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Low plasma eicosapentaenoic acid and depressive symptomatology are independent predictors of dementia risk[1–3]

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ABSTRACT

Background: The potential preventive role of polyunsaturated fatty acids (PUFAs) in Alzheimer disease has aroused increasing interest. Plasma n−3 PUFAs have been shown to be inversely related to the risk of dementia and to depression, which is frequently associated with dementia.

Objective: The objective was to ascertain whether plasma PUFAs predict the risk of incident dementia in a cohort of older persons, independently of their depressive status.

Design: Of 1214 nondemented participants in the Three-City Study from Bordeaux (France) who were followed up for 4 y, 65 developed dementia. The association between the proportion of plasma fatty acids at baseline and the risk of incident dementia was assessed by multivariate proportional hazard models, taking into account depressive status assessed on the basis of the Center for Epidemiologic Studies Depression scale.

Results: A higher plasma eicosapentaenoic acid (EPA) concentration was associated with a lower incidence of dementia [hazard ratio (HR) for 1 SD = 0.69; 95% CI: 0.48, 0.98], independently of depressive status and after adjustment for age, education, apolipoprotein E ε4 allele, diabetes, and baseline plasma vitamin E and triacylglycerol. The relations between docosahexaenoic acid (DHA), total n−3 PUFAs, and incident dementia did not remain significant in multivariate models. Higher ratios of arachidonic acid (AA) to DHA and of n−6 to n−3 fatty acids were related to an increased risk of dementia, particularly in depressive subjects ($n = 90$): ratio of AA to DHA (HR: 2.65; 95% CI: 1.07, 6.56) and ratio of n−6 to n−3 (HR: 1.61; 95% CI: 1.04, 2.47).

Conclusions: A high plasma EPA concentration may decrease the risk of dementia, whereas high ratios of n−6 to n−3 fatty acids and of AA to DHA may increase the risk of dementia, especially in depressed older persons. The role of EPA in dementia warrants further research. *Am J Clin Nutr* 2008;88:714–21.

INTRODUCTION

Alzheimer disease (AD) is the most frequent cause of dementia in older persons. The main risk factor of late-onset or sporadic AD is genetic; possession of the ε4 allele of the apolipoprotein E (apo E) gene increases the risk. Given the paucity of modifiable risk factors of AD, the potential preventive role of nutrition has aroused increasing interest. Several epidemiologic studies have shown that regular fish consumers have a decreased risk of dementia or AD (1, 2) and better cognitive performances (3–5). The protective effect of fish consumption has been attributed to its high content of long-chain n−3 polyunsaturated fatty acids (n−3 PUFAs), particular eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). The beneficial effect of long-chain n−3 PUFAs against dementia may be explained by their major structural and functional roles in neurone membranes, their vascular and antiinflammatory properties, as well as their potential ability to modulate neuroinflammation and the expression of neuronal-plasticity-related genes (6). The biosynthesis of EPA and DHA from their precursor α-linolenic acid (ALA) is limited and seems to decrease with aging (7). Thus, the major source of EPA and DHA is diet, mainly via fatty fish consumption (8). High dietary intake of long-chain n−3 PUFAs has been shown to be associated with a lower risk of dementia or cognitive decline (3, 9). However, some studies have not shown such a protective association (4, 10). Such inconsistent results may be explained by the weak association between dietary intake and the bioavailability of fatty acids. Indeed, recent studies have reported that fish and fish oil intake explain only partially the variability in plasma n−3 PUFAs (11). Therefore, biological data may be more accurate than dietary data in studying the putative protective effect of PUFAs on dementia. Cross-sectional studies that evaluated the

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relation between plasma fatty acids and cognitive decline or dementia provide limited evidence because they cannot ascertain causality (12, 13). Longitudinal studies of this relation, although scarce, have shown that total or long-chain n−3 PUFAs in plasma or erythrocyte membranes are related to slower cognitive decline (14–17). The 2 longitudinal studies that assessed the relation between plasma long-chain PUFAs and incidence of dementia show conflicting results. The first study found no association (18), whereas the most recent study reported that plasma DHA concentrations are inversely related to the risk of incident dementia and AD (19).

However, these studies may have been limited by residual confounding. Indeed, several studies have linked a low level of long-chain n−3 PUFAs, particularly EPA, with a high level of depressive symptoms in older persons (20). Moreover, depression is a frequent comorbid condition in patients with dementia, even at its early phase of mild cognitive impairment (21, 22). Increasing evidence shows that depression is a risk factor for incident dementia (22–25). Depression could therefore act as a confounder in the relation between plasma EPA and dementia risk. The aim of this longitudinal study was to ascertain whether plasma fatty acids predict the risk of incident dementia in a cohort of older persons, independently of their depressive status.

SUBJECTS AND METHODS

Subjects

The study was conducted among participants in the Three-City (3C) Study, a large ongoing prospective cohort study of vascular risk factors for dementia that included 9294 community dwellers in Bordeaux ($n = 2104$), Dijon ($n = 4931$), and Montpellier ($n = 2259$), France, at baseline in 1999–2000. To be eligible for recruitment into the 3C Study, individuals had to be living in 1 of these 3 French cities, had to be aged ≥65 y, and had to not be institutionalized. The methods of the study and baseline characteristics are described elsewhere (26). The protocol of the 3C Study was approved by the Consultative Committee for the Protection of Persons participating in Biomedical Research of the Kremlin-Bicêtre University Hospital (Paris). All participants signed an informed consent form.

The baseline data collection included sociodemographic and lifestyle characteristics, symptoms and complaints, main chronic conditions, neuropsychological testing, a physical examination, a brief food-frequency questionnaire and blood sampling. Two follow-up examinations were performed, 2 and 4 y after the baseline examination.

Plasma fatty acids were measured in the 1518 participants of the Bordeaux sample of the 3C Study who agreed to have a blood sample collected at baseline; 1419 of these persons had a physical examination and followed the screening procedure for dementia described below. We excluded 54 demented participants at baseline and 3 subjects for whom there was a technical problem with the measurement of plasma fatty acids. Thus, the initial study sample consisted of 1362 nondemented participants. During the second round of the study (2001–2002), 1167 participants were reexamined (86% of the initial sample), 28 died, and 167 refused or were lost to follow-up. During the third round (2003–2004), 1049 participants were examined (79% of the survivors); the cumulative number of deaths was 95 and 246 refused or were lost to follow-up. Finally, 1214 (89% of the nondemented participants at baseline) participants had at least one follow-up reexamination over the 4 y and were included in the present study.

Diagnosis of dementia

The diagnosis of dementia was based on a 3-step procedure (26).Trained psychologists administered a battery of neuropsychological tests at baseline and at each follow-up examination. All participants were examined by a neurologist at baseline. At follow-up, only the participants who were suspected of dementia on the basis of their neuropsychological performance were examined by the neurologist. Finally, an independent committee of neurologists reviewed all potential prevalent and incident cases of dementia to obtain a consensus on its diagnosis and etiology according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (27).

Assessment of plasma fatty acids

Fasting blood samples were collected at the baseline visit into heparinized evacuated tubes and centrifuged at 1000 × *g* for 10 min. Total lipids were extracted from plasma with 5 mL of hexane/isopropanol (3:2, by vol). The plasma fatty acid composition was determined from 2 mL of the lipid extract after transformation into isopropyl esters (28). Separation of isopropyl esters was made on a gas chromatograph (Trace, Thermoelectron, Cergy-Pontoise, France) using a 25-m Carbowax capillary column (internal diameter: 0.32 mm). Column conditions were 180 °C for 5 min, increasing by 7.5 °C/min to 220 °C for 30 min. The injector was set at 60 °C and the flame ionization detector at 250 °C. Helium was used as the carrier gas (flow rate: 2 mL/min). The peaks were identified by comparison with reference fatty acid esters (Sigma Chemical Co, Lyon, France), and peak areas were measured with an automatic integrator (DP700; Fisons Instruments, Arcueil, France). The results for each fatty acid were expressed as a percentage of total fatty acids. Plasma triacylglycerol was analyzed enzymatically using a multiparameter automated analyzer (LX20; Coulter-Beckman, Paris, France) and was used as a proxy of overall lipidic status in our analysis.

Assessment of depressive status

Depressive symptoms were assessed during the baseline home interview using the validated, 20-item Center for Epidemiologic Studies-Depression (CES-D) scale (29). The CES-D scale has been reported to constitute a valid and reliable measure of depressive symptomatology in elderly persons (30). Scores range from 0 to 60 according to the frequency of the depressive symptoms during the previous week. Scores of ≥17 in men and of ≥23 in women were used as indicators of a clinically relevant level of depressive symptomatology (31). If the CES-D scale was not fully completed, the interviewers were to mention whether this was because of severe depression. If >4 of 20 items were missing because of severe depression, as ascertained by the psychologist, the participant was considered to be depressive.

Other variables

Sociodemographic information recorded at baseline included age, sex, education [6 educational levels grouped into 4 classes: no education or primary school only, secondary (middle) school, high school or vocational school, and university], and income (4 classes: <750, 750–1500, 1500–2250, and >2250 euros/mo).

Vascular risk factors at baseline included body mass index [computed as weight (kg)/height^2 (m)], smoking status in pack-years (average number of packs of cigarettes smoked a day multiplied by number of years of smoking), history of cardiovascular or cerebrovascular disease, hypertension (if systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg), and diabetes (fasting glucose ≥7.0 mmol/L or antidiabetic treatment). Frequency of consumption of fish and raw or cooked fruit and vegetables was recorded in 6 classes ranging from never to daily. We classified as "regular fish consumers" those eating fish or seafood at least once a week and "frequent fruit and vegetable consumers" those eating raw fruit and raw vegetables and cooked fruit or vegetables every day.

Genetic risk of dementia was assessed by apo E genotyping, which was conducted at the genopole in Lille (France). Plasma vitamin E concentration was quantified by reversed-phase HPLC and used as a marker of overall oxidative status.

Statistical analysis

We used the individual fatty acid proportion of total fatty acids in the analyses. We calculated the proportion of n−6 PUFAs as the sum of linoleic acid (LA), γ-linolenic acid, and arachidonic acid (AA); the proportion of n−3 PUFAs was calculated as the sum of ALA, EPA, docosapentaenoic acid and DHA. Furthermore, we calculated the ratio of n−6 to n−3 PUFAs and the ratios of AA to EPA, AA to DHA, and LA to ALA.

Cox proportional hazard models with delayed entry and age as a time scale (32) were performed separately to estimate the risk of incident dementia as a function of each baseline plasma fatty acid proportion or ratio expressed as continuous variables. Hazard ratios (HRs) were estimated for an increase of 1 SD for each fatty acid, for one unit for the ratios.

For each fatty acid selected in previous univariate analyses, the relative risks of dementia with an increase of 1 SD were estimated after adjustment for potential confounders determined as follows. Separate Cox proportional hazard regressions were run to identify the baseline variables that were associated with incident dementia at a significance level of $P \leq 0.15$. These variables were then used as adjustment variables in a first set of adjusted models for each selected fatty acid or ratio significant at $P \leq 0.05$ (model 1). The plasma triacylglycerol concentration was systematically considered as a major adjustment variable because it was reported to be inversely associated with EPA and DHA intake (33). Further adjustment on depressive status was then performed (model 2). Log transformation of plasma fatty acid concentrations was additionally performed and did not change the results.

The interaction of each plasma fatty acid proportion with apo E genotype (possession of at least one ε4 allele) was tested. Interactions of plasma fatty acids with depressive status, plasma vitamin E and plasma triacylglycerol were also assessed. Any variable involved in an interaction term that was associated with incident dementia at a significance level of $P \leq 0.10$ was selected as a potential effect modification factor. Stratified analyses according to the interaction factor were then performed.

In all Cox proportional hazard models, the proportional hazard assumption and the log-linearity hypothesis were satisfied. Statistical analyses were performed with SAS Statistical package release 9.1 (SAS institute Inc, Cary, NC).

RESULTS

Of the 1214 participants, 65 incident cases of dementia were diagnosed over the 4 y of follow-up (**Table 1**). The overall incidence rate was 1.49 cases/100 person-years (95% CI: 1.13, 1.85).

The baseline characteristics of the sample according to future diagnosis of dementia are presented in Table 1. Incident cases of dementia were older (mean age at baseline: 78.3 y compared with 74.1 y for nondemented subjects; $P < 0.001$ using Student's t test). Subjects in the 2 groups were similar for sex, BMI, smoking status, educational level, and income. There was no significant difference in the prevalence of history of cardiovascular events and hypertension between the 2 groups. Risk of incident dementia was significantly higher in apo E ε4 carriers, depressed or diabetic participants, and increased with increasing plasma triacylglycerol concentration. Higher plasma vitamin E was associated with a higher risk of dementia with borderline significance.

Several plasma fatty acids were associated with the incidence of dementia in crude analyses (**Table 2**). An increase of 1 SD in palmitoleic acid was related to a 25% increased risk of dementia. Conversely, higher plasma EPA or DHA as well as total n−3 PUFA proportions were significantly associated with lower risks of dementia. Higher ratios of n−6 to n−3 and of AA to DHA were significantly associated with a higher incidence of dementia, whereas there was no association with the ratios of LA to ALA or of AA to EPA.

Accordingly, regular fish consumption was associated with a lower risk of dementia (91.1% of regular fish consumers in nondemented subjects compared with 79.7% in future demented subjects; crude hazard ratio for dementia = 0.38; 95% CI: 0.20, 0.69; $P = 0.002$).

Multivariate analyses of the association between plasma fatty acid proportions and incidence of dementia are presented in **Table 3**. After adjustment for educational level, possession of the apo E ε4 allele, diabetes, plasma triacylglycerol, and plasma vitamin E, the relation between a higher plasma EPA concentration and a lower incidence of dementia remained significant. Further adjustment on depressive status did not change the estimation of the risk ratio nor its significance. The associations with palmitoleic acid, DHA, and n−3 PUFAs were no longer significant in multivariate models. However, when triacylglycerol was not taken into account in model 1, the inverse association with incident dementia was significant for total n−3 PUFAs (HR = 0.73; 95% CI: 0.55, 0.97; $P = 0.03$) and was nearly significant for DHA (HR = 0.78; 95% CI: 0.59, 1.02; $P = 0.07$). Depressive status was significantly and strongly related to risk of dementia in all models.

The interactions of the ratios of n−6 to n−3 fatty acids and of AA to DHA with depressive status for the risk of dementia were statistically significant ($P = 0.08$ and $P = 0.05$, respectively). Thus, model 1 was performed separately for each stratum of the interaction factor (ie, depressive compared with nondepressive subjects) (**Table 4**). Because the subgroup of depressive subjects was of relatively small size ($n = 90$), educational level was coded as a binary adjustment variable (first level compared with other levels) for these analyses to minimize the loss of power. The risk ratio for dementia for an increment of 1 unit of the ratio of AA to DHA in depressive subjects was 2 times that in nondepressive

TABLE 1
Baseline characteristics of participants according to future diagnosis of dementia over 4 y in the Bordeaux sample of the Three-City Study (n = 1214), 1999–2004

	Incident cases of dementia		
	Yes (n = 65)	No (n = 1149)	P for risk of dementia[1]
Age (y)	78.3 ± 5.45[2]	74.1 ± 4.77	—
Sex, male (%)	38.5	38.4	0.58
BMI (kg/m^2)	25.9 ± 4.24	26.5 ± 4.17	0.45
Smoking (packs/y)	9.4 ± 27.39	8.7 ± 17.55	0.39
Education (%)			0.11
No or primary	46.0	32.3	—
Secondary	15.9	27.5	—
High school	23.8	21.8	—
University	14.3	18.4	—
Monthly income (%)			0.76
<750€	13.8	8.0	—
750–1500€	37.9	35.6	—
1500–2250€	22.4	25.2	—
≥2250€	25.9	31.2	—
ApoE ε4 allele (%)	32.3	18.5	0.001
CES-D score[3]	11.0 ± 9.10	7.2 ± 7.40	0.003
Depressive status (%)	18.5	6.8	0.006
History of cardiovascular disease (%)	32.3	32.1	0.33
Hypertension (%)	63.1	56.4	0.44
Diabetes (%)	21.9	9.4	0.02
Plasma triacylglycerol (mmol/L)	1.6 ± 0.93	1.3 ± 0.62	<0.001
Plasma vitamin E (mmol/L)	16.6 ± 5.90	15.8 ± 4.94	0.09

[1] Cox proportional hazard models with delayed entry and age as a time scale.
[2] $\bar{x}$ ± SD (all such values).
[3] CES-D, Center for Epidemiologic Studies Depression scale.

subjects, whereas the ratio of n−6 to n−3 fatty acids was related to an increased risk of dementia in depressive subjects only.

We performed additional models adjusting for frequent fruit and vegetable consumption instead of plasma vitamin E. The results were mostly unchanged (data not shown), except for the PUFA ratios. The multivariate association between a higher ratio of AA to DHA and risk of dementia was strengthened in depressive subjects (HR = 2.96; 95% CI: 1.08, 8.12; P = 0.04), whereas it was unchanged in nondepressive subjects (HR = 1.11; 95% CI: 1.04, 1.19; P = 0.003). The multivariate association between higher ratios of n−6 to n−3 fatty acids and risk of dementia was slightly lowered in depressive subjects (HR = 1.48; 95% CI: 1.04, 2.47; P = 0.06) but was unchanged in nondepressive participants (HR = 1.09; 95% CI: 0.99, 1.19; P = 0.09).

DISCUSSION

In the present study, a higher proportion of plasma EPA was associated with a lower incidence of dementia, independently of depressive status. The relation between plasma DHA proportion and incidence of dementia did not remain significant in the adjusted models. In addition, higher ratios of n−6 to n−3 and of AA to DHA were related to an increased risk of dementia, particularly in depressive subjects.

Some potential limitations to our findings must be stressed. Plasma PUFA concentrations reflect a shorter-term lipid intake than do PUFAs from red blood cell (RBC) membranes (34). Because plasma PUFA turnover is more rapid than that of RBC PUFA turnover, direct measures of PUFA in plasma may better reflect their bioavailability as precursors of other active molecules, such as eicosanoids, particularly for EPA (35). We adjusted for many potential confounders, some of which were not considered in previous studies. In particular, adjustment for plasma triacylglycerol may be important because EPA and DHA have triacylglycerol-lowering effects (33), and higher triacylglycerol concentrations were related to an increased risk of dementia in our study. Plasma antioxidants could also confound the relation between plasma PUFAs and dementia, because they may exert a protective effect against dementia by decreasing lipid peroxidation (36). We adjusted for plasma vitamin E as a marker of overall oxidative status (37). Moreover, our results were unchanged after adjustment for fruit and vegetables, which are good dietary sources of antioxidants. However, we cannot exclude that other unmeasured lifestyle characteristics associated with a "healthy" diet, such as physical and cognitive activities, may decrease dementia risk (38) and thus acted as residual confounders in our study.

One of the major strengths of the present study was that it considered depression as a potential confounding or effect modification factor in the relation between plasma PUFAs and dementia. Indeed, depression was reported to be a risk factor for dementia (24) and was related to plasma EPA (20). Therefore, depression could either be the mediator in the relation between higher EPA and lower risk of dementia or could confound this relation as an independent risk factor. Our longitudinal study provided convincing evidence that both low EPA concentrations and depression were independent predictors of dementia. Indeed, further adjustment for depressive

TABLE 2
Proportions of plasma fatty acids according to future diagnosis of dementia and age-adjusted risk of dementia by 1-SD changes in fatty acid proportion: the Bordeaux sample of the Three-City Study (n = 1214), 1999–2004[1]

	Incident cases of dementia		Risk of dementia for a 1-SD change in plasma fatty acids[2]		
Fatty acids	Yes (n = 65)	No (n = 1149)	HR	95% CI	P
SFA	40.22 ± 6.61	40.97 ± 8.40	0.93	0.70, 1.24	0.62
Myristic acid	1.27 ± 0.41	1.24 ± 0.46	1.03	0.79, 1.32	0.84
Palmitic acid	28.19 ± 4.97	28.14 ± 5.76	1.03	0.80, 1.33	0.81
Stearic acid	10.75 ± 2.45	11.58 ± 3.34	0.78	0.57, 1.06	0.11
MUFA	24.02 ± 4.10	22.67 ± 4.31	1.27	0.98, 1.65	0.07
Oleic acid	21.39 ± 3.50	20.34 ± 3.78	1.23	0.95, 1.60	0.12
Palmitoleic acid	2.63 ± 0.98	2.32 ± 0.96	1.25	1.00, 1.57	0.05
PUFA	35.76 ± 6.47	36.37 ± 6.90	0.93	0.73, 1.19	0.57
n−6 PUFA	31.83 ± 6.13	32.06 ± 6.38	0.98	0.76, 1.26	0.89
LA	24.91 ± 5.29	24.90 ± 5.40	1.01	0.78, 1.30	0.95
γ-linolenic acid	0.42 ± 0.18	0.41 ± 0.23	1.12	0.96, 1.30	0.15
AA	6.50 ± 1.75	6.75 ± 1.84	0.91	0.71, 1.17	0.45
n−3 PUFA	3.93 ± 1.14	4.31 ± 1.36	0.74	0.57, 0.97	0.03
ALA	0.44 ± 0.2	0.41 ± 0.18	1.08	0.93, 1.26	0.30
EPA	0.83 ± 0.450	1.03 ± 0.609	0.67	0.48, 0.94	0.02
Docosapentaenoic acid	0.45 ± 0.123	0.47 ± 0.177	0.90	0.64, 1.26	0.53
DHA	2.20 ± 0.790	2.41 ± 0.805	0.76	0.59, 0.99	0.04
Plasma fatty acid ratios					
AA-to-EPA	9.44 ± 4.762	8.37 ± 4.701	1.03[3]	0.99, 1.07[3]	0.16[3]
AA-to-DHA	3.63 ± 3.869	3.01 ± 1.063	1.10[3]	1.03, 1.17[3]	0.004[3]
LA-to-ALA	66.58 ± 30.981	70.20 ± 31.922	0.99[3]	0.99, 1.01[3]	0.46[3]
n−6-to-n−3 PUFA	8.72 ± 2.829	7.99 ± 2.491	1.09[3]	1.01, 1.19[3]	0.04[3]

[1] SFA, saturated fatty acid; MUFA, monounsaturated fatty acid; PUFA, polyunsaturated fatty acid; LA, linoleic acid; AA, arachidonic acid; ALA, α-linolenic acid; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid; HR, hazard ratio.
[2] Cox proportional hazard models with delayed entry and age as a time scale.
[3] Values are for one unit of ratio.

status in our multivariate analyses did not change either the significance or the size of the HR. In addition, depression was an effect modification factor in the relation between the ratios of n−6 to n−3 and of AA to DHA and the incidence of dementia, suggesting a synergistic deleterious effect of a relative excess of n−6 PUFAs and depressive status on the risk of the disease.

The incidence of dementia in our study was lower than previously reported (39), but comparisons between studies are limited

TABLE 3
Associations between each plasma fatty acid proportion, depressive status, and 4-y incident dementia in the Bordeaux sample of the Three-City Study (n = 1214), 1999–2004[1]

	Risk of dementia					
	Model 1[2]			Model 2[3]		
Plasma fatty acids	HR	95% CI	P	HR	95% CI	P
Palmitoleic acid						
For 1 SD of plasma proportion	1.09	0.85,1.39	0.51	1.09	0.85,1.40	0.49
Depressive status	—	—	—	2.16	1.08,4.35	0.03
n−3 PUFA						
For 1 SD of plasma proportion	0.78	0.58,1.06	0.11	0.78	0.58,1.05	0.10
Depressive status	—	—	—	2.18	1.09,4.39	0.03
EPA						
For 1 SD of plasma proportion	0.69	0.48,0.98	0.04	0.69	0.48,0.98	0.04
Depressive status	—	—	—	2.16	1.08,4.34	0.03
DHA						
For 1 SD of plasma proportion	0.84	0.63,1.11	0.21	0.83	0.62,1.10	0.19
Depressive status	—	—	—	2.22	1.10,4.46	0.03

[1] HR, hazard ratio; PUFA, polyunsaturated fatty acid; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid.
[2] Separate Cox proportional hazard models with delayed entry and age as a time scale and adjusted for education (4 levels), apolipoprotein E allele, diabetes, plasma triacylglycerol, and plasma vitamin E.
[3] Model 1 + depressive status (separate models).

TABLE 4
Associations between the ratios of arachidonic acid (AA) to docosahexaenoic acid (DHA) and of n−6 to n−3 fatty acids and 4-y incident dementia by stratum of depressive status in the Bordeaux sample of the Three-City Study (n = 1214), 1999–2004

	Risk of dementia					
	Model 1[1] in depressive subjects (n = 90)			Model 1 in nondepressive subjects (n = 1124)		
	HR[2]	95% CI	P	HR[2]	95% CI	P
AA-to-DHA ratio						
For 1 unit of ratio	2.65	1.07, 6.56	0.03	1.11	1.04, 1.19	0.002
n−6-to-total n−3 PUFA ratio						
For 1 unit of ratio	1.61	1.04, 2.47	0.03	1.09	0.99, 1.19	0.08

[1] Separate Cox proportional hazard models with delayed entry and age as a time scale and adjusted for education (4 levels), apolipoprotein E ε4 allele, diabetes, plasma triacylglycerol, plasma vitamin E.
[2] HR, hazard ratio.

by different diagnosis criteria for dementia or sample characteristics. Likewise, direct comparisons of PUFA status across studies are difficult because of the different compartments used to measure PUFA concentrations. Overall, our total plasma PUFA concentrations were close to those measured in plasma phospholipids (18, 40). Interestingly, studies that measured fatty acid proportions in RBCs (14, 17) found much higher DHA proportions but similar EPA proportions. Our ratio of AA to DHA was close to the ratios previously described in RBCs. Contrarily to a recent study (17), the present study found no interaction between fatty acids and apo E genotype. A single previous longitudinal study found that only the plasma phosphatidylcholine DHA content was associated with a 47% reduction in the risk of dementia for the top quartile compared with the lowest quartile (19). Although comparability is limited, our findings are only partially divergent because plasma DHA was related to the incidence of dementia in our crude models. However, adjustment for plasma triacylglycerol considerably weakened this relation. Our results suggest a positive association between the ratios of n−6 to n−3 fatty acids and the risk of dementia, in accordance with a previous study that found an inverse relation between the ratio of n−3 to n−6 fatty acids in RBC membranes and cognitive decline (14). However, that study did not consider depressive status. No interventional study with EPA or DHA supplementation for the primary prevention of dementia was ever published (41). The OmegAD randomized clinical trial found a positive effect of EPA+DHA supplementation on cognitive functioning in a small subgroup of patients with very mild AD (42). A small pilot study on the efficacy of ethyl-EPA in the treatment of AD did not evidence any effect on cognition in a 12-wk period (43).

The specific role of EPA in dementia may have been underestimated. EPA may have specific effects on neuroprotection during aging (44), independent and complementary of those of DHA, which, as the major n−3 PUFA of neurone membranes, may more be implied in brain signal transduction and neuroplasticity (45). EPA could stimulate ketogenesis, which would help to compensate impaired brain glucose uptake in AD patients (44). Because recent findings suggested that inflammatory biomarkers were associated with a higher risk of AD (46), the protective role of EPA could also be related to specific antiinflammatory properties (47). The excessive production of proinflammatory eicosanoids derived from AA are competitively compensated by the antiinflammatory products of EPA metabolism (48). Plasma may be the best compartment to reflect EPA antiinflammatory bioactive derivatives (49), which may explain why EPA was strongly associated with dementia risk in our study, unlike DHA and AA. Incorporation of DHA into the brain could be modeled more efficiently by RBC membranes, and AA brain contents, because they are metabolized very rapidly to bioactive eicosanoids, may not adequately be reflected by any of these compartments (50). However, although isolated plasma AA and DHA concentrations were not associated with dementia risk in our study, the ratio of AA to DHA was. Our findings confirm, therefore, the major structural role of AA and DHA and the importance of their balance and turnover in neuronal function (49). The protective effect of long-chain n−3 PUFAs was related to a higher fish consumption in our study. However, some regulatory mechanisms of long-chain n−3 PUFA metabolism can also explain our results, because n−3 biosynthesis is limited beyond EPA, and retroconversion of DHA to EPA may occur (51).

Because depression and dementia share common vascular risk factors (24, 52), the vascular properties of EPA could contribute to decrease depression and dementia risk simultaneously. The effect modification found in the present study between depressive status and ratio of n−6 to n−3 fatty acids, based on a statistically significant interaction, raises some interesting physiologic hypotheses. Depression and higher ratios of n−6 to n−3 may exert synergistic effects on neuropathological processes implied in dementia. Rather than being a prodrome of dementia, depression could play a causal role in the disease (24), as suggested by a study that found more pronounced AD-specific lesions in the hippocampus of patients with a lifetime history of major depression (53). This assumption is also supported by the "glucocorticoid cascade" hypothesis (24). Glucocorticoids, secreted during stress, may have long-term neurotoxic effects in the hippocampus, the primary target of AD neuropathology, leading to its atrophy (54). Furthermore, fish oils have stress-reduction properties, and PUFA reduces cortisol concentrations (55). Together, these findings may explain how ratios of n−6 to n−3 and depression could interact in the pathological processes implied in dementia.

Our results provide evidence that both lower plasma EPA and higher depression may increase the risk of dementia and that higher ratios of n−6 to n−3 and of AA to DHA are associated with higher dementia risk, especially among depressive subjects. However, randomized controlled trials are necessary before recommending EPA supplementation in depressed older persons to decrease their dementia risk. Further research is also needed to

better understand the protective role of plasma EPA against dementia.

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