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Plasma ω-3 and ω-6 PUFA Concentrations and Risk of Atrial Fibrillation: The Multi-Ethnic Study of Atherosclerosis

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ABSTRACT

Background: Current literature examining the prospective relation of circulating omega-3 (n–3) and omega-6 (n–6) PUFAs and atrial fibrillation (AF) is limited to predominantly white populations.

Objectives: We investigated the association of circulating n–3 and n–6 PUFAs with incident AF in participants from the Multi-Ethnic Study of Atherosclerosis.

Methods: A total of 6229 participants (mean age = 62 y; 53% female; 39% white, 27% black, 22% Hispanic, and 12% Chinese) who were free of baseline AF and with plasma phospholipid PUFAs measured at baseline using GC were prospectively followed for the development of AF. Incident AF was ascertained using International Classification of Diseases-9 codes from hospital discharge records and Medicare claims data with follow-up through 2014. Multivariable Cox proportional hazards regression analysis was performed to determine the risk of incident AF.

Results: During a median follow-up of 12.9 y, 813 (13%) participants developed AF. Each higher SD increment in arachidonic acid (AA; 20:4n–6) concentrations was associated with an 11% decreased risk of incident AF (HR: 0.89; 95% CI: 0.82, 0.96). Similarly, higher overall n–6 PUFA concentrations were also associated with a reduced AF risk (HR per SD increment: 0.93; 95% CI: 0.87, 1.00). Although no significant overall associations were observed for any individual n–3 PUFAs, higher circulating concentrations of DHA (22:6n–3) and EPA (20:5n–3) were associated with a decreased AF risk in blacks and Hispanics (DHA only) but not whites or Chinese Americans.

Conclusions: In a multiethnic cohort of individuals free of baseline cardiovascular disease, higher plasma concentrations of n–6 PUFAs, particularly AA, were associated with a reduced risk of incident AF. Important differences in AF risk were also noted across race/ethnicity for the n–3 PUFAs DHA and EPA. *J Nutr* 2021;151:1479–1486.

Keywords: fatty acids, arachidonic acid, atrial fibrillation, cardiovascular disease, primary prevention

Introduction

Atrial fibrillation (AF) is the most frequently encountered cardiac arrhythmia in clinical practice, with an estimated prevalence of 11 million people in Europe and 9 million people in the United States (1, 2). The presence of AF is associated with an >2-fold increased risk of stroke, heart failure, and cardiovascular mortality (3). After accounting for known modifiable risk factors, nearly half of the population attributable risk of AF development still remains unexplained (4).

Long-chain omega-3 (n–3) PUFAs have been suggested to have a variety of biological effects that may reduce AF incidence. Increased intake of n–3 PUFAs provides anti-inflammatory and antifibrotic effects that may reduce long-term atrial remodeling and limit substrate for AF development (5–7). Cellular studies suggest n–3 PUFAs may also have direct antiarrhythmic effects as well (8–10). The protective effects of long-chain ω-6 (n–6) PUFAs are less clear. Arachidonic acid (AA; 20:4n–6) has been reported, in some studies, to give rise to a range of eicosanoids considered to be proinflammatory and prothrombotic (11–13). Other studies, however, suggest AA is also the precursor to key anti-inflammatory metabolites (14).

Current literature examining the prospective relation of circulating PUFAs and AF is limited to predominantly white populations (15–18). A Mendelian randomization analysis of >500,000 individuals found that plasma concentrations of n–3 and n–6 PUFAs were not associated with AF risk (18). In contrast, REDUCE-IT (the Reduction of Cardiovascular Events with Icosapent Ethyl–Intervention Trial) recently reported an increased risk of hospitalized AF in those randomly assigned

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to Icosapent Ethyl, a purified version of EPA (20:5n–3) (19). Over 90% of participants in these studies, however, were white. The risk of developing AF is not evenly distributed among the various racial and ethnic groups. Despite underrepresented racial and ethnic groups experiencing a higher burden of traditional AF risk factors and a poorer AF-associated outcome profile, a paradox exists in that the overall incidence and prevalence of AF in these groups are nearly half of what is observed for whites (20, 21). Continued investigation into identifying additional risk factors is important to improve our understanding of not only the mechanisms that underlie AF but also the differences in AF incidence observed across various racial and ethnic groups.

The purpose of this study is to evaluate associations of circulating concentrations of both n–3 and n–6 PUFAs with the risk of incident AF in the Multi-Ethnic Study of Atherosclerosis (MESA).

Methods

Study participants

MESA is a prospective cohort study designed to investigate risk factors associated with subclinical cardiovascular disease across race/ethnicities. MESA recruited, in 6 US study centers, 6814 male and female white, black, Hispanic, and Chinese-American participants aged 45–84 y at baseline (2000–2002) who were free of clinical cardiovascular disease, including AF, at that time (22). There were 585 participants excluded from the present analysis (missing PUFA measurements, $n = 306$; missing follow-up AF data, $n = 5$; missing covariate data, $n = 274$). Protocols were approved by local institutional review boards, and all participants gave written informed consent.

Plasma n–3 and n–6 PUFA measurements

α-Linolenic acid (ALA; 18:3n–3), EPA, docosapentaenoic acid (DPA; 22:5n–3), DHA (22:6n–3), linoleic acid (LA; 18:2n–6), and arachidonic acid (AA; 20:4n–6) were measured at baseline. The band of phospholipids was then harvested and individual phospholipid fatty acids were extracted from EDTA plasma using a chloroform/methanol extraction method (23) and subsequently separated from cholesterol esters, triglycerides, and free fatty acids by TLC. Individual phospholipid fatty acids were derivatized to methyl esters and detected by GC flame ionization. Phospholipid fatty acid measurements were expressed as a percentage of total fatty acids. Our primary focus of interest was n–3 PUFAs (ALA; EPA; DPA; DHA; EPA + DPA + DHA) and n–6 PUFAs (LA; AA; AA + LA). For each fatty acid, the limit of detection was 0.03%. Interassay CVs were 13.5% (ALA), 7.6% (EPA), 8.3% (DPA), 8.5% (DHA), 6.8% (LA), and 7.4% (AA).

AF

After the baseline examination, participants were followed up every 9–12 mo by telephone to obtain information on hospitalizations and medical records, including discharge diagnoses. Incident AF through December 2014 was identified from study electrocardiograms verified for AF at Visit 5 (2010–2012), International Classification of Diseases-9 hospital discharge diagnoses consistent with AF (427.31 or 427.32), and, for participants enrolled in fee-for-service Medicare, inpatient and outpatient AF claims data.

Covariates

Standardized questionnaires were used at baseline to obtain demographic information, level of education, annual household income, physical activity, smoking history, alcohol use, and medication usage, including antihypertensive and antidiabetic use. BMI was calculated as kg/m^2. Three separate systolic and diastolic blood pressure measurements were taken in seated participants at rest, with the last 2 measurements being averaged for analysis. Physical activity was recorded as participant-reported number of intentional exercise metabolic equivalent-minutes per week. Cigarette smoking was calculated in pack-years and also defined as current, former, or never. Total and HDL cholesterol, triglycerides, and glucose were measured from fasting blood samples. LDL cholesterol was calculated by the Friedewald equation in those with triglyceride concentrations <400 mg/dL. Diabetes was defined as a fasting glucose concentration >125 mg/dL or use of antidiabetic medications.

Statistical analysis

Descriptive statistics were reported for baseline variables according to *1*) total n–3 PUFA concentrations, *2*) total n–6 PUFA concentrations, and *3*) race/ethnicity. Pearson correlation coefficients were calculated between the different n–3 and n–6 PUFAs. We used Cox regression models to estimate the HRs and 95% CIs of risk of incident AF according to each circulating PUFA, with time at risk until the first AF event, death, or last follow-up. Associations with each circulating fatty acid were evaluated in quartiles and continuously per SD increment. The linear relation between continuous PUFA measures and risk of AF was examined using splines and showed no violation. Models were adjusted for age, race/ethnicity, sex, education, income, site, height, BMI, cigarette smoking, diabetes, systolic blood pressure, diastolic blood pressure, antihypertensive medication, physical activity, total cholesterol, HDL cholesterol, and alcohol consumption. The covariates were modeled (continuous compared with categorical) as described in **Tables 1** and **2**. Effect modification by race/ethnicity was evaluated by stratifying and comparing models with and without interaction terms. Statistical significance was defined as $P < 0.05$. Stata version 15.1 (StataCorp LLC) was used for all analyses. The proportional hazard assumption was examined on the basis of Schoenfeld residuals after the Cox regression was fitted. There was no evidence of violation of the proportional hazard assumption in our data. The functional form (linearity) of continuous fatty acid measures was examined using Martingale residuals and the smoothing technique.

Results

A total of 6229 participants were included in the prospective analysis (mean age ± SD: 61.6 ± 10 y; 53% female; 39% white, 27% black, 22% Hispanic, and 12% Chinese American). Eight hundred and thirteen (13%) participants developed AF (incidence rate per 1000 person-years = 11.6; person-years of follow-up = 70,205 y) over a median follow-up of 12.9 y. Baseline characteristics for included participants according to total n–3 PUFA and n–6 PUFA concentrations are presented in Tables 1 and 2, respectively. Participants with higher total n–3 PUFA concentrations were older, reported a higher level of education and income, and were more likely to drink alcohol (Table 1). Opposite trends were noted in these baseline characteristics for participants with higher total n–6 PUFA concentrations (Table 2). In addition, participants with higher total n–3 PUFA concentrations were less likely to be Hispanic, whereas those with higher total n–6 PUFA concentrations were

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Abbreviations used: AA, arachidonic acid; AF, atrial fibrillation; ALA, α-linolenic acid; DPA, docosapentaenoic acid; LA, linoleic acid; MESA, Multi-Ethnic Study of Atherosclerosis; REDUCE-IT, Reduction of Cardiovascular Events with Icosapent Ethyl–Intervention Trial.

TABLE 1 Multi-Ethnic Study of Atherosclerosis participant baseline characteristics according to plasma n–3 PUFA concentrations[1]

Characteristic	Quartile 1 (0.51–1.46)	Quartile 2 (1.46–1.77)	Quartile 3 (1.77–2.21)	Quartile 4 (2.21–15.97)	*P* value
n	1568	1545	1558	1558	
Age, y	61 ± 10	62 ± 10	62 ± 10	63 ± 10	0.002
Male	755 (48.2)	753 (48.7)	734 (47.1)	700 (44.9)	0.15
Race/ethnicity					
White	543 (34.6)	605 (39.2)	641 (41.1)	633 (40.6)	<0.001
Chinese-American	141 (9.0)	142 (9.2)	170 (10.9)	326 (20.9)	
Black	343 (21.9)	422 (27.3)	454 (29.1)	411 (26.4)	
Hispanic	541 (34.5)	376 (24.3)	293 (18.8)	188 (12.1)	
Education					
High school or less	660 (42.1)	589 (38.1)	530 (34.0)	445 (28.6)	<0.001
Some college	467 (29.8)	457 (29.6)	440 (28.2)	407 (26.1)	
College or more	441 (28.1)	499 (32.3)	588 (37.7)	706 (45.3)	
Income, $					
<25,000	582 (37.1)	504 (32.6)	456 (29.3)	410 (26.3)	<0.001
25,000–49,999	462 (29.5)	463 (30.0)	451 (28.9)	418 (26.8)	
50,000–74,999	262 (16.7)	263 (17.0)	286 (18.4)	253 (16.2)	
≥75,000	262 (16.7)	315 (20.4)	365 (23.4)	477 (30.6)	
Height, cm	166 ± 10	167 ± 10	167 ± 10	166 ± 9.7	<0.001
BMI, kg/m^2	29 ± 5.6	29 ± 5.7	28 ± 5.5	27 ± 4.9	<0.001
Smoking status					
Never	753 (48.0)	726 (47.0)	808 (51.9)	862 (55.3)	<0.001
Former	573 (36.5)	585 (37.9)	551 (35.4)	560 (35.9)	
Current	242 (15.4)	234 (15.1)	199 (12.8)	136 (8.7)	
Pack-years smoking	13 ± 23	12 ± 26	11 ± 21	9.3 ± 19	<0.001
Alcohol consumption					
Never	326 (20.8)	293 (19.1)	312 (20.1)	335 (21.6)	<0.001
Former	451 (28.8)	376 (24.5)	350 (22.5)	279 (18.0)	
Current	788 (50.4)	866 (56.4)	892 (57.4)	937 (60.4)	
Physical activity, MET-min/wk	5704 ± 5984	5982 ± 5944	6163 ± 5836	5465 ± 6041	0.006
Diabetes	215 (13.7)	188 (12.2)	191 (12.3)	163 (10.5)	0.051
SBP, mm Hg	126 ± 22	126 ± 21	127 ± 22	125 ± 21	0.25
DBP, mm Hg	72 ± 10	72 ± 10	72 ± 10	72 ± 10	0.42
Plasma total cholesterol, mg/dL	191 ± 37	195 ± 36	196 ± 35	196 ± 34	<0.001
Plasma HDL cholesterol, mg/dL	49 ± 14	49 ± 14	52 ± 15	53 ± 15	<0.001
Plasma triglycerides, mg/dL	135 ± 88	137 ± 105	133 ± 84	123 ± 74	<0.001
Antihypertensive use	538 (34.3)	571 (37.0)	566 (36.3)	572 (36.7)	0.40

[1] $n = 6229$. Values are mean ± SD or *n* (%) unless otherwise indicated. n–3 PUFA concentrations are the sum of DHA, n–3 docosapentaenoic acid, and EPA. DBP, diastolic blood pressure; MET, metabolic equivalent; SBP, systolic blood pressure.

less likely to be white. **Supplemental Table 1** reports baseline characteristics according to race/ethnicity. **Supplemental Table 2** shows correlations between each of the measured n–3 and n–6 PUFAs.

In adjusted analyses, higher circulating concentrations of total n–3 PUFAs were not found to be associated with a reduced risk of AF development (**Table 3**). When each individual n–3 PUFA was examined separately, although some significant interquartile associations were observed, results were similar (Table 3).

Table 4 shows the risk of incident AF according to baseline n–6 PUFA concentrations. Higher overall concentrations of n–6 PUFAs (LA + AA) were associated with a 7% reduced risk of incident AF in adjusted analyses. When each individual n–6 PUFA was examined separately, AA was significantly associated with lower risk of AF, with a 29% and 21% lower risk in the third and fourth quartiles, respectively, than in the lowest. When evaluated continuously, each SD increment in AA was associated with an 11% lower risk of AF. No significant association was observed for LA concentrations and risk of developing AF.

Table 5 presents race/ethnicity-stratified analyses for each of the n–3 and n–6 PUFAs. Differing associations with risk of incident AF were noted across race/ethnicity for circulating concentrations of EPA and DHA, with *P* values for interaction of 0.031 and 0.016, respectively. When comparing the 2 extreme groups of fatty acid concentrations (fourth compared with first quartile), higher concentrations of EPA or DHA were not associated with AF risk in whites or Chinese Americans but were associated with a decreased risk in blacks (EPA HR: 0.62; 95% CI: 0.39, 0.99 and DHA HR: 0.47; 95% CI: 0.27, 0.79) and Hispanics (DHA HR: 0.52; 95% CI: 0.27, 0.98).

Discussion

In a multiethnic cohort of individuals, higher plasma concentrations of n–6 PUFAs, particularly AA, were associated with a

TABLE 2 Multi-Ethnic Study of Atherosclerosis participant baseline characteristics according to plasma n–6 PUFA concentrations[1]

Characteristic	Quartile 1 (8.23–29.95)	Quartile 2 (29.95–32.03)	Quartile 3 (32.03–34.00)	Quartile 4 (34.00–47.30)	*P* value
n	1562	1557	1545	1565	
Age, y	63 ± 10	62 ± 10	62 ± 10	60 ± 10	<0.001
Male	685 (43.9)	694 (44.6)	738 (47.8)	825 (52.7)	<0.001
Race/ethnicity					
White	799 (51.2)	653 (41.9)	556 (36.0)	414 (26.5)	<0.001
Chinese-American	102 (6.5)	128 (8.2)	195 (12.6)	354 (22.6)	
Black	361 (23.1)	412 (26.5)	428 (27.7)	429 (27.4)	
Hispanic	300 (19.2)	364 (23.4)	366 (23.7)	368 (23.5)	
Education					
High school or less	512 (32.8)	559 (35.9)	555 (35.9)	598 (38.2)	0.002
Some college	425 (27.2)	449 (28.8)	468 (30.3)	429 (27.4)	
College or more	625 (40.0)	549 (35.3)	522 (33.8)	538 (34.4)	
Income, $					
<25,000	440 (28.2)	491 (31.5)	488 (31.6)	533 (34.1)	0.018
25,000–49,999	446 (28.6)	462 (29.7)	448 (29.0)	438 (28.0)	
50,000–74,999	269 (17.2)	269 (17.3)	264 (17.1)	262 (16.7)	
≥75,000	407 (26.1)	335 (21.5)	345 (22.3)	332 (21.2)	
Height, cm	166 ± 9.9	166 ± 10	166 ± 10	167 ± 9.8	0.68
BMI, kg/m^2	28 ± 5.5	29 ± 5.5	28 ± 5.7	27 ± 5.0	<0.001
Smoking status					
Never	780 (49.9)	782 (50.2)	789 (51.1)	798 (51.0)	0.37
Former	600 (38.4)	563 (36.2)	557 (36.1)	549 (35.1)	
Current	182 (11.7)	212 (13.6)	199 (12.9)	218 (13.9)	
Pack-years smoking	13 ± 28	11 ± 21	11 ± 21	9.9 ± 19	0.002
Alcohol consumption					
Never	266 (17.1)	331 (21.3)	316 (20.5)	353 (22.7)	<0.001
Former	357 (22.9)	308 (19.8)	394 (25.6)	397 (25.5)	
Current	933 (60.0)	914 (58.9)	829 (53.9)	807 (51.8)	
Physical activity, MET-min/wk	5567 ± 5827	5947 ± 6209	5790 ± 5879	6007 ± 5899	0.17
Diabetes	155 (9.9)	187 (12.0)	204 (13.2)	211 (13.5)	0.009
SBP, mm Hg	127 ± 21	127 ± 22	127 ± 22	124 ± 21	<0.001
DBP, mm Hg	72 ± 10	72 ± 10	72 ± 10	72 ± 9.9	0.74
Plasma total cholesterol, mg/dL	195 ± 36	197 ± 35	194 ± 35	191 ± 36	<0.001
Plasma HDL cholesterol, mg/dL	51 ± 16	50 ± 14	51 ± 14	51 ± 15	0.11
Plasma triglycerides, mg/dL	138 ± 83	137 ± 76	132 ± 89	122 ± 104	<0.001
Antihypertensive use	589 (37.7)	565 (36.3)	609 (39.4)	484 (30.9)	<0.001

[1] *n* = 6229. Values are mean ± SD or *n* (%) unless otherwise indicated. n–6 PUFA concentrations are the sum of arachidonic acid and linoleic acid. DBP, diastolic blood pressure; MET, metabolic equivalent; SBP, systolic blood pressure.

reduced risk of AF. Important differences in AF risk were also noted across race/ethnicity for the n–3 PUFAs EPA and DHA.

The mechanisms by which n–6 PUFAs can affect the cardiovascular system are not clear. LA, the dietary source of n–6 PUFAs, has favorable effects on inflammation, blood pressure, and body composition (24–26). The conversion of LA into AA, however, is reported to give rise to a range of eicosanoids considered to be proinflammatory and prothrombotic (11–13). The level of conversion of LA to AA in humans in stable isotope studies and actual effects of increasing dietary LA on plasma and adipose tissue AA concentrations in trials appear limited, however (24, 27, 28). In addition, other studies suggest AA is also the precursor to key anti-inflammatory metabolites and other mediators that actively resolve inflammation (14). It also gives rise to prostacyclin, a potent antiaggregatory and vasodilatory molecule (29). A large recent meta-analysis of 30 cohort studies found that higher circulating concentrations of LA and possibly AA were associated with lower risk of major cardiovascular events (30).

Prior studies evaluating the relation between n–6 PUFAs and incident AF have not demonstrated an association. The Danish Diet, Cancer, and Health cohort assessed dietary intakes of LA and AA in >50,000 participants at baseline and found that neither were associated with AF risk over a median follow-up time of 13.5 y (31). LA is an essential fatty acid not synthesized by humans and is the main dietary n–6 PUFA. In contrast, the dietary intake of AA is limited and plasma concentrations are largely dependent upon the endogenous conversion of LA into AA. Prior studies evaluating the correlation between circulating and dietary n–6 PUFAs have found a weakly significant relation (32–35). In a prior analysis of 2593 participants in this same MESA cohort, correlations for circulating and dietary n–6 PUFAs were 0.05 for AA and 0.13 for LA, whereas correlations for the n–3 PUFAs EPA and DHA were 0.34 and 0.43, respectively (32). Similarly, in a smaller French study of 257 individuals, circulating and dietary intakes of AA, LA, EPA, and DHA were all significantly correlated with their respective percentages in plasma total fatty acids but only

TABLE 3 HRs of incident atrial fibrillation according to baseline n–3 PUFA concentrations in Multi-Ethnic Study of Atherosclerosis participants[1]

	Quartiles of plasma phospholipid FAs[2]				
PUFA	Quartile 1	Quartile 2	Quartile 3	Quartile 4	SD increment[3]
Phospholipid ALA, % total FA (median = 0.16)					
n cases/total	182/1563	219/1572	215/1538	197/1556	813/6229
HR (95% CI)	1 (referent)	1.19 (0.98, 1.46)	1.10 (0.90, 1.35)	1.12 (0.91, 1.38)	1.00 (0.94, 1.07)
Phospholipid EPA, % total FA (median = 0.67)					
n cases/total	197/1567	187/1545	208/1558	221/1559	813/6229
HR (95% CI)	1 (referent)	0.88 (0.72, 1.08)	0.95 (0.78, 1.16)	0.93 (0.76, 1.15)	1.03 (0.96, 1.10)
Phospholipid n–3 DPA, % total FA (median = 0.90)					
n cases/total	227/1563	196/1562	180/1548	210/1556	813/6229
HR (95% CI)	1 (referent)	0.83 (0.68, 1.00)	0.78 (0.64, 0.95)[4]	0.88 (0.72, 1.06)	0.96 (0.89, 1.03)
Phospholipid DHA, % total FA (median = 3.58)					
n cases/total	200/1567	200/1561	219/1547	194/1554	813/6229
HR (95% CI)	1 (referent)	0.81 (0.66, 0.99)[4]	0.89 (0.71, 1.10)	0.78 (0.62, 0.98)[4]	0.95 (0.87, 1.03)
Phospholipid EPA + DHA + n–3 DPA, % total FA (median = 1.77)					
n cases/total	208/1568	190/1545	205/1558	210/1558	813/6229
HR (95% CI)	1 (referent)	0.88 (0.72, 1.07)	0.90 (0.74, 1.10)	0.88 (0.72, 1.08)	0.98 (0.90, 1.06)

[1] Cox proportional hazard model adjusted for age, race/ethnicity, sex, education, income, site, height, BMI, cigarette smoking, diabetes, blood pressure, antihypertensive medication, physical activity, and alcohol consumption. ALA, α-linolenic acid; DPA, docosapentaenoic acid; FA, fatty acid.
[2] Quartile ranges were as follows: ALA: first, 0.03–0.12; second, 0.12–0.16; third, 0.16–0.20; fourth, 0.20–2.54; EPA: first, 0.09–0.48; second, 0.48–0.67; third, 0.67–0.99; fourth, 0.99–14.46; n–3 DPA: first, 0.04–0.77; second, 0.77–0.90; third, 0.90–1.05; fourth, 1.05–2.42; DHA: first, 0.57–2.71; second, 2.71–3.58; third, 3.58–4.68; fourth, 4.68–10.56; EPA + DHA + n–3 DPA: first, 0.51–1.46; second, 1.46–1.77; third, 1.77–2.21; fourth, 2.21–15.97.
[3] SD increment = 0.08 (phospholipid ALA), 0.79 (phospholipid EPA), 0.23 (phospholipid n–3 DPA), 1.48 (phospholipid DHA), and 0.93 (phospholipid DHA + n–3 DPA + EPA).
[4] $0.01 < P < 0.05$.

mildly (coefficients between 0.16 and 0.28) (33). Although this may explain the difference in results seen here, more cohort studies are needed to better discern whether a true difference exists.

A recent Mendelian randomization analysis including >500,000 individuals, however, evaluated whether genetic predisposition to higher concentrations of the n–3 and n–6 PUFAs was associated with AF risk and also found no relation (18). The risk of developing AF is not evenly distributed among the various racial and ethnic groups and this study was comprised of an almost exclusively white population. Although race/ethnicity did not significantly influence the relation of AA with incident AF in our study, power was limited and the HRs for black and Hispanic participants were considerably lower than for whites.

Prior prospective studies evaluating the relation of circulating n–3 PUFAs and incident AF were limited to predominantly white populations (15–17). The Kuopio Ischemic Heart Disease Risk Factor Study and the Cardiovascular Health Study found that participants in the highest quartile of DHA concentrations were at a 42% and a 23% reduced risk of incident AF compared with participants in the lowest quartile, respectively (15, 16). Unlike these previous studies, we did not find a significantly decreased AF risk for higher overall or individual n–3 PUFA concentrations.

Our study builds upon the previous n–3 PUFA literature by evaluating associations in a multiethnic cohort. We observed significant differences across race/ethnicity for EPA and DHA. The reasons for such differences are unclear. Heterogeneous associations across races/ethnicities with respect to n–3 PUFAs

TABLE 4 HRs of incident atrial fibrillation according to baseline n–6 PUFA concentrations in Multi-Ethnic Study of Atherosclerosis participants[1]

	Quartiles of plasma phospholipid FAs[2]				
PUFA	Quartile 1	Quartile 2	Quartile 3	Quartile 4	SD increment[3]
Phospholipid LA, % total FA (median = 20.1)					
n cases/total	221/1544	188/1545	201/1568	203/1572	813/6229
HR (95% CI)	1 (referent)	0.87 (0.71, 1.06)	0.95 (0.78, 1.16)	1.04 (0.84, 1.29)	1.02 (0.94, 1.10)
Phospholipid AA, % total FA (median = 11.55)					
n cases/total	229/1577	238/1562	169/1565	177/1525	813/6229
HR (95% CI)	1 (referent)	1.03 (0.86, 1.24)	0.71 (0.58, 0.87)[4]	0.79 (0.64, 0.98)[5]	0.89 (0.82, 0.96)[4]
Phospholipid LA + AA, % total FA (median = 32.03)					
n cases/total	234/1562	214/1557	185/1545	180/1565	813/6229
HR (95% CI)	1 (referent)	0.98 (0.81, 1.18)	0.88 (0.72, 1.07)	0.89 (0.72, 1.09)	0.93 (0.87, 1.00)

[1] Cox proportional hazard model adjusted for age, race/ethnicity, sex, education, income, site, height, BMI, cigarette smoking, diabetes, blood pressure, antihypertensive medication, physical activity, and alcohol consumption. AA, arachidonic acid; FA, fatty acid; LA, linoleic acid.
[2] Quartile ranges: LA: first, 5.66–18.00; second, 18.00–20.10; third, 20.10–22.33; fourth, 22.33–36.13; AA: first, 1.71–9.84; second, 9.84–11.53; third, 11.53–13.32; fourth, 13.32–22.17; LA + AA: first, 8.23–29.95; second, 29.95–32.03; third, 32.03–34.00; fourth, 34.00–47.30.
[3] SD increment = 3.30 (phospholipid LA), 2.54 (phospholipid AA), and 3.27 (phospholipid AA + LA).
[4] $0.001 < P < 0.01$.
[5] $0.01 < P < 0.05$.

TABLE 5 HRs of incident atrial fibrillation according to baseline n–3 and n–6 PUFA concentrations (fourth compared with first quartile) in Multi-Ethnic Study of Atherosclerosis participants stratified by race/ethnicity[1]

PUFA	White	Chinese American	Black	Hispanic	*P*-interaction
Phospholipid ALA					
n cases/total	390/2422	105/779	171/1630	147/1398	
HR (95% CI)	1.20 (0.87, 1.65)	1.22 (0.67, 2.23)	1.09 (0.69, 1.73)	1.09 (0.68, 1.75)	0.82
Phospholipid EPA					
n cases/total	390/2422	105/779	171/1630	147/1398	
HR (95% CI)	1.02 (0.74, 1.40)	1.11 (0.61, 2.03)	0.62 (0.39, 0.99)[2]	0.94 (0.55, 1.61)	0.031
Phospholipid n–3 DPA					
n cases/total	390/2422	105/779	171/1630	147/1398	
HR (95% CI)	0.81 (0.60, 1.09)	1.08 (0.63, 1.84)	0.86 (0.57, 1.30)	0.69 (0.41, 1.16)	0.10
Phospholipid n–3 DHA					
n cases/total	390/2422	105/779	171/1630	147/1398	
HR (95% CI)	1.02 (0.73, 1.41)	0.53 (0.18, 1.51)	0.47 (0.27, 0.79)[3]	0.52 (0.27, 0.98)[2]	0.016
Phospholipid LA					
n cases/total	390/2422	105/779	171/1630	147/1398	
HR (95% CI)	0.99 (0.72, 1.35)	0.70 (0.31, 1.59)	0.91 (0.52, 1.58)	1.04 (0.64, 1.69)	0.70
Phospholipid AA					
n cases/total	390/2422	105/779	171/1630	147/1398	
HR (95% CI)	0.90 (0.66, 1.22)	0.92 (0.47, 1.79)	0.59 (0.36, 0.97)[2]	0.71 (0.43, 1.20)	0.55

[1] Cox proportional hazard model adjusted for age, sex, education, income, site, height, BMI, cigarette smoking, diabetes, blood pressure, antihypertensive medication, physical activity, and alcohol consumption. AA, arachidonic acid; ALA, α-linolenic acid; DPA, docosapentaenoic acid; LA, linoleic acid.
[2] $0.01 < P < 0.05$.
[3] $0.001 < P < 0.01$.

have been reported in the MESA cohort before. Circulating DPA concentrations were inversely associated with cardiovascular disease in whites and Chinese Americans, but not for other races/ethnicities (32). Genetic variants of enzymes involved in the metabolic conversion of n–3 DPA have been associated with altered inflammatory responses and risk of coronary heart disease (36, 37). Mean concentrations of both EPA and DHA, however, do not differ across race/ethnicity in MESA, with the exception of Chinese participants having significantly higher DHA concentrations than Hispanic participants (38). More importantly, associations for mean concentrations of these fatty acids with biomarkers of inflammation and endothelial function were not modified by race/ethnicity (38). Whether race/ethnic-specific genetic or biochemical differences in n–3 PUFA metabolism could also explain the observed heterogeneity by race/ethnicity in the present study still requires more investigation.

The findings reported here are also important in the context of the REDUCE-IT trial which found that individuals randomly assigned to icosapent ethyl, a highly purified and stable EPA ester, were at significantly increased risk of hospitalized AF. Over a median follow-up of nearly 5 y, 1 more individual out of every 100 randomly assigned to 4 g icosapent ethyl experienced AF than the same number assigned to placebo (14). The REDUCE-IT trial participants were overwhelmingly white (90%) and it would be of interest to determine whether race plays a role in AF risk for individuals on very-high-dose EPA. Prior studies have also demonstrated that increased supplemental EPA is associated with a reduction in overall n–6 PUFA and AA concentrations (39–42). It is possible that AA concentrations observed in the lowest quartile of study participants were low enough that the ability of AA to maintain eicosanoid functions, particularly those related to immunity, vasodilation, and inflammation, was compromised, which then led to an increased susceptibility to AF.

Our study has limitations. Although we used physician claims for those in fee-for-service Medicare, our method for AF detection was not sensitive to cases of paroxysmal AF that either were asymptomatic or did not require hospitalization, and these cases were missed. Because no information regarding symptom presence or the paroxysmal compared with permanent nature of AF was available, we could not determine whether specific PUFAs may have had stronger associations with certain AF subtypes. Imprecision in the measurement of circulating PUFAs may have resulted in exposure misclassification, attenuating measures of association toward the null. Thus, our findings could have underestimated the true associations. Power for the analyses stratified by race/ethnicity was limited, particularly for Chinese-American participants, and the presence of additional significant associations cannot be excluded based on these results. Finally, this is an observational study and we cannot exclude residual confounding, despite adjusting for potential covariates.

In conclusion, higher concentrations of long-chain n–6 PUFAs, particularly AA, were associated with a lower incident AF risk. In addition, higher circulating concentrations of EPA and DHA were not associated with AF risk in whites or Chinese Americans but were associated with a decreased risk in blacks and Hispanics (DHA only). Studies in other prospective cohorts are needed to corroborate associations found for AA and further research is needed to better understand potential racial/ethnic differences.

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aspects of the work ensuring integrity and accuracy, and read and approved the final manuscript.

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