Intakes of long-chain n–3 polyunsaturated fatty acids and fish in relation to measurements of subclinical atherosclerosis1–3

Ka He, Kiang Liu, Martha L Davgulis, Elisabeth Mayer-Davis, Nancy Swords Jenny, Rui Jiang, Pamela Ouyang, Lyn M Steffen, David Siscovick, Colin Wu, R Graham Barr, Michael Tsai, and Gregory L Burke

ABSTRACT

Background: Data on the relations of different types of fish meals and long-chain n–3 polyunsaturated fatty acids (PUFAs) to measures of atherosclerosis are sparse.

Objective: We examined intakes of long-chain n–3 PUFAs and fish in relation to clinical measures of subclinical atherosclerosis.

Design: A cross-sectional study was conducted in a multiethnic group of 5488 adults aged 45–84 y and free of clinical cardiovascular disease. Diet was assessed by using self-administered food-frequency questionnaires. Subclinical atherosclerosis was determined by measurements of common carotid intima–media thickness (cCIMT, >80th percentile), internal CIMT (iCIMT, >80th percentile), coronary artery calcium score (CAC score, >0), or ankle-brachial index (ABI, <0.90).

Results: After adjustment for potential confounders, intakes of long-chain n–3 PUFAs and nonfried (broiled, steamed, baked, or raw) fish were inversely related to subclinical atherosclerosis determined by cCIMT but not by iCIMT, CAC score, or ABI. The multivariate odds ratio comparing the highest to the lowest quartile of dietary exposures in relation to subclinical atherosclerosis determined by cCIMT was 0.69 (95% CI: 0.55, 0.86; P for trend <0.01) for n–3 PUFA intake; 0.80 (95% CI: 0.64, 1.01; P = 0.054) for nonfried fish consumption; and 0.90 (95% CI: 0.73, 1.11; P = 0.38) for fried fish consumption.

Conclusions: This study indicates that the dietary intake of long-chain n–3 PUFAs or nonfried fish is associated with a lower prevalence of subclinical atherosclerosis classified by cCIMT, although significant changes in iCIMT, CAC score, or ABI were not observed. Our findings also suggest that the association of fish and atherosclerosis may vary depending on the type of fish meal consumed and the measures of atherosclerosis. Am J Clin Nutr 2008;88:1111–8.

INTRODUCTION

Observational studies and randomized trials have indicated that higher intakes of long-chain (LC) n–3 polyunsaturated fatty acids (PUFAs), including eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), and of fish are associated with a lower risk of cardiovascular disease (CVD) (1–4). Possible mechanisms underlying this cardioprotective effect include a reduction in serum triglycerides (5), a decrease in platelet aggregability (6), and the presence of antiarrhythmic effects (6). Whereas the hypotriglyceridemic effects of supplementation with high-dose LC n–3 PUFAs are well established (7), these fatty acids may also increase LDL cholesterol (8, 9) and enhance the oxidation of LDL cholesterol (10, 11). Indeed, previous studies did not provide a clear picture of the effects of LC n–3 PUFAs or fish on subclinical atherosclerosis. Data from both animal models (12–14) and humans (15–17) are inconsistent.

Computed tomography scanning of the coronary arteries for calcium is widely used as a noninvasive method of assessing early coronary artery disease. The presence of coronary artery calcium (CAC) is a predictor of a greater risk of future coronary events (18, 19). The ultrasonographic evaluation of the carotid intimal–medial thickness (CIMT) is also used to assess carotid atherosclerosis (20, 21). In addition, a low ankle-brachial index (ABI) has been reported to be associated with greater risks of death, total CVD, coronary heart disease, congestive heart failure, and symptomatic peripheral arterial disease (22–25). Although these measurements are widely employed as markers of subclinical atherosclerosis in various epidemiologic studies, few studies have used these measurements simultaneously in a single cohort.

To determine whether the previous inconsistent findings on fish and subclinical atherosclerosis can be partially explained by the different clinical measures used and to ascertain how different types of fish meals related to atherosclerosis, we examined fish consumption and LC n–3 PUFA intake in relation to clinical measures of atherosclerosis including common CIMT (cCIMT),

1 From the School of Public Health and School of Medicine, University of North Carolina at Chapel Hill, Chapel Hill, NC (KH and EM-D); the Feinberg School of Medicine, Northwestern University, Chicago, IL (KL and MLD); the University of Vermont College of Medicine, Colchester, VT (NSJ); the Columbia University Medical Center, New York, NY (RJ and RGB); the Johns Hopkins University School of Medicine, Baltimore, MD (PO); the School of Public Health, University of Minnesota, Minneapolis, MN (LMS and MT); the School of Medicine, University of Washington, Seattle, WA (DS); the National Heart, Lung, and Blood Institute, Bethesda, MD (CW); and the Wake Forest University of Health Sciences, Winston-Salem, NC (GLB).

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3 Reprints not available. Address correspondence to K He, Departments of Nutrition and Epidemiology, School of Public Health, University of North Carolina at Chapel Hill, 2202 McGavran-Greenberg Hall, CB# 7461, Chapel Hill, NC 27599. E-mail: kahe@unc.edu.

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internal CIMT (iCIMT), CAC score, and ABI in a multiethnic cohort of middle-aged and older men and women.

PARTICIPANTS AND METHODS

Study population

The Multi-Ethnic Study of Atherosclerosis (MESA) is a population-based study of 6814 men and women aged 45–84 y who are without clinical CVD and were recruited from 6 US communities. Participants were enrolled between August 1, 2000, and July 30, 2002. The self-identified ethnic background of the cohort is 38.5% white, 27.8% African American, 21.9% Hispanic, and 11.8% Chinese American. The primary goal of MESA is to determine the characteristics associated with subclinical CVD and its progression. Details of the sampling and recruitment procedures were published elsewhere (26). Participants completed a set of measurements of subclinical CVD and assessment of standard CVD risk factors, sociodemographic factors, diet, lifestyle, and psychosocial factors. In the present analysis, we excluded those who had missing data on diet (n = 577), ABI (n = 70), cCIMT (n = 74), iCIMT (n = 98), and who had extreme total energy intake (<600 or >6000 kcal/d, n = 285). We also excluded participants without information on covariates used in the analysis (n = 222). After these exclusions, a total of 5488 participants remained in the analysis.

All participants provided informed consent. The MESA protocol was approved by institutional review boards at all participating sites.

Dietary assessment

Dietary information was assessed by using a self-administered food frequency questionnaire (FFQ) and dietary supplement form. The FFQ was based on an FFQ used in the multiethnic (non-Hispanic white, African American, and Hispanic) Insulin Resistance Atherosclerosis Study and was modified for the Diabetes Prevention Program to include foods typically consumed by a Chinese American population and to collect supplemental information (26, 27). Participants were asked to identify the usual frequency of consumption of the food items during the past year and the average serving size consumed. Nine frequency responses were available in the questionnaire, ranging from “never or rare” to “>2 times/d,” and 3 serving sizes were specified: small, medium, and large. In the present study, fish consumption was defined as fish and other seafood intake. Participants were asked to indicate how often they consumed 1) fried fish or fish sandwich, fried shrimp, or calamari; 2) shrimp, lobster, crab, oysters, or mussels (not fried); 3) tuna, salmon, or sardines (including sashimi or sushi); and 4) other broiled, steamed, baked, or raw fish (eg, trout, sole, halibut, poke, or grouper).

Studies have suggested that the preparation method—in particular, frying—may substantially alter the fatty acid content of a fish meal (28) and that the associations with CVD risk may be different (29). In addition, the LC n–3 PUFA content in shellfish is relatively low. Therefore, we divided fish consumption into 3 groups: fried fish (including fried shellfish), nonfried fish (broiled, steamed, baked, or raw fish), and nonfried fish + shellfish. Because nearly 50% of participants reported no shellfish consumption, we were not able to analyze shellfish separately. The questionnaire also includes 3 questions related to mixed fish dishes such as the Chinese dishes of stir-fried shrimp or fish with vegetables or non-Chinese dishes such as pasta with seafood and seafood gumbo. Because we were not able to determine the exact portion of seafood in a mixed fish dish, we did not include mixed fish dishes in the main analyses. However, we included mixed fish dishes in the secondary analyses by assigning a weight 0.4, 0.5, or 0.6 for calculating the amount of fish in the mixed fish dishes. We converted fish consumption into servings per day and adjusted for serving size (ie, small = 0.5 × medium; medium = standard age- and sex-specific serving size; large = 1.5 × medium) (30). Nutrients including LC n–3 PUFAs were derived from the Minnesota Nutrition Data System NDS software (version 4.02/30; Nutrition Coordinating Center, University of Minnesota, Minneapolis, MN) (31). Information on the dose of supplements including fish oil was acquired. The doses of supplements also were included in the estimation of nutrient intake.

Although the FFQ has not been validated in MESA, the Insulin Resistance Atherosclerosis Study questionnaire has shown reasonable validity and reliability in a diverse cohort (32). Compared with the average of eight 24-h recalls, the mean correlation coefficients of nutrient intake were 0.62 for non-Hispanic whites, 0.5 for African Americans, and 0.41 for Hispanics. The somewhat lower observed correlations among Hispanics were largely accounted for by differences in education across the ethnicities. For reliability, the mean correlation coefficient for nutrients evaluated was 0.62; it did not differ by ethnic subgroup.

Measures of subclinical atherosclerosis

In the present study, subclinical atherosclerosis was defined by CAC score, cCIMT, iCIMT, and ABI. The CAC score was measured by using 2 scans obtained on the same occasion in all participants during the clinical examination using electron beam computed tomography or multidetector computed tomography (33). The presence of CAC (Agatston score >0) was considered as a marker of subclinical atherosclerosis.

Intimal-media thickness (IMT) was measured between the lumen-intima and media-adventitia interfaces of near and far walls of the common carotid artery (the 1-cm segment proximal to the bifurcation) and the internal carotid artery (including the bifurcation and 1 cm distal to the bifurcation) with B-mode ultrasound [Logiq 700 ultrasound machine; General Electric Medical Systems, Waukesha, WI] (34). Subclinical atherosclerosis was defined by the values of cCIMT or the iCIMT index of >80th percentile values.

All participants were evaluated in the supine position after ≥5 min of rest. Systolic blood pressure was measured in arms and in the right and left posterior tibial and dorsalis pedis artery. The resting ABI was determined for each leg by dividing the systolic blood pressure at the ankle by the brachial pressure; the lower of the ABI values obtained in each leg was used in the data analysis (35). An ABI value < 0.9 was classified as subclinical atherosclerosis in this analysis.

Assessment of other covariates

Demographic and major lifestyle variables were collected via questionnaire; they included age, sex, race-ethnicity, education level, household income, smoking status, medical conditions, and current medication use. Body weight and height were directly measured according to standard procedures. Body mass index (BMI; in kg/m²) was calculated. Physical activity was
measured by using a detailed, semiquantitative questionnaire adopted from the Cross-Culture Activity Participation Study (26). Total physical activity was computed as the total intentional exercise [all light, moderate, and vigorous activities (min/wk)] multiplied by the activities’ individual metabolic equivalent values.

Statistical analysis

Quartiles of fish consumption and LC n–3 PUFA intake were created and used in the analysis. Age-, sex-, and race-adjusted means and SEs or proportions were computed for selected variables by quartiles of LC n–3 PUFA intake. Logistic regression analyses were used to examine the associations of fish consumption and LC n–3 PUFA intake with subclinical atherosclerosis, which are classified by cCIMT (>80th percentile), iCIMT (>80th percentile), CAC (Agatston score >0), or ABI (<0.90).

We considered a number of potential confounders in the multivariable models, including age, race-ethnicity, sex, BMI, physical activity, household income, smoking status, systolic blood pressure, antihypertensive medication use, and several dietary variables. We first ran a basic model by including a few demographic variables. Other major lifestyle factors and dietary variables were included in the analysis as potential confounders based on previous studies and statistical tests. Covariates were added to the basic regression model in a hierarchical fashion so that we can assess the effect of adjustment for specific confounders on the association of each combination of dietary exposure and clinical measures of atherosclerosis. In addition, we adjusted for fried fish when examining nonfried fish and vice versa. Test for trends across quartiles was evaluated by using the mean values of each quartile of fish and LC n–3 PUFA intake. In a sensitivity analysis, different cutoffs (ie, 10, 50, 100, or 200) were used for CAC score to determine whether the results for fish or LC n–3 PUFAs and CAC score were robust. All P values were 2-sided, and P < 0.05 was considered statistically significant. SAS software (version 9; SAS Institute Inc, Cary, NC) was used for all analyses.

RESULTS

Age-, sex-, and race- adjusted characteristics of the study population according to dietary intake of LC n–3 PUFA are shown in Table 1. The median daily intakes of LC n–3 PUFA across quartiles were 40, 80, 120, and 220 mg, respectively. Compared with participants in the lowest quartile of LC n–3 PUFA intake, those in the highest quartile were more likely to have higher education and household income; they also exercised more and were less likely to be current smokers. Moreover, participants in the highest quartile of LC n–3 PUFA intake had lower intakes of alcohol, total energy, saturated fat, and trans fat and a higher intake of α-linolenic acid.

In multivariate analysis, a significant inverse association was observed between LC n–3 PUFA intake and subclinical atherosclerosis as determined by cCIMT. The odds of having cCIMT > 80th percentile was 31% lower [odds ratio (OR): 0.69; 95% CI: 0.55, 0.86; P for trend = 0.005] for participants in the highest quartile of LC n–3 PUFA intake than for those in the lowest quartile (Table 2). Greater nonfried fish consumption was related to lower odds of cCIMT > 80th percentile (OR: 0.80; 95% CI: 0.64, 1.01; P for trend = 0.054), but this inverse association was attenuated by including shellfish (OR: 0.84; 95% CI: 0.67, 1.04; P for trend = 0.15). Fried fish was not related to cCIMT. In addition, no inverse associations were observed for LC n–3 PUFA, nonfried fish, nonfried fish + shellfish, or fried fish intake and subclinical atherosclerosis classified by iCIMT, CAC score, or ABI (Table 2).

After adjustment for potential confounders, LC n–3 PUFA intake and fish consumption were significantly inversely related to blood triglyceride concentrations. In addition, intakes of LC n–3 PUFAs and nonfried fish were positively associated with blood HDL–cholesterol concentrations. The ratio of total to HDL cholesterol (total: HDL cholesterol) has been suggested as a powerful predictor of coronary heart disease (36). In the present study, dietary LC n–3 PUFA intake (but not fish consumption) was significantly inversely related to total: HDL cholesterol (Table 3).

By stratifying data, we found that the inverse associations between nonfried fish consumption or LC n–3 PUFA intake and cCIMT were not appreciably modified by sex. The P values for the sex × LC n–3 PUFA and sex × nonfried fish interactions were 0.95 and 0.57, respectively. In addition, the observed inverse associations remained in whites but not other races-ethnicities (data not shown).

In sensitivity analyses (data not shown), we used different cutoffs (ie, 10, 50, 100, or 200) for CAC score, but the results were not materially altered. In addition, ≈4% of participants used fish-oil supplements. The results remained when we excluded the supplement users in the analyses. In the present study, we were not able to analyze shellfish separately because nearly half of the participants reported no shellfish consumption. Nevertheless, no association with any of the clinical markers was observed with dichotomizing shellfish consumption. Moreover, we included mixed fish dishes in the analysis by assigning a weight of 0.4, 0.5, or 0.6, respectively, to mixed fish dishes. The observed inverse associations were slightly attenuated.

DISCUSSION

In this cross-sectional study, we found that dietary intake of LC n–3 PUFAs and nonfried fish consumption were associated with a lower OR of subclinical atherosclerosis classified by cCIMT but not iCIMT, CAC score, or ABI. The inverse associations were consistent in men and in women.

Despite potential benefits of dietary LC n–3 PUFAs in the reduction of coronary heart disease mortality (3), it is not clear whether LC n–3 PUFAs have a direct effect on the pathogenesis of atherosclerosis. A randomized controlled trial among 59 patients with angiographically documented coronary heart disease showed that fish-oil treatment (6 g/d of EPA and DHA) for 2 y had no major favorable effect on the diameter of atherosclerotic coronary arteries (15). Another randomized, double-blind, placebo-controlled trial in 223 patients with angiographically proven coronary artery disease found that a fish-oil intake of ≈1.65 g/d of EPA and DHA for 2 y modestly mitigated the course of human coronary atherosclerosis (16) but had no effect on progression of carotid atherosclerosis (37). A change in the extent of atherosclerosis in carotid arteries and in coronary arteries in these patients during the same period was not correlated (37). The association of fish or LC n–3 PUFA with atherosclerosis was also examined in observational studies. A cross-sectional study conducted in 470 Japanese found that serum LC n–3 PUFA...
Concentrations were inversely related to the probability of common carotid plaques (38). In addition, a prospective cohort study of postmenopausal women with coronary artery disease (n = 229) found that fish consumption was associated with significantly less progression of coronary atherosclerosis (17).

The effects of LC n–3 PUFAs on atherosclerosis may be mediated through PUFAs’ roles in lipoprotein metabolism. In the present study, we found that fish and LC n–3 PUFA intakes were associated with lower triglyceride concentrations. LC n–3 PUFAs and nonfried fish were positively related to HDL. LC n–3 PUFAs also were inversely associated with total HDL cholesterol. No statistically significant associations were found for LDL and total cholesterol. A recent meta-analysis of 21 randomized controlled trials summarized the effects of fish-oil supplementation on lipid values (39). The meta-analysis suggests that fish-oil consumption significantly reduces serum triglycerides and modestly improves HDL. However, fish-oil intake increases the concentration of LDL cholesterol and has no effect on total cholesterol. It is uncertain how these combined effects of LC n–3 PUFAs with lipids, anti-inflammatory effects and may improve endothelial function (43, 44). The associations of LC n–3 PUFAs with atherosclerosis may reflect the integrative effects of LC n–3 PUFAs with lipids, anti-inflammatory effects and may improve endothelial function (43, 44). The associations of LC n–3 PUFAs with atherosclerosis may reflect the integrative effects of LC n–3 PUFAs with lipids, anti-inflammatory effects and may improve endothelial function (43, 44).
### TABLE 2
Multivariate-adjusted odds ratios (ORs) (and 95% CIs) of subclinical atherosclerosis determined by various biomarkers by quartile (Q) of dietary intake of fish and long-chain (LC) n–3 polyunsaturated fatty acids (PUFAs)—MESA, 2000–2002

<table>
<thead>
<tr>
<th>LC n–3 PUFA (mg/d)</th>
<th>cCIMT</th>
<th>iCIMT</th>
<th>CAC</th>
<th>ABI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects with cCIMT &gt;80th percentile</td>
<td>OR (95% CI)</td>
<td>Subjects with iCIMT &gt;80th percentile</td>
<td>OR (95% CI)</td>
<td>Subjects with CAC &gt; 0</td>
</tr>
<tr>
<td>LC n–3 PUFA (mg/d)</td>
<td>Median intake</td>
<td>n</td>
<td>OR</td>
<td>n</td>
</tr>
<tr>
<td>Q1 (n = 1372)</td>
<td>40</td>
<td>317</td>
<td>1.00</td>
<td>299</td>
</tr>
<tr>
<td>Q2 (n = 1372)</td>
<td>80</td>
<td>275</td>
<td>0.77 (0.63, 0.95)</td>
<td>268</td>
</tr>
<tr>
<td>Q3 (n = 1372)</td>
<td>120</td>
<td>263</td>
<td>0.78 (0.63, 0.96)</td>
<td>285</td>
</tr>
<tr>
<td>Q4 (n = 1372)</td>
<td>220</td>
<td>234</td>
<td>0.69 (0.55, 0.86)</td>
<td>245</td>
</tr>
<tr>
<td>P for trend</td>
<td>0.005</td>
<td>0.87</td>
<td>0.09</td>
<td>0.18</td>
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</table>

<table>
<thead>
<tr>
<th>Nonfried fish (servings/wk)</th>
<th>cCIMT</th>
<th>iCIMT</th>
<th>CAC</th>
<th>ABI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects with cCIMT &gt;80th percentile</td>
<td>OR (95% CI)</td>
<td>Subjects with iCIMT &gt;80th percentile</td>
<td>OR (95% CI)</td>
<td>Subjects with CAC &gt; 0</td>
</tr>
<tr>
<td>Q1 (n = 1422)</td>
<td>0</td>
<td>316</td>
<td>1.00</td>
<td>310</td>
</tr>
<tr>
<td>Q2 (n = 1257)</td>
<td>0.3</td>
<td>256</td>
<td>0.95 (0.77, 1.18)</td>
<td>252</td>
</tr>
<tr>
<td>Q3 (n = 1468)</td>
<td>0.8</td>
<td>281</td>
<td>0.88 (0.72, 1.09)</td>
<td>281</td>
</tr>
<tr>
<td>Q4 (n = 1341)</td>
<td>2.0</td>
<td>236</td>
<td>0.80 (0.64, 1.01)</td>
<td>254</td>
</tr>
<tr>
<td>P for trend</td>
<td>0.054</td>
<td>0.80</td>
<td>0.94</td>
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</table>

<table>
<thead>
<tr>
<th>Nonfried fish and shellfish (servings/wk)</th>
<th>cCIMT</th>
<th>iCIMT</th>
<th>CAC</th>
<th>ABI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects with cCIMT &gt;80th percentile</td>
<td>OR (95% CI)</td>
<td>Subjects with iCIMT &gt;80th percentile</td>
<td>OR (95% CI)</td>
<td>Subjects with CAC &gt; 0</td>
</tr>
<tr>
<td>Q1 (n = 1491)</td>
<td>0</td>
<td>344</td>
<td>1.00</td>
<td>334</td>
</tr>
<tr>
<td>Q2 (n = 1243)</td>
<td>0.5</td>
<td>237</td>
<td>0.90 (0.73, 1.11)</td>
<td>231</td>
</tr>
<tr>
<td>Q3 (n = 1383)</td>
<td>1.0</td>
<td>261</td>
<td>0.83 (0.67, 1.02)</td>
<td>273</td>
</tr>
<tr>
<td>Q4 (n = 1371)</td>
<td>2.5</td>
<td>247</td>
<td>0.84 (0.67, 1.04)</td>
<td>259</td>
</tr>
<tr>
<td>P for trend</td>
<td>0.15</td>
<td>0.98</td>
<td>0.26</td>
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</table>

<table>
<thead>
<tr>
<th>Fried fish (servings/wk)</th>
<th>cCIMT</th>
<th>iCIMT</th>
<th>CAC</th>
<th>ABI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects with cCIMT &gt;80th percentile</td>
<td>OR (95% CI)</td>
<td>Subjects with iCIMT &gt;80th percentile</td>
<td>OR (95% CI)</td>
<td>Subjects with CAC &gt; 0</td>
</tr>
<tr>
<td>Q1 (n = 2240)</td>
<td>0</td>
<td>435</td>
<td>1.00</td>
<td>442</td>
</tr>
<tr>
<td>Q2 and Q3 (n = 1789)</td>
<td>0.2</td>
<td>341</td>
<td>0.92 (0.77, 1.11)</td>
<td>331</td>
</tr>
<tr>
<td>Q4 (n = 1459)</td>
<td>0.8</td>
<td>313</td>
<td>0.90 (0.73, 1.11)</td>
<td>324</td>
</tr>
<tr>
<td>P for trend</td>
<td>0.38</td>
<td>0.09</td>
<td>0.34</td>
<td>0.78</td>
</tr>
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</table>

1. cCIMT, common carotid intima–media thickness; iCIMT, internal carotid intima–media thickness; CAC, coronary artery calcium (score); ABI, ankle-brachial index. The numbers of participants in the fish quartiles are different because of a tie in the values for the amount of fish consumption. Data were obtained by using logistic regression models. The ORs were adjusted for age, race, sex, BMI, physical activity, household income, smoking status (current, former, or never smoker), systolic blood pressure, antihypertensive medication use, alcohol consumption, and intakes of saturated fat, α-linolenic acid, trans fatty acids, and total energy; further adjusted for fried fish and shellfish (for nonfried fish) or fried fish (for nonfried fish + shellfish) or nonfried fish and shellfish (for fried fish).

2. Includes broiled, steamed, baked, or raw fish.

3. Includes fried fish and fried shellfish.

4. Q2 and Q3 were combined because only a small number of participants were ranked in Q2 as a result of a tie in the values for fried fish consumption.
may be different surrogates of the atherosclerotic process. For example, ABI is generally thought of as the best clinical marker of diffuse atherosclerosis, the CAC score may reflect atherosclerosis in coronary arteries, and cCIMT and iCIMT are considered to be markers of carotid atherosclerosis. Second, because dietary intake was self-reported, the inevitable measurement errors in estimation from media sources. This diet change could dilute any inverse association between nonfried fish and cCIMT was attenuated by the inclusion of shellfish. Although it was modestly inversely related to blood triglyceride concentrations, we found no beneficial effects of fried fish consumption on atherosclerosis. Our findings are biologically plausible, because frying may affect a fish meal’s fatty acid composition (28), at least partly by reducing LC n–3 PUFA content and producing trans unsaturated fatty acids. These changes in fatty acid profile of cooked fish meals may somewhat attenuate or cancel the potential benefit of fish consumption.

The present study had some limitations. First, given the cross-sectional analysis, the possibility of reverse causation cannot be completely excluded. In addition, we could not account for the effects of changes in diet on atherosclerosis. For example, some participants who were at high risk of CVD may have changed their diet (eg, increased fish consumption or started taking a fish-oil supplement) on the advice of physicians or due to information from media sources. This diet change could dilute any inverse association of LC n–3 PUFA intake could bias our results. Third, although we adjusted for a number of potential confounders in the analysis, residual confounding and may be different surrogates of the atherosclerotic process. For example, ABI is generally thought of as the best clinical marker of diffuse atherosclerosis, the CAC score may reflect atherosclerosis in coronary arteries, and cCIMT and iCIMT are considered to be markers of carotid atherosclerosis. Our findings are biologically plausible, because frying may affect a fish meal’s fatty acid composition (28), at least partly by reducing LC n–3 PUFA content and producing trans unsaturated fatty acids. These changes in fatty acid profile of cooked fish meals may somewhat attenuate or cancel the potential benefit of fish consumption.

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possible confounding from unmeasured dietary and nondietary factors could not be ruled out. For example, information on mercury and other contaminants in fish was not available. A study has suggested that mercury may increase the risk of myocardial infarction (46). Thus, mercury in fish may confound our findings. Fourth, nearly 20% participants were excluded in the analyses, mainly because of missing data. Although the characteristics of these 2 groups did not differ significantly, the results may be affected by the exclusions. Finally, the relatively small numbers of participant with ABI < 0.90 may limit our capability to examine the associations by using the ABI as the measure of subclinical atherosclerosis.

In summary, the present study indicates that dietary intakes of LC n–3 PUFA and nonfried fish are inversely associated with subclinical atherosclerosis determined by cCIMT but not iCIMT, CAC score, or ABI. Our findings also suggest that results of clinical and epidemiologic research may differ according to the measures used to assess atherosclerosis and the type of fish meal consumed.

We thank the other investigators and the staff of the Multi-Ethnic Study of Atherosclerosis (MESA) for their valuable contributions. A full list of participating investigators and institutions can be found at http://www.mesa-nhlbi.org. We also thank Laura Colangelo for her assistance in statistic analyses and SAS programming.

The authors’ responsibilities were as follows—KH: designed the study, conducted the analyses, and drafted the manuscript; KL: provided statistical advice and helped revise the manuscript; and MLD, EMD, NSJ, RJ, PO, LMS, DS, CW, RGB, MT, and GLB critically revised the manuscript for important intellectual content. None of the authors had a personal or financial conflict of interest.

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