Circulating and dietary α-linolenic acid and incidence of congestive heart failure in older adults: the Cardiovascular Health Study[1–3]

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ABSTRACT

Background: Few studies have evaluated the association between the n−3 fatty acid α-linolenic acid (ALA) and the incidence of congestive heart failure (CHF).

Objective: We investigated whether plasma phospholipid concentrations and estimated dietary consumption of ALA are associated with incident CHF.

Design: We used data from the Cardiovascular Health Study, a prospective cohort study of cardiovascular diseases among adults aged ≥65 y, from 4 US communities. A total of 2957 participants free of prevalent heart disease and with available fatty acid measurements were included in biomarker analyses (30,722 person-years and 686 incident CHF events). A total of 4432 participants free of prevalent heart disease were included in dietary analyses (52,609 person-years and 1072 events). We investigated the association of ALA with incident CHF by using Cox regression.

Results: After adjustment for age, sex, race, education, smoking status, BMI, waist circumference, and alcohol consumption, plasma phospholipid ALA was not associated with incident CHF (HR for the highest compared with the lowest quartile: 0.97; 95% CI: 0.79, 1.21; *P*-trend = 0.85). Likewise, dietary ALA was not associated with incident CHF (adjusted HR for the highest compared with the lowest quartile: 0.96; 95% CI: 0.82, 1.20; *P*-trend = 0.97). We observed no association of biomarker or dietary ALA with nonvalvular CHF subtype. We also found little evidence of an association between ALA and CHF in subgroups based on age, sex, diabetes, fish consumption, BMI, or *FADS2* genotype (rs1535).

Conclusion: ALA intake is not associated with incident CHF in older adults. This trial was registered at clinicaltrials.gov as NCT00005133. *Am J Clin Nutr* 2012;96:269–74.

INTRODUCTION

Congestive heart failure (CHF)[4] is a disabling condition with high rates of rehospitalization and mortality (1, 2). Incidence increases dramatically with advancing age, making CHF a particular burden in the elderly (1, 3). Nutritional factors may play a role in the prevention of CHF, indirectly by lowering risk factors for CHF such as hypertension or ischemic heart disease (IHD) or directly by improving cardiac systolic or diastolic function. For example, nutritional factors that are part of a healthy lifestyle (4), higher fish consumption (5, 6), and higher dietary omega-3 (n−3) fatty acids from seafood (EPA and DHA) (6) have been found to be associated with a lower incidence of CHF.

α-Linolenic acid (ALA) is an essential n−3 fatty acid of plant origin that can be converted to EPA. Whereas EPA and DHA have shown benefits on cardiovascular disease risk factors that might prevent CHF and have been studied for physiologic and mortality benefits in patients with established CHF (7), much less is known about ALA. Given the challenges of sustainability of fish sources and a far greater potential supply of ALA, it would be important to know whether ALA has cardiovascular benefits. In brief (1 y) randomized trials, ALA supplementation (∼3–5 g/d) did not significantly reduce IHD risk, but in trials of longer duration (≥2 y), dietary patterns that included ALA-rich foods substantially reduced IHD risk (7, 8). However, these trials were largely confined to individuals with known IHD (ie, secondary prevention) and did not evaluate CHF. The study of ALA with the use of estimated dietary intake is difficult, in part related to the challenges of estimating ALA intake from questionnaires, which requires precise assessment of very specific foods. A handful of retrospective case-control studies that used

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[4] Abbreviations used: ALA, α-linolenic acid; ARIC, Atherosclerosis Risk in Communities; CHF, congestive heart failure; CHS, Cardiovascular Health Study; IHD, ischemic heart disease.

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a biomarker of ALA exposure found protective associations with nonfatal myocardial infarction (9, 10). Whether such an association extended to CHF, a related but distinct outcome, has not been evaluated. Far fewer studies of the effects of ALA, than of EPA and DHA, on physiologic risk factors and cardiovascular endpoints have been conducted. Nevertheless, reported beneficial effects on IHD (9, 11), markers of IHD (12, 13), blood lipids (14–16), and inflammation (17) suggest possible mechanisms by which ALA can reduce CHF risk.

Plasma phospholipid concentrations of ALA (18, 19), and other n−3 fatty acids (20, 21), are an objective biomarker of intake of these fatty acids. With the use of this biomarker, we showed an association of EPA and DHA with lower CHF risk in the Cardiovascular Health Study (CHS) (22)—a prospective cohort of risk factors for cardiovascular disease among older adults (23). By using the same cohort, we tested the hypothesis that higher ALA intake, assessed with a biomarker of intake and directly from the diet, may be associated with a lower risk of incident CHF.

SUBJECTS AND METHODS

Study population

CHS is a prospective, population-based cohort study of cardiovascular disease among older adults (23). Participants were recruited from 4 US communities (Forsyth County, NC; Sacramento County, CA; Washington County, MD; Allegheny County, PA) as a random sample generated from the Health Care Financing Administration files. Among eligible adults who were contacted, 57% agreed to participate. The cohort consisted of 5201 noninstitutionalized men and women aged ≥65 y, recruited in 1989–1990, plus an additional 687 black participants recruited in 1992–1993. Each center's institutional review board approved the study, and all participants provided informed written consent to participate in the study. Participants who did not consent to genetic analyses were excluded from the gene-by-environment portion of the study.

Phospholipid fatty acids were measured in specimens drawn in 1992–1993—the baseline of the phospholipid ALA analyses. We excluded from these analyses participants censored before 1992–1993 (n = 623), participants with prevalent CHF (n = 344) or prevalent IHD (n = 946), and participants with missing fatty acid measurements (n = 1018). The remaining 2957 participants were included in the phospholipid ALA analysis.

Dietary habits were assessed in 1989–1990 and again in 1995–1996. Participants recruited in 1992–1993 entered the diet analysis at the time of the second assessment. We excluded participants with prevalent CHF (n = 275) or IHD (n = 979) at the time of their first diet assessment and participants with missing diet assessment (n = 202). The remaining 4432 participants were included in the diet analysis.

Plasma phospholipid ALA

Blood was drawn, after the subjects had fasted for 12 h, into tubes containing EDTA, and plasma specimens were stored at −70°C. Plasma lipids were extracted by using the method of Folch (24). Phospholipids were separated by thin-layer-chromatography in the presence of the antioxidant butylated hydroxytoluene; fatty acid methyl esters were prepared by direct *trans*-esterification of the phospholipid fraction (25) and were separated by gas chromatography by using a fused-silica 100-m capillary column as previously described (22). Plasma phospholipid ALA was expressed as a percentage of total fatty acids. The interassay CV was 3.1%.

Dietary ALA

Dietary habits were assessed in 1989–1990 by using a picture-sort food-frequency questionnaire validated against 6 detailed 24-h dietary recall interviews spaced ∼1 mo apart (26) and again in 1995–1996 by using the Willett food-frequency questionnaire (27). We used dietary ALA expressed as a percentage of total fat intake, because it correlated better with phospholipid ALA, measured 3 y later (r = 0.20), than with absolute ALA intake or ALA intake expressed as a percentage of total energy.

Other risk factors

Information on medical history, lifestyle, and clinical risk factors was collected at annual clinic visits. Physical activity was assessed at the 1992–1993 visit by using a modified Minnesota Leisure-Time Activities questionnaire (28). The covariates measured at the same 1992–1993 visit used for blood sampling were used in the plasma phospholipid ALA analyses. Covariates measured at the same visits used for diet assessments were used in the dietary analyses.

Ascertainment of CHF

The participants were followed by means of annual study-clinic examinations with interim phone contacts for 10 y and telephone contacts every 6 mo thereafter. Incident CHF was adjudicated by a centralized CHS committee by using information from outpatient and inpatient medical records, diagnostic tests and consultations, and interviews. Confirmation of definite CHF required each of 3 criteria: *1*) CHF diagnosis by a treating physician; *2*) either CHF symptoms (shortness of breath, fatigue, orthopnea, and paroxysmal nocturnal dyspnea) plus signs (edema, rales, tachycardia, gallop rhythm, and displaced apical impulse) or supportive clinical findings on echocardiography, contrast ventriculography, or chest radiography; and *3*) medical therapy for CHF, defined as diuretics plus either digitalis or a vasodilator (angiotensin-converting-enzyme inhibitors, hydralazine, and long-acting nitrates) (29). In addition, CHF was subclassified as valvular or nonvalvular based on medical record information on catheterization results, ejection fraction, wall-motion abnormalities, and presence of valvular disease.

Statistical analysis

ALA concentrations were evaluated in quartiles as indicator variables, with the significance of trends across categories evaluated by entering the categorical variable as an ordinal variable. Cox proportional hazards were used to estimate the HR of incident CHF, with time-at-risk until first diagnosis, death, or latest adjudicated date of follow-up in 2008. Missing covariates (most factors <2%) were imputed by single regressions with demographic and risk-factor variables; the results excluding subjects with missing values were similar.

Estimated ALA consumption was updated over time as a time-varying exposure by using cumulative updating (averaging first and second dietary estimates at the time of the second dietary assessment) (27). To account for development of IHD between the dietary questionnaires that could be either a confounder or a mediator of a potential association with CHF, we did not update after a diagnosis of incident IHD. We also performed sensitivity analyses in which we excluded participants who had developed IHD at the time of their second diet assessment and weighted the nonexcluded participants with 2 diet assessments by their inverse probability of not developing IHD by this time (30).

We performed additional analyses limited to the midpoint of follow-up (7 y) to minimize exposure misclassification with increasing duration of follow-up. By using information on ejection fraction available on half of the CHF events, we estimated the HRs of incident diastolic CHF (CHF with preserved ejection fraction) and incident systolic CHF (CHF with depressed ejection fraction) associated with plasma phospholipid and dietary ALA.

Effect modification was evaluated for age (continuous), sex, diabetes, BMI (continuous), genotype at rs1535 (a single nucleotide polymorphism in the *FADS2* gene with minor allele frequency of 0.28 reportedly associated with plasma phospholipid concentrations of ALA; 31), concentrations of linoleic acid, low fish consumption (defined as <0.6 servings/wk, the 25th percentile), and no fish consumption/no fish-oil supplement use. Statistical significance was assessed via the Wald test for the multiplicative interaction term, in models in which ALA was modeled continuously. The analyses used Stata10.1 (StataCorp).

RESULTS

Plasma phospholipid ALA and CHF

The mean (5th, 95th percentile) plasma phospholipid concentration of ALA was 0.15% of total fatty acids (0.08, 0.25). In unadjusted analyses, ALA concentrations were associated with female sex, white race, greater education, less smoking, less diabetes, smaller BMI and waist circumference, and lower fasting glucose and fasting insulin (**Table 1**). In addition, ALA concentrations were associated with dietary ALA estimated 3 y earlier, lower energy intake from total fat, greater energy intake from carbohydrate, and consumption of fish, salad dressing, and alcohol.

During 30,722 person-years of follow-up, there were 686 cases of incident CHF. The incidence rate was 2.2/100 person-years, and the cumulative incidence was 23.2% over 16 y. Whereas the crude incidence rate of CHF was lower in higher quartiles of ALA, plasma phospholipid ALA was not associated with CHF after adjustment for age and sex or after adjustment for other demographic, cardiovascular, and lifestyle risk factors (**Table 2**). Similarly, when we examined nonvalvular CHF, an outcome that might be more plausibly affected by dietary factors, no association with plasma phospholipid ALA was found (Table 2). Further adjustments for other risk factors, including diabetes, history of stroke, atrial fibrillation, hypertension, fish consumption, and phospholipid concentrations of long-chain n−3 fatty acids and linoleic acid, or exclusion of fish-oil supplement users (3.5% of study population) did not appreciably alter the results (data not shown). In exploratory analyses, phospholipid ALA was not associated with risk of either systolic or diastolic CHF (data not shown).

TABLE 1
Baseline characteristics of 2957 participants in the Cardiovascular Health Study cohort according to quartiles of plasma phospholipid α-linolenic acid

	Quartile of plasma phospholipid α-linolenic acid			
	1 (n = 756)	2 (n = 751)	3 (n = 713)	4 (n = 737)
α-Linolenic acid (% of total plasma phospholipid fatty acids)	0.09 (0.05–0.11)[1]	0.13 (0.11–0.14)	0.16 (0.14–0.18)	0.22 (0.18–0.47)
Age (y)	72.0 ± 5.0[2]	72.1 ± 5.1	72.1 ± 5.2	72.3 ± 5.3
Sex, male (%)	45.9	36.4	33.8	30.9
Race, white (%)	82.9	87.5	87.8	91.5
Education, >high school (%)	68.0	73.6	77.5	79.5
Current smoker (%)	11.5	11.6	7.0	8.2
Diabetes mellitus (%)	29.5	25.3	20.2	19.7
Atrial fibrillation (%)	5.9	5.9	6.0	5.3
History of stroke (%)	5.4	5.1	3.2	2.7
Treated hypertension (%)	41.3	42.5	38.6	40.6
BMI (kg/m^2)	27.7 ± 5.0	26.8 ± 4.5	26.6 ± 4.5	25.5 ± 4.2
Fasting glucose (mmol/L)	6.1 ± 2.2	6.0 ± 2.0	5.8 ± 1.6	5.8 ± 1.7
Fasting insulin (pmol/L)	96.3 ± 130.8	95.6 ± 124.3	91.8 ± 136.1	78.2 ± 83.0
Waist circumference (cm)	100.0 ± 13.5	96.9 ± 12.7	96.4 ± 13.2	93.8 ± 13.0
Physical activity (kcal/wk)	1092 ± 1413	969 ± 1346	1040 ± 1376	1149 ± 1557
Alcohol (drinks/wk)	1.6 ± 4.0	1.8 ± 4.7	2.2 ± 5.4	2.9 ± 9.8
Tuna/dark fish (servings/wk)	1.6 ± 1.4	1.5 ± 1.2	1.5 ± 1.4	1.7 ± 1.5
Salad dressing (servings/wk)	1.8 ± 0.8	1.9 ± 0.8	2.0 ± 0.8	2.0 ± 0.8
Fat intake (% of energy)	32.4 ± 6.4	32.3 ± 5.5	32.2 ± 5.9	31.7 ± 6.0
Carbohydrate intake (% of energy)	51.9 ± 8.2	52.0 ± 7.6	52.5 ± 7.7	52.9 ± 7.9
Total energy intake (kcal/d)	2044 ± 656	2036 ± 676	2008 ± 639	1992 ± 612
α-Linolenic acid intake (% of total fat)	2.2 ± 0.6	2.3 ± 0.6	2.3 ± 0.6	2.5 ± 0.6

[1] Mean; range in parentheses (all such values).
[2] Mean ± SD (all such values).

TABLE 2
HRs (95% CIs) for the association of plasma phospholipid α-linolenic acid with incident congestive heart failure and nonvalvular congestive heart failure in 2957 participants in the Cardiovascular Health Study[1]

	Quartile of plasma phospholipid α-linolenic acid				
	1	2	3	4	*P*-trend
Total congestive heart failure					
Person-years	7838	7570	7469	7846	
No. of incident cases	191	169	161	165	
Model 1	Reference	0.95 (0.77, 1.17)	0.91 (0.74, 1.13)	0.88 (0.72, 1.09)	0.23
Model 2	Reference	0.97 (0.78, 1.20)	0.98 (0.79, 1.22)	0.97 (0.79, 1.21)	0.85
Nonvalvular congestive heart failure					
Person-years	7838	7570	7469	7846	
No. of incident cases	123	109	92	107	
Model 1	Reference	0.93 (0.72, 1.21)	0.80 (0.61, 1.05)	0.88 (0.68, 1.15)	0.22
Model 2	Reference	0.98 (0.75, 1.28)	0.88 (0.67, 1.16)	1.03 (0.79, 1.34)	0.95

[1] HRs and 95% CIs were calculated by using multivariate Cox proportional hazard regression. Model 1 was adjusted for age (y) and sex. Model 2 was adjusted as for model 1 with additional adjustment for enrollment site (4 sites), race (white, nonwhite), education (<high school, high school, college), smoking (never, former, current), leisure-time physical activity (kcal/wk), BMI (kg/m^2), waist circumference (cm), and alcohol consumption (g/d).

There was little evidence that the association of phospholipid ALA with CHF varied according to age, sex, diabetes, BMI, genotype at rs1535, phospholipid linoleic acid, or low or no fish consumption (8 comparisons; *P*-interaction > 0.29 for each), and stratified analyses did not suggest any association in any subgroup (data not shown). However, the subgroup that reported no fish consumption and no supplement use was too small (121 study subjects and 32 events) to provide meaningful risk estimates. We also observed similar results in analyses censored at the midpoint of follow-up to minimize effects of exposure misclassification over time (data not shown).

Dietary ALA and CHF

Of the 4432 participants in the dietary analyses, mean (5th, 95th percentile) estimated dietary ALA was 2.2% (1.4, 3.2) of total fat intake. During 52,609 person-years of follow-up, there were 1072 cases of incident CHF. After adjustment for demographic, cardiovascular, and lifestyle risk factors, dietary ALA was not associated with incident total CHF (*P*-trend = 0.97) or incident nonvalvular CHF (*P*-trend = 0.59) (**Table 3**). Further adjustment for other risk factors, including diabetes, history of stroke, atrial fibrillation, hypertension, and dietary linoleic acid and fish consumption, did not appreciably affect the results (data not shown). In exploratory analyses, dietary ALA was associated with a lower risk of systolic CHF (n = 253 cases), with fully adjusted HRs across quartiles of ALA of 1.0 (reference), 0.65 (0.47, 0.91), 0.66 (0.47, 0.94), and 0.66 (0.45, 0.98) (*P*-trend = 0.02). Dietary ALA was not associated with risk of diastolic CHF (data not shown).

The association of dietary ALA with CHF did not significantly vary according to subgroups of age, sex, diabetes, BMI, dietary

TABLE 3
HRs (95% CIs) for the association of dietary α-linolenic acid with incident congestive heart failure and nonvalvular congestive heart failure in 4432 participants in the Cardiovascular Health Study[1]

	Quartile of dietary α-linolenic acid				
	1	2	3	4	*P*-trend
Total congestive heart failure					
Person-years	12,753	13,472	13,387	12,997	
No. of incident cases	319	280	258	215	
Model 1	Reference	0.83 (0.71, 0.98)	0.88 (0.74, 1.04)	0.89 (0.75, 1.07)	0.26
Model 2	Reference	0.83 (0.71, 0.98)	0.92 (0.77, 1.09)	0.99 (0.82, 1.20)	0.97
Nonvalvular congestive heart failure					
Person-years	12,753	13,472	13,387	12,997	
No. of incident cases	207	186	167	136	
Model 1	Reference	0.88 (0.72, 1.08)	0.90 (0.73, 1.10)	0.85 (0.68, 1.07)	0.18
Model 2	Reference	0.88 (0.72, 1.08)	0.92 (0.74, 1.14)	0.93 (0.74, 1.18)	0.59

[1] HRs and 95% CIs were calculated by using multivariate Cox proportional hazard regression. Model 1 was adjusted for age (y) and sex. Model 2 was adjusted as for model 1 with additional adjustment for enrollment site (4 sites), race (white, nonwhite), education (<high school, high school, college), smoking (never, former, current), BMI (kg/m^2), waist circumference (cm), alcohol consumption (g/d), and total energy intake (kcal/d).

linoleic acid, fish consumption, or genotype at rs1535 (8 comparisons; *P*-interaction > 0.23 for each). For example, in the subgroup that reported no fish intake and no supplement use (n = 732), the HR associated with higher quartiles of dietary ALA were 0.9 (0.6, 1.4), 0.9 (0.5, 1.4), and 1.4 (0.8, 2.2) compared with the lowest quartile.

DISCUSSION

In this large, prospective cohort study of older US adults without heart disease at baseline, plasma phospholipid concentrations of ALA, a biomarker of intake, and estimated dietary intake of ALA were not associated with incidence of total or nonvalvular CHF. The results were similar in subgroups based on age, sex, diabetes, BMI, fatty fish consumption, and *FADS2* genotype at rs1535.

Dietary ALA is difficult to estimate from questionnaires because of challenges in estimating the ALA content of foods. This likely explains, at least in part, the low correlation (0.20) between estimated dietary ALA and phospholipid ALA. Additionally, although measurement of the biomarker is more precise from a laboratory standpoint, with only 3% CV, how well plasma phospholipid ALA reflects usual diet is not well known, because phospholipids reflect only a few weeks of diet, and ALA is also extensively metabolized after consumption. In short-term intervention studies, high doses of ALA supplements (eg, 10 g/d) result in higher concentrations of tissue ALA (32); however, tracer studies show that only a small proportion of dietary ALA is incorporated into phospholipids (33). In addition, circulating ALA was measured at baseline, and fluctuations over time would result in exposure misclassification during follow-up. However, the biomarker association did not change in analyses restricted to the first 7 y of follow-up. Overall, we cannot exclude the possibility that measurement error in both the dietary and biomarker estimates may account for the null findings, but the consistency of the findings with both biomarker and dietary estimates strengthens the study conclusion of no overall association of ALA with incident CHF.

Our findings are consistent with those of a prior study of circulating ALA and incident CHF in the Atherosclerosis Risk in Communities (ARIC) Study (34). In that cohort of predominantly middle-aged US adults, 2 biomarker compartments, plasma phospholipid ALA and cholesterol-ester ALA, showed no association with CHF risk. Because the ARIC study population was younger (aged 45–64 y at baseline) than the CHS population and included fewer CHF events (n = 197), our findings suggest the generalizability of no association from middle age to elderly and also that statistical power is a less likely explanation for their null findings.

The absence of association of plasma phospholipid ALA with incident CHF contrasts with our findings of a lower CHF risk associated with higher plasma phospholipid EPA in CHS (22) and a lower CHF risk associated with estimated fish consumption in CHS (6) and in the Women's Health Initiative (5). Together with the findings from the ARIC cohort, the current results suggest that plant-derived ALA might not be considered a substitute for long-chain n−3 fatty acids in the prevention of CHF.

In the liver, ALA can be converted to EPA—a long-chain n−3 fatty acid. However, the extent of conversion in humans appears to be low (35) or requires large doses of ALA (36), which may explain the lack of benefits of ALA. In a meta-analysis that included CHS and other cohort studies, we showed that the association of plasma phospholipid ALA with EPA is lower among carriers of a genetic variant in the desaturase gene *FADS2*, which suggests less conversion (31). In the current study, we did not find that *FADS2* genotype modified the association of ALA biomarker or dietary ALA with CHF risk. In the Health Professionals Follow-Up Study, we reported a stronger association of dietary ALA with lower IHD risk among men with lower seafood intake (37). However, we found no evidence of an interaction of dietary ALA with seafood intake and no evidence of an interaction of biomarker ALA with plasma phospholipid long-chain n−3 fatty acids in the current study.

This was an observational analysis, and residual confounding by unknown factors is possible. However, results were robust to adjustment for multiple CHF risk factors. The study was conducted among older adults with modest fish intake, and the results may not be generalizable to other populations with a very low fish intake, in whom ALA could have greater effects, or to younger populations. Information on ejection fraction was available for only half of the CHF events. The association of dietary ALA with lower incidence of systolic CHF in subgroup analyses was not confirmed with the biomarker and may be a chance finding.

The strengths of the study included its prospective design, population-based enrollment, large number of events, and rich information on demographics, cardiovascular risk factors, and lifestyle habits. In conclusion, we found no association of ALA, measured either with a biomarker or from dietary questionnaires, with incident CHF. Unlike the seafood-derived n−3 fatty acids EPA and DHA, plant n−3 fatty acid ALA was not associated with a lower risk of CHF.

A full list of principal CHS investigators and institutions can be found at http://www.chs-nhlbi.org/pi.htm.

The authors' responsibilities were as follows—RNL: designed the research (project conception), performed the statistical analysis, wrote the manuscript, and had primary responsibility for the final content; IBK: conducted the research (data collection) and obtained funding; XS: conducted the research (data collection); CS: performed the statistical analysis; DS, FMS, and EBR: wrote the manuscript and obtained funding; BM and LD: wrote the manuscript; and DM and DSS: conducted the research (data collection), wrote the manuscript, and obtained funding. DM reports receiving research grants from GlaxoSmithKline, Sigma Tau, Pronova, and the NIH for an investigator-initiated, not-for-profit clinical trial; travel reimbursement, honoraria, or consulting fees from the International Life Sciences Institute, Aramark, Unilever, SPRIM, and Nutrition Impact; and royalties from UpToDate. None of the other authors declared a conflict of interest.

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