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# Omega-3 Fatty Acid Biomarkers and Incident Atrial Fibrillation

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## ABSTRACT

**BACKGROUND** The relationship between omega-3 fatty acids and atrial fibrillation (AF) remains controversial.

**OBJECTIVES** This study aimed to determine the prospective associations of blood or adipose tissue levels of eicosapentaenoic acid (EPA), docosapentaenoic acid (DPA), and docosahexaenoic acid (DHA) with incident AF.

**METHODS** We used participant-level data from a global consortium of 17 prospective cohort studies, each with baseline data on blood or adipose tissue omega-3 fatty acid levels and AF outcomes. Each participating study conducted a de novo analyses using a prespecified analytical plan with harmonized definitions for exposures, outcome, covariates, and subgroups. Associations were pooled using inverse-variance weighted meta-analysis.

**RESULTS** Among 54,799 participants from 17 cohorts, 7,720 incident cases of AF were ascertained after a median 13.3 years of follow-up. In multivariable analysis, EPA levels were not associated with incident AF, HR per interquintile range (ie, the difference between the 90th and 10th percentiles) was 1.00 (95% CI: 0.95-1.05). HRs for higher levels of DPA, DHA, and EPA+DHA, were 0.89 (95% CI: 0.83-0.95), 0.90 (95% CI: 0.85-0.96), and 0.93 (95% CI: 0.87-0.99), respectively.

**CONCLUSIONS** In vivo levels of omega-3 fatty acids including EPA, DPA, DHA, and EPA+DHA were not associated with increased risk of incident AF. Our data suggest the safety of habitual dietary intakes of omega-3 fatty acids with respect to AF risk. Coupled with the known benefits of these fatty acids in the prevention of adverse coronary events, our study suggests that current dietary guidelines recommending fish/omega-3 fatty acid consumption can be maintained.
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Atrial fibrillation (AF) is the most common chronic cardiac arrhythmia, affecting approximately 9% of adults age ≥65 years. Long-chain omega-3 polyunsaturated fatty acids have been shown in experimental settings to have possible antiarrhythmic properties.[1] Observational studies and randomized controlled trials (RCTs) have demonstrated that omega-3 fatty acids may reduce the risk of sudden cardiac death, with mechanisms related to prevention of acute, ischemia-induced ventricular arrhythmias.[2-4] However, the potential effects of omega-3 fatty acids on other arrhythmias, particularly AF, remain less well understood.

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Prior RCTs have tested short-term supplemental doses of omega-3 fatty acids on the development of AF, predominantly among patients undergoing elective cardiac surgery. A meta-analysis showed that omega-3 fatty acid supplementation did not affect overall risk of postsurgical AF, with significant heterogeneity.[5] Recently, several RCTs conducted among individuals with pre-existing cardiovascular disease (CVD) or at high cardiovascular (CV) risk found that high-dose (up to 4 g/d) omega-3 fatty acids *increased* risk of AF hospitalization, although these were mostly secondary or exploratory outcomes.[3,6,7] On the other hand, the VITAL (VITamin D and OmegA-3 TriaL)-Rhythm,[8] an RCT testing 1 g/d of eicosapentaenoic acid (EPA) + docosahexaenoic acid (DHA) among individuals without a history of CVD, did not demonstrate significant benefits or harms with omega-3 fatty acids on AF incidence.

Due to the relatively short duration of these RCTs (median duration ~5 years), frequent use of high-dose omega-3 preparations, and the enrichment for individuals with elevated CV risk, their generalizability to habitual dietary intakes of omega-3 fatty acid-rich foods among the general population is uncertain. Several prospective cohort studies assessing self-reported estimates of dietary fish or omega-3 fatty acid intake have shown beneficial or neutral associations with AF.[9] However, self-reported estimates of omega-3 fatty acid intake have the limitations of measurement error as well as potential recall and memory biases. Moreover, most of these reports were in Western populations, and studies on the association between omega-3 fatty acids and AF risk outside of Europe and the United States remain sparse.

**ABBREVIATIONS AND ACRONYMS**

**AF** = atrial fibrillation
**CVD** = cardiovascular disease
**DHA** = docosahexaenoic acid
**DPA** = docosapentaenoic acid
**EPA** = eicosapentaenoic acid
**RCT** = randomized controlled trial

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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**TABLE 1 Baseline Characteristics of Studies Assessing Omega-3 Fatty Acid Biomarker Levels and Incident AF**

| Study | Country | Study Design[a] | Baseline Years | AF Cases, n/N | Median Follow-Up, y | Mean Age, y | Women, % | Mean BMI, kg/m$^2$ | Baseline ASCVD, %[b] | Baseline HF, % |
|---|---|---|---|---|---|---|---|---|---|---|
| 60YO | Sweden | Prospective cohort | 1997-1999 | 3,987/581 | 16.5 | 60.0 | 51.7 | 26.8 | 8.2 | 1.2 |
| ARIC | USA | Prospective cohort | 1987 | 3,821/896 | 29.1 | 54.0 | 52.0 | 27.1 | 5.3 | 3.5 |
| CHS | USA | Prospective cohort | 1992-1993 | 3,526/1,459 | 9.5 | 74.9 | 60.0 | 26.8 | 24.3 | 4.9 |
| DCH | Denmark | Prospective cohort | 1993-1997 | 3,187/183 | 13.5 | 56.7 | 46.1 | 26.2 | 3.0 | 0.2 |
| EPIC-Norfolk | UK | Prospective cohort | 1993-1998 | 7,383/1,070 | 14.3 | 63.3 | 19.2 | 26.6 | 5.0 | - |
| FHS | USA | Prospective cohort | 2005-2008 | 2,488/329 | 11.3 | 65.9 | 55.5 | 28.2 | 13.1 | 1.1 |
| Hisayama | Japan | Prospective cohort | 2002-2003 | 3,126/153 | 9.0 | 62.0 | 57.5 | 23.0 | 5.6 | - |
| HPFS | USA | Prospective cohort | 1994 | 1,529/64 | 17.4 | 64.6 | 0.0 | 25.8 | 0.0 | 0.0 |
| KIHD | Finland | Prospective cohort | 1998-2001 | 1,774/435 | 18.1 | 62.8 | 53.0 | 27.8 | 30.1 | 6.7 |
| MERLIN TIMI-36 | 17 countries[c] | Prospective case-cohort | 2004 | 1,769/161 | 0.9 | 63.2 | 37.4 | 29.1 | 100.0 | 21.0 |
| MESA | USA | Prospective cohort | 2000 | 6,203/816 | 12.9 | 62.0 | 52.7 | 28.2 | 0.0 | 0.0 |
| PIVUS | Sweden | Prospective cohort | 2001-2004 | 950/205 | 15.0 | 70.2 | 51.1 | 27.0 | 10.0 | 4.7 |
| PRE-DETERMINE | USA and Canada | Prospective cohort | 2007-2013 | 4,732/505 | 7.9 | 63.0 | 23.9 | 30.2 | 100.0 | 23.3 |
| RS | Netherlands | Prospective cohort | 2002-2005 | 2,361/299 | 9.9 | 74.9 | 58.8 | 27.4 | 14.7 | 4.9 |
| RUTI-HF | Spain | Prospective cohort | 2006-2020 | 700/84 | 2.9 | 64.8 | 30.4 | 27.4 | 32.4 | 100.0 |
| ULSAM | Sweden | Prospective cohort | 1971-1974 | 2,006/406 | 33.3 | 49.7 | 0.0 | 25.0 | 1.2 | 2.7 |
| WHIMS | USA | Prospective cohort | 1995 | 5,257/74 | 6.0 | 70.0 | 100.0 | 28.3 | 18.1 | 0.8 |
| Total | | | | 54,799/7,720 | 13.3 | 63.4 | 46.7 | 27.3 | 19.6 | 6.6 |

[a]Study details are available in the Supplemental Appendix. [b]ASCVD is defined as a prior diagnosis of coronary heart disease, stroke, or peripheral artery disease. [c]Included participants from Austria, Belgium, Canada, Czech Republic, France, Georgia, Germany, Hungary, Israel, Italy, the Netherlands, Poland, Russia, South Africa, Spain, United Kingdom, and the United States.

60YO = The Stockholm Cohort of 60-year-olds; AF = atrial fibrillation; ARIC = Atherosclerosis Risk In Communities Study; ASCVD = atherosclerotic cardiovascular disease; CHS = Cardiovascular Health Study; DCH = Danish Diet, Cancer and Health Study; EPIC-Norfolk = European Prospective Investigation into Cancer and Nutrition-Norfolk; FHS = Framingham Heart Study; HF = heart failure; Hisayama = Hisayama Study; HPFS = Health Professionals Follow-up Study; KIHD = Kuopio Ischaemic Heart Disease Risk Factor Study; MERLIN TIMI-36 = The Metabolic Efficiency With Ranolazine for Less Ischemia in Non-ST-Elevation Acute Coronary Syndromes - Thrombolytics in Myocardial Infarction 36 Trial; MESA = Multi-Ethnic Study of Atherosclerosis; PIVUS = Prospective Investigation of Vasculature in Uppsala Seniors; PRE-DETERMINE = PRE-DETERMINE Biologic Markers and Sudden Cardiac Death Study; RS = Rotterdam Study; RUTI-HF = Can Ruti Heart Failure Cohort; ULSAM = Uppsala Longitudinal Study of Adult Men; WHIMS = Women's Health Initiative Memory Study.

Few studies have examined circulating or tissue omega-3 fatty acids as objective measures of endogenous omega-3 status as well as a reliable biomarker of habitual dietary intake[10] in relation to incident AF. To our knowledge, only 5 prospective cohort studies from the United States and Europe have examined this question.[11-15] Interestingly, all 5 studies tended to show inverse associations between omega-3 fatty acids and AF, with DHA being most consistently associated with lower risk. Moreover, the widespread exposure to omega-3 fatty acids through intake of fish/seafood or fortified foods as well as supplements renders the association between these fatty acids and incident AF an important clinical and public health question. Notably, as highlighted by recent RCTs, possible heterogeneity among high-risk vs general populations may also exist for the effect of omega-3 fatty acid on AF, which has not been examined in prior studies. The limited statistical power in prior analyses to assess potential effect modification by baseline CV risk, as well as publication bias in both studies of fish intake and omega-3 fatty acid biomarkers with respect to AF risk, are indications that further studies are warranted.

In the context of these questions, we evaluated the relationship between circulating and tissue omega-3 fatty acids across 17 prospective international studies with data on incident AF.

## METHODS

**STUDY SELECTION.** We used the same methodological approach as prior studies from the FORCE (Fatty Acids and Outcomes Research Consortium), the details of which have been previously published.[16,17] In our study, 17 cohorts were included based on availability of ascertained AF, fatty acid exposures (1 or more of EPA, docosapentaenoic acid [DPA], and docosahexaenoic acid [DHA]), and prospective design (cohort or nested case-cohort). Participants were included if they were age ≥18 years and free of prevalent or a history of AF at the time of blood/adipose tissue collection. Participating studies received approval from their corresponding institutional review boards, and all participants gave informed consent. Cohort-specific inclusion/exclusion criteria at baseline enrollment are provided in the Supplemental Methods.

**EXPOSURE ASSESSMENT.** Each cohort measured fatty acids using gas chromatography in 1 or more of the following lipid compartments: erythrocyte or plasma/serum phospholipids, total plasma/serum, cholesterol esters, and adipose tissue. Fatty acids of interest were quantified as a percentage of the total measured fatty acids. Detailed information on the measurement protocol, specific fatty acids assessed, and coefficients of variation can be found in the Supplemental Methods.

**ASCERTAINMENT OF INCIDENT AF.** Incident AF was assessed using 1 or more of the following criteria: 1) characteristic findings on standard 12-lead ECG or event monitors; 2) hospital discharge or outpatient diagnostic codes (International Classification of Diseases [ICD]-8: 427.4; ICD-9: 427.3; ICD-10: I48); or 3) medical record review. We did not include incident cases that were diagnosed using self-report only. Cohort-specific methods for AF ascertainment can be found in Supplemental Table 1.

**STATISTICAL ANALYSES.** Spearman's correlation coefficients were used to assess the correlations between individual omega-3 fatty acids. In each cohort, multivariable-adjusted Cox proportional hazards models were used to calculate the HR and 95% CIs per interquintile range (difference between the 90th and 10th percentile of each fatty acid). We also analyzed the associations by cohort-specific quintiles. Multivariable models were adjusted for the following prespecified covariates: age (years), sex (male, female), field site (when applicable), race/ethnicity (when applicable), education (<high school, high school graduate, college or higher), physical activity, smoking (never, former, current), alcohol use (drinks/d), body mass index (BMI) (kg/m$^2$), beta-blocker use (yes, no), biomarker levels of linoleic acid (18:2n-6) and arachidonic acid (20:4n-6) (both assessed as a % of total fatty acids), prevalent hypertension (yes, no), dyslipidemia (yes, no), diabetes (yes, no), atherosclerotic CVD (coronary heart disease, stroke, or peripheral artery disease) (yes, no), or heart failure (HF) (yes, no). In a secondary model, we additionally adjusted for intakes of fish/seafood, fruits, vegetables, and coffee/tea (servings/d or grams/d).

For the pooled analysis, we used inverse-variance weighted meta-analysis to calculate the HR and 95% CI, overall and within each lipid fraction. Because some cohorts measured omega-3 fatty acids in multiple lipid fractions, for the overall analysis we used the following order to select one lipid fraction that best reflects long-term dietary intake: adipose tissue > erythrocyte phospholipid > plasma/serum phospholipid > total plasma/serum > cholesterol ester. Heterogeneity was calculated using the $I^2$-statistic.

To test for possible nonlinear associations between each of the omega-3 fatty acids and AF, we conducted a pooled analysis of the cohort-specific quintiles. We additionally modeled the associations with meta-regression restricted cubic splines using the median % fatty acid in each cohort-specific quintile and the respective multivariable-adjusted HR and 95% CI. Due to variations in omega-3 fatty acid concentrations in each lipid compartment, this analysis was done for each compartment separately. We used 3 knots placed at the 10th, 50th, and 90th percentiles.

**SUBGROUP AND SENSITIVITY ANALYSES.** To explore for heterogeneity and effect modification, we prespecified 3 subgroup analyses, each evaluated within each cohort and then pooled. These included by age (<65 or ≥65 years), by sex (male, female), and among individuals with elevated CV risk at baseline (defined as 1 or more of the following: established atherosclerotic CVD, heart failure, diabetes mellitus, baseline triglycerides ≥150 mg/dL [≥1.70 mmol/L], or, if triglyceride data was unavailable, non-high-density lipoprotein cholesterol ≥160 mg/dL [≥4.14 mmol/L]). We used meta-regressions to assess the statistical significance of between-subgroup heterogeneity. Due to the exploratory nature of subgroup analyses, we used a Bonferroni-adjusted $P$ value of 0.004 (0.05 divided by 4 fatty acid exposures × 3 subgroups) to denote statistically significant heterogeneity. We additionally conducted a post hoc subgroup analysis by global region, for which we also used meta-regressions to assess for between-subgroup heterogeneity. Finally, we conducted a meta-regression analysis to assess for potential heterogeneity by duration of follow-up (above and below the median duration of follow-up).

## RESULTS

**BASELINE CHARACTERISTICS.** The 17 cohort studies comprised 54,799 participants from 21 nations from North America, Europe, Asia, and Africa. The baseline characteristics for each study are shown in **Table 1**. Sixteen studies employed a prospective cohort design, and 1 (MERLIN TIMI-36 [The Metabolic Efficiency With Ranolazine for Less Ischemia in Non-ST-Elevation Acute Coronary Syndromes Thrombolysis In Myocardial Infarction-36]) trial, a prospective case-cohort design. The mean age of participants was 63 years, and approximately one-half were women. Mean BMI was in the overweight range

**FIGURE 1** Pooled HR of Incident Atrial Fibrillation for EPA, DPA, DHA, and EPA+DHA

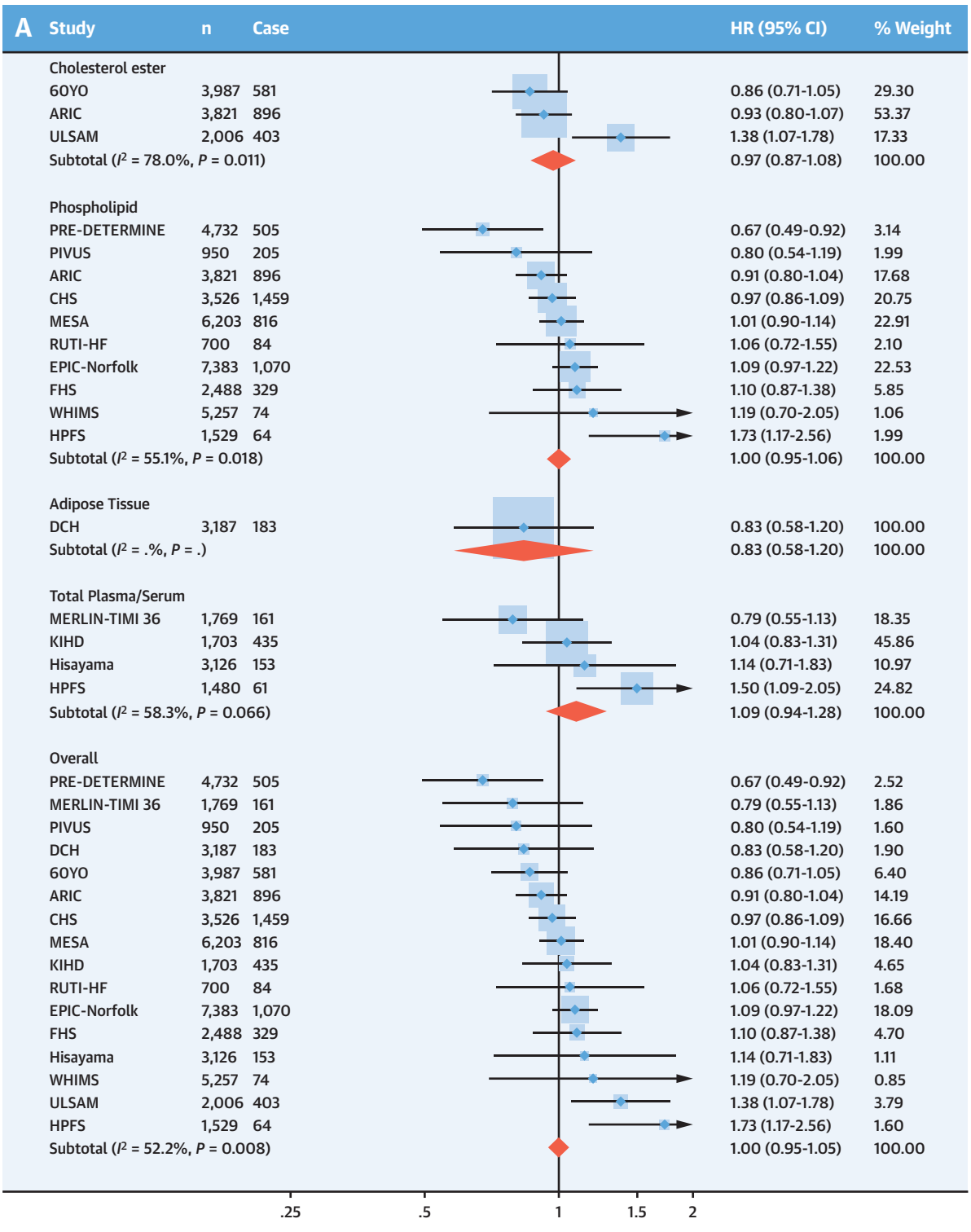


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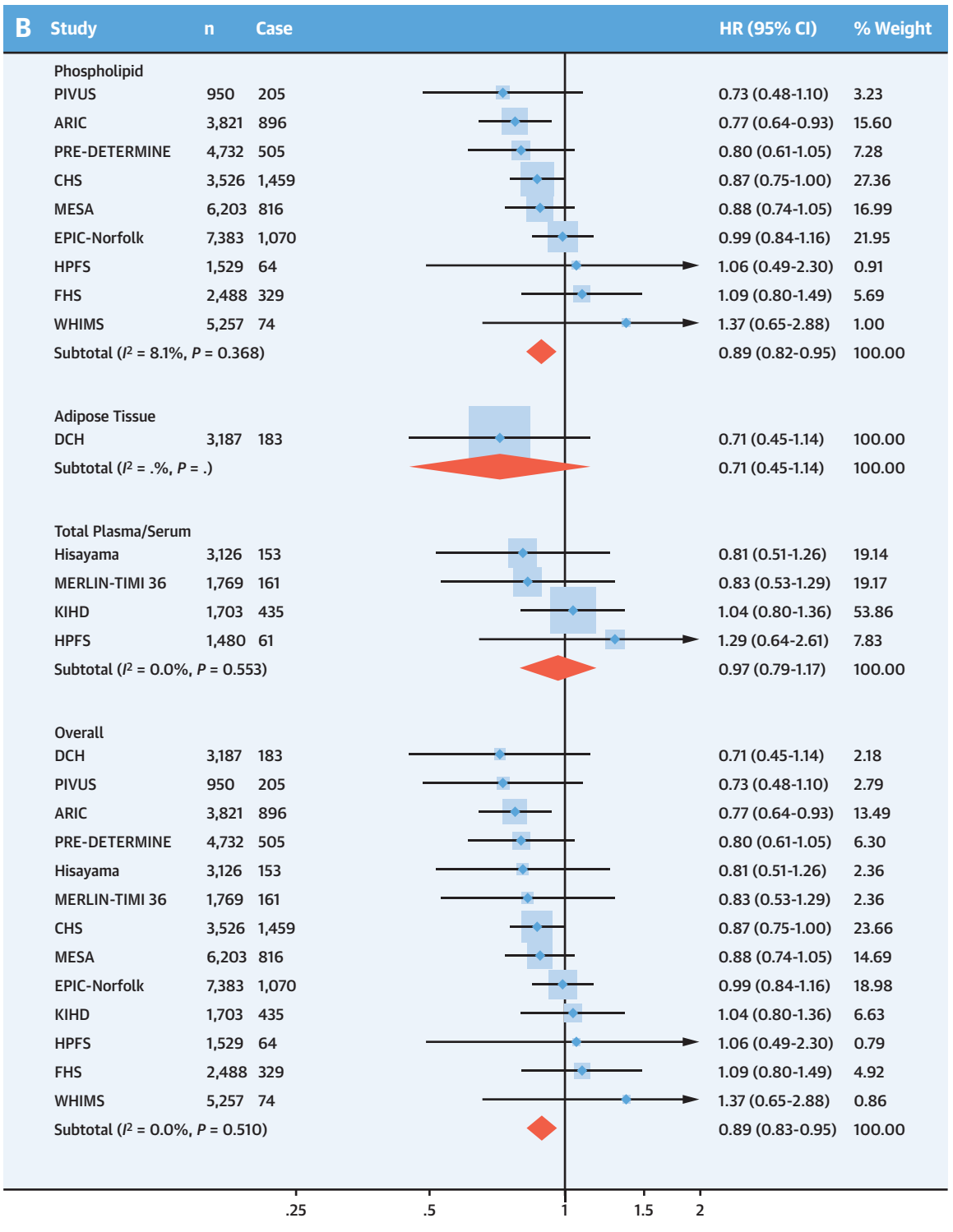
**FIGURE 1 Continued**

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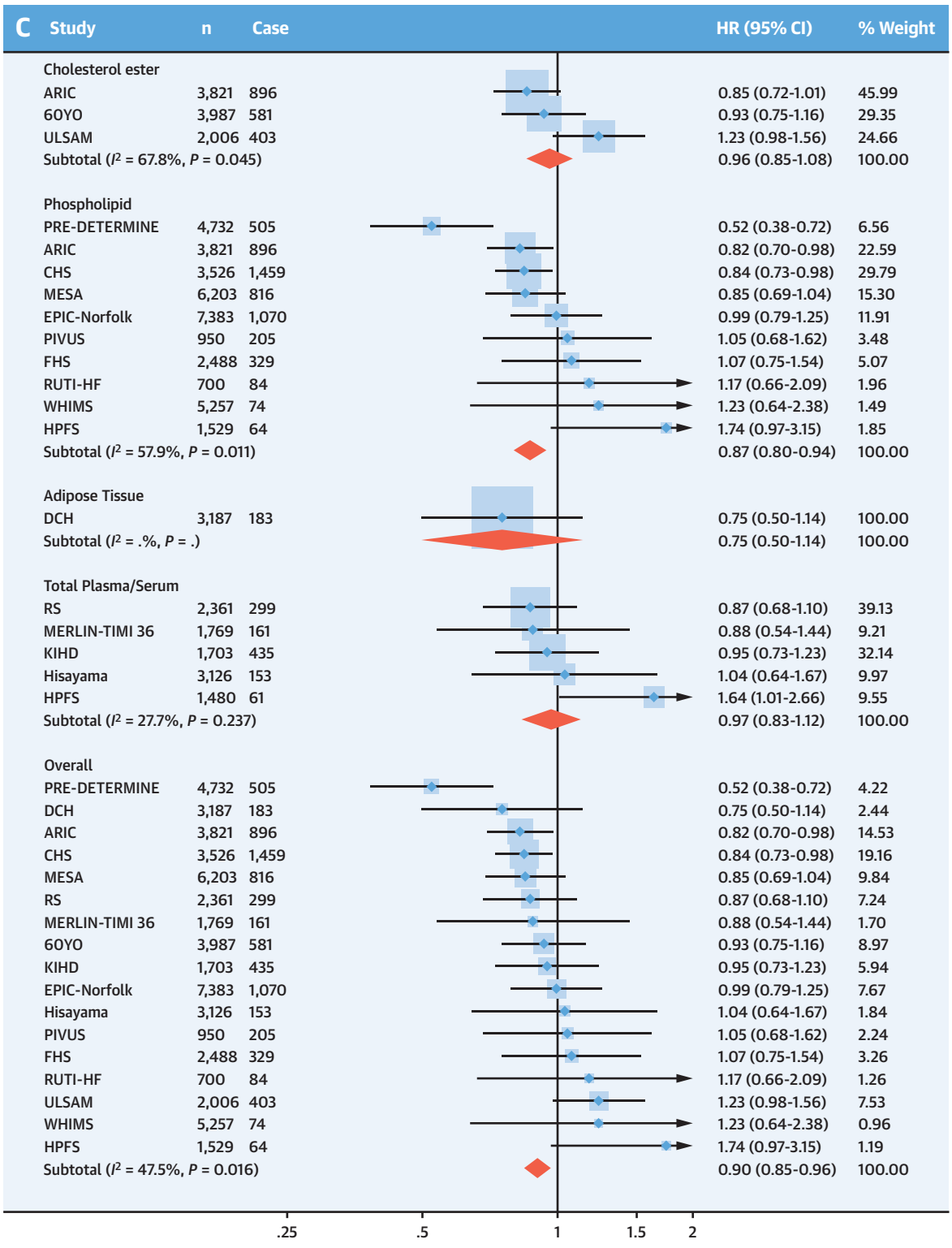


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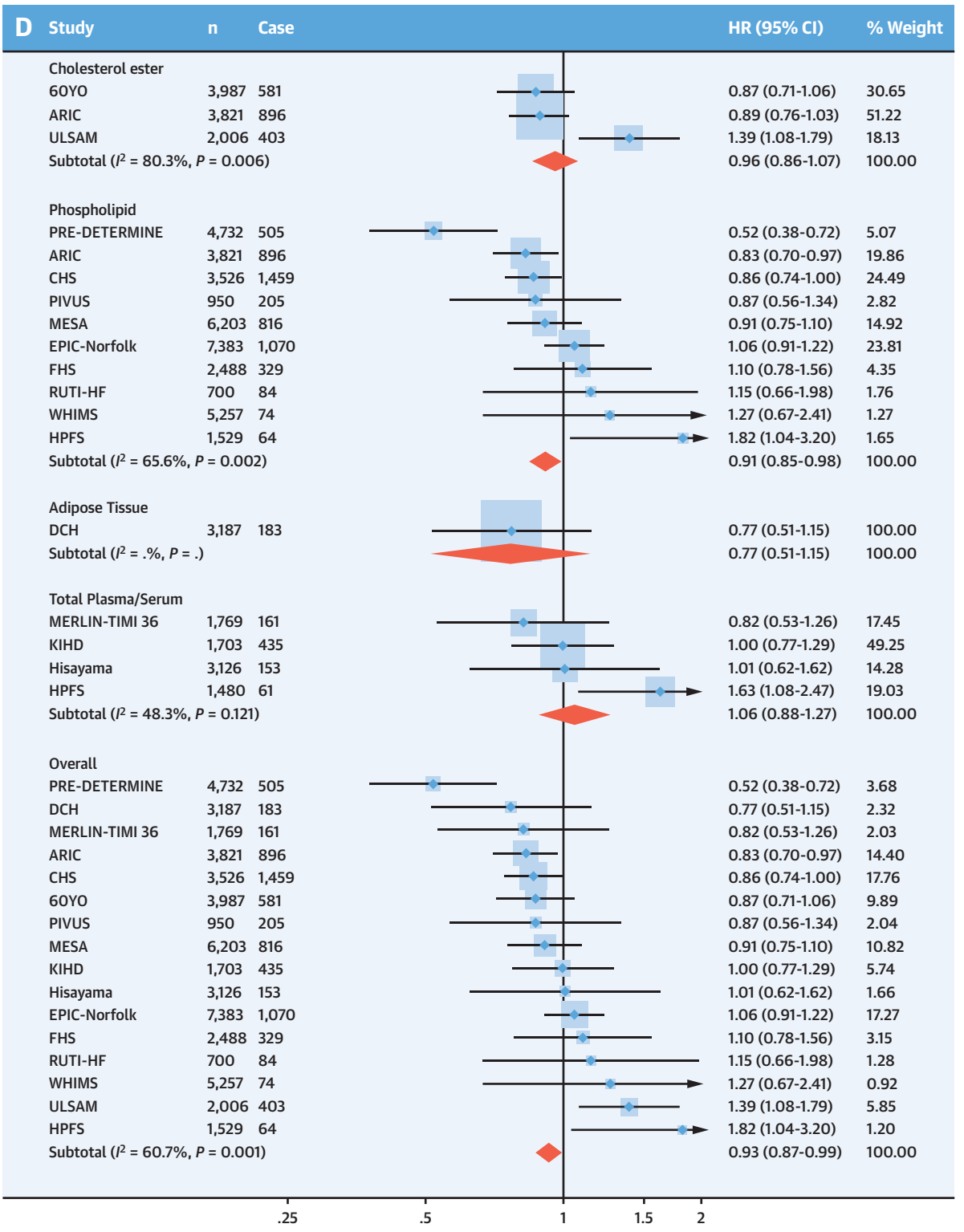


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**TABLE 2 Association Between Omega-3 Fatty Acid Biomarker Levels[a] and Incident Atrial Fibrillation**

| | | | Continuous Analysis Per Interquintile Range[b] | | Categorical Analysis Comparing Q5 vs Q1[c] | |
|---|---|---|---|---|---|---|
| Exposure | No. of Studies | No. of Cases | HR (95% CI) | $I^2$ (%) | HR (95% CI) | $I^2$ (%) |
| EPA | | | | | | |
| Phospholipids | 10 | 5,502 | 1.00 (0.95-1.06) | 55.1 | 0.92 (0.83-1.02) | 60.1 |
| Total plasma/serum | 4 | 810 | 1.09 (0.94-1.28) | 58.3 | 0.97 (0.75-1.25) | 62.5 |
| Cholesterol ester | 3 | 1,880 | 0.97 (0.87-1.08) | 78.0 | 1.06 (0.90-1.26) | 43.6 |
| Adipose tissue | 1 | 183 | 0.83 (0.58-1.20) | – | 0.86 (0.54-1.37) | – |
| Overall | 16 | 7,421 | 1.00 (0.95-1.05) | 52.2 | 0.94 (0.86-1.02) | 49.6 |
| DPA | | | | | | |
| Phospholipids | 9 | 5,418 | 0.89 (0.82-0.95) | 8.1 | 0.87 (0.79-0.97) | 0.0 |
| Total plasma/serum | 4 | 810 | 0.97 (0.79-1.17) | 0.0 | 1.17 (0.91-1.51) | 0.0 |
| Adipose tissue | 1 | 183 | 0.71 (0.45-1.14) | – | 0.72 (0.42-1.23) | – |
| Overall | 13 | 6,350 | 0.89 (0.83-0.95) | 0.0 | 0.90 (0.82-0.98) | 0.0 |
| DHA | | | | | | |
| Phospholipids | 10 | 5,502 | 0.87 (0.80-0.94) | 57.9 | 0.84 (0.76-0.92) | 44.7 |
| Total plasma/serum | 5 | 1,109 | 0.97 (0.83-1.12) | 27.7 | 0.91 (0.74-1.11) | 0.0 |
| Cholesterol ester | 3 | 1,880 | 0.96 (0.85-1.08) | 67.8 | 0.94 (0.81-1.10) | 73.5 |
| Adipose tissue | 1 | 183 | 0.75 (0.50-1.14) | – | 0.73 (0.45-1.19) | – |
| Overall | 17 | 7,720 | 0.90 (0.85-0.96) | 47.5 | 0.87 (0.80-0.94) | 38.4 |
| EPA + DHA | | | | | | |
| Phospholipids | 10 | 5,502 | 0.91 (0.85-0.98) | 65.6 | 0.84 (0.76-0.92) | 57.1 |
| Total plasma/serum | 4 | 810 | 1.07 (0.90-1.27) | 32.0 | 0.95 (0.74-1.23) | 28.7 |
| Cholesterol ester | 3 | 1,880 | 0.96 (0.86-1.07) | 80.3 | 1.00 (0.84-1.18) | 76.9 |
| Adipose tissue | 1 | 183 | 0.77 (0.51-1.15) | – | 0.73 (0.44-1.20) | – |
| Overall | 16 | 7,421 | 0.93 (0.87-0.99) | 60.7 | 0.88 (0.81-0.95) | 57.1 |

[a]Multiple lipid fractions were available for some studies, but only one lipid fraction was used for the overall analysis. [b]An interquintile range refers to the difference between the 10th to 90th percentile of the respective fatty acid in each cohort. [c]Q1 and Q5 refer to the first and the fifth groups categorized by quintile values in each cohort. Effect estimates were pooled using inverse-variance weighted fixed-effect meta-analysis.

DHA = docosahexaenoic acid; DPA = docosapentaenoic acid; EPA = eicosapentaenoic acid.

(25.0-29.9 kg/m$^2$, except in the Hisayama Study, where mean BMI was 23.0 kg/m$^2$), and each cohort included participants with a wide range of BMI values. Baseline CVD prevalence was generally <20%, except for 5 cohorts with baseline CVD prevalence >20% and 3 cohorts with HF prevalence >20%. Baseline year of blood or adipose tissue collection ranged from the 1990s to early 2000s, with the

**FIGURE 1 Continued**

The association between marine omega-3 fatty acid levels and incident AF were assessed in multivariable models for each cohort, and the results were pooled using inverse-variance weighted fixed-effect meta-analysis for **(A)** EPA, **(B)** DPA, **(C)** DHA, and **(D)** EPA+DHA. In each cohort, a multivariable model was used to assess the association with adjustment for age; sex; field site (if applicable); race/ethnicity; education; smoking; alcohol use; body mass index; beta-blocker use; linoleic acid (18:2n-6) level; arachidonic acid (20:4n-6) level; and prevalent hypertension, dyslipidemia, diabetes mellitus, atherosclerotic CVD (defined as the presence of one or more of the following: coronary heart disease, stroke, or peripheral artery disease), and heart failure. If multiple biomarkers were available for a study, only one was used for the overall analysis based on the best ability to reflect long-term dietary intake (in the following order of preference): adipose tissue, erythrocyte phospholipids, plasma/serum phospholipids, total plasma/serum, and cholesterol ester. Please note that phospholipids include both erythrocyte and plasma/serum phospholipids. 60YO = The Stockholm Cohort of 60-year-olds; ARIC = Atherosclerosis Risk in Communities Study; ASCVD = atherosclerotic cardiovascular disease; CHS = Cardiovascular Health Study; DCH = Danish Diet, Cancer and Health Study; EPIC-Norfolk = European Prospective Investigation into Cancer and Nutrition-Norfolk; FHS = Framingham Heart Study; HF = heart failure; Hisayama = Hisayama Study; HPFS = Health Professionals Follow-up Study; KIHD = Kuopio Ischaemic Heart Disease Risk Factor Study; MERLIN TIMI-36 = The Metabolic Efficiency With Ranolazine for Less Ischemia in Non-ST-Elevation Acute Coronary Syndromes - Thrombolysis In Myocardial Infarction 36 Trial; MESA = Multi-Ethnic Study of Atherosclerosis; PIVUS = Prospective Investigation of Vasculature in Uppsala Seniors; PRE-DETERMINE = PRE-DETERMINE Biologic Markers and Sudden Cardiac Death Study; RS = Rotterdam Study; RUTI-HF = Can Ruti Heart Failure Cohort; ULSAM = Uppsala Longitudinal Study of Adult Men; WHIMS = Women's Health Initiative Memory Study.

**TABLE 3 Stratified Analysis of Omega-3 Fatty Acid Biomarkers and Incident Atrial Fibrillation**

| | EPA | | DPA | | DHA | | EPA + DHA | |
|---|---|---|---|---|---|---|---|---|
| | HR (95% CI)[a] | $P_{het}$[b] | HR (95% CI)[a] | $P_{het}$[b] | HR (95% CI)[a] | $P_{het}$[b] | HR (95% CI)[a] | $P_{het}$[b] |
| Overall estimate | 1.00 (0.95-1.05) | | 0.89 (0.83-0.95) | | 0.90 (0.85-0.96) | | 0.93 (0.87-0.99) | |
| Elevated CV risk[c] | 0.94 (0.88-1.02) | | 0.88 (0.80-0.96) | | 0.89 (0.82-0.97) | | 0.91 (0.85-0.98) | |
| Global region | | 0.54 | | 0.34 | | 0.09 | | 0.12 |
| North America | 0.98 (0.92-1.05) | | 0.86 (0.79-0.94) | | 0.85 (0.78-0.92) | | 0.86 (0.79-0.94) | |
| Europe | 1.04 (0.94-1.14) | | 0.96 (0.85-1.09) | | 0.97 (0.88-1.07) | | 1.00 (0.89-1.12) | |
| East Asia | 1.14 (0.71-1.83) | | 0.81 (0.51-1.26) | | 1.04 (0.64-1.67) | | 1.01 (0.62-1.62) | |
| Age, y | | 0.29 | | 0.77 | | 0.56 | | 0.92 |
| <65 | 0.97 (0.89-1.05) | | 0.88 (0.78-0.99) | | 0.94 (0.86-1.04) | | 0.93 (0.85-1.03) | |
| ≥65 | 1.02 (0.96-1.09) | | 0.90 (0.82-0.97) | | 0.91 (0.84-0.98) | | 0.94 (0.86-1.02) | |
| Sex | | 0.33 | | 0.31 | | 0.39 | | 1.00 |
| Male | 0.98 (0.92-1.05) | | 0.86 (0.78-0.95) | | 0.94 (0.87-1.02) | | 0.94 (0.88-1.01) | |
| Female | 1.03 (0.96-1.11) | | 0.93 (0.84-1.03) | | 0.89 (0.82-0.98) | | 0.94 (0.87-1.02) | |

[a]Effect estimates were per study-specific interquintile range (10th to 90th percentile), multivariable-adjusted as described in the figure legends, and pooled using inverse-variance weighted fixed-effect meta-analysis. [b]$P_{het}$ between subgroups was calculated using meta-regression. [c]Elevated CV risk was defined as possessing 1 or more of the following: 1) fasting triglycerides ≥150 mg/dL (or ≥1.70 mmol/L); 2) non-high-density lipoprotein cholesterol ≥160 mg/dL (or ≥4.14 mmol/L); 3) diabetes mellitus; 4) atherosclerotic cardiovascular disease, including coronary heart disease, stroke, or peripheral artery disease; or 5) heart failure.

Abbreviations as in Table 2.

exception of ULSAM (Uppsala Longitudinal Study of Adult Men), where blood collection was performed in the 1970s. Fatty acid distributions for each cohort are shown in Supplemental Figures 1A to 1D. There were moderate correlations between each of the individual omega-3 fatty acids as well as with EPA+DHA, in the 0.5 to 0.9 range (Supplemental Table 2).

**ASSOCIATION WITH INCIDENT AF.** During a median follow-up ranging from 0.9 to 29.1 years (weighted median: 13.3 years), 7,720 incident AF cases were ascertained (**Table 1**). In multivariable-adjusted analyses, EPA levels were not associated with incident AF: HR per interquintile range 1.00 (95% CI: 0.95-1.05), with moderate heterogeneity, $I^2 = 52.2\%$ (**Figure 1A**). In contrast, each of DPA, DHA, and EPA+DHA were associated with lower incidence of AF, with HRs of 0.89 (95% CI: 0.83-0.95), 0.90 (95% CI: 0.85-0.96), and 0.93 (95% CI: 0.87-0.99), respectively (**Figures 1B to 1D**). The pooled categorical analyses comparing extreme quintiles yielded similar associations (**Table 2**, Supplemental Figures 2 to 5). There was low heterogeneity for DPA ($I^2 = 0\%$) and moderate heterogeneity for DHA ($I^2 = 47.5\%$) and EPA+DHA ($I^2 = 60.7\%$).

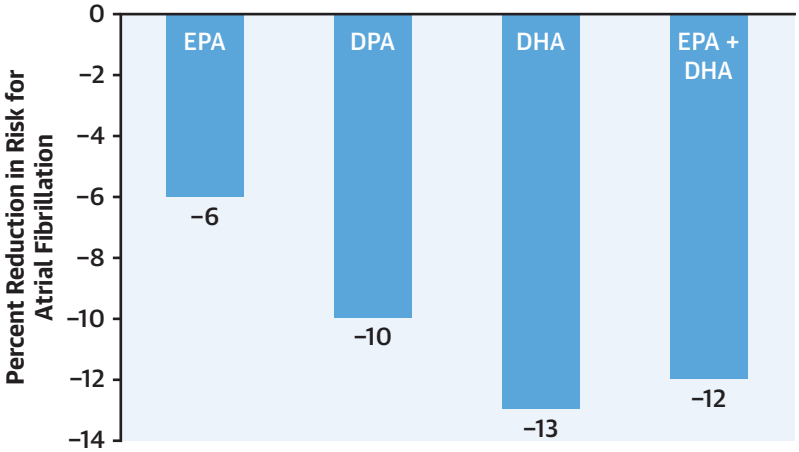
**SUBGROUP AND SENSITIVITY ANALYSES.** We found little evidence that the associations significantly varied by age, sex, or global region, or across the various lipid compartments ($P_{het} > 0.05$ for each fatty acid exposure) (**Table 3**). Moreover, the relationship between omega-3 fatty acids and AF did not significantly differ among individuals at higher CV risk (**Table 3**). In 13 of the 17 cohorts with dietary information, additional adjustment for dietary intakes did not appreciably alter these associations (Supplemental Figure 6). The pooled categorical analyses did not demonstrate apparent nonlinear trends (Supplemental Table 3). Restricted cubic splines of the compartment-specific associations were suggestive of possible nonlinear relationships between plasma phospholipid DPA, DHA, and EPA+DHA with incident AF, although the confidence limits did not exclude one (Supplemental Figures 7A to 7N). No such plateauing was seen for erythrocyte phospholipid DPA, DHA, and EPA+DHA. We also did not find any evidence of heterogeneity by the duration of follow-up in meta-regression analyses ($P_{het} > 0.05$ for each fatty acid exposure).

## DISCUSSION

In this global consortium of 17 cohort studies including 54,799 participants from 21 nations with 7,720 incident cases of AF, we observed that circulating and adipose tissue EPA was not associated with incident AF and that higher levels of DPA, DHA, and EPA+DHA were each associated with a statistically significant lower risk of AF (**Central Illustration**). Associations were generally consistent by lipid compartments, demographic characteristics, and global region.

Our findings are consistent with, and greatly expand upon, the limited number of prior observational studies demonstrating an inverse association between omega-3 fatty acid biomarkers and incident AF.[12-15] However, our results are in contrast to those

**CENTRAL ILLUSTRATION Omega-3 Levels and Risk for Atrial Fibrillation**




**Qian F, et al. J Am Coll Cardiol. 2023;82(4):336-349.**

Compared with individuals in the lowest quintile, those in the highest quintile of blood/tissue omega-3 levels had between 6% and 13% lower risk for developing atrial fibrillation. These multivariable-adjusted estimates were derived from a pooled study of 17 cohorts including 54,799 individuals followed for a median of 13.3 years and analyzed using prespecified and harmonized outcome definitions, covariates, and statistical methods. DHA = docosahexaenoic acid; DPA = docosapentaenoic acid; EPA = eicosapentaenoic acid.

of a recent meta-analysis of intervention trials, which found that treatment with omega-3 fatty acid products, particularly at high doses (1.8-4 g/d), was associated with increased risk of AF.[18] There are several potential reasons why the results of the present study may differ from recent omega-3 RCTs. First, the majority of the participants included in our study were community-dwelling individuals who were free of CVD or at relatively low CV risk. In contrast, except for VITAL-Rhythm,[8] the studies included in the aforementioned meta-analysis typically enrolled individuals with baseline CVD or were at elevated CV risk. It is conceivable that the effects of omega-3 fatty acids on atrial arrhythmias may differ in those with existing CVD vs without. To afford a more direct comparison to the populations in the typical trials represented in the meta-analysis, we prespecified a subgroup analysis to examine a "REDUCE-IT"-like cohort, with established CVD and/or elevated CV risk. In this subgroup, we observed a lack of association for EPA and inverse associations for DPA, DHA, and EPA+DHA with incident AF.

Second, the prevalence of omega-3 fatty acid supplement use in our cohorts was very low,[16,19] meaning that biomarker levels of these fatty acids largely reflect habitual dietary intake. Based on a global survey of seafood omega-3 intake by country,[20] the mean intake in the countries represented in our study was 0.43 ± 0.35 g/d, far less than the >1.8 g/d added to the background diets in the RCTs. RCTs of generally short-term, high-dose encapsulated omega-3 agents are unlikely to mimic the long-term impact of habitual dietary omega-3 fatty acid intake on AF risk. Moreover, the duration of follow-up in the majority of our cohorts was longer than that for most RCTs. In particular, as omega-3 fatty acids appear to exert influences on multiple upstream risk factors related to AF such as blood pressure,[3,21-23] type 2 diabetes,[16,24] systemic inflammation,[25] and chronic sympathetic activation,[26] the timeline to seeing a possible benefit with respect to AF may be longer than what can be feasibly achieved in an RCT, particularly coupled with the typical decline in adherence to study therapy over time.[27] More research is needed to confirm our findings and to explore potential mechanisms for which long-term dietary omega-3 fatty acid intake may relate to lower AF risk.

The modest protective association of omega-3 fatty acid levels with incident AF appeared to be more prominent in phospholipids, as compared with cholesterol esters or total plasma. The reason for this difference is unclear, although it might relate to the larger number of studies in our consortium that

assessed fatty acid in phospholipids, which would increase statistical power and precision. Future studies are warranted to assess how fatty acid levels in different lipid compartments may influence AF.

To our knowledge, our study is the largest investigation to date to examine the association between in vivo omega-3 fatty acid status and incident AF. Whether these associations represent a true independent effect or merely a reflection of the correlation with seafood intake and related lifestyle factors warrants further research. The difference in associations for EPA vs DHA, both of which are correlated with seafood consumption, and the significantly lower risk for DPA, which is endogenously regulated and very weakly correlated with diet, suggest that confounding by diet and lifestyle is unlikely to fully explain our observations. Our novel results highlight the need for additional studies to examine how varying intakes of dietary omega-3 fatty acids and omega-3 formulations (eg, DHA-rich products) may affect intermediary risk factors, such as blood pressure, type 2 diabetes, and inflammation, as well as clinical AF.

**STUDY STRENGTHS AND LIMITATIONS.** The strengths of our study include the harmonized exposure, outcome, and analysis plan, which can reduce between-study heterogeneity. Nevertheless, moderate unexplained heterogeneity remained for EPA and DHA. By identifying and contacting the majority of cohorts with the necessary exposure and outcome information, and conducting de novo analyses in each of the cohorts, our study reduces the likelihood of publication bias and is thus more likely to present accurate and unbiased associations for omega-3 fatty acids and incident AF. We adjusted for a wide range of major AF risk factors in a harmonized fashion, reducing the potential for residual confounding. Heterogeneity was generally low to moderate in the overall pooled analyses. The large number of AF events allowed for greater statistical precision in the estimation of the overall associations as well as in several subgroups, including among participants at elevated CV risk.

Due to the observational nature of our study, we cannot rule out residual or unmeasured confounding as possible explanations for the associations we observed despite extensive adjustments for known AF risk factors. Nevertheless, the robustness of our findings from pooling multiple cohorts from different populations with varying dietary backgrounds and baseline AF risk, as well as in sensitivity analyses, suggest that our findings are likely not merely caused by uncontrolled confounding or chance. We did not prespecify within-cohort subgroup analyses by race/ethnicity or BMI, and thus potential effect modification by these factors was not explored. There was moderate heterogeneity for several of the fatty acid exposures, as evidenced by the $I^2$-statistic (ranging from 47.5% to 60.7%), for which we were not readily able to identify the source of through subgroup and meta-regression analyses. To partially account for this heterogeneity, we also conducted a random-effects meta-analysis for each fatty acid exposure and found similar risk estimates (data not shown). Individuals with paroxysmal AF may have only been partially captured. Fatty acids were only measured at one time point, and changes in dietary intakes, other lifestyle exposures, and health conditions over time may alter the endogenous levels of omega-3 fatty acids. Nevertheless, previous studies have shown reasonable reproducibility for omega-3 fatty acid levels over time, ranging from 0.59 to 0.80 for EPA, DPA, and DHA over 6 to 13 years of follow-up.[28] At the same time, because all of the included cohorts were conducted in a prospective fashion, changes in omega-3 fatty acid levels over time would likely be nondifferential with respect to the outcome of interest, and would generally tend to bias associations toward the null.

## CONCLUSIONS

In a global, harmonized, pooled analysis, higher circulating and tissue omega-3 fatty acid biomarkers were not associated with an increased incidence of AF. Our data indicates that high-dose omega-3 supplementation in populations with established CVD or who are at high risk for CVD may not necessarily be generalizable to lower-dose habitual dietary omega-3 intakes. Coupled with the more consistent benefits of these fatty acids in the prevention of adverse coronary events, our study suggests that current dietary guidelines recommending fish/omega-3 fatty acid consumption should be maintained.

## FUNDING SUPPORT AND AUTHOR DISCLOSURES

The Fatty Acid Research Institute retrospectively provided a small honorarium to a subset of the analysts who participated in this study, but it had no role in the design, analysis, manuscript writing, nor decision to submit for publication. Detailed funding information for the individual cohorts can be found in the Supplemental Appendix, specifically Supplemental Table 4. None of the funders/sponsors played any role in the collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; or decision to submit the manuscript for publication. Dr O'Donoghue is a member of the TIMI Study Group, which has received institutional research grant support through Brigham and Women's Hospital from Amgen, Novartis, Janssen, and AstraZeneca; and has received consulting fees from Amgen, Novartis, Janssen, and

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## PERSPECTIVES

**COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS:** Dietary intake of long-chain omega-3 polyunsaturated fatty acids, reflected by circulating fatty acid biomarkers, does not increase the risk of AF in the general population.

**TRANSLATIONAL OUTLOOK:** Future clinical trials of omega-3 polyunsaturated fatty acid supplementation should include AF as an adjudicated outcome.

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**KEY WORDS** biomarkers, docosapentaenoic acid, docosahexaenoic acid, eicosapentaenoic acid, observational epidemiology

**APPENDIX** For an expanded Methods section as well as supplemental tables and figures, please see the online version of this paper.