Dietary α-Linolenic Acid Intake and Risk of Sudden Cardiac Death and Coronary Heart Disease

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Background—α-Linolenic acid, an intermediate-chain n-3 fatty acid found primarily in plants, may decrease the risk of fatal coronary heart disease (CHD) through a reduction in fatal ventricular arrhythmias and sudden cardiac death (SCD).

Methods and Results—We prospectively examined the association between dietary intake of α-linolenic acid assessed via updated food-frequency questionnaires and the risk of SCD, other fatal CHD, and nonfatal myocardial infarction (MI) among 76 763 women participating in the Nurses’ Health Study who were free from cancer and completed a dietary questionnaire at baseline in 1984. During 18 years of follow-up, we identified 206 SCDs, 641 other CHD deaths, and 1604 nonfatal MIs. After controlling for coronary risk factors and other fatty acids, including long-chain n-3 fatty acids, the intake of α-linolenic acid was inversely associated with the risk of SCD (P for trend, 0.02) but not with the risk of other fatal CHD or nonfatal MI. Compared with women in the lowest quintile of α-linolenic acid intake, those in the highest 2 quintiles had a 38% to 40% lower SCD risk. This inverse relation with SCD risk was linear and remained significant even among women with high intakes of long-chain n-3 fatty acids.

Conclusions—These prospective data suggest that increasing dietary intake of α-linolenic acid may reduce the risk of SCD but not other types of fatal CHD or nonfatal MI in women. The specificity of the association between α-linolenic acid and SCD supports the hypothesis that these n-3 fatty acids may have antiarrhythmic properties. (Circulation. 2005;112:3232-3238.)

Key Words: death, sudden ■ women ■ arrhythmia ■ nutrition ■ fatty acids

The long-chain n-3 fatty acids found in fish have been associated with reduced risks of coronary heart disease (CHD), particularly mortality from CHD1-3 and sudden cardiac death (SCD).4-5 However, fatty fish is not readily available or palatable to all populations, and concerns have been raised about mercury contamination of the fish supply6 and depletion of ocean fisheries.7 Therefore, other sources of n-3 fatty acids should also be investigated. α-Linolenic acid (ALA) is an intermediate-chain n-3 fatty acid found in high concentrations in flaxseed, soybean, and canola oils and other foods of plant origin. After ingestion, ALA is partly converted (≈4% to 8%) into the long-chain n-3 fatty acids found in fish.8 In addition, ALA has direct antiarrhythmic properties in animal models9 and beneficial effects on thrombosis.10

Inverse associations between the intake of ALA and risk of fatal CHD have been observed in most11-14 but not all15 prospective cohort studies. In a prior report from this cohort,13 a single baseline measure of ALA intake was associated with a lower risk of fatal but not with nonfatal CHD during 10 years of follow-up. Similar to the long-chain n-3 fatty acids, ALA may influence CHD risk by reducing the risk of fatal arrhythmias without affecting the incidence of nonfatal myocardial infarction (MI). To address this hypothesis, we examined the relation of ALA intake (while controlling for long-chain n-3 fatty acid intake) specifically to the risk of SCD and report on the associations for other coronary death and nonfatal MI during 18 years of follow-up.

Methods

The Nurses’ Health Study Cohort

The Nurses’ Health Study began in 1976 when 121 701 registered nurses, 30 to 55 years of age, completed a questionnaire about their medical history, cardiovascular risk factors, menopausal status, and lifestyle factors. The cohort has been followed up every 2 years with mailed questionnaires that update exposure information and inquire about newly diagnosed medical illnesses.

Study Population

A total of 97 423 women returned the baseline 1984 questionnaire, the first to include food items critical for the assessment of ALA intake. We excluded women who did not complete the dietary

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questionnaire and those with 10 or more blank items or implausible reported food intakes (ie, <660 or >3500 kcal per day), leaving 81 757 women. After excluding women with a history of cancer (except nonmelanoma skin cancer) before 1984, 76 763 women remained for the primary analyses. Women who reported a history of prior cardiovascular disease (CVD; angina, MI, coronary revascularization, or stroke) at baseline or who reported CVD during follow-up were not excluded from the primary analyses. Instead, in those analyses, we controlled for any report of CVD that occurred before the development of 1 of the study end points throughout the follow-up period. Subjects or family members provided written, informed consent, and the study was approved by the institutional review board of Partners HealthCare System, Boston, Mass.

Dietary Assessment
In 1984, 1986, 1994, and 1998, a semiquantitative food-frequency questionnaire (FFQ) was mailed to participants. Use of the FFQ in estimating dietary intake16 and the calculation of ALA13 have been described in detail elsewhere. Because the US Department of Agriculture database contains values only for total linolenic acid17 and ALA constitutes the vast majority of total dietary linolenic acid, we used total linolenic acid values as a surrogate for ALA.13 The correlation coefficient between the calculated dietary linolenic acid from the FFQ and the proportion of linolenic acid in adipose tissue was 0.34 (P<0.001)18. The correlation coefficients for linolenic acid intake were 0.57 between the 1984 and 1986 questionnaires and 0.48 between the 1986 and 1990 questionnaires.13

End-PointAscertainment and Definitions
The study end points comprised incident cases of SCDS, other fatal CHD, and nonfatal MI that occurred after return of the 1984 questionnaire and before June 1, 2002. All women who reported having a nonfatal MI were asked for permission to review their medical records. MIs were confirmed according to World Health Organization criteria18 by physicians blinded to exposure status. MIs that required hospital admission and for which confirmatory information was obtained by interview or letter, but for which no medical records were available, were designated as probable (20%). Analyses excluding these events revealed similar results.

Deaths were either reported by next of kin or postal authorities or identified through a search of the National Death Index. Death certificates were obtained to confirm deaths, and we sought permission to obtain further information from medical records or family members. The next of kin were interviewed about the circumstances surrounding the death if not adequately documented in the medical record.

The classification of SCD is described in detail elsewhere.20 In brief, cardiac deaths were considered sudden if the death or cardiac arrest that precipitated death occurred within 1 hour of symptom onset. To increase our specificity for “arrhythmic death,” we excluded women with evidence of circulatory collapse (hypotension, exacerbation of congestive heart failure, or altered mental status) before the disappearance of the pulse.21 Unwitnessed deaths that could have occurred within 1 hour of symptom onset and with autopsy findings consistent with SCD were considered probable SCDS (10%) and not included in the analysis. Analyses excluding these events revealed similar results.

Fatal CHD was defined as ICD-9 codes 410 to 412 if confirmed by hospital records or autopsy or if CHD was the most probable cause and was listed as the cause of death on the death certificate, along with evidence of prior CHD. We designated as presumed CHD (24% of fatal cases) those cases in which CHD was the underlying cause on the death certificate but for which no medical records concerning the death were available. CHD deaths that did not also fulfill the criteria for SCD described earlier were designated “other CHD deaths” for these analyses.

Statistical Analysis
Age-adjusted means or proportions of cardiovascular risk factors were computed across quintiles of ALA intake. For each woman, person-months of follow-up were calculated from the date of return of the 1984 questionnaire to the date of the first end point, death or June 1, 2002, whichever came first. Because of the long follow-up period, dietary and other variables were updated to better represent both short- and long-term dietary patterns. Because ALA is largely metabolized and not stored and the mechanism of action is hypothesized to be either arrhythmogenic or antithrombotic,22 we postulated that short-term intake might be more likely to affect risk. Therefore, we performed a simple updated analysis that used the most recent dietary intake22 and carried forward the last observation for those with missing values (24% of updated observations).23

Proportional-hazards models were used to compute age- and multivariate-adjusted hazard ratios as estimates of relative risk across quintiles of ALA. Two multivariate models were performed (see the footnote to Table 2 for the list of covariates). The first multivariate model simultaneously controlled for coronary risk factors, updated prior report of CVD, alcohol intake, aspirin, vitamin supplements, and postmenopausal hormone use. The second multivariate model included these covariates and additionally controlled for intake of other fatty acids that resulted in a change of >10% in the parameter estimate for ALA intake. All variables, including dietary variables, were treated as time-varying covariates, with the most recent exposure used to predict outcome. Tests for linear trend were performed by assigning the median value to each quintile and modeling this as a continuous variable in separate proportional-hazards models. We also examined the possibility of a nonlinear relation between ALA intake and SCD risk nonparametrically by using restricted cubic spline transformations24,25 and tested for nonlinearity with the likelihood ratio test.

To determine whether the effect of ALA might differ in secondary or primary prevention, similar analyses were performed after stratifying the population by the presence or absence of a confirmed cardiovascular event (angina, MI, coronary revascularization, or stroke). Because ALA may act in part through elongation to long-chain n-3 fatty acids (eicosapentaenoic acid [EPA] and docosahexaenoic acid [DHA]), we performed stratified analyses that tested for an effect modification by long-chain n-3 fatty acids. We also examined plausible interactions with aspirin intake, age (<60 versus 60+ years), and n-6 fatty acids by adding cross-product terms between ALA and the exposure of interest into the full multivariate model. Statistical analysis was performed with SAS statistical software (SAS Institute Inc) version 8.2.

Results
Among the 76 763 women included in this analysis, ALA was the predominant n-3 fatty acid consumed, with intake ranging from 0.37% of total energy intake in the lowest quintile to 0.74% in the highest; corresponding percentages for combined EPA and DHA were 0.03% to 0.23%, respectively. The median absolute intake of ALA was 0.66 g/d in the lowest and 1.39 g/d in the highest quintile. Women who consumed greater amounts of ALA were older, more likely to be obese, have a history of diabetes, drink light to moderate amounts of alcohol, and smoke cigarettes (Table 1). They were less likely to have reported a prior history of CVD, drink larger amounts of alcohol (>15 g/d), and use aspirin or multivitamin supplements on a regular basis.

During 18 years of follow-up, we documented 206 SCDS, 641 other CHD deaths, and 1604 nonfatal MIs. In age-adjusted analyses, greater ALA intake was associated with a trend toward a lower risk of SCD (Table 2). After controlling for multiple coronary risk factors (see the footnote to Table 2, multivariate model 1), the inverse relation with SCD became significant. These relations remained significant when other fatty acids, including the long-chain n-3 fatty acids, were included in the model (Table 2, multivariate model 2). In
contrast, ALA intake was not significantly related to other (nonsudden) fatal CHD events or to nonfatal MI in any of the age-adjusted or multivariate models (Table 2). In the quintile analysis, the inverse association with SCD appeared linear, and reductions in risk became significant in the fourth quintile of intake, corresponding to a median absolute intake of 1.16 g/d. The test for nonlinearity was not significant, and multivariate spline regression confirmed a linear relation (P for linear trend, 0.02). For every 0.1% increase in energy intake from ALA, the associated hazard ratio was 0.88 (95% confidence interval [CI], 0.80 to 0.98).

To explore whether the association between ALA and SCD might differ in primary versus secondary prevention, we stratified the population by the presence or absence of a confirmed cardiovascular event (angina, MI, coronary revascularization, or stroke) before the incident event. In these secondary analyses, the dose-response relation between ALA and SCD was only apparent among women without a history of prior CVD (Table 3). However, with only 47 cases among women with prior CVD, we had limited ability to detect such a relation. Although the inverse association appeared stronger in the women without prior CVD, the CIs widely overlapped, and the test for interaction was not significant (P = 0.55).

To explore potential interactions between ALA and long-chain n-3 fatty acid intake (EPA+DHA), we computed the relative risk of SCD in 9 groups according to EPA+DHA intake (above versus below the median) and ALA intake (in quintiles) as compared with those with the lowest intake for both fatty acids (the Figure). The inverse relation between ALA intake and SCD in women was slightly more apparent in those above the median (P for trend, 0.049) versus below the median (P for trend, 0.12) of EPA+DHA intake; however, the test for an interaction between ALA and EPA+DHA intake was not significant (P for interaction, 0.64). The lowest risks for SCD were among those with the highest intakes of both fatty acids. Compared with those with the lowest intakes, the relative hazard for SCD was 0.41 (95% CI, 0.21 to 0.79, P = 0.008) among those in the highest

**TABLE 1. Relationship of Quintiles of Linolenic Acid Intake to Coronary Heart Disease Risk Factors**

Among 76,763 Women at Baseline in 1984

<table>
<thead>
<tr>
<th>Variable</th>
<th>Quintile of α-Linolenic Acid</th>
<th>Quintile of α-Linolenic Acid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median (% Energy)</td>
<td>1 (0.37)</td>
<td>2 (0.45)</td>
</tr>
<tr>
<td>No. of women (total = 76,763)</td>
<td>15363</td>
<td>15362</td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>50.7 (7.3)</td>
<td>50.4 (7.2)</td>
</tr>
<tr>
<td>Smoking†</td>
<td>Past</td>
<td>4610 (30.0)</td>
</tr>
<tr>
<td>Current 1–14 cigarettes/d</td>
<td>1138 (7.4)</td>
<td>1103 (7.2)</td>
</tr>
<tr>
<td>Current 15–24 cigarettes/d</td>
<td>1450 (9.4)</td>
<td>1497 (9.7)</td>
</tr>
<tr>
<td>Current ≥25 cigarettes/d</td>
<td>1121 (7.3)</td>
<td>1022 (6.6)</td>
</tr>
<tr>
<td>Reported diagnosis of</td>
<td>Diabetes, n (%)</td>
<td>473 (3.1)</td>
</tr>
<tr>
<td>High cholesterol, n (%)</td>
<td>1465 (9.6)</td>
<td>1322 (8.8)</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>3475 (22.7)</td>
<td>3270 (21.7)</td>
</tr>
<tr>
<td>CVD, n (%)</td>
<td>608 (3.9)</td>
<td>511 (3.4)</td>
</tr>
<tr>
<td>Body mass index ≥29 kg/m²</td>
<td>2301 (15.0)</td>
<td>2432 (15.9)</td>
</tr>
<tr>
<td>Parental history of MI before age 60 y</td>
<td>2240 (14.6)</td>
<td>2310 (15.0)</td>
</tr>
<tr>
<td>Alcohol intake</td>
<td>0.1–4.9 g/d</td>
<td>4681 (30.4)</td>
</tr>
<tr>
<td>≥15.0 g/d</td>
<td>2816 (18.3)</td>
<td>3108 (20.2)</td>
</tr>
<tr>
<td>Aspirin use (≥7 times per week, %)</td>
<td>2970 (19.3)</td>
<td>2792 (18.3)</td>
</tr>
<tr>
<td>Postmenopausal hormone use (current)</td>
<td>2106 (13.8)</td>
<td>1956 (13.0)</td>
</tr>
<tr>
<td>Physical activity (moderate and vigorous)</td>
<td>2–3.9 h/wk</td>
<td>2641 (17.2)</td>
</tr>
<tr>
<td>4–6.9 h/wk</td>
<td>4389 (28.6)</td>
<td>4403 (28.6)</td>
</tr>
<tr>
<td>≥7 h/wk</td>
<td>538 (3.5)</td>
<td>450 (2.9)</td>
</tr>
<tr>
<td>Vitamin supplement use</td>
<td>Vitamin E, n (%)</td>
<td>2870 (18.7)</td>
</tr>
<tr>
<td>Multivitamin, n (%)</td>
<td>6217 (40.5)</td>
<td>5679 (37.0)</td>
</tr>
</tbody>
</table>

*All percentages are standardized for age to the total cohort.
†Data are expressed as No. (%) unless otherwise indicated
‡Prior history of angina, MI, coronary revascularization, or stroke.
quintile of ALA intake who were also above the median for EPA/DHA intake. We found no evidence for an interaction between ALA intake and aspirin use, n-6 fatty acid intake, or age (60 versus 60 years).

**Discussion**

In this large, long-term, prospective cohort study of women, ALA intake was inversely associated with the risk of SCD but not with other types of fatal CHD or nonfatal MI. The inverse association with SCD risk persisted after controlling for other dietary fats, including the long-chain n-3 fatty acids found in fish. Women in the 2 highest quintiles of ALA intake had a 38% to 40% lower SCD risk, and the risk reduction appeared linear. When examined continuously, every 0.1% increase in energy intake from ALA was associated with a 12% reduction in SCD risk. In stratified analyses, inverse associations were most apparent for women without a history of prior CVD and those above the median for EPA/DHA intake. However, tests for interaction were not significant.

The specificity of the association with SCD, as opposed to other types of cardiac events, supports the hypothesis that ALA may influence cardiovascular risk through effects on arrhythmogenesis and fatal ventricular arrhythmias. Intravenous infusions of ALA reduced the risk of ventricular fibrillation during coronary artery ischemia in animal models,9 and dietary linolenic acid is associated with a reduced risk of abnormally prolonged repolarization in men and women.26 Also, after ingestion, ALA can be converted into EPA and, to a lesser extent, DHA,8 both of which have antiarrhythmic effects.27,28 Other plausible mechanistic pathways through which ALA may exert favorable effects on coronary and SCD risk include endothelial function, inflammation,29 and thrombosis.10

If ALA acts through the same pathway as EPA/DHA, with a threshold intake above which no further benefit is observed,10 one would expect to observe a weaker association between ALA intake and SCD risk among those who consumed higher amounts of EPA/DHA. Such an interaction between EPA/DHA and ALA was recently reported for total CHD in the Health Professional Follow-Up Study.31 However, our data suggest that increased ALA intake was associated with a lower risk of SCD, even among those with a lower risk of SCD.
higher intake of EPA+DHA. Those in the highest intake category for both n-3 fatty acids had the lowest risk, and therefore, additive effects of these fatty acids may also be plausible. Further studies are warranted to examine the interaction between ALA intake and long-chain n-3 fatty acids.

These data should be placed in the context of prior studies on ALA and CHD risk. In a prior report from this cohort, baseline ALA intake in 1984 was associated with a lower risk of total CHD death but not nonfatal MI during 10 years of follow-up. Unlike the present study, sudden death was not separated from other fatal CHD events in that report. The prior report also did not control for or examine the effect modification by the long-chain n-3 fatty acids. The present study, which included 8 more years of follow-up and used updated measures of ALA intake, confirms the prior null findings for nonfatal MI and provides an explanation for the disparate findings for fatal and nonfatal events observed in the prior report. Based on the present data, the benefit on fatal CHD observed in the prior study was likely due to a benefit on sudden CHD death, which accounts for a higher proportion of CHD death in younger women.

Other studies on ALA and CHD risk have been conducted in men. The Multiple Risk Factor Intervention trial \(^{14}\) and the Finnish Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study \(^{12}\) reported inverse associations between ALA intake and CHD death, whereas no relation was found for fatal or total CHD in the smaller Zutphen Elderly Study. \(^{15}\) The original report from the Health Professionals Follow-Up Study \(^{11}\) reported a significant inverse association with total CHD, especially nonfatal events. In the updated report from the Health Professionals Follow-Up Study, \(^ {31}\) only a trend toward an overall inverse association with total CHD persisted, primarily in men with low intakes of EPA+DHA, and no significant association with SCD was found.

These seemingly contradictory findings with regard to SCD raise the possibility that associations may differ in men versus women. Although conversion of ALA to EPA+DHA is limited, fractional conversion appears to be greater in women, potentially mediated through estrogen.\(^ {8,33}\) Also, a greater proportion of ALA appears to be β-oxidized in men and metabolized as an energy source,\(^ {8}\) potentially leading to lower plasma levels at similar intakes. Consistent with these potential sex differences in metabolism, a recent study reported that women achieved higher plasma levels of DHA compared with men on the same diet.\(^ {33}\) Alternatively, our contradictory findings could reflect differences in the classification of SCD among studies or could be due to chance.

There are limitations of the present study that warrant consideration. As with any observational study, ours cannot prove causality, because the association between ALA consumption and SCD could, at least in part, have been caused by residual confounding. However, ALA intake was directly associated with several coronary risk factors (age, obesity, diabetes, and smoking) and did not appear to be associated with others (hypertension, physical activity). Therefore, it is also possible that a more complete control for risk factors would have strengthened the inverse associations observed.

### Table 3: Primary vs Secondary Prevention: Relative Risks (95% Confidence Interval)\(^ *\) of Sudden Cardiac Death From 1984 to 2002, According to Quintiles of Linolenic Acid Intake, Stratified by History of Nonfatal CVD Before the SCD

<table>
<thead>
<tr>
<th>Quintiles of Linolenic Acid</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>P for Trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>No prior history of CVD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (% energy)</td>
<td>0.37</td>
<td>0.45</td>
<td>0.52</td>
<td>0.60</td>
<td>0.74</td>
<td></td>
</tr>
<tr>
<td>No of cases</td>
<td>40</td>
<td>34</td>
<td>34</td>
<td>24</td>
<td>27</td>
<td></td>
</tr>
<tr>
<td>Person-years</td>
<td>252 241</td>
<td>251 981</td>
<td>251 869</td>
<td>251 644</td>
<td>251 727</td>
<td></td>
</tr>
<tr>
<td>Incidence rate†</td>
<td>16</td>
<td>13</td>
<td>14</td>
<td>10</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Age-adjusted</td>
<td>1.0</td>
<td>0.92 (0.58–1.45)</td>
<td>0.92 (0.58–1.47)</td>
<td>0.65 (0.39–1.09)</td>
<td>0.68 (0.41–1.12)</td>
<td>0.06</td>
</tr>
<tr>
<td>Multivariate‡</td>
<td>1.0</td>
<td>0.89 (0.56–1.41)</td>
<td>0.86 (0.54–1.39)</td>
<td>0.60 (0.35–1.03)</td>
<td>0.59 (0.34–1.02)</td>
<td>0.03</td>
</tr>
<tr>
<td>Prior history of CVD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (% energy)</td>
<td>0.35</td>
<td>0.43</td>
<td>0.49</td>
<td>0.58</td>
<td>0.72</td>
<td></td>
</tr>
<tr>
<td>No of cases</td>
<td>13</td>
<td>9</td>
<td>6</td>
<td>10</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Person-years</td>
<td>13 007</td>
<td>12 965</td>
<td>12 936</td>
<td>12 907</td>
<td>12 841</td>
<td></td>
</tr>
<tr>
<td>Incidence Rate†</td>
<td>100</td>
<td>69</td>
<td>46</td>
<td>77</td>
<td>70</td>
<td></td>
</tr>
<tr>
<td>Age-adjusted</td>
<td>1.0</td>
<td>0.67 (0.28–1.58)</td>
<td>0.44 (0.16–1.16)</td>
<td>0.75 (0.32–1.75)</td>
<td>0.65 (0.27–1.57)</td>
<td>0.50</td>
</tr>
<tr>
<td>Multivariate‡</td>
<td>1.0</td>
<td>0.68 (0.28–1.64)</td>
<td>0.38 (0.14–1.06)</td>
<td>0.76 (0.30–1.88)</td>
<td>0.53 (0.19–1.45)</td>
<td>0.33</td>
</tr>
</tbody>
</table>

SCD indicates sudden cardiac death.

*95% confidence intervals shown in parentheses.

†Incidence per 100 000 person years.

‡Adjusted for age, calories (continuous), smoking status (never, past, current 1–14 cigarettes/d, 15–24 cigarettes/d, ≥25 cigarettes/d), body mass index (<22, 22–22.9, 23–24.9, 25–28.9, ≥29 kg/m²), alcohol intake (0, <5, 5–14, ≥15 g/d), menopausal status and postmenopausal hormone use, vigorous to moderate activity (<2, 2–3.9, ≥4 h/wk), usual aspirin use (<1 wk, 1–6 wk, and ≥7 wk), multivitamin use (yes vs no), vitamin E supplement use (yes vs no), history of hypertension (yes vs no), hypercholesterolemia (yes vs no), diabetes (yes vs no) family history of MI (no, before age 60 y, after age 60 y), intakes of trans-unsaturated fat, ratio of polyunsaturated fat to saturated fat, and omega-3 fatty acids (all in quintiles).
Multivariate, adjusted relative hazard of SCD across increasing quintiles of α-linolenic acid intake stratified at the median for long-chain n-3 fatty acid intake. Relative hazard was adjusted for age, calories (continuous), smoking status (never; past; current 1 to 14, 15 to 24, or ≥25 cigarettes/d), body mass index (<22, 22 to 22.9, 23 to 24.9, 25 to 28.9, or ≥29 kg/m²), alcohol intake (0, <5, 5 to 14, or ≥15 g/d), menopausal status and postmenopausal hormone use, vigorous to moderate activity (<2, 2 to 3.9, ≥4 h/wk), usual aspirin use (<1, 1 to 6, and ≥7 h/wk), multivitamin use (yes vs no), history of hypertension (yes vs no), hypercholesterolemia (yes vs no), diabetes (yes vs no), family history of MI (no, yes before 60, yes after age 60), history of prior CVD (yes vs no), intake of trans-polyunsaturated fat, and ratio of polyunsaturated fat to saturated fat intake (all in quintiles). High EPA/DHA was defined as values greater than or equal to the median value of the cohort (0.09% of energy intake); low was defined as values less than or equal to the median value.

Second, information on coronary risk factors and diet was ascertained by self-report, potentially leading to some misclassification. However, numerous validation studies have established that the nurses accurately reported diet and coronary risk factors. Additionally, a unique advantage of this study is that coronary risk factors and dietary intake were assessed on several occasions, and changes in these dietary and nondietary covariates were taken into account in the analysis. However, there is still the chance for misclassification because of both missing data on subsequent questionnaires and the time lag between questionnaire years. If present, such misclassification might have biased our results toward the null if, as hypothesized, short-term intake is more likely to affect risk. Although the long follow-up period provided sufficient power for the main analyses, we had inadequate power to detect subtle interactions that might have existed. Finally, the selective nature of the cohort, US female registered nurses, may limit the generalizability of the findings, and as mentioned earlier, it is possible that these findings may not apply to men.

In conclusion, these prospective data provide evidence for an inverse association between ALA intake and SCD risk among women. Because the majority of women who die suddenly do not have a history of CVD and few cardiac arrest victims survive to hospital discharge, any substantial reduction in SCD will require prevention efforts in the general population as well as in those with a history of CVD. If diets and/or supplements enriched with ALA were found to have antiarrhythmic properties or to reduce the risk of SCD in randomized trials, the public health impact of such a low-cost and easily accessible intervention could be significant.

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