The American Journal of Clinical Nutrition 118 (2023) 406–411

The American Journal of CLINICAL NUTRITION

journal homepage: https://ajcn.nutrition.org/

Original Research Article

Dietary ω-3 fatty acids and the incidence of atrial fibrillation in the Million Veteran Program

Eric T. Guardino [1,2,*], Yanping Li [1], Xuan-Mai Nguyen [1], Peter W.F. Wilson [3,4], J. Michael Gaziano [1,2], Kelly Cho [1], Emelia J. Benjamin [5,6], Luc Djoussé [1,2,7]

[1] *Massachusetts Veterans Epidemiology Research and Information Center (MAVERIC), VA Boston Healthcare System, Boston, MA, United States;* [2] *Division of Aging, Brigham & Women's Hospital and Harvard Medical School, Boston, MA, United States;* [3] *Atlanta VA Healthcare System, Decatur, GA, United States;* [4] *Emory Clinical Cardiology Research Institute, Atlanta, GA, United States;* [5] *Department of Medicine, Boston University Chobanian & Avedisian School of Medicine/Boston Medical Center, Boston, MA, United States;* [6] *Department of Epidemiology, Boston University School of Public Health, Boston, MA, United States;* [7] *Department of Nutrition, Harvard T. H. Chan School of Public Health, Boston, MA, United States*

A B S T R A C T

Background: Although recent large randomized clinical trials have reported an increased risk of atrial fibrillation (AF) with marine ω-3 fatty acid supplements, it is unclear whether dietary marine ω-3 fatty acids assessed through food frequency questionnaires are associated with AF risk.

Objectives: We sought to test the hypothesis that dietary eicosapentaenoic acid/docosahexaenoic acid/docosapentaecnoic acid (EPA/DHA/DPA) is associated with a higher risk of AF in a large prospective cohort of US Veterans.

Methods: We analyzed data from Million Veteran Program participants who completed self-reported food frequency questionnaires. We used multivariable Cox regression to estimate the HRs of AF across quintiles of ω-3 fatty acid consumption and a cubic spline analysis to assess the dose–response relations between ω-3 fatty acids and AF.

Results: Of the 301,294 veterans studied, the median intake of ω-3 fatty acids (EPA/DHA/DPA) was 219 mg/d (IQR: 144–575), and the mean age was 64.9 y (SD: 12.0); 91% were men, and 84% were White. Consumption of EPA/DHA/DPA exhibited a nonlinear inverse relation with incident AF characterized by an initial decline to 11% at 750 mg/d of marine ω-3 fatty acid intake followed by a plateau.

Conclusions: Contrary to our hypothesis, dietary EPA/DHA/DPA was not associated with a higher risk of AF but was inversely related to AF risk in a nonlinear manner.

Keywords: ω-3 fatty acids, atrial fibrillation, nutrition, veterans, cardiology, arrhythmia

Introduction

Consumption of marine ω-3 fatty acids (ie, EPA, DHA, and DPA) is common in the United States primarily through foods (ie, fish and other seafood products or supplements). Recent large clinical trials evaluating the effects of EPA/DHA supplements on cardiovascular outcomes have reported an increased risk of atrial fibrillation (AF) [1,2] with EPA/DHA supplements. AF is the most common sustained cardiac arrhythmia and affects at least 5.2 million adults in the United States with costs to the United States health care system of about $26 billion to $28 billion annually [3–5].

Previous research evaluating the relation of ω-3 fatty acids with the risk of AF has been inconsistent. A large Danish cohort study of 55,246 participants reported a U-shaped relationship between the consumption of marine ω-3 fatty acids (EPA, DHA, and DPA) and incidence of AF over 13.6 y, with the lowest risk occurring at 630 mg/d of marine ω-3 intake [6]. A randomized controlled trial (RCT) evaluating the incidence of AF with EPA/DHA supplementation (840 mg/d) among 6270 patients found no increase in the incidence of AF in the EPA/DHA group over a median follow-up of 5.3 y [7]. The Reduction of Cardiovascular Events with Icosapent Ethyl–Intervention Trial (REDUCE-IT) trial reported that an intervention with 4 g/d of icosapent ethyl led to a 3.1% risk of hospitalization for AF or atrial flutter compared with 2.1% in the control group [1]. A meta-analysis of large scale RCTs identified that supplementation with EPA/DHA increased the risk of AF events by 25% compared with a placebo, and this risk was higher for patients taking

Abbreviations: AF, atrial fibrillation; EHR, electronic health record; MVP, Million Veteran Program; RCT, randomized controlled trial; DHA, docosahexaenoic acid; DPA, docosapentaenoic acid.

* Corresponding author.
E-mail address: eguardino@une.edu (E.T. Guardino).

https://doi.org/10.1016/j.ajcnut.2023.06.001
Received 6 March 2023; Received in revised form 22 May 2023; Accepted 1 June 2023; Available online 20 June 2023
0002-9165/Published by Elsevier Inc. on behalf of American Society for Nutrition.

more than 1000 mg/d of EPA/DHA supplements [8]. Two recent trials assessing biomarkers of ω-3 fatty acids, 1 in adipose tissue and 1 in plasma, showed an inverse relationship between ω-3 fatty acid concentrations and the risk of AF [9,10].

Given the paucity of data on the role of dietary intake of marine ω-3 fatty acids on the risk of developing AF, we sought to evaluate whether dietary intake of EPA/DHA/DPA was associated with a higher risk of AF among US Veterans enrolled in the Million Veteran Program (MVP) [11]. We hypothesized that there is a positive linear relation between EPA/DHA/DPA assessed using a food frequency questionnaire and incident AF.

Methods

Study population

This study consists of US Veterans enrolled in the MVP. The MVP is a prospective cohort study designed to help better understand how health is affected by genetic and nongenetic characteristics. Veterans enrolled in the program provide blood samples, fill out questionnaires, and consent to allowing access to their medical records [11]. All participants gave informed consent and the study was approved by the Veterans Affairs Central Institutional Review Board. In total, 819,417 veterans were enrolled in the MVP at the end of 2020, and 379,852 had completed the MVP Lifestyle Survey, which contains information about dietary habits [12]. Of the Veterans who completed this survey, we excluded Veterans with a history of AF (Supplemental Figure 1). A comparison of baseline characteristics among those who completed the MVP Lifestyle Survey and those who did not can be found in Supplemental Table 1.

Dietary assessment of EPA/DHA/DPA

The MVP Lifestyle Survey contains a section with a self-reported food frequency questionnaire that was based on a previously validated questionnaire [13]. The Veterans were asked how often they consumed standard portions of different food items in the past year. The prespecified responses were: "never or less than once per month," "once a week," "2–4 per week," "5–6 per week," "once a day," "2–3 per day," "4–5 per day," and "≥6 per day." This information was used to calculate the average daily intake of the different food items and then the amount of ω-3 fatty acid intake was calculated using nutrient content from the Harvard University Food Composition Database [14]. Additionally, the MVP Lifestyle Survey collected information on dietary supplement use, including ω-3 supplements, which were accounted for when computing total ω-3 intake.

Assessment of AF

AF was defined using ICD-9 and ICD-10 codes within the Veterans Affairs electronic health record (EHR). The EHR is housed within the Corporate Data Warehouse, and ICD-9 codes *427.3x* and ICD-10 codes *I48.x* were included. Veterans were classified as having an AF event if they had ≥1 diagnosis as an inpatient or ≥2 diagnoses as an outpatient within the follow-up period.

Relevant covariates

Baseline data on age, sex, race, ethnicity, and BMI were cross-referenced with the EHR, and the other covariates were taken from the self-reported MVP Baseline Survey.

Statistical analysis

We presented the baseline characteristics (mean ± SD for continuous and normally distributed variables and number and percentage for categorical variables) of the study population according to the quintile of dietary ω-3 fatty acid intake. The person-years of follow-up were calculated as the time between the date of completion of the MVP Lifestyle Survey and the closure date of the current data, which was defined as the earliest of: time of the first occurrence of AF, death, date of the last update in the EHR, or September 30, 2020, if the last visit in the EHR took place on or after October 1, 2020.

We examined Cox proportional hazards models to estimate HRs with 95% CIs comparing higher quintiles to the lowest quintile of dietary ω-3 fatty acid intake with simultaneous adjustment for covariates using 4 different models. Model 1 only adjusted for age (continuous). Model 2 further adjusted for sex (male or female), race (White, Black, Asian, other), ethnicity, education level (less than or equal to high school or general educational development, some college, or college or above), income level (<$30,000, $30,000–$59,000, or ≥$60,000), smoking status (current, former, or never smoking), physical activity in metabolic equivalents (continuous), calorie intake (continuous), alcohol intake (continuous), and BMI (continuous). Model 3 was further adjusted for history of diabetes, hypertension, chronic kidney disease, heart failure, and coronary artery/coronary heart disease (includes angina) at baseline (yes vs. no). Model 4 further adjusted for dietary nutrient intake including protein, saturated fat, monounsaturated fatty acid, trans fat, and ω-6 fatty acid, which was used for the rest of our analysis as it best accounted for potential confounders. We assessed the proportional hazard assumption using a likelihood ratio test comparing the model with and without an interaction term between time periods and dietary ω-3 fatty acid intake.

To quantify a linear trend of relative risk of AF across quintiles of ω-3 fatty acid intake, we assigned the median within each quintile and modeled this variable continuously; the Wald test was used for statistical significance. The potential nonlinearity in the association between ω-3 fatty acid intake and the risk of AF was examined using restricted cubic spline regression with 3 knots applied to flexibly model the association with the first percentile of ω-3 fatty acid intake as the reference level. The nonlinearity in the dose–response relationship of ω-3 fatty acid intake and the incidence of AF was tested by comparing the model with the linear term to the model with the linear and cubic spline terms using the likelihood ratio test. We examined the interaction between races and ω-3 fatty acids using a likelihood method comparing the model with and without interaction terms between races (White, Black, Asian, and others) and ω-3 fatty acid intake (by quintiles) with a degree of freedom of 12.

Results

Baseline characteristics

We analyzed data from 301,294 US Veterans with a mean age of 64.9 y (SD: 12), 91% men, and 84% White. The median intake of dietary EPA/DHA/DPA was 219 mg/d (IQR: 144–575). Higher consumption of marine ω-3 fatty acids was positively associated with physical activity, prevalent coronary artery disease, hypertension, having a college degree, and making more than $60,000 per year, whereas the reverse was true for alcohol intake, current smoking, having an education level of a high school degree or less, and making less than $30,000 per year (Table 1).

Primary outcome

Overall, consumption of marine ω-3 fatty acids was not associated with a higher incidence of AF in this population. Multivariable adjusted HRs (95% CIs) across consecutive quintiles of dietary ω-3 fatty acid intake for the incidence of AF were 1.00 (reference), 1.01 (95% CI: 0.96, 1.05), 0.95 (95% CI: 0.91, 1.00), 0.97 (95% CI: 0.92, 1.02), and

TABLE 1
Baseline characteristics[1]

Characteristic and category	All participants	Quintiles of dietary ω-3 (EPA, DHA, DPA) intake				
		Q1	Q2	Q3	Q4	Q5
N	301,294	60,340	60,141	60,397	60,201	60,215
ω-3, mg/d	394 ± 375	79 ± 31	158 ± 17	223 ± 25	473 ± 126	1038 ± 286
EPA, mg/d	139 ± 179	16 ± 7	33 ± 7	46 ± 10	139 ± 78	458 ± 129
DPA, mg/d	56 ± 35	22 ± 8	33 ± 7	45 ± 9	72 ± 17	105 ± 35
DHA, mg/d	200 ± 174	41 ± 22	92 ± 12	131 ± 17	262 ± 67	474 ± 160
Age, mean, y	64.9 ± 12.0	64.5 ± 12.2	65.1 ± 12.1	64.8 ± 12.1	64.9 ± 12.2	65.1 ± 11.4
Sex, n (%)						
Male	274,881 (91.2)	54,762 (90.8)	55,594 (92.4)	55,431 (91.8)	54,549 (90.6)	54,548 (90.6)
Female	26,413 (8.8)	5577 (9.2)	4557 (7.6)	4963 (8.2)	5651 (9.4)	5665 (9.4)
BMI, mean ± SD, kg/m^2	29.4 ± 5.5	29.0 ± 5.7	29.2 ± 5.5	29.6 ± 5.6	29.4 ± 5.5	29.5 ± 5.3
Race, *n* (%)						
White	253,144 (84.0)	53,569 (88.8)	51,822 (86.2)	49,498 (82.0)	47,563 (79.0)	50,692 (84.2)
Black	34,469 (11.4)	4271 (7.1)	5891 (9.8)	8,150 (13.5)	9738 (16.2)	6419 (10.7)
Asian	2868 (1.0)	284 (0.5)	392 (0.7)	543 (0.9)	768 (1.3)	881 (1.5)
Other[2]	10,813 (3.6)	2216 (3.7)	2036 (3.4)	2206 (3.7)	2132 (3.5)	2223 (3.7)
Ethnicity: Hispanic or Latino, *n* (%)	19,943 (6.6)	3824 (6.3)	3584 (6.0)	4071 (6.7)	4060 (6.7)	4404 (7.3)
Comorbidities, *n* (%)						
Coronary artery disease	38,550 (14.4)	6923 (12.9)	7206 (13.5)	7534 (14.1)	7746 (14.5)	9141 (16.8)
Heart failure	11,905 (4.4)	2294 (4.3)	2319 (4.3)	2439 (4.6)	2481 (4.7)	2371 (4.4)
Diabetes	69,190 (25.8)	12,476 (23.3)	12,971 (24.3)	14,641 (27.5)	14,114 (26.5)	14,988 (27.5)
Chronic kidney disease	14,705 (5.5)	2727 (5.1)	2746 (5.1)	2969 (5.6)	3088 (5.8)	3175 (5.8)
Hypertension	164,714 (61.5)	31,573 (58.9)	32,580 (61.0)	33,220 (62.3)	33,030 (61.9)	34,311 (63.0)
Physical activity, MET-h/wk	4.7 ± 5.5	3.7 ± 5.0	4.3 ± 5.2	4.5 ± 5.3	5.3 ± 5.9	5.7 ± 6.0
Alcohol intake, g/d	7.9 ± 14.7	9.1 ± 18.4	8.7 ± 15.5	7.3 ± 13.1	7.1 ± 12.5	7.1 ± 13.0
Energy intake, kcal/d	1430 ± 620	1465 ± 673	1456 ± 583	1256 ± 496	1635 ± 722	1339 ± 526
DASH score	24.1 ± 5.0	22.4 ± 5.1	23.3 ± 4.8	23.9 ± 4.8	24.9 ± 4.9	25.8 ± 4.8
Ever smoking, *n* (%)	160,471 (53.8)	30,669 (51.3)	31,988 (53.6)	32,474 (54.3)	31,762 (53.3)	33,578 (56.2)
Currently smoking, *n* (%)	41,865 (14.0)	11,900 (19.9)	9771 (16.4)	7933 (13.3)	7303 (12.3)	4958 (8.3)
Annual family income, *n* (%), $						
<30,000	79,126 (33.0)	19,440 (40.5)	16,178 (33.7)	15,079 (31.6)	15,020 (31.6)	13,409 (27.7)
30,000–59,000	86,283 (36.0)	17,027 (35.4)	17,895 (37.2)	17,148 (35.9)	16,707 (35.1)	17,506 (36.2)
≥60,000	74,433 (31.0)	11,587 (24.1)	13,968 (29.1)	15,532 (32.5)	15,862 (33.3)	17,484 (36.1)
Education level, *n* (%)						
High school or lower or GED	61,650 (23.3)	16,028 (30.3)	13,718 (26.0)	12,314 (23.4)	10,321 (19.6)	9269 (17.2)
Some college (no degree)	79,591 (30.1)	16,599 (31.4)	16,266 (30.9)	15,911 (30.2)	15,527 (29.5)	15,288 (28.4)
College or above	123,305 (46.6)	20,224 (38.3)	22,730 (43.1)	24,386 (46.4)	26,773 (50.9)	29,192 (54.3)
Intake of nutrient, g/d						
Protein	78.1 ± 19.2	66.7 ± 17.5	73.2 ± 15.2	82.1 ± 15.9	85.3 ± 19.8	83.3 ± 20.1
Saturated fat	19.3 ± 5.0	19.7 ± 5.9	19.8 ± 4.9	19.7 ± 4.5	18.9 ± 4.7	18.5 ± 4.7
MUFA	20.6 ± 4.9	20.1 ± 5.6	20.6 ± 4.7	21.1 ± 4.5	20.7 ± 4.8	20.3 ± 4.8
Trans fat	0.9 ± 0.3	1.0 ± 0.3	1.0 ± 0.3	0.9 ± 0.3	0.9 ± 0.3	0.8 ± 0.3
LA	8.9 ± 2.6	8.7 ± 3.0	8.9 ± 2.6	9.1 ± 2.4	9.0 ± 2.6	9.1 ± 2.6
AA	0.3 ± 0.1	0.2 ± 0.1	0.2 ± 0.1	0.3 ± 0.1	0.3 ± 0.1	0.3 ± 0.1

Abbreviations: EPA, eicosapentaenoic acid; GED, general educational development; MET, metabolic equivalent of task.
[1] Baseline characteristics of veterans enrolled in the Million Veteran Program with data about their marine ω-3 fatty acid intake on food frequency questionnaires.
[2] The "other" category includes American Indian, Pacific Islander, and unknown.

0.93 (95% CI: 0.88, 0.98), respectively (Table 2). A cubic spline analysis suggested an inverse and nonlinear relation with an HR of 0.89 (95% CI: 0.84, 0.95) at 2 SDs (750 mg/d) of ω-3 fatty acid intake (Figure 1). The tests for the proportional hazard assumption did not indicate a violation of the assumption.

In secondary analyses, we observed similar associations of dietary ω-3 fatty acids (EPA, DPA, and DHA) with the incidence of AF (Supplemental Figures 2–4). There was no evidence of interaction between race and dietary ω-3 intake and incidence of AF ($P > 0.05$).

Discussion

In this prospective study of more than 300,000 veterans without AF at baseline, dietary intake of total marine ω-3 fatty acids was associated with lower risk of AF in a nonlinear manner. Additionally, we observed similar findings with dietary EPA, DHA, and DPA.

A Danish study of 55,246 individuals (mean age: 57 y) with a median consumption of 630 mg/d of marine ω-3 fatty acids reported a U-shaped relationship between dietary marine ω-3 fatty acid intake (both total and individual) and the incidence of AF [6]. Despite the difference in the shape of the relationship, our results were similar. AF incidence was 11% versus 13% lower at a similar ω-3 fatty acid intake of 750 mg/d versus 630 mg/d in our study compared to theirs. The difference in the shape of the relationship between the 2 studies could be related to the difference in our study populations or that the average ω-3 fatty acid intake in their fifth quintile was 1250 mg/d compared with 1038 mg/d in our fifth quintile. A biomarker study reported an inverse association between EPA concentration in adipose tissue and

TABLE 2
Adjusted HRs for the incidence of atrial fibrillation[1]

	Quintiles of dietary ω-3 fatty acid intake, mg/d					*P* for trend
	Q1 (15–128)	Q2 (129–186)	Q3 (187–277)	Q4 (278–708)	Q5 (708–6085)	
Cases	4327	4473	4194	4360	4398	
Person-years	258,841	260,587	258,143	261,698	274,984	
Model 1[2] HR (95% CI)	1.00	0.99 (0.95, 1.04)	0.96 (0.92, 1.00)	0.97 (0.93, 1.01)	0.93 (0.89, 0.97)	<0.001
Model 2[3] HR (95% CI)	1.00	1.02 (0.97, 1.06)	0.99 (0.95, 1.04)	1.05 (1.00, 1.09)	1.00 (0.96, 1.05)	0.864
Model 3[4] HR (95% CI)	1.00	1.02 (0.98, 1.06)	0.98 (0.93, 1.02)	1.01 (0.97, 1.06)	0.97 (0.92, 1.01)	0.094
Model 4[5] HR (95% CI)	1.00	1.01 (0.96, 1.05)	0.95 (0.91, 1.00)	0.97 (0.92, 1.02)	0.93 (0.88, 0.98)	0.005

[1] Adjusted HRs for the incidence of atrial fibrillation among US Veterans based on their dietary intake of ω-3 fatty acids.
[2] Model 1: adjusted age (continuous).
[3] Model 2: further adjusted sex, races (White, Black, Asian, others), Hispanic, education levels, income, smoking status, physical activity metabolic equivalent of tasks (continuous), calorie intakes (continuous), alcohol intake (continuous), and BMI (continuous).
[4] Model 3: model 2 + chronic conditions at baseline including diabetes mellitus, hypertension, coronary artery disease, heart failure, and chronic kidney disease.
[5] Model 4: model 3 + nutrients, including protein, saturated fat, MUFA, trans fat, and ω-6 fatty acid.

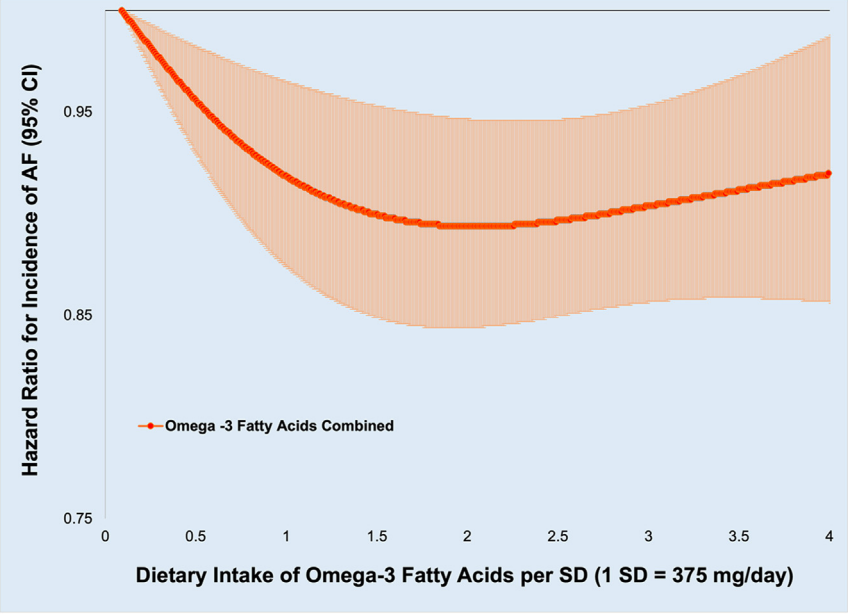

FIGURE 1. Cubic spline of HR for the incidence of atrial fibrillation (AF). Cubic spline of the HR for the incidence of AF among US Veterans enrolled in the Million Veteran Program with information on ω-3 fatty acid intake per SD of ω-3 fatty acid intake (1 SD = 375 mg/d). There is an initial decline in the incidence of AF with consumption of ω-3 fatty acids with a HR of 0.89 (95% CI: 0.84, 0.95) at 2 SD (750 mg/d) of ω-3 fatty acid intake. This is then followed by a plateau in the incidence of AF with higher levels of ω-3 fatty acid consumption. Therefore, consumption of dietary ω-3 fatty acids is protective against the development of AF up to about 750 mg/d with no additional benefit from consuming additional dietary ω-3 fatty acids.

risk of AF among men and women; however, concentration of adipose tissue DHA was inversely associated with AF risk among women but not in men [9].

Recent large RCTs of ω-3 fatty acids that evaluated the risk of AF and cardiovascular outcomes reported a different result [1,2,7,15–18]. These 7 trials showed a trend toward increased AF incidence (new onset, hospitalization for AF, or worsening AF) with greater ω-3 fatty acid intake, but only REDUCE-IT [1] and Long-Term Outcomes Study to Assess Statin Residual Risk with Epanova in High Cardiovascular Risk Patients with Hypertriglyceridemia (STRENGTH) [2] demonstrated a statistically significant increase in AF. Both of these trials used dosages of 4000 mg/d (REDUCE-IT used 3992 mg/d of icosapent ethyl [1], and STRENGTH used 2200 mg/d of EPA and 800 mg/d of DHA [19]), whereas in the other trials, 1 used 1800 mg/d [18] and the rest used 1000 mg/d. A relatively small number of people consume enough ω-3 fatty acids in their diet to approach the 4000 mg/d given in these 2 above trials. The median intake of ω-3 fatty acids among all participants in our study was 219 mg/d, and only 0.03% (n = 89) of the participants consumed 4000 mg/d or more. In the Danish study, the median intake of ω-3 fatty acids was 630 mg/d [6].

The mechanism as to why ω-3 fatty acids could be proarrhythmic is uncertain. One potential mechanism is that ω-3 fatty acids can block sodium channels and shorten action potentials, which can favor re-entry-based arrhythmias [20]. One study involving intravenous EPA/DHA found atrial conduction slowing and decreased inducibility of AF but enhanced flutter inducibility [21]. Additionally, ω-3 fatty acids have been shown to increase vagal tone, which can predispose to AF [22].

It is possible that there is a dose-dependent mechanism that would help to explain the difference in AF incidence between our study and

the 2 RCTs that found increased AF. Our observational study involved dietary and supplemental marine ω-3 fatty acids intake but did not have many individuals consuming the large amounts of ω-3 fatty acids that were given in the RCTs. To further evaluate this possible dose–response, a trial involving varying amounts of ω-3 fatty acid supplementation could examine if small amounts of ω-3 fatty acids are protective for developing AF, but larger amounts may put patients at risk of AF. Additionally, the populations studied in these 2 RCTs differ from our study population. REDUCE-IT only included patients with established cardiovascular disease or patients with diabetes and other risk factors who were on a statin with elevated triglycerides [1]. STRENGTH evaluated participants on statins with high cardiovascular risk and elevated triglycerides and low high-density lipoprotein cholesterol [2]. None of the above criteria applied to the MVP population.

Our study has several strengths, including large sample size, large number of events, comprehensive EHR to identify most episodes of AF, and the accounting of multiple covariates to minimize confounding.

One limitation of our study is that it only includes Veterans, and the participants were mostly White and men; hence, our findings may not be generalizable to a more diverse patient population. Performing a similar study among a more diverse patient population and including participants from other countries would help improve the generalizability. Another limitation is the fact that dietary ω-3 fatty acid intake was derived from a food frequency questionnaire obtained at a single point in time. Incorporating multiple food frequency questionnaires over time could account for changes in dietary habits, and measuring blood levels of ω-3 fatty acids could help reduce misclassification of ω-3 fatty acids from self-reported food frequency questionnaires in future studies. Many of the covariates were self-reported and hence may have been misclassified, limiting the ability to fully account for confounding. This study also varies from the clinical trials in that there could be other factors in the foods that contain ω-3 fatty acids that have an effect on AF that are not present when using an ω-3 fatty acid supplement; however, we adjusted for nutrient intake and compared dietary scores to limit this confounding. Another limitation is that episodes of AF were determined using ICD codes, which can lead to missed diagnoses of AF, especially in a subject with paroxysmal AF. Using patient level data such as electrocardiograms or clinical notes may capture more episodes of AF. Additionally, given the observational nature of our study, we cannot exclude residual or unmeasured confounding as an explanation of our observed findings.

Our data did not show a higher risk of AF with dietary marine ω-3 fatty acid intake. Our findings demonstrated an inverse and nonlinear relation of dietary ω-3 fatty acids with the incidence of AF among US Veterans. Confirmation in the general population is warranted.

Acknowledgments

The authors thank the members of the Million Veteran Program Core, those who have contributed to the Million Veteran Program, and especially the Veteran participants for their generous contributions (see supplement file for full acknowledgments).

Author contributions

The authors' responsibilities were as follows – ETG, LD: designed research; YL, X-MN, JMG, LD: curation of food frequency questionnaires and nutrient data; YL: performed statistical analysis; ETG, YL, X-MN, PWFW, JMG, KC, EJB, LD: contributed to data analysis and interpretation of the results; ETG, LD: wrote the paper; LD: supervised the project and had primary responsibility for final content; and all authors: read and approved the final manuscript.

Funding

This research is based on data from the Million Veteran Program, Office of Research and Development, Veterans Health Administration, and was supported by award #MVP000 and VA grant BX004821 (to PWFW and KC). EJB was supported in part by NIH, National Heart, Lung, and Blood Institute grant 2R01HL092577 and American Heart Association: 18SFRN34110082. LD was supported by grants R01 AG053325-01 and 1R01HL131687-01A1 from the NIH.

Conflict of interest

The authors report no conflicts of interest.

Data availability

Data described in the manuscript, code book, and analytic code will not be made available to other researchers for purposes of reproducing the results or replicating the procedure, in order to comply with current Veterans Affairs privacy regulations pursuant to the US Department of Veterans Administration policies on compliance with the confidentiality of US Veterans' data [23].

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ajcnut.2023.06.001.

References

[1] D.L. Bhatt, P.G. Steg, M. Miller, E.A. Brinton, T.A. Jacobson, S.B. Ketchum, et al., Cardiovascular risk reduction with icosapent ethyl for hypertriglyceridemia, N. Engl. J. Med. 380 (1) (2019) 11–22, https://doi.org/10.1056/NEJMoa1812792.

[2] S.J. Nicholls, A.M. Lincoff, M. Garcia, D. Bash, C.M. Ballantyne, P.J. Barter, et al., Effect of high-dose omega-3 fatty acids vs corn oil on major adverse cardiovascular events in patients at high cardiovascular risk: the STRENGTH randomized clinical trial, JAMA 324 (22) (2020) 2268–2280, https://doi.org/10.1001/jama.2020.22258.

[3] S. Colilla, A. Crow, W. Petkun, D.E. Singer, T. Simon, X. Liu, Estimates of current and future incidence and prevalence of atrial fibrillation in the U.S. adult population, Am. J. Cardiol. 112 (8) (2013) 1142–1147, https://doi.org/10.1016/j.amjcard.2013.05.063.

[4] M. Birger, A.S. Kaldjian, G.A. Roth, A.E. Moran, J.L. Dieleman, B.K. Bellows, Spending on cardiovascular disease and cardiovascular risk factors in the United States: 1996 to 2016, Circulation 144 (4) (2021) 271–282, https://doi.org/10.1161/CIRCULATIONAHA.120.053216.

[5] J.L. Dieleman, J. Cao, A. Chapin, C. Chen, Z. Li, A. Liu, et al., US health care spending by payer and health condition, 1996-2016, JAMA 323 (9) (2020) 863–884, https://doi.org/10.1001/jama.2020.0734.

[6] T.A. Rix, A.M. Joensen, S. Riahi, S. Lundbye-Christensen, A. Tjønneland, et al., A U-shaped association between consumption of marine n-3 fatty acids and development of atrial fibrillation/atrial flutter-a Danish cohort study, Europace 16 (11) (2014) 1554–1561, https://doi.org/10.1093/europace/euu019.

[7] C.M. Albert, N.R. Cook, J. Pester, M.V. Moorthy, C. Ridge, J.S. Danik, et al., Effect of marine omega-3 fatty acid and vitamin D supplementation on incident atrial fibrillation: a randomized clinical trial, JAMA 325 (11) (2021) 1061–1073, https://doi.org/10.1001/jama.2021.1489.

[8] B. Gencer, L. Djousse, O.T. Al-Ramady, N.R. Cook, J.E. Manson, C.M. Albert, Effect of long-term marine ω-3 fatty acids supplementation on the risk of atrial fibrillation in randomized controlled trials of cardiovascular outcomes: a systematic review and meta-analysis, Circulation 144 (25) (2021) 1981–1990, https://doi.org/10.1161/CIRCULATIONAHA.121.055654.

[9] T.A. Rix, P. Dinesen, S. Lundbye-Christensen, A.M. Joensen, S. Riahi, K. Overvad, et al., Omega-3 fatty acids in adipose tissue and risk of atrial fibrillation, Eur. J. Clin. Invest. 52 (1) (2022), e13649, https://doi.org/10.1111/eci.13649.

[10] K. Kapoor, A. Alfaddagh, M. Al Rifai, D.L. Bhatt, M.J. Budoff, K. Nasir, et al., Association between omega-3 fatty acid levels and risk for incident major bleeding events and atrial fibrillation: MESA, J. Am. Heart Assoc. 10 (11) (2021), e021431, https://doi.org/10.1161/JAHA.121.021431.

[11] J.M. Gaziano, J. Concato, M. Brophy, L. Fiore, S. Pyarajan, J. Breeling, et al., Million Veteran Program: a mega-biobank to study genetic influences on health and disease, J. Clin. Epidemiol. 70 (2016) 214–223, https://doi.org/10.1016/j.jclinepi.2015.09.016.

[12] D.D. Wang, Y. Li, X.T. Nguyen, R.J. Song, Y.L. Ho, F.B. Hu, et al., Dietary sodium and potassium intake and risk of non-fatal cardiovascular diseases: the Million Veteran Program, Nutrients 14 (5) (2022) 1121, https://doi.org/10.3390/nu14051121.

[13] S. Salvini, D.J. Hunter, L. Sampson, M.J. Stampfer, G.A. Colditz, B. Rosner, et al., Food-based validation of a dietary questionnaire: the effects of week-to-week variation in food consumption, Int. J. Epidemiol. 18 (4) (1989) 858–867, https://doi.org/10.1093/ije/18.4.858.

[14] Harvard T.H, Nutrition Questionnaire Service Center, Chan School of Public Health Nutrition Department: Food Composition Table Download Site. [Internet]. Available from: https://regepi.bwh.harvard.edu/health/nutrition/.

[15] ASCEND Study Collaborative Group, L. Bowman, M. Mafham, K. Wallendszus, W. Stevens, G. Buck, et al., Effects of n-3 fatty acid supplements in diabetes mellitus, N. Engl. J. Med. 379 (16) (2018) 1540–1550, https://doi.org/10.1056/NEJMoa1804989.

[16] Risk and Prevention Study Collaborative Group, M.C. Roncaglioni, M. Tombesi, F. Avanzini, S. Barlera, V. Caimi, et al., n-3 fatty acids in patients with multiple cardiovascular risk factors, N. Engl. J. Med. 368 (19) (2013) 1800–1808, https://doi.org/10.1056/NEJMoa1205409.

[17] A. Aleksova, S. Masson, A.P. Maggioni, D. Lucci, G. Fabbri, L. Beretta, et al., n-3 polyunsaturated fatty acids and atrial fibrillation in patients with chronic heart failure: the GISSI-HF trial, Eur. J. Heart Fail. 15 (11) (2013) 1289–1295, https://doi.org/10.1093/eurjhf/hft103.

[18] A.A. Kalstad, P.L. Myhre, K. Laake, S.H. Tveit, E.B. Schmidt, P. Smith, et al., Effects of n-3 fatty acid supplements in elderly patients after myocardial infarction: a randomized, controlled trial, Circulation 143 (6) (2021) 528–539, https://doi.org/10.1161/CIRCULATIONAHA.120.052209.

[19] J.J. Kastelein, K.C. Maki, A. Susekov, M. Ezhov, B.G. Nordestgaard, B.N. Machielse, et al., Omega-3 free fatty acids for the treatment of severe hypertriglyceridemia: the EpanoVa fOr Lowering Very high triglyceridEs (EVOLVE) trial, J. Clin. Lipidol. 8 (1) (2014) 94–106, https://doi.org/10.1016/j.jacl.2013.10.003.

[20] H.M. den Ruijter, G. Berecki, T. Opthof, A.O. Verkerk, P.L. Zock, R. Coronel, Pro- and antiarrhythmic properties of a diet rich in fish oil, Cardiovasc. Res. 73 (2) (2007) 316–325, https://doi.org/10.1016/j.cardiores.2006.06.014.

[21] S. Kumar, F. Sutherland, J.M. Lee, T. Robinson, P.M. Heck, M.C. Wong, et al., Effects of high dose intravenous fish oil on human atrial electrophysiology: implications for possible anti- and pro-arrhythmic mechanisms in atrial fibrillation, Int. J. Cardiol. 168 (3) (2013) 2754–2760, https://doi.org/10.1016/j.ijcard.2013.03.053.

[22] C.S. Bork, P.L. Myhre, E.B. Schmidt, Do omega-3 fatty acids increase risk of atrial fibrillation? Curr. Opin. Clin. Nutr. Metab. Care. 26 (2) (2023) 78–82, https://doi.org/10.1097/MCO.0000000000000090.7.

[23] Ethics Principles for Access to and Use of Veteran Data - DigitalVA, [Internet], 2021. Available from: https://digital.va.gov/employee-resources/ethics-principles-for-access-to-and-use-of-veteran-data/.