HHS Public Access

Author manuscript

Arterioscler Thromb Vasc Biol. Author manuscript; available in PMC 2019 March 01.

Published in final edited form as:

Arterioscler Thromb Vasc Biol. 2018 March ; 38(3): 653–659. doi:10.1161/ATVBAHA.117.310366.

Plasma n-3 and n-6 fatty acids are differentially related to carotid plaque and its progression: the Multi-Ethnic Study of Atherosclerosis

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Abstract

Objective—Omega-3 (n-3) fatty acids (FAs) have long been considered healthful dietary components, yet recent clinical trials have questioned their cardiovascular benefits. By contrast, the omega-6 (n-6) FAs have been considered harmful, pro-atherogenic macronutrients despite an absence of empirical evidence supporting this hypothesis. We aimed to determine whether plasma n-3 and n-6 FAs are related to risk of carotid plaque and its progression in 3,327 participants of the Multi-Ethnic Study of Atherosclerosis.

Approach and Results—Carotid plaque was assessed using ultrasonography at baseline and following a median period of 9.5 years. Plasma phospholipid n-3 and n-6 FAs were determined using gas chromatography-flame ionization detection. Relative risk regression analyses assessed the relations of FAs with the presence or progression of carotid plaque adjusted for typical cardiovascular disease risk factors. At baseline, it was found that participants in the 4th quartile of n-3 docosahexaenoic acid showed a 9% lower risk of carotid plaque (p=0.05) while those in the 2nd quartile of n-3 alpha-linolenic acid showed an 11% greater risk compared to respective referent quartiles (p=0.02). In prospective analyses, individuals in the top quartile of

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DISCLOSURES

The authors have no competing interests to disclose.

docosahexaenoic acid showed a 12% lower risk of carotid plaque progression over 9.5 years compared to those in the referent quartile (p=0.002). No significant relations were observed among n-6 FAs and plaque outcomes. No significant race/ethnicity interactions were found.

Conclusion—These findings support docosahexaenoic acid as an atheroprotective macronutrient, while null findings for n-6 FAs challenge the view that they promote atherosclerosis.

Keywords

fatty acids; atherosclerosis; plaque; risk factors

Subject code

Epidemiology; Cardiovascular Disease; Risk Factors; Race and Ethnicity

INTRODUCTION

Atherosclerosis is a pathophysiological process involving an insult to the vascular endothelium followed by inflammation, endothelial activation, oxidative stress, and lipid accumulation in the arterial wall resulting in an atherosclerotic plaque and vessel occlusion. Atherogenesis has been shown to occur as early as adolescence (1), and it is therefore imperative that modifiable risk factors be identified and controlled at a young age. Among these, long-chain omega-3 (n-3) and omega-6 (n-6) polyunsaturated fatty acids (FAs) have been respectively characterized as anti- and pro-atherogenic dietary components, yet findings among studies are inconsistent, and no large multi-ethnic prospective study has examined these FAs in relation to subclinical atherosclerosis outcomes.

The n-3 FAs are a well-studied class of macronutrients considered to be atheroprotective and include the plant-derived alpha-linolenic acid (ALA) and fish oil eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). Their plasma concentrations have been shown to be inversely associated with inflammation and endothelial activation (2–7) and have been associated with lower risk of cardiovascular (CV) outcomes in cohort studies (8,9). And yet, null results from recent meta-analyses and large randomized controlled trials (10–12) have cast uncertainty as to the CV health benefits of n-3 FAs.

In contrast to the n-3 FAs, the n-6's are not as well-studied but have previously been suggested to be pro-inflammatory, pro-atherogenic compounds (13). This view likely originated with the observation that the essential n-6 FA, linoleic acid (LA) can be converted to arachidonic acid (AA)—a substrate for eicosanoid lipid mediators that promote vascular disease (13,14). However, this presumption has been shifting (15), and it has since been shown that both LA and AA may have CV benefits (5, 16–19). By contrast, the n-6 FAs gamma-linolenic acid (GLA) and dihomo-gamma-linolenic acid (DGLA)—primarily synthesized de-novo from LA—have been associated with inflammation and endothelial activation (5,19), but it is unknown whether higher levels have implications for atherosclerosis. No large prospective cohort study has examined plasma n-6 FAs and atherosclerosis outcomes to date.

The current study of 3,283 Multi-Ethnic Study of Atherosclerosis (MESA) participants without apparent cardiovascular disease at baseline examined whether objectively measured plasma levels of n-3 or n-6 fatty acids were associated with the presence of carotid plaque or occurrence of plaque progression over a median 9.5 year study period and whether race/ethnicity modified any observed associations.

MATERIALS AND METHODS

Materials and Methods are available in the online-only Data Supplement.

RESULTS

Demographic and clinical characteristics of 3,283 MESA participants are presented in Table 1, stratified by the presence of carotid plaque at baseline. Compared to individuals with carotid plaque at baseline, those without carotid plaque had a lower mean age ($p<0.001$), were more likely to be female ($p=0.003$) and more likely to have never smoked ($p<0.001$). Those without carotid plaque additionally had lower mean systolic blood pressure ($p<0.001$), were less likely to have diabetes ($p<0.001$), had lower levels of total cholesterol ($p<0.001$) and greater levels of plasma LA ($p<0.001$) and DHA ($p=0.03$).

Characteristics of MESA participants were stratified by the occurrence of carotid plaque progression in Table 2. Significant differences were found between those who exhibited plaque progression and those who did not over the median 9.5-year study period. Individuals in whom plaque progression did not occur had a lower mean age ($p<0.001$), BMI ($p=0.016$), systolic blood pressure ($p<0.001$), total cholesterol ($p=0.04$), had fewer current and former smokers ($p<0.001$), and fewer individuals taking medication for hypertension ($p<0.001$) or lipids ($p<0.001$). In addition, this group was found to have greater levels of HDL-C ($p=0.002$), plasma DHA ($p=0.005$) and plasma LA ($p=0.003$) compared to those who exhibited plaque progression.

Risk of carotid plaque at baseline was evaluated in 3,314 MESA participants and is presented across quartiles of plasma n-3 and n-6 FAs in Table 3. Individuals in the 2nd quartile of the n-3 ALA were found to have a significantly 11% greater risk of having plaque than those in the referent ($p=0.02$) though no significant relations were observed in 3rd or 4th quartiles. Participants in the 4th quartiles of DHA and in n-3/n-6 ratio were found to have 9% and 17% lower risk of carotid plaque compared to referent quartiles. Additional analyses of highly unsaturated n-6 FAs docosapentaenoic acid (n-6 DPA, 22:5) and adrenic acid (22:4) were conducted, and no relations with carotid plaque at baseline were found. Interaction analysis revealed no modification effect of race/ethnicity on associations between fatty acids and baseline carotid plaque.

Risk of carotid plaque progression in 3,283 MESA participants is presented across quartiles of plasma n-3 and n-6 FAs in Table 4. Carotid plaque progression was treated as a logistical variable (0 or 1). Individuals in the top quartile of DHA showed a 12% lower risk of carotid plaque progression than those in the referent ($p=0.002$). No significant relations of n-6 FAs DPA and adrenic acid with carotid plaque progression were observed. Interaction analysis

revealed no modification effect of race/ethnicity on associations between fatty acids and carotid plaque progression.

Secondary analyses of n-3 and n-6 exposure variables with carotid plaque outcomes were conducted (Supplemental Table I). Those in the top quartile of the n-3/n-6 ratio were found to be at significantly lower risk of having carotid plaque at baseline (p=0.03), while those in the top quartiles of EPA+DHA and total n-3 FAs were found to be at lower risk of plaque progression (p=0.01 and p=0.02, respectively). No significant relations between total n-6 FAs and either the presence or progression of carotid plaque were observed.

DISCUSSION

In this prospective study of 3,314 MESA participants, individuals in the top quartile of plasma DHA were found to have a 9% lower risk of carotid plaque at baseline and 12% lower risk of carotid plaque progression over the 9.5-year follow-up period compared to referent quartiles. These findings support previous evidence that DHA promotes CV health. By contrast, individuals in the 2nd quartile of ALA were found to have an 11% greater risk for carotid plaque compared to the referent quartile at baseline, but no significant risk was observed for those in subsequent quartiles and no associations were observed in prospective analyses. The null findings for plasma n-6 FAs with carotid atherosclerosis outcomes dispute the hypothesis that they are pro-atherogenic macronutrients. Additional secondary analyses of plasma n-3 and n-6 exposure variables were conducted. Plasma EPA+DHA, total n-3 FAs, and the ratio of n-3 to n-6 FAs showed inverse associations with plaque outcomes similar to those of DHA alone (although incrementally weaker). Total n-6 FA levels were not associated with the presence or progression of carotid plaque.

Fish oil n-3 FAs

Fish oil FAs have been shown to have numerous CV benefits that would be expected to constrain atherogenesis including, but not limited to, reducing elevated triglyceride levels, modestly raising HDL-C (20), enhancing endothelial function (21), and lowering blood pressure (22). More recently, EPA and DHA have been shown to actively resolve inflammation through metabolism in to potent lipid signaling compounds (23–25) and may also facilitate efferocytosis (26,27)—i.e., the process by which apoptotic cells are removed by phagocytic cell, critical in suppressing necrotic plaque formation (28). Consistent with these anti-atherogenic effects, observational studies have shown that higher levels of EPA and/or DHA are associated with lower prevalence of coronary and carotid atherosclerosis as determined by angiography (29) and ultrasound (30,31), though null findings have also been reported (32–34).

Our results indicate that individuals in the top quartiles of plasma DHA (>4.8% of total phospholipids), but not EPA, have lower risks of showing atherosclerotic plaque or experiencing plaque progression over an approximate 10-year period. The magnitude of associations for DHA (9% lower risks for plaque prevalence and 12% for plaque progression) suggests a modest to moderate preventive influence on plaque outcomes when compared to other well-documented risk factors. For example, in this sample, current cigarette smokers showed a 38% greater risk of plaque progression compared to non-

smokers (p<0.001; data not shown). It may be speculated that the comparatively lower strength of associations for DHA may have contributed to the mixed findings among previous studies, particularly in those with shorter follow-up periods.

The null findings for EPA were unexpected and counter to the above observational studies as well as intervention studies that have shown that EPA supplementation reduces atherosclerosis (35–38). It may be speculated that the relatively low EPA levels in MESA participants may have contributed to the null results. This is supported by a cross-sectional study that examined associations of serum EPA with carotid atherosclerosis in White Americans, Japanese Americans, and native Japanese (34). High serum EPA levels were found to be related to lower carotid intima media thickness (p=0.004), but only in native Japanese. It was concluded that higher intakes of fish in Japanese living in Japan resulted in higher serum EPA concentrations (EPA 2.5%) and accounted for the lower carotid atherosclerosis—a relation not observed in White (EPA=0.8%) or Japanese American (EPA=1.0%) participants (34). Given that the mean EPA level in MESA participants was 0.9%, low levels may have resulted in the null finding and may also have contributed to the above modest findings for DHA. Study samples with greater fish intakes would provide a more comprehensive assessment of the anti-atherogenic potential of the fish oil n-3 FAs.

Plant-derived n-3 ALA

Compared to the fish oil FAs, the plant-derived n-3 ALA is less well-researched, but has also been proposed to be anti-atherogenic. And yet, plasma ALA concentrations have previously been shown to be unrelated to coronary atherosclerosis (29), and randomized controlled trials and intervention studies have shown that ALA has no effect on markers of inflammation, endothelial activation, lipid levels (39, 40), or carotid atherosclerosis (7). In the present analysis, the greater risk of carotid plaque observed in the 2nd quartile of ALA at baseline was unexpected, but null findings in subsequent quartiles and for the plaque progression outcome suggest that ALA levels are not a risk factor for carotid plaque.

Omega-6 FAs

In contrast with the n-3 FAs, the n-6's have been characterized, and potentially mischaracterized, as pro-inflammatory and pro-atherogenic FAs that are over-represented in Western diets (13, 14). And while it has been suggested that dietary LA metabolizes to AA and subsequently to inflammatory eicosanoids (which may then promote atherogenesis), there is little empirical evidence to support this. First, these processes are tightly regulated and not driven by principles of mass action. Higher dietary LA intakes do not increase plasma or cell membrane AA levels (41), and intervention studies in humans have failed to demonstrate that LA or AA supplementation results in greater leukotriene synthesis or inflammation (42–45).

To date, no large cohort studies have examined n-6 FAs and atherosclerosis outcomes, but studies of CV events have been conducted. A meta-analysis of 25 case-control and prospective studies showed that plasma LA was associated with lower risk of incident non-fatal CHD (p<0.01), but not fatal CHD (p=0.51) (17). Similar to LA, higher plasma phospholipid AA levels have been shown to be associated with 35% and 14% lower risk of

incident CHD in two cohort studies (18, 46), though a previous meta-analysis of 18 prospective studies found no relation of plasma phospholipid AA with CHD events (17). Our results for AA are similar to the meta-analysis findings, as no relations between n-6 FAs and carotid atherosclerosis were observed. Overall, our findings suggest n-6 FAs have no influence on atherosclerosis, but given the limited research in this area, further studies of n-6's and atherosclerosis outcomes are warranted.

Future research

Previous n-3 and n-6 research has largely focused on typical atherogenic mechanisms including inflammation, endothelial function, and blood lipids. Yet growing evidence suggests that n-3 FAs also affect plaque phenotype. For example, it has been shown that patients administered short-term n-3 FA treatment have atherosclerotic plaques with greater proportions of n-3 FAs and thicker fibrous caps, indicating greater plaque stability (47). Additional studies in cell culture and animal models have found that n-3 FAs stimulate efferocytosis (26, 48) which would, in turn, promote plaque stability. Whether these experimental findings translate to reduced clinical events and whether n-6 FAs may affect plaque phenotype requires further research.

Strengths and Limitations

The present study represents one of the largest prospective analyses of plasma phospholipid FAs and carotid atherosclerosis in a multi-ethnic cohort and is the first to examine plasma n-6 FAs and atherosclerotic plaque outcomes. The prospective design and approximate 10-year follow up period allowed for temporality of associations to be evaluated. In addition, ultrasound measurement precision was strong with inter-reader and intra-reader reproducibility of 0.95 and 0.99, respectively. In terms of limitations, all study participants in this subcohort completed Exam 5, and a selection bias for healthier individuals with less carotid atherosclerosis than those in the entire cohort is therefore possible. Plasma phospholipids were measured at Exam 1, and the possibility of subsequent changes in plasma FA levels cannot be evaluated. In addition, null results for GLA, n-6 DPA, and adrenic acid should be interpreted with caution due to their low plasma concentrations (mean levels <0.5%) and relatively higher coefficients of variation compared to other long-chain FA measurements. Adjustments were made for demographic and clinical risk factors in the statistical model, but residual confounding remains possible. Finally, MESA is a U.S. cohort study, and findings may not be generalizable to other populations.

Conclusions

Our findings support a protective influence of DHA on atherosclerotic plaque burden, while null findings for the n-6 FAs challenge the notion that they promote atherosclerosis. Continued research is necessary to further scrutinize the roles of n-3 and particularly the n-6 FAs in atherosclerotic plaque development, progression, and stability as well as hard CV endpoints.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The authors thank the other investigators, the staff, and the participants of the MESA study for their valuable contributions. A full list of participating MESA investigators and institutions can be found at http://www.mesa-nhlbi.org.

SOURCES OF FUNDING

This research was supported by contracts HHSN268201500003I, N01-HC-95159 through N01 HC 95169 from the National Heart, Lung, and Blood Institute, grants UL1-TR-000040, UL1-TR-001079, and UL1-TR-001420 from NCATS, and the Multi-Ethnic Study of Atherosclerosis and Air Pollution, funded by grant RD 831697 from the Environmental Protection Agency Science to Achieve Results (STAR) Program.

NONSTANDARD ABBREVIATIONS AND ACRONYMS

N-3	Omega-3
N-6	Omega-6
FAs	Fatty acids
MESA	Multi-Ethnic Study of Atherosclerosis
ALA	Alpha-linolenic acid
EPA	Eicosapentaenoic acid
DHA	Docosahexaenoic acid
CV	Cardiovascular
LA	Linoleic acid
AA	Arachidonic acid
GLA	Gamma-linoleic acid
DGLA	Dihomo-gamma linoleic acid
HR	Hazard ratio

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HIGHLIGHTS

- Plasma omega-3 and omega-6 fatty acids were differentially related to carotid plaque prevalence and progression over an approximate 10-year period in 3,327 participants of a multi-ethnic US cohort
- High levels of the fish oil omega-3, docosahexaenoic acid, were related to lower risk of atherosclerotic plaque prevalence and progression
- No relations were found among omega-6 fatty acids and carotid plaque
- No influence of race was observed
- The results support the narrative that fish oil has cardiovascular health benefits independent of race/ethnicity, while omega-6's did not appear to be pro-atherogenic in this sample

Table 1

Demographic and clinical characteristics of 3,327 MESA participants by the presence of carotid plaque at baseline

	All	(+) Presence of Plaque	(−) Absence of Plaque	p-value
N	3327	1566	1761	
Age, years (SD)	60.3 (9.4)	63.0 (9.2)	57.9 (8.9)	<0.001
Sex, n (% female)	1565 (47.0)	780 (49.8)	785 (44.6)	0.003
Race/ethnicity, n (%)				<0.001
White	1303 (39.2)	684 (43.7)	619 (35.2)	
Chinese	439 (13.2)	159 (10.2)	280 (15.9)	
Black	870 (26.1)	411 (26.2)	459 (26.1)	
Hispanic	715 (21.5)	312 (19.9)	403 (22.9)	
Smoking, n (%)				<0.001
Never	1727 (52.0)	720 (46.0)	1007 (57.3)	
Former	1216 (36.6)	633 (40.5)	583 (33.2)	
Current	379 (11.4)	211 (13.5)	168 (9.6)	
BMI (kg/m^2), mean (SD)	28.3 (5.3)	28.4 (5.2)	28.1 (5.3)	0.11
SBP (mm Hg), mean (SD)	124.3 (20.2)	128.0 (20.7)	121.0 (19.1)	<0.001
Hypertension medication, n (%)	1163 (35.0)	656 (41.9)	507 (28.8)	<0.001
Lipid lowering medication, n (%)*	542 (16.3)	338 (21.6)	204 (11.6)	<0.001
Diabetes, n (%)	330 (9.9)	213 (13.6)	117 (6.7)	<0.001
Total cholesterol (mmol/L), mean (SD)	5.03 (0.91)	5.10 (0.95)	4.96 (0.85)	<0.001
HDL-C (mmol/L), mean (SD)	1.32 (0.39)	1.31 (0.39)	1.33 (0.38)	0.32
Omega-3 PUFAs, mean (SD)†				
ALA	0.17 (0.074)	0.17 (0.080)	0.17 (0.068)	0.57
EPA	0.93 (0.84)	0.93 (0.87)	0.93 (0.81)	0.84
DHA	3.88 (1.49)	3.82 (1.46)	3.94 (1.51)	0.030
Omega-6 PUFAs, mean (SD)				
LA	20.24 (3.27)	19.96 (3.18)	20.50 (3.33)	<0.001
GLA	0.11 (0.055)	0.12 (0.054)	0.11 (0.056)	0.16
DGLA	3.18 (0.83)	3.20 (0.81)	3.17 (0.84)	0.33
AA	11.8 (2.54)	11.9 (2.54)	11.7 (2.53)	0.06

Definitions: SBP=systolic blood pressure; BMI=body mass index; diabetes=treated or untreated; HDL-C=high density lipoprotein-cholesterol; LDL-C=low density lipoprotein-cholesterol; PUFAs=polyunsaturated fatty acid; ALA=alpha-linolenic acid; EPA=eicosapentaenoic acid; DHA=docosahexaenoic acid; LA=linoleic acid; GLA=gamma-linolenic acid; DGLA=dihomo-gamma linolenic acid; AA=arachidonic acid

*at baseline

†PUFAs are expressed as % of total plasma phospholipid fatty acids

Table 2

Demographic and clinical characteristics of 3,296 MESA participants by the occurrence of carotid plaque progression over the 9.5-year study period

	All	(+) Plaque Progression	(−) No Plaque Progression	p-value
N	3296	1854	1442	
Age, years (SD)	60.3 (9.4)	62.3 (9.2)	57.7 (8.9)	<0.001
Sex, n (% female)	1547 (46.9)	917 (49.5)	630 (43.7)	<0.001
Race/ethnicity, n (%)				0.002
White	1292 (39.2%)	775 (41.8%)	517 (35.9%)	
Chinese	435 (13.2%)	218 (11.8%)	217 (15.0%)	
Black	862 (26.2%)	471 (25.4%)	391 (27.1%)	
Hispanic	707 (21.5%)	390 (21.0%)	317 (22.0%)	
Smoking, n (%)				<0.001
Never	1707 (51.9%)	876 (47.3%)	831 (57.7%)	
Former	1208 (36.7%)	727 (39.3%)	481 (33.4%)	
Current	376 (11.4%)	248 (13.4%)	128 (8.9%)	
BMI (kg/m^2), mean (SD)	28.3 (5.3)	28.4 (5.2)	28.0 (5.3)	0.016
SBP (mm Hg), mean (SD)	124.3 (20.2)	127.1 (20.4)	120.6 (19.3)	<0.001
Hypertension medication, n (%)	1150 (34.9%)	743 (40.1%)	407 (28.2%)	<0.001
Lipid lowering medication, n (%) *	1297 (39.4%)	816 (44.0%)	481 (33.4%)	<0.001
Diabetes, n (%)	328 (10.0%)	236 (12.7%)	92 (6.4%)	<0.001
Total cholesterol (mmol/L), mean (SD)	5.02 (0.91)	5.05 (0.92)	4.99 (0.89)	0.04
HDL-C (mmol/L), mean (SD)	1.32 (0.39)	1.30 (0.38)	1.34 (0.39)	0.002
Omega-3 PUFAs, mean (SD) †				
ALA	0.17 (0.07)	0.17 (0.08)	0.17 (0.07)	0.9
EPA	0.93 (0.84)	0.92 (0.83)	0.94 (0.86)	0.5
DHA	3.88 (1.49)	3.82 (1.46)	3.97 (1.52)	0.005
Omega-6 PUFAs, mean (SD)				
LA	20.2 (3.27)	20.1 (3.24)	20.4 (3.30)	0.003
GLA	0.11 (0.06)	0.16 (0.05)	0.11 (0.06)	0.20
DGLA	3.18 (0.83)	3.20 (0.82)	3.16 (0.84)	0.13
AA	11.8 (2.54)	11.8 (2.56)	11.7 (2.51)	0.36

Definitions: SBP=systolic blood pressure; BMI=body mass index; diabetes=treated or untreated; HDL-C=high density lipoprotein-cholesterol; LDL-C=low density lipoprotein-cholesterol; PUFAs=polyunsaturated fatty acid; ALA=alpha-linolenic acid; EPA=eicosapentaenoic acid; DHA=docosahexaenoic acid; LA=linoleic acid; GLA=gamma-linolenic acid; DGLA=dihomo-gamma linolenic acid; AA=arachidonic acid

*At the time of Exam 5

†PUFAs are expressed as % of total plasma phospholipid fatty acids

Table 3

Risk of carotid plaque (absent or present) at baseline is presented across quartiles of plasma n-3 and n-6 fatty acids in 3,314 MESA participants. First quartiles serve as referents. Adjustments were made for age, sex, race/ethnicity, BMI, smoking status, systolic blood pressure, hypertension medication use, diabetes, lipid lowering medication use, HDL-C, and total cholesterol. Values are expressed as relative risk (95% confidence intervals).

	Fatty acid quartile			
	1	**2**	**3**	**4**
Omega-3 FAs				
ALA (18:3)	Ref	**1.11 (1.02 – 1.21)** *	1.05 (0.96 – 1.16)	1.06 (0.97 – 1.17)
EPA (20:5)	Ref	1.02 (0.93 – 1.12)	1.00 (0.91 – 1.10)	0.99 (0.90 – 1.09)
DHA (22:6)	Ref	0.95 (0.87 – 1.04)	0.96 (0.88 – 1.05)	**0.91 (0.82 – 0.99)** *
Omega-6 FAs				
LA (18:2)	Ref	1.06 (0.97 – 1.15)	1.03 (0.94 – 1.12)	0.99 (0.89 – 1.09)
GLA (18:3)	Ref	1.02 (0.92 – 1.12)	1.03 (0.94 – 1.13)	1.00 (0.91 – 1.10)
DGLA (20:3)	Ref	1.04 (0.95 – 1.14)	0.97 (0.89 – 1.07)	1.04 (0.94 – 1.14)
AA (20:4)	Ref	1.08 (0.98 – 1.18)	1.02 (0.93 – 1.12)	1.06 (0.96 – 1.17)

* $p<0.05$

FAs=fatty acids; ALA=alpha-linolenic acid; EPA=eicosapentaenoic acid; DHA=docosahexaenoic acid; LA=linoleic acid; GLA=gamma-linolenic acid; DGLA=dihomo-gamma linolenic acid; AA=arachidonic acid

Table 4

Risk of carotid plaque progression is presented across quartiles of plasma omega-3 and omega-6 fatty acids in 3,283 MESA participants. First quartiles serve as referents. Adjustments were made for age, sex, race/ethnicity, BMI, hypertension medication use, smoking status, systolic blood pressure, diabetes, lipid lowering medication use (as a time dependent variable), HDL-C, and total cholesterol. Carotid plaque progression was treated as a logistical variable, and values are expressed as relative risk (95% confidence intervals).

	Fatty acid quartile			
	1	**2**	**3**	**4**
Omega-3 FAs				
ALA (18:3)	Ref	1.08 (1.00 – 1.17)	1.05 (0.97 – 1.13)	1.08 (1.00 – 1.17)
EPA (20:5)	Ref	1.03 (0.95 – 1.11)	1.03 (0.95 – 1.11)	0.98 (0.91 – 1.07)
DHA (22:6)	Ref	0.94 (0.88 – 1.01)	0.93 (0.86 – 1.00)	**0.88 (0.81 – 0.95)** *
Omega-6 FAs				
LA (18:2)	Ref	1.01 (0.93 – 1.09)	1.01 (0.93 – 1.08)	0.98 (0.91 – 1.07)
GLA (18:3)	Ref	1.01 (0.93 – 1.09)	1.01 (0.93 – 1.09)	1.00 (0.93 – 1.09)
DGLA (20:3)	Ref	1.05 (0.97 – 1.13)	0.98 (0.90 – 1.06)	1.05 (0.97 – 1.14)
AA (20:4)	Ref	1.00 (0.92 – 1.08)	1.05 (0.97 – 1.13)	1.04 (0.96 – 1.13)

* $p<0.01$

FAs=fatty acids; ALA=alpha-linolenic acid; EPA=eicosapentaenoic acid; DHA=docosahexaenoic acid; LA=linoleic acid; GLA=gamma-linolenic acid; DGLA=dihomo-gamma linolenic acid; AA=arachidonic acid