Dietary linolenic acid and carotid atherosclerosis: the National Heart, Lung, and Blood Institute Family Heart Study[1–3]

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ABSTRACT

Background: Dietary intake of linolenic acid is associated with a lower risk of cardiovascular disease mortality. However, it is unknown whether linolenic acid is associated with a lower risk of carotid atherosclerosis.

Objective: The objective was to examine the association between dietary linolenic acid and the presence of atherosclerotic plaques and the intima-media thickness of the carotid arteries.

Design: In a cross-sectional design, we studied 1575 white participants of the National Heart, Lung, and Blood Institute Family Heart Study who were free of coronary artery disease, stroke, hypertension, and diabetes mellitus. High-resolution ultrasound was used to assess intima-media thickness and the presence of carotid plaques beginning 1 cm below to 1 cm above the carotid bulb. We used logistic regression and a generalized linear model for the analyses.

Results: From the lowest to the highest quartile of linolenic acid intake, the prevalence odds ratio (95% CI) of a carotid plaque was 1.0 (reference), 0.47 (0.30, 0.73), 0.38 (0.22, 0.66), and 0.49 (0.26, 0.94), respectively, in a model that adjusted for age, sex, energy intake, waist-to-hip ratio, education, field center, smoking, and the consumption of linoleic acid, saturated fat, fish, and vegetables. Linoleic acid, fish long-chain fatty acids, and fish consumption were not significantly related to carotid artery disease. Linolenic acid was inversely related to thickness of the internal and bifurcation segments of the carotid arteries but not to the common carotid artery.

Conclusion: Higher consumption of total linolenic acid is associated with a lower prevalence odds of carotid plaques and with lesser thickness of segment-specific carotid intima-media thickness. *Am J Clin Nutr* 2003;77:819–25.

KEY WORDS Linolenic acid, n−3 fatty acids, n−6 fatty acids, diet, carotid artery disease, National Heart, Lung, and Blood Institute Family Heart Study

INTRODUCTION

Epidemiologic studies have indicated that a higher consumption of n−3 fatty acids is related to a lower risk of coronary artery disease (CAD) incidence and mortality (1–7). In the Lyon Diet Heart Study (2), α-linolenic acid was associated with a decreased risk of recurrent fatal and nonfatal myocardial infarction. Other large prospective studies and a cross-sectional study reported an inverse association between linolenic acid and the risk of CAD or fatal CAD mortality (5, 8–10). In animal models, a higher concentration of linolenic acid was associated with a lower incidence of ventricular fibrillation and cardiac deaths (11). Linolenic acid may also reduce the risk of CAD through its antithrombotic effects (12). It is unclear whether linolenic acid is related to early signs of atherosclerosis such as carotid artery plaques or increased wall thickness detectable with ultrasound. Underlying physiologic mechanisms by which linolenic acid affects the risk of CAD in humans are not well established.

We used data collected from 1575 white participants of the National Heart, Lung, and Blood Institute (NHLBI) Family Heart Study to assess whether dietary consumption of total linolenic acid (α- and γ-linolenic acid) was associated with carotid artery plaques and intima-media thickness (IMT) of the carotid arteries. In addition, we evaluated whether the intakes of n−6 fatty acids, fish, and long-chain n−3 fatty acids were related to carotid artery atherosclerosis.

SUBJECTS AND METHODS

Study population

Study participants were members of the NHLBI Family Heart Study, which is a multicenter, population-based study designed to identify and evaluate genetic and nongenetic determinants of CAD, preclinical atherosclerosis, and cardiovascular risk factors. A detailed description of the NHLBI Family Heart Study was published (13). Families in the study were chosen, either at random or on the basis of a higher than expected risk of CAD, from previously established population-based cohort studies: the Framingham Heart Study in Framingham, MA; the Atherosclerosis Risk in Communities Study (cohorts from North Carolina and Minnesota); and the Utah Health Family Tree Study in Salt Lake City. The high-risk group was defined on the basis of a family risk score, which related the family's age- and sex-specific incidence of CAD to that expected in the general population (14).

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Briefly, between 1993 and 1995, groups of persons participating in each of the parent studies were selected at random and invited to furnish an updated family health history that contained information on their parents, children, and siblings. Of 4679 persons contacted, responses were obtained from 3150 (67%); their family members were then contacted, and self-reported health data were obtained from a total of 22 908 persons (86% of those contacted). From the families responding to the health questionnaire, 588 families were chosen at random, and 566 families were selected on the basis of a higher than expected risk of CAD. All members of these families were invited to come to 1 of the 4 study clinics for a 4-h clinical evaluation. The evaluation consisted of a detailed medical and lifestyle history, obtained through interview, and laboratory measurements, including a carotid artery ultrasound examination.

The current analyses are based on data from 1575 participants, who were members of the randomly selected families and who were free of stroke, CAD, hypertension, renal insufficiency, and diabetes mellitus at the time of clinic examination. Most of the participants from the random sample were white. Informed consent was obtained from each participant, and the study protocol was reviewed and approved by each of the participating institutions.

Carotid artery ultrasound

Using high-resolution B-mode ultrasound, trained technicians measured carotid IMT according to the Atherosclerosis Risk in Communities Study protocol (15). Carotid artery assessments were completed bilaterally on 3 segments: the common carotid artery (1 cm proximal to the dilatation of the carotid bulb), the bifurcation (the 1-cm segment proximal to the flow divider), and the internal carotid artery (the 1-cm segment in the internal branch distal to the flow divider). B-mode images were recorded on high-resolution cassettes. Recorded images were read at the central reading station by trained readers. The presence of an atherosclerotic plaque was determined by using 3 criteria: regularity or irregularity of surface, overall thickness, and ecogenicity. A plaque was ascertained at the visualized segment if ≥2 of these criteria were present. For each subject, the total number of plaques was recorded. For these analyses, carotid atherosclerosis was present if at least one plaque was detected in any of the segments visualized. The interreader reproducibility was very good (κ statistic: 0.76 for plaque and 0.77, 0.73, and 0.70 for mean carotid far-wall IMT at the bifurcation, internal artery, and common carotid artery, respectively).

Dietary assessment

Data on dietary linolenic acid and other dietary information were collected through a staff-administered semiquantitative food-frequency questionnaire developed by Willett (16, 17). Although we did not have the opportunity to test the reproducibility of the questionnaires in this study, the reproducibility and validity of this food-frequency questionnaire were documented elsewhere (18). The intake of specific nutrients was computed by multiplying the frequency of consumption of an item by the nutrient content of specified portions. The composition values for linolenic acid, linoleic acid, and other nutrients were obtained from the Harvard University Food Composition Database derived from US Department of Agriculture sources (19) and manufacturer information. We were unable to differentiate α- from γ-linolenic acid. Thus, we used total linolenic acid in this study because the relation of α-linolenic acid to CAD has been shown to be very similar to that of total linolenic acid to CAD (8). In addition, it has been reported that the main sources of γ-linolenic acid are beef fats and other animal fats and that the γ-linolenic acid concentration in these fats is small (20).

Other variables

Information on cigarette smoking, alcohol intake, and education were obtained by interview during the clinic visit. Use of aspirin and vitamins was assessed with the use of a questionnaire and medication inventory. Subjects were asked about the type of oil they used for cooking and the type of salad dressing they consumed. The frequency of fish, nut, and vegetable consumption was obtained with the use of the food-frequency questionnaire. Possible response categories were as follows: almost never, 1–3 times/mo, 1 time/wk, 2–4 times/wk, 5–6 times/wk, 1 time/d, 2–3 times/d, 4–6 times/d, and >6 times/d. Level of physical activity during the previous year was estimated through self-reports. Anthropometric data were collected while the participants were wearing scrub suits. LDL was measured by using the method of Friedewald et al (21), except for participants with triacylglycerol concentrations >4.5 mmol/L, whose LDL concentrations were measured by ultracentrifugation. Triacylglycerol was measured by using a peroxidase-coupled method. Total cholesterol was measured by using a commercial cholesterol oxidase method on a Roche COBAS-FARA centrifugal analyzer (Boehringer Mannheim Diagnostics, Indianapolis). HDL cholesterol was measured after precipitation of the other lipoprotein fractions by dextran sulfate (22).

Statistical analyses

Of the 2169 white participants from the randomly selected families who had a clinic examination and for whom data on linolenic acid were available, 125 were excluded because of missing ultrasound data. In addition, 469 subjects were excluded because of missing data on smoking status (n = 17) or preexisting conditions that can influence carotid artery disease: CAD or stroke (n = 130), diabetes mellitus (n = 86), hypertension (n = 225), or renal insufficiency (n = 11). Analyses were based on the remaining 1575 subjects.

Because energy intake and dietary patterns differ between men and women, we initially conducted sex-specific analyses. Within each sex, we created quartiles of linolenic acid because we did not assume linear relations between linolenic acid intake and prevalent carotid atherosclerosis. However, because dietary linolenic acid was associated with a lower odds of carotid artery plaques in both sexes and there was no interaction between sex and linolenic acid (P = 0.85), we reported combined data for men and women.

We used a logistic regression model to estimate the prevalence odds ratio of carotid artery plaques, adjusting for age (5-y categories), sex, energy intake (quartiles), education (up to high school, vocational school, and college), field center, waist-to-hip ratio (quartiles), smoking status (never and former smokers, and current smokers of 1–20 and ≥21 cigarettes/d), saturated fat (quartiles), fish consumption (0, 1, and ≥2 servings/wk), vegetable intake (≤1, 2, and 3 and ≥4 servings/wk), and linoleic acid intake (quartiles). We created 3 indicator variables, comparing subjects in the upper 3 quartiles with those in the lowest quartile of linolenic acid intake. Additional adjustment for alcohol intake (0, 1–12, 13–24, and ≥24 g/d), physical activity (quartiles), systolic blood pressure (continuous), triacylglycerol (quartiles), HDL and LDL cholesterol (quartiles), dietary fiber (quartiles), aspirin use (yes or no), and multivitamin use (yes or no) did not alter the results substantially and thus were excluded from the final model.

Because linolenic acid is converted to long-chain fatty acids [eicosapentaenoic acid (EPA) and docosahexaenoic

TABLE 1
Characteristics of the male participants in the National Heart, Lung, and Blood Institute Family Heart Study at baseline

	Quartile of total linolenic acid intake				
	1 (Low) 0.45 (0.23–0.57) g/d[1] (n = 173)	2 0.66 (0.58–0.75) g/d (n = 174)	3 0.85 (0.76–0.97) g/d (n = 176)	4 (High) 1.30 (0.98–3.48) g/d (n = 175)	P[2]
Age (y)	46.8 ± 13.4[3]	49.9 ± 13.3	49.0 ± 12.5	47.5 ± 14.1	0.77
Waist-to-hip ratio	0.94 ± 0.09	0.95 ± 0.06	0.95 ± 0.06	0.95 ± 0.07	0.20
Systolic blood pressure (mm Hg)	115.0 ± 11.8	114.1 ± 10.7	113.1 ± 9.7	113.2 ± 10.7	0.07
Exercise (min/d)	39.9 ± 41.9	34.0 ± 36.6	34.9 ± 37.3	37.4 ± 45.1	0.62
Triacylglycerol (mmol/L)	1.59 ± 1.32	1.74 ± 1.17	1.69 ± 1.33	1.64 ± 0.98	0.83
LDL cholesterol (mmol/L)	3.19 ± 0.88	3.30 ± 0.82	3.26 ± 0.82	3.07 ± 0.86	0.13
Dietary intake					
EPA and DHA (g/d)[4]	0.18 ± 0.18	0.21 ± 0.21	0.25 ± 0.26	0.26 ± 0.28	0.0002
Linoleic acid (g/d)	5.18 ± 2.30	7.24 ± 2.39	8.84 ± 2.71	12.18 ± 4.4	<0.0001
Fiber (g/d)	13.5 ± 6.4	16.4 ± 7.0	18.2 ± 7.8	23.3 ± 10.7	<0.0001
Total fat (g/d)	39.5 ± 11.7	56.9 ± 11.6	71.4 ± 14.0	102.6 ± 26.8	<0.0001
Monounsaturated fat (g/d)	15.5 ± 5.2	22.6 ± 5.3	28.3 ± 6.3	40.3 ± 11.4	<0.0001
Polyunsaturated fat (g/d)	6.0 ± 2.4	8.4 ± 2.4	10.3 ± 2.8	14.2 ± 4.6	<0.0001
Saturated fat (g/d)	14.2 ± 4.4	20.6 ± 4.4	26.3 ± 5.7	38.9 ± 11.5	<0.0001
Cholesterol (g/d)	0.16 ± 0.06	0.22 ± 0.07	0.28 ± 0.09	0.39 ± 0.16	<0.0001
Energy (kJ)	5492 ± 1237	7188 ± 1558	8495 ± 1639	11 124 ± 2412	<0.0001
Vegetables (servings/d)	1.43 ± 0.96	1.58 ± 0.96	1.67 ± 1.07	1.95 ± 1.29	<0.0001
Education (%)					0.0031
High school or less	17.3	25.3	20.6	28.0	
College or more	82.7	74.7	79.4	72.0	
Smoking status (%)					0.17
Never smokers	57.2	59.8	59.1	54.3	
Former smokers	29.5	31.6	26.7	25.7	
Current smokers	13.3	8.6	14.2	20.0	
Fish intake (%)					0.17
0 servings/wk	33.0	27.0	21.6	21.7	
1 serving/wk	40.5	48.9	48.9	48.6	
≥2 servings/wk	26.5	24.1	29.5	29.7	
Use of canola oil (%)	3.5	8.1	4.6	3.4	0.15
Mayonnaise consumption (%)	50.0	73.6	77.3	86.1	<0.0001
Nut consumption (%)	59.0	59.2	69.9	73.1	0.0012

[1] $\bar{x}$; range in parentheses.
[2] Obtained by using ANOVA for continuous variables and the chi-square test for categorical variables.
[3] $\bar{x}$ ± SD.
[4] EPA, ecosapentaenoic acid; DHA, docosahexaenoic acid.

acid (DHA)], which are also present in fish, we conducted a sensitivity analysis to explore whether the observed association between linolenic acid and carotid plaques was independent of EPA and DHA. For this, we repeated the analyses in 445 subjects who did not consume fish. Finally, we assessed whether the intakes of long-chain fatty acids, canola oil, mayonnaise, and nuts were associated with carotid plaques. We created categories of each exposure variable and used a logistic regression to estimate prevalence odds ratios. We used generalized estimating equations to account for the correlation among family members.

We also evaluated the association between total linolenic acid and carotid IMT as a continuous variable. We created quartiles of total linolenic acid and evaluated each segment (common, bifurcation, and internal carotid artery) separately. For each segment, we used the side with the greatest IMT and a fitted generalized linear model (PROC MIXED in SAS; SAS Institute Inc, Cary, NC) to estimate adjusted means of IMT. The model was adjusted for age (5-y categories), energy (quartiles), waist-to-hip ratio (quartiles), field center, and smoking status (never, former, and current smokers of 1–20 and ≥ 21 cigarettes/d). Additional adjustment for lifestyle and metabolic factors did not alter the results.

Because energy intake was positively correlated with dietary linolenic acid, we also conducted stratified analyses by quartiles of energy. Specifically, we created sex-, age-, and energy-specific quartiles of linolenic acid. However, the results were very similar to those obtained with the use of the initial analysis approach (data not shown). The α level was set at 0.05 for statistical significance. All analyses were performed by using PC-SAS (version 6.12; SAS Institute Inc).

RESULTS

Of the 1575 white participants included in the detailed analysis, 698 were men and 877 were women. The mean (± SD) age of the men was 48.3 ± 18.4 y and of the women was 50.4 ± 13.0 y. The total prevalence of any carotid artery plaque was 17.8% (n = 132 cases in men and 149 cases in women). The mean intake of linolenic acid in men was 0.82 ± 0.36 g/d and in women was 0.69 ± 0.29 g/d. The sex-specific baseline characteristics of the subjects, by quartiles of linolenic acid, are shown in **Tables 1**

TABLE 2
Characteristics of the female participants in the National Heart, Lung, and Blood Institute Family Heart Study at baseline

	Quartile of total linolenic acid intake				
	1 (Low) 0.38 (0.17–0.48) g/d[1] (n = 221)	2 0.56 (0.49–0.63) g/d (n = 221)	3 0.74 (0.64–0.84) g/d (n = 223)	4 (High) 1.09 (0.85–2.08) g/d (n = 212)	P[2]
Age (y)	51.2 ± 12.7[3]	51.0 ± 12.9	50.2 ± 12.8	49.0 ± 13.8	0.06
Waist-to-hip ratio	0.87 ± 0.09	0.86 ± 0.08	0.87 ± 0.09	0.87 ± 0.08	0.64
Systolic blood pressure (mm Hg)	109.6 ± 12.2	110.3 ± 13.2	109.0 ± 12.9	109.7 ± 14.2	0.83
Exercise (min/d)	23.9 ± 30.8	25.1 ± 27.7	24.5 ± 27.6	25.2 ± 30.0	0.72
Triacylglycerol (mmol/L)	1.40 ± 0.92	1.56 ± 1.12	1.47 ± 0.82	1.40 ± 0.75	0.79
LDL cholesterol (mmol/L)	3.16 ± 0.85	2.99 ± 0.85	3.06 ± 0.89	3.17 ± 0.86	0.74
Dietary intake					
EPA and DHA (g/d)[4]	0.16 ± 0.15	0.19 ± 0.20	0.23 ± 0.19	0.26 ± 0.22	<0.0001
Linoleic acid (g/d)	4.10 ± 1.65	5.44 ± 1.95	7.31 ± 2.76	10.28 ± 3.70	<0.0001
Fiber (g/d)	12.8 ± 5.6	16.5 ± 7.2	18.4 ± 6.1	23.09 ± 8.9	<0.0001
Total fat (g/d)	31.1 ± 9.2	44.2 ± 10.2	58.4 ± 13.7	84.0 ± 21.4	<0.0001
Monounsaturated fat (g/d)	11.9 ± 4.0	17.0 ± 4.6	22.5 ± 5.9	32.6 ± 8.8	<0.0001
Polyunsaturated fat (g/d)	4.8 ± 1.7	6.4 ± 2.0	8.6 ± 2.8	12.0 ± 3.9	<0.0001
Saturated fat (g/d)	11.3 ± 3.8	16.5 ± 4.2	21.9 ± 5.6	31.9 ± 9.2	<0.0001
Cholesterol (g/d)	0.13 ± 0.05	0.18 ± 0.06	0.23 ± 0.08	0.33 ± 0.12	<0.0001
Energy (kJ)	4594 ± 1252	6046 ± 1402	7119 ± 1458	9390 ± 2099	<0.0001
Vegetables (servings/d)	1.58 ± 0.94	1.81 ± 1.17	1.87 ± 1.00	1.85 ± 0.97	0.0050
Education (%)					0.55
High school or less	34.8	35.3	29.2	33.5	
College or more	65.2	64.7	70.8	66.5	
Smoking status (%)					0.024
Never smokers	59.7	62.9	68.2	67.5	
Former smokers	29.0	30.8	22.4	18.4	
Current smokers	11.3	6.3	9.4	14.1	
Fish intake (%)					
0 servings/wk	29.4	33.5	31.8	25.9	
1 serving/wk	49.8	43.0	39.9	42.0	
≥2 servings/wk	20.8	23.5	28.3	32.1	0.08
Use of canola oil (%)	10.9	10.0	14.8	14.6	0.29
Mayonnaise consumption (%)	57.6	52.3	65.8	70.1	0.04
Nut consumption (%)	40.7	48.9	53.4	63.7	<0.0001

[1] $\bar{x}$; range in parentheses.
[2] Obtained by using ANOVA for continuous variables and the chi-square test for categorical variables.
[3] $\bar{x}$ ± SD.
[4] EPA, ecosapentaenoic acid; DHA, docosahexaenoic acid.

and **2**, for men and women, respectively. In both men and women, a higher intake of dietary linolenic acid was associated with a higher consumption of EPA and DHA (P = 0.0002 for men and <0.0001 for women), linoleic acid, dietary fiber, total fat, mono- and polyunsaturated fat, saturated fat, dietary cholesterol, and energy intake (P < 0.0001 for each variable). In addition, linolenic acid intake was positively associated with vegetable consumption (P < 0.0001 for men and <0.005 for women).

In a logistic regression adjusting for age, sex, energy intake, education, waist-to-hip ratio, field center, smoking status, and intakes of linoleic acid, saturated fat, fish, and vegetables, we showed an inverse relation between linolenic acid and the prevalence odds of carotid plaques. From the lowest to the highest quartile of linolenic acid intake, the prevalence odds ratio (95% CI) of carotid plaques was 1.0 (referent), 0.47 (0.30, 0.73), 0.38 (0.22, 0.66), and 0.49 (0.26, 0.94), respectively (**Table 3**). Additional adjustment for systolic blood pressure, alcohol consumption, dietary fiber intake, HDL and LDL cholesterol, triacylglycerol, physical activity, and multivitamin use did not alter the results substantially (data not shown). This inverse association persisted when the analyses were restricted to 445 subjects who did not report any fish consumption and, thus, had minimal intakes of EPA and DHA (median: 0.07 g/d; range: 0–0.70 g/d). In this subgroup, the prevalence odds ratios (95% CI) were 1.0 (reference), 0.24 (0.10, 0.63), 0.21 (0.07, 0.70), and 0.46 (0.13, 1.55; NS) from the lowest to the highest quartile of linolenic acid intake, respectively, suggesting that the observed association was independent of EPA and DHA intakes. No interaction between fish consumption and linolenic acid intake on the studied association was observed (P = 0.47).

The consumption of linoleic acid, fish, and fish long-chain fatty acids was not associated with prevalent carotid plaques (data not shown). In another multivariate analysis, there was a suggestive (nonsignificant) indication for an inverse association between consumption of mayonnaise and canola oil and the prevalence odds of carotid plaques. Compared with nonusers of mayonnaise, the prevalence odds ratio of any carotid plaque was 0.86 (0.53, 1.39; NS) in subjects who used mayonnaise for salad dressing. The odds ratio associated with the use of canola oil was 0.95 (0.58, 1.54; NS). In addition, the odds ratio associated with some consumption of nuts (compared with no consumption) was 1.13 (0.84, 1.50; NS).

Using IMT as the outcome, total linolenic acid intake was inversely related to the internal and bifurcation segment, but not

TABLE 3
Prevalence odds ratio (and 95% CI) of any carotid artery plaques according to linolenic fatty acid intake in men and women combined

Quartile of linolenic acid intake[1]	No. of cases	No. of subjects	Odds ratio (95% CI)	
			Model 1[2]	Model 2[3]
1: 0.40 g/d (0.17–0.51) g/d, low	78	390	1.0	1.0
2: 0.60 g/d (0.52–0.68) g/d	63	396	0.47 (0.32, 0.71)	0.47 (0.30, 0.73)
3: 0.79 g/d (0.69–0.89) g/d	65	393	0.43 (0.27, 0.68)	0.38 (0.22, 0.66)
4: 1.19 g/d (0.90–3.48) g/d, high	75	396	0.58 (0.34, 0.97)	0.49 (0.26, 0.94)
P for trend[4]			0.030	0.065

[1] $\bar{x}$; range in parentheses.
[2] Used generalized estimation equations adjusted for age (5-y categories), sex, energy intake (quartiles), education (3 categories), and linoleic acid intake (quartiles).
[3] Used generalized estimation equations adjusted for age (5-y categories), sex, energy (quartiles), education (3 categories), field center (4 categories), smoking status (4 categories), waist-to-hip ratio (quartiles), and intakes of linoleic acid (quartiles), saturated fat (continuous), fish (0, 1, or ≥2 servings/wk), and vegetables (4 categories).
[4] *P* for interaction between sex and linolenic acid intake = 0.85.

with the common carotid artery (**Table 4**). From the lowest to the highest quartile of linolenic acid intake, mean IMT values were 0.70, 0.63, 0.60, and 0.64 mm, respectively, for the internal carotid artery (*P* for trend = 0.014) in a model that adjusted for age, sex, energy intake, waist-to-hip-ratio, field center, and smoking status. Corresponding means were 0.99, 0.91, 0.86, and 0.94 mm, respectively, for the bifurcation (*P* for trend = 0.0008) and 0.72, 0.70, 0.70, and 0.71 mm, respectively, for the common carotid artery (*P* for trend = 0.31).

DISCUSSION

In this cross-sectional study, we found that dietary linolenic acid was associated with a lower prevalence odds ratio of carotid artery plaques. There was little evidence for a dose-response relation. This association was independent of long-chain n−3 fatty acid intake. After adjustment for major risk factors for atherosclerosis, dietary linoleic acid, fish consumption, and fish n−3 fatty acid intake were not related significantly to prevalent carotid plaques. When examined as a continuous variable, total linolenic acid intake was inversely associated with IMT at 2 of the 3 sites.

Although the potential benefits of dietary n−3 fatty acids have been shown for CAD incidence and mortality (1–3, 7), it is not known whether n−3 fatty acids have a direct effect on the pathogenesis of carotid atherosclerosis. Contrary to the finding of no association between linolenic acid intake and CAD among men in the Zutphen Elderly Study (23), several prospective studies have reported an inverse association. In the Lyon Diet Heart Study, de Lorgeril et al (2) showed a significantly lower incidence of death from recurrent cardiovascular disease in the group of patients with CAD randomly assigned to consume a Mediterranean diet enriched with α-linolenic acid than in the subjects who received usual care. In addition, Hu et al (8) compared the highest with the lowest quintile of α-linolenic acid in the Nurses Health Study and found a 45% reduction in incident fatal myocardial infarction. In the Multiple Risk Factor Intervention Trial (5), a greater α-linolenic intake was associated with a lower total mortality rate. Our findings suggest that a cardioprotective effect of linolenic acid may be observed at an early stage of the atherosclerotic process, reflected by plaque formation in the carotid arteries.

Physiologic mechanisms by which linolenic acid might protect against carotid artery disease or CAD are not well known. The effects of linolenic acid could be mediated through the synthesis of long-chain polyunsaturated fatty acids with cardioprotective effects: after ingestion, α-linolenic acid is readily converted to EPA and slowly to DHA (24). Both EPA and DHA have been shown to reduce cardiac arrhythmia (25, 26). EPA may also protect against thrombosis (27, 28) through the inhibition of platelet cyclooxygenase. Lowering plasma triacylglycerol (29, 30), increasing endothelial nitric oxide (31), and attenuating inflammation (32) have also been proposed as additional mechanisms by which linolenic acid might favorably influence the risk of atherosclerosis.

The present study has some limitations. First, given the cross-sectional design of our study, we were unable to infer causality between linolenic acid intake and carotid artery disease. Second, dietary nutrients were computed on the basis of information obtained through a

TABLE 4
Adjusted mean values of carotid intima-media thickness according to dietary linolenic acid intake and carotid artery segments[1]

Quartile of linolenic acid intake[2]	Intima-media thickness
Internal carotid artery	
1: 0.40 (0.18–0.51) g/d, low	0.70 ± 0.03 [184]
2: 0.60 (0.52–0.68) g/d	0.63 ± 0.02 [191]
3: 0.78 (0.69–0.88) g/d	0.60 ± 0.02 [181]
4: 1.17 (0.89–2.11) g/d, high	0.64 ± 0.03 [189]
P for trend	0.014
Bifurcation segment of the carotid artery	
1: 0.40 (0.17–0.51) g/d, low	0.99 ± 0.03 [288]
2: 0.59 (0.52–0.67) g/d	0.91 ± 0.03 [272]
3: 0.78 (0.68–0.89) g/d	0.86 ± 0.03 [284]
4: 1.19 (0.90–2.26) g/d, high	0.94 ± 0.03 [276]
P for trend	0.0008
Common carotid artery	
1: 0.40 (0.17–0.51), g/d low	0.72 ± 0.01 [340]
2: 0.60 (0.52–0.67) g/d	0.70 ± 0.01 [331]
3: 0.78 (0.68–0.89) g/d	0.70 ± 0.01 [348]
4: 1.20 (0.90–3.48) g/d, high	0.71 ± 0.01 [332]
P for trend	0.31

[1] $\bar{x}$ ± SE; *n* in brackets. Means were adjusted for sex, age (continuous), energy (quartiles), waist-to-hip ratio (quartiles), field center, and smoking status (never, former, and current smokers of 1–20 or ≥21 cigarettes/d) by using a random-effects model (PROC MIXED; SAS Institute Inc, Cary, NC).
[2] $\bar{x}$; range in parentheses.

food-frequency questionnaire, which may have resulted in reporting bias and affected the results. Third, because different components of the diet are strongly intercorrelated, it is difficult to conclude with certainty that our results were due to linolenic acid and not to other dietary components. Fourth, the generalizability of our findings was limited by the fact that our random sample was limited to white subjects. Fifth, we were unable to differentiate between α- and γ-linolenic acid; however, in apolipoprotein E knockout mice, dietary γ-linolenic acid significantly reduced atherosclerotic lesions and reduced aortic IMT at 20 and 30 wk (33). Nevertheless, there were strengths of the study, including the large sample size, the collection of data with the use of standardized and valid techniques, the availability of data for both men and women, and the multicenter design that allowed the collection of data from white subjects throughout the country. In conclusion, our findings indicate that a higher intake of dietary linolenic acid is related to a lower prevalence odds ratio of carotid artery plaques and may be inversely related to carotid IMT.

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LD designed the project, completed the data analyses, and prepared the manuscript; ARF participated in the data collection and critical review of the manuscript; MAP and SCH participated in the study design, data collection and cleaning, and critical review of the manuscript; RCE participated in the study design, data collection and cleaning, data analyses, and critical review of the manuscript. None of the coauthors had a conflict of interest to disclose.

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