Circulation: Arrhythmia and Electrophysiology

ORIGINAL ARTICLE

Effects of Omega-3 Fatty Acid Treatment on Risk for Atrial Fibrillation: An Updated Meta-Analysis of 35 Trials including 114 592 Individuals

Nada R. Abuknesha, PhD; James H O'Keefe, MD; Frank Qian, MD, MPH; Nathan L. Tintle, PhD; Yidie Lin, MB; Yue Sun, MB; Han-Zhu Qian, MD, PhD; Paul S. Aisen, MD; Christine M. Albert, MD, MPH; William J. Aronson, MD; Abdul Aziz A. Asbeutah, MD; Heike A. Bischoff-Ferrari, DrPH, MD; Matthew J. Budoff, MD; Nicholas R. Burns, PhD; Cecilia A. Cardenas, BS; Cynthia M. Carlsson, MD, MS; Emily Y. Chew, MD; Neal J. Cohen, MD; Léopold K. Fezeu, MD, PhD; Amana Liddell, BS; Pilar Galan, MD, PhD; Mark A. Hull, PhD, FRCP; Tsuo-Hung Lan, MD, PhD; Pan-Yen Lin, MD, PhD; Alexia Mengelberg, PhD; Anne-Marie Minihane, PhD; Joseph F. Quinn, MD; Thomas A.B. Sanders, DSc, PhD, FAFN, FHEA, FRSM; Andrew Scholey, PhD; David A. Schoenfeld, PhD; Kirsty Sprange, PhD; Kuan-Pin Su, MD, PhD; Christopher H. van Dyck, MD; Carol A. Van Hulle, PhD; David Vauzour, PhD; Claire Weber, PhD; Francine K. Welty, MD, PhD; Gary Wittert, MBBch, MD, FRACP; William S. Harris, PhD

BACKGROUND: Recent meta-analyses of randomized controlled trials have raised concerns that treatment with omega-3 fatty acids may increase the risk of atrial fibrillation (AF). However, these meta-analyses included at most 8 trials. The aim of this current meta-analysis was to expand the search by including other eligible omega-3 randomized controlled trials with AF incidence data, incorporating both published and unpublished data.

METHODS: Eligible studies were randomized controlled trials investigating daily doses of ≥500 mg/d of docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA). Additional inclusion criteria included ≥12 months of treatment with EPA/DHA, participants ≥50 years of age, and, where possible, the absence of known AF/atrial flutter at baseline. The primary outcome was the occurrence of new-onset AF. Our primary hypothesis was that risk for AF would simultaneously depend on both omega-3 dose (above or below 1500 mg/d) and background cardiovascular disease risk status, and that their combined impact on AF risk would be synergistic.

RESULTS: A total of 35 randomized controlled trials (37 data sets; n=114 592) were included in this meta-analysis. Only studies including patients at high-risk for cardiovascular disease who were treated with high-doses of EPA/DHA (>1500 mg/d) showed a statistically significant increase in AF risk with a pooled odds ratio (OR) of 1.43 (95% CI, 1.14–1.79) and an absolute risk difference of 0.8% (0.40%–1.1%). None of the other 3 groups showed statistically significant levels of AF risk (odds ratios, 1.07 [high risk–low dose], 1.06 [low risk–low dose], and 1.03 [low risk–high dose]).

CONCLUSIONS: This meta-analysis suggests that high-dose EPA/DHA treatment is associated with an increased risk of AF in patients at high cardiovascular disease risk, whereas low-dose EPA/DHA does not appear to increase AF risk, even in high-risk populations. Further prospective studies are needed to evaluate any potential increased risk of higher doses balanced against potential benefits.

GRAPHIC ABSTRACT: A graphic abstract is available for this article.

Key Words: atrial fibrillation ■ atrial flutter ■ cardiovascular diseases ■ docosahexaenoic acid ■ eicosapentaenoic acid

Correspondence to: Nada R. Abuknesha, PhD, The Fatty Acid Research Institute (FARI), 4600 W Nobel St, Ste 123, Sioux Falls, SD 57107. Email nada@faresinst.com
Supplemental Material is available at https://www.ahajournals.org/doi/suppl/10.1161/CIRCEP.125.014785.

Circulation: Arrhythmia and Electrophysiology is available at www.ahajournals.org/journal/circep

WHAT IS KNOWN?

- Previous meta-analyses of omega-3 fatty acid randomized controlled trials have reported a dose-response relationship with risk for atrial fibrillation (AF), but these have included no more than 8 trials.
- Emerging evidence has challenged these findings, with observational biomarker studies suggesting higher circulating marine omega-3 fatty acid levels may be associated with lower AF risk (particularly at low-to-intermediate doses), while concerns have also been raised regarding inconsistent AF ascertainment and selective outcome reporting in prior analyses.

WHAT THE STUDY ADDS

- This meta-analysis incorporated both published and underutilized data sources, including adverse event records, trial registry data, and investigator-provided unpublished AF data, thereby substantially expanding the evidence base on omega-3 fatty acids and AF risk.
- Stratification by omega-3 dose and baseline cardiovascular disease risk provided a more clinically relevant understanding of how lower-dose omega-3 supplementation (including doses commonly achievable through diet or standard nutritional supplementation) may affect AF risk across different patient populations, as distinct from the effects observed with high-dose pharmaceutical omega-3 products.
- Increased AF risk was observed primarily in high-risk cardiovascular disease populations receiving high-dose omega-3s (>1500 mg/d eicosapentaenoic acid+docosahexaenoic acid), whereas lower doses (≤1500 mg/d) were not associated with increased AF risk, even in high-risk populations.

Nonstandard Abbreviations and Acronyms

AF	atrial fibrillation
ASCEND	A Study of Cardiovascular Events in Diabetes
CVD	cardiovascular disease
DHA	docosahexaenoic acid
EPA	eicosapentaenoic acid
FA	fatty acid
GISSI-HF	Gruppo Italiano per lo Studio della Sopravvivenza nell'Insufficienza Cardiaca
HR-HD	high risk-high dose
HR-LD	high risk-low dose
LR-HD	low risk-high dose
LR-LD	low risk-low dose
OR	odds ratio
PI	principal investigator
RCT	randomized controlled trial
REDUCE-IT	Reduction of Cardiovascular Events With Icosapent Ethyl–Intervention Trial
RESPECT-EPA	Randomized Trial for Evaluation in Secondary Prevention Efficacy of Combination Therapy–Statin and Eicosapentaenoic Acid

Recent meta-analyses of randomized controlled trials (RCTs) have raised concerns that omega-3 fatty acid (FA) supplementation may increase the risk of incident atrial fibrillation (AF), potentially in a dose-dependent manner. Gencer et al[1] reviewed 7 RCTs focused on cardiovascular outcomes and found that the risk for AF was increased by 25% with omega-3 treatment. Bae et al[2] reported similar associations, and Jia et al[3] found a lower risk for AF among the 5 low-dose omega-3 FA studies compared with the risk in 3 higher risk studies.

Emerging evidence, however, has called these findings into question. For example, a 2023 biomarker-based meta-analysis of 17 prospective cohorts found that higher circulating levels of marine omega-3 FAs were inversely associated with incident AF, suggesting a potential protective impact of low to intermediate doses known to produce such blood levels.[4] Furthermore, methodological concerns have been raised regarding prior interventional analyses, including inconsistent reporting of AF outcomes, potential informative censoring due to longer survival in omega-3 treated groups compared with placebo groups,[5] and discrepancies in AF case ascertainment.[6] These factors may have contributed to an overestimation of AF risk in prior analyses.

According to PubMed (August 16, 2025), over the last 40 years, there have been over 3900 published RCTs involving omega-3 FAs, there is a significant opportunity to reexamine the omega-3/AF issue using a broader evidence base by including supplementation studies where AF was not a prespecified outcome but would have been recorded as an adverse event had it developed. The goal of this analysis was to conduct a more comprehensive review of the literature and to perform an updated meta-analysis of RCTs to better understand the relationship between omega-3 supplementation and AF risk.

In contrast to earlier meta-analyses,[1–3] we integrated both published and underutilized data sources, including trial registries and unpublished data sets, to reduce selective reporting bias. We further ensured that trials reporting no AF events contributed to the pooled evidence base. Finally, we applied a cardiovascular disease (CVD) risk/dose stratification framework to distinguish between doses largely achievable through diet or typical supplementation versus approved doses of pharmacological formulations.

METHODS

The protocol for this study is registered at the International Prospective Register of Systematic Reviews (PROSPERO, CRD420251233813). The conduct and reporting of this systematic review and meta-analysis adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 guidelines.[7]

This meta-analysis included published data and unpublished summary data provided by individual study investigators. Restrictions apply to the availability of unpublished data, which were obtained with permission for the purposes of this study and are not publicly available. Studies contributing unpublished data are identified in Table S1. All analytic methods are described within the Methods section, with additional procedural details provided in the Supplemental Methods. Requests for access to underlying data should be directed to the original study investigators or relevant data custodians.

Institutional review board approval and written informed consent were obtained in the original studies, as reported by the respective investigators.

Eligibility Criteria

Eligible studies were parallel-group RCTs investigating omega-3 FA supplementation containing eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), administered in capsule or liquid oil form, at a dosage meeting or exceeding ≥500 mg/d of EPA+DHA, consistent with international intake recommendations.[8–10] This followed the precedent of all prior meta-analyses, which only included studies where EPA+DHA intakes exceeded this threshold. There was no upper limit on dosage. Trials were required to have a minimum treatment duration of 12 months and to enroll participants aged ≥50 years, reflecting the age at which AF risk begins to increase.[11] There were no restrictions on EPA:DHA ratio or chemical form (eg, ethyl esters, triglycerides, phospholipids). Multicomponent intervention studies were eligible if data from an appropriate nonomega-3 control group were available. We excluded trials that: administered omega-3s solely through dietary sources or food-based delivery formats; relied on dietary or lifestyle counseling as the sole intervention; used omega-3s in the comparator arm; or lacked a placebo or control group. Studies were also excluded if intervention and control groups were not treated in parallel for at least 12 months. Studies were included regardless of participants' baseline health status. All individuals with known AF (paroxysmal, persistent, or permanent) at baseline were excluded. For studies enrolling participants both with and without prior AF, data from participants with documented baseline AF were excluded where possible. Additional eligibility details are provided in the Supplemental Methods.

Search Strategy

A systematic search was conducted across multiple bibliographic databases, clinical trial registries, and data repositories, including PubMed, ClinicalTrials.gov, International Standard Randomised Controlled Trial Number Registry, Clinical Drug Experience Knowledgebase, medRxiv, and other relevant sources. Searches were conducted through November 2025 and were updated approximately monthly. Reference lists of prior systematic reviews and key primary studies were also screened to ensure comprehensive coverage.

Titles and abstracts were screened by 1 reviewer (N.A.), with all exclusions independently checked by a second reviewer (W.H.). Full-text eligibility was assessed independently by both reviewers, with disagreements resolved through discussion or consultation with a third reviewer (F.Q.). Screening was performed in an unblinded manner. Full search terms, registry-specific strategies, and targeted searches for unpublished or registry-only trials are detailed in the Supplemental Methods.

Outcome

The primary outcome was the occurrence of new-onset AF/flutter as determined through central adjudication, ECG, electronic medical records, insurance claims, and patient-reported adverse events.

Data Collection and Extraction

One reviewer (N.A.) extracted all relevant data, which were independently verified by a second reviewer (W.H.). Extracted variables included trial name, registration number, publication year, study design, comparator, omega-3 dose and formulation, supplementation duration, sample size, participant characteristics, target population, and outcomes of interest. Definitions of end points were not standardized across studies. Trial quality was assessed using the modified Jadad scale (0–8), with scores ≥5 indicating high quality.

Published AF data were defined as new-onset AF events reported in peer-reviewed publications, Supplemental Materials, publicly accessible safety reports, clinical trial registries, or other secondary sources. Adverse and serious adverse events, reported using standardized adverse event classification systems,[12–16] were systematically reviewed to identify AF events. Broader event categories (eg, cardiac events or palpitations) were not classified as AF unless clarified by principal investigators (PIs).

For studies that did not prespecify AF and did not report AF-related events, zero events were not assumed unless outcome ascertainment procedures and investigator confirmation justified this classification. Detailed procedures for adverse event review, AF ascertainment, zero-event classification, and investigator verification are described in the Supplemental Methods.

Acquiring Unpublished Data

To minimize reporting bias, we proactively contacted PIs of eligible trials to determine whether AF outcomes had been collected or could be verified. For the purposes of this review, unpublished data were defined as AF/flutter outcome data not reported in peer-reviewed publications or publicly accessible sources, irrespective of whether the primary trial results had already been published. This included investigator-provided data, nonpublic data sets obtained through formal access requests, and data from completed registered trials for which primary results were not yet published at the time of the meta-analysis. Studies were included only when AF outcome status could be confirmed or when monitoring procedures justified the absence of reported events.

A maximum of 3 follow-up attempts were made to contact coauthors in cases of nonresponding lead authors over a period of ≈6 months. All direct investigator outreach efforts were

concluded in December 2025. All responses from PIs, including confirmations, clarifications, and statements of unavailable or unreliable AF data, are documented in Tables S1 and S2. Expanded descriptions of investigator contact procedures, follow-up strategy, and interpretation of unavailable AF data are provided in the Supplemental Methods.

Data Synthesis

Since CVD risk status and the EPA/DHA dose may each plausibly influence the development of AF, and this influence may be synergistic, we prespecified analyses that simultaneously stratified by both variables to explore their potential modifying effects. Trials were classified into 4 strata: high risk-high dose (HR-HD), high risk-low dose (HR-LD), low risk-high dose (LR-HD), and low risk-low dose (LR-LD).

CVD risk status was defined based on baseline atherosclerotic cardiovascular disease or the presence of multiple CVD risk factors. Low CVD risk was defined as the absence of diagnosed atherosclerotic cardiovascular disease, including trials enrolling participants for non-cardiovascular indications or general wellness.

Omega-3 dose was categorized as ≤1500 mg/d or >1500 mg/d to distinguish intakes achievable through diet or dietary supplements from those requiring pharmacological formulations. This threshold was selected based on several factors: it is below the lowest approved daily dose of pharmaceutical-grade omega-3 products (ie, Vascepa 1800 mg/d) and it has been shown to produce upper quintile levels of the omega-3 index (ie, erythrocyte EPA+DHA, a validated biomarker of omega-3 intake[17,18]) which have been associated with the lowest risk of AF,[4,19] stroke,[20] and all-cause mortality[21] in large long-term epidemiological studies. Further details on the rationale used to distinguish EPA/DHA intakes from dietary supplements versus pharmacological agents can be found in Supplemental Appendix 1.

AF event counts and denominators were extracted separately for intervention and control arms. Where multiple omega-3 dose arms were present, arms were pooled or stratified as appropriate to avoid double-counting comparators. Trials with unresolved AF outcome status after investigator contact were excluded from the meta-analysis (Table S2). Additional details on trial stratification, CVD risk classification, and arm pooling procedures are provided in the Supplemental Methods.

Data Analysis

Absolute risk for AF was computed as the number of reported AF events divided by the number of subjects in the treatment group. The relative risk for AF was computed by dividing the absolute risk in the omega-3 group by that of the control group.

Unadjusted logistic regression models predicting AF status (yes/no) by treatment group (omega-3/control), with Firth correction (brglm2 package, version 1.0.1) to adjust for small sample sizes, were fit on each cohort when predicting odds ratios (ORs). Cohort-specific, unadjusted ORs were then pooled by inverse-variance weighted, random effects meta-analysis (restricted maximum likelihood) using the metafor package (v. 4.4.0) in R (v. 4.3.2). As a sensitivity analysis, we also conducted meta-analysis on the absolute risk difference (Figure S1) using the meta (v. 8.1.0) package in R. A second sensitivity analysis excluded studies which did not assess prevalent AF status at baseline (Figure S2). In all cases, heterogeneity was assessed by I^2 and Cochran Q statistics and further explored by meta-analyzing prespecified subgroups as created by classifying cohorts based on participants baseline CVD risk (high versus low), and the omega-3 dose (≤1500 mg/d or >1500 mg/d). A significance level of 0.05 was used for all analyses.

RESULTS

Results of the Search

Figure 1 presents the study selection process and the acquisition of unpublished data, following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 guidelines.[7] The electronic search yielded 3688 records, of which 1962 were duplicates and removed. Title and abstract screening of the remaining 1726 records led to the exclusion of 1646 studies. The primary reasons for exclusion were trial duration <12 months and mean participant age <50 years (n=1273). Additional reasons for exclusion are shown in Figure 1.

After full-text assessment of the remaining 80 RCTs that met the inclusion criteria, 20 had available published data on incident AF, while 60 were identified as studies potentially containing unpublished data. Formal data access requests were submitted where applicable (n=1), or PIs were contacted directly (n=58). One data set was obtained via internal collaboration from a coauthor (F.Q.) who had previously received the data set.

Among the 58 PIs contacted, 33 responded. Of these, 13 provided usable AF data, 8 confirmed that AF data was not collected in their study,[22–30] 2 confirmed relevant data collected but not shareable- either because the data is pending first presentation[31] (n=1), or the article is under review[32] (n=1). Ten investigators could not confirm the status of AF data. This was due to the inability to access or review raw data sets or uncertainty regarding whether AF events were captured within broader AE categories[33–37] (n=5), ongoing trials with no available safety data[38] (n=1), or responses indicating they were unable to assist without clarifying whether AF data existed[39] (n=1). In addition, some investigators indicated that institutional approvals would be required to determine data availability, but did not confirm whether such data had been collected or respond to further correspondence[40] (n=1), while others suggested that relevant data (eg, ECG abnormalities or AE data sets) could be reviewed, but did not provide confirmation despite follow-up requests[41,42] (n=2). 25 PIs did not respond after 3 follow-up attempts.[43–67] Detailed study-level characteristics, investigator responses, and reasons for exclusion of eligible RCTs not included in the meta-analysis are provided in Table S2.

In total, 35 RCTs were included in the meta-analysis. This included 20 RCTs with published AF data[68–87] and 15 with unpublished AF data[88–102] (13 obtained directly from PIs,[88–93,95–100,102] 1 via a granted database request,[103] and 1 through internal collaboration[104]). Published data sources included original research articles[69–73,77,81,82] (n=8),

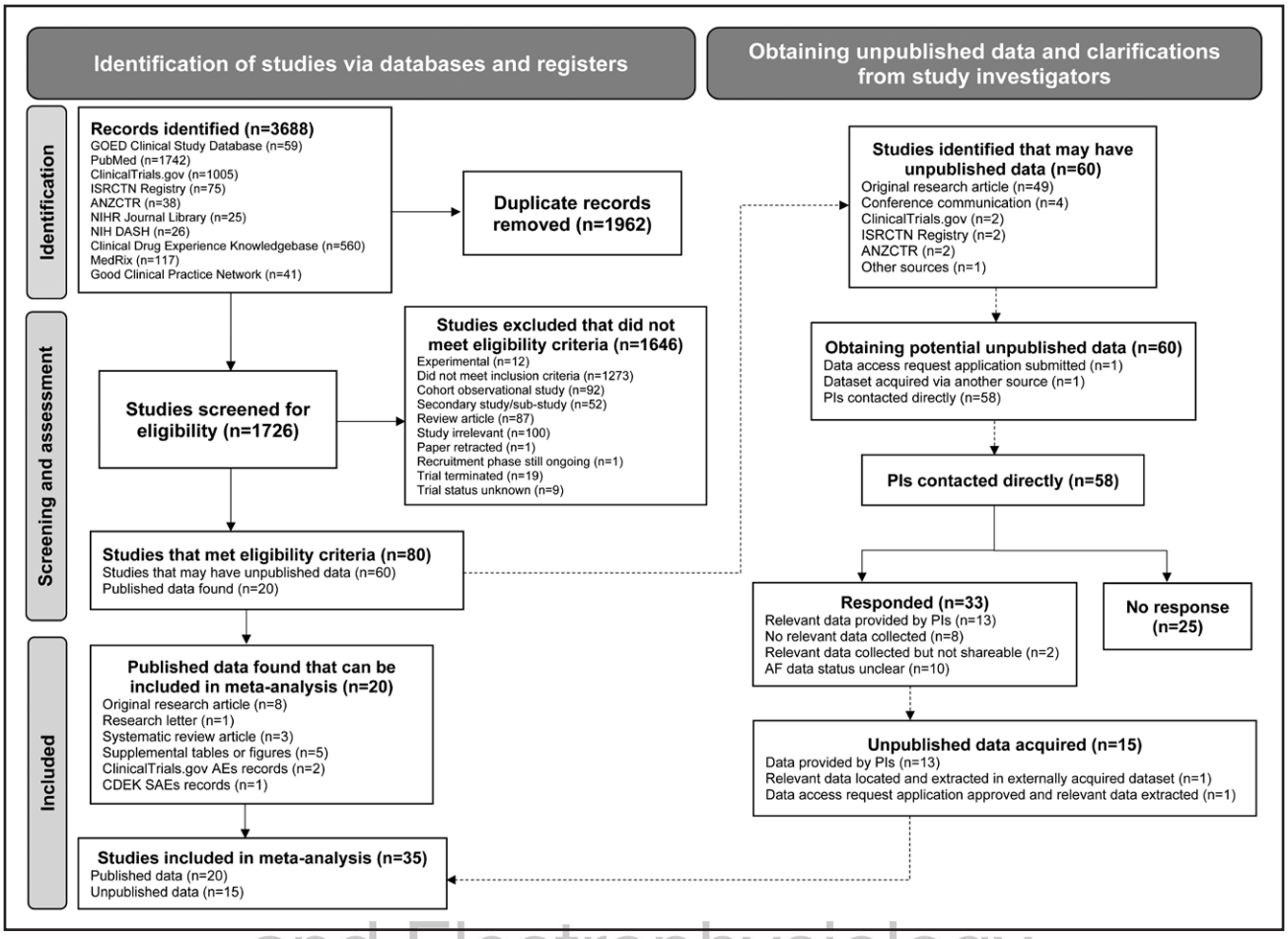

Figure 1. PRISMA 2020 flow diagram of study selection and acquisition of unpublished data.
Records were identified through bibliographic databases, clinical trial registries, and additional sources through November 2025. After duplicate removal, records underwent title/abstract screening and full-text assessment according to predefined eligibility criteria. The diagram also summarizes investigator contact procedures and acquisition of unpublished atrial fibrillation (AF) outcome data from principal investigators (PIs), registry sources, and shared data sets. Detailed investigator responses and study-level data availability are provided in Tables S1 and S2. CDEK indicates Clinical Drug Experience Knowledgebase; GOED, Global Organization of Omega-3 EPA and DHA; ISRCTN, International Standard Randomised Controlled Trial Number Registry; NIH, National Institutes of Health; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; and SAE, serious adverse event. Adapted from the PRISMA 2020 statement.[7]

research letter[6] (n=1), systematic review[105] (n=3), supplemental tables or figures[76,78,84,85,87] (n=5), ClinicalTrials.gov[106,107](n=2), and Clinical Drug Experience Knowledgebase[108] (n=1) adverse event records. For 2 studies, additional publicly accessible sources[109,110] were used to clarify or supplement AF outcome reporting from the original reports.[6,69] Detailed study-level information on publication status, AF data sources, and how AF outcome data were identified or obtained for each trial is provided in Table S1.

Characteristics of Trials

Among the 35 RCTs there were 37 data sets comprising 114 592 participants (Table). In the pooled data set, the mean baseline age was 66 years (range, 53–78) with 61% men. Daily omega-3 doses ranged from 600 to 4000 mg/d, and EPA/DHA was most commonly administered in either an ethyl ester[69,71,73–80,85,87–92,95,97,101] (57%) or triglyceride-based formulation[72,82–84,86,93,94,96,98–100,102] (34%). The duration of interventions ranged from 12 to 88.8 months. Most studies employed a double-blind, placebo-controlled design. Control groups most commonly received oil-based placebos. A subset of trials adopted factorial or multi-factorial designs (45%), combining omega-3 supplementation with other active interventions. These included pharmacological therapies,[71,73,76,79,82,83,85,92] nutritional supplements,[80,86,87,91,100–102] or structured lifestyle interventions.[74,99,102] Trials were conducted across 46 countries and included 5 multinational studies.[69,70,92,100,102] Detailed study characteristics are presented in Table S3.

Rates of New-Onset AF by Dose/Risk Group

After stratifying the studies by dose and CVD risk status (Table), there were 12 studies in the HR-HD

Table. Summary of 35 RCTs (37 Data Sets) Including Data From 114 592 Subjects and the Observed AF Rates* Segregated by High Versus Low Dose EPA+DHA (≤ Versus >1500 mg/d) and by High Versus Low Risk for CVD

Trial/authors, y	Omega-3 EPA/DHA			Comparator			Study characteristics		
High dose >1500 mg E+D/d	AF Events	N	AF%	AF events	N	AF%	Dosage EPA/DHA, mg/d	Duration, mo	Omega-3 formulation
HR-HD									
Yokote et al (2020)†	0	306	0.0%	0	77	0.0%	2250	12	O3CA
REDUCE-IT (2023)‡	103	3721	2.8%	80	3707	2.2%	4000	58.8	IPE
STRENGTH (2020)§	144	6539	2.2%	86	6539	1.3%	3000	42	O3CA
FAAT (2005)	3	164	1.8%	3	164	1.8%	2600	12	O3AEE
PEACH (2018)‖	0	73	0.0%	0	144	0.0%	1800	12	IPE
OMEMI (2023)	28	387	7.2%	15	372	4.0%	1800	24	rTG
EVAPORATE (2020)	0	31	0.0%	0	37	0.0%	4000	18	IPE
HEARTS (2025)	8	111	7.2%	5	102	4.9%	3360	30	O3AEE
SAREPITASO (2018)	0	38	0.0%	0	38	0.0%	1800	12	IPE
Derosa et al (2016)	1	128	0.8%	3	130	2.3%	2550	18	EE
OFAMI (2001)	8	150	5.3%	15	150	10.0%	3360	18	O3AEE
RESPECT-EPA (2024)	39	1244	3.1%	20	1251	1.6%	1800	60	IPE
Weighted	334	12892	2.6%	227	12711	1.8%	2693	26.4	…
HR-LD									
GISSI-HF (2013)¶	278	2492	11.2%	244	2499	9.8%	870	46.8	O3AEE
Risk & Prevention (2013)	113	6239	1.8%	92	6266	1.5%	925	60	EE
ASCEND (2018)	595	7740	7.7%	582	7740	7.6%	840	88.8	O3AEE
GISSI-Prevenzione (2001)#	40	2835	1.4%	46	2828	1.6%	860	42	O3AEE
SU.FOL.OM3 (2010)	33	1253	2.6%	32	1248	2.6%	600	56.4	EE
ORIGIN (2012)	288	6281	4.6%	259	6255	4.1%	840	74.4	O3AEE
Weighted	1347	26840	5.0%	1255	26836	4.7%	823	61.4	…
LR-HD									
RCT-EPA (2023)	0	61	0.0%	0	60	0.0%	3000	14	MAG-EPA
Mengelberg et al (2022)	0	37	0.0%	0	35	0.0%	1842	12	TG
seAFOod Polyp Prevention (2018)	3	347	0.9%	0	350	0.0%	2000	12	FFA/TG
EnRGISE (2019)**	0	148	0.0%	4	141	2.8%	2100	12	TG
ADCS-DHA (2010)	2	238	0.8%	1	164	0.6%	2040	18	TG
Lin et al (2022)††	0	40	0.0%	0	40	0.0%	1600	24	EE
MARINA (2011)††	0	92	0.0%	0	88	0.0%	1800	24	TG
BRAVE-EPA (2025)	0	63	0.0%	2	68	2.9%	4000	18	IPE
EPOCH (2018)	2	195	1.0%	1	196	0.5%	2320	18	rTG
DREAM (2018)	2	349	0.6%	1	186	0.5%	3000	12	TG
CAPFISH-3 (2024)	1	50	2.0%	0	50	0.0%	2200	12	TG
Sandhu et al (2016)	0	107	0.0%	0	159	0.0%	3360	24	O3AEE
Weighted	10	1727	0.6%	9	1537	0.6%	2439	16.7	…
LR-LD									
Shinto et al (2014)	1	34	2.9%	0	33	0.0%	1275	18	TG
VITAL Rythym (2021)‡‡	469	12542	3.7%	431	12577	3.4%	840	63.6	O3AEE
CANN (2023)	0	125	0.0%	0	121	0.0%	1500	12	TG
AREDS2 (2013)	242	2123	11.4%	238	2032	11.7%	1000	57.6	EE
MARINA (2011)††	0	187	0.0%	0	88	0.0%	675	24	TG
Lin et al (2022)††	0	83	0.0%	0	40	0.0%	925	24	EE
DO-HEALTH (2025)	34	1027	3.3%	28	1037	2.7%	990	36	TG

(*Continued*)

Table. Continued

Trial/authors, y	Omega-3 EPA/DHA			Comparator			Study characteristics		
High dose >1500 mg E+D/d	AF Events	N	AF%	AF events	N	AF%	Dosage EPA/DHA, mg/d	Duration, mo	Omega-3 formulation
Weighted	746	16121	4.6%	697	15928	4.4%	1029	33.6	…

Summary AF rates were based on weighted analysis by sample size. ADCS-DHA indicates Alzheimer's Disease Cooperative Study–Docosahexaenoic Acid; AF, atrial fibrillation; AREDS2, Age-Related Eye Disease Study 2; ASCEND, A Study of Cardiovascular Events in Diabetes; BRAVE-EPA, Brain Amyloid and Vascular Effects of Eicosapentaenoic Acid; CANN, Cognitive Ageing Nutrition and Neurogenesis Trial; CAPFISH-3, CAncer Prostate FISH Oil Trial Phase 3; CVD, cardiovascular disease; DHA, docosahexaenoic acid; DO-HEALTH, Vitamin D3–Omega-3–Home Exercise–Healthy Ageing and Longevity Trial; DREAM, Dry Eye Assessment and Management Study; EE, ethyl ester; ENRGISE, Enabling Reduction of Low-Grade Inflammation in Seniors; EPA, eicosapentaenoic acid; EPOCH, Older People, Omega-3, and Cognitive Health Trial; EVAPORATE, Effect of Vascepa on Improving Coronary Atherosclerosis in People With High Triglycerides Taking Statin Therapy; FAAT, Fatty Acid Antiarrhythmia Trial; FFA, free fatty acid; GISSI-HF, Gruppo Italiano per lo Studio della Sopravvivenza nell'Insufficienza Cardiaca; GISSI-Prevenzione, Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico–Prevenzione; HEARTS, Slowing HEART Disease With Lifestyle and Omega-3 Fatty Acids; MARINA, Modulation of Atherosclerosis Risk by Increasing Doses of n-3 Fatty Acids; OFAMI, Omega-3 Fatty Acids in Myocardial Infarction; OMEMI, OMega-3 Fatty Acids in Elderly Patients With Myocardial Infarction; ORIGIN, Outcome Reduction With an Initial Glargine Intervention; PEACH, Pitavastatin and Combined Omega-3 Health Study; RCT-EPA, Effects of EPA on Prostate Cancer Cell Proliferation and Quality of Life; REDUCE-IT, Reduction of Cardiovascular Events With Icosapent Ethyl–Intervention Trial; RESPECT-EPA, Randomized Trial for Evaluation in Secondary Prevention Efficacy of Combination Therapy–Statin and Eicosapentaenoic Acid; SAREPITASO, Sarpogrelate-EPA-Pitavastatin-ASO Study; seAFOod Polyp Prevention, Systematic Evaluation of Aspirin and Fish Oil Polyp Prevention Trial; STRENGTH, Outcomes Study to Assess Statin Residual Risk Reduction With EpaNova in High Cardiovascular Risk Patients With Hypertriglyceridemia; SU.FOL.OM3, SUpplementation with FOlate, Vitamin B6 and B12 and/or OMega-3 Fatty Acids; and VITAL Rhythm, VITamin D and Omega-3 Trial–Rhythm Study.

*Details of AF definition/outcome classification and ascertainment methods for each RCT are provided in Table S1, and all study characteristics are reported in Table S3.

†Yokote et al investigated 2 EPA doses (2*g*/d and 4g/d) in high-risk participants. Here we report the mean of the 2 doses.

‡For REDUCE-IT, the primary report (Bhatt et al, 2019) presented AF/flutter treatment-emergent adverse events (TEAEs), which included both incident AF and worsening of preexisting AF, and were not stratified by baseline AF status. Subsequent analyses (Olshansky et al, 2023) reported adjudicated AF/flutter hospitalizations (≥24 h) stratified by prior AF status. For the present meta-analysis, AF/flutter hospitalization events among participants without prior AF were extracted and supplemented with serious AF/flutter adverse events reported in ClinicalTrials.gov (NCT01492361). This approach was chosen to minimize the inclusion of recurrent AF events. Full details are provided in Table S1.

§For STRENGTH, AF event counts are based on the primary publication (Nicholls et al, 2020), which reported investigator-reported AF as a prespecified tertiary end point (144/6539 vs 86/6539; 2.2% vs 1.3%). A subsequent secondary analysis (Wang et al, 2026), restricted to participants without prior AF and based on adjudicated events, reported different event counts (126/6000 vs 75/6012; 2.1% vs 1.2%) and was not included, as these data became available only after Revision 2 had been submitted to the Journal. The differences in relative risks were virtually the same (before 1.69 and after 1.75) and thus would not have altered the overall findings. Further details are provided in Table S1.

‖PEACH investigated EPA 1.8 g/d administered with either 2 mg/d or 4 mg/d pitavastatin. As the EPA dose was identical across both statin strata, these 2 groups were combined in our analyses.

¶For GISSI-HF, AF events were defined as incident AF events among patients without AF on baseline ECG, among patients without a history of AF at baseline. Further details are given in Table S1.

#In GISSI-Prevenzione, AF data were available only from participants in the omega-3 alone and control groups; data from other randomized groups were not accessible and were therefore not included. Further details are given in Table S1.

**EnRGISE participants received 1.4 g/d of fish oil for the first 6 mo, after which the dose was escalated to 2.8 g/d for the subsequent 6 mo. Here we report the average daily dose.

#MARINA and Lin et al, investigated multiple doses of omega-3 in low-risk participants. As a result, their low-dose arms were included in the LR-LD category, and their high-dose arms were included in the LR-HD category in the stratified analyses. We report the mean of the 2 low doses in MARINA (0.45*g*, 0.9g EPA+DHA) and Lin et al (0.7g DHA, 1150 mg EPA+DHA).

††VITAL-rhythm is an ancillary trial of the VITAL trial (NCT01169259)- our meta-analysis was performed using VITAL-rhythm data.

stratum[68–76,88–90] including 25603 patients given an average of 2693 mg EPA+DHA/d. The 6 HR-LD studies[77–80,91,92] included 53676 patients with an average dose of 823 mg/d. The LR-HD stratum[81–85,93–99] included 12 studies with 3264 subjects given a mean dose of 2439 mg/d, and the LR-LD group[86,87,95,96,100–102] included 7 studies, 32049 individuals with a mean dose of 1029 mg/d. A summary of all included trials, including AF event counts and stratified rates, is presented in the Table. Detailed study-level information on AF ascertainment and outcome definitions is provided in Table S1.

Meta-Analysis

Looking at each of the 4 groups separately, only the HR-HD group[68–76,88–90] (ie, individuals at elevated cardiovascular risk receiving ≥1500 mg/d of EPA/DHA) showed a statistically significant increase in AF risk with a pooled OR of 1.43 (Figure 2). The ORs for the other 3 categories were not statistically significant (1.07 for HR-LD[77–80,91,92]; 1.03 for LR-HD[81–85,93–99]; and 1.06 for LR-LD[86,87,95,96,100–102]). We also note that only 2 studies[70,76] (both in the HR-HD group) found a statistically significant increase in risk of AF. In all 4 strata, residual heterogeneity estimates were <16% and not statistically significant (all 4; P>0.41). Across all studies, risk for AF was significantly increased by 14%.

Posthoc comparisons, using the HR-HD group as the reference, demonstrated the following (Figure 2). The HR-LD group exhibited a significantly lower AF risk (OR=0.73 [95% CI, 0.60–0.88]; P=0.0012). Second, the LR-LD group had a significantly lower AF risk (OR=0.72 [95% CI, 0.59–0.88]; P=0.0015). Finally, the LR-HD group showed the largest reduction in AF risk (OR=0.71 [95% CI, 0.30–1.64]) as compared with the HR-HD group, although this was not statistically significant (P=0.49).

Sensitivity Analysis: Risk Difference

Figure S1 illustrates a similar pattern of results when considering the risk difference instead of ORs. Namely,

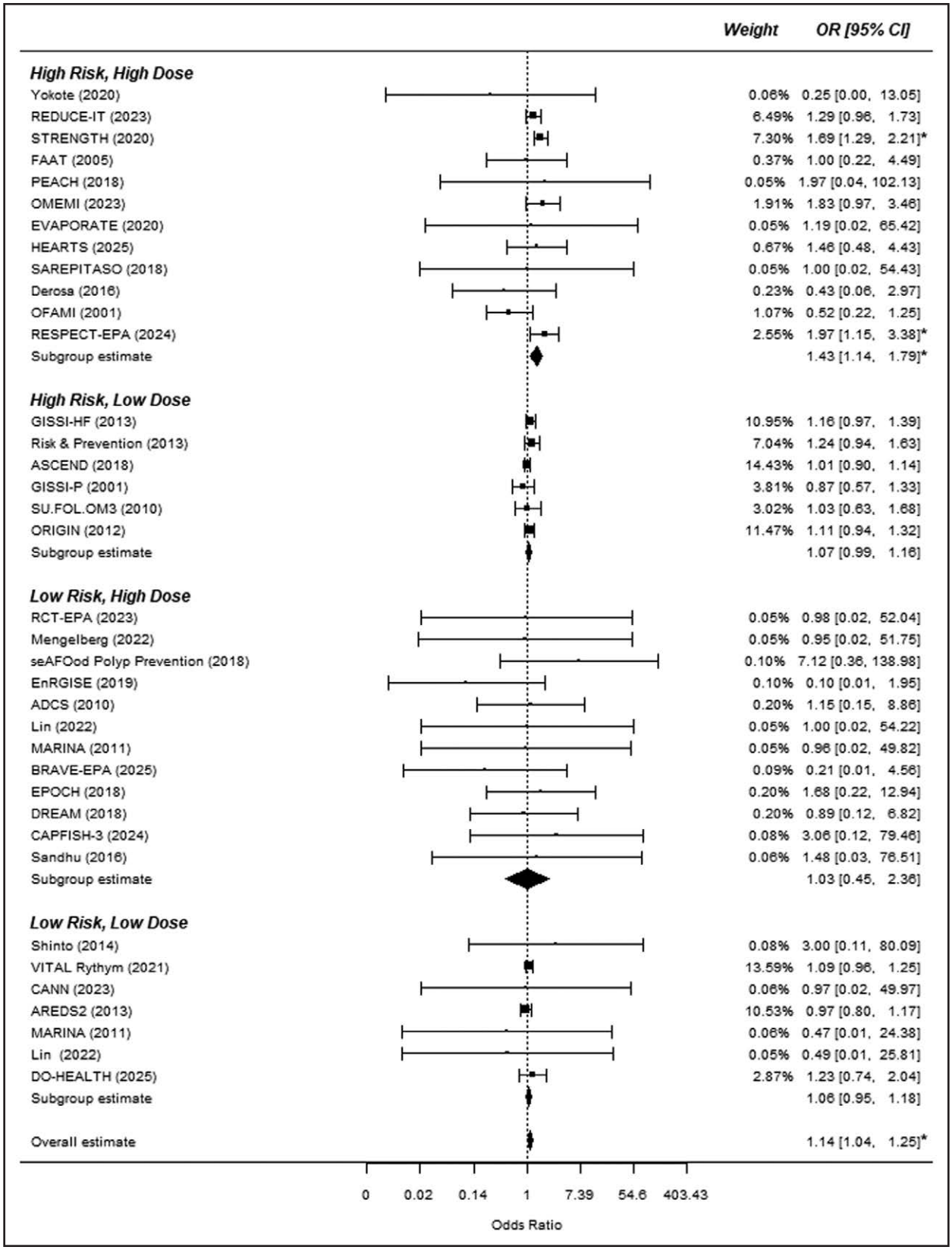

Figure 2. Meta-analysis of incident atrial fibrillation (AF) according to omega-3 fatty acid dose and cardiovascular disease (CVD) risk status across 35 randomized controlled trials (RCTs).

Forest plot demonstrates pooled odds ratios (ORs) for incident AF from 35 RCTs (37 data sets), including 114 592 participants. Cohort-specific unadjusted ORs were estimated using logistic regression with Firth correction and pooled using inverse-variance weighted random-effects meta-analysis with restricted maximum likelihood (REML) estimation. Studies were stratified according to baseline (*Continued*)

only the HR-HD group showed a statistically significant increased risk (risk difference, 0.8% [95% CI, 0.40–1.1]; $P<0.0001$).

Figure S2 illustrates a similar pattern of results in sensitivity analyses restricted to studies with a confirmed absence of prevalent AF at baseline.[6,68,69,72,75–77,82–84,87–90,96,97,101,102] In 3 of the 4 strata, ORs were nearly identical to those in the primary analysis (Figure 2; HR-HD: 1.46 versus 1.43; HR-LD: 1.07 versus 1.07; LR-LD: 1.06 versus 1.06), and the HR-HD group remained the only statistically significant stratum. Although the LR-HD OR differed numerically (0.68 versus 1.03), CIs were wide, and neither estimate was statistically significant.

DISCUSSION

Recent meta-analyses reporting that DHA and EPA increase the risk of AF,[1–3] have raised doubts among physicians and the public about the safety of omega-3 products, whether dietary supplements or pharmaceutical preparations. As noted earlier, these previous meta-analyses included no more than 8 RCTs, whereas the present analysis now includes 35 RCTs. By examining how both background CVD risk and omega-3 dose influence AF outcomes, our findings provide a more nuanced perspective on the relationship between omega-3 FAs and risk for AF.

We found a statistically significant, 43% increase in the relative risk of AF (Figure 2) and an absolute risk increase of <1% in the HR-HD group (Figure S1). In contrast, the HR-LD, LR-HD, and LR-LD strata (Figure 2) showed pooled risk estimates that were substantially lower than those of the HR-HD group (ORs ≈1.0), and none were statistically significant. Importantly, post hoc comparisons using HR-HD as the reference, HR-LD, and LR-LD groups each showed approximately null and significantly lower AF risk (OR ≈0.70). Although not formally assessed, the increased AF risk observed in the HR-HD group was evident across trials employing different omega-3 formulations (Table), including EPA ethyl esters,[69] carboxylic acids,[70,111] and reesterified triglycerides.[72] This consistency across formulations suggests that the observed AF signal in high-risk patients is unlikely to be attributable to a single omega-3 formulation, but rather appears to be linked to dose and background CVD risk.

Among LR individuals, the mean intake in the HD group was ≈2400 mg/d (Table), and this intake was associated with a reduced AF risk (OR=0.71) as compared with the HR-HD group, with a pooled OR of 1.03 (Figure 1). This suggests that in the general population, EPA/DHA intakes at this level are safe to consume (vis-à-vis risk for AF). This finding, however, was based on relatively few events; therefore should be considered tentative. Nevertheless, this is consistent with the Food and Drug Administration's designation of EPA/DHA intakes of up to 3000 mg/d as generally recognized as safe.[112]

There are a variety of other considerations that would support the safety vis-à-vis AF in the general population. For example, on average, North American adults eat <1 serving per week of fish/seafood; thus, the mean intake of DHA+EPA in the United States is only ≈100 mg/d.[113] This is associated with a mean DHA+EPA level in red blood cells (ie, the omega-3 index[17,18]) of ≈5.5% in the United States.[114] Observational studies consistently show that an omega-3 index of ≥8% is ideal for reducing risk of major adverse cardiovascular events,[115] stroke,[20] and all-cause mortality.[116] For typical Americans, achieving this would require an intake of ≈1000 mg/d of DHA+EPA.[18] In Japan, where average omega-3 intake approximates this level,[117] age-adjusted AF incidence is substantially lower than in the United States.[118,119] These ecological considerations are at least consistent with the

Figure 2 Continued. CVD risk (high vs low) and omega-3 fatty acid dose (high dose >1500 mg/d eicosapentaenoic acid [EPA] + docosahexaenoic acid [DHA] vs low dose ≤1500 mg/d EPA+DHA). Squares represent individual study effect estimates, with square size proportional to study weighting; horizontal lines indicate 95% CIs; diamonds represent subgroup and overall pooled estimates. The vertical dashed line denotes the null effect (OR=1). Statistical heterogeneity was assessed using the Cochran Q and I^2 statistics. ADCS-DHA indicates Alzheimer's Disease Cooperative Study–Docosahexaenoic Acid; AREDS2, Age-Related Eye Disease Study 2; ASCEND, A Study of Cardiovascular Events in Diabetes; GISSI-Prevenzione, Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico–Prevenzione; BRAVE-EPA, Brain Amyloid and Vascular Effects of Eicosapentaenoic Acid; CANN, Cognitive Ageing Nutrition and Neurogenesis Trial; CAPFISH-3, CAncer Prostate FISH Oil Trial Phase 3; DO-HEALTH, Vitamin D3–Omega-3–Home Exercise–Healthy Ageing and Longevity Trial; DREAM, Dry Eye Assessment and Management Study; ENRGISE, Enabling Reduction of Low-Grade Inflammation in Seniors; EPOCH, Older People, Omega-3, and Cognitive Health Trial; EVAPORATE, Effect of Vascepa on Improving Coronary Atherosclerosis in People With High Triglycerides Taking Statin Therapy; FAAT, Fatty Acid Antiarrhythmia Trial; GISSI-HF, Gruppo Italiano per lo Studio della Sopravvivenza nell'Insufficienza Cardiaca; HEARTS, Slowing HEART Disease With Lifestyle and Omega-3 Fatty Acids; MARINA, Modulation of Atherosclerosis Risk by Increasing Doses of n-3 Fatty Acids; OFAMI, Omega-3 Fatty Acids in Myocardial Infarction; OMEMI, OMega-3 Fatty Acids in Elderly Patients With Myocardial Infarction; ORIGIN, Outcome Reduction With an Initial Glargine Intervention; PEACH, Pitavastatin and Combined Omega-3 Health Study; RCT-EPA, Effects of EPA on Prostate Cancer Cell Proliferation and Quality of Life; REDUCE-IT, Reduction of Cardiovascular Events With Icosapent Ethyl–Intervention Trial; RESPECT-EPA, Randomized Trial for Evaluation in Secondary Prevention Efficacy of Combination Therapy–Statin and Eicosapentaenoic Acid; SAREPITASO, Sarpogrelate-EPA-Pitavastatin-ASO Study; seAFOod Polyp Prevention, Systematic Evaluation of Aspirin and Fish Oil Polyp Prevention Trial; STRENGTH, Outcomes Study to Assess STatin Residual Risk Reduction With EpaNova in HiGh Cardiovascular Risk PatienTs With Hypertriglyceridemia; SU.FOL.OM3, SUpplementation with FOlate, Vitamin B6 and B12 and/or OMega-3 Fatty Acids; and VITAL Rhythm, VITamin D and Omega-3 Trial–Rhythm Study.

view that in the general population, even relatively high doses (1–1.5 g/d) do not increase risk, and indeed may decrease risk, for AF.

There are several potential mechanisms that might explain the increased risk for AF in patients with HR taking high-dose omega-3. Omega-3 treatment has been shown to reduce resting heart rate[120] through increasing vagal tone even at relatively low doses of about 500 mg/d.[120,121] These dose-dependent vagotonic actions of omega-3 suggest a mechanism that may in part explain the divergent effects on risk of developing AF, whereby low-dose omega-3 does not significantly increase AF risk and may actually reduce risk, but high-doses can increase AF, especially in high-risk individuals.[122] These patients frequently have underlying structural heart disease and are commonly treated with medications such as beta blockers, which may further increase vagal tone through sympathetic inhibition. The dose-dependent vagal-stimulating effects are likely to be especially problematic for individuals at high risk for bradycardia-dependent AF.[123] This includes individuals who perform high volumes of strenuous endurance exercise, patients with untreated obstructive sleep apnea, sick sinus syndrome, and chronically slow heart rates.[123] Reanalysis of high-dose omega-3 RCTs examining interactions between baseline heart rate, omega-3 intake, and AF incidence may help clarify this potential relationship.

Considering that stroke is the major complication of AF, it is paradoxical that higher omega-3 intake and blood levels have been repeatedly associated with a lower risk of stroke. Specifically, a comprehensive meta-analysis (n>180 000 subjects) found patients in the top quintile of marine omega-3 blood levels had an 18% lower risk of ischemic stroke, and no effect on hemorrhagic stroke compared with patients in the lowest quintile of omega-3.[20] Similarly, in the REDUCE-IT (Reduction of Cardiovascular Events With Icosapent Ethyl–Intervention Trial),[69,124] which was comprised of high-CVD risk patients, high-dose EPA (4000 mg/d) reduced relative risk of stroke by 28% despite increasing relative risk of AF by 35%.[125] Even those in the EPA arm of the REDUCE-IT study who developed AF experienced lower risks of stroke and major adverse cardiovascular events compared with those in the control group who developed AF.[125] This presumed protective effect against stroke may relate to the mild anti-thrombotic effects of EPA and DHA.[126,127] Still, for high-risk individuals with a history of AF, Olshansky et al reported a nonsignificantly higher risk for developing AF on EPA than similar patients in REDUCE-IT without a history of AF.[69] Accordingly, a lower omega-3 target dose of <1500 mg/d of DHA/EPA may be a safer level of intake for patients with CVD with a history of AF.

The potential risk of AF must be considered within the broader risk-benefit profile of omega-3 therapy, particularly in high-risk populations where higher doses are typically used. Across several major RCTs, such as REDUCE-IT,[69,124] RESPECT-EPA (Randomized Trial for Evaluation in Secondary Prevention Efficacy of Combination Therapy–Statin and Eicosapentaenoic Acid),[76] GISSI-HF (Gruppo Italiano per lo Studio della Sopravvivenza nell'Insufficienza Cardiaca),[77] and ASCEND (A Study of Cardiovascular Events in Diabetes)[6,79]; the magnitude of cardiovascular benefit equaled or exceeded the observed increase in AF risk. For example, in REDUCE-IT, the 1.0% absolute increase in AF hospitalization with 4 g/d EPA was offset by a 4.8% absolute reduction in major adverse cardiovascular events,[69] a trade-off that strongly favors treatment given that events, such as myocardial infarction, ischemic stroke, or cardiovascular death, carry far greater clinical consequences than increased risk for new-onset AF. This interpretation aligns with recent cost-effectiveness analyses demonstrating that the reduction in major adverse cardiovascular events more than compensates for increased AF risk, supporting an overall favorable benefit-risk balance for high-dose omega-3 therapy.[128]

Meta-analyses of prospective cohort studies focusing on omega-3 blood levels as the exposure have reported lower risk for mortality from all causes and from CVD, cancer, and other causes.[21] Other biomarker-based studies have found higher levels of omega-3s to be associated with lower risk for atherosclerotic cardiovascular disease,[115] Alzheimer's disease[129] and total dementia,[129] heart failure,[130] diabetes,[131] suicidal ideation/self-harm,[132] poor lung function,[133] colorectal cancer,[134] and several other malignancies,[135] atopic dermatitis,[136] hospitalization for sepsis,[137] liver cirrhosis,[138] chronic kidney disease,[139] frailty[140] and hip fractures.[141] These associations, in addition to a lower risk for AF,[4,19] support a generalized overall benefit of omega-3 in human health.

STRENGTHS AND LIMITATIONS

This meta-analysis represents a substantial advance in our understanding of the relationship between omega-3 treatment and risk for AF. Unlike earlier work that relied almost exclusively on published reports, we systematically integrated underutilized data sources, including trial registry adverse event records and unpublished data sets (Table S1); thereby reducing selective reporting bias. Importantly, we also incorporated trials in which no AF events were observed (where, had they occurred, they would have been noted), ensuring that such data contributed to the overall evidence base rather than being excluded. A further novel contribution is our risk-dose stratification framework, which moves 1 step beyond the high-dose versus low-dose paradigm used in past studies.[1] This approach provides a clearer understanding of how simple dietary supplementation might affect risk for AF as opposed to the use of high-dose phar major adverse cardiovascular events utical products. It also illuminates

the importance of patient substrate, as we found limited evidence of an increase in AF risk even in high-risk CVD patients who are taking relatively low omega-3 doses (<1500 mg/d). Finally, by including populations outside of high-risk CVD cohorts, our analysis broadens generalizability and offers more nuanced insight into how AF risk may differ across clinical contexts. There are also limitations to this work, chief among them being the inability to ensure that all relevant studies were included in the analysis[43–67] (Table S2). In addition, for many RCTs, the status of AF outcomes was unclear, as PIs no longer had access to the original raw datasets[33–37] and were, therefore, unable to confirm whether AF events were systematically collected or adjudicated (Table S2).

CONCLUSIONS

This meta-analysis demonstrates a clear dose-dependent association between omega-3 FA supplementation and AF risk. Importantly, low-dose omega-3 supplementation does not appear to increase AF risk, even among patients at high CVD risk, providing reassurance regarding the safety of commonly used nutritional doses. In contrast, high doses of omega-3 FAs (typically from pharmacological products) administered to patients at high CVD risk were associated with a ≈40% to 45% increase in AF risk, although the absolute risk increase is modest (0.8%). These findings suggest that omega-3 supplementation providing <1500 mg of EPA+DHA per day (and possibly up to 2400 mg) can be used safely with respect to AF risk, whereas doses exceeding 3000 mg/d in high-risk CVD populations may warrant caution. Given that elevated blood omega-3 levels (achieved through diet and supplementation) are associated with reduced atherosclerotic cardiovascular disease risk and other favorable health outcomes, the small AF signal in HR-HD populations should be weighed against the substantial cardiovascular benefits when making treatment decisions.

Future prospective RCTs designed to evaluate the risk-benefit ratio of high-dose omega-3 supplementation in high-risk populations should incorporate systematic AF detection, including wearable-based monitoring, and objective biomarkers of omega-3 exposure, such as the omega-3 index.

ARTICLE INFORMATION

Received December 16, 2025; accepted June 16, 2026.

Affiliations

Fatty Acid Research Institute, Sioux Falls, SD (N.R.A., J.H.O.K., N.L.T., W.S.H.). Saint Luke's Mid America Heart Institute & University of Missouri-Kansas City (J.H.O.K.). Section of Cardiovascular Medicine, Boston Medical Center & Boston University Chobanian & Avedisian School of Medicine, MA (F.Q.). Department of Epidemiology & Health Statistics, West China School of Public Health & West China Fourth Hospital, Sichuan University, Chengdu (Y.L., Y.S.). GlaxoSmithKline, Rockville, MD (H.-Z.Q.). Alzheimer's Therapeutic Research Institute, Keck School of Medicine, University of Southern California, San Diego (P.S.A.). Department of Cardiology, Smidt Heart Institute, Cedars-Sinai Medical Center, Los Angeles, CA (C.M.A.). Department of Medicine (C.M.A., D.A.S.) and Department of Biostatistics (D.A.S.), Massachusetts General Hospital, Boston. Division of Nutrition, Harvard Medical School, Boston, MA (F.K.W.). Department of Urology, David Geffen School of Medicine, University of California Los Angeles (W.J.A., A.L.). VA Medical Center Greater Los Angeles Healthcare System, CA (W.J.A., A.L.). Department of Medicine, Division of Cardiovascular Medicine, University of Wisconsin-Madison Hospitals & Clinics (A.A.A.A.). Division of Cardiovascular Medicine, Department of Medicine, Beth Israel Deaconess Medical Center, Boston, MA (A.A.A.A., F.K.W.). Department of Aging Medicine, University of Basel, Felix Platter, Switzerland (H.A.B.-F.). Swiss Campus for Healthy Longevity, University of Basel, Switzerland (H.A.B.-F.). Department of Medicine, Lundquist Institute at Harbor-UCLA Medical Center, Torrance, CA (M.J.B.). School of Psychology, University of Adelaide, Australia (N.R.B.). School of Medicine, University of Adelaide, Australia (G.W.). Division of Geriatrics, Department of Medicine, University of Wisconsin School of Medicine & Public Health (C.A.C., C.M.C., C.A.V.H.). Wisconsin Alzheimer's Disease Research Center, University of Wisconsin School of Medicine & Public Health (C.A.C., C.M.C., C.A.V.H.). William S. Middleton Memorial Veterans Hospital, Madison, WI (C.M.C.). Division of Epidemiology & Clinical Applications, National Eye Institute/National Institute of Health, Bethesda, MD (E.Y.C., C.W.). Beckman Institute for Advanced Science & Technology, University of Illinois at Urbana-Champaign, Urbana (N.J.C.). Université Sorbonne Paris Nord & Université Paris Cité, INSERM, INRAE, CNAM, Centre for Research in Epidemiology & StatisticS (CRESS), Nutritional Epidemiology Research Team (EREN), Bobigny, France (L.K.F., P.G.). Keck School of Medicine, University of Southern California, Los Angeles (A.L.). Leeds Institute of Medical Research, University of Leeds, St James's University Hospital, United Kingdom (M.A.H.). Tsaotun Psychiatric Center, Ministry of Health and Welfare, Nantou (T.-H.L.). Department of Psychiatry, School of Medicine, National Yang Ming Chiao Tung University, Taipei (T.-H.L.). Institute of Clinical Medicine, National Yang Ming Chiao Tung University, Taipei. Center for Neuropsychiatric Research, National Health Research Institute, Miaoli (T.-H.L.). Department of Psychiatry & Mind-Body Interface Laboratory (MBI-Lab), China Medical University Hospital (P.-Y.L., K.-P.S.). PhD program for Aging, College of Medicine, China Medical University, Taichung (P.-Y.L., K.-P.S.). Department of Psychiatry, Wei Gong Memorial Hospital, Miaoli, Taiwan (P.-Y.L.). School of Psychology, Massey University, Wellington, New Zealand (A.M.). Department of Nutrition & Preventive Medicine, Norwich Medical School, BCRE (A.-M.M., D.V.). Norwich Institute of Healthy Ageing (NIHA), University of East Anglia, Norwich, United Kingdom (A.-M.M., D.V.). Department of Neurology, Oregon Health & Science University, Portland (J.F.Q.). Department of Nutritional Sciences, King's College London (T.A.B.S.). School of Psychology, Northumbria University, Newcastle-upon-Tyne, United Kingdom (A.S.). Centre for Human Psychopharmacology, Swinburne University, Melbourne, Australia (A.S.). Nottingham Clinical Trials Unit, School of Medicine, University of Nottingham, United Kingdom (K.S.). An-Nan Hospital, China Medical University, Tainan, Taiwan (K.-P.S.). Department of Psychiatry, Yale University, New Haven, CT (C.H.D.). Endocrine Unit, Royal Adelaide Hospital (G.W.). South Australian Health & Medical Research Institute, Adelaide (G.W.). Department of Internal Medicine, Sanford School of Medicine, University of South Dakota, Sioux Falls (W.S.H.).

Acknowledgments

The authors thank Hertzel Gerstein, MD, for providing access to data from the ORIGIN trial (NCT00069784). Data from the ADCS-DHA trial (NCT00440050) used in the preparation of this article were obtained from the University of California, San Diego Alzheimer's Disease Cooperative Study (ADCS) legacy database (https://www.adcs.org/). Data collection and sharing for this project were funded by the ADCS (National Institutes of Health, grant U19 AG010483). Data from the AREDS2 trial (NCT00345176) were obtained from the National Eye Institute, National Institutes of Health, and are available through dbGaP (accession phs002015.v2. p1).

Sources of Funding

The authors declare that financial support was received for the research and publication of this article. The project was supported in part by The Global Organization of Omega-3 EPA and DHA (GOED), which had no role in the research design or conduct; data analysis or interpretation; preparation, review, or approval of the article; or the decision to submit the article for publication. Dr Qian is supported by the National Heart, Lung, and Blood Institute of the National Institutes of Health under award number T32HL125232 (Multidisciplinary Training Program in Cardiovascular Epidemiology).

Disclosures

Dr Abuknesha reports receiving the GOED Clinical Study Database Research Award (2023), which supported participation in clinical trial database research

activities related to omega-3 RCTs. Dr O'Keefe is the Chief Medical Officer of CardioTabs, a company that sells omega-3 products. Dr Harris holds stock in OmegaQuant Analytics, LLC, a laboratory that offers blood fatty acid testing (including the Omega-3 Index) for researchers, clinicians, and consumers. The other authors report no conflicts.

Supplemental Material

Supplemental Methods
Tables S1–S3
Figures S1 and S2
Supplemental Appendix
References 18,142–156

REFERENCES

1. Gencer B, Djousse L, Al-Ramady OT, Cook NR, Manson JE, Albert CM. Effect of long-term marine ω-3 fatty acids supplementation on the risk of atrial fibrillation in randomized controlled trials of cardiovascular outcomes: a systematic review and meta-analysIS. *Circulation*. 2021;144:1981–1990. doi: 10.1161/CIRCULATIONAHA.121.055654
2. Bae JH, Lim H, Lim S. The potential cardiometabolic effects of long-chain ω-3 polyunsaturated fatty acids: recent updates and controversies. *Adv Nutr*. 2023;14:612–628. doi: 10.1016/j.advnut.2023.03.014
3. Jia X, Gao F, Pickett JK, Al Rifai M, Birnbaum Y, Nambi V, Virani SS, Ballantyne CM. Association between omega-3 fatty acid treatment and atrial fibrillation in cardiovascular outcome trials: a systematic review and meta-analysis. *Cardiovasc Drugs Ther*. 2021;35:793–800. doi: 10.1007/s10557-021-07204-z
4. Qian F, Tintle N, Jensen PN, Lemaitre RN, Imamura F, Feldreich TR, Nomura SO, Guan W, Laguzzi F, Kim E, et al; Fatty Acids and Outcomes Research Consortium (FORCE). Omega-3 fatty acid biomarkers and incident atrial fibrillation. *J Am Coll Cardiol*. 2023;82:336–349. doi: 10.1016/j.jacc.2023.05.024
5. Samuel M, Nattel S. Fish oil supplements may increase the risk for atrial fibrillation: What does this mean? *Circulation*. 2021;144:1991–1994. doi: 10.1161/CIRCULATIONAHA.121.057464
6. Parish S, Mafham M, Offer A, Barton J, Wallendszus K, Stevens W, Buck G, Haynes R, Collins R, Bowman L, et al; ASCEND Study Collaborative Group. Effects of omega-3 fatty acid supplements on arrhythmias. *Circulation*. 2020;141:331–333. doi: 10.1161/CIRCULATIONAHA.119.044165
7. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, Shamseer L, Tetzlaff JM, Akl EA, Brennan SE, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021;372:n71. doi: 10.1136/bmj.n71
8. International Society for the Study of Fatty Acids and Lipids. *ISSFAL policy statement 3: recommendations for intake of polyunsaturated fatty acids in healthy adults*. 2004. https://issfal.memberclicks.net/assets/issfal%2003%20pufaintakereccomdfinalreport.pdf
9. Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail (ANSES). *Avis de l'Agence française de sécurité sanitaire des aliments relatif à l'actualisation des apports nutritionnels conseillés pour les acides gras*. 2006. https://www.anses.fr/fr/system/files/NUT2006sa0359.pdf
10. Vannice G, Rasmussen H. Position of the academy of nutrition and dietetics: dietary fatty acids for healthy adults. *J Acad Nutr Diet*. 2014;114:136–153. doi: 10.1016/j.jand.2013.11.001
11. Kannel WB, Wolf PA, Benjamin EJ, Levy D. Prevalence, incidence, prognosis, and predisposing conditions for atrial fibrillation: population-based estimates. *Am J Cardiol*. 1998;82:2N–9N. doi: 10.1016/s0002-9149(98)00583-9
12. National Heart, Lung, and Blood Institute (NHLBI). *NHLBI adverse event and unanticipated problem reporting policy*. National Institutes of Health. https://www.nhlbi.nih.gov/grants-and-training/policies-and-guidelines/nhlbi-adverse-event-and-unanticipated-problem-reporting-policy
13. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). *Medical Dictionary for Regulatory Activities (MedDRA), version 20.1*. McLean (VA): ICH; 2017. https://www.meddra.org
14. World Health Organization. *International Classification of Diseases (ICD)*. World Health Organization; https://www.who.int/standards/classifications/classification-of-diseases
15. National Cancer Institute. *Common Terminology Criteria for Adverse Events (CTCAE) version 4.03*. U.S. Department of Health and Human Services, National Institutes of Health; 2010. https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf
16. SNOMED International. *SNOMED CT: systematized nomenclature of medicine clinical terms*. SNOMED International. https://www.snomed.org/snomed-ct
17. Harris WS, von Schacky C. The Omega-3 Index: A new risk factor for death from coronary heart disease? *Prev Med*. 2004;39:212–220. doi: 10.1016/j.ypmed.2004.02.030
18. Walker RE, Jackson KH, Tintle NL, Shearer GC, Bernasconi A, Masson S, Latini R, Heydari B, Kwong RY, Flock M, et al. Predicting the effects of supplemental EPA and DHA on the omega-3 index. *Am J Clin Nutr*. 2019;110:1034–1040. doi: 10.1093/ajcn/nqz161
19. O'Keefe EL, O'Keefe JH, Tintle NL, Franco WG, Westra J, Harris WS. Associations between plasma omega-3 and fish oil use with risk of atrial fibrillation in the UK Biobank. *J Am Heart Assoc*. 2025;14:e043031. doi: 10.1161/JAHA.125.043031
20. O'Keefe JH, Tintle NL, Harris WS, O'Keefe EL, Sala-Vila A, Attia J, Garg GM, Hure A, Bork CS, Schmidt EB, et al. Omega-3 blood levels and stroke risk: a pooled and harmonized analysis of 183 291 participants from 29 prospective studies. *Stroke*. 2024;55:50–58. doi: 10.1161/STROKEAHA.123.044281
21. O'Keefe EL, O'Keefe JH, Tintle NL, Westra J, Albuisson L, Harris WS. Circulating docosahexaenoic acid and risk of all-cause and cause-specific mortality. *Mayo Clin Proc*. 2024;99:534–541. doi: 10.1016/j.mayocp.2023.11.026
22. Lok CE, Moist L, Hemmelgarn BR, Tonelli M, Vazquez MA, Dorval M, Oliver M, Donnelly S, Allon M, Stanley K; Fish Oil Inhibition of Stenosis in Hemodialysis Grafts (FISH) Study Group. Effect of fish oil supplementation on graft patency and cardiovascular events among patients with new synthetic arteriovenous hemodialysis grafts: a randomized controlled trial. *JAMA*. 2012;307:1809–1816. doi: 10.1001/jama.2012.3473
23. Nosaka K, Miyoshi T, Iwamoto M, Kajiya M, Okawa K, Tsukuda S, Yokohama F, Sogo M, Nishibe T, Matsuo N, 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;228:173–179. doi: 10.1016/j.ijcard.2016.11.105
24. Baleztena J, Ruiz-Canela M, Sayon-Orea C, Pardo M, Anorbe T, Gost JI, Gomez C, Ilarregui B, Bes-Rastrollo M. Association between cognitive function and supplementation with omega-3 PUFAs and other nutrients in ≥ 75 years old patients: a randomized multicenter study. *PLoS One*. 2018;13:e0193568. doi: 10.1371/journal.pone.0193568
25. Brouwer IA, Zock PL, Camm AJ, Böcker D, Hauer RN, Wever EF, Dullemeijer C, Ronden JE, Katan MB, Lubinski A, et al; SOFA Study Group. 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;295:2613–2619. doi: 10.1001/jama.295.22.2613
26. Dangour AD, Allen E, Elbourne D, Fasey N, Fletcher AE, Hardy P, Holder GE, Knight R, Letley L, Richards M, et al. Effect of 2-y n−3 long-chain polyunsaturated fatty acid supplementation on cognitive function in older people: a randomized, double-blind, controlled trial. *Am J Clin Nutr*. 2010;91:1725–1732. doi: 10.3945/ajcn.2009.29121
27. Cockayne NL, Duffy SL, Bonomally R, English A, Amminger PG, Mackinnon A, Christensen HM, Naismith SL, Hickie IB. The Beyond Ageing Project Phase 2 - a double-blind, selective prevention, randomised, placebo-controlled trial of omega-3 fatty acids and sertraline in an older age cohort at risk for depression: study protocol for a randomized controlled trial. *Trials*. 2015;16:336. doi: 10.1186/s13063-015-0762-6
28. ISRCTN Registry. *Effect of icosapent ethyl on inflammation in the vessel wall assessed by the fat attenuation Index Score (IRIS-FAI) (ISRCTN15140257)*. https://www.isrctn.com/ISRCTN15140257
29. Delpech JC. *Investigating the impact of an n-3 PUFA combined with vitamin A supplementation on cognition and plasma EV signature in aged individuals [conference abstract]*. Presented at: International Society for the Study of Fatty Acids and Lipids (ISSFAL) Congress; 2025
30. NUTRIMEMO Trial Investigators. *NUTRIMEMO (NCT02626247)*. ClinicalTrials.gov. https://clinicaltrials.gov/study/NCT02626247
31. Lok CE, Hemmelgarn B, Moist LM, Polkinghorne K, Tomlinson G, Tam PY, Tonelli M. Protection against incidences of serious cardiovascular events study with daily fish oil supplementation in patients on dialysis (PISCES). *J Am Soc Nephrol*. 2025;36(10 Supp):10–1681. doi: 10.1681/asn.2025pdej0qvx
32. Yassine HN, Arellanes IC, Mazmanian A, De La Cruz L, Martinez J, Contreras L, Kono N, Liu BS, Badie D, Bantugan MA, et al. Baseline findings of prevente4: a double-blind placebo controlled clinical trial testing

high dose DHA in APOE4 carriers before the onset of dementia. *J Prev Alzheimers Dis*. 2023;10:810–820. doi: 10.14283/jpad.2023.77
33. Einvik G, Klemsdal TO, Sandvik L, Hjerkinn EM. A randomized clinical trial on n-3 polyunsaturated fatty acids supplementation and all-cause mortality in elderly men at high cardiovascular risk. *Eur J Cardiovasc Prev Rehabil*. 2010;17:588–592. doi: 10.1097/HJR.0b013e328339cc70
34. Andrieu S, Guyonnet S, Coley N, Cantet C, Bonnefoy M, Bordes S, Bories L, Cufi M-N, Dantoine T, Dartigues J-F, et al; MAPT Study Group. 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;16:377–389. doi: 10.1016/S1474-4422(17)30040-6
35. Scorletti E, Bhatia B, McCormick K, Clough G, Nash K, Hodson L, et al. Potential benefits of purified long chain omega-3 fatty acid treatment in Non-Alcoholic Fatty Liver Disease (NAFLD): a potential treatment for early NAFLD in metabolic syndrome and type 2 diabetes? Results from the WELCOME study. *Diabet Med*. 2014;31:31
36. Yokoyama M, Origasa H, Matsuzaki M, Matsuzawa Y, Saito Y, Ishikawa Y, Oikawa S, Sasaki J, Hishida H, Itakura H, et al; Japan EPA lipid intervention study (JELIS) Investigators. Effects of eicosapentaenoic acid on major coronary events in hypercholesterolaemic patients (JELIS): a randomised open-label, blinded endpoint analysis. *Lancet*. 2007;369:1090–1098. doi: 10.1016/S0140-6736(07)60527-3
37. Sanyal AJ, Abdelmalek MF, Suzuki A, Cummings OW, Chojkier M, Study Group EPE-A. No significant effects of ethyl-eicosapentanoic acid on histologic features of nonalcoholic steatohepatitis in a phase 2 trial. *Gastroenterology*. 2014;147:377–384.e1. doi: 10.1053/j.gastro.2014.04.046
38. Hull MA, Ow PL, Ruddock S, Brend T, Smith AF, Marshall H, Song M, Chan AT, Garrett WS, Yilmaz O, et al. Randomised, placebo-controlled, phase 3 trial of the effect of the omega-3 polyunsaturated fatty acid Eicosapentaenoic Acid (EPA) on colorectal cancer recurrence and survival after surgery for resectable liver metastases: EPA for Metastasis Trial 2 (EMT2) study protocol. *BMJ Open*. 2023;13:e077427. doi: 10.1136/bmjopen-2023-077427
39. Souied EH, Delcourt C, Querques G, Bassols A, Merle B, Zourdani A, Smith T, Benlian P; Nutritional AMD Treatment 2 Study Group. Oral docosahexaenoic acid in the prevention of exudative age-related macular degeneration: the Nutritional AMD Treatment 2 study. *Ophthalmology*. 2013;120:1619–1631. doi: 10.1016/j.ophtha.2013.01.005
40. Nolan JM, Power R, Howard AN, Bergin P, Roche W, Prado-Cabrero A, Pope G, Cooke J, Power T, Mulcahy R. Supplementation with carotenoids, omega-3 fatty acids, and vitamin E Has a positive effect on the symptoms and progression of Alzheimer's disease. *J Alzheimers Dis*. 2022;90:233–249. doi: 10.3233/JAD-220556
41. Shinto LH, Murchison CF, Silbert LC, Dodge HH, Lahna D, Rooney W, Kaye J, Quinn JF, Bowman GL. ω-3 PUFA for secondary prevention of white matter lesions and neuronal integrity breakdown in older adults. *JAMA Netw Open*. 2024;7:e2426872. doi: 10.1001/jamanetworkopen.2024.26872
42. Nutrition Interventions for Cognitive Enhancement (NICE). ClinicalTrials.gov. 2019
43. Rauch B, Schiele R, Schneider S, Diller F, Victor N, Gohlke H, Gottwik M, Steinbeck G, Del Castillo U, Sack R, et al; OMEGA Study Group. OMEGA, a randomized, placebo-controlled trial to test the effect of highly purified omega-3 fatty acids on top of modern guideline-adjusted therapy after myocardial infarction. *Circulation*. 2010;122:2152–2159. doi: 10.1161/CIRCULATIONAHA.110.948562
44. 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;77:31–36. doi: 10.1016/s0002-9149(97)89130-8
45. Tande KS, Vo TD, Lynch BS. Clinical safety evaluation of marine oil derived from Calanus finmarchicus. *Regul Toxicol Pharmacol*. 2016;80:25–31. doi: 10.1016/j.yrtph.2016.05.030
46. Nakao K, Noguchi T, Miura H, Asaumi Y, Morita Y, Takeuchi S, Matama H, Sawada K, Doi T, Hosoda H, et al. Effect of eicosapentaenoic acid/docosahexaenoic acid on coronary high-intensity plaques detected using non-contrast T1-weighted imaging: the AQUAMARINE EPA/DHA randomized study. *J Atheroscler Thromb*. 2024;31:122–134. doi: 10.5551/jat.64063
47. Duan H, Yang T, Li C, Xu N, Wang M, Zhang C, Zhao J, Chen Y, Yan J, Li W, et al. Supplementation of medium-chain triglycerides combined with docosahexaenoic acid improves cognitive function in Chinese older adults with mild cognitive impairment: a randomized double-blind, placebo-controlled trial. *J Affect Disord*. 2025;378:263–270. doi: 10.1016/j.jad.2025.03.008
48. von Schacky C, Angerer P, Kothny W, Theisen K, Mudra H. The effect of dietary omega-3 fatty acids on coronary atherosclerosis. A randomized, double-blind, placebo-controlled trial. *Ann Intern Med*. 1999;130:554–562. doi: 10.7326/0003-4819-130-7-199904060-00003
49. Zhuang P, Wu Y, Yao J, Liu X, Liu H, Wan X, Jia W, Wang T, Zhang Y, Jiao J. Marine n-3 polyunsaturated fatty acids slow sleep impairment progression by regulating central circadian rhythms in type 2 diabetes. *Cell Rep Med*. 2025;6:102128. doi: 10.1016/j.xcrm.2025.102128
50. Piñas García P, Hernández Martínez FJ, Aznárez López N, Castillón Torre L, Tena Sempere ME. Supplementation with a highly concentrated Docosahexaenoic Acid (DHA) in non-proliferative diabetic retinopathy: a 2-year randomized double-blind placebo-controlled study. *Antioxidants (Basel)*. 2022;11:116. doi: 10.3390/antiox11010116
51. García-Layana A, Recalde S, Hernandez M, Abraldes MJ, Nascimento J, Hernández-Galilea E, Olmedilla-Alonso B, Escobar-Barranco JJ, Zapata MA, Silva R, et al. A randomized study of nutritional supplementation in patients with unilateral wet age-related macular degeneration. *Nutrients*. 2021;13:1253. doi: 10.3390/nu13041253
52. Ahn J, Park SK, Park TS, Kim JH, Yun E, Kim SP, Lee HW, Oh J-H, Choi JH, Cha KS, et al. Effect of n-3 polyunsaturated fatty acids on regression of coronary atherosclerosis in statin treated patients undergoing percutaneous coronary intervention. *Korean Circ J*. 2016;46:481–489. doi: 10.4070/kcj.2016.46.4.481
53. Raitt MH, Connor WE, Morris C, Kron J, Halperin B, Chugh SS, McClelland J, Cook J, MacMurdy K, Swenson R, et al. Fish oil supplementation and risk of ventricular tachycardia and ventricular fibrillation in patients with implantable defibrillators: a randomized controlled trial. *JAMA*. 2005;293:2884–2891. doi: 10.1001/jama.293.23.2884
54. Brox J, Olaussen K, Osterud B, Elvevoll EO, Bjørnstad E, Brattebøg G, Iversen H. A long-term seal- and cod-liver-oil supplementation in hypercholesterolemic subjects. *Lipids*. 2001;36:7–13. doi: 10.1007/s11745-001-0661-4
55. Puri BK, Leavitt BR, Hayden MR, Ross CA, Rosenblatt A, Greenamyre JT, Hersch S, Vaddadi KS, Sword A, Horrobin DF, et al. Ethyl-EPA in Huntington disease: a double-blind, randomized, placebo-controlled trial. *Neurology*. 2005;65:286–292. doi: 10.1212/01.wnl.0000169025.09670.6d
56. Sabour H, Norouzi Javidan A, Latifi S, Shidfar F, Heshmat R, Emami Razavi SH, Vafa MR, Larijani B. Omega-3 fatty acids' effect on leptin and adiponectin concentrations in patients with spinal cord injury: a double-blinded randomized clinical trial. *J Spinal Cord Med*. 2015;38:599–606. doi: 10.1179/2045772314Y.0000000251
57. Olendzki BC, Leung K, Van Buskirk S, Reed G, Zurier RB. Treatment of rheumatoid arthritis with marine and botanical oils: influence on serum lipids. *Evid Based Complement Alternat Med*. 2011;2011:827286. doi: 10.1155/2011/827286
58. Svensson M, Schmidt EB, Jørgensen KA, Christensen JH; OPACH Study Group. N-3 fatty acids as secondary prevention against cardiovascular events in patients who undergo chronic hemodialysis: a randomized, placebo-controlled intervention trial. *Clin J Am Soc Nephrol*. 2006;1:780–786. doi: 10.2215/CJN.00630206
59. Volpe G, Skinner S, Gerrior-Schofield J, Zhang FF, Tang A, Kuvin J, Mangili A, Wanke C. A randomized controlled trial of omega-3 fatty acids in Human Immunodeficiency Virus (HIV): long-term effects on lipids and vascular function. *Open Forum Infect Dis*. 2016;3(Suppl 1):951. doi: 10.1093/ofid/ofw194.91
60. Li M, Li T, Yang T, Huang L, Zhao J, Liu H, Chen Y, Li W, Zhu Y, Ma F, et al. Cognitive benefits of folic acid, docosahexaenoic acid, and a combination of both nutrients in mild cognitive impairment: possible alterations through mitochondrial function and DNA damage. *Gerontology*. 2024;70:940–949. doi: 10.1159/000540021
61. Lafuente M, Ortín L, Argente M, Guindo JL, López-Bernal MD, López-Román FJ, Domingo JC, Lajara J. 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. *Retina*. 2019;39:1083–1090. doi: 10.1097/IAE.0000000000002114
62. Garbagnati F, Cairella G, De Martino A, Multari M, Scognamiglio U, Venturiero V, Paolucci S. Is antioxidant and n-3 supplementation able to improve functional status in poststroke patients? Results from the Nutristroke Trial. *Cerebrovasc Dis*. 2009;27:375–383. doi: 10.1159/000207441
63. Power R, Nolan JM, Prado-Cabrero A, Roche W, Coen R, Power T, Mulcahy R. Omega-3 fatty acid, carotenoid and vitamin E supplementation improves working memory in older adults: a randomised clinical trial. *Clin Nutr*. 2022;41:405–414. doi: 10.1016/j.clnu.2021.12.004
64. Blok WL, Deslypere JP, Demacker PNM, van der Ven-Jongekrijg J, Hectors MPC, van der Meer JWM, Katan MB. Pro- and anti-inflammatory cytokines in healthy volunteers fed various doses of fish oil for 1 year. *Eur J Clin Invest*. 1997;27:1003–1008. doi: 10.1046/j.1365-2362.1997.2240775.x

65. *IcoSApent ethyL to Slow Down Aortic VAlve Stenosis proGrEssion (SALVAGE)*. 2023. https://clinicaltrials.gov/ct2/show/NCT06466278
66. *Testosterone-Omega Three (DHA) — Amyloid Lowering (ToTAL) Study*. 2018. https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=373908
67. Hearon CM Jr, Dias KA, MacNamara JP, Hieda M, Mantha Y, Harada R, Samels M, Morris M, Szczepaniak LS, Levine BD, et al. 1 year HIIT and omega-3 fatty acids to improve cardiometabolic risk in stage-a heart failure. *JACC Heart Fail*. 2022;10:238–249. doi: 10.1016/j.jchf.2022.01.004
68. Yokote K, Niwa K, Hakoda T, Oh F, Kajimoto Y, Fukui T, Kim H, Noda Y, Lundström T, Yajima T. Short-term efficacy (at 12 weeks) and long-term safety (up to 52 weeks) of omega-3 free fatty acids (AZD0585) for the treatment of japanese patients with dyslipidemia - a randomized, double-blind, placebo-controlled, phase III study. *Circ J*. 2020;84:994–1003. doi: 10.1253/circj.CJ-19-0358
69. Olshansky B, Bhatt DL, Miller M, Steg PG, Brinton EA, Jacobson TA, Ketchum SB, Doyle RT, Juliano RA, Jiao L, et al; REDUCE-IT Investigators. Cardiovascular benefits of icosapent ethyl in patients with and without atrial fibrillation in REDUCE-IT. *J Am Heart Assoc*. 2023;12:e026756. doi: 10.1161/JAHA.121.026756
70. Nicholls SJ, Lincoff AM, Garcia M, Bash D, Ballantyne CM, Barter PJ, Davidson MH, Kastelein JJP, Koenig W, McGuire DK, 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;324:2268–2280. doi: 10.1001/jama.2020.22258
71. Miyoshi T, Kohno K, Asonuma H, Sakuragi S, Nakahama M, Kawai Y, Uesugi T, Oka T, Munemasa M, Takahashi N, et al; PEACH Investigators. Effect of Intensive and standard pitavastatin treatment with or without eicosapentaenoic acid on progression of coronary artery calcification over 12 months - prospective multicenter study. *Circ J*. 2018;82:532–540. doi: 10.1253/circj.CJ-17-0419
72. Myhre PL, Berge T, Kalstad AA, Tveit SH, Laake K, Schmidt EB, Solheim S, Arnesen H, Seljeflot I, Tveit A. Omega-3 fatty acid supplements and risk of atrial fibrillation and 'micro-atrial fibrillation': a secondary analysis from the OMEMI trial. *Clin Nutr*. 2023;42:1657–1660. doi: 10.1016/j.clnu.2023.07.002
73. Nomura S, Taniura T, Shouzu A, Omoto S, Suzuki M, Okuda Y, Ito T. Effects of sarpogrelate, eicosapentaenoic acid and pitavastatin on arterioslcerosis obliterans-related biomarkers in patients with type 2 diabetes (SAREPITASO study). *Vasc Health Risk Manag*. 2018;14:225–232. doi: 10.2147/VHRM.S171143
74. Derosa G, Cicero AFG, 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;42:316–322. doi: 10.1002/biof.1275
75. 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;74:50–56. doi: 10.1093/ajcn/74.1.50
76. Miyauchi K, Iwata H, Nishizaki Y, Inoue T, Hirayama A, Kimura K, Ozaki Y, Murohara T, Ueshima K, Kuwabara Y, et al; RESPECT-EPA Investigators. Randomized trial for evaluation in secondary prevention efficacy of combination therapy-statin and eicosapentaenoic acid (RESPECT-EPA). *Circulation*. 2024;150:425–434. doi: 10.1161/CIRCULATIONAHA.123.065520
77. Aleksova A, Masson S, Maggioni AP, Lucci D, Fabbri G, Beretta L, Mos L, Paino AM, Nicolosi GL, Marchioli R, et al. n-3 Polyunsaturated fatty acids and atrial fibrillation in patients with chronic heart failure: the GISSI-HF trial. *Eur J Heart Fail*. 2013;15:1289–1295. doi: 10.1093/eurjhf/hft103
78. Risk and Prevention Study Collaborative Group. n-3 Fatty acids in patients with multiple cardiovascular risk factors. *N Engl J Med*. 2013;368:1800–1808. doi: 10.1056/NEJMoa1205409
79. Bowman L, Mafham M, Wallendszus K, Stevens W, Buck G, Barton J, Murphy K, Aung T, Haynes R, Cox J, et al; ASCEND Study Collaborative Group. Effects of n-3 fatty acid supplements in diabetes mellitus. *N Engl J Med*. 2018;379:1540–1550. doi: 10.1056/NEJMoa1804989
80. Marchioli R, Schweiger C, Tavazzi L, Valagussa F. Efficacy of n-3 polyunsaturated fatty acids after myocardial infarction: results of GISSI-prevenzione trial. *Lipids*. 2001;36(Suppl):S119–S126. doi: 10.1007/s11745-001-0694-8
81. Moussa H, Robitaille K, Pelletier JF, Tourigny R, Fradet Y, Lacombe L, Toren P, Lodde M, Tiguert R, Dujardin T, et al. Effects of concentrated long-chain omega-3 polyunsaturated fatty acid supplementation on quality of life after radical prostatectomy: a phase II randomized placebo-controlled trial (RCT-EPA). *Nutrients*. 2023;15:1369. doi: 10.3390/nu15061369
82. Hull MA, Sprange K, Hepburn T, Tan W, Shafayat A, Rees CJ, Clifford G, Logan RF, Loadman PM, Williams EA, et al; seAFOod Collaborative Group. Eicosapentaenoic acid and aspirin, alone and in combination, for the prevention of colorectal adenomas (seAFOod Polyp Prevention trial): a multicentre, randomised, double-blind, placebo-controlled, 2 × 2 factorial trial. *Lancet*. 2018;392:2583–2594. doi: 10.1016/S0140-6736(18)31775-6
83. Pahor M, Anton SD, Beavers DP, Cauley JA, Fielding RA, Kritchevsky SB, Leeuwenburgh C, Lewis KH, Liu CK, Lovato LC, 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: Ser A*. 2018;74:1612–1619. doi: 10.1093/gerona/gly277
84. Asbell PA, Maguire MG, Pistilli M, Ying GS, Szczotka-Flynn LB, Hardten DR, Lin MC, Shtein RM; Dry Eye Assessment and Management Study Research Group. n-3 fatty acid supplementation for the treatment of dry eye disease. *N Engl J Med*. 2018;378:1681–1690. doi: 10.1056/NEJMoa1709691
85. Sandhu N, Schetter SE, Liao J, Hartman TJ, Richie JP, McGinley J, Thompson HJ, Prokopczyk B, DuBrock C, Signori C, 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;9:275–282. doi: 10.1158/1940-6207.CAPR-15-0235
86. Shinto L, Quinn J, Montine T, Dodge HH, Woodward W, Baldauf-Wagner S, Waichunas D, Bumgarner L, Bourdette D, Silbert L, 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;38:111–120. doi: 10.3233/JAD-130722
87. Albert CM, Cook NR, Pester J, Moorthy MV, Ridge C, Danik JS, Gencer B, Siddiqi HK, Ng C, Gibson H, et al. Effect of marine omega-3 fatty acid and vitamin D supplementation on incident atrial fibrillation: a randomized clinical trial. *JAMA*. 2021;325:1061–1073. doi: 10.1001/jama.2021.1489
88. Leaf A, Albert CM, Josephson M, Steinhaus D, Kluger J, Kang JX, Cox B, Zhang H, Schoenfeld D; Fatty Acid Antiarrhythmia Trial Investigators. Prevention of fatal arrhythmias in high-risk subjects by fish oil n-3 fatty acid intake. *Circulation*. 2005;112:2762–2768. doi: 10.1161/CIRCULATIONAHA.105.549527
89. Budoff MJ, Bhatt DL, Kinninger A, Lakshmanan S, Muhlestein JB, Le VT, May HT, Shaikh K, Shekar C, Roy SK, et al. Effect of icosapent ethyl on progression of coronary atherosclerosis in patients with elevated triglycerides on statin therapy: final results of the EVAPORATE trial. *Eur Heart J*. 2020;41:3925–3932. doi: 10.1093/eurheartj/ehaa652
90. 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;6:e006981. doi: 10.1161/JAHA.117.006981
91. Blacher J, Czernichow S, Paillard F, Ducimetiere P, Hercberg S, Galan P. Cardiovascular effects of B-vitamins and/or N-3 fatty acids: the Su.Fol.Om3 trial. *Int J Cardiol*. 2013;167:508–513. doi: 10.1016/j.ijcard.2012.01.060
92. Trial Investigators ORIGIN. n-3 fatty acids and cardiovascular outcomes in patients with dysglycemia. *N Engl J Med*. 2012;367:309–318. doi: 10.1056/NEJMoa1203859
93. Mengelberg A, Leathem J, Podd J, Hill S, Conlon C. The effects of docosahexaenoic acid supplementation on cognition and well-being in mild cognitive impairment: a 12-month randomised controlled trial. *Int J Geriatr Psychiatry*. 2022;37:10.1002/gps.5707. doi: 10.1002/gps.5707
94. Quinn JF, Raman R, Thomas RG, Yurko-Mauro K, Nelson EB, Van Dyck C, Galvin JE, Emond J, Jack CR, Weiner M, et al. Docosahexaenoic acid supplementation and cognitive decline in Alzheimer disease: a randomized trial. *JAMA*. 2010;304:1903–1911. doi: 10.1001/jama.2010.1510
95. Lin PY, Cheng C, Satyanarayanan SK, Chiu LT, Chien YC, Chuu CP, Lan T-H, Su K-P. Omega-3 fatty acids and blood-based biomarkers in Alzheimer's disease and mild cognitive impairment: a randomized placebo-controlled trial. *Brain Behav Immun*. 2022;99:289–298. doi: 10.1016/j.bbi.2021.10.014
96. Sanders TA, Hall WL, Maniou Z, Lewis F, Seed PT, Chowienczyk PJ. Effect of low doses of long-chain n-3 PUFAs on endothelial function and arterial stiffness: a randomized controlled trial. *Am J Clin Nutr*. 2011;94:973–980. doi: 10.3945/ajcn.111.018036
97. Cardenas CA, Van Hulle CA, Zylstra H, Cronin K, Cole A, Beckman E, Eierman AC, Blazel M, Lazar KK, Johnson KM, et al. Impact of icosapent ethyl on lipids, blood pressures, and adverse events in cognitively healthy veterans participating in the BRAVE study. *Alzheimer's Dement*. 2024;20(Suppl):e094881. doi: 10.1002/alz.094881
98. Danthiir V, Hosking DE, Nettelbeck T, Vincent AD, Wilson C, O'Callaghan N, Calvaresi E, Clifton P, Wittert GA. An 18-mo randomized, double-blind, placebo-controlled trial of DHA-rich fish oil to prevent age-related cognitive decline in cognitively normal older adults. *Am J Clin Nutr*. 2018;107:754–762. doi: 10.1093/ajcn/nqx077

99. Aronson WJ, Grogan T, Liang P, Jardack P, Liddell AR, Perez C, Elashoff D, Said J, Cohen P, Marks LS, et al. High omega-3, low omega-6 diet with fish oil for men with prostate cancer on active surveillance: the CAPFISH-3 randomized clinical trial. *J Clin Oncol*. 2025;43:800–809. doi: 10.1200/JCO.24.00608
100. Vauzour D, Scholey A, White DJ, Cohen NJ, Cassidy A, Gillings R, Irvine MA, Kay CD, Kim M, King R, et al. A combined DHA-rich fish oil and cocoa flavanols intervention does not improve cognition or brain structure in older adults with memory complaints: results from the CANN randomized, controlled parallel-design study. *Am J Clin Nutr*. 2023;118:369–381. doi: 10.1016/j.ajcnut.2023.06.008
101. Bonds DE, Harrington M, Worrall BB, Bertoni AG, Eaton CB, Hsia J, Robinson J, Clemons TE, Fine LJ, Chew EY. Effect of long-chain ω-3 fatty acids and lutein+zeaxanthin supplements on cardiovascular outcomes. *JAMA Intern Med*. 2014;174:763–771. doi: 10.1001/jamainternmed.2014.328
102. Gaengler S, Sadlon A, Molino CDGRC, Willett WC, Manson JE, Vellas B, Steinhagen-Thiessen E, Von Eckardstein A, Ruschitzka F, Rizzoli R, et al. Effects of vitamin D, omega-3 and a simple strength exercise programme in cardiovascular disease prevention: the DO-HEALTH randomized controlled trial. *J Nutr Health Aging*. 2024;28:100037. doi: 10.1016/j.jnha.2023.100037
103. Alzheimer's Disease Cooperative Study (ADCS). *(2007–2010) Docosahexaenoic Acid (DHA) clinical trial dataset*. University of California; Alzheimer's Disease Cooperative Study. Accessed: February 2025. https://www.adcs.org
104. National Eye Institute (NEI). *(2012) Age-Related Eye Disease Study 2 (AREDS2) clinical trial dataset*. National Institutes of Health, U.S. Department of Health and Human Services. Accessed: March 2025. https://www.nei.nih.gov/research/clinical-trials/age-related-eye-disease-study-2-areds2
105. Hooper L, Abdelhamid A, Brainard J, Brown T, Hanson S, Thorpe G, et al. *Set of systematic reviews of RCTs on the health effects of omega-3 polyunsaturated fats in adults*. World Health Organization; 2017
106. *The ENRGISE (ENabling Reduction of Low-Grade Inflammation in SEniors) Pilot Study (ENRGISE)*. U.S. National Library of Medicine. https://clinicaltrials.gov/study/NCT02676466
107. *Lipoic Acid and Omega-3 Fatty Acids for Alzheimer's Disease*. U.S. National Library of Medicine. https://clinicaltrials.gov/study/NCT01058941
108. AZD0585 Phase III Long-Term Study Investigators. *A randomized, double-blind, placebo-controlled Phase III trial (NCT02463071) evaluating AZD0585 versus placebo in Japanese patients with hypertriglyceridemia and hyperlipidemia*. CDEK/Clinical Drug Experience Knowledgebase. https://cdek.pharmacy.purdue.edu/trial/NCT02463071/
109. REDUCE-IT Investigators. *A study of AMR101 to evaluate its ability to reduce cardiovascular events in high-risk patients with hypertriglyceridemia and on statin (REDUCE-IT)*. 2011. https://clinicaltrials.gov/ct2/show/NCT01492361
110. Parish S, Armitage J. *Effects of omega-3 fatty acid supplements on arrhythmias in ASCEND*. Presented at: ESC Congress together with World Congress of Cardiology; 2019. https://www.svcardiologia.com/wp-content/uploads/2019/09/ASCEND_Omega_3_trial_ESC_2019.pdf
111. Wang TKM, Nicholls SJ, Tan C, Liao BYW, Wolski K, St John J, Nissen SE. Novel risk model for predicting incident atrial fibrillation in patients taking ω-3 fatty acid: sub-analysis of the STRENGTH randomized trial. *Am J Prev Cardiol*. 2026;28:101583. doi: 10.1016/j.ajpc.2026.101583
112. FDA. *GRAS notices for menhaden oil. Federal Register*. 1997. Accessed: 24 September 2024. https://www.fda.gov/ohrms/dockets/dockets/95s0316/95s-0316-rpt0299-053-Appendix-A-Tab-F-Ref-047-FDA-1997B-vol2.pdf
113. Gebauer SK, Psota TL, Harris WS, Kris-Etherton PM. n-3 fatty acid dietary recommendations and food sources to achieve essentiality and cardiovascular benefits. *Am J Clin Nutr*. 2006;83(6 Suppl):1526S–1535S. doi: 10.1093/ajcn/83.6.1526S
114. Schuchardt JP, Cerrato M, Ceseri M, DeFina LF, Delgado GE, Gellert S, Hahn A, Howard BV, Kadota A, Kleber ME, et al. Red blood cell fatty acid patterns from 7 countries: focus on the Omega-3 index. *Prostaglandins Leukot Essent Fatty Acids*. 2022;179:102418. doi: 10.1016/j.plefa.2022.102418
115. Harris WS, Del Gobbo L, Tintle NL. The Omega-3 Index and relative risk for coronary heart disease mortality: estimation from 10 cohort studies. *Atherosclerosis*. 2017;262:51–54. doi: 10.1016/j.atherosclerosis.2017.05.007
116. Harris WS, Tintle NL, Imamura F, Qian F, Korat AVA, Marklund M, Djoussé L, Bassett JK, Carmichael P-H, Chen Y-Y, et al; Fatty Acids and Outcomes Research Consortium (FORCE). Blood n-3 fatty acid levels and total and cause-specific mortality from 17 prospective studies. *Nat Commun*. 2021;12:2329. doi: 10.1038/s41467-021-22370-2
117. Iso H, Kobayashi M, Ishihara J, Sasaki S, Okada K, Kita Y, Kokubo Y, Tsugane S; JPHC Study Group. Intake of fish and n3 fatty acids and risk of coronary heart disease among Japanese: the Japan Public Health Center-Based (JPHC) Study Cohort I. *Circulation*. 2006;113:195–202. doi: 10.1161/CIRCULATIONAHA.105.581355
118. Oltman CG, Kim TP, Lee JWY, Lupu JD, Zhu R, Moussa ID. Prevalence, management, and comorbidities of adults with atrial fibrillation in the United States, 2019 to 2023. *JACC Adv*. 2024;3:101330. doi: 10.1016/j.jacadv.2024.101330
119. Inoue H, Fujiki A, Origasa H, Ogawa S, Okumura K, Kubota I, Aizawa Y, Yamashita T, Atarashi H, Horie M, et al. Prevalence of atrial fibrillation in the general population of Japan: an analysis based on periodic health examination. *Int J Cardiol*. 2009;137:102–107. doi: 10.1016/j.ijcard.2008.06.029
120. Mozaffarian D, Geelen A, Brouwer IA, Geleijnse JM, Zock PL, Katan MB. Effect of fish oil on heart rate in humans: a meta-analysis of randomized controlled trials. *Circulation*. 2005;112:1945–1952. doi: 10.1161/CIRCULATIONAHA.105.556886
121. Christifano DN, Chollet-Hinton L, Mathis NB, Gajewski BJ, Carlson SE, Colombo J, Gustafson KM. DHA Supplementation during pregnancy enhances maternal vagally mediated cardiac autonomic control in humans. *J Nutr*. 2023;152:2708–2715. doi: 10.1093/jn/nxac178
122. O'Keefe JH, Abuissa H, Sastre A, Steinhaus DM, Harris WS. Effects of omega-3 fatty acids on resting heart rate, heart rate recovery after exercise, and heart rate variability in men with healed myocardial infarctions and depressed ejection fractions. *Am J Cardiol*. 2006;97:1127–1130. doi: 10.1016/j.amjcard.2005.11.025
123. O'Keefe EL, O'Keefe JH, Abuissa H, Metzinger M, Murray E, Franco WG, et al. Omega-3 and risk of atrial fibrillation: vagally-mediated double-edged sword. *Prog Cardiovasc Dis*. 2024;91:3–9. doi: 10.1016/j.pcad.2024.11.003
124. Bhatt DL, Steg PG, Miller M, Brinton EA, Jacobson TA, Ketchum SB, Doyle RT, Juliano RA, Jiao L, Granowitz C, et al; REDUCE-IT Investigators. Cardiovascular risk reduction with icosapent ethyl for hypertriglyceridemia. *N Engl J Med*. 2019;380:11–22. doi: 10.1056/NEJMoa1812792
125. Ballantyne CM, Jia X. Omega-3 fatty acids and risk for atrial fibrillation: Big fish or small fry? *J Am Coll Cardiol*. 2023;82:350–352. doi: 10.1016/j.jacc.2023.05.026
126. Javaid M, Kadhim K, Bawamia B, Cartlidge T, Farag M, Alkhalil M. Bleeding risk in patients receiving omega-3 polyunsaturated fatty acids: a systematic review and meta-analysis of randomized clinical trials. *J Am Heart Assoc*. 2024;13:e032390. doi: 10.1161/JAHA.123.032390
127. Wachira JK, Larson MK, Harris WS. n-3 Fatty acids affect haemostasis but do not increase the risk of bleeding: clinical observations and mechanistic insights. *Br J Nutr*. 2014;111:1652–1662. doi: 10.1017/S000711451300425X
128. Bernasconi AA, Maki KC, Finkelstein EA. Cost-effectiveness of long-chain omega-3 supplementation for the secondary prevention of cardiovascular disease in the United States. *Value Health*. 2025;28:1481–1487. doi: 10.1016/j.jval.2025.07.005
129. Sala-Vila A, Satizabal CL, Tintle N, Melo van Lent D, Vasan RS, Beiser AS, Seshadri S, Harris WS. Red blood cell DHA is inversely associated with risk of incident Alzheimer's disease and all-cause dementia: Framingham Offspring Study. *Nutrients*. 2022;14:2408. doi: 10.3390/nu14122408
130. Jawad MA, O'Keefe JH, Tintle N, O'Keefe EL, Franco WG, Djoussé L, Ryder N, Harris WS. Association of plasma omega-3 levels with incident heart failure and related mortalities. *Mayo Clin Proc*. 2024;99:1895–1904. doi: 10.1016/j.mayocp.2024.08.007
131. Qian F, Ardisson Korat AV, Imamura F, Marklund M, Tintle N, Virtanen JK, Zhou X, Bassett JK, Lai H, Hirakawa Y, et al; Fatty Acids and Outcomes Research Consortium (FORCE). n-3 fatty acid biomarkers and incident type 2 diabetes: an individual participant-level pooling project of 20 prospective cohort studies. *Diabetes Care*. 2021;44:1133–1142. doi: 10.2337/dc20-2426
132. Franco WG, Tintle NL, Westra J, O'Keefe EL, O'Keefe JH, Harris WS. The association between plasma omega-3 fatty acids and suicidal ideation/self-harm in the United Kingdom Biobank. *Lipids Health Dis*. 2025;24:364. doi: 10.1186/s12944-025-02689-1
133. Zheng Z, Wu Q, Fang Y, Di H, Zhang M, Ding X, Liu Q, Chen Z, Yang S, Wang B, et al. The relationship of fish oil supplements and plasma fatty acids with lung function decline. *Eur J Nutr*. 2025;64:183. doi: 10.1007/s00394-025-03702-0
134. Aldoori J, Zulyniak MA, Toogood GJ, Hull MA. Plasma n-3 polyunsaturated fatty acid levels and colorectal cancer risk in the UK

biobank: evidence of nonlinearity, as well as tumor site- and sex-specificity. *Cancer Epidemiol Biomarkers Prev*. 2025;34:394–404. doi: 10.1158/1055-9965.EPI-24-1154
135. Zhang Y, Sun Y, Song S, Khankari NK, Brenna JT, Shen Y, Ye K. Associations of plasma omega-6 and omega-3 fatty acids with overall and 19 site-specific cancers: a population-based cohort study in UK Biobank. *Int J Cancer*. 2025;156:1154–1172. doi: 10.1002/ijc.35226
136. Mao R, Meng X, Zhang T, Wang F, Zhong Y, Li J. Evaluating the impact of omega-3 fatty acids and genetic susceptibility on atopic dermatitis in adults. *Mol Nutr Food Res*. 2025;69:e70002. doi: 10.1002/mnfr.70002
137. Narayan D, Vlasschaert C, Day AG, Norman P, Rauh MJ, Maslove DM. Association of omega-3 status with long-term risk of hospitalization for sepsis. *Crit Care Med*. 2025;53:e763–e771. doi: 10.1097/CCM.0000000000006593
138. Guo C, Liu Z, Fan H, Wang H, Zhang X, Zhao S, Li Y, Wang T, Dai L, Huang J, et al. Nonlinear relationships of circulating polyunsaturated fatty acids with the complications of liver cirrhosis: a prospective, longitudinal cohort study. *Clin Nutr*. 2024;43:2083–2091. doi: 10.1016/j.clnu.2024.07.027
139. Koh HB, Kim HW, Joo YS, Jung CY, Kim HJ, Chang TI, Park JT, Yoo T-H, Kang S-W, Han SH. Plasma levels of polyunsaturated fatty acids and adverse kidney outcomes. *Am J Kidney Dis*. 2024;84:179–194.e1. doi: 10.1053/j.ajkd.2023.12.020
140. Kim J, Kim M, Won CW, Park Y. Erythrocyte levels of n-3 polyunsaturated fatty acids and incidence of frailty after a 6-year follow-up: the Korean frailty and aging cohort study. *Front Nutr*. 2025;12:1569832. doi: 10.3389/fnut.2025.1569832
141. Orchard TS, Ing SW, Lu B, Belury MA, Johnson K, Wactawski-Wende J, Jackson RD. The association of red blood cell n-3 and n-6 fatty acids with bone mineral density and hip fracture risk in the Women's health initiative. *J Bone Miner Res*. 2013;28:505–515. doi: 10.1002/jbmr.1772
142. Manson JE, Cook NR, Lee IM, Christen W, Bassuk SS, Mora S, Gibson H, Albert CM, Gordon D, Copeland T, et al; VITAL Research Group. Marine n-3 fatty acids and prevention of cardiovascular disease and cancer. *N Engl J Med*. 2019;380:23–32. doi: 10.1056/NEJMoa1811403
143. Guertin MH, Robitaille K, Pelletier JF, Duchesne T, Julien P, Savard J, Bairati I, Fradet V. Effects of concentrated long-chain omega-3 polyunsaturated fatty acid supplementation before radical prostatectomy on prostate cancer proliferation, inflammation, and quality of life: study protocol for a phase IIb, randomized, double-blind, placebo-controlled trial. *BMC Cancer*. 2018;18:64. doi: 10.1186/s12885-017-3979-9
144. Irvine MA, Scholey A, King R, Gillings R, Vauzour D, Demichele SJ, Das T, Wesnes KA, Sut-ton BP, Cassidy A, et al. The Cognitive Ageing, Nutrition and Neurogenesis (CANN) trial: design and progress. *Alzheimers Dement (N Y)*. 2018;4:591–601. doi: 10.1016/j.trci.2018.08.001
145. Bischoff-Ferrari HA, de Godoi Rezende Costa Molino C, Rival S, Vellas B, Rizzoli R, Kressig RW, Kanis JA, Manson JE, Dawson-Hughes B, Orav EJ, et al; DO-HEALTH Research Group. DO-HEALTH: vitamin d3 - omega-3 - home exercise - healthy aging and longevity trial - design of a multinational clinical trial on healthy aging among European seniors. *Contemp Clin Trials*. 2021;100:106124. doi: 10.1016/j.cct.2020.106124
146. Martin SS, Aday AW, Allen NB, Almarzooq ZI, Anderson CAM, Arora P, Avery CL, Baker-Smith CM, Bansal N, Beaton AZ, et al; American Heart Association Council on Epidemiology and Prevention Statistics Committee and Stroke Statistics Committee. 2025 heart disease and stroke statistics: a report of US and global data from the American Heart Association. *Circulation*. 2025;151:e41–e660. doi: 10.1161/CIR.0000000000001303
147. Schuchardt JP, Beinhorn P, Hu XF, Chan HM, Roke K, Bernasconi A, Hahn A, Sala-Vila A, Stark KD, Harris WS. Omega-3 world map: 2024 update. *Prog Lipid Res*. 2024;95:101286. doi: 10.1016/j.plipres.2024.101286
148. Sugano M, Hirahara F. Polyunsaturated fatty acids in the food chain in Japan. *Am J Clin Nutr*. 2000;71(1 Suppl):189S–196S. doi: 10.1093/ajcn/71.1.189S
149. Rix TA, Joensen AM, Riahi S, Lundbye-Christensen S, Tjønneland A, Schmidt EB, Overvad K. A U-shaped association between consumption of marine n-3 fatty acids and development of atrial fibrillation/atrial flutter-a Danish cohort study. *Europace*. 2014;16:1554–1561. doi: 10.1093/europace/euu019
150. Guardino ET, Li Y, Nguyen XM, Wilson PWF, Gaziano JM, Cho K, et al. Dietary ω-3 fatty acids and the incidence of atrial fibrillation in the million veteran program. *Am J Clin Nutr*. 202306;118:4–411. doi: 10.1016/j.ajcnut.2023.06.001
151. Zhang J, Cai A, Chen G, Wang X, Cai M, Li H, Nissen SE, Lip GYH, Lin H. Habitual fish oil supplementation and the risk of incident atrial fibrillation: findings from a large prospective longitudinal cohort study. *Eur J Prev Cardiol*. 2022;29:1911–1920. doi: 10.1093/eurjpc/zwac192
152. Chen G, Qian ZM, Zhang J, Zhang S, Zhang Z, Vaughn MG, Aaron HE, Wang C, Lip GY, Lin H. Regular use of fish oil supplements and course of cardiovascular diseases: prospective cohort study. *BMJ Med*. 2024;3:e000451. doi: 10.1136/bmjmed-2022-000451
153. Micha R, Khatibzadeh S, Shi P, Andrews KG, Engell RE, Mozaffarian D; Global Burden of Diseases Nutrition and Chronic Diseases Expert Group (NutriCoDE). Global, regional and national consumption of major food groups in 1990 and 2010: a systematic analysis including 266 country-specific nutrition surveys worldwide. *BMJ Open*. 2015;5:e008705. doi: 10.1136/bmjopen-2015-008705
154. Flock MR, Skulas-Ray AC, Harris WS, Etherton TD, Fleming JA, Kris-Etherton PM. Determinants of erythrocyte omega-3 fatty acid content in response to fish oil supplementation: a dose-response randomized controlled trial. *J Am Heart Assoc*. 2013;2:e000513. doi: 10.1161/JAHA.113.000513
155. Davis CG. *Seafood consumption per capita drifts higher in the United States. Charts of Note*. 2024. Accessed: 24 September 2024. https://www.ers.usda.gov/data-products/charts-of-note/chart-detail?chartId=108936#:~:text=U.S.%20residents%20consumed%20an%20average,shellfish%E2%80%94per%20capita%20in%202021
156. Jackson KH, Polreis JM, Tintle NL, Kris-Etherton PM, Harris WS. Association of reported fish intake and supplementation status with the omega-3 index. *Prostaglandins Leukot Essent Fatty Acids*. 2019;142:4–10. doi: 10.1016/j.plefa.2019.01.002