

Relation between dietary linolenic acid and coronary artery disease in the National Heart, Lung, and Blood Institute Family Heart Study¹⁻³

Luc Djoussé, James S Pankow, John H Eckfeldt, Aaron R Folsom, Paul N Hopkins, Michael A Province, Yuling Hong, and R Curtis Ellison

ABSTRACT

Background: Epidemiologic studies suggest that a higher consumption of eicosapentaenoic acid and docosahexaenoic acid is associated with a reduced risk of cardiovascular disease. Studies in humans and animals also reported an inverse association between α -linolenic acid and cardiovascular disease morbidity and mortality.

Objective: We examined the relation between dietary linolenic acid and prevalent coronary artery disease (CAD).

Design: We studied 4584 participants with a mean (\pm SD) age of 52.1 \pm 13.7 y in the National Heart, Lung, and Blood Institute Family Heart Study in a cross-sectional design. Participants' diets were assessed with a semiquantitative food-frequency questionnaire. For each sex, we created age- and energy-adjusted quintiles of linolenic acid, and we used logistic regression to estimate prevalent odds ratios for CAD.

Results: From the lowest to the highest quintile of linolenic acid, the prevalence odds ratios of CAD were 1.0, 0.77, 0.61, 0.58, and 0.60 for the men (P for trend = 0.012) and 1.0, 0.57, 0.52, 0.30, and 0.42 for the women (P for trend = 0.014) after adjustment for age, linoleic acid, and anthropometric, lifestyle, and metabolic factors. Linoleic acid was also inversely related to the prevalence odds ratios of CAD in the multivariate model (0.60 and 0.61 in the second and third tertiles, respectively) after adjustment for linolenic acid. The combined effect of linoleic and linolenic acids was stronger than the individual effects of either fatty acid.

Conclusions: A higher intake of either linolenic or linoleic acid was inversely related to the prevalence odds ratio of CAD. The 2 fatty acids had synergistic effects on the prevalence odds ratio of CAD. *Am J Clin Nutr* 2001;74:612-9.

KEY WORDS Linolenic acid, linoleic acid, n-3 fatty acids, n-6 fatty acids, diet, coronary artery disease, food-frequency questionnaire, National Heart, Lung, and Blood Institute Family Heart Study

INTRODUCTION

A high consumption of n-3 fatty acids is associated with a lower risk of coronary artery disease (CAD) incidence and mortality (1-6). In animal experiments, a higher concentration of α -linolenic acid was associated with a lower incidence of ven-

tricular fibrillation and cardiac deaths (7, 8). α -Linolenic acid may also reduce the risk of CAD because of its antithrombotic effects (9). Data on the effects of linolenic acid in humans are limited. de Lorgeril et al (4) showed the protective effects of α -linolenic acid in a secondary prevention trial of myocardial infarction. In a large prospective study, a higher concentration of α -linolenic acid was associated with a reduced risk of fatal ischemic heart disease in women (10). The mechanisms by which linolenic acid affects the risk of CAD in humans are not well known. In addition, it is not known whether this effect is modified by 1) the ratio of linoleic to linolenic acid or 2) the ratio of polyunsaturated to saturated fatty acids (P:S). The conversion of α -linolenic acid to eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) may be affected by the concentration of linoleic acid because linoleic and linolenic acids use the same set of enzymes for desaturation and chain elongation (11). The largest proportion of total linolenic acid is in the α form. Linolenic acid is found mostly in flaxseed oil, soy oil, canola oil, and English walnuts, and in smaller concentrations in green leafy vegetables, corn oil, almonds, and hazelnuts (12, 13).

The purpose of the present study was to assess the relation between reported intake of linolenic acid and prevalent CAD in 4584 male and female participants of the National Heart, Lung, and Blood Institute (NHLBI) Family Heart Study and to examine whether such a relation was influenced by 1) fish consumption,

¹From the Section of Preventive Medicine and Epidemiology, Evans Department of Medicine, the School of Medicine, Boston University; the Department of Epidemiology, the School of Public Health, University of North Carolina at Chapel Hill; the Department of Laboratory Medicine and Pathology, Fairview-University Medical Center, Minneapolis; the Division of Epidemiology, University of Minnesota, Minneapolis; the Department of Cardiovascular Genetics, University of Utah, Salt Lake City; and the Division of Biostatistics, Washington University, St Louis.

²Supported in part by the National Heart, Lung, and Blood Institute cooperative agreement grants U01 HL56563, U01 HL56564, U01 HL56565, U01 HL56566, U01 HL56567, U01 HL56568, and U01 HL56569 and the Institute on Lifestyle and Health, School of Medicine, Boston University.

³Reprints not available. Address correspondence to L Djoussé, School of Medicine, Boston University, Room B-612, 715 Albany Street, Boston, MA 02118. E-mail: ldjouss@bu.edu.

Received August 15, 2000.

Accepted for publication January 17, 2001.

2) the P:S, and 3) the ratio of linoleic to linolenic acid. In a secondary analysis, we assessed the relation between linoleic acid and CAD, adjusting for linolenic fatty acid and the interaction between the 2 fatty acids.

SUBJECTS AND METHODS

Subjects

The NHLBI Family Heart Study is a multicenter, population-based study designed to identify and evaluate genetic and non-genetic determinants of CAD, preclinical atherosclerosis, and cardiovascular disease risk factors. A description of the methods and design was previously published (14). Families in the study were chosen either at random (random group) or on the basis of a higher-than-expected risk of CAD (high-risk group) from previously established population-based cohort studies: the Framingham Heart Study (in Framingham, MA), the Atherosclerosis Risk in Communities (ARIC) study in 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 reflects a comparison of the family's age- and sex-specific incidence of CAD with that expected in the general population (15).

Between 1993 and 1995, individuals participating in each of the parent studies were selected at random and invited to provide an updated family-health history that contained information about their parents, children, and siblings. Of the 4679 individuals contacted, 3150 (67%) responded. Their family members were then contacted and self-reported health data were obtained from a total of 22908 individuals (86% of those contacted). Of the families who responded to the health questionnaire, 588 were chosen randomly and 566 were selected on the basis of a higher-than-expected risk of CAD. All members of these families were invited to attend 1 of the 4 study clinics for a clinical evaluation lasting ≈ 4 h. The evaluation included a detailed medical and lifestyle history, which was obtained through an interview. All interviewers were trained centrally and required periodic certification; standardization of interviews was facilitated by a periodic review of sound recorded interviews and by the frequent circulation of the distributions of responses obtained by the different interviewers and the different centers. The study protocol was reviewed and approved by each of the participating institutions.

Dietary assessment

Dietary information was collected with the use of a semi-quantitative food-frequency questionnaire that was administered by the staff and developed by Willett (16, 17). The reproducibility and validity of the food-frequency questionnaire was documented elsewhere (18). From the food-frequency questionnaire, intake of specific nutrients was computed by multiplying the frequency of consumption of an item by the nutrient content of specified portions. The compositions of linolenic and linoleic acids and other nutrients were obtained from the HARVARD UNIVERSITY FOOD COMPOSITION DATABASE (Boston, MA), which was created from sources from the US Department of Agriculture (19) and from the food manufacturers' information. This database only provides the content of total linolenic acid. We used the total linolenic acid content in the present analyses because 1) the relation of α -linolenic acid to CAD was similar to the association of total linolenic acid to ischemic heart disease in a large prospective study (10), and 2) it was reported

that the main sources of dietary γ -linolenic acid are beef fats and other animal fats and that γ -linolenic concentrations in these fats are very low (20).

Ascertainment of CAD

Prevalent CAD was assessed from the participants' medical history and a 12-lead electrocardiogram. Individuals were considered to have CAD if they reported a history of myocardial infarction, percutaneous transluminal coronary angioplasty, or coronary artery bypass graft that could be validated by a review of their medical records, or if abnormal Q waves (Minnesota codes 1.1–1.2) were detected on a resting 12-lead electrocardiogram (21).

Other variables

The participants were interviewed about cigarette smoking, alcohol intake, and education levels during the clinic visit, and their use of aspirin, multivitamins, vitamins E or C, or hormone replacement therapy was assessed by using a questionnaire and a medication inventory. Information about the type of oil the participants used to deep-fry food, the frequency of their fish intake, and their vegetable consumption was obtained with the food-frequency questionnaire. Physical activity levels for the previous year were estimated by using their self-reports. Anthropometric data were collected while the participants were wearing scrub suits. A balance scale was used to measure body weight and a wall-mounted vertical ruler was used to measure height. Diabetes mellitus was defined as the following: 1) a self-reported history of diabetes, 2) a fasting glucose concentration ≥ 7.8 mmol/L, or 3) the current use of a hypoglycemic agent. LDL-cholesterol concentrations were measured by using the method of Friedewald (22), except for participants with triacylglycerol concentrations > 4.5 mmol/L, for whom concentrations were measured by ultracentrifugation (23). Triacylglycerol concentrations were measured by using a peroxidase-coupled method (24). Total cholesterol concentrations were measured by using a commercial cholesterol oxidase method on a Roche Cobas Fara centrifugal analyzer (Boehringer Mannheim Diagnostics, Indianapolis) (25). HDL cholesterol was measured after precipitation of the other lipoprotein fractions by using dextran sulfate (26).

Statistics

Of the 5975 participants who had a clinic examination, 1391 were excluded from the analysis because of missing covariates ($n = 275$) or probable errors on their food-frequency questionnaires ($n = 1116$), ie, unreliable answers or 18 questions were left blank ($n = 682$) or energy intakes were outside a priori ranges [acceptance range: 3347.2–17572.8 kJ for the men (16) and 2510.4–14644 kJ for the women (27) ($n = 434$)].

Data on the African Americans were limited. There were only 15 prevalent cases of CAD in 178 African Americans (5 cases in 57 men; 10 cases in 121 women). We did not assume that the relation between linolenic acid and CAD in African Americans was similar to that of the whites because the African Americans had a higher mean intake of linolenic acid (0.83 compared with 0.74 g/d), and they were older than the whites (53.7 compared with 52.11 y). In addition, the African Americans had a higher prevalence of diabetes mellitus (14.6% compared with 6.1%) and smoking (25% compared with 14%), a higher proportion of fish consumption (92% compared with 73%), a higher mean systolic blood pressure, higher concentrations of linoleic acid and fish $n-3$ fatty acids, and higher HDL-cholesterol concentrations than did the whites. Because the limited number of prevalent cases of

TABLE 1
Baseline characteristics of 2024 white men in the National Heart, Lung, and Blood Institute Family Heart Study¹

Characteristics	Age- and energy-adjusted quintiles of total linolenic acid intake					P for trend ²
	1 (low) 0.53 (0.19–0.97) g/d ² (n = 392)	2 0.67 (0.35–1.18) g/d (n = 408)	3 0.78 (0.41–1.35) g/d (n = 414)	4 0.90 (0.45–1.73) g/d (n = 411)	5 (high) 1.14 (0.55–3.48) g/d (n = 399)	
Age (y)	51.3 ± 14.0 ⁴	51.4 ± 14.3	52.1 ± 13.8	52.0 ± 14.1	52.0 ± 13.6	0.38
Waist-to-hip ratio	0.95 ± 0.06	0.96 ± 0.08	0.96 ± 0.06	0.96 ± 0.07	0.97 ± 0.07	0.03
Systolic BP (mm Hg)	120.1 ± 16.8	120.2 ± 16.5	119.4 ± 16.4	119.4 ± 17.1	118.2 ± 15.5	0.07
Education (y)	16.9 ± 4.0	16.8 ± 3.8	16.7 ± 3.9	16.4 ± 4.0	15.9 ± 3.9	0.0001
Physical activity (min/d)	39.7 ± 48.4	36.1 ± 42.8	36.7 ± 39.7	33.9 ± 37.6	32.3 ± 38.9	0.01
LDL cholesterol (mmol/L)	3.3 ± 0.9	3.2 ± 0.8	3.3 ± 0.8	3.3 ± 0.9	3.3 ± 0.8	0.53
EPA and DHA (g/d)	0.23 ± 0.20	0.25 ± 0.23	0.25 ± 0.23	0.23 ± 0.22	0.22 ± 0.20	0.21
P:S	0.47 ± 0.16	0.43 ± 0.14	0.41 ± 0.13	0.40 ± 0.13	0.41 ± 0.14	0.0001
Linoleic:linolenic acid	12.3 ± 5.1	11.1 ± 3.7	10.5 ± 3.2	10.0 ± 2.8	9.0 ± 2.6	0.0001
Dietary fiber intake (g/d)	16.7 ± 8.4	17.2 ± 7.9	17.9 ± 7.9	18.5 ± 9.1	18.1 ± 9.2	0.006
High-risk group (%)	57.9	50.0	47.6	52.3	52.4	0.32
Diabetes mellitus (%)	4.1	5.6	5.6	8.5	9.0	0.002
Aspirin use (%)	43.4	39.7	41.8	37.5	35.1	0.01
Current smokers (%)	13.5	13.0	15.5	15.1	17.0	0.10
Alcohol drinkers (%)	53.1	44.6	43.9	34.5	33.6	0.0001
Canola oil use (%)	7.6	6.9	7.0	7.5	8.8	0.45
Olive oil use (%)	0.8	0.3	1.5	2.7	1.1	0.49
Multivitamin use (%)	21.4	20.1	19.1	19.7	19.8	0.59
Fish intake of ≥ 1 serving/wk (%)	74.7	76.9	76.1	76.4	73.9	0.68

¹EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid; P:S, ratio of polyunsaturated to saturated fatty acids; BP, blood pressure.

² \bar{x} ; range in parentheses.

³Midpoints of each quintile were used as continuous variables in a linear or logistic model.

⁴ $\bar{x} \pm$ SD.

CAD in the African Americans yielded unstable estimations in stratified analyses, the reported analyses are limited to the whites.

We created sex-specific quintiles of linolenic acid and adjusted them for age and energy intake for the following reasons: 1) eating patterns (number of servings and the amount of energy) differed by sex; 2) energy intake, which is influenced by body size, physical activity levels, and metabolic efficiency (28), differed by sex; and 3) we did not assume linear relations between linolenic acid and prevalent CAD. For each sex, we created quintiles of age. Within each sex-specific age category, we created quintiles of energy. Within each of the 25 age- and energy-specific groups, we generated quintiles of linolenic acid (referred to as age- and energy-adjusted quintiles of linolenic acid).

We used a stepwise regression model to select covariates for adjustment (P for selection < 0.2). Model 1 included CAD as an outcome, and age, age squared, the risk group for CAD (random group compared with high-risk group), field center (4 categories), and 4 indicator variables that compared individuals in the upper 4 quintiles with those in the lowest quintile of linolenic acid intake. Model 2 included all the variables that were in model 1 and the participants' waist-to-hip ratios (3 categories), their education level, prevalent diabetes mellitus, amount of smoking (3 categories), alcohol intake, physical activity level, systolic blood pressure, linoleic acid intake (tertiles), the P:S (tertiles), fish consumption (3 categories), dietary fiber intake, multivitamin use, aspirin use, and LDL-cholesterol, HDL-cholesterol, and triacylglycerol concentrations. Additional adjustments for the use of vitamin E or C and hormone replacement therapy for women did not alter the results. To test for a linear trend across increasing categories of linolenic acid intake, we treated the categories as a continuous variable and used the median linolenic acid intake of each category as the correspond-

ing value. We used a logistic model for categorical variables or a generalized linear model for continuous variables.

To assess the influence of fish intake (rich in n-3 fatty acid) on the studied association, we created 3 categories of fish consumption: 0, 1, and ≥ 2 servings/wk and conducted a stratified analysis comparing prevalence odds ratio of CAD in the upper 4 quintiles with the lowest quintile of linolenic acid. We also evaluated the relation between linoleic acid and CAD across tertiles of the ratio of linoleic to linolenic acid, the P:S, and linoleic acid intake. To assess the combined effects of linolenic and linoleic acid intake, we cross-classified tertiles of linoleic acid and tertiles of linolenic acid and created 8 dummy variables by using the group with the lowest tertile of each of the 2 fatty acids as a reference category. We used a bootstrap method in a logistic regression model to correct for the correlation among family members. The bootstrap method, which randomly selects one individual per family for modeling, ran > 300 replications. 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, Cary, NC).

RESULTS

Of the 4406 whites included in the detailed analysis, 2024 were men and 2382 were women. The mean age (\pm SD) of the men was 51.8 ± 13.9 y and of the women was 52.4 ± 13.6 y. The total prevalence of CAD was 11% [n = 362 cases in the men (90 in the random group and 272 in the high-risk group) and n = 123 cases in the women (20 in the random group and 103 in the high-risk group)]. The mean intake of linolenic acid was 0.81 ± 0.35 g/d for the men and 0.68 ± 0.29 g/d for the women. Sex-specific baseline characteristics by age- and energy-adjusted quintiles of linolenic acid intake are shown in **Tables 1** and **2**. In

TABLE 2

Baseline characteristics of 2382 white women in the National Heart, Lung, and Blood Institute Family Heart Study¹

Characteristics	Age- and energy-adjusted quintiles of total linolenic acid intake					P for trend ³
	1 (low) 0.46 (0.13–0.84) g/d ² (n = 455)	2 0.58 (0.26–1.13) g/d (n = 484)	3 0.65 (0.031–1.16) g/d (n = 486)	4 0.76 (0.40–1.35) g/d (n = 484)	5 (high) 0.96 (0.48–2.29) g/d (n = 473)	
Age (y)	51.9 ± 13.9 ⁴	52.3 ± 13.9	52.7 ± 13.5	52.4 ± 13.4	52.5 ± 13.6	0.57
Waist-to-hip ratio	0.87 ± 0.09	0.88 ± 0.09	0.88 ± 0.08	0.88 ± 0.09	0.88 ± 0.08	0.008
Systolic BP (mm Hg)	113.9 ± 17.9	115.2 ± 18.5	115.5 ± 18.9	114.5 ± 19.2	115.5 ± 18.7	0.35
Education (y)	15.6 ± 3.6	15.9 ± 3.6	15.4 ± 3.7	15.6 ± 3.7	15.2 ± 3.6	0.05
Physical activity (min/d)	27.7 ± 39.4	27.1 ± 32.7	21.6 ± 28.0	22.7 ± 22.0	22.0 ± 32.0	0.002
LDL cholesterol (mmol/L)	3.2 ± 0.9	3.2 ± 0.9	3.2 ± 0.9	3.1 ± 0.9	3.2 ± 0.9	0.59
EPA and DHA (g/d)	0.19 ± 0.19	0.23 ± 0.20	0.24 ± 0.23	0.24 ± 0.23	0.23 ± 0.22	0.04
P:S	0.47 ± 0.18	0.43 ± 0.15	0.42 ± 0.15	0.41 ± 0.16	0.40 ± 0.15	0.0001
Linoleic:linolenic acid	12.3 ± 6.1	10.7 ± 3.9	10.2 ± 3.2	9.3 ± 3.0	8.4 ± 2.3	0.0001
Dietary fiber intake (g/d)	16.6 ± 7.8	18.0 ± 7.8	17.8 ± 8.1	18.0 ± 8.2	17.7 ± 8.5	0.09
High-risk group (%)	51.2	54.6	57.2	48.6	53.9	0.98
Diabetes mellitus (%)	4.2	6.2	8.0	3.3	6.8	0.42
Aspirin use (%)	32.3	30.2	32.1	30.6	32.1	0.95
Current smokers (%)	13.6	10.0	11.1	13.0	16.5	0.04
Alcohol drinkers (%)	34.5	32.4	25.9	20.7	21.1	0.0001
Canola oil use (%)	9.9	13.2	13.6	12.0	16.7	0.007
Olive oil use (%)	1.3	2.5	2.3	2.5	1.7	0.84
Multivitamin use (%)	30.8	28.7	25.7	26.0	22.8	0.004
Fish intake of ≥ 1 serving/wk (%)	67.0	71.5	72.0	70.3	69.1	0.77

¹EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid; P:S, ratio of polyunsaturated to saturated fatty acids; BP, blood pressure.

² \bar{x} ; range in parentheses.

³Midpoints of each quintile were used as continuous variables in a linear or logistic model.

⁴ $\bar{x} \pm SD$.

the men (Table 1), a higher intake of dietary linolenic acid was associated with a higher waist-to-hip ratio, a significantly lower education level, a significantly lower physical activity level, a significantly lower P:S and ratio of linoleic to linolenic acid, a significantly higher dietary fiber intake, a significantly higher prevalence of diabetes mellitus, a lower prevalence of aspirin use, and a significantly lower prevalence of current alcohol drinkers. In the women (Table 2), a higher intake of dietary linolenic acid was associated with a significantly higher waist-to-hip ratio, a significantly lower physical activity level, a higher concentration of EPA and DHA, a significantly lower P:S and ratio of linoleic to linolenic acid, a higher prevalence of current

smokers, a significantly lower prevalence of current alcohol drinkers, a significantly higher percentage of canola oil use, and a significantly lower percentage of multivitamin use.

Linolenic acid intake was inversely associated with the prevalence odds ratio of CAD (Table 3). From the lowest to the highest quintile of linolenic acid, the prevalence odds ratios were 1.0 (reference), 0.77, 0.61, 0.58, and 0.60 in the men and 1.0, 0.57, 0.52, 0.30, and 0.42 in the women after adjustment for age, age squared, field center (4 categories), risk group, energy intake, linoleic acid intake, fish intake, plasma cholesterol, and anthropometric, lifestyle, and metabolic factors. When limited to randomly selected study participants, the data suggested an inverse

TABLE 3

Prevalence odds ratios (95% CIs) of coronary artery disease (CAD) in the National Heart, Lung, and Blood Institute Family Heart Study¹

	Age- and energy-adjusted quintiles of linolenic acid intake ²					P for trend
	1 (low) (n = 392 M, 455 W)	2 (n = 408 M, 484 W)	3 (n = 414 M, 486 W)	4 (n = 411 M, 484 W)	5 (high) (n = 399 M, 473 W)	
Men						
Cases of CAD	93	76	66	65	62	
Model 1	1.0	0.60 (0.43, 0.83) ³	0.54 (0.38, 0.74)	0.53 (0.38, 0.77)	0.53 (0.38, 0.74)	0.0004
Model 2	1.0	0.77 (0.52, 1.13)	0.61 (0.39, 0.96)	0.58 (0.38, 0.87)	0.60 (0.39, 0.92)	0.012
Women						
Cases of CAD	27	23	32	20	21	
Model 1	1.0	0.66 (0.36, 1.19)	0.70 (0.39, 1.28)	0.49 (0.27, 0.89)	0.66 (0.40, 1.10)	0.09
Model 2	1.0	0.57 (0.29, 1.10)	0.52 (0.24, 1.13)	0.30 (0.13, 0.68)	0.42 (0.22, 0.84)	0.014

¹Model 1 used bootstrap logistic regression (>300 replications) and adjusted for the following variables: age, age squared, field center (4 categories), and risk group; model 2 adjusted for the variables of model 1 in addition to the following variables: diabetes mellitus, alcohol intake (g/d), smoking status (3 categories), LDL cholesterol, HDL cholesterol, triacylglycerol, systolic blood pressure, education level, dietary fiber intake, multivitamin use, aspirin use, linoleic acid intake (tertiles), ratio of polyunsaturated to saturated fatty acids, fish intake (3 categories), and waist-to-hip ratio (3 categories).

²The mean intakes (g/d) from the lowest to the highest quintile are 0.53 (range: 0.19–0.97), 0.67 (0.35–1.18), 0.78 (0.41–1.35), 0.90 (0.45–1.73), and 1.14 (0.55–3.48) for the men and 0.46 (0.13–0.84), 0.58 (0.26–1.13), 0.65 (0.31–1.16), 0.76 (0.40–1.35), and 0.96 (0.48–2.29) for the women.

TABLE 4

Influence of fish consumption on the relation of linolenic acid intake to the prevalence odds ratios (95% CIs) of coronary artery disease in the National Heart, Lung, and Blood Institute Family Heart Study¹

Fish intake	Age- and energy-adjusted quintiles of total linolenic acid intake ²					P for trend
	1 (low)	2	3	4	5 (high)	
0 serving/wk (n = 1207)	1.0	0.71 (0.23, 2.18)	0.81 (0.33, 2.30)	0.62 (0.16, 2.33)	0.38 (0.12, 1.27)	0.17
1 serving/wk (n = 1976)	1.0	1.11 (0.59, 2.11)	2.19 (1.01, 4.78)	0.71 (0.25, 1.96)	0.94 (0.28, 3.12)	0.67
≥2 servings/wk (n = 1223)	1.0	0.70 (0.41, 1.23)	1.01 (0.51, 2.03)	0.47 (0.28, 1.00)	0.35 (0.14, 0.92)	0.05

¹Determined by bootstrap logistic regression (>300 replications) and adjusted for age, age squared, sex, field center (4 categories), risk group, diabetes mellitus, alcohol intake (g/d), smoking status (3 categories), LDL cholesterol, HDL cholesterol, triacylglycerol, systolic blood pressure, education level, dietary fiber intake, multivitamin use, aspirin use, linoleic acid intake (tertiles), ratio of polyunsaturated to saturated fatty acids (tertiles), and waist-to-hip ratio (3 categories).

²The mean intakes (g/d) from the lowest to the highest quintile are 0.37 (0.18–0.46), 0.53 (0.47–0.59), 0.65 (0.60–0.72), 0.81 (0.73–0.92), and 1.20 (0.93–2.50) for 0 serving/wk; 0.37 (0.13–0.47), 0.55 (0.48–0.61), 0.69 (0.62–0.77), 0.87 (0.78–0.97), and 1.26 (0.98–2.49) for 1 serving/wk; and 0.39 (0.23–0.49), 0.57 (0.50–0.63), 0.71 (0.64–0.78), 0.88 (0.79–0.98), and 1.27 (0.99–3.48) for ≥2 servings/wk.

relation between linolenic acid intake and CAD [β coefficient \pm SE for linolenic acid (g): -0.81097 ± 2.54504].

Stratified analyses

When stratified by the number of fish servings per week, the trend suggested an inverse relation between linolenic acid intake and CAD in the noneaters of fish and in the category with the highest weekly fish intake (**Table 4**). Fish n-3 fatty acid intake was inversely related to the prevalence odds ratio of CAD (data not shown) in the multivariate analysis. After adjustment for fish n-3 fatty acid intake, fish intake was not associated with CAD in the current study; from the lowest to the highest category of fish intake, the prevalence odds ratios of CAD were 1 (reference), 1.16 (0.64–2.11), and 1.19 (0.61–2.32). When the analysis was repeated to assess whether the relation was influenced by the P:S, the trend indicated an inverse association, mostly in the first 2 tertiles, of the P:S (NS; **Table 5**). Last, the inverse association between linolenic acid and the prevalence odds ratio of CAD was seen in all tertiles of the ratio of linoleic to linolenic acid although the trend was significant only in the lowest tertile of the ratio of linoleic to linolenic acid (range: 2.3–8.4; **Table 6**).

TABLE 5

Influence of the ratio of polyunsaturated to saturated fatty acids on the relation of linolenic acid intake to the prevalence odds ratios (95% CIs) of coronary artery disease in the National Heart, Lung, and Blood Institute Family Heart Study¹

Tertiles of the ratio of polyunsaturated to saturated fatty acids	Age- and energy-adjusted quintiles of total linolenic acid intake ²					P for trend
	1 (low)	2	3	4	5 (high)	
1: 0.28 (0.10–0.34) ³ (n = 1468)	1.0	0.72 (0.28, 1.81)	0.82 (0.26, 2.51)	0.60 (0.18, 1.98)	0.65 (0.09, 4.55)	0.57
2: 0.40 (0.35–0.46) (n = 1469)	1.0	0.57 (0.23, 1.42)	0.78 (0.32, 1.95)	0.36 (0.12, 1.10)	0.43 (0.12, 1.50)	0.14
3: 0.59 (0.47–1.86) (n = 1469)	1.0	1.36 (0.76, 2.41)	1.56 (0.86, 2.81)	1.64 (0.88, 3.09)	0.86 (0.36, 2.05)	0.86

¹Determined by bootstrap logistic regression (>300 replications) and adjusted for age, age squared, sex, field center (4 categories), risk group, diabetes mellitus, alcohol intake (g/d), smoking status (3 categories), LDL cholesterol, HDL cholesterol, triacylglycerol, systolic blood pressure, education level, dietary fiber intake, multivitamin use, aspirin use, linoleic acid intake (tertiles), fish intake (3 categories), and waist-to-hip ratio (3 categories). None of the trends were significant.

²The mean intakes (g/d) from the lowest to the highest quintile are 0.41 (0.19–0.51), 0.59 (0.52–0.66), 0.73 (0.67–0.81), 0.90 (0.82–1.00), and 1.32 (1.01–2.50) for tertile 1; 0.39 (0.13–0.49), 0.56 (0.50–0.63), 0.70 (0.64–0.77), 0.87 (0.78–0.98), and 1.23 (0.99–2.42) for tertile 2; and 0.34 (0.17–0.42), 0.49 (0.43–0.55), 0.62 (0.56–0.68), 0.78 (0.69–0.88), and 1.18 (0.89–3.48) for tertile 3.

³ \bar{x} ; range in parentheses.

Relation between the linoleic acid intake and the prevalence odds ratio of CAD

In the multivariate logistic model that adjusted for linolenic acid intake and all other relevant covariates, linoleic acid intake was associated with a 39% lower prevalence odds ratio of CAD when the third and the first tertiles of linoleic acid were compared (**Table 7**). As shown in **Table 8**, both linoleic acid and linolenic acid intakes were independently and jointly associated with lower prevalence odds ratio of CAD. Participants in the highest tertile of both linoleic acid and linolenic acid intakes had 56% lower prevalence odds ratio than did the participants in the lowest tertile of both fatty acid intakes (95% CI: 0.17, 1.17). Additional analysis, which was limited to the randomly selected participants, suggested an inverse relation between linoleic acid and CAD [β coefficient \pm SE for linoleic acid (g): -0.17088 ± 0.17029].

DISCUSSION

We found an inverse relation between age- and energy-adjusted indexes of reported intake of linolenic acid and prevalent CAD for both men and women. This reduction in the risk of

TABLE 6

Influence of the ratio of linoleic to linolenic acid on the relation of linolenic acid intake to the prevalence odds ratios (95% CIs) of coronary artery disease in the National Heart, Lung, and Blood Institute Family Heart Study¹

Tertiles of the ratio of linoleic to linolenic acid	Age-, sex-, and energy-adjusted quintiles of linolenic acid intake ²					P for trend
	1 (low)	2	3	4	5 (high)	
1: 6.94 (2.3–8.4) ³ (n = 1468)	1.0	1.11 (0.59, 2.10)	0.73 (0.34, 1.60)	0.58 (0.23, 1.47)	0.47 (0.15, 1.50)	0.06
2: 9.76 (8.5–11.1) (n = 1469)	1.0	0.82 (0.31, 2.20)	1.69 (0.67, 4.26)	0.30 (0.10, 0.86)	0.45 (0.13, 1.56)	0.17
3: 14.40 (11.2–64.0) (n = 1469)	1.0	0.63 (0.33, 1.19)	1.07 (0.59, 1.91)	0.68 (0.32, 1.44)	0.44 (0.14, 1.31)	0.40

¹Determined by bootstrap logistic regression (>300 replications) and adjusted for age, age squared, sex, field center (4 categories), risk group, diabetes mellitus, alcohol intake (g/d), smoking status (3 categories), LDL cholesterol, HDL cholesterol, triacylglycerol, systolic blood pressure, education level, dietary fiber intake, multivitamin use, aspirin use, linoleic acid intake (tertiles), ratio of polyunsaturated to saturated fatty acid (tertiles), fish intake (3 categories), and waist-to-hip ratio (3 categories).

²The mean intakes (g/d) from the lowest to the highest quintile are 0.40 (0.19–0.50), 0.57 (0.51–0.64), 0.72 (0.65–0.80), 0.90 (0.81–1.01), and 1.36 (1.02–3.48) for tertile 1; 0.39 (0.13–0.49), 0.57 (0.50–0.63), 0.71 (0.64–0.78), 0.88 (0.79–0.99), and 1.26 (1.00–2.42) for tertile 2; and 0.35 (0.17–0.43), 0.51 (0.44–0.56), 0.63 (0.57–0.69), 0.78 (0.70–0.88), and 1.12 (0.89–2.30) for tertile 3.

³ \bar{x} (range).

CAD appeared to be independent of fish consumption. In addition, linoleic fatty acid was inversely associated with prevalence odds ratio of CAD independently of linolenic acid intake, and our data suggest a synergistic relation between the 2 fatty acid intakes and the prevalence odds ratio of CAD.

A higher intake of α -linolenic acid is recommended for primary and secondary prevention of CAD because of its cardioprotective effects. In an animal model, rats fed an α -linolenic acid-enriched diet showed a reduced incidence of ventricular fibrillation and cardiac mortality (7, 8). Epidemiologic studies also suggested that a higher dietary intake of α -linolenic acid is associated with cardioprotective effects. In a large secondary prevention trial, de Lorgeril et al (4, 29) showed a significant reduction of cardiovascular mortality in the group assigned to consume a Mediterranean diet enriched with α -linolenic acid compared with subjects who consumed their usual diet. In addition, Hu et al (10) reported a 45% reduction in incident fatal myocardial infarction when the highest and lowest quintiles of α -linolenic acid intake were compared in the Nurses Health Study. Other epidemiologic studies documented inverse associations between α -linolenic acid and ischemic heart disease (2, 30). Our findings are consistent with the results of these previous studies.

Plausible biologic mechanisms by which α -linolenic acid may protect against CAD incidence and mortality have been proposed. It has been suggested that a higher intake of α -linolenic acid could raise the threshold for arrhythmia. Additional effects of linolenic acid could be mediated through synthesis of long-chain polyunsaturated fatty acids with cardioprotective effects: after ingestion, α -linolenic acid is quickly converted to EPA but slowly converted to DHA (11). Both EPA and DHA have been shown to reduce cardiac arrhythmia (31–35). EPA may also protect against thrombosis (36, 37) through the inhibition of platelet cyclooxygenase. In addition, lowering plasma triacylglycerol concentrations (38–40) and increasing endothelial nitric oxide (12) and attenuation of inflammation (41) are other potential mechanisms by which n-3 fatty acids protect against CAD.

A higher intake of linoleic acid may also reduce the incidence of CAD. Riemersma et al (42) reported that linoleic acid con-

centrations in adipose tissue are inversely related to mortality from CHD. In addition, a diet rich in linoleic acid was shown to lower cholesterol and apolipoprotein B concentrations (43). Although linoleic and linolenic acids use the same enzyme set for their metabolic pathway, linolenic acid has a competitive disadvantage because intakes of linoleic acid are higher than those of linolenic acid (44). It was suggested that the optimal ratio of linoleic to linolenic acid in the diet should be 2.3/1 (13) to maximize the rate of conversion of α -linolenic acid to DHA (45). Because linoleic and α -linolenic acids compete for desaturase and elongase enzymes, the amount of linoleic acid in the diet can affect the conversion of α -linolenic acid to EPA and DHA in vivo. In our study, the highest quintile of linolenic acid intake was associated with a lower prevalence odds ratio of CAD in all tertiles of the ratio of linoleic to linolenic acid. However, the results according to the tertiles of both fatty acids (Table 8) indicated that a combined intake was associated with a greater reduction in the prevalence odds ratio of CAD in the category with the highest values of both fatty acids.

TABLE 7

Relation of linoleic acid to the prevalence odds ratios (95% CIs) of coronary artery disease in the National Heart, Lung, and Blood Institute Family Heart Study¹

Tertiles of linoleic acid intake ²	Prevalence odds ratio
1 (low)	1.0
2	0.60 (0.34, 1.07)
3 (high)	0.61 (0.30, 1.25)

¹Determined by bootstrap logistic regression (>300 replications) and adjusted for age, age squared, sex, field center (4 categories), risk group, diabetes mellitus, alcohol intake (g/d), smoking status (3 categories), LDL cholesterol, HDL cholesterol, triacylglycerol, systolic blood pressure, education level, dietary fiber intake, multivitamin use, aspirin use, ratio of polyunsaturated to saturated fatty acids (tertiles), fish intake (3 categories), linolenic acid intake (quintiles), and waist-to-hip ratio (3 categories).

²The mean intakes (g/d) from the lowest to the highest tertile are 3.97 (1.09–5.40), 6.76 (5.41–8.26), and 11.68 (8.27–36.80).

TABLE 8

Relation of the combined effects of linoleic and linolenic acids to the prevalence odds ratios (95% CIs) of coronary heart disease in the National Heart, Lung, and Blood Institute Family Heart Study¹

	Tertiles of linoleic acid intake		
	1 (low) 3.86 (1.09–5.23) g/d ² (n = 1358)	2 6.65 (5.24–8.24) g/d (n = 1567)	3 (high) 11.66 (8.25–36.80) g/d (n = 1481)
Tertiles of linolenic acid intake ³			
1 (low) (n = 1445)	1.0	0.69 (0.31, 1.54)	— ⁴
2 (n = 1338)	0.91 (0.34, 2.38)	0.83 (0.41, 1.70)	1.04 (0.40, 2.73)
3 (high) (n = 1633)	0.72 (0.02, 28.96)	0.46 (0.17, 1.21)	0.44 (0.17, 1.17)


¹Determined by bootstrap logistic regression (>300 replications) and adjusted for age, age squared, sex, field center (4 categories), risk group, diabetes mellitus, alcohol intake (g/d), smoking status (3 categories), LDL cholesterol, HDL cholesterol, triacylglycerol, systolic blood pressure, education level, dietary fiber intake, multivitamin use, aspirin use, the ratio of polyunsaturated to saturated fatty acids (tertiles), fish intake (3 categories), and waist-to-hip ratio (3 categories).

² \bar{x} ; range in parentheses.

³The mean intakes (g/d) from the lowest to the highest tertile are 0.43 (0.13–0.56) for tertile 1, 0.67 (0.57–0.78) for tertile 2, and 1.07 (0.79–3.48) for tertile 3.

⁴Numbers in cell were too small for a stable estimate.

The present study has some limitations. We used an abbreviated version of a standardized food-frequency questionnaire to estimate the intake of linolenic and linoleic acids. Although we did not have the opportunity to validate the food-frequency questionnaire in this study, Willett et al (17, 18) showed that estimation of nutrients with a similar but more comprehensive semiquantitative food-frequency questionnaire was reasonably valid and reproducible. Because of the cross-sectional design of this study, we can only speculate about the temporal relation of linoleic acid and prevalent CAD. People with CAD are more likely to modify their diet on the basis of medical advice and may also have dietary recall patterns that bias the results. This type of bias would not account completely for the observed association. On the other hand, if subjects with CAD were advised to consume more fish or fish capsules, this would dilute the association between n-3 fatty acid intake and CAD and bias the effect measure toward the null. The fact that we found an inverse relation between n-3 fatty acid intake and CAD suggests that the true prevalence odds ratio would indicate stronger protection without such bias. The strong intercorrelation of the different components of the diet was a methodologic challenge, which made it difficult to assess the independent effects of linolenic acid intake on prevalent CAD. Our inference was not affected by the large number of participants selected because of their higher-than-expected risk of CAD. We know this because an analysis restricted to randomly selected participants indicated a similar trend for an inverse relation of linolenic acid intake to CAD. The large sample size and the multicenter design of the study that incorporated different regions of the US population were strengths of this study.

In summary, the results of this study suggest that a higher intake of either linolenic acid or linoleic acid is associated with a lower prevalence odds ratio of CAD in both men and women. The results also indicate that the combined intake of both fatty acids had synergistic effects. 

This paper is presented on behalf of the investigators of the NHLBI Family Heart Study. The participating institutions and principal staff of the study are as follows. University of North Carolina: Gerardo Heiss, HA Tyröler, Jeannette T Bensen, Catherine Paton, Delilah Posey Amy Haire, and James Pankow; Wake Forest University: Stephen Rich and Greg Evans; Field Center, University of Minnesota: Donna K Arnett, Aaron R Folsom, Larry Atwood, James Peacock, and Greg Feitl; Framingham Field Center, Boston University: R Curtis Ellison, Richard H Myers, Yuqing Zhang, Andrew G Bostom,

Luc Djoussé, Jemma B Wilk, and Greta Lee Splansky; Field Center, University of Utah: Steven C Hunt, Roger R Williams (deceased), Paul N Hopkins, Hilary Coon, and Jan Skuppin; Coordinating Center, Washington University: Michael A Province, DC Rao, Ingrid B Borecki, Yuling Hong, Mary Feitosa, Jeanne Cashman, and Avril Adelman; Central Biochemistry Laboratory, University of Minnesota: John H Eckfeldt, Catherine Leiendecker-Foster, Michael Y Tsai, and Greg Rynders; Central Molecular Laboratory, University of Utah: Mark F Leppert, Jean-Marc Lalouel, Tena Varvil, and Lisa Baird; Project Office, NHLBI: Phyliss Sholinsky, Millicent Higgins (retired), Jacob Keller (retired), Sarah Knox, and Lorraine Silsbee.

REFERENCES

1. von Schacky C. Prophylaxis of atherosclerosis with marine omega-3 fatty acids—a comprehensive strategy. *Ann Intern Med* 1987;107:890–9.
2. Dolecek TA. Epidemiological evidence of relationships between dietary polyunsaturated fatty acids and mortality in the multiple risk factor trial. *Proc Soc Exp Biol Med* 1992;200:177–82.
3. Ascherio A, Rimm EB, Stampfer MJ, Giovannucci EL, Willett WC. Dietary intake of marine n-3 fatty acids, fish intake, and the risk of coronary disease among men. *N Engl J Med* 1995;332:977–82.
4. de Lorgeril M, Salen P, Martin JL, Monjaud I, Delaye J, Mamelle N. Mediterranean diet, traditional risk factors, and the rate of cardiovascular complications after myocardial infarction: final report of the Lyon Diet Heart Study. *Circulation* 1999;99:779–85.
5. Siscovick DS, Raghunathan TE, King I, et al. Dietary intake of long-chain n-3 polyunsaturated fatty acids and the risk of primary cardiac arrest. *Am J Clin Nutr* 2000;71(suppl):208S–12S.
6. von Schacky C. n-3 Fatty acids and the prevention of coronary atherosclerosis. *Am J Clin Nutr* 2000;71(suppl):224S–7S.
7. Siebert BD, McLennan PL, Woodhouse JA, Charnock JS. Cardiac arrhythmia in rats in response to dietary n-3 fatty acids from red meat, fish oil and canola oil. *Nutr Res* 1993;13:1407–18.
8. McLennan PL, Dallimore JA. Dietary canola oil modifies myocardial fatty acids and inhibits cardiac arrhythmias in rats. *J Nutr* 1995;125:1003–9.
9. Owren PA. Coronary thrombosis. Its mechanism and possible prevention by linolenic acid. *Ann Intern Med* 1965;63:167–84.
10. Hu FB, Stampfer MJ, Manson JE, et al. Dietary intake of α -linolenic acid and risk of fatal ischemic heart disease among women. *Am J Clin Nutr* 1999;69:890–7.
11. Gerster H. Can adults adequately convert α -linolenic acid (18:3n-3) to eicosapentaenoic acid (20:5n-3) and docosahexaenoic acid (22:6n-3)? *Int J Vitam Nutr Res* 1988;68:159–73.
12. Connor WE. α -Linolenic acid in health and disease. *Am J Clin Nutr* 1999;69:827–8 (editorial).

13. Kris-Etherton PM, Taylor DS, Yu-Poth S, et al. Polyunsaturated fatty acids in the food chain in the United States. *Am J Clin Nutr* 2000;71(suppl):179S–88S.
14. Higgins M, Province M, Heiss G, et al. NHLBI Family Heart Study: objectives and design. *Am J Epidemiol* 1996;143:1219–28.
15. Hunt SC, Williams RR, Barlow GK. A comparison of positive family history definitions for defining risk of future disease. *J Chronic Dis* 1986;39:809–21.
16. Stein AD, Shea S, Basch CE, Contento IR, Zybert P. Consistency of the Willett semiquantitative food frequency questionnaire and 24-hour dietary recalls in estimating nutrient intakes of preschool children. *Am J Epidemiol* 1992;135:667–77.
17. Rimm EB, Giovannucci EL, Stampfer MJ, Colditz GA, Litin LB, Willett WC. Reproducibility and validity of an expanded self-administered semiquantitative food frequency questionnaire among male health professionals. *Am J Epidemiol* 1992;135:1114–26.
18. Willett WC, Sampson L, Stampfer MJ, et al. Reproducibility and validity of a semiquantitative food frequency questionnaire. *Am J Epidemiol* 1985;122:51–65.
19. US Department of Agriculture. Composition of foods: raw, processed, and prepared, 1963–1988. Agriculture handbook no. 8 Washington, DC: US Government Printing Office, 1989.
20. Nettleton JA. Omega-3 fatty acids: comparison of plant and seafood sources in human nutrition. *J Am Diet Assoc* 1991;91:331–7.
21. Blackburn H, Keys A, Simonson E, Rautaharju P, Punsar S. The electrocardiogram in population studies: a classification system. *Circulation* 1960;21:1160–75.
22. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. *Clin Chem* 1972;18:499–502.
23. David JA, Paksi J, Naito NK. Separation of lipoprotein (Lp) fraction by the Beckman TL-100 table-top ultracentrifuge (UC). *Clin Chem* 1986;32:1094 (abstr).
24. McGovan MW, Artiss JD, Strandbergh DR, Zork B. A peroxidase-coupled method for the colorimetric determination of serum triglycerides. *Clin Chem* 1983;29:538–42.
25. Allain CC, Poon LS, Chan C, Richmond W, Fu PC. Enzymatic determination of total serum cholesterol. *Clin Chem* 1974;20:470–5.
26. Warnick GR, Benderson J, Albers JJ. Dextran sulfate-Mg²⁺ precipitation procedure for quantitation of high-density-lipoprotein cholesterol. *Clin Chem* 1982;28:1379–88.
27. Salmeron J, Manson JE, Stampfer MJ, Colditz GA, Wing AL, Willett WC. Dietary fiber, glycemic load, and risk of non-insulin dependent diabetes mellitus in women. *JAMA* 1997;277:472–7.
28. Willett WC, Stampfer MJ. Total energy intake: implications for epidemiologic analyses. *Am J Epidemiol* 1986;124:17–27.
29. de Lorgeril M, Renaud S, Mamelle N, et al. Mediterranean α -linolenic acid-rich diet in secondary prevention of coronary heart disease. *Lancet* 1994;343:1454–9.
30. Ascherio A, Rimm EB, Giovannucci EL, Spiegelman D, Stampfer MJ, Willett WC. Dietary fat and risk of coronary heart disease in men: cohort follow-up study in the United States. *BMJ* 1996;313:84–90.
31. Kang JX, Leaf A. Prevention and termination of arrhythmias induced by lysophosphatidyl choline and acylcarnitine in neonatal rat cardiac myocytes by free omega-3 fatty acids. *Eur J Pharmacol* 1996;297:97–106.
32. Kang JX, Leaf A. Antiarrhythmic effects of polyunsaturated fatty acids: recent studies. *Circulation* 1996;94:1774–80.
33. Billman GE, Kang JX, Leaf A. Prevention of sudden cardiac death by dietary pure n-3 polyunsaturated fatty acids in dogs. *Circulation* 1999;99:2452–7.
34. Kang JX, Leaf A. Prevention of fatal cardiac arrhythmias by polyunsaturated fatty acids. *Am J Clin Nutr* 2000;71(suppl):202S–7S.
35. Leaf A, Kang JX, Xiao YF, Billman GE. Omega-3 fatty acids in the prevention of cardiac arrhythmias. *Lipids* 1999;34(suppl):S187–9.
36. Knapp HR. Dietary fatty acids in human thrombosis and hemostasis. *Am J Clin Nutr* 1997;65(suppl):1687S–98S.
37. Ferretti A, Flanagan VP. Antithromboxane activity of dietary α -linolenic acid: a pilot study. *Prostaglandins Leukot Essent Fatty Acids* 1996;54:451–5.
38. Harris WS. Fish oils and plasma lipid and lipoprotein metabolism in humans: a critical review. *J Lipid Res* 1989;30:785–807.
39. Roche HM, Gibney MJ. Postprandial triacylglycerolaemia: the effect of low-fat dietary treatment with and without fish oil supplementation. *Eur J Clin Nutr* 1996;50:617–24.
40. Roche HM, Gibney MJ. Effect of long-chain n-3 polyunsaturated fatty acids on fasting and postprandial triacylglycerol metabolism. *Am J Clin Nutr* 2000;71(suppl):232S–7S.
41. Wallace JM, Turley E, Gilmore WS, Strain JJ. Dietary fish oil supplementation alters leukocyte function and cytokine production in healthy women. *Arterioscler Thromb Vasc Biol* 1995;15:185–9.
42. Riemersma RA, Wood DA, Butler S, et al. Linoleic acid content in adipose tissue and coronary heart disease. *Br Med J (Clin Res)* 1986;292:1423–7.
43. Herrmann W, Biermann J, Kostner GM. Comparison of effects of n-3 to n-6 fatty acids on serum level of lipoprotein(a) in patients with coronary artery disease. *Am J Cardiol* 1995;76:459–62.
44. Budowski P. Omega-3 fatty acids in health and disease. *World Rev Nutr Diet* 1988;57:241–74.
45. Masters C. n-3 Fatty acids and the peroxisome. *Mol Cell Biochem* 1996;165:83–93.