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Fish consumption, n−3 fatty acids, and subsequent 5-y cognitive decline in elderly men: the Zutphen Elderly Study[1–4]

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ABSTRACT

Background: Indications have been seen of a protective effect of fish consumption and the intake of n−3 fatty acids on cognitive decline. However, studies are scarce and results inconsistent.

Objective: The objective of the study was to examine the associations between fish consumption, the intake of the n−3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) from fish and other foods, and subsequent 5-y cognitive decline.

Design: Data on fish consumption of 210 participants in the Zutphen Elderly Study, who were aged 70–89 y in 1990, and data on cognitive functioning collected in 1990 and 1995 were used in the study. The intake of EPA and DHA (EPA+DHA) was calculated for each participant. Multivariate linear regression analysis with multiple adjustments was used to assess associations.

Results: Fish consumers had significantly ($P = 0.01$) less 5-y subsequent cognitive decline than did nonconsumers. A linear trend was observed for the relation between the intake of EPA+DHA and cognitive decline ($P = 0.01$). An average difference of ≈380 mg/d in EPA+DHA intake was associated with a 1.1-point difference in cognitive decline ($P = 0.01$).

Conclusions: A moderate intake of EPA+DHA may postpone cognitive decline in elderly men. Results from other studies are needed before definite conclusions about this association can be drawn. *Am J Clin Nutr* 2007;85:1142–7.

KEY WORDS Fish, n−3 fatty acids, cognition, elderly

INTRODUCTION

Dementia and Alzheimer disease are preceded by a progressive degenerative cognitive decline. Evidence is accumulating that fish consumption and the intake of the n−3 polyunsaturated fatty acids (PUFAs) eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) may protect against dementia and Alzheimer disease (1–3). Most epidemiologic studies suggested a protective effect of fish or n−3 PUFAs, but one did not (4).

Less evidence with respect to cognitive functioning is available. A cross-sectional analysis of a Dutch study showed that both fish consumption and EPA+DHA intake were inversely associated with cognitive impairment in middle-aged men and women (5). In the Zutphen Elderly Study (6), fish consumption tended to be inversely associated with cognitive impairment and with 3-y cognitive decline, although the results were not significant after multiple adjustments [odds ratio (OR): 0.63; 95% CI: 0.33, 1.21 and OR: 0.45; 95% CI: 0.17, 1.16]. In addition, the intake of n−3 PUFAs was not related to cognitive impairment or cognitive decline. The Canadian Study of Health and Aging also did not find a protective effect of n−3 PUFAs in plasma on cognitive decline or on dementia after a 5-y follow-up (7). The Chicago Health and Aging Project showed that fish consumption was associated with less cognitive decline, but no evidence was found for an association between the intake of n−3 fatty acids and the rate of cognitive decline (8).

Several mechanisms have been suggested for the association between n−3 fatty acids and cognitive functioning. n−3 Fatty acids have antiinflammatory and cardiovascular protective effects (9) and may therefore reduce the risk of atherothrombotic complications such as stroke (10) and subsequent cognitive decline. Furthermore, n−3 fatty acids may improve the composition of cell membranes and therefore stimulate the development and regeneration of nerve cells (11).

EPA and DHA are frequently called fish fatty acids. However, recent results of fatty acid analysis showed that these n−3 fatty acids are present not only in fish and seafood but also in other animal foods, such as meat and eggs, and in plant foods, such as leek and cereal-based products (12). To study the association between the intake of n−3 fatty acids and cognitive decline, it is necessary also to take into account the intake of n−3 fatty acids in foods other than fish and seafood.

This prospective cohort study used longitudinal data and was focused on changes in cognitive functioning. New data recently became available on the content of EPA and DHA in fish and seafood and in other animal foods and plant foods. On the basis of these new data, we calculated the EPA+DHA content of the diet consumed by the participants in the Zutphen Elderly Study in 1990 and 1995, in order to examine both the association between fish consumption and cognitive decline and that between

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the intake of EPA+DHA from different foods and cognitive decline.

SUBJECTS AND METHODS

Study population

The Zutphen Elderly Study is a prospective cohort study of men born between 1900 and 1920 who lived in Zutphen, a town in the eastern part of the Netherlands. In 1985, 939 elderly men were examined (response rate: 74%); in 1990 and 1995, follow-up examinations in which information was collected on cognitive functioning were carried out. In 1990, 556 men aged 70–89 y participated in the survey (response rate: 77%); in 1995, 307 of those 556 men, then aged 75–94 y, participated. Because poor health status at baseline may influence both cognitive functioning and food consumption, we selected men without myocardial infarction, stroke, diabetes, or cancer at baseline (n = 228). Complete information on possible confounding factors was available for 210 men.

Written informed consent was obtained from all participants. The Zutphen Elderly Study was approved by the Medical Ethics Committee of the University of Leiden (Leiden, Netherlands).

Dietary intake assessment

Information about habitual food consumption was collected in 1990 by using the cross-check dietary history method (13), which is reproducible (13) and valid (14). Spearman correlation coefficient for fish consumption in 1990 and 1995 was 0.62 and that for the intake of EPA+DHA was 0.47.

Dietitians interviewed the participants in their homes with respect to their usual food-consumption patterns. A checklist providing information on the frequencies and quantities of foods consumed during the previous 2–4 wk was used to verify the participants' food-consumption patterns. Total fish consumption per day was calculated by adding the amount of different types of fish. Energy, fatty acid, and antioxidant (vitamins C and E and β-carotene) intakes for each participant were calculated with the use of the computerized version of the Dutch Food Composition Table (15). The fatty acid content of the foods consumed was estimated for each participant. For EPA and DHA, we used recently available data on the content of these fatty acids not only in fish and seafood but also in other animal foods (eggs and meat) and in plant foods (vegetables and cereal-based products) (12).

Assessment of cognitive functioning

The Mini-Mental State Examination (MMSE) was used in 1990 and 1995 as a screening test to assess global cognitive functioning (16); it includes questions on orientation to time and place, registration, attention and calculation, recall, language, and visual construction. The maximum score is 30 points, and a higher score indicates better cognitive functioning. If a subject did not answer ≥4 individual items (of a total of 20), the total MMSE score was considered missing. If <4 items were missing, these items were rated as errors and a total MMSE score was calculated (17). Originally, the MMSE was created for clinical use, but it is now used extensively in epidemiologic studies, has a good test-retest reliability, and is a valid indicator of cognitive functioning (18–20).

Other measurements

Demographic, lifestyle, and other information was obtained with standardized questionnaires in 1990. Education was assessed as the number of years of education. Subjects' smoking status was categorized as current smokers and nonsmokers and their alcohol consumption as alcohol users and nonusers. Physical activity was assessed by a validated questionnaire especially designed for retired men and categorized into quartiles (21). Depressive symptoms were measured with a Self-rating Depression Scale (SDS) developed by Zung (22). A value of ≥50 was used to indicate the presence of depressive symptoms (yes or no). Information about the prevalence of myocardial infarction, stroke, diabetes, and cancer was collected by standardized questionnaires (yes or no) and validated by hospital registries, information obtained from general practitioners, or both.

Statistical analysis

Differences in baseline variables among different categories of fish consumers were evaluated by using the Kruskal-Wallis test for skewed variables, and analysis of variance was used for normally distributed continuous variables. Categorical data were tested for differences with the chi-square test. EPA+DHA intake is highly correlated (Spearman correlation coefficient: 0.88); therefore, we used the sum of EPA and DHA in the analyses.

To investigate fish consumption as well as the intake of EPA+DHA in 1990 in relation to cognitive functioning and cognitive decline, different multivariate linear regression models were used. Fish consumption (yes or no and classes of 0, >0–20, and >20 g/d) and the intake of EPA+DHA (in tertiles of 0–56, >56–148, and >148 mg/d) in 1990 were entered as class variables into the model, and the outcome variables baseline cognitive functioning and 5-y cognitive decline (MMSE 1995 − MMSE 1990), which were used singly in the different analyses, were treated as continuous variables. Dose-response relations were tested for trend by using a linear regression model.

Adjustments were made for the well-known confounding factors age and education (23). Because fish consumption may be associated with a healthier lifestyle, we also adjusted for energy intake, alcohol consumption, smoking status, and physical activity. In longitudinal analyses, we adjusted for baseline cognitive functioning because the level of baseline cognitive functioning may influence cognitive decline. Additional adjustments were made for dietary antioxidants on the assumption that fish consumers are more likely than are fish nonconsumers to follow a healthy diet rich in fruit and vegetables (24). Dietary antioxidants may protect against cognitive decline by scavenging free radicals. Furthermore, a low intake of unsaturated fatty acids may be associated with a high intake of *trans* fatty acids, which are associated with a greater risk of Alzheimer disease (25). Therefore, we also adjusted for these fatty acids. Because depression may be associated with both fish consumption and cognitive functioning, we adjusted for depressive symptoms (24). Finally, to reduce reporting bias due to impaired cognitive functioning, we excluded participants with an MMSE score <24 (impaired cognition; 20) in 1990 (n = 25).

All statistical analyses were carried out with SAS software (version 9.1; SAS Institute Inc, Cary, NC). A 2-sided P value of ≤0.05 was considered significant.

TABLE 1
Baseline characteristics and daily nutrient intakes of 210 healthy men aged 70–89 y according to fish consumption in 1990[1]

Characteristic	Fish consumption: 0 g/d (n = 51)	>0–20 g/d (n = 86)	>20 g/d (n = 73)	P^2
Age (y)	76.1 ± 4.5[3]	75.8 ± 4.3	74.1 ± 3.9	<0.01
MMSE score[4]	26.1 ± 2.4	26.3 ± 2.2	26.7 ± 2.0	0.30
Education (y)	9.6 ± 3.3	11.1 ± 4.2	11.5 ± 4.7	0.04
Physical activity (min/wk)	570.8 ± 358.2	696.4 ± 668.1	541.4 ± 337.2	0.65
Alcohol consumers (%)	71	78	85	0.16
Current smoker (%)	9	24	18	0.10
Depressive symptoms (%)[5]	6	1	1	0.16
Energy intake (MJ/d)	8.8 ± 1.8	8.9 ± 1.9	9.1 ± 2.0	0.82
Total fat (g)	88.2 ± 25.8	91.3 ± 28.1	92.4 ± 29.7	0.88
Saturated fat (g)	37.9 ± 13.3	39.6 ± 12.9	37.7 ± 13.5	0.39
Monounsaturated fatty acid (g)	31.7 ± 8.6	32.2 ± 10.6	33.1 ± 10.9	0.95
trans Fatty acid (g)	7.2 ± 3.4	6.1 ± 3.2	6.7 ± 4.1	0.14
Polyunsaturated fatty acid (g)	15.7 ± 8.5	16.4 ± 9.5	18.2 ± 9.0	0.11
Linoleic acid (g)	13.4 ± 8.7	14.1 ± 9.3	15.4 ± 8.7	0.19
α-Linolenic acid (g)	1.1 ± 3.2	1.1 ± 3.7	1.2 ± 5.8	0.29
EPA and DHA (mg)	14.7 ± 11.1	126.1 ± 103.0	346.8 ± 291.0	<0.001
Vitamin C (mg/d)	95.9 ± 45.9	102.3 ± 63.4	94.9 ± 44.8	0.98
Vitamin E (mg/d)	9.5 ± 8.2	14.0 ± 25.1	10.4 ± 7.8	0.38
β-Carotene (mg/d)	2.2 ± 1.2	2.0 ± 1.3	2.1 ± 1.4	0.64

[1] MMSE, Mini-Mental State Examination; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid.
[2] Based on Kruskal-Wallis test, ANOVA, or chi-square test.
[3] $\bar{x}$ ± SD (all such values).
[4] Cognitive functioning measured with the MMSE (range: 0–30).
[5] Depressive feelings measured with the Self-rating Depression Scale (range: 25–100) developed by Zung (21). A value of ≥50 was used to indicate the presence of depressive symptoms; n = 49, 86, and 71 for the 0, >0–20, and >20 g/d groups, respectively.

RESULTS

In 1990, 24% of the participants did not consume fish, 41% consumed between >0 and 20 g fish/d, and 35% consumed >20 g fish/d. Fish consumption in the current study consisted of lean fish (67%; raw lean fish contains <12 g fat), fatty fish (32%; raw fatty fish contains ≥12 g fat), and crustacean and shellfish (1%).

Overall, few differences were found in characteristics and daily nutrient intakes between men in the different categories of fish consumption (**Table 1**). Men who did not consume fish were the oldest and had the fewest years of education. Men who did not consume fish had an average EPA+DHA intake of 15 mg/d because of the small amounts of these fatty acids in animal foods other than fish and in plant foods.

Some men did not participate in the current study because they died before 1995, they did not respond in 1995, or they had poor health status or missing values in 1990. These men overall were older, had fewer years of education, had lower baseline cognitive test scores, were less physically active, and had a lower percentage of alcohol users than did the men who participated. These nonparticipants also had lower fish consumption and EPA+DHA intake in 1990 than did men who participated in the current study (data not shown).

In the 210 men with complete information, cognitive functioning in 1990 did not differ between those who consumed or did not consume fish in 1990, after adjustment for age, education, alcohol consumption, smoking status, physical activity, and energy intake (**Figure 1**). However, men who did not consume fish had a subsequent cognitive decline of 1.2 points, which was 4 times the decline in men who consumed fish (P = 0.01).

Cognitive functioning in 1990 did not differ among the categories of fish consumers (**Table 2**). However, the decline in cognitive functioning was 1.0 point stronger in men who did not than in those who did consume fish.

No differences in cognitive functioning were found in 1990 among the tertiles of EPA+DHA intake (**Table 3**). However, a dose-response relation was noted between tertiles of EPA+DHA intake and 5-y cognitive decline (P = 0.01). The difference in cognitive decline between the highest and the lowest tertiles of EPA+DHA intake was 1.1 points.

Additional adjustments for the intakes of *trans* fatty acids and antioxidants and for depressive symptoms did not attenuate our results. The exclusion of men with impaired cognitive functioning (MMSE score < 24) in 1990 also did not change the results.

DISCUSSION

This study showed that fish consumption in older men was associated with less subsequent 5-y cognitive decline than was no fish consumption. Furthermore, a dose-response relation was noted between the combined intake of the n−3 fatty acids EPA and DHA and cognitive decline, which suggests that a higher intake of EPA+DHA was associated with less cognitive decline.

The strengths of the current study are its prospective population-based design, the availability of detailed information on n−3 fatty acids, the ability to adjust for multiple possible confounding factors, and the availability of repeated measurements of cognitive functioning. The study has also limitations.

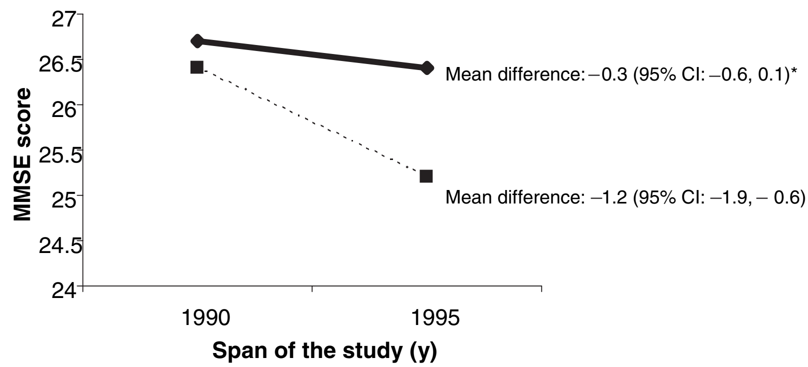

FIGURE 1. Multivariate linear regression analysis of 5-y cognitive decline in 210 elderly men in relation to fish consumption in 1990, showing the mean change in cognitive functioning between 1990 and 1995, adjusted for age, education, alcohol consumption, smoking status, physical activity, energy intake, and baseline cognitive functioning. MMSE, Mini-Mental Status Examination. ♦, Fish consumers; ■, fish nonconsumers. *Significantly different from cognitive decline in 51 fish nonconsumers, $P = 0.01$.

Selection bias due to death and nonresponse could have influenced the results. However, that bias would probably have led only to an underestimation of the strength of the associations, because the men who dropped out of the current study consumed less fish and had a lower intake of EPA+DHA and lower cognitive test scores.

Bias due to cognitive impairment in 1990 could have influenced our results, because men with an impaired cognition could have changed their dietary habits or they may have given imprecise information about their actual food consumption. To reduce this differential misclassification, we also excluded men who were cognitively impaired (MMSE score < 24) in 1990 (20). The results did not change after the exclusion of these men. Therefore, differential misclassification was not a major problem in the current study. Although we adjusted for many possible confounding factors, we cannot exclude residual confounding by risk factors that we did not measure.

Because multiple measurements of cognitive functioning were available, we were able to investigate associations for both cognitive impairment and cognitive decline. The results of the current study show that fish consumption and EPA+DHA intake are not significantly related to cognitive impairment but are significantly related to cognitive decline. This finding emphasizes the importance of repeated measures of cognitive functioning. Because the MMSE is a screening test that assesses overall cognitive functioning, we recommend that future studies include a more extensive battery of cognitive tests to obtain information about different cognitive domains.

Only a few studies have investigated the relations between fish consumption and the intake of n−3 fatty acids and cognitive decline. Results of the current study differ from earlier results of the Zutphen Elderly Study, in which no clear inverse association between fish consumption and 3-y cognitive decline could be shown (6). In the current study, we observed a strong inverse association between the EPA+DHA intake and cognitive decline. Possible explanations for the discrepancy between the earlier results of the Zutphen Elderly Study and the current findings could be the longer follow-up period in the current study and the availability of data on the EPA and DHA content of animal and plant foods in addition to fish and seafood. However, in the Canadian Study of Health and Aging, an inverse relation between n−3 PUFA in plasma (an indicator of the total dietary intake of EPA+DHA) and cognitive decline was not found (7). The Chicago Health and Aging Project showed that fish consumption but not the intake of n−3 fatty acids (from different food items) was associated with less cognitive decline (8).

Although fish is the major source of the EPA and DHA consumed (71%), these fatty acids are also contained in other foods, such as meat (20%), eggs (6%), and plant foods (such as leek and cereal-based products; 3%) (12). In the past few years, several foods have been enriched with n−3 fatty acids because of the suggested positive effect of these n−3 fatty acids on health. Therefore, information on the EPA and DHA content of all foods in the diet is now required when associations between these fatty acids and cognitive functioning are studied.

TABLE 2
Cognitive functioning of 210 elderly men per fish consumption category in 1990[1]

	Fish consumption			
	0 g/d (n = 51)	>0–20 g/d (n = 86)	>20 g/d (n = 73)	P for trend[2]
Cognitive functioning in 1990[3]	26.4 (25.8, 26.9)[4]	26.8 (26.4, 27.3)	26.5 (26.0, 27.0)	0.81
5-y cognitive decline[5]	−1.2 (−1.9, −0.6)	−0.2 (−0.7, 0.3)	−0.3 (0.9, 0.2)	0.07

[1] $\bar{x} \pm$ SD consumption was 11 ± 6 and 37 ± 21 g/d in the >0–20 and >20 g/d groups, respectively.
[2] Based on a multivariate linear regression.
[3] Adjusted for age, education, alcohol consumption, smoking status, physical activity, and energy intake.
[4] $\bar{x}$; 95% CI in parentheses (all such values).
[5] Adjusted for age, education, alcohol consumption, smoking status, physical activity, energy intake, and baseline cognitive functioning.

TABLE 3
Cognitive functioning of 210 elderly men per tertile of eicosapentaenoic acid and docosahexaenoic acid (EPA+DHA) intake in 1990[1]

	EPA+DHA intake			
	Lowest tertile ($n = 69$)	Middle tertile ($n = 70$)	Highest tertile ($n = 71$)	*P* for trend[2]
Cognitive functioning in 1990[3]	26.3 (25.8, 26.8)[4]	26.9 (26.4, 27.4)	26.6 (26.1, 27.1)	0.36
5-y cognitive decline[5]	−0.9 (−1.5, −0.3)	−0.7 (−1.3, 0.2)	0.2 (−0.4, 0.7)	0.01

[1] $\bar{x} \pm$ SD intake was 20 ± 15, 104 ± 27, and 398 ± 269 mg/d in the lowest, middle, and highest tertile, respectively.
[2] Based on a multivariate linear regression.
[3] Adjusted for age, education, alcohol consumption, smoking status, physical activity, and energy intake.
[4] $\bar{x}$; 95% CI in parentheses (all such values).
[5] Adjusted for age, education, alcohol consumption, smoking status, physical activity, energy intake, and baseline cognitive functioning.

Several biological mechanisms have been suggested for the associations observed in the current study. The n−3 fatty acids EPA and DHA provide protection against cardiovascular disease (10, 26) by lowering blood triacylglycerols, improving platelet aggregation and endothelial function (9, 27), and increasing antiarrhythmia (28). They may also stabilize atherosclerotic plaques and reduce the risk of atherothrombotic complications. Furthermore, the n−3 fatty acids have antiinflammatory effects (9) by inhibiting the synthesis of cytokines and mitogens (29). High levels of inflammation, possibly due to β-amyloid peptides, could contribute to cognitive decline (30). Finally, animal studies have shown that n−3 PUFAs have an effect on membrane excitability, play a role in brain development by stimulating synaptic plasticity and increasing neurotransmission (11, 31), and increase memory abilities (32).

Our results suggest that the n−3 fatty acids EPA and DHA may protect against cognitive decline. Elderly men who consumed an average of ≈400 mg EPA and DHA/d had less (by 1.1 points) cognitive decline than did those who consumed ≈20 mg EPA and DHA/d. In the population in the current study, fish is the main source of EPA+DHA intake, and it is therefore recommended as a first choice to increase the intake of these fatty acids. However, the results of the current study also show that approximately one-third of EPA+DHA ingested comes from foods other than fish—eg, meat, eggs, leek, and cereal products—and thus their consumption can also contribute to higher EPA+DHA intake.

In conclusion, the current study provides evidence that a combined daily intake of ≈400 mg n−3 PUFAs EPA and DHA [similar to 6 servings of ≈140 g lean fish/wk (total: ≈850 g) or 1 serving of 140 g fatty fish (such as mackerel and herring)/wk] is associated with less subsequent cognitive decline in elderly men. Fish is the most important source of these fatty acids in the diet, and its consumption is inversely associated not only with cognitive decline but also with cardiovascular disease (10, 26). To prevent cardiovascular disease mortality, the American Heart Association recommends the consumption of fish (preferably fatty fish) at least twice a week (33). That recommendation is compatible with the results of the current study. However, results of other prospective cohort and intervention studies are needed to make more definitive statements on the association between n−3 fatty acids and cognitive decline.

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All authors contributed substantially to the conception and design of the study; BMvG prepared part of the database; SK and DK were responsible for data collection; BMvG was responsible for and all authors contributed to the analysis of the data; BMvG, MT, SK, and DK wrote the draft of the manuscript; and BMvG, SK, and DK contributed to revisions of the manuscript and approved the final version. DK is the principal investigator of the Zutphen Elderly Study. None of the authors had a personal or financial conflict of interest.

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