

Polyunsaturated Fatty Acids, Antioxidants, and Cognitive Function in Very Old Men

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Atherosclerosis and thrombosis may lead to cognitive impairment through cerebral infarcts or white matter hyperintensities. Oxidative stress is now seen as a major contributor to the process of atherogenesis. High intake of polyunsaturated fatty acids, e.g., linoleic acid, or low intake of antioxidants can increase oxidative stress. High intake of n-3 polyunsaturated fatty acids and its main source, fish, may reduce the risk of thrombosis. Little is known, however, about the relation between these dietary factors and cognitive function. The authors investigated this relation with data derived from a cohort of men, aged 69–89 years, who were participants in the Zutphen Elderly Study. The 30-point Mini-Mental State Examination was used to assess cognitive impairment in 1990 (score ≤ 25 in 153/476 men, 32%) and cognitive decline from 1990 to 1993 (drop > 2 points in 51/342 men, 15%). Food intake was estimated in 1985 and 1990 by the cross-check dietary history method. High linoleic acid intake was associated with cognitive impairment after adjustment for age, education, cigarette smoking, alcohol consumption, and energy intake (odds ratio (OR) for highest vs. lowest tertile = 1.76, 95% confidence interval (CI) 1.04–3.01). Intake of n-3 polyunsaturated fatty acids was not associated with cognitive impairment, whereas high fish consumption tended to be inversely associated with cognitive impairment (OR = 0.63, 95% CI 0.33–1.21) and cognitive decline (OR = 0.45, 95% CI 0.17–1.16). Intakes of beta-carotene, vitamins C and E, and flavonoids were not inversely associated with cognitive impairment or decline. This study raises the possibility that high linoleic acid intake is positively associated with cognitive impairment and high fish consumption inversely associated with cognitive impairment. *Am J Epidemiol* 1997;145:33–41.

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Cognitive performance decreases with increasing age. Cognitive impairment is a major component of dementia and influences the individual's ability to function independently. Due to aging of the population, the prevalence of cognitive impairment is expected to increase. Therefore, it is important to elucidate possible modifiable risk factors for impaired cognitive function, such as diet.

Polyunsaturated fatty acids and antioxidants may affect the development of cognitive impairment through their impact on atherosclerosis and thrombosis. These processes have been associated with an increased risk of stroke, lacunar infarcts, and white

matter changes, as seen on neuroimaging, which can subsequently lead to cognitive impairment (1–4). Oxidative stress is now seen as an important contributor to the process of atherogenesis (5). Polyunsaturated fatty acids are highly susceptible to oxidation, and may increase the oxidative modification of low density lipoprotein (LDL) cholesterol, making it more atherogenic (6, 7). Because linoleic acid, which is an n-6 polyunsaturated fatty acid, constitutes nearly 90 percent of the polyunsaturated fatty acids in LDL cholesterol, it is the major substrate of LDL oxidation (6). Dietary antioxidants, such as vitamin E, beta-carotene, and flavonoids, may protect against oxidative damage and thus reduce the risk of atherosclerosis (8–10).

Polyunsaturated fatty acids may also influence the risk of thrombosis. N-3 polyunsaturated fatty acids, such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), compete with linoleic acid in the eicosanoid metabolism (11). A high linoleic acid intake may lead to increased production of the proaggregatory thromboxane A_2 . N-3 polyunsaturated fatty acids, on the other hand, reduce the production of thromboxane A_2 and increase the production of the

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Abbreviations: CI, confidence interval; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; MMSE, Mini-Mental State Examination; OR, odds ratio; SD, standard deviation.

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antiaggregatory prostacyclin PGI_2 , consequently reducing the risk of thrombosis (11).

Therefore, we examined the association of polyunsaturated fatty acids and antioxidants with cognitive function. We also investigated the association between fish consumption and cognitive function, because fish is the main source of n-3 polyunsaturated fatty acids. We investigated these associations in a community-based longitudinal study of very old men.

MATERIALS AND METHODS

Study population

The Zutphen Elderly Study is a longitudinal study on risk factors for chronic diseases in men who live in Zutphen, a town in the eastern part of the Netherlands (12). It is the continuation of the Zutphen Study, which was initiated in 1960 as the Dutch contribution to the Seven Countries Study (13). In 1985, 555 subjects from the original cohort, born between 1900 and 1920, were still alive. In addition, 711 men of the same age (64–84 years) were randomly selected from all other men living in Zutphen. This resulted in a population of 1,266 men, of which 939 participated (response rate, 74 percent). In 1990, 560 of 718 surviving men (78 percent) were reexamined. The examinations were repeated in 1993 on 390 of 553 surviving men (71 percent). The study has been approved by the medical ethics committee of the University of Leiden, the Netherlands, and informed consent was obtained from all participants.

Examinations

In the spring of 1985 and 1990, interviews and examinations were carried out at home and in a study center. In the spring of 1993, interviews were conducted at home. Dietary intake was assessed in 1985 and 1990 and cognitive function was tested in 1990 and 1993. For the analyses on prevalent cognitive impairment, information on cognitive function in 1990 was used; complete information on dietary and other risk factors was available for 476 men. For the longitudinal analyses on cognitive decline, information on cognitive function in 1990 and 1993 was used; complete information was available for 342 men.

Food and beverage intake was estimated by the cross-check dietary history method (14) adapted to the Dutch situation (15). This method provides information about the usual food consumption pattern during the 2–4 weeks preceding the interview. The interviews were carried out by well-trained dietitians in 1985 and 1990, using the same methodology in both years. All subjects were interviewed at home, preferably in the

presence of the partner. First, the usual food consumption pattern of a person was assessed during weekdays and weekends. Thereafter, a checklist with an extensive number of foods was reviewed, and the frequencies and amounts consumed were recorded. Portion sizes were estimated by a portable scale. The results were checked by comparing the average consumption of foods during a week with the quantities of food purchased for the family during a week. At the same time, the use of prescribed diets, diet products, vitamins, and health food products was assessed by a standardized questionnaire. The whole interview took approximately one and a half hours.

Food intake data were coded and converted into energy and nutrients using a computerized version of the Dutch food table (Uniform Food Encoding food table, 1984, and NEVO table, 1989), updated with information on beta-carotene, vitamin E, and flavonoids (10), and with additional information on the n-3 polyunsaturated fatty acids EPA and DHA (16). The flavonoid content was defined as the sum of quercetin, kaempferol, myricetin, apigenin, and luteolin, the five major antioxidant food flavonoids. The average daily intake of 1985 and 1990 combined was calculated for all dietary factors of interest and used for the analyses, because this gives a more reliable estimate of a subject's true intake than only one measurement (17). The average intake was then categorized into tertiles, and the first tertile, which corresponded to the lowest intake, used as the reference. Fish consumption was divided into three categories: 0 g/day, >0–20 g/day, and >20 g/day. We defined use of vitamin C or E supplements as use in 1985 or 1990, either during the whole year or during winter time only. Users of vitamin C and E supplements were assigned to the highest vitamin C and E tertiles.

Global cognitive function was tested with the Dutch version of the 30-point Mini-Mental State Examination (MMSE) (18, 19). The MMSE includes questions on orientation to time and place, registration, attention and calculation, recall, language, and visual construction. This screening test was originally created for a clinical setting (18), and is extensively used in epidemiologic studies (20). Although it tests a limited set of cognitive functions, these are important to daily functioning and severely affected in dementia. In 1990, it was administered in a controlled hospital setting, while in 1993, it was administered at the subject's homes. Research assistants were uniformly trained to administer the MMSE and the scoring was checked by the same person in 1990 and 1993 with strict scoring criteria. If less than four individual items (out of a total of 20 items) were not answered by the subject, these were rated as errors (21). If items could not be per-

formed because of severe physical disability, a weighted total score was given. If a subject did not answer four or more individual items, the total MMSE score was considered missing. We used a score of ≤ 25 as the cut-off point, because this is indicative of cognitive impairment (22). Cognitive decline was defined as a drop of more than two points in the MMSE over a 3-year period (>1 standard deviation (SD), which corresponds to the 15th percentile of change).

We considered the following potentially confounding variables in our analyses: age (continuous); education, obtained from a self-administered questionnaire (≤ 6 , 7–12, and >12 years of education); cigarette smoking in 1990 (current: yes/no), assessed by a trained physician with the use of a standardized questionnaire (23); usual alcohol consumption in 1990, obtained from the cross-check dietary history (none, <1 drink/day (<13.2 g), ≥ 1 drink/day) (23); and energy intake (continuous).

Statistical analysis

Univariate associations were tested with the non-parametric Mann-Whitney test for continuous variables. We used logistic regression with cognitive impairment (MMSE score >25 as reference) and cognitive decline (change in MMSE score ≤ 2 points as reference) as dependent variables and the following dietary factors as independent variables: polyunsaturated fatty acids, which were divided into the n-6 fatty acid linoleic acid and the n-3 fatty acids EPA and DHA; fish; and the antioxidants beta-carotene, vitamin C, vitamin E, and flavonoids. Age, education, current cigarette smoking, alcohol consumption, and energy intake were added to the model as potential confounding factors. In the analyses on cognitive decline, we also adjusted for baseline MMSE score. When analyzing intake of vitamin E, we in addition adjusted for polyunsaturated fatty acids intake, because these variables were highly correlated ($r = 0.6$).

Because high antioxidant intake may diminish the oxidation of LDL induced by linoleic acid (6), and thereby may attenuate the relation between linoleic acid and cognitive impairment, we examined the interaction between intake of linoleic acid and antioxidants. This was done by including the product terms of the linoleic acid and antioxidant dummy variables into the adjusted model. We investigated the interaction between antioxidants and smoking in the same manner to see whether antioxidants were more strongly associated with cognition in smokers, in whom the increased free radical load may lead to an increased need for antioxidants (24). All tests were two-sided and a p value of less than 0.05 was considered to be statisti-

cally significant. We used SAS program version 6.09 software in the analyses (25).

RESULTS

Description of the sample

The median MMSE score was 27 (10th centile: 22; 90th centile: 29). Twenty-two percent of subjects currently smoked. Mean energy intake decreased from $9,668 \pm 2,078$ kJ in 1985 to $8,858 \pm 1,951$ kJ in 1990. Fifty-two subjects (11 percent) used vitamin C supplements in 1985 or 1990, and seven subjects (1 percent) used vitamin E supplements. Eighty-six percent of the men consumed fish.

Cognitive impairment

Thirty-two percent of the subjects were cognitively impaired in 1990 (MMSE score ≤ 25). Subjects with cognitive impairment were older (19) and concluded less years of education (data not shown). To determine whether cognitive impairment altered dietary intake, we investigated the change in nutrients of interest from 1985 to 1990 in subjects who were cognitively impaired in 1990 and in those who were unimpaired. We found no significant differences in change in total energy and polyunsaturated fatty acid intake between these two groups (table 1) or in change in antioxidant intake (data not shown). The 1985–1990 average intakes of total fat, polyunsaturated fatty acids, and linoleic acid were higher in subjects with cognitive impairment, while total energy, fish, EPA, and DHA intake were lower (table 2).

Cognitive impairment was associated with high linoleic acid intake, after adjustment for potential confounding (table 3). The intake of n-3 polyunsaturated fatty acids was not independently related to cognitive impairment. Compared with no fish consumption, fish consumption of >20 g per day was inversely associated with cognitive impairment in the crude analysis (odds ratio (OR) = 0.43, 95 percent confidence interval (CI) 0.23–0.78, p trend = 0.004). This association was weakened after adjustment (OR = 0.63, 95 percent CI 0.33–1.21, p trend = 0.13). There was no relation between cognitive function and intake of any of the antioxidants. The results reported above did not change essentially after exclusion of subjects with stroke or myocardial infarction ($n = 83$). Likewise, the results did not change when we excluded subjects who were on a prescribed diet in 1990 (18 percent). There were no significant interactions between linoleic acid intake and any of the antioxidants, nor between antioxidants and smoking ($p > 0.1$).

TABLE 1. Mean change (standard deviation) in daily intake of selected nutrients and fish from 1985 to 1990 by level of cognitive function: the Zutphen Elderly Study

	Cognitive function in 1990		<i>P</i> value [§]
	Normal [†] (<i>n</i> = 323)	Impaired [‡] (<i>n</i> = 153)	
Total energy (kJ)	-196.7 (447.9)	-172.9 (427.8)	0.7
n-6 PUFA*			
Linoleic acid (en%)	0.65 (2.77)	1.02 (3.38)	0.3
n-3 PUFA			
EPA* (mg)	-15.4 (189.0)	10.5 (148.8)	0.6
DHA* (mg)	-19.6 (224.2)	10.7 (173.5)	0.7
Fish (g)	-1.54 (21.66)	-3.13 (22.81)	0.8

* PUFA, polyunsaturated fatty acids; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid.

[†] As measured by the Mini-Mental State Examination: score >25.

[‡] As measured by the Mini-Mental State Examination: score ≤25.

[§] As determined by the Mann-Whitney test.

Cognitive decline

The 3-year decline in MMSE score was studied in 342 men who took part in both examination years. Participants did not differ from nonparticipants in nutrients of interest, except in vitamin C intake in 1990, which was lower in the 1993 nonparticipants (mean intake 87.3 mg vs. 98.6 mg, *p* = 0.03). The baseline MMSE score was lower in the nonparticipants as well (median MMSE score 26 vs. 27, *p* = 0.005). The associations between the nutrients of interest and cog-

nitive impairment in 1990 were not different for the nonparticipants compared with the participants.

Mean 3-year decline in MMSE score was 0.27 (standard deviation = 2.62). Fifteen percent of the men (*n* = 51) showed a decline of more than two points. After adjustment for possible confounding factors, there was no association between linoleic acid intake and cognitive decline (table 4). Fish consumption was inversely but not significantly associated with cognitive decline (adjusted OR = 0.45, 95 percent CI 0.17–1.16, *p* trend = 0.09). Vitamin C intake was positively related to decline of cognitive function (table 4). All results were essentially the same when subjects who were on a prescribed diet (18 percent) were excluded from the analyses. To examine whether the mechanism behind the observed associations was more acute (i.e., thrombosis), we performed an analysis with 1990 diet and cognitive decline from 1990 to 1993. The results for fish or for the other nutrients did not change.

In addition, we investigated the incidence of cognitive impairment at 3 years of follow-up by excluding subjects with cognitive impairment at baseline (1990, *n* = 105/342). High linoleic acid intake was associated with an increased risk of becoming cognitively impaired (adjusted OR = 2.57, 95 percent CI 1.05–6.27, *p* trend = 0.04). For fish, the risk was similar to the risk of cognitive decline.

TABLE 2. Mean (standard deviation) daily intake* of selected nutrients and fish by level of cognitive function: the Zutphen Elderly Study

	Cognitive function in 1990		<i>P</i> value [§]
	Normal [†] (<i>n</i> = 323)	Impaired [‡] (<i>n</i> = 153)	
Energy (kJ)	9,364 (1,774)	8,975 (1,799)	0.03
Total fat (en%)	38.8 (5.6)	40.0 (5.1)	0.02
Saturated fat (en%)	16.7 (3.1)	16.8 (2.5)	0.6
MUFA [†] (en%)	14.3 (2.8)	14.7 (2.6)	0.2
PUFA [†] (en%)	6.5 (2.5)	7.3 (2.7)	0.002
n-6 PUFA			
Linoleic acid (en%)	5.4 (2.5)	6.1 (2.8)	0.006
n-3 PUFA			
EPA [†] (mg)	88.2 (137.2)	78.6 (129.6)	0.1
DHA [†] (mg)	103.0 (156.8)	89.5 (147.6)	0.05
Fish (g)	18.8 (18.4)	14.9 (15.7)	0.02
Antioxidants			
Beta-carotene (mg)	1.42 (0.52)	1.42 (0.61)	0.6
Vitamin C (mg)	97.3 (40.4)	96.9 (38.9)	0.9
Vitamin E (mg)	8.49 (2.23)	8.44 (2.03)	0.7
Flavonoids (mg)	26.8 (12.9)	26.6 (10.8)	0.6

* Average of intake in 1985 and 1990.

[†] MUFA, monounsaturated fatty acids; PUFA, polyunsaturated fatty acids; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid.

[‡] As measured by the Mini-Mental State Examination: score >25.

[§] As measured by the Mini-Mental State Examination: score ≤25.

[¶] As determined by the Mann-Whitney test.

TABLE 3. Adjusted odds ratios (OR) (95% confidence intervals (CI)) for the association between nutrient intake* and prevalent cognitive impairment† in 476 men: the Zutphen Elderly Study

	Daily intake tertile			<i>p</i> trend
	Low	Medium	High	
Linoleic acid (g)				
Range	2.8–9.3	9.3–15.3	15.3–48.7	
OR‡	1.00	1.23	1.76	0.04
95% CI	–	0.73–2.07	1.04–3.01	
n-3 Fatty acid§ (mg)				
Range	0–37.5	37.5–155.5	155.5–2,110.5	
OR	1.00	1.09	0.96	0.9
95% CI	–	0.65–1.80	0.57–1.62	
Beta-carotene (mg)				
Range	0.55–1.14	1.14–1.54	1.54–4.81	
OR	1.00	0.87	1.26	0.4
95% CI	–	0.52–1.47	0.76–2.09	
Vitamin C (mg)¶				
Range	18.0–74.4	74.4–108.8	108.8–295.6	
OR	1.00	1.00	1.19	0.8
95% CI	–	0.60–1.65	0.71–1.97	
Vitamin E (mg)¶, #				
Range	3.3–7.5	7.5–9.1	9.1–17.5	
OR	1.00	1.19	1.40	0.3
95% CI	–	0.69–2.07	0.71–2.77	
Flavonoids (mg)				
Range	2.4–20.7	20.7–30.0	30.0–96.1	
OR	1.00	1.50	1.44	0.2
95% CI	–	0.90–2.48	0.86–2.41	

* Average of intake in 1985 and 1990, categorized into tertiles.

† Mini-Mental State Examination 1990 with score >25 as reference.

‡ Odds ratios adjusted for age, education, cigarette smoking, alcohol consumption, and energy intake.

§ Eicosapentaenoic acid and docosahexaenoic acid.

¶ Vitamin C and E supplement users were assigned to the highest tertile.

Also adjusted for polyunsaturated fatty acids.

DISCUSSION

Our data suggested that high linoleic acid intake was associated with cognitive impairment. High fish consumption was inversely associated with cognitive impairment and decline in the univariate analysis, although this was weakened after adjustment for confounding. None of the antioxidants we investigated were inversely related to cognitive impairment. These results could not be explained by differences in age, education, smoking behavior, alcohol, or energy intake.

Linoleic acid and fish

We found a positive association between intake of linoleic acid and cognitive impairment. The most important food groups that predicted absolute intake of linoleic acid in this population were margarines (with

>40 g linoleic acid added), butter, baking fats, sauces, and cheese. Studies have shown that replacement of saturated fatty acid intake by linoleic acid decreases serum total and LDL cholesterol concentrations (26) and that linoleic acid intake is inversely related to coronary heart disease (27). On the other hand, high linoleic acid intake may increase the susceptibility of LDL to oxidation, which makes it more atherogenic (5–7). However, the association between linoleic acid and atherosclerosis is not consistent. Some studies show an inverse association (28), some a positive association (29–31), and others no association (32, 33). Our findings are consistent with the hypothesis that linoleic acid is atherogenic. Apart from the role of oxidation in atherogenesis, several in vitro and in vivo studies have shown that free radicals may increase vasogenic edema after cerebral ischemia and that they may aggravate the neurologic consequences of is-

TABLE 4. Adjusted odds ratios (OR) (95% confidence intervals (CI)) for the association between nutrient intake* and risk of cognitive decline† (1990–1993) in 342 men: the Zutphen Elderly Study

	Daily intake tertile			<i>p</i> trend
	Low	Medium	High	
Linoleic acid (g)				
OR‡	1.00	0.95	1.05	0.9
95% CI	–	0.45–2.05	0.49–2.27	
n-3 Fatty acid§ (mg)				
OR	1.00	0.85	0.78	0.5
95% CI	–	0.40–1.82	0.35–1.73	
Beta-carotene (mg)				
OR	1.00	0.83	0.67	0.3
95% CI	–	0.39–1.77	0.30–1.48	
Vitamin C¶ (mg)				
OR	1.00	1.42	2.02	0.09
95% CI	–	0.62–3.25	0.90–4.52	
Vitamin E¶,# (mg)				
OR	1.00	1.13	1.20	0.7
95% CI	–	0.48–2.62	0.43–3.31	
Flavonoids (mg)				
OR	1.00	0.89	0.86	0.7
95% CI	–	0.41–1.93	0.39–1.89	

* Average of intake in 1985 and 1990, categorized into tertiles.

† >2 points decline in the Mini-Mental State Examination score.

‡ Odds ratio adjusted for age, education, cigarette smoking, alcohol consumption, energy intake, and baseline Mini-Mental State Examination score.

§ Eicosapentaenoic acid and docosahexaenoic acid.

¶ Vitamin C and E supplement users were assigned to the highest tertile.

Also adjusted for polyunsaturated fatty acids.

chemia, which could increase the risk of vascular-related cognitive impairment (34, 35). The association between linoleic acid and cognitive impairment was not modified by any of the antioxidants, including the relatively high correlated vitamin E ($r = 0.6$).

We did not observe an association between linoleic acid intake and cognitive decline. This may be due to regression toward the mean (36); subjects with the lowest MMSE scores, and also the highest linoleic acid intake, in our sample will on average have a smaller decline. Furthermore, the mechanisms by which linoleic acid may affect cognitive function could be more chronic, in which case a follow-up period of 3 years would be too short. Theoretically, cognitive impairment could have led to a high linoleic acid intake. It is conceivable that subjects with cognitive impairment have a higher prevalence of cardiovascular disease and therefore might have changed their diet, favoring linoleic acid above saturated fatty acids. However, exclusion of subjects who were on a prescribed diet or of subjects with a history of stroke or myocardial infarction did not change the results. Moreover, confining the analyses to subjects with nor-

mal cognitive function at baseline (1990) showed a significantly increased risk of becoming cognitively impaired for subjects with high linoleic acid intake, which is consistent with the analyses on cognitive impairment.

A diet with a high intake of n-3 polyunsaturated fatty acids or fish may reduce the risk of thrombosis (11). In addition, n-3 polyunsaturated fatty acids are important for the development of the brain and play a role in the functioning of cerebral membranes. Several studies on infants (37–39) have suggested that breastfeeding, which leads to higher DHA concentrations in the brain, or supplementation with DHA, is related to better cognitive performance at later age. An inverse association between fish consumption and cognitive impairment and decline was suggested by our results. However, we found no association between the n-3 polyunsaturated fatty acids, EPA and DHA, and cognitive function, despite the fact that consumption of even small amounts of fish has been shown to be reflected in the concentration of plasma phospholipid EPA and DHA (40). Possibly, other nutrients than the n-3 polyunsaturated fatty acids in fish play a role in the

protection against cognitive impairment, such as selenium, which has antioxidant properties (41). Or maybe non-fish eaters are different in factors that are related to cognitive impairment.

Antioxidants

We observed no protective effect from any of the antioxidants on cognitive impairment or decline. In contrast, vitamin C was associated with a higher risk of cognitive decline. We found no interaction between antioxidants and smoking. This study may be too small to examine interaction, and we suggest that larger studies examine this issue. Most studies that have investigated the association between antioxidants and cognition have been cross-sectional. They found no clear association of vitamin E and C to dementia (42, 43) and an inverse association between a high intake of beta-carotene and cognitive impairment (44). In the cohort of the Honolulu Heart Program (45), users of vitamins E and C and multivitamin supplements 4 years prior performed better on cognitive tests. Two intervention studies on geriatric patients (41, 46) found improvement of cognitive capacities after one year of supplementation with a mixture of antioxidants.

In the present study, the intake of antioxidants was relatively low and only a few people used supplements. The positive association between vitamin C and cognitive decline did not change appreciably after exclusion of subjects who used a prescribed diet. Stroke and myocardial infarction were more prevalent in subjects with the highest vitamin C intake, but exclusion of these subjects did not alter the results. Perhaps unknown and unmeasured confounding factors account for this association. However, it is possible that vitamin C behaves as a pro-oxidant in the presence of free iron (47), which is highly concentrated in the brain.

Methodological considerations

Habitual food intake of the participants was assessed with the cross-check dietary history method. The validity and reproducibility of this method have been well described (15, 48). The average intake between 1985 and 1990 was used to obtain a more reliable estimate of the diet during the 5 years prior to measurement of cognitive function. Nevertheless, differential misclassification could have influenced the results, because subjects with poor cognitive function might give less precise information on their food intake (49). This could either lead to overestimation or underestimation of the association between diet and

cognitive function. Yet, we found that change in dietary intake from 1985 to 1990 was not different in subjects who were cognitively impaired in 1990 compared with those who were unimpaired. Still, we can not be completely sure that cognitive impairment did not alter the report of dietary intake, because subjects could already have been impaired in 1985.

The Mini-Mental State Examination was used to assess cognitive function. It has proven to be a reliable and valid indicator of cognitive impairment, with a test-retest reliability generally between 0.80 and 0.95 (22). The MMSE can measure a substantial decline in cognitive function that may result from a strong risk factor, such as the apolipoprotein e4 allele (50). Nevertheless, dietary risk factors may be associated with small effects on cognitive decline, which may not be detected with the MMSE (51).

It could be argued that selective participation may have affected the validity of our results. Subjects who did not participate in 1993 had a significantly lower baseline MMSE score and a lower vitamin C intake than subjects who did participate. However, the cross-sectional association between cognitive function and intake of vitamin C or other nutrients in 1990 was essentially the same for the nonparticipants and the participants. Thus, it is unlikely that selection bias accounted for our results.

In conclusion, this study raises the possibility that high linoleic acid intake is positively and high fish consumption inversely associated with cognitive impairment in elderly men. None of the antioxidants were protective. Because this is one of the first studies on this subject, caution is called for in the interpretation of our findings. Modest associations are difficult to detect with dietary data in a relatively small study. The present findings therefore need confirmation in large prospective studies, preferably with a longer follow-up period, or using a more sensitive measure of cognitive decline.

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