

n-3 Polyunsaturated fatty acids, fatal ischemic heart disease, and nonfatal myocardial infarction in older adults: the Cardiovascular Health Study¹⁻³

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ABSTRACT

Background: Little is known about the relation of the dietary intake of n-3 polyunsaturated fatty acids, ie, docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) from fatty fish and α -linolenic acid from vegetable oils, with ischemic heart disease among older adults.

Objective: We investigated the associations of plasma phospholipid concentrations of DHA, EPA, and α -linolenic acid as biomarkers of intake with the risk of incident fatal ischemic heart disease and incident nonfatal myocardial infarction in older adults.

Design: We conducted a case-control study nested in the Cardiovascular Health Study, a cohort study of adults aged ≥ 65 y. Cases experienced incident fatal myocardial infarction and other ischemic heart disease death ($n = 54$) and incident nonfatal myocardial infarction ($n = 125$). Matched controls were randomly selected ($n = 179$). We measured plasma phospholipid concentrations of n-3 polyunsaturated fatty acids in blood samples drawn ≈ 2 y before the event.

Results: A higher concentration of combined DHA and EPA was associated with a lower risk of fatal ischemic heart disease, and a higher concentration of α -linolenic acid with a tendency to lower risk, after adjustment for risk factors [odds ratio: 0.32 (95% CI: 0.13, 0.78; $P = 0.01$) and 0.52 (0.24, 1.15; $P = 0.1$), respectively]. In contrast, n-3 polyunsaturated fatty acids were not associated with nonfatal myocardial infarction.

Conclusions: Higher combined dietary intake of DHA and EPA, and possibly α -linolenic acid, may lower the risk of fatal ischemic heart disease in older adults. The association of n-3 polyunsaturated fatty acids with fatal ischemic heart disease, but not with nonfatal myocardial infarction, is consistent with possible antiarrhythmic effects of these fatty acids. *Am J Clin Nutr* 2003;77:319-25.

KEY WORDS Fatty acids, n-3 fatty acids, phospholipids, ischemic heart disease, myocardial infarction, nested case-control studies, docosahexaenoic acid, eicosapentaenoic acid, older adults, Cardiovascular Health Study

INTRODUCTION

There is growing evidence that diets high in long-chain n-3 polyunsaturated fatty acids (PUFAs), ie, docosahexaenoic acid (DHA; 22:6n-3) and eicosapentaenoic acid (EPA; 20:5n-3), decrease the risk of fatal ischemic heart disease (IHD) (1-11). On the basis of this research, the American Heart Association now

recommends eating 1 or 2 fish meals weekly, particularly fatty fish (12). However, most of the research on n-3 PUFAs and IHD was done in middle-aged adults. Whether the benefits of a diet high in n-3 PUFAs extend to the elderly has received limited attention (3).

In experimental studies in primates and dogs, high dietary intakes of DHA and EPA decreased the risk of ventricular fibrillation, suggesting an antiarrhythmic mechanism of action (13-16). In our own research, we have shown that both high concentrations of DHA and EPA in the diet and high concentrations of DHA and EPA in red blood cell membranes are associated with a lower risk of primary cardiac arrest (out-of-hospital cardiac arrest due to heart disease) (4). Life-threatening cardiac arrhythmias are major contributors to fatal IHD. On this basis, we hypothesized that n-3 PUFAs would be associated with a lower risk of fatal IHD but not nonfatal myocardial infarction (MI).

α -Linolenic acid (18:3n-3) is another dietary n-3 PUFA, of intermediate-chain length, found in vegetable oils such as canola oil and soybean oil. There is limited information on the relation of α -linolenic acid intake to the risk of IHD, and findings have been inconsistent (5, 17-23). A report from the Nurses' Health Study suggests an inverse association of dietary α -linolenic acid with risk of fatal IHD among women (22). However, dietary intake of α -linolenic acid is difficult to measure with dietary questionnaires, and α -linolenic acid was not associated with fatal IHD in a study using a biomarker of α -linolenic acid intake (19).

The primary objectives of this study were to investigate the associations of n-3 PUFAs, specifically, the long-chain DHA and EPA and the intermediate-chain α -linolenic acid, with fatal IHD

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and nonfatal MI in an elderly population. A secondary study objective was to investigate the associations of linoleic acid, an abundant dietary PUFA from vegetable seed oil (eg, safflower and cottonseed oils) of the $n-6$ family, with fatal IHD and nonfatal MI. To assess intake, we measured plasma phospholipid concentrations of $n-3$ PUFAs and linoleic acid as a biomarker of intake over the previous 4–6 wk (24, 25).

SUBJECTS AND METHODS

We conducted a case-control study nested in the Cardiovascular Health Study, a prospective cohort study of cardiovascular disease risk factors and outcomes among adults aged ≥ 65 y at baseline. The study was approved by the institutional review board at each study site.

Study participants

The Cardiovascular Health Study cohort consists of 5201 non-institutionalized men and women aged ≥ 65 y recruited in June 1989 from 4 US communities (Forsyth County, NC; Sacramento County, CA; Washington County, MD; and Pittsburgh (Allegheny County), PA) and 687 additional African American adults recruited from June 1992 on. Participants were sampled randomly from the Medicare eligibility lists of the Health Care Financing Administration.

In the present study, cases were defined as Cardiovascular Health Study participants, free of IHD and stroke at baseline, who experienced either an incident fatal IHD event (fatal MI or other IHD death) or an incident nonfatal MI during follow-up through June 1996. Myocardial infarction was defined on the basis of cardiac enzymes, chest pain, and serial electrocardiogram changes (26). IHD deaths were defined as fatal MI or fatal events that did not meet the criteria for definite MI in which the participant had chest pain within 72 h of death or had a history of chronic IHD. All IHD events were classified by a Morbidity and Mortality Committee (26). The committee also assigned a mechanism of death, including arrhythmia, congestive heart failure, cardiac procedure, and multiple mechanisms, whenever possible.

For each case, one control of the same sex, clinical site, and entry cohort; of similar age (± 5 y); and whose follow-up was at least as long as that of the case was randomly selected from the Cardiovascular Health Study participants who remained free of IHD during follow-up. Because our emphasis was on a biomarker of diet, we excluded cases and controls who reported using fish oil supplements at baseline ($n = 10$). With the use of these matching criteria, 54 cases of fatal IHD, 125 cases of nonfatal MI, and 179 individually matched controls were selected for these analyses. Of the 54 fatal IHD cases, 36 (67%) were thought to be due to arrhythmia, 9 were thought to be due to congestive heart failure, 2 were due to other mechanisms, and 7 were of unknown mechanism.

Measurement of plasma phospholipid polyunsaturated fatty acids

Blood samples were obtained at baseline and in the third year of follow-up. Because relatively short time changes in $n-3$ PUFA dietary intake may influence the risk of life-threatening arrhythmias, we used blood samples collected closest to (before) the IHD event. We used baseline blood samples for cases who experienced their event before the third-year follow-up visit and for their matched controls and we used blood samples obtained in the third

year of follow-up for cases who experienced their incident event after their third year blood draw and for their matched controls. The median time elapsed between blood collection and the IHD event was 1.76 y.

Plasma samples were stored at -70°C until analyzed. Total lipids were extracted from plasma by the method of Folch et al (27). Phospholipids were separated from neutral lipids by one-dimensional thin-layer chromatography with the use of 250- μm Silica Gel G plates (Analtech Inc, Newark, DE) and a 67.5:15:0.75 hexane:ether:acetic acid development solvent with 0.005% butylated hydroxytoluene. The phospholipid fractions were then directly transesterified to prepare fatty acid methyl esters with the use of the method of Lepage and Roy (28). Fatty acid methyl esters of individual fatty acids were separated by gas chromatography as previously described (29). Interassay CVs were 2.9%, 3.0%, 4.8%, and 1.3% for DHA, EPA, α -linolenic acid, and linoleic acid, respectively. Laboratory personnel were blinded to the case-control status of the plasma samples.

PUFAs were expressed as percentages of total fatty acids by weight. Because DHA and EPA are usually found together in fatty fish, plasma phospholipid concentrations of DHA and EPA were correlated ($r = 0.54$). In preliminary analyses, DHA and EPA were both associated with a lower risk of fatal IHD. Thus, we summed the concentrations of DHA and EPA to use as a single variable. Plasma phospholipid concentrations of combined DHA and EPA were correlated with the number of servings of nonfried fish reported to be consumed at baseline by 320 study participants who were administered a picture-sort dietary questionnaire (30; Spearman correlation: 0.49, $P = 0.0001$).

Assessment of other risk factors

At baseline and in the third year of follow-up, participants completed standard questionnaires on medical history, health status, and personal habits and underwent a clinic examination including sitting blood pressure, anthropometric measurements, and venipuncture (31).

Statistical analysis

All statistical analyses were done by using STATA 6.0 (Stata Corporation, College Station, TX). Fatal IHD and nonfatal MI were treated as separate outcomes. Because controls were individually matched to cases, there were 2 mutually exclusive control groups: one group of controls matched to cases of fatal IHD and one matched to cases of nonfatal MI. In descriptive analyses, we compared the prevalence of risk factors and means of plasma phospholipid PUFA concentrations among cases and their matched controls with the use of paired t tests.

We used conditional logistic regression to obtain estimates of the relative risk (odds ratio) of incident fatal IHD and the relative risk of incident nonfatal MI associated with higher plasma phospholipid concentrations of PUFAs. Preliminary analyses using quartiles of plasma phospholipid PUFAs were consistent with inverse linear relations of $n-3$ PUFAs with the risk of fatal IHD. Therefore, $n-3$ and $n-6$ PUFAs were included as linear terms in the conditional logistic regression analyses. The addition of quadratic terms did not improve the fit of any of the models. Results presented are the odds ratios associated with a 1-SD increase in the concentration of plasma phospholipid PUFAs; the SDs were from the PUFA distributions in all the controls.

The covariates used in the analyses were from the exam of the blood collection, except for demographic characteristics, which were collected only at baseline. The conditional logistic regression analyses accounted for the sampling variables (age, sex, clinic site, and entry cohort) and were adjusted for age, systolic



TABLE 1
Characteristics of the study population

	Cases of fatal ischemic heart disease ¹ (n = 54)	Controls ^{2,3} (n = 54)	Cases of nonfatal myocardial infarction (n = 125)	Controls ^{2,4} (n = 125)
Age (y)	79.1 ± 7.5 ⁵	78.2 ± 6.8	75.4 ± 5.5	75.2 ± 5.5
Male sex (%)	57.4	57.4	64.0	64.0
White race (%)	81.5	87.0	86.4	86.4
High school graduates (%)	55.6	72.2	68.8	71.8
Congestive heart failure (%)	9.3	3.7	3.2	1.6
Treated diabetes (%)	24.1	14.8	15.2	10.5
Treated hypertension (%)	42.6	31.5	40.0	29.0
Weight (kg)	71.4 ± 13.9	74.5 ± 13.0	73.5 ± 13.8	74.9 ± 14.1
Systolic blood pressure (mm Hg)	140.4 ± 21.2	133.7 ± 21.6	143.5 ± 20.7 ⁶	137.3 ± 21.8
Diastolic blood pressure (mm Hg)	71.0 ± 12.2	69.6 ± 9.8	73.0 ± 11.4	73.3 ± 10.8
Family history of myocardial infarction (%)	35.4	31.1	35.9 ⁶	23.7
Current smokers (%)	18.5	7.4	9.6	8.8
Alcohol users (%)	31.5	46.3	49.6	52.0
Daily aspirin users (%)	16.7	22.2	18.4	15.2
Total cholesterol (mmol/L)	5.1 ± 1.0	5.3 ± 1.0	5.3 ± 1.1	5.3 ± 1.0
HDL cholesterol (mmol/L)	1.3 ± 0.3	1.3 ± 0.3	1.3 ± 0.4	1.4 ± 0.4
Triacylglycerol (mmol/L)	1.7 ± 0.9	1.6 ± 0.8	1.7 ± 0.9	1.6 ± 0.9
Fasting glucose (mmol/L)	7.5 ± 3.5 ⁶	5.9 ± 1.2	6.3 ± 2.0	6.5 ± 3.6
Fasting insulin (pmol/L)	27.0 ± 57.4	16.0 ± 12.1	17.9 ± 31.6	13.8 ± 12.1
Fibrinogen (μmol/L)	9.8 ± 1.9	9.3 ± 1.6	9.8 ± 1.7	9.6 ± 2.7

¹Cases were selected from participants in the Cardiovascular Health Study, a cohort study of cardiovascular disease risk factors and outcomes among older adults; participants selected as cases were free of myocardial infarction and stroke at entry in the cohort and experienced an ischemic heart disease event during follow-up between 1989 and 1996.

²Controls were randomly sampled from the Cardiovascular Health Study participants who were free of myocardial infarction and stroke at entry in the cohort and who did not experience an event. Controls were individually matched to cases by age, sex, clinic site, and length of follow-up.

³Controls individually matched to fatal ischemic heart disease cases.

⁴Controls individually matched to nonfatal myocardial infarction cases.

⁵ $\bar{x} \pm SD$.

⁶Significantly different from matched controls, $P < 0.05$ (paired t test).

blood pressure, weight, educational attainment (high school graduation), and fasting plasma glucose. The analyses were based on the updated Cardiovascular Health Study databases, which incorporated minor corrections up to March 2000.

RESULTS

Traditional IHD risk factors were generally more prevalent in cases than in controls, although few of the differences were significant (**Table 1**). Cases of fatal IHD had on average higher fasting plasma glucose concentrations than did their matched controls ($P = 0.002$), and cases of nonfatal MI were more likely than their matched controls to have higher systolic blood pressure ($P = 0.02$) and to have a family history of heart disease ($P = 0.047$). Of note, cases of fatal IHD were on average older than cases of nonfatal MI ($P = 0.0003$).

Overall, study participants who subsequently experienced an incident fatal IHD event had significantly lower baseline plasma phospholipid concentrations of combined DHA and EPA than did their matched controls ($P = 0.02$) and higher concentrations of linoleic acid ($P = 0.03$) (**Table 2**). In contrast, mean baseline PUFA concentrations did not differ significantly among participants who subsequently experienced a nonfatal MI and their matched controls.

In analyses adjusted for age, systolic blood pressure, weight, education, and fasting plasma glucose, higher plasma phospholipid concentrations of combined DHA and EPA were associated

with a lower risk of incident fatal IHD events (**Table 3**). For a 1-SD increase in plasma phospholipid combined DHA and EPA, there was an associated 70% lower risk of fatal IHD (odds ratio: 0.30; 95% CI: 0.12, 0.76; $P = 0.01$). Similarly, for a 1-SD increase in α -linolenic acid, there was an associated 50% lower risk of fatal IHD (odds ratio: 0.48; 95% CI: 0.24, 0.96; $P = 0.04$). In contrast, linoleic acid was associated with an associated higher risk of incident fatal IHD (**Table 3**). None of the PUFAs were associated with the risk of nonfatal MI (**Table 3**).

Further adjustments for smoking, alcohol use, triacylglycerol concentrations, HDL-cholesterol concentrations, treated hypertension, treated diabetes, congestive heart failure, claudication, heart rate, family history of MI, fibrinogen concentrations, and kilocalories of physical activity did not change these results. In analyses of fatal IHD restricted to 38 matched pairs with dietary information, adjustment for total fat intake and total energy intake, or for saturated fat intake and total energy intake, also had little effect on the estimated odds ratios of fatal IHD associated with each PUFA. We also did not find evidence that the associations of the PUFAs with fatal IHD were modified by traditional risk factors.

When the analyses of fatal IHD were limited to only the cases for which the mechanism was thought to be due to life-threatening arrhythmia (36 cases), we obtained odds ratios similar to the ones presented in **Table 3**: the estimated odds ratios of fatal IHD associated with each 1-SD increase in plasma phospholipid concentrations of DHA+EPA, α -linolenic acid, and linoleic acid were 0.23 (95% CI: 0.06, 0.83), 0.43 (95% CI: 0.17, 1.12), and 2.66

TABLE 2Plasma phospholipid polyunsaturated fatty acid concentrations in blood samples drawn from the study population on average 2 y before the event¹

Polyunsaturated fatty acid	Cases of fatal ischemic heart disease (n = 54)	Controls (n = 54)	Cases of nonfatal myocardial infarction (n = 125)	Controls (n = 125)
	% of total fatty acids			
Combined DHA (22:6n-3) and EPA (20:5n-3)	3.3 ± 0.8 ²	3.8 ± 1.3	3.6 ± 1.1	3.7 ± 1.2
Linolenic acid (18:3n-3)	0.16 ± 0.06	0.17 ± 0.06	0.17 ± 0.06	0.17 ± 0.06
Linoleic acid (18:2n-6)	20.1 ± 2.3 ²	19.2 ± 2.4	20.3 ± 2.5	20.0 ± 2.7

¹ $\bar{x} \pm SD$. Fatty acid concentrations are expressed as percentage of total plasma phospholipid fatty acids. DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid.

²Significantly different from matched controls, $P < 0.05$ (paired t test).

(95% CI: 1.04, 6.79), respectively, after adjustment for age, weight, and fasting plasma glucose concentrations.

The associations shown in Table 3 were independent of traditional risk factors. However, PUFA concentrations were correlated. In particular, plasma phospholipid concentrations of linoleic acid were inversely related to concentrations of combined DHA and EPA ($r = -0.33$, $P < 0.0001$) and positively related to concentrations of α -linolenic acid ($r = 0.30$, $P < 0.0001$). We therefore investigated whether the associations of each PUFA type with risk of fatal IHD and nonfatal MI were independent of the other PUFAs. Similar results were obtained when the associations of combined DHA and EPA and α -linolenic acid were investigated simultaneously (Table 4) or separately (Table 3), and when the associations of α -linolenic acid and linoleic acid were investigated simultaneously (Table 4) or separately (Table 3). When the associations of all 3 types of PUFAs were investigated simultaneously, the association of linoleic acid with fatal IHD was noticeably diminished (Table 4).

DISCUSSION

In this nested case-control study conducted among older adults, we found that higher plasma phospholipid concentrations of the long-chain n-3 PUFAs DHA and EPA were associated with a lower risk of incident fatal IHD, whereas the intermediate-chain n-3 PUFA α -linolenic acid was associated with a tendency to lower risk. In contrast, higher concentrations of linoleic acid, an n-6 PUFA, were not associated with a lower risk of fatal IHD. None of these PUFAs were associated with the risk of nonfatal MI.

The strengths of our study include the prospective study design, the reliable ascertainment of cardiovascular events, and

the availability of information on numerous clinical characteristics collected from the study participants. The study limitations include the relatively small number of incident fatal IHD events and the indirect assessment of dietary PUFAs.

There is strong supporting evidence from epidemiologic studies (1, 4, 6, 7, 10) and secondary prevention trials in post-MI patients (2, 5, 8, 32) that a diet high in DHA and EPA is associated with a lower risk of fatal IHD and sudden cardiac death among middle-aged adults. The study results suggest that the benefits of high DHA and EPA consumption extend to the prevention of fatal IHD in older adults (on average 78 y old in the present study).

Both studies of isolated cells and animal-experimental studies suggest potential mechanisms that underlie the observed association of plasma phospholipid DHA and EPA with fatal IHD but not with nonfatal MI. Studies of isolated myocytes and voltage clamping suggest that long chain n-3 PUFAs alter electrophysiologic function in a manner that reduces vulnerability to ventricular fibrillation (13-16). In animal studies, dietary intake of long-chain n-3 PUFAs decreases the risk of life-threatening cardiac arrhythmias in the setting of provocative stimuli (13-16). We reported in a previous study that higher concentrations of both dietary DHA and EPA and red blood cell membrane DHA and EPA are associated with lower risk of primary cardiac arrest (4). In a recent report from the Physicians' Health Study, higher blood concentrations of long-chain n-3 fatty acids were also associated with reduced risk of sudden death (11). In the GISSI-Prevenzione Trial, the observed decrease in risk of IHD with long-chain n-3 PUFA supplementation was largely accounted for by a decreased risk of sudden cardiac death (8) that is detected early (32). A lack of association of DHA and EPA with nonfatal IHD may also explain in part the negative results obtained in the Health Professionals Follow-up Study (33).

TABLE 3Odds ratios and 95% CIs of fatal ischemic heart disease and nonfatal myocardial infarction associated with a 1-SD increase in plasma phospholipid polyunsaturated fatty acid concentration¹

	Fatal ischemic heart disease (54 cases and 54 controls)		Nonfatal myocardial infarction (125 cases and 125 controls)	
	Odds ratio	<i>P</i>	Odds ratio	<i>P</i>
Combined DHA (22:6n-3) and EPA (20:5n-3)	0.30 (0.12, 0.76)	0.01	0.97 (0.71, 1.33)	0.8
Linolenic acid (18:3n-3)	0.48 (0.24, 0.96)	0.04	1.07 (0.81, 1.41)	0.6
Linoleic acid (18:2n-6)	2.42 (1.07, 5.43)	0.03	1.10 (0.83, 1.46)	0.5

¹Odds ratios were obtained from separate statistical models assessing one polyunsaturated fatty acid at a time with the use of conditional logistic regression to take into account the matching on sex, clinical site, entry cohort, and age, and with further adjustment for systolic blood pressure, weight, education, and fasting plasma glucose. DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid.

TABLE 4

Odds ratios and 95% CIs of fatal ischemic heart disease and nonfatal myocardial infarction associated with 1-SD increases in plasma phospholipid polyunsaturated fatty acid (PUFA) concentrations, examined simultaneously¹

	Fatal ischemic heart disease (54 cases and 54 controls)		Nonfatal myocardial infarction (125 cases and 125 controls)	
	Odds ratio	P	Odds ratio	P
Long-chain and intermediate-chain n-3 PUFAs examined simultaneously				
Combined DHA (22:6n-3) and EPA (20:5n-3)	0.32 (0.13, 0.78)	0.01	0.96 (0.70, 1.32)	0.8
α -Linolenic acid (18:3n-3)	0.52 (0.24, 1.15)	0.1	1.07 (0.81, 1.42)	0.6
Intermediate-chain n-3 and n-6 PUFAs examined simultaneously				
α -Linolenic acid (18:3n-3)	0.48 (0.25, 0.92)	0.03	1.04 (0.77, 1.40)	0.8
Linoleic acid (18:2n-6)	2.73 (1.09, 6.87)	0.03	1.08 (0.79, 1.47)	0.6
Long-chain n-3 and intermediate-chain n-3 and n-6 PUFAs examined simultaneously				
Combined DHA (22:6n-3) and EPA (20:5n-3)	0.41 (0.15, 1.14)	0.09	0.98 (0.71, 1.36)	0.9
α -Linolenic acid (18:3n-3)	0.52 (0.25, 1.10)	0.09	1.04 (0.77, 1.41)	0.8
Linoleic acid (18:2n-6)	1.63 (0.50, 5.26)	0.4	1.07 (0.78, 1.48)	0.7

¹Odds ratios were obtained from conditional logistic regression models including the 2 or 3 PUFAs listed in each grouping and adjusted as reported in Table 3. DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid.


The association of higher concentrations of plasma phospholipid α -linolenic acid with lower risk of fatal IHD agrees with findings from the Multiple Risk Factor Intervention Trial (17) and the Nurses' Health Study (22) obtained with dietary questionnaires. Evidence from 3 other prospective studies among men is inconclusive (20, 21, 23). In the Nurses' Health Study, a higher dietary intake of α -linolenic acid was associated with a lower risk of fatal IHD among women but not with a lower risk of MI (22). Because intake of dietary α -linolenic acid is strongly associated with intake of dietary linoleic acid (22), confirmation of these findings is important. The similarity of results in our study, obtained in elderly men and women with the use of a biomarker of α -linolenic acid intake, and in the Nurses Health study, obtained in women by use of a food-frequency questionnaire, brings further support to the possibility that higher consumption of dietary α -linolenic acid may decrease the risk of fatal IHD.

In contrast, serum phospholipid α -linolenic acid concentrations were not associated with the risk of incident IHD in a small (94 cases) nested case-control study among men enrolled in the Multiple Risk Factor Intervention Trial (19). However, there was a long time interval between the events and the blood collection in the 1970s, during which dietary intake may have changed. Furthermore, the study combined nonfatal MI and IHD deaths. If α -linolenic acid was inversely associated with fatal IHD but not associated with MI, as was the case for long-chain n-3 PUFAs, then combining fatal and nonfatal outcomes may have diminished the power to detect associations in that study (19).

Because α -linolenic acid is a precursor of long chain n-3 PUFAs, antiarrhythmic effects are a possible mechanism underlying the observed inverse association of α -linolenic acid with fatal IHD, although the extent of the conversion to long chain n-3 PUFAs is not known. Limited animal-experimental evidence also suggests that α -linolenic acid itself may have antiarrhythmic effects (15, 34).

We found no evidence for a lower risk of fatal IHD or nonfatal MI associated with higher plasma phospholipid concentrations of linoleic acid, the principal dietary n-6 PUFA, and in some analyses, higher concentrations of linoleic acid were associated with a higher risk of fatal IHD. Prospective studies using dietary

questionnaires suggest no association of linoleic acid with fatal IHD (17, 20, 21) or an inverse association (35). In our study, plasma phospholipid concentrations of linoleic acid were inversely associated with concentrations of combined DHA and EPA, and adjustment for DHA and EPA reduced the association of linoleic acid with fatal IHD. It is therefore possible that study subjects who ate more foods containing linoleic acid ate less foods containing DHA and EPA (ie, fatty fish), and the higher risk associated with higher linoleic acid may have been confounded by lower fatty fish intake. In the context of other published studies (17, 20, 21, 36), our results suggest that higher intake of linoleic acid, compared with less, is not associated with lower risk of fatal IHD. On the other hand, when substituted for saturated fat intake, higher intake of linoleic acid decreases LDL cholesterol in feeding studies (37), decreases ventricular fibrillation in experimental animal studies (14), and is associated with lower risk of fatal IHD (35).

In conclusion, our results suggest that in older adults, higher dietary intake late in life of the long-chain n-3 PUFAs DHA and EPA, found in fatty fish, is associated with a lower risk of fatal IHD. Higher dietary intake of the intermediate-chain n-3 PUFA α -linolenic acid, found in canola oil and soybean oil, also appears to be associated with a lower risk of fatal IHD. Association of the n-3 PUFAs with lower risk of fatal IHD, but not nonfatal MI, is consistent with possible antiarrhythmic properties of n-3 PUFAs. 

RNL analyzed the data and wrote the manuscript, IBK provided the fatty acid measurements and contributed to the writing of the manuscript, DM contributed to the interpretation of the data analyses and the writing of the manuscript, LHK reviewed the manuscript critically and provided significant advice, RPT provided the blood samples from the study participants and reviewed the manuscript critically, and DSS designed the study and contributed to data collection, data analyses, and writing of the manuscript. None of the authors had any financial or personal interest in any company or organization sponsoring the research, including advisory board affiliations.

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