SUPPLEMENTAL MATERIAL

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Supplemental Methods

Eligibility criteria

RCTs administering EPA and/or DHA via liquid oil preparations (e.g., cod liver, seal, or tuna oil) were also eligible. Multi-component intervention studies (i.e., those combining omega-3 supplementation with pharmaceutical agents, antioxidant vitamins, or lifestyle interventions such as exercise regimens, low-fat diets and/or incorporated as part of a multi-nutrient supplement) were eligible if data from appropriate non-omega-3 control group were available.

We excluded trials that 1) administered omega-3 through dietary sources (e.g., oily fish meals), or through food/beverage-delivery based formats (e.g., fortified in margarine or a milkshake); 2) employed dietary regimen or lifestyle counselling as the sole intervention (e.g., Mediterranean diet) or advice to increase consumption of oily fish; 3) used omega-3 in the comparator arm (e.g., low vs high dose omega-3, or given dietary advice to increase oily fish intake, etc.); and 4) did not include a control/placebo or comparator group. Studies were also excluded if the intervention and control groups were not treated in parallel for at least 12 months, such as in delayed-start or open-label extension designs where the control group received the active intervention partway through the study.

Search strategy

A systematic search was conducted across nine databases: the Global Organization for EPA and DHA Omega-3s (GOED) Clinical Study Database, ResearchGate, PubMed, ClinicalTrials.gov, the International Standard Randomised Controlled Trial Number (ISRCTN) Registry, Australian New Zealand Clinical Trials Registry (ANZCTR), the National Institute for Health and Care Research (NIHR) Journal Library, the National Institutes of Health (NIH) Data Sharing and Archiving for Human Studies (DASH), medRxiv, Good Clinical Practice Network (GCP), and the Clinical Drug Experience Knowledgebase (CDEK). These databases were re-searched approximately monthly to detect newly published reports. The search was terminated on November 29th 2025.

Search terms included different combinations of keywords related to the intervention and outcome of interest: ‘omega-3 fatty acid’, ‘fish oil’, ‘seal oil’, ‘cod-liver oil’, ‘tuna oil’, ‘algae oil’, ‘krill oil’, ‘calanus oil’, ‘icosapent ethyl’, ‘DHA’, ‘EPA’, ‘lovaza’, ‘omega-3 acid ethyl esters’, ‘vascepa’, ‘omacor’, ‘epanova’, ‘docosahexaenoic’, and/or ‘eicosapentaenoic’. Outcome terms included ‘incident atrial fibrillation,’ ‘new-onset atrial fibrillation,’ and ‘atrial flutter.’ These terms were applied to titles and topic fields where database search functionality allowed. To minimize omission of eligible studies, the search strategy also incorporated terms related to dietary and nutritional supplements containing omega-3 fatty acids as part of multi-component interventions, recognizing that such trials may not be indexed primarily under omega-3-specific terminology alone. Relevant indexing terms included ‘dietary supplements,’ ‘nutraceuticals,’ and related nutritional intervention terminology.

To minimize reporting bias and maximize capture of relevant data, an expanded and targeted search strategy was implemented to identify RCTs meeting eligibility criteria irrespective of whether incident AF was a prespecified outcome, explicitly reported, or whether the primary focus of the trial was CV in nature. Trials were considered regardless of publication status.

Reference lists of prior systematic reviews on omega-3 fatty acids were screened to identify eligible RCTs. This included reviews spanning CV and non-CV outcomes (e.g., metabolic, neurocognitive, oncological, and inflammatory conditions), recognizing that such populations may still be at risk of incident AF.

To identify RCTs that may have collected relevant data but for which primary trial results had not yet been published in peer-reviewed journals, additional searches were conducted for study design publications and trial registry entries. Using the same keywords listed above, clinical trial registries (e.g., ClinicalTrials.gov, ISRCTN, ANZCTR, and GCP) were systematically screened irrespective of trial status (i.e., ongoing, or completed) and primary disease focus. Trials were considered irrespective of publication status; however, those that were still recruiting, in the intervention phase, terminated early, or had an unknown status were excluded.

A targeted search of ResearchGate was conducted specifically to identify potentially relevant conference communications. This approach enabled identification of eligible RCTs prior to publication of primary results and facilitated subsequent contact with investigators to obtain relevant outcome data.

Data collection and extraction

For the current review, published data were defined as reports of new-onset AF or atrial flutter events extracted from peer-reviewed publications (including primary reports, secondary analyses, and research letters/short communications) and/or their accompanying supplementary materials. These events could be reported as SAEs, AEs, treatment-emergent adverse events (TEAEs), predefined safety endpoints, or prespecified primary, secondary, tertiary, or exploratory outcomes (**Table S1**).

Published data included AF/flutter events identified through linked data sources reported within trial publications, such as electronic health records (EHRs), electronic medical records (EMRs), administrative or insurance claims databases, and hospitalization records. Events reported as AF-related hospitalizations or documented within broader clinical event collections were included where explicitly specified.

Published data also included AF/flutter events reported in publicly accessible sources, such as ClinicalTrials.gov AEs records, CDEK safety databases, NIHR safety reports, systematic reviews, supplementary files accompanying trial publications, other secondary reports, preprints (medRxiv), and publicly available datasets (e.g., NIH DASH), even if these data were not included in the primary trial publication. All available sources were systematically reviewed to identify cases of new-onset AF/flutter.

In trials where AEs monitoring followed a standardized classification system (e.g., National Institutes of Health [NIH] adverse event reporting frameworks[12], Medical Dictionary for Regulatory Activities[13] [MedDRA], International Classification of Diseases [ICD] coding[14], National Cancer Institute Common Terminology Criteria for Adverse Events[15] [CTCAE], or Systematized Nomenclature of Medicine- Clinical Terms[16] [SNOMED CT]), which includes CV and arrhythmia-related events such as AF/flutter

events reported under broader or indirect categories (e.g., ‘cardiovascular events,’ ‘cardiac events,’ ‘arrhythmic events,’ ‘cardiac disorders,’ ‘palpitations,’ ‘medication changes,’ or ‘cardiovascular hospitalizations’) were not considered equivalent to AF, unless explicitly attributed to new-onset AF/flutter within the publication or accompanying materials, or further clarification could be obtained from principal investigators (PIs).

In contrast, RCTs where cardiac safety/monitoring was a prespecified outcome, and/or AE monitoring included systematic cardiac assessments (e.g., scheduled ECGs or repeated CV evaluations during follow-up), and investigators explicitly reported the types of cardiac events observed without identifying AF/flutter, or explicitly stated that no CV events occurred- these findings were considered indicative of no AF occurrence. In such cases, a value of zero AF events was assigned to both trial arms in the current meta-analysis.

Acquisition of unpublished data

To maximize ascertainment of incident AF, we sought to obtain additional data beyond that reported in primary trial publications by proactively contacting PIs or corresponding authors of all eligible RCTs. Trials were contacted irrespective of whether incident AF/flutter was prespecified, or explicitly mentioned in the publication.

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 data obtained from non-public datasets (provided directly by investigators or through formal data access requests), investigator-confirmed data following review of study records (including confirmation of zero events), and data from completed registered trials for which primary results had not yet been published at the time of the meta-analysis.

Where primary trial results had not yet been published, or where published reports did not include AF/flutter outcomes, we systematically screened published study design

papers (e.g., via PubMed), study protocols and/or statistical analysis plans (SAPs) uploaded onto registries (when available), and trial registry entries. These sources were reviewed as they provide detailed information on planned outcomes, safety monitoring procedures, and data collection methods, which are often not fully reported in primary publications. Trials were evaluated for indications that relevant data may have been collected, including (but not limited to) planned AEs monitoring, CV or cardiac safety assessments, ECG monitoring, collection of CV hospitalizations or clinical event data, or explicit inclusion of new-onset AF as a prespecified clinical or safety outcome.

Where such data were expected to have been collected but could not be located (e.g., trial remains unpublished, data under embargo, article in press, or datasets not publicly accessible). PIs were contacted to inquire and/or request access to the relevant data. Formal trial database access applications were also submitted where applicable.

For published RCTs where no trial registry entries, study protocols, or SAPs were available, investigators were contacted to determine whether relevant data had been collected but not publicly reported. A similar approach was applied to trials with available publications or registry documentation where AF-related data were incomplete, insufficiently detailed, or reported under broader categories. In such cases, investigators were contacted to clarify outcome definitions, ascertainment methods, and to request additional or disaggregated AF/flutter data (e.g., event counts by treatment arm or differentiation of AF from related events). Where it was evident that relevant data likely existed but could not be accessed (e.g., due to non-response or unavailable records), this was documented and reported in **Tables S1-S2** where applicable.

In addition, baseline characteristics and eligibility criteria reported in trial publications were reviewed to identify indirect indicators that AF-related data may have been collected. Specifically, reporting of AF history at baseline (e.g., ‘history of AF, n [%]’) or exclusion of participants with prior AF suggested that incident AF may have been monitored or recorded during follow-up. Similarly, trials incorporating cardiac rhythm surveillance procedures (e.g., implantable cardioverter-defibrillator [ICD] monitoring, continuous rhythm monitoring, or detection/reporting of ventricular arrhythmias) were considered potentially to have captured atrial arrhythmia data, including AF/flutter

events. Such trials were considered potentially informative, and PIs were contacted to clarify availability of incident AF data.

Importantly, trials were not excluded based on whether AF was a prespecified outcome or explicitly reported as an AE- we did not assume absence of events. Instead, investigators were contacted and, where possible, asked to review AE datasets, CRFs, EMRs, or other relevant sources (e.g. ECGs) if applicable, to identify potential AF events.

In all cases, if investigators confirmed that AF/flutter events had been recorded, these data were included into the present meta-analysis. If investigators confirmed that no AF events had been observed or recorded, and the study's monitoring procedures (e.g., systematic AE collection, cardiac or safety monitoring, and/or regular follow-up) were deemed sufficient to capture such events if present, these studies were included and coded as zero events in both trial arms.

Conversely, studies were not coded as zero events if investigators were unable to confirm absence of AF or if available data were insufficient to support this assumption (**Table S2**). Investigators were not asked to perform additional adjudication or retrospective chart review beyond existing study data, unless voluntarily offered.

Communication with principal investigators/corresponding authors

Investigators who responded with non-specific statements (e.g., 'unable to assist' or 'no information available') were contacted with follow-up inquiries to clarify whether this reflected absence of AF data collection, inability to access or share existing data, or uncertainty regarding whether AF outcomes had been recorded. Where initial responses indicated that AF was not a prespecified outcome, additional clarification was sought regarding whether AF events may nevertheless have been captured through AE monitoring systems, clinical records, or other study data sources.

Responses were subsequently categorized based on whether (i) relevant data were available and shareable, (ii) data had not been collected, (iii) data were collected but not

accessible or not shareable, or (iv) the status of AF data remained unclear despite follow-up (**Table S2**). In all cases, absence of confirmation was not interpreted as absence of AF events unless explicitly verified by the investigator and supported by the study's monitoring procedures.

Data synthesis

Pooling of omega-3 arms depended on whether all doses fell within the same predefined category. If all doses were in the same category (e.g., low dose), they were combined into a single treatment group, and the mean dose calculated. When a study investigated multiple omega-3 doses, each dose arm was stratified separately according to the high-dose vs low-dose criteria, and the non-omega-3 comparator group was necessarily included in both strata to allow for appropriate comparisons.

For all included trials, AF event counts and denominators were checked for completeness and internal consistency. When AF data were missing, incomplete, or unclear, study investigators were contacted to request clarification. If AF data remained unresolved after these inquiries, these RCTs were not included in the meta-analysis. However, studies with partially missing data were retained when analyzable arms were available.

Table S1. 35 RCTs meeting eligibility and included in meta-analysis stratified by cardiovascular risk and omega-3 dosage (high dose ≥1500 mg E+D/d), with publication status, data source, AF definition/outcome classification, and method of AF ascertainment.

Trial/ Authors (Year)	Trial Acronym and/ or Official Study Title Trial Registration No.	Publication Status Data Source	AF Definition/Outcome Classification Method of AF Ascertainment
High Risk High Dose (HR-HD)			
Yokote et al (2020)*[68]	AZD0585 Phase III Long-term Study in Japan NCT02463071	Published data Data extracted from Clinical Drug Experience Knowledgebase AEs records[109].	AF not a prespecified outcome of Yokote et al (2020), however, safety was a primary outcome of the study[68]. Safety evaluations included treatment-emergent adverse events (TEAEs), laboratory parameters, electrocardiograms (ECGs), vital signs, and physical examinations conducted at 4-5 visits during follow-up over the 12-mos treatment period[68]. Adverse events (AEs) were classified using the Medical Dictionary for Regulatory Activities (MedDRA) by system organ class and preferred term. While serious cardiac events (e.g. myocardial ischemia and atrioventricular block) were reported[109], no AF events were identified. AF was therefore coded as zero events in the current meta-analysis.
REDUCE-IT (2023)[69]	Reduction of Cardiovascular Events with Icosapent Ethyl-Intervention Trial A Study of AMR101 to Evaluate Its Ability to Reduce Cardiovascular Events in High-Risk Patients With Hypertriglyceridemia and on Statin NCT01492361	Published data. Data reported in research article[69] and clinicaltrials.gov AEs records[110]	AF and atrial flutter reported as prespecified exploratory tertiary endpoints in REDUCE-IT, adjudicated by the Clinical Endpoint Committee. AF/atrial flutter hospitalizations (≥24 hours) were captured under 'arrhythmia requiring hospitalization.' Additional AF/flutter events not meeting endpoint adjudication criteria were captured through standard AE reporting as TEAEs. TEAEs were defined as events first occurring or worsening

			in severity on or after study drug initiation and within 30 days after treatment discontinuation. Events positively adjudicated as clinical endpoints (i.e., AF/flutter hospitalizations) were excluded from the TEAE dataset. Annual ECGs were performed during follow-up but were not mandated to determine the presence or absence of AF. AEs were coded using MedDRA (v.20.1) Multiple publications from REDUCE-IT report AF/flutter outcomes using different definitions. The main trial publication[125] reported AF/flutter TEAEs, which include both incident AF and worsening of pre-existing AF and were not stratified by baseline AF status (215/4089 vs. 159/4090)[125]. Post-hoc analyses subsequently reported adjudicated AF/flutter hospitalizations stratified by prior AF status[69]. However, equivalent stratification was not reported for TEAE-level AF events[125]. As AF events not meeting hospitalization endpoint criteria were captured only through AE reporting, incident AF/flutter among participants without prior AF (n=7,428)[69] could not be isolated from the TEAE dataset[125]. Attempts were made to contact the investigators for clarification, but no response was received. Serious AF/flutter AEs were also identified from results posted on ClinicalTrials.gov (uploaded in 2022)[110], which report SAEs under the MedDRA cardiac disorders category. These events represent serious safety events recorded during the trial but are separate from adjudicated endpoint events. For the present meta-analysis, AF/flutter hospitalization events among participants without prior AF (81/3721 vs. 60/3707) reported in the post-hoc analyses[69] were extracted and supplemented with AF/flutter SAEs reported in ClinicalTrials.gov[110] (AF [21 vs. 17] and atrial flutter [1 vs. 3]). This approach was chosen to minimize inclusion of recurrent AF events among participants with pre-existing AF.

STRENGTH (2020)[70]	A Long-Term Outcomes Study to Assess STatin Residual Risk Reduction with EpaNova in HiGh Cardiovascular Risk PatienTs with Hypertriglyceridemia NCT02104817	Published data. Data reported in research article[70].	AF reported as a prespecified tertiary efficacy endpoint in STRENGTH, defined as first occurrence of new-onset AF during follow-up. Events were investigator-reported based on ECGs, and presented as time-to-first event (Kaplan-Meier). According to the primary publication[70] and the accompanying study protocol[70], AF events were not centrally adjudicated. Participants were followed at outpatient visits at -3 and -6 mos, and every 6- mos thereafter over a mean follow-up period of 3.5-yrs. In a subsequent secondary analysis of STRENGTH[112], incident AF was instead reported as a safety AE outcome and restricted to participants without a documented history of AF (n=12,012). In this analysis, AF events were adjudicated by a clinical events committee, and case ascertainment based on investigator-reported ECG findings without a strict duration criterion[112]. For the current meta-analysis, AF data was extracted from the primary trial report (144/6539 vs. 86/6539; 2.2% vs 1.3%)[70]. Updated events from the secondary report (126/6000 vs. 75/6012; 2.1% vs 1.2%)[112] were not extracted as these data became available after completion of the meta-analysis. 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.
FAAT (2005)[88]	Fatty Acid Antiarrhythmia Trial NCT00004559	Unpublished data. Data acquired directly from PIs.	AF not a prespecified outcome of FAAT. PIs confirmed that patients were monitored for the development of arrhythmias (including AF) during follow-up, with events requiring therapy captured via the case report form (CRF) medication-change field over the 12-mos study period. Participants attended follow-up visits at 3-mos intervals.

			PIs reviewed AEs records for FAAT and confirmed that recorded medication changes reflected new-onset AF. As AF events were not separately reported, incidence was inferred from these data rather than directly adjudicated.
PEACH (2018)[71]	The PEACH (Pitavastatin And Combined Omega-3 Health) Study Effect of Pitavastatin and EPA on coronary artery calcification detected by computed tomography UMIN000003171	Published data. Data reported in research Article[71].	AF not a prespecified outcome of PEACH. Safety was assessed by recording all SAEs and AEs of special interest (including arrhythmias). These were reported by site investigators to the PI, and then to the Data and Safety Monitoring Board (DSMB), which constituted of cardiologists. Investigators explicitly report that no CV events were observed in patients[71]. AF was therefore coded as zero events in the current meta-analysis.
OMEMI (2023)[72]	OMega-3 fatty acids in Elderly patients with Acute Myocardial Infarction study NCT01841944	Published data. Data reported in research Article[72].	AF reported as a prespecified secondary outcome of OMEMI, defined as the occurrence of new-onset AF in participants without prior AF. New-onset AF events were identified by a standard 12-lead ECG or single-lead ECG tracing ≥30 sec showing irregular RR intervals without discernible P waves. AF ascertainment included scheduled 12-lead ECGs at -3, -12, and 24-mos, supplemented by clinical detection (including hospital admissions) and active screening using intermittent handheld single-lead ECG monitoring (Zenicor; twice daily 30-sec recordings for 14 days at 12 mos). All events were adjudicated centrally by an independent endpoint committee blinded to treatment allocation.

EVAPORATE (2020)[89]	Effect of Vascepa on Improving Coronary Atherosclerosis in People With High Triglycerides Taking Statin Therapy NCT02926027	Unpublished data. Data acquired directly from PI.	AF reported as a prespecified safety outcome of EVAPORATE, as confirmed by the PI. AF ascertainment (per investigator communication) included ECGs, patient reports, physical examinations, and review of hospital/clinic records at scheduled visits (-3, -9, -12, and 18-mos, with interim telephone follow-up at 15-mos). AEs were monitored throughout the study period with SAEs reported within 24 hrs and overseen by an independent DSMB. PI confirmed that no AF events were detected during the study; this was coded as zero events in our meta-analysis.
HEARTS (2025)[90]	Slowing HEART diSease With Lifestyle and Omega-3 Fatty Acids NCT01624727	Unpublished data. Data acquired directly from PI.	AF reported as a prespecified safety endpoint of HEARTS, as confirmed by the PI. Cardiac events, including first occurrence of AF/flutter, were prospectively monitored throughout the 30-mos intervention period. Participants attended scheduled follow-up visits (6 wks and -3, -6, -9, -12, -18, -24, and 30-mos), during which clinical assessments, including ECG; were performed. AEs were systematically collected via questionnaires at each visit. Medical records were obtained to confirm reported AF/flutter events.
SAREPITASO (2018)†[73]	SARpogrelate-EPA-PITavastatin-ASO Study Effects of sarpogrelate, eicosapentaenoic acid and pitavastatin on arterioslcerosis obliterans-related biomarkers in patients with type 2 diabetes	Published data. Data reported in research article[73].	AF not a prespecified outcome of SAREPITASO. CV events were monitored throughout the study (-3, -6 and 12- mos). PIs explicitly report no CV events were observed or reported by patients[73], therefore AF coded as zero events in our meta-analysis.

Derosa et al (2016)*†[74]	Effects of n-3 pufas on fasting plasma glucose and insulin resistance in patients with impaired fasting glucose or impaired glucose tolerance	Published data. Data extracted from systematic review[106].	AF not a prespecified outcome of Derosa et al (2016). Specific AF ascertainment details were not directly reported; however, the primary publication reported that 12-lead ECGs were conducted at baseline, 9- and 18-mos during the trial period[74]. Therefore, AF detection may have been captured as part of safety monitoring, but this was not explicitly reported by investigators. Contact with PI was attempted to confirm this but received no response.
OFAMI (2001)[75]	Omega-3 Fatty Acids in Myocardial Infarction study Effects of High-dose n-3 Fatty Acids on Clinical Outcome and Serum Lipids - Omacor Following Acute Myocardial Infarction (OFAMI) NCT01422317	Published data. Data extracted from systematic review[106]	AF not a prespecified outcome of OFAMI. Specific AF ascertainment details were not directly reported; however, the primary publication reported that repeated ECG recordings at 6 wks, 6-, 12- and 18-mos, and for several patients at 24-mos post-randomization were conducted[75]. Therefore, AF detection may have been captured as part of safety monitoring, but this was not explicitly reported by investigators. Contact with PI was attempted to confirm this but received no response.
RESPECT-EPA (2024)[76]	Randomized Trial for Evaluation in Secondary Prevention Efficacy of Combination Therapy-Statin and Eicosapentaenoic Acid UMIN000012069	Published data. Data extracted from supplemental table[76].	AF reported as a prespecified secondary endpoint of RESPECT-EPA. According to the supplementary appendix of the primary publication, events were captured under ‘cardiac disease-related events’ and defined as newly identified AF on ECG during the study period[76]. AF events were systematically monitored at annual visits over 3 yrs using ECGs and recorded under both clinical outcomes and AEs reporting. AEs were evaluated as a safety endpoint. All endpoint events were adjudicated by an independent clinical endpoint committee blinded to treatment assignment.

High Risk Low Dose (HR-LD)			
GISSI-HF (2013)[77]	The Gruppo Italiano per lo Studio della Sopravvivenza nell'Insufficienza Cardiaca (Italian Group for the Study of the Survival in Heart Failure) GISSI-HF- Effects of n-3 PUFA and Rosuvastatin on Mortality-Morbidity of Patients With Symptomatic CHF NCT00336336	Published data. Data reported in research article[77].	AF was reported as a predefined secondary outcome in GISSI-HF and investigated among participants without AF on baseline ECG, irrespective of prior history of AF. AF occurrence was defined as the presence of AF on ECG performed at study visits, or AF identified as a clinical event between visits (including AF causing or worsening heart failure, AF leading to hospitalization, or AF occurring during hospitalization). AF events were ascertained from scheduled ECGs and clinical events, supported by hospitalization records and clinical documentation. Participants attended follow-up visits at 1, 3, 6, 12, 18, 24, 30, and 36 months. Commonly reported AF event counts in GISSI-HF (Population 1: 444/2921 vs. 408/2914)[77] included participants with a prior history of AF. For the present analysis, we incorporated event counts from Population 2 (244/2499 vs. 278/2492)[77], which excludes individuals with a history of AF. This approach was chosen to minimize misclassification of recurrent AF as incident AF.
Risk & Prevention (2013)[78]	Rischio and Prevenzione Risk and Prevention Study: Evaluation of the Efficacy of n-3 PUFA in Subjects at High Cardiovascular Risk NCT00317707	Published data. Data extracted from supplemental table[78].	While AF was not specifically defined as an independent outcome in Risk & Prevention (R&P), hospitalization for CV reasons was a prespecified primary endpoint of the study, within which AF-related hospital admissions were reported in the results[78]. Hospitalizations for CV causes were defined as any admission coded using International Classification of Diseases [ICD-9]) codes 390–459 or procedures 35–39). Events were documented with narrative summaries and supporting clinical documentation, and adjudicated by a

			blinded committee using pre-agreed definitions and procedures. Only AF hospitalizations are reported in R&P[78]; it is unclear whether non-hospitalized or AE-level AF was systematically captured. Although AEs and SAEs were reported in the trial publication[78], AF was not separately described within these categories. Attempts to contact the investigators for clarification were unsuccessful.
ASCEND (2018)[79]	A Study of Cardiovascular Events iN Diabetes NCT00135226	Published data. Data reported in research letter[105] and extracted from conference presentation[111].	AF reported as a prespecified exploratory vascular outcome in ASCEND, but was not adjudicated clinically. Outcomes ascertained via hospitalizations, SAEs reported by participants during the trial, ICD-10 code diagnoses and Office of Population Censuses and Surveys Classification of Interventions and Procedures (OPCS-4, v.4) procedure codes in electronic health records (EHR- [Hospital Episode Statistics data]) covering 97% of participants with a 14-yr look-back[105]. Participants were followed up approximately twice yearly (≈6-monthly) via postal questionnaires (with later use of online and telephone follow-up). Analyses were restricted to participants without known prior AF at baseline. Most events were identified via EHRs (890 EHR-only; 231 both EHR and self-report), with a small proportion based on self-report alone (n=56)[111]. Although AF incidence was reported in the research letter[105], detailed event counts by treatment arm were not provided. Therefore, event counts were obtained from a conference presentation[111] of the same trial population and outcome are included in the current meta-analyses.

GISSI-Prevenzione (2001)†[80]	Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico – Prevenzione (Italian Group for the Study of the Survival of Myocardial Infarction – Prevention)	Published data. Data extracted from systematic Review[106]	AF not a prespecified outcome of GISSI-Prevenzione. Specific AF ascertainment details were not directly reported in original research article[80]. Contact with PI was attempted to clarify this but received no response. From GISSI-Prevenzione, only AF events reported in the n-3 alone and control groups[106] are included in our dataset; AF data from other multi-factorial groups (vitamin E alone, n=2,830; n-3 + vitamin E, n=5,660) were excluded in the systematic review[106], for reasons that remain unclear. Attempts to obtain these data from PI were unsuccessful.
SU.FOL.OM3 (2010)[91]	SUpplementation with FOlate, vitamin B6 and B12 and/or OMega-3 fatty acids ISRCTN41926726	Unpublished data. Data acquired directly from PI.	AF was a prespecified secondary endpoint of SU.FOL.OM3, as confirmed by the PI. Participants attended annual in-person follow-up visits (T1, T2, T3, T5), during which physical examinations and biological assessments were performed; AF was ascertained and recorded using ECGs. Between visits, participants completed semi-annual mailed questionnaires capturing new diagnoses and hospitalizations, with non-responders followed up by telephone interview. Reported CV events (including AF) were verified using medical records, hospital discharge summaries, death certificates, and autopsy data, and adjudicated centrally according to ICD-10 criteria.
ORIGIN (2012)[92]	Outcome Reduction with an Initial Glargine Intervention NCT00069784	Unpublished data. Data acquired directly from PI.	AF was not a prespecified outcome in ORIGIN. The PI confirmed that AF events were reported by individual study sites as part of routine safety monitoring and were not centrally adjudicated. As described in the study protocol provided in the supplementary appendix of the main trial publication[92], safety events (including AEs and SAEs), were collected prospectively at scheduled study visits (2-, 4-, 8-, and 16-wks post-randomization and every 4-mos thereafter) and documented by investigators using CRFs. AEs were coded using the MedDRA dictionary and reported by system organ class and preferred term.

Low Risk High Dose (LR-HD)			
RCT-EPA (2023)[81]	Effects of EPA on Prostate Cancer Cells Proliferation and Quality of Life (RCT-EPA) NCT02333435	Published data. Data reported in research Article[81].	AF not a prespecified outcome in RCT-EPA. The study protocol[144] reported that AEs would be collected and monitored at each post-prostatectomy visit (6 wks, 3-, 6-, 9-, and 12-mos) using NIH AE criteria (v4.03, June 2010), which include CV/arrhythmic events. In the published article, all AEs were listed, and none were cardiac events[81]; therefore, AF coded as zero events in the current meta-analysis.
Mengelberg et al (2022)[*93]	The effects of docosahexaenoic acid supplementation on cognition and well-being in mild cognitive impairment: A 12-month randomised controlled trial ACTRN12614000874617	Unpublished data. Data acquired directly from PIs.	AF was not a prespecified outcome in Mengelberg et al (2022). PI confirmed that any AF events would have been captured under AEs which were monitored throughout the study period, with collection at scheduled assessments (-6, -9, and 12-mos). PI confirmed no AF was reported by patients- this was coded as zero events in our analysis.
seAFOod Polyp Prevention (2018)[82]	The seAFOod (Systematic Evaluation of Aspirin and Fish Oil) Polyp Prevention trial ISRCTN05926847	Published data. Data extracted from research article[82].	AF was not a prespecified outcome of seAFOod Polyp Prevention, However, AEs were a prespecified secondary outcome of the study and were systematically collected according to standard CTIMP pharmacovigilance procedures. AEs were coded using MedDRA system organ classes, under which AF falls within the cardiac disorders category. Therefore, while AF/flutter was not defined as a specific endpoint, any events that occurred were captured as part of routine AEs monitoring. Telephone consultations were conducted at -2, -12, and -38 wks after randomization to assess AEs, in addition to routine in person follow-up. PI further confirmed that ECGs were not performed.

ENRGISE (2019)[83]	The ENRGISE (ENabling Reduction of Low-Grade Inflammation in SEniors) Study NCT02676466	Published data. Data extracted from ClinicalTrials.gov AEs records[107]	AF not a prespecified outcome in ENRGISE. AF events were captured under both SAEs (2 AF hospitalizations grouped under 'cardiac disorders')[107] and non-SAEs (2 AF events grouped under 'general disorders')[107], using MedDRA system organ classes. AEs were systematically collected from screening through study closeout, with participants followed for 12 mos. Participants were assessed at quarterly (3-mos) in-person visits, during which clinical evaluations, laboratory testing, safety reviews, and structured participant interviews were conducted; participants could also report events between visits. Notably, the main trial publication[83] explicitly report that study treatment was discontinued in the event of new-onset AF, indicating that incident AF was actively monitored within the safety framework, despite not being a prespecified outcome of the study.
ADCS-DHA (2010)[94]	DHA (Docosahexaenoic Acid), an Omega 3 Fatty Acid, in Slowing the Progression of Alzheimer's Disease Alzheimer's Disease Cooperative Study NCT00440050	Unpublished data. Data were extracted from the AEs raw dataset, accessed via formal data application request to ADCS data repository[103]	AF was not a prespecified outcome in ADCS-DHA. AF/flutter events were captured under AEs, which were collected systematically at follow-up visits conducted every 3 mos during treatment (follow-up visits at -3, -6, -9, -12, -15, and 18-mos). According to the study dataset[103] (accessed via approved application) and confirmed by the PI, AF/flutter events were recorded within the AEs dataset and ascertained through multiple sources, including medical records, ECGs, participant self-report, and other clinical documentation. Additional cardiac-related events (e.g., arrhythmia, palpitations/flutter, heart murmur) were also recorded but not further adjudicated to our knowledge; therefore, only explicitly documented AF/flutter events were included in the present meta-analysis.

MARINA (2011)[‡96]	The Modulation of Atherosclerosis Risk by Increasing doses of N3 fatty Acids study Vascular effects of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA): the MARINA study ISRCTN66664610	Unpublished data. Data acquired directly from PIs.	AF not a prespecified outcome of MARINA. PI checked raw dataset (AEs, reasons for non-compliance, dropouts) and confirmed no cases of AF were recorded during the study. Although AF was not an outcome of MARINA, the incidence of AF would have been detected by 24h heart rate monitoring with an Actiheart device (Cambridge Neurotechnology Ltd, Cambridge, UK) that was conducted at baseline, 6- and 12 mos of treatment (heart rate variability defined as a prespecified secondary outcome of MARINA). PI is confident that no cases of AF were missed- this was coded as zero events in our analysis.
Lin et al (2022)[*‡95]	The Protective Effect of Omega-3 Fatty Acid on Cognitive Function Among Patients with Mild Dementia NCT04972643	Unpublished data. Data acquired directly from PIs.	AF not a prespecified outcome of Lin et al (2022). PI confirmed that any AF events would have been captured under AEs reporting. Participants were followed over a 24-month treatment period, with scheduled in-person visits (-6, -12, -18, and 24-mos) for AEs monitoring[95]. PI confirmed no AF was reported by patients- this was coded as zero events in our analysis.
BRAVE-EPA (2025)[97]	Brain Amyloid and Vascular Effects of Eicosapentaenoic Acid Study NCT02719327	Unpublished data. Data acquired directly from PIs.	AF not a prespecified outcome in BRAVE-EPA. As confirmed by the PI, AF events were captured as AEs within the cardiac disorders category (Systematized Nomenclature of Medicine-Clinical Terms [SNOMED-CT]). AF was reported among 'other adverse events not including serious adverse events'. AF ascertainment was based on patient self-report and routine clinical assessment. Participants were evaluated for AEs every 3-mos during the 18-mos trial duration.

EPOCH (2018)[98]	The Older People, Omega-3, and Cognitive Health (EPOCH) trial ACTRN12607000278437	Unpublished data. Data acquired directly from PI.	AF not a prespecified outcome in EPOCH. PI confirmed AF captured under SAEs, based on patient self-report. AEs were systematically recorded at each follow-up visit conducted at 3-mos intervals (-3, -6, -9, -12, -15, and 18-mos). Adverse effects suspected to be related to the intervention were reviewed by the trial physician as needed. Participants completed self-report questionnaires prior to each visit, and AEs were documented during in-person assessments.
DREAM (2019)[84]	DRy Eye Assessment and Management (DREAM©) Study NCT02128763	Published data. Data extracted from supplemental table[84].	AF not a prespecified outcome in DREAM. AF/flutter were recorded as part of SAEs captured under 'cardiac disorders' coded using MedDRA (v4.0). Coordinators systematically elicited AEs during each in-person visit (-3, -6, and 12-mos) and via telephone at 9-mos.
CAPFISH-3 (2024)[99]	CAncer Prostate FISH oil trial (Phase 3) Low-Fat Diet and Fish Oil in Men on Active Surveillance for Prostate Cancer NCT02176902	Unpublished data. Data acquired directly from PIs.	AF not a prespecified outcome of CAPFISH-3, however, safety was a predefined secondary endpoint of the study. PI confirmed that AF was self-reported and recorded as part of AE reporting during in-person and phone visits monthly for the omega-3 group and in-person visits at -6 and -12 mos for the control group. Incidence of AEs graded according to National Cancer Institute (NCI) Common Toxicity Criteria (v. 4.0). Therefore, while AF was not defined as a specific endpoint, any events that occurred were captured as part of routine AEs monitoring.

Sandhu et al (2016)*[85]	Nutritional Supplements and Hormonal Manipulations for Breast Cancer Prevention NCT00723398	Published data. Data extracted from supplemental table[85].	AF not a prespecified outcome in Sandhu et al (2016). CV events were monitored throughout the study (-12 and -24 mos) as SAEs using NCI Common Terminology Criteria for Adverse Events (CTCAE) (v. 3.0). Reported CV events included coronary artery disease, chest pain, valvular heart disease, and hypertension[85]. No AF events were reported- this was coded as zero events in the current meta-analysis.
Low Risk Low Dose (LR-LD)			
Shinto et al (2014)*[86]	Lipoic Acid and Omega-3 Fatty Acids for Alzheimer's Disease NCT01058941	Published data. Data extracted from ClinicalTrials.gov AEs records[108]	AF not a prespecified outcome in Shinto et al (2014). Events were collected by systematic assessment and captured within SAEs and coded under 'cardiac disorders' using MedDRA (version not specified). AEs were monitored monthly during the 18-mos trial period; clinic visits and by phone. Safety monitoring included participant and study partner reports, laboratory tests, vital signs, and physical examinations[48].
VITAL Rhythm (2021)[87]	VITamin D and Omega-3 Trial – Rhythm Study NCT02178410	Published data. Data extracted from research article[87] and supplemental table[87]	AF was reported as a prespecified primary outcome of VITAL-Rhythm, and defined as a confirmed diagnosis of AF or atrial flutter occurring during follow-up. Case ascertainment was conducted via two complementary pathways: participant self-report on annual questionnaires and linkage to administrative claims data (Centers for Medicare & Medicaid Services [CMS]/insurance) using ICD-9 and ICD-10 diagnostic codes for AF and atrial flutter, respectively. For all potential cases identified through either method, permission was sought to obtain relevant medical records.

			An independent endpoint adjudication committee confirmed events based on predefined criteria, requiring either ECG evidence of AF/atrial flutter or physician documentation of the diagnosis. The date of onset was defined as the earliest documented occurrence in the medical record. If questionnaires were not returned, participants were assumed not to have developed AF unless identified through claims data or medical record review. A total of 900 confirmed incident AF events were identified by self-report and/or CMS claims during the trial period. Among these, 72.9% (n=656) were supported by ECG documentation and 27.1% (n=244) by physician diagnosis, consistent with the adjudication criteria. 7.3% (n=66) of cases occurred in the postoperative setting, and 5.8% (n=52) had only atrial flutter documented in medical records[87]. VITAL-Rhythm is an ancillary study of the VITAL trial[143]; the current meta-analysis was performed using data reported in VITAL-Rhythm[87].
CANN (2023)[100]	The Cognitive Ageing Nutrition and Neurogenesis (CANN) Trial NCT02525198	Unpublished data. Data acquired directly from PIs.	AF was not a prespecified outcome in CANN. PI confirmed that any AF events would have been captured under AEs. According to supplemental appendices accompanying the study design[145], AEs were actively monitored, with participants encouraged to report events at any time, and events systematically documented in CRFs. AEs were reviewed at in-person visits at -3 and 12-mos, with additional follow-up via telephone when events were reported. PI confirmed no AF was reported by patients- this was coded as zero events in the current meta-analysis.

AREDS2 (2013)[101]	Age-Related Eye Disease Study 2 NCT00345176	Unpublished data. Data were extracted from the AEs raw dataset[104], obtained through internal collaboration with the trial investigators.	AF reported as a predefined secondary safety endpoint in AREDS2, as confirmed by the PI. Events were captured within SAEs and coded under 'cardiac disorders' using MedDRA (v 10.0). PI confirmed that CV events, including AF, were initially self-reported by participants, with medical record verification when available. Formal adjudication of CV events was conducted by a medical committee comprising cardiologists, internists, and neurologists. AEs were ascertained through annual study visits, supplemented by telephone follow-up at 3 mos post-randomization and at 6-mos intervals between visits across a 5 yr-period.
MARINA (2011)‡[96]	The Modulation of Atherosclerosis Risk by Increasing doses of N3 fatty Acids study Vascular effects of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA): the MARINA study ISRCTN66664610	Unpublished data. Data acquired directly from PIs.	Same information as detailed in LR-HD group‡
Lin et al (2022)*‡[95]	The Protective Effect of Omega-3 Fatty Acid on Cognitive Function Among Patients with Mild Dementia NCT04972643	Unpublished data. Data acquired directly from PIs.	Same information as detailed in LR-HD group‡
DO-HEALTH (2025)[102]	VitaminD3-Omega3-Home Exercise-HeALTHy Ageing and Longevity Trial NCT01745263	Unpublished data. Data acquired directly from PI.	AF reported as a predefined safety endpoint in DO-HEALTH as confirmed to us by PI. According to the study protocol[146] events were captured through systematic AE monitoring based on participant self-report at each study contact, including structured telephone interviews every 3 mos and in-person clinic

			visits at -12, -24, and 36-mos over the 3-yr follow-up period. AF events were classified using ICD-10 (v. 2010) terminology, and reflected physician-diagnosed events within the trial's safety monitoring system. SAEs were subject to standardized, protocol-driven reporting procedures, including rapid reporting to the sponsor and regulatory oversight bodies.

Abbreviations: AF: atrial fibrillation; AEs: adverse events; CRF: case report form; CTCAE: Common Terminology Criteria for Adverse Events (National Cancer Institute); CTIMP: clinical trial of an investigational medicinal product; CV: cardiovascular; DHA: docosahexaenoic acid; DSMB: Data and Safety Monitoring Board; ECG: electrocardiogram; EHR: electronic health records; EPA: eicosapentaenoic acid; HF: heart failure; ICD: implantable cardioverter-defibrillator; ICD: International Classification of Diseases; MedDRA: Medical Dictionary for Regulatory Activities; mos: months; N: number of participants randomized; NCI: National Cancer Institute; OPCS: Office of Population Censuses and Surveys Classification of Interventions and Procedures; PIs: principal investigators; RCT: randomized controlled trial; SAEs: serious adverse events; SNOMED CT: Systematized Nomenclature of Medicine – Clinical Terms; wks: weeks; yr: year.

*Studies without a trial name did not report a trial acronym/name in the publication and/or registry entry.

†Studies without a registered trial identification number did not report a registry entry in the primary publication or could not be identified in trial registries.

‡MARINA[96] and Lin et al.[95], 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.

Table S2. RCTs meeting eligibility criteria but excluded from the meta-analysis due to principal investigators (PIs)/corresponding authors were unable to provide data or did not respond to repeated requests (after 3x attempts at follow-up).

Trial/ Authors (Year)	Trial Acronym and/ or Official Study Title Trial Registration No. Country	Intervention (Treatment & Comparator) Study Duration (Months)	Sample Size (N) Study Population	PIs Response
Responded- no relevant data collected				
FISH (2012)[22]	Fish oil Inhibition of Stenosis in Hemodialysis grafts study ISRCTN15838383 Canada and United States	MEG-3® 4000mg/d (EPA 1600mg/d + 800mg/d DHA) Placebo (corn oil) 12 months	N=232 Chronic hemodialysis patients who needed new graft access.	PI confirmed that AF was not a pre-specified outcome of FISH; no relevant data collected.
Nosaka et al (2017)[*23]	Clinical effect of early loading of eicosapentaenoic acid after percutaneous coronary intervention in patients with acute coronary syndrome UMIN000016723 Japan	Vascepa® 1800mg/d (1800mg/d EPA +2mg/d Pitavastatin) Control (2mg/d Pitavastatin) 12 months.	N=241 Patients w/ acute coronary syndrome patients treated w/ successful percutaneous coronary intervention within 24 hrs.	PI confirmed they do not have data on incidence AF.
Baleztena et al (2018)[*24]	Dietary Supplement for the Prevention of Cognitive Decline in a Very Elderly Population. NCT01817101 Spain	Omega-3 1050 mg/d (120mg/d EPA + 750mg/d DHA) Placebo (gelatin). 12 months	N=99 ≥75-year-old nursing home resident's w/o CI or with mild cognitive impairment (MCI).	PI confirmed AF was not recorded and was not a pre-specified outcome; access to EMRs for AF assessment not possible due to lack of consent and participant availability.

SOFA (2006)[25]	Study on Omega-3 Fatty acids and ventricular Arrhythmia NCT00110838 Europe	Omega-3 2000mg/d (EPA 450mg/d + DHA 350mg/d) Placebo (inert oil unspecified) 12 months	N=546 Patients w/implantable cardioverter defibrillators (ICD) and prior documented malignant VT or VF.	PI confirmed all arrhythmias captured under AEs in SOFA were ventricular (ICD-detected); AF could not be isolated from VF or VF. Therefore, no relevant data collected in SOFA.
OPAL (2010)[26]	The Older People And n-3 Long-chain polyunsaturated fatty acids study United Kingdom ISRCTN72331636	Omega-3 1000mg/d (EPA 200mg/d + DHA 500mg/d) Placebo (olive oil) 24 months	N=867 Cognitively healthy adults aged 70-79 yrs.	PI confirmed that AF was not a pre-specified outcome of OPAL and that no relevant data are available for inclusion. Follow-up regarding AEs data also confirmed that no AF-related information was collected.
The Beyond Ageing Project (2017)[27]	The Beyond Ageing Project: A selective prevention trial using novel pharmacotherapies in an older age cohort at risk for depression ACTRN12610000032055 Australia	Omega-3 2000mg/d (1200mg/d EPA + 800mg/d DHA) or 50mg/d Sertraline hydrochloride Placebo (paraffin oil). 12 months	N=450 A community-based sample subjects w/previously reported sub-threshold depressive symptoms, aged 60-74 yrs.	PI confirmed AF was not a pre-specified outcome of Beyond Ageing Project; no relevant data collected.
IRIS-FAI (2024)[28]	Effect of Icosapent ethyl on inflammation in the vessel wall assessed by the Fat Attenuation Index Score ISRCTN15140257 United Kingdom	Vazkepa® (icosapent ethyl) x2 capsules (1920mg/d EPA) combined w/ standard care Control (standard care only) 12 months	N=100 (target) High-risk adults w/ established cardiovascular disease and elevated triglyceride levels.	PI was unable to assist without providing further clarification (response in September 2025). IRIS-FAI was terminated in October 2025 owing to recruitment challenges[28].

NUTRIMEMO (2015)[29, 30]	Effect of Lipidic Nutrients on Memory and Well Being in Healthy Aging Adults NCT02626247 France	Omega-3 combined w/ Vitamin A x3 capsules/d (EPA+DHA 900mg/d) Placebo (unspecified) 12 months	N=340 Healthy elderly subjects independently living at home aged 60-70 yrs.	PI confirmed that AF was not a pre-specified endpoint of NUTRIMEMO and no ECGs were performed. PI re-examined the NUTRIMEMO study database and found no recorded AF or major CV events; however, after consultation with the cohort PI, it was concluded by the investigators that AF and CV events were not systematically collected or verifiable.
Responded- relevant data collected but not shareable				
PISCES (2025)[31]	Protection against Incidences of Serious Cardiovascular Events Study with daily fish oil supplementation in dialysis patients ISRCTN00691795 United States, Canada, and Australia	Omega-3 4000mg/d (EPA 1600mg/d + DHA 800mg/d) Placebo (corn oil) 42 months	N=1100 Patients w/ end-stage kidney disease who requires chronic hemodialysis 3 or 4 times/wk.	PI confirmed that arrhythmia data including atrial and ventricular arrhythmias were collected in PISCES; however, these data are not currently shareable. The team plans to present the arrhythmia results in mid-2026.
Prevent E4 (2023)[32]	The Brain DHA Delivery Trial NCT03613844 United States	Omega-3 2000mg/d (DHA 2000mg/d) Placebo (corn and soy oil) 24 months	N=365 Cognitively unimpaired individuals aged 55-80 yrs, with at least one CV or dementia risk factor (obesity, hypertension, hyperlipidemia, or physical inactivity).	PI confirmed that AF was recorded as an AE in Prevent E4, but could not provide the data until the main trial results are published in a peer-reviewed Journal.

Responded- AF data status unclear				
DOIT (2010)[†33]	Diet and Omega-3 Intervention Trial (DOIT) on atherosclerosis Norway	Pikasol® 2400mg/d (EPA 840mg/d + DHA 480mg/d) combined w/ or w/o dietary counselling (Mediterranean) Control (dietary counselling) Placebo (corn oil). 36 months	N= 563 Elderly men aged 65-75 yrs w/ longstanding dyslipidemia or hypertension.	Co-investigator confirmed that AF was not a pre-specified outcome of DOIT and indicated they do not have access to the raw dataset to review AEs. The PI may hold the dataset, but multiple contact attempts by us received no response.
MAPT (2019)[34]	Omega-3 Fatty Acids and/or Multi-domain Intervention in the Prevention of Age-related Cognitive Decline (MAPT) NCT00672685 France and Monaco	Omega-3 1025mg/d (800mg/d DHA + 225mg/d EPA) combined w/ or w/o multi-domain intervention (nutrition, physical exercise, cognitive stimulation, social activities). Placebo (unspecified) 36 months	N=1680 Community-dwelling participants aged ≥70 yrs non-demented, but w/ memory complaint and limitations in one instrumental activity of daily living, or slow gait speed.	PI confirmed that AF was not a pre-specified outcome of MAPT and that AF cases may be identifiable within AE records, however this analysis has not been conducted. The PI did not respond to follow-up requests asking whether AE data could be reviewed for AF events.
NAT2 (2013)[39]	Nutritional AMD Treatment 2 Study ISRCTN98246501 France	Omega-3 840mg/d (DHA 840mg/day) Placebo (olive oil) 36 months	N=263 Patients aged 55-85 yrs w/early lesions of age-related maculopathy.	PI was unable to assist and provided no further information. It remains unclear whether AF-related data were collected or exist within the NAT2 study records.
JELIS (2007)[36]	Japan EPA Lipid Intervention Study NCT00231738 Japan	Vascepa® 1800mg/d combined w/ 10mg/d Pravastatin or 5mg/d Simvastatin (EPA 1800mg/d) Control (Statin therapy alone) 55 months (mean follow-up)	N= 18,645 Patients' w/ Hypercholesterolemia undergoing statin therapy.	Co-investigators confirmed that AF was not a pre-specified outcome of JELIS and do not have access to the raw dataset to review AEs. It remains unclear whether AF-related data were collected or exist within the JELIS study records.

EPE-A (2014)[37]	Double-Blind, Placebo-Controlled Study of Two Doses of EPA-E in Patients With Non-Alcoholic Steatohepatitis NCT01154985 United States	Omega-3 1800mg/d or 2700mg/d (EPA 1800mg/d or 2700mg/d; chemical formulation unspecified) Placebo (unspecified) 12 months	N=243 Patients w/nonalcoholic steatohepatitis and/or non-alcoholic fatty liver disease.	PI confirmed that AF was not a pre-specified outcome of EPE-A. PI does not have access to raw dataset to review AEs; data are held exclusively by the study sponsor.
Re-MIND (2022)[40]	Memory Intervention with Nutrition for Dementia ISRCTN11892249 Ireland	Omega-3 1000mg/d (DHA 500mg/d + EPA 150mg/d) Placebo (sunflower oil) 24 months	N=120 Patients w/ mild-moderate Alzheimer Disease.	Discussion with PI planned to address IRB ethical approval for secondary data use; follow-up was made, but received no response.
EMT2 (2023)[38]	EPA for Metastasis Trial 2 A randomised placebo-controlled phase III trial of the effect of the omega-3 fatty acid eicosapentaenoic acid (EPA) on colorectal cancer recurrence and survival after surgery for resectable liver metastases NCT03428477 United Kingdom	Vascepa® 4000mg/d (EPA 3656mg/d) Placebo (mineral oil) 24-36 months	N=448 Patients undergoing liver resection surgery for advanced colorectal cancer liver metastasis with curative intent.	PI confirmed that the trial is ongoing and remains blinded, with participants still in the intervention phase. Relevant outcome data have not yet been generated or finalized (prior to data cleaning, database lock, and unblinding). The PI indicated that AF events may have occurred but could not provide analyzable data while the blind is maintained.
PUFA (2024)[41]	Prevention of Cerebral Small Vessel Disease and Inflammation in Aging NCT01953705 United States	ProOmega-3® 1650mg/d (EPA 975mg/d + DHA 650mg/d) Placebo (soybean oil) 36 months	N=102 Participants w/o dementia but with mild cognitive impairment (MCI) aged ≥75 yrs (mean age: 81.1 yrs, 61% female).	PI recalled 21 abnormal ECGs at 12 months (≈10 in omega-3 group, ≈11 in placebo), with no between-group differences. Reasons for abnormalities unclear; confirmation would require reading ECGs. PI initially agreed to revisit the ECGs to verify whether any represented AF; however, no further responses were received despite several follow-up attempts.

NICE (2024)[42]	Nutrition Interventions for Cognitive Enhancement Enhanced Mediterranean Diet for Alzheimer's Disease Prevention NCT03841539 United States	Omega-3 2000mg/d combined w/ dietary counselling- Mediterranean or Low-fat. (Ratio EPA/DHA unspecified) Placebo (unspecified) 12 months	N=209 Cognitively normal older adults aged ≥65 yrs.	PI confirmed that AF was not a prespecified outcome in NICE. PI could not recall any AEs related to AF but would require confirmation. No further responses were received regarding our request to review the AEs dataset.
WELCOME (2014)[35]	Wessex Evaluation of fatty Liver and Cardiovascular markers in NAFLD with Omacor thErapy NCT00760513 United Kingdom	Omacor® 4000mg/d (1840mg/d EPA + 1520mg/d DHA) Placebo (olive oil) 18 months	N=103 Patients w/non-alcoholic fatty liver disease (NALFD).	PI confirmed that AF was not a pre-specified outcome of WELCOME. AEs data not available in an electronic format for review; review of paper CRFs was not feasible.
No response				
OMEGA (2013)[43]	Effect of Omega 3-Fatty Acids on the Reduction of Sudden Cardiac Death After Myocardial Infarction NCT00251134 Germany	Zodin® 1000mg/d (EPA 460mg/d + DHA 380mg/d) Placebo (olive oil) 12 months	N=3851 Patients who survived acute myocardial infarction.	New-onset AF data reported in systematic review[106] which required further clarification from PIs who did not respond to our request.
SHOT (1996)†[44]	Scandinavian Heart Omega-3 Trial Denmark	Omacor® 4000mg/d combined w/ 15mg/d Warfarin or 300mg/d Aspirin (1840mg/d EPA + 1520mg/d DHA) Placebo (margarine) 12 months	N=610 Patients admitted for coronary bypass grafting surgery.	No response.
Tande et al (2016)*†[45]	Clinical safety evaluation of marine oil derived from Calanus finmarchicus Norway	Calanus oil 2000mg/d (EPA/DHA dosage unspecified) Placebo (unspecified) 12 months	N=127 Healthy subjects with BMI 25-35 kg/m^2	No response.

AQUAMARINE EPA/DHA (2024)[46]	The Attempts at Plaque Vulnerability Quantification with Magnetic Resonance Imaging Using Non contrast T1-weighted Technic EPA/DHA study Japan UMIN 000015316	Lotriga® 2000mg/d or 4000mg/d (EPA 930mg/d + DHA 750mg/d or EPA 1860mg/d + 1500mg/d) Control (standard statin therapy) 12 months	N=84 Patients' w/ CAD receiving statin therapy.	No response.
Duan et al (2025)*[47]	Effects of medium chain triglycerides combined with DHA on ameliorating cognitive decline by brain energy metabolism in the elderly with mild cognitive impairment China ChiCTR2200059641	Algae oil 2000mg/d (DHA 900-1100mg/d) Placebo (corn oil) 24 months	N=240 Elderly individuals with mild cognitive impairment (MCI).	No response.
SCIMO (2001)†[48]	Study on Prevention of Coronary Atherosclerosis with Marine Omega-3 Fatty Acids The Netherlands	Omega-3 6000mg/d (1650mg/d EPA + DHA) for the first 3 months then for the following 21 months 3000mg/d (1500mg/d EPA + DHA) Placebo (composition reflecting average European diet). 24 months	N=223 Patients w/angiographically proven CAD.	No response.
PNMD (2025)[49]	The Precision Nutritional Management for Diabetes (PNMD) trial NCT03708887 China	MEG-3® 3000mg/d or 1500mg/d (EPA 1440mg/d + DHA 570mg/d or EPA 720mg/d + DHA 285mg/d) Placebo (refined olive oil) 14 months	N=415 Patients aged 40-75 yrs (mean age 63 yrs) w/ type-2 diabetes or obesity (BMI ≥28).	No response.

PAOXRED (2022)†[50]	Protección AntiOXidante en la REtinopatía Diabética (Antioxidant Protection in Diabetic Retinopathy) Spain	Brudyretina® 1500mg/d (EPA 127mg/d + DHA 1050mg/d) Placebo (olive oil) 24 months	N=170 Patients w/non-proliferative diabetic retinopathy.	No response.
Garcia Layana et al (2021)*[51]	Study of Nutritional Supplementation in Patients With Unilateral Wet AMD Spain NCT04756310	Retilut® x2 capsules/d (DHA 800mg/d) Control (Theavit® nutritional supplement w/o DHA) 12 months	N=109 Patients w/diagnosed unilateral exudative age-related macular degeneration.	No response.
Ahn et al (2016)*†[52]	Effect of n-3 Polyunsaturated Fatty Acids on Regression of Coronary Atherosclerosis in Statin Treated Patients Undergoing Percutaneous Coronary Intervention Korea	Omega-3 (3000mg/d) (EPA 1395mg/d + DHA 1125mg/d) Placebo (unspecified) 12 months.	N=74 Patients undergoing percutaneous coronary intervention w/ stent implantation and undergoing statin therapy.	No response.
Raitt et al (2005)*†[53]	Fish Oil Supplementation and Risk of Ventricular Tachycardia and Ventricular Fibrillation in Patients With Implantable Defibrillators A Randomized Controlled Trial United States	Omega-3 1800mg/d (EPA 756mg/d + DHA 540mg/d) Placebo (olive oil) 24 months	N=200 Patients with implantable cardioverter defibrillators (ICD) and recent episode of sustained VT or VF.	Investigators report a total of 47 AF events identified through ICD electrogram review[53]; however, it is unclear whether these represented new-onset or pre-existing AF, and the allocation of events to the omega-3 or placebo groups could not be determined. Attempts to obtain clarification from the PI received no response.

Brox et al (2001)*†[54]	A Long-Term Seal- and Cod-Liver-Oil Supplementation in Hypercholesterolemic Subjects Norway	Cod-liver oil 15ml/d (EPA 1500mg/d + DHA 1800mg/d) or Seal oil 15ml/d (EPA 1100mg/d + DHA 1500mg/d) Control (nothing given) 14 months	N=120 Subjects with moderate hypercholesterolemia.	No response.
Puri et al (2005)*[55]	A multicentre, multinational, double blind, randomised, parallel group, placebo-controlled study of ethyl-eicosapentaenoate (EPA) in patients with Huntington's disease (HD) ISRCTN79170611 United Kingdom	Omega-3 2000mg/d (EPA 2000mg/d) Placebo (unspecified) 12 months	N=135 Patients w/ Huntington disease.	No response.
Sabour et al (2015)*[56]	Omega 3 in Intervention Spinal Cord Injured People Omega-3 fatty acids' effect on leptin and adiponectin concentrations in patients with spinal cord injury: A double-blinded randomized clinical trial Iran NCT01311375	MorDHA® x2 capsules/d (EPA 130mg/d + DHA 870mg/d) Placebo (unspecified) 14 months.	N=110 Chronic traumatic spinal cord-injured patients.	No response.
Olendzki et al (2011)*†[57]	Treatment of Rheumatoid Arthritis with Marine and Botanical Oils: Influence on Serum Lipids United States	Omega-3 3500mg/d combined w/ 1800mg/d borage oil (GLA) (2100mg/d EPA + 1400mg/d DHA) Placebo (sunflower oil) 18 months	N=146 Rheumatoid arthritis patients w/ active joint inflammation'	No response.

OPACH (2006)[58]	Omacor in Prevention of Cardiovascular Events in Patients Undergoing Chronic Hemodialysis Denmark NCT00257283	Omacor® 2000mg/d (EPA 920mg/d + DHA 760mg/d) Placebo (olive oil) 24 months	N=206 Patients w/ documented CVD, undergoing chronic hemodialysis for at least 6 mos.	No response.
HOST (2016)[59]	The Impact of Omega Three Fatty Acids on Vascular Function in HIV NCT01041521 United States	Lovaza® 4000mg/d (EPA 1860mg/d + DHA 1500mg/d) Placebo (sugar pill) 24 months	N=129 HIV-infected individuals with elevated levels of triglycerides (≥150 mg/dl).	No response.
Li et al (2024)[*†60]	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 China	Omega-3 800mg/d combined w/ or w/o 800µg/d folic acid (DHA 800mg/d) Placebo (unspecified) 12 months.	N=280 Mild cognitive impairment (MCI) participants aged ≥60 yrs.	No response.
Lafuente et al (2017)[*61]	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 EudraCT 2015-001082-74 Spain	Brudyretina® 1500mg/d combined w/ 0.5mg/d Ranibizumab (EPA 127mg/d + DHA1050mg/day) Control (0.5mg/d Ranibizumab) 36 months	N=55 Patients w/ type 2 diabetes who presented decreased vision due to central-involved diabetic macular edema.	No response.

NutriStroke (2009)[†62]	The Role of Nutrition in the Rehabilitation of Patients With Eating Disorders After a Vascular Stroke Italy	Omega-3 500mg/d combined w/ or w/o antioxidants (EPA 250mg/d + DHA 250mg/d) Placebo (identical supplement but contained no antioxidants or omega-3) 12 months	N=72 Stroke patients admitted to a rehabilitation hospital for sequelae of first-ever ischemic stroke.	No response.
CARES (2022)[63]	Cognitive impAiRmEnt Study: Changes in brain function among individuals with a mild memory impairment ISRCTN10431469 Ireland	Omega-3 1000mg/d combined w/ carotenoids (lutein, zeaxanthin, and meso-zeaxanthin) (DHA 430mg/d + EPA 90mg/d) Placebo (sunflower oil) 24 months	N=60 Individuals w/ mild cognitive impairment aged ≥65 yrs.	No response.
Blok et al (1997)[*†64]	Pro- and anti-inflammatory cytokines in healthy volunteers fed various doses of fish oil for 1 year The Netherlands	Omega-3 3000mg/d (EPA+DHA 1060mg/d) or Omega-3 6000mg/d (EPA+DHA 2130mg/d) or Omega-3 9000mg/d (EPA+DHA 3190mg/d) Placebo (identical supplement w/o omega-3). 12 months	N=58 Healthy monks (mean age 56 yrs).	No response.
SALVAGE (2024)[65]	IcoSApent ethyL to Slow Down Aortic VAlve Stenosis proGrEssion Study on Icosapent Ethyl for Slowing Aortic Valve Stenosis Progression in Patients with Aortic Valve Stenosis NCT06466278 The Netherlands	Vazkepa® 4000mg/d (EPA 3656mg/d) Placebo (unspecified) 24 months	N=110 (estimated) Patients w/ mild to moderate to aortic valve stenosis aged ≥50 yrs.	No response.

TotAL (2018)[66]	Testosterone-Omega Three (DHA) - Amyloid Lowering (TotAL) study Australia ACTRN12618000761268	Omega-3 x4 capsules/d (1720mg DHA) combined w/ or w/o intramuscular testosterone injections every ~12 weeks Placebo (corn oil) 14-18 months approx.	N=200 Males aged between 60-80 yrs w/ subjective memory complaints, and amyloid-positive PET scans.	No response.
Hearon et al (2022)*[67]	Improving Metabolic Health in Patients With Diastolic Dysfunction (MTG) NCT03448185 United States	Lovaza® 2000mg/d combined w/ high-intensity interval training (HIIT) or yoga (EPA 930mg/d + DHA 750mg/d) Placebo (olive oil) 12 months	N=80 Obese middle-aged adults (mean age 50 yrs) at high-risk of heart failure (HF).	No response

Abbreviations: AF: atrial fibrillation; AEs: adverse events; CAD: coronary artery disease; CV: cardiovascular; CVD: cardiovascular disease; DHA: docosahexaenoic acid; ECGs: electrocardiograms; EPA: eicosapentaenoic acid; HF: heart failure; HIIT: high-intensity interval training; HIV: human immunodeficiency virus; ICD: implantable cardioverter-defibrillator; IRB: institutional review board; MCI: mild cognitive impairment; mg/d: milligrams per day; mos: months; N: number of participants randomized; PET: positron emission tomography; PIs: principal investigators; RCT: randomized controlled trial; SAEs: serious adverse events; VT: ventricular tachycardia; VF: ventricular fibrillation; wks: weeks; yr: year

*Studies without a trial name did not report a trial acronym/name in the publication or registry entry.

†Studies without a registered trial identification number did not report a registry entry in the primary publication or could not be identified in trial registries.

Table S3. Characteristics of the 35 RCTs included in the meta-analysis stratified by cardiovascular risk and omega-3 dosage (high dose ≥1500 mg E+D/d).

Trial/ Authors (Year)	Country	N	Study Population	Mean Age Males (%)	Omega-3 Formulation	Intervention (Treatment & Comparator)	Month	Ratio (EPA:DHA)
High Risk High Dose (HR-HD)								
Yokote et al (2020)*[68]	Japan	383	Patients' w/ hyperlipidemia accompanied by hypertriglyceridemia.	56.9 78%	O3CA	Epanova® 2000mg/d (EPA 1100mg/d + DHA 400mg/d) Epanova® 4000mg/d (EPA 2200mg/d + DHA 800mg/d Placebo (corn oil)	12	2.75:1
REDUCE-IT (2023)[69]	Multi-national	8,179	Statin-treated patients w/ hypertriglyceridemia, and high risk of/or established ASCVD and/or TD1/2.	64 71%	IPE	Vascepa® 4000 mg/day (EPA 4000mg/d) Placebo (mineral oil)	58.8	NA
STRENGTH (2020)[70]	Multi-national	13,078	Statin-treated patients w/ hypertriglyceridemia, low HDL, and high risk of/or established ASCVD and/or TD1/2.	62.5 65%	O3CA	Epanova® 4000mg/d (EPA 2200mg/d + DHA 800mg/d) Placebo (corn oil)	42	2.75:1
FAAT (2005)[88]	USA	402	Patients' w/ implantable cardioverter/defibrillators at high risk of fatal ventricular arrhythmias.	65 85%	O3AEE	Omacor® 4000mg/d (EPA+DHA 2600 mg/d) Placebo (olive oil)	12	1.24:1
PEACH (2018)[71]	Japan	157	Patients' w/ hypercholesterolemia undergoing statin therapy.	67 53%	IPE	Vascepa® 1800mg/d combined w/ Pitavastatin 2mg/d (EPA 1800mg/d) Control (Pitavastatin 2mg/d or 4mg/d)	12	NA

OMEMI (2023)[72]	Norway	1,027	Elderly patients (70-82 yrs) w/recent MI 2-8 wks prior.	74 71%	rTG	Omega-3 1800mg/d (EPA 930mg/d + DHA 660mg/d) Placebo (corn oil)	24	1.4:1
EVAPORATE (2020)[89]	USA	80	Patients w/ coronary atherosclerosis under-going statin therapy, and have persistently elevated triglyceride levels.	57.4 54%	IPE	Vascepa® 4000 mg/day (EPA 4000mg/d) Placebo (mineral oil).	18	NA
HEARTS (2025)[90]	USA	285	Patients' w/stable CAD on statin therapy.	63 85%	O3AEE	Lovaza® 3360mg/d (EPA 1860mg/d +DHA 1500mg/d) Control (standard care)	30	1.24:1
SAREPITASO (2018)†[73]	Japan	76	Patients w/ T2DM and non-diabetic controls.	74 47%	IPE	Vascepa® 1800mg/d (EPA 1800mg/d combined w/ Pitavastatin 2mg/d) Control (Sarpogrelate 300mg/d + Pitavastatin 2mg/d	12	NA
Derosa et al (2016)*†[74]	Italy	281	Overweight/obese patients w/ impaired fasting glucose or impaired glucose tolerance.	53.5 50%	EE	Omega-3 3000mg/d combined w/ diet and physical activity. (EPA+DHA dose unspecified) Placebo (sucrose, mannitol and mineral salts)	18	0.9:1.5
OFAMI (2001)[75]	Norway	300	Patients w/ existing CVD following MI (recruited 4-8 days after confirmed MI).	64 74%	O3AEE	Omacor® 4000mg/d (~3400-3500 mg/d EPA + DHA) Placebo (corn oil)	18	1.24:1
RESPECT-EPA (2024)[76]	Japan	2,506	Patients w/ stable CAD and a low EPA/AA ratio.	68 80%	IPE	Vascepa® 1800mg/d combined w/ standard statin therapy (EPA 1800mg/d) Control (standard statin therapy only)	60	NA

High Risk Low Dose (HR-LD)								
GISSI-HF (2013)[77]	Italy	5,835	Patients w/heart failure irrespective of cause and left ventricular ejection fraction.	66 80%	O3AEE	Omacor® 1000mg/d (EPA+DHA ~866mg/d) Placebo (olive oil)	46.8	1.24:1
Risk & Prevention (2013)[78]	Italy	12,505	Patients w/multiple CV risk factors (at least 4 of the following: hypertension, hypercholesterolemia, current smoker, obesity, family history of premature CVD), clinical evidence of ASCVD, or any other condition placing the patient at high CV risk, but no MI.	64 61%	EE	Omega-3 1000mg/d (EPA+DHA ~870mg/d) Placebo (olive oil)	60	1:1.2
ASCEND (2018)[79]	UK	15,480	Patients' w/T2DM but w/o ASCVD	63.3 62%	O3AEE	Omacor® 1000mg/d combined w/ 100mg/d aspirin (2x2) (EPA 460mg/d + DHA 380mg/d) Placebo (olive oil)	88.8	1.2:1
GISSI-Prevenzione (2001)†[80]	Italy	11,324	Patients who had experienced a recent MI (within the previous 3 mos) and under-going preventive pharmacological interventions, alongside following Mediterranean dietary guidelines.	59 85%	O3AEE	Omacor® 1000mg/d combined w/ 300mg/d vitamin E (2x2) (EPA+DHA ~866mg/d) Control (nothing given)	42	1.24:1
SU.FOL.OM3 (2010)[91]	France	2,501	Patients' w/ a history of MI, unstable angina, or ischemic stroke in the previous year.	61.4 79%	EE	Omega-3 600mg/d combined w/ 560µg/d folate, 3mg/d vitaminB6, 20µg/d vitamin B12 (2x2) (EPA 400mg/d + DHA 200mg/d) Placebo (gelatin)	56.4	2:1

ORIGIN (2012)[92]	Multi-national	12,536	Patients' w/ T2DM, or impaired glucose tolerance, or prior MI, stroke, or revascularization, or angina w/ documented ischemia, or PAD, or microalbuminuria, or LVH.	63.5 65%	O3AEE	Omacor® 1000mg/d combined w/ insulin glargine (2x2) (EPA 465mg/d + DHA 375mg/d) Control (standard care combined w/olive oil or insulin [Lantus®; OptiPen® Pro 1])	74.4	1.24:1
Low Risk High Dose (LR-HD)								
RCT-EPA (2023)[81]	Canada	121	Men w/ prostate cancer who have has chosen to undergo radical prostatectomy.	63 100%	MAG-EPA	Omega-3 3750mg/d (EPA 3000mg/d) Placebo (high oleic sunflower oil)	14	NA
Mengelberg et al (2022)[*93]	New Zealand	76	Patients (60-90 yrs) w/ mild cognitive impairment.	72.8 42%	TG	Omega-3 3000mg/d (EPA 351mg/d +DHA 1491mg/d) Placebo (linoleic acid)	12	1:4.25
seAFOod Polyp Prevention (2018)[82]	UK	709	Patients' (55-73 yrs) identified as 'high risk' of bowel cancer (detection of ≥5 small adenomas or ≥3 adenomas with at least one being ≥10 mm in diameter) after their 1st screening colonoscopy.	65 80%	FFA/TG[‡]	ALFA® x2 capsules/d (FFA) or 2780mg/d TGs combined w/ or w/o 300mg aspirin (2x2) (EPA 2000mg/d) Placebo (capric and caprylic acid medium-chain TGs)	12	NA
ENrGISE (2019)[83]	USA	289	Patients aged ≥70 yrs w/ self-reported walking or stair-climbing difficulty and therefore at high risk for mobility disability and had evidence of low-grade chronic inflammation.	78.3 52%	TG	Omega-3 1400-2800mg/d combined w/ 50-100mg/d losartan (2x2) (EPA 800-1200mg/d + DHA 400-600mg/d) Placebo (corn oil)	12	2:1
ADCS-DHA (2010)[94]	USA	402	Patients w/mild to moderate Alzheimer disease.	76 47%	TG	Neuromins® 2000mg/d (DHA 2000mg/d) Placebo (corn or soy oil)	18	NA

MARINA (2011)[§95]	UK	163	Non-smoking participants aged 45-70yrs w/ mild-to-moderate increased risk of CVD.	55 39%	TG	Omega-3 1800mg/d (EPA ~1083mg/d + DHA ~717mg/d) Placebo (olive oil)	24	1.51:1
Lin et al (2022)[*§96]	Taiwan	312	Patients ≥65yrs w/mild cognitive impairment or Alzheimer's Disease living in Veteran Retirement Centers.	77.5 65%	EE	Omega-3 2000mg/d (EPA 1600mg/d) Placebo (isocaloric oil)	24	NA
BRAVE-EPA (2025)[97]	USA	131	Cognitively healthy male veterans aged 50-70 yrs at risk for Alzheimer's Disease.	65.5 100%	IPE	Vascepa® 4000mg/d (EPA 4000mg/d) Placebo (mineral oil)	18	NA
EPOCH (2018)[98]	New Zealand	403	Cognitively healthy community-dwelling adults aged 65-90 yrs.	72.9 46%	rTG	Omega-3 2320mg/d (EPA 600mg/d + DHA 1720mg/d) Placebo (olive oil)	18	~1:2.85
DREAM (2019)[84]	USA	535	Patients w/ chronic, symptomatic moderate to severe dry eye disease.	58 19%	TG	Omega-3 3000mg/d (EPA 2000mg/d + DHA 1000mg/d) Placebo (olive oil)	12	2:1
CAPFISH-3 (2024)[99]	USA	100	Men on active surveillance for prostate cancer.	64 100%	TG	Omega-3 2200mg/d combined w/ dietary counselling (low-fat diet) (2200mg/d EPA+DHA) Control (nothing given)	12	Unspecified
Sandhu et al (2016)[*85]	USA	266	Healthy postmenopausal women at increased risk of breast cancer based on high breast density detected on their routine screening mammograms.	57.4 0%	O3AEE	Lovaza® 4000mg/d alone or combined w/ 30mg Raloxifene (EPA 1860mg/d + DHA 1500mg/d) or 30mg Raloxifene alone or 60mg Raloxifene alone Control (nothing given)	24	NA

Low Risk Low Dose (LR-LD)								
Shinto et al (2014)[*86]	USA	67	Patients aged ≥55yrs w/ probable Alzheimer dementia diagnosis.	74.7 47%	TG	Omega-3 3000mg/d combined w/ 600mg lipoic acid (EPA 975mg/d + DHA 675mg/d) Placebo (soybean oil)	18	1.4:1
VITAL Rhythm (2021)[‖87]	USA	900	Healthy adults aged ≥55yrs w/o history of CVD or cancer.	66.7 50%	O3AEE	Omacor®1000mg/d combined w/ 2000IU/d vitamin D3 (2x2) (EPA 460mg/d + DHA 380mg/d) Placebo (olive oil)	63.6	1.24:1
CANN (2023)[100]	UK, USA, and Australia	259	Older adults aged ≥55yrs w/ either subjective or mild cognitive impairment but without a diagnosis or evidence of dementia, or significant depression or other neurological disorders.	65.5 43%	TG	Omega-3 1500mg/d combined w/ 500mg cocoa plant-derived flavanols (EPA 400mg/d + DHA 1100mg/d) Placebo (corn and palm oil blend fatty acid composition typical of a UK or Australian diet)	12	1:2.8
AREDS2 (2013)[101]	USA	4,203	Patients aged 50-85 yrs w/intermediate advanced age-related macular degeneration (AMD) in both eyes or intermediate AMD in one and advanced AMD in the other eye.	74 43%	EE	AREDS2® 2x capsules/d (EPA 650mg/d + DHA 350mg/d combined w/ 500 mg/d vitamin C, 440IU/d vitamin E, 15mg/d beta-carotene, 80mg/d zinc oxide and 2mg/d cupric oxide (2x2). Control: standard AREDS® supplement w/o omega-3.	57.6	~1.9:1
MARINA (2011)[§96]	UK	163	Non-smoking participants aged 45-70yrs w/ mild-to-moderate increased risk of CVD.	55 39%	TG	Omega-3 450mg/d (EPA ~270mg/d + DHA ~179mg/d) or Omega-3 900mg/d (EPA ~542mg/d + DHA ~359mg/d) Placebo (olive oil)	24	1.51:1

Lin et al (2022)[*§95]	Taiwan	312	Patients ≥65yrs w/mild cognitive impairment or Alzheimer's Disease living in Veteran Retirement Centers.	77.5 65%	EE	Omega-3 1000mg/d (DHA 700mg/d) or Omega-3 2000mg/d (EPA+DHA 1150mg/d) Placebo (isocaloric oil)	24	Unspecified
DO-HEALTH (2025)[102]	Europe	2157	Community-dwelling adults aged ≥70 yrs generally healthy and active, w/no major health events (e.g., cancer or MI) in the 5 yrs prior to enrollment.	74 38%	TG	Omega-3 1000mg/d combined w/ 2000IU/d vitamin D3 and strength exercise 3x /wk. (2x2x2) (EPA 330mg/d + DHA 660mg/d) Placebo (sunflower oil)	36	1:2

Abbreviations: AREDS: Age-Related Eye Disease Study; ASCVD: atherosclerotic cardiovascular disease; CAD: coronary artery disease; CVD: cardiovascular disease; DHA: docosahexaenoic acid; EE: ethyl ester; EPA: eicosapentaenoic acid; FFA: free fatty acid; HDL: high-density lipoprotein; HR-HD: high risk, high dose; HR-LD: high risk, low dose; IPE: icosapent ethyl; LR-HD: low risk, high dose; LR-LD: low risk, low dose; LVH: left ventricular hypertrophy; MAG: monoacylglyceride; mg/d: milligram per day; MI: myocardial infarction; mos: months; N: number of participants randomized; NA: not applicable; O3AEE: omega-3 acid ethyl esters; O3CA: omega-3 carboxylic acids; PAD: peripheral artery disease; RCT: randomized controlled trial; rTG: re-esterified triglyceride; TD1/2: type 1/2 diabetes mellitus; TG: triglyceride; UK: the United Kingdom; USA: the United States of America; wks: weeks; yrs: years

[*]Studies without a trial name did not report a trial acronym/name in the publication and/or registry entry.

[†]Studies without a registered trial identification number did not report a registry entry in the primary publication or could not be identified in trial registries.

[‡]In seAFOod Polyp Prevention[82], the omega-3 intervention formulation was modified mid-trial due to discontinuation of the original product. Participants initially received 2000 mg/day of >99% pure EPA (FFA); when supply ceased, ~one-third were switched to an equivalent EPA dose provided as 2780 mg/day of 90% EPA in TG form.

[§]MARINA[96] and Lin et al.[95], 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.

[‖]VITAL-rhythm[87] is an ancillary trial of the VITAL trial[142]- our meta-analysis was performed using VITAL-rhythm data.

Figure S1. Risk differences (RD) sensitivity analysis of 35 RCTs (37 datasets) including data from 114,592 participants, and the observed AF rates segregated by high vs low dose EPA+DHA (≤ vs > 1500 mg/d) and by high vs low risk for CVD.

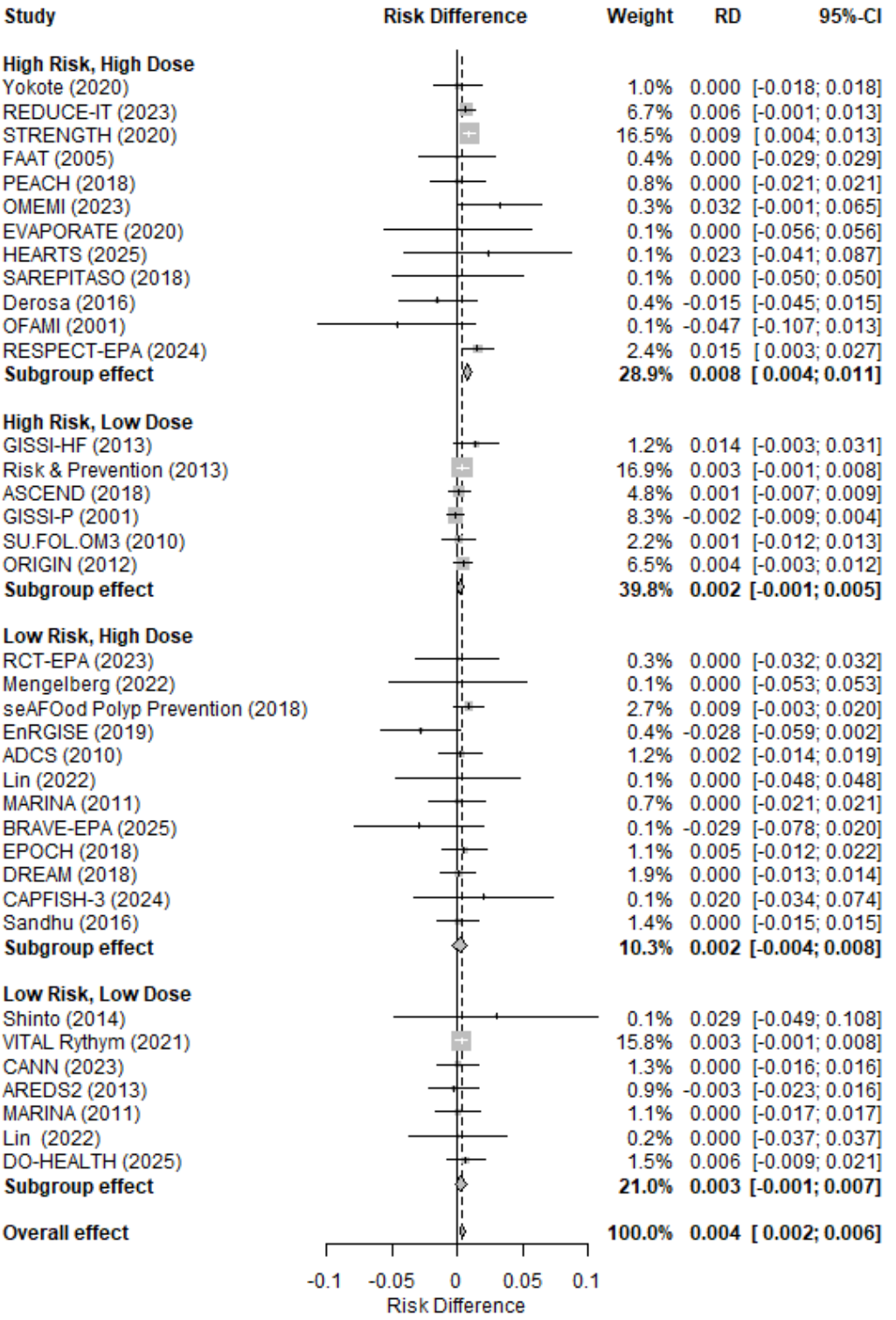
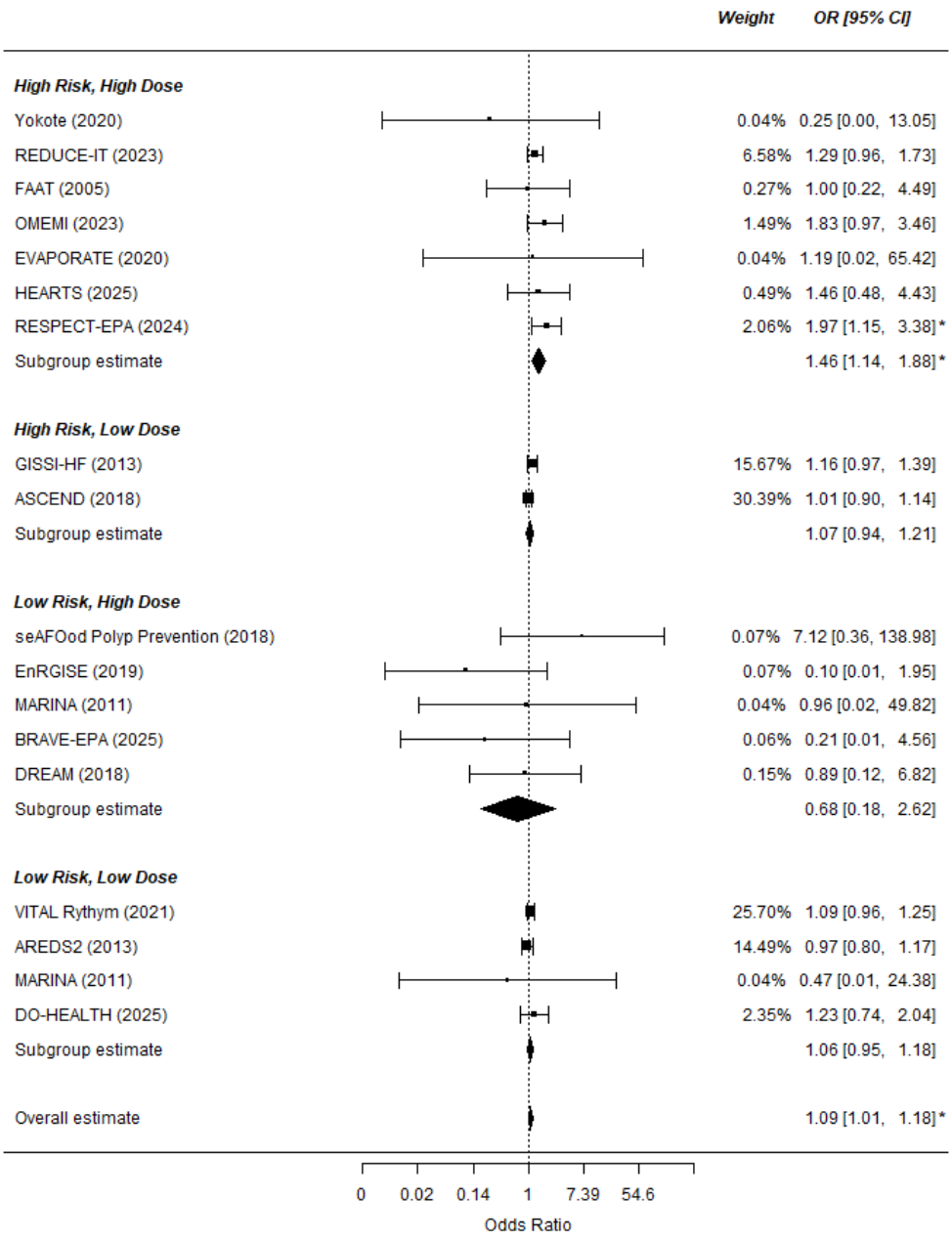


Figure S2. Sensitivity analysis of the odds ratio (OR) of 17 RCTs (18 datasets) including 65,590 participants that explicitly excluded individuals with a history of/prevalent AF at baseline*. Observed AF rates segregated by high vs low dose EPA+DHA (≤ vs > 1500 mg/d) and by high vs low risk for CVD.



*HEARTS[90], OFAMI[75], OMEMI[72], FAAT[88], RESPECT-EPA[76], DO-HEALTH[102], VITAL[87], REDUCE-IT[69], and AREDS2[101] enrolled mixed populations, including participants with baseline AF, but reported baseline AF status, allowing exclusion of participants with prior/history of AF from these analyses. GISSI-HF[77] assessed AF at baseline using ECGs and history of paroxysmal AF. ASCEND[79] indirectly excluded known AF through anticoagulant exclusion criteria, later validated through electronic health record linkage. MARINA[96] confirmed absence of AF using 24-hour heart-rate monitoring. DREAM[84], ENRGISE[83], and EVAPORATE[89] excluded participants with prior or persistent/paroxysmal AF. Yokote et al.[68], BRAVE-EPA[97], and SeaFOod Polyp Prevention[82] excluded participants receiving anticoagulant therapy, thereby indirectly excluding many individuals with prior AF.

Supplemental Appendix 1. Rationale for setting an intake of 1500 mg/d for EPA/DHA to differentiate dietary/supplement intake levels from pharmaceutical dose levels

Ecological data. The age-standardized global prevalence of AF in 2021 was reported in a 2025 update from the American Heart Association[147]. The rate of AF in the US, which has an average Omega-3 Index (O3I, erythrocyte EPA+DHA%) of 5%[148], is >1000 pr 100,000 people. Compared with this, Japan, a country with an average O3I of ~10%[149], has an AF rate of <400 per 100,000. In a 2000 publication, Sugano stated, "Fish and shellfish now provide 5–6 g fat and **<1–2 g** n3 PUFA per person per day in Japan." Clearly, there are multiple differences between the US and the Japanese populations, but this observation is at least consistent with the hypothesis that higher intakes and tissue levels of omega-3 PUFAs are associated with lower risk for AF. Importantly, data from a prospective cohort study in Japan including about 42,000 individuals between 40 and 59 years of age reported that the median EPA+DHA intake in the cohort was **900** mg/d, and the intake in the highest quintile – where risks for total MI and nonfatal coronary events were the lowest - was **2100** mg/d[118]. AF risk was not tracked in this report.

Omega-3 Intake data. A large observational study from Denmark found that consumption of around **600** mg/d of EPA+DPA+DHA (quintile 3, Q3; **Table 1**) was associated with the lowest risk of AF compared with lower and higher levels, i.e., there was a U-shaped relationship[150]. However, intakes in Q4 and Q5 were not significantly different from Q1 (reference) in any of the three models tested (**Table 1**). Q5 was >**0.99** g/d. Data from the Million Veterans study[151] suggested that risk for AF was reduced maximally at about **500 mg/d** but remained significantly reduced up to **~1300** mg/d of EPA+DHA (**Figure 1**).

Table 1. Associations between quintiles of omega-3 intake and risk for AF. Taken from Rix et al.

	Crude			Primary adjusted model[a]			Secondary model[b]		
	HR	95% CI	P	HR	95% CI	P	HR	95% CI	P
Q1 <0.39 g/day	1	–	–	1	–	–	1	–	–
Q2 0.39–0.53 g/day	0.92	0.82–1.03	0.14	0.92	0.82–1.03	0.16	0.92	0.82–1.04	0.18
Q3 0.54–0.73 g/day	0.87	0.77–0.97	0.02	0.87	0.78–0.98	0.02	0.87	0.78–0.98	0.02
Q4 0.74–0.99 g/day	0.95	0.85–1.07	0.40	0.96	0.86–1.08	0.49	0.96	0.86–1.08	0.52
Q5 >0.99 g/day	1.06	0.95–1.18	0.30	1.05	0.93–1.18	0.42	1.05	0.93–1.18	0.43

PUFA, polyunsaturated fatty acids; HR, hazard ratio; CI, confidence interval; Q, quintile.
[a]Adjusted for age, sex, hypertension, systolic blood pressure, body-mass index, waist circumference, smoking, alcohol intake, years in school, hypercholesterolaemia and/or cholesterol treatment, total serum cholesterol, angina pectoris, diabetes mellitus, myocardial infarction, heart failure, and total energy intake.
[b]Sensitivity analysis further adjusted for consumption of fruits, vegetables, red meat, poultry, and fatty dairy products.

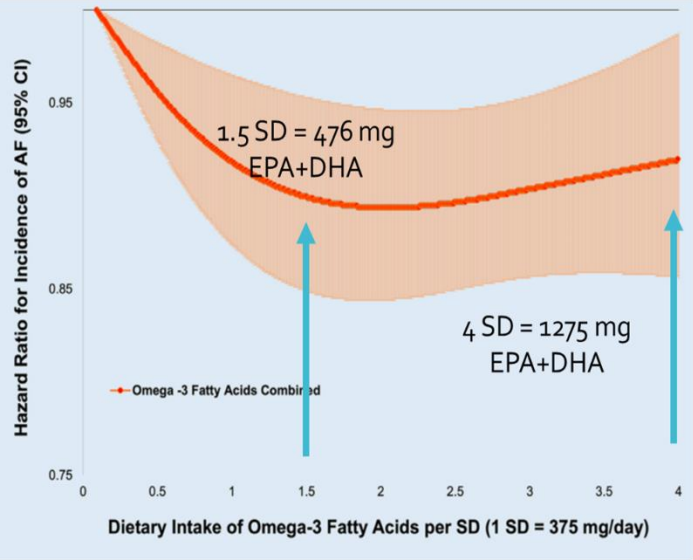


Figure 1. Association between reported EPA+DHA intake and risk for AF in a Veterans cohort. Risk for AF was significantly and maximally reduced (compared with no intake) between about 476 and 1270 mg EPA+DHA per day. From Guardino et al.

Fish oil supplement use data. An alternative approach to this question is to determine the extent to which reported fish oil supplement (FOS) use is associated with risk for AF. Two such studies (from the same research group) have been reported in the UK Biobank (UKBB). Both Zhang et al.[152] and Chen et al.[153] concluded that the use of FOS was associated with an increased risk (10-13%) for AF. (Importantly, Chen et al. also reported that FOS use was favorably associated with five other CVD outcomes in the same study)[153]. These findings have been re-examined by O'Keefe et al.[19] and found to be in error, that being the failure to adjust for age properly (i.e., continuously, instead of dichotomously as was done in the earlier studies). Thus, there is no association between FOS use and risk for AF in the UKBB.

Blood omega-3 data. As dietary intake (and FOS use) data are subject to a number of uncertainties (faulty memory, old FA data in food databases, compliance with and doses of FOS, etc.), biomarkers of omega-3 PUFA status (whether in plasma, plasma phospholipids, whole blood and/or erythrocytes) provides a more objective measure of

tissue exposure. Accordingly, two recent studies from the Fatty Acids and Outcomes Research Consortium (FORCE group) are important in this regard. First, a meta-analysis of de novo data from 17 observational cohorts around the world including about 55,000 individuals found that those individuals with the highest EPA+DHA levels (compared with the lowest; 90th vs 10th percentiles), were 12% less likely to develop AF after a median follow-up of 13 years (**Figure 2**)[4]. The second report took the same approach but focused on risk for stroke. That study included data from 29 cohorts and over 183,00 individuals followed for a median of 14 years. As was seen with AF, the risk for stroke was significantly reduced in a dose dependent manner (**Figure 3**)[20]. In both of these studies, the estimated O3I of the highest quintile was about 8% compared to <4% in the reference group.

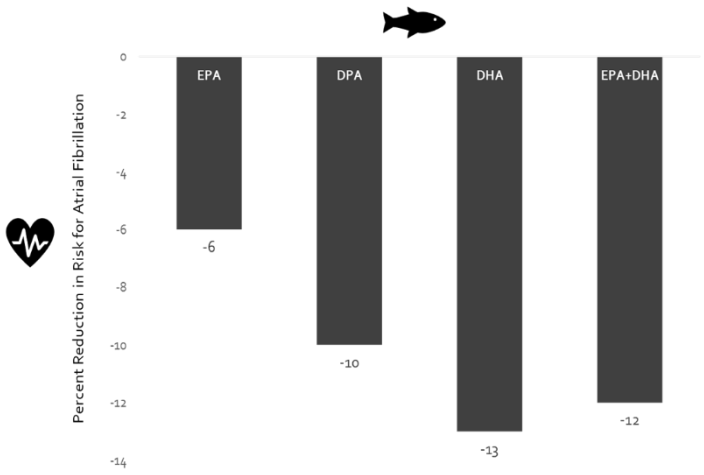


Figure 2. Association between circulating n-3 PUFA levels and odds for atrial fibrillation. From Qian et al.

Second, a study conducted only within the UK Biobank (UKBB) confirmed the findings of Qian et al. That study[19] included data on 261,108 UKBB participants followed for 12.7 years for new onset AF. The higher levels (quintiles 2-5) for total omega-3, DHA and non-DHA omega-3 were all significantly reduced compared with quintile 1 (**Figure 4**). When these new data were combined with the original meta-analysis of Qian et al.[4], the relationships between omega-3 levels and risk for AF were confirmed and strengthened (**Table 2**). Multiple other FORCE studies comparing disease outcomes as a function of blood omega-3 levels have consistently shown the greatest protection at the highest blood levels (**Figure 5**), again levels associated with intakes of up to 1500 mg/d.

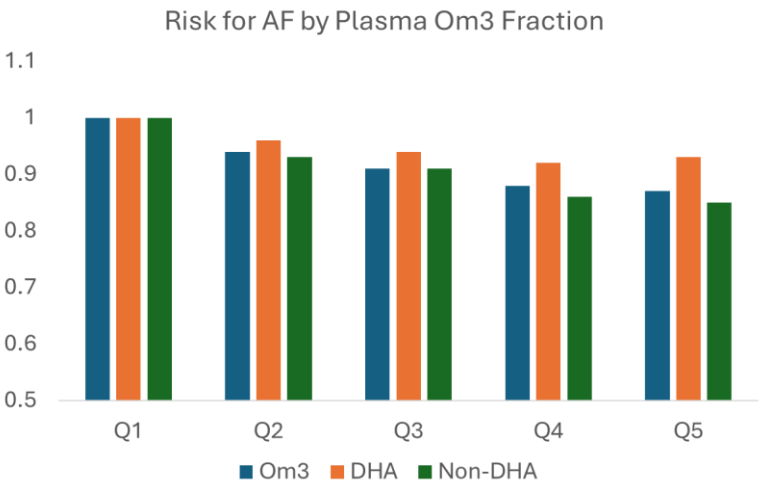


Figure 4. Association between plasma n-3 PUFA levels and odds for atrial fibrillation. All Q2-Q5 HRs lower than Q1 (p<0.01). From O'Keefe (ms under review JAHA 7/2025).

Randomized trials with fish oils in the general population. The only large RCT to address the question of how omega-3 supplementation affects risk for AF is the VITAL study[143]. Here 25,119 men and women over age 50 were randomized to **840** mg EPA+DHA/day (and/or vitamin D) and followed for incident AF for 5.3 years. The risk for AF was 9% higher in the treated group than the placebo group but this difference was not statistically significant (p=0.19). Thus, there was no reduction in risk for AF as the longer-term observational data suggested, but at least in this group of older patients treated for 5 years with omega-3, there was no increase in risk for AF. Hence, the safety of that dose vis-à-vis AF was confirmed as also suggested by the FOS use studies in the UKBB.

Table 2. Association between plasma n-3 PUFA levels and odds for atrial fibrillation. All Q2-Q5 HRs lower than Q1 (p<0.01)

	Analysis	Adjusted Hazard Ratio[1]
DHA	Original meta-analysis	0.90 (0.85, 0.96) **
	UK Biobank alone	0.93 (0.89, 0.97) ***
	Updated meta-analysis	**0.92 (0.89, 0.96) *****
EPA	Original meta-analysis	1.00 (0.95, 1.05)
	UK Biobank alone	0.92 (0.88, 0.95) ***
	Updated meta-analysis	**0.94 (0.92, 0.97) *****
DPA	Original meta-analysis	0.89 (0.83, 0.95) ***
	UK Biobank alone	0.91 (0.87, 0.94) ***
	Updated meta-analysis	**0.90 (0.88, 0.93) *****
EPA + DHA	Original meta-analysis	0.93 (0.87, 0.99) *
	UK Biobank alone	0.92 (0.88, 0.95) ***
	Updated meta-analysis	**0.92 (0.90, 0.95) *****

Further considerations of the EPA+DHA intake that does not increase the risk for AF.

However, estimates can also be made based on the blood biomarker data from the two FORCE studies, Qian et al.[4] and O'Keefe et al.[20]. In the former, the authors noted that the mean (SD) marine omega-3 intake in the 10 countries from which the 17 cohorts were drawn was about **430 (350)** mg/day[154]. Assuming a normal distribution (which it probably is not), the 95th percentile intake would be **1130**

mg/day. In the latter study, the estimated O3I in the highest EPA+DHA quintile was about 8% [which is consistent with the originally-proposed O3I target of >8% for minimizing risk of CVD death[17]]. In the UKBB, where the highest quintiles of plasma omega-3 were associated with the lowest risk of both AF and stroke, the estimated O3I was 7-8%. Thus, what intake is associated with an O3I of around 8%? Unfortunately, the actual intakes of omega-3 across the quintiles of plasma omega-3 in the UKBB are not known. However, we know that a dose of **1800** mg/day of EPA+DHA was shown to increase the O3I from 4.3% to 9.5% after 5 months of treatment, and a dose of **900** mg/day raised the O3I to 7.5%[155].

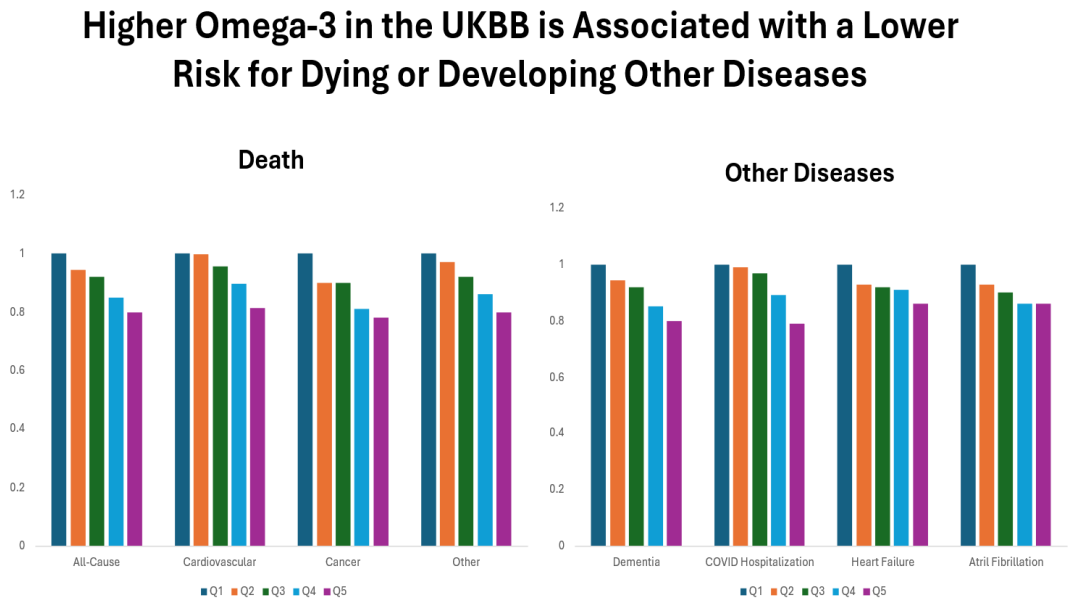


Figure 5. Summary of relationships between quintiles of blood omega-3 levels and several incident diseases from the UKBB

In 2021, the typical adult American ate ~1.5 serving/week of fish or seafood[156]; and the average intake of DHA + EPA in the United States is approximately 100 mg/d[18, 157]. This corresponds to an average DHA + EPA level in red blood cells (i.e., O3I) in the United States of about 5.4%[115, 148]. The estimated median O3I in Q5 in the Qian study was 8.62%. A pooled analysis of individual-level data from 14 omega-3 supplementation studies allowed for the construction of an equation that would predict the amount of EPA+DHA needed to achieve an O3I of 8% from different starting levels[18]. Using this

equation, the amount of EPA+DHA needed to raise an *average* O3I of 5.4% to 8% is **900** mg/d. For 95% of the population (not just 50%) to achieve an O3I of 8% would require an increase of approximately **1500** mg/d of DHA + EPA[115, 158].

In light of these considerations and recognizing that the lowest approved dose of an omega-3 pharmaceutical product (Epanova®) is **1800 mg/day**, we consider that a reasonable dividing line between "low" intakes from food and/or dietary supplements and "high" doses used in drug studies would be ~1500 mg EPA+DHA per day. This value was thus applied to the updated meta-analysis of omega-3 RCTs and risk for AF. As noted above, an intake of ~1500 mg/d is also associated with the highest quintile O3I levels, and these levels are linked with the lowest risk for AF[4, 19] [not to mention stroke[20] and total mortality[117]].