevention of fatal arrhythmias in high-risk subjects by fish oil n-3 fatty acid intake. Circulation. 2005;112(18):2762-8.
10. Puri BK, Leavitt BR, Hayden MR, et al. Ethyl-EPA in Huntington disease: a double-blind, randomized, placebo-controlled trial. Neurology. 2005;65(2):286-92.
11. Raitt MH, Connor WE, Morris C, et al. Fish oil supplementation and risk of ventricular tachycardia and ventricular fibrillation in patients with implantable defibrillators: a randomized controlled trial. JAMA. 2005;293(23):2884-91.
12. Baldassarre D, Amato M, Eligini S, et al. Effect of n-3 fatty acids on carotid atherosclerosis and haemostasis in patients with combined hyperlipoproteinemia: a double-blind pilot study in primary prevention. Ann Med. 2006;38(5):367-75.
13. Brouwer IA, Zock PL, Camm AJ, et al. Effect of fish oil on ventricular tachyarrhythmia and death in patients with implantable cardioverter defibrillators: the Study on Omega-3 Fatty Acids and Ventricular Arrhythmia (SOFA) randomized trial. JAMA. 2006;295(22):2613-9.
14. Yokoyama M, Origasa H, Matsuzaki M, et al. Effects of eicosapentaenoic acid on major coronary events in hypercholesterolaemic patients (JELIS): a randomised open-label, blinded endpoint analysis. Lancet. 2007;369(9567):1090-8.

15. Feagan BG, Sandborn WJ, Mittmann U, et al. Omega-3 free fatty acids for the maintenance of remission in Crohn disease: the EPIC Randomized Controlled Trials. JAMA. 2008;299(14):1690-7.
16. Tavazzi L, Maggioni AP, Marchioli R, et al. Effect of n-3 polyunsaturated fatty acids in patients with chronic heart failure (the GISSI-HF trial): a randomised, double-blind, placebo-controlled trial. Lancet. 2008;372(9645):1223-30.
17. Garbagnati F, Cairella G, De Martino A, et al. Is antioxidant and n-3 supplementation able to improve functional status in poststroke patients? Results from the Nutristroke Trial. *Cerebrovasc Dis*. 2009;27(4):375–383.
18. Zimmer R, Riemer T, Rauch B, et al. Effects of 1-year treatment with highly purified omega-3 fatty acids on depression after myocardial infarction: results from the OMEGA trial. J Clin Psychiatry. 2013;74(11):e1037-45.
19. Kromhout D, Giltay EJ, Geleijnse JM. n-3 fatty acids and cardiovascular events after myocardial infarction. N Engl J Med. 2010;363(21):2015-26.
20. Hjerkinn EM, Abdelnoor M, Breivik L, et al. Effect of diet or very long chain omega-3 fatty acids on progression of atherosclerosis, evaluated by carotid plaques, intima-media thickness and by pulse wave propagation in elderly men with hypercholesterolaemia. Eur J Cardiovasc Prev Rehabil. 2006;13(3):325-33.
21. Blacher J, Czernichow S, Paillard F, et al. Cardiovascular effects of B-vitamins and/or N-3 fatty acids: the SU.FOL.OM3 trial. Int J Cardiol. 2013;167(2):508-13.

22. Nodari S, Triggiani M, Campia U, et al. Effects of n-3 polyunsaturated fatty acids on left ventricular function and functional capacity in patients with dilated cardiomyopathy. J Am Coll Cardiol. 2011;57(7):870-9.
23. Kumar S, Sutherland F, Morton JB, et al. Long-term omega-3 polyunsaturated fatty acid supplementation reduces the recurrence of persistent atrial fibrillation after electrical cardioversion. *Heart Rhythm*. 2012;9(4):483–491.
24. Bosch J, Gerstein HC, Dagenais GR, et al. n-3 fatty acids and cardiovascular outcomes in patients with dysglycemia. N Engl J Med. 2012;367(4):309-18.
25. Nigam A, Talajic M, Roy D, et al. Fish oil for the reduction of atrial fibrillation recurrence, inflammation, and oxidative stress. J Am Coll Cardiol. 2014;64(14):1441-8.
26. Macchia A, Grancelli H, Varini S, et al. Omega-3 fatty acids for the prevention of recurrent symptomatic atrial fibrillation: results of the FORWARD (Randomized Trial to Assess Efficacy of PUFA for the Maintenance of Sinus Rhythm in Persistent Atrial Fibrillation) trial. J Am Coll Cardiol. 2013;61(4):463-8.
27. Roncaglioni MC, Tombesi M, Avanzini F, et al. n-3 fatty acids in patients with multiple cardiovascular risk factors. N Engl J Med. 2013;368(19):1800-8.
28. Nosaka K, Miyoshi T, Iwamoto M, et al. Early initiation of eicosapentaenoic acid and statin treatment is associated with better clinical outcomes than statin alone in patients with acute coronary syndromes: 1-year outcomes of a randomized controlled study. Int J Cardiol. 2017;228:173-9.

29. Sanyal AJ, Abdelmalek MF, Suzuki A, Cummings OW, Chojkier M. No significant effects of ethyl-eicosapentanoic acid on histologic features of nonalcoholic steatohepatitis in a phase 2 trial. Gastroenterology. 2014;147(2):377-84.e1.
30. Shinto L, Quinn J, Montine T, et al. A randomized placebo-controlled pilot trial of omega-3 fatty acids and alpha lipoic acid in Alzheimer's disease. *J Alzheimers Dis*. 2014;38(1):111–120.
31. Proudman SM, Cleland LG, Metcalf RG, Sullivan TR, Spargo LD, James MJ. Plasma n-3 fatty acids and clinical outcomes in recent-onset rheumatoid arthritis. Br J Nutr. 2015;114(6):885-90.
32. Derosa G, Cicero AF, D'angelo A, Borghi C, Maffioli P. Effects of n-3 pufas on fasting plasma glucose and insulin resistance in patients with impaired fasting glucose or impaired glucose tolerance. Biofactors. 2016;42(3):316-22.
33. Hill CL, March LM, Aitken D, et al. Fish oil in knee osteoarthritis: a randomised clinical trial of low dose versus high dose. Ann Rheum Dis. 2016;75(1):23-9.
34. Sandhu N, Schetter SE, Liao J, et al. Influence of Obesity on Breast Density Reduction by Omega-3 Fatty Acids: Evidence from a Randomized Clinical Trial. Cancer Prev Res (Phila). 2016;9(4):275-82.
35. Alfaddagh A, Elajami TK, Ashfaque H, Saleh M, Bistrian BR, Welty FK. Effect of Eicosapentaenoic and Docosahexaenoic Acids Added to Statin Therapy on Coronary Artery Plaque in Patients With Coronary Artery Disease: A Randomized Clinical Trial. J Am Heart Assoc. 2017 Dec 15;6(12):e006981.

36. Andrieu S, Guyonnet S, Coley N, et al. Effect of long-term omega 3 polyunsaturated fatty acid supplementation with or without multidomain intervention on cognitive function in elderly adults with memory complaints (MAPT): a randomised, placebo-controlled trial. Lancet Neurol. 2017;16(5):377-389.
37. Bowman L, Mafham M, Wallendszus K, et al. Effects of n-3 Fatty Acid Supplements in Diabetes Mellitus. N Engl J Med. 2018;379(16):1540-50.
38. Pahor M, Anton SD, Beavers DP, et al. Effect of Losartan and Fish Oil on Plasma IL-6 and Mobility in Older Persons. The ENRGISE Pilot Randomized Clinical Trial. *J Gerontol A Biol Sci Med Sci*. 2019;74(10):1612–1619.
39. Bhatt DL, Steg PG, Miller M, et al. Cardiovascular Risk Reduction with Icosapent Ethyl for Hypertriglyceridemia. N Engl J Med. 2019;380(1):11-22.
40. Manson JE, Cook NR, Lee IM, et al. Marine n-3 Fatty Acids and Prevention of Cardiovascular Disease and Cancer. N Engl J Med. 2019;380(1):23-32.
41. Kalstad AA, Myhre PL, Laake K, et al. Effects of n-3 Fatty Acid Supplements in Elderly Patients After Myocardial Infarction: A Randomized, Controlled Trial. *Circulation*. 2021;143(6):528-539. doi:10.1161/CIRCULATIONAHA.120.052209
42. Nicholls SJ, Lincoff AM, Garcia M, et al. Effect of High-Dose Omega-3 Fatty Acids vs Corn Oil on Major Adverse Cardiovascular Events in Patients at High Cardiovascular Risk: The STRENGTH Randomized Clinical Trial. *JAMA*. 2020;324(22):2268-2280. doi:10.1001/jama.2020.22258

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A4 Primary prevention trials, or trials with some primary prevention participants

Trial	Population	n (treated/control)	Dose (mg/day)	Composition	Publication Year	Length (months)
Brox	Subjects with moderate hypercholesterolemia.	120 (80/40)	3000	EPA+DHA	1990	12
AREDS2	Participants who were at risk for developing late age-related macular degeneration	4203 (2147/2056)	1000	EPA+DHA	1996	24
Puri	Patients with Huntington disease.	121 (60/61)	1900	EPA only	1999	12
Baldassare	Patients with combined hyperlipoproteinemia.	64 (32/32)	1800	EPA+DHA	1999	42
JELIS	Hypercholesterolaemic patients on statins.	18645 (9326/9319)	1800	EPA only	2001	24
EPIC-1	Patients with quiescent Crohn disease.	374 (188/186)	3000	EPA+DHA	2001	14
DO-IT	Elderly men with hypercholesterolaemia.	563 (282/281)	1320	EPA+DHA	2003	24
ORIGIN	Patients with dysglycemia and at a high risk for cardiovascular events.	12536 (6281/6255)	840	EPA+DHA	2005	60
EPE-A	Subjects with NASH and nonalcoholic fatty liver disease (NAFLD) activity scores ≥ 4, with minimum scores of 1 for steatosis and inflammation, along with either ballooning or at least stage 1a fibrosis.	243 (168/75)	2700	EPA only	2005	12

Shinto	Patients 55+ with a diagnosis of probable Alzheimer's disease	26 (13/13)	1650	EPA+DHA	2006	24
Proudman	Patients with recent-onset rheumatoid arthritis.	140 (87/53)	5500	EPA+DHA	2006	24
Derosa	Patients with impaired fasting glucose or impaired glucose tolerance.	258 (128/130)	2550	EPA+DHA	2007	12
FOSTAR	Patients with knee osteoarthritis and regular knee pain.	202 (101/101)	4500	EPA+DHA	2008	60
Sandhu	Healthy postmenopausal women with high breast density as detected on routine screening mammograms.	213 (107/106)	3360	EPA+DHA	2008	52
MAPT	Elderly adults with memory complaints	1652 (820/832)	1030	EPA+DHA	2009	47
ASCEND	Patients with diabetes but without evidence of atherosclerotic cardiovascular disease	15480 (7740/7740)	840	EPA+DHA	2009	12
ENRGISE	Patients aged 70+, with self-reported mobility impairment.	289 (148/141)	1800	EPA+DHA	2010	12
REDUCE-IT	Patients with established cardiovascular disease or with diabetes and other risk factors, receiving statin therapy and with a fasting triglyceride level of 135 -499 mg/dl.	8179 (4089/4090)	3880	EPA only	2010	40
VITAL	Participants without a prior history of heart disease, stroke, or cancer.	25871 (12933/12938)	840	EPA+DHA	2010	36

STRENGTH	Statin-treated participants at high cardiovascular risk, with hypertriglyceridemia and low HDL-C.	13078(6539/6539)	3000	EPA+DHA	2011	48