

Cognitive performance among the elderly and dietary fish intake: the Hordaland Health Study¹⁻³

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ABSTRACT

Background: Increasing evidence suggests that cognitive impairment and dementia in older subjects might be influenced by a diet including seafood.

Objective: The objective was to examine the cross-sectional relation between intake of different amounts of various seafood (fish and fish products) and cognitive performance.

Design: The subjects ($n = 2031$ subjects; 55% women), aged 70–74 y, were recruited from the general population in Western Norway and underwent cognitive testing. A cognitive test battery included the Kendrick Object Learning Test, Trail Making Test (part A), modified versions of the Digit Symbol Test, Block Design, Mini-Mental State Examination, and Controlled Oral Word Association Test. Poor cognitive performance was defined as a score in the highest decile for the Trail Making Test and in the lowest decile for all other tests.

Results: Subjects whose mean daily intake of fish and fish products was ≥ 10 g/d ($n = 1951$) had significantly better mean test scores and a lower prevalence of poor cognitive performance than did those whose intake was < 10 g/d ($n = 80$). The associations between total intake of seafood and cognition were strongly dose-dependent; the maximum effect was observed at an intake of ≈ 75 g/d. Most cognitive functions were influenced by fish intake. The effect was more pronounced for nonprocessed lean fish and fatty fish.

Conclusions: In the elderly, a diet high in fish and fish products is associated with better cognitive performance in a dose-dependent manner. *Am J Clin Nutr* 2007;86:1470–8.

KEY WORDS Cognitive deficit, cognition, elderly, fish, fish oils, processed fish, seafood

INTRODUCTION

Modern studies of the role of nutrition in cognition among the elderly began in the 1980s and were reviewed by Rosenberg and Miller (1). In 1997 Grant (2) highlighted the possible role of diet in the development of Alzheimer disease (AD). After the initiation of large-scale observational epidemiologic studies in the Netherlands in the 1990s (3), it was suggested that the intake of fish might protect the elderly from developing cognitive impairment or dementia (4, 5). This idea has been supported by several independent studies (2, 6–12) that have led to a debate about whether modification of the diet might be one way to prevent cognitive decline and dementia in the elderly (13, 14). It is clearly important to resolve the question of whether such a relatively simple change in lifestyle as eating more fish can reduce the

burden on the individual and on society of cognitive decline and dementia in the elderly (15). Although intervention studies ultimately will be required to answer this question, it is possible to test some hypotheses by additional observational studies.

The purpose of this cross-sectional study on community-dwelling elderly people was to seek answers to the following questions: 1) Is the intake of fish and fish products associated with better cognitive performance? 2) Is dietary intake of seafood associated with the performance of all, or only some, cognitive abilities? 3) Is there any relation between the type of seafood product consumed and cognitive test results? and 4) Is there any relation between the amount of fish consumed and cognitive test results? We had the opportunity to examine these issues among >2000 elderly men and women, who represented a subset of subjects within the Hordaland Health Study (HUSK).

SUBJECTS AND METHODS

Study population

The HUSK study was conducted from 1997 to 1999 as a collaboration between the University of Bergen, University of Oslo, local health services, and the Norwegian Institute of Public Health. In a subsample of the study, 4338 individuals born in 1925–1927 who had participated in the Hordaland Homocysteine Study (16) in 1992–1993, were invited to participate in HUSK to examine age effects. Recruitment into the Cognitive Substudy is described on the Web (Internet: www.uib.no/isf/)

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husk/Vedlegg_dokumenter/Cognitive_Sub_study.pdf). Briefly, the recruitment was among subjects born in 1925–1927 who participated in both 1992–1993 and in 1997–1999. Altogether, 2841 individuals were invited to participate in the cognitive tests, 2197 (77.3%) of whom agreed and constitute the Cognitive Substudy. In this report, we confined the analysis to 2031 (71.5%) individuals who also completed a food-frequency questionnaire. All participating subjects gave their written informed consent. The study protocol was approved by the Regional Committee for Medical Research Ethics of Western Norway.

Data collection

Cognitive testing was performed at the study location by trained nurses after the standard cardiovascular examinations of the National Health Screening Service (17) were completed. The cognitive test battery included 6 tests.

Kendrick Object Learning Test

The Kendrick Object Learning Test (KOLT; episodic memory) (18) is designed to assess dementia status and memory performance among noninstitutionalized elderly. The maximum possible KOLT score is 70.

Trail Making Test

The Trail Making Test, part A (TMT-A; executive function) (19) is a test of visual conceptual and visuomotor tracking, involving motor speed and attention functions. The score is the total time in seconds to complete the items. The shortest and longest times in our population were 16 and 331 s.

Modified version of the Digit Symbol Test

The modified version of the Digit Symbol Test (m-DST; perceptual speed) (20) is regarded as a measure of focused attention, visuomotor coordination, and psychomotor speed. In the present version, the number of correct matches between digits and symbols in 30 s was recorded.

Block Design

The Block Design (m-BD; visuospatial skills) (20) tests visuospatial and motor skills. The short form, used in the present study, included 4 of the 10 patterns (patterns 1, 2, 5, and 6) in the full test. Every correct matching gives 4 points; thus, a possible maximum score on the m-BD short form is 16.

Modified version of the Mini-Mental State Examination

A modified version of the Mini-Mental State Examination (m-MMSE; global cognition) (21) covers various aspects of cognitive function, including orientation to time and place, naming, repeating, writing, copying, instantaneous recall, short-term memory, backward spelling, and performing a 3-stage command (22). The m-MMSE consists of 12 of the 20 items in the full version of the MMSE and has been shown to be just as effective as the full version when the purpose is to identify elderly subjects with cognitive impairment (22).

Abridged version of the Controlled Oral Word Association Test

The abridged version (S-task) of the Controlled Oral Word Association Test (access to semantic memory) (23) is a test of

verbal fluency and psychomotor speed. The subjects were required to generate as many words as possible beginning with the letter S within 60 s. The maximum possible score is theoretically infinite; in our subjects it was 39.

Dietary habits

To assess habitual food consumption, a modified version of a comprehensive food-frequency questionnaire created at the Department of Nutrition, University of Oslo (24, 25), was handed out on the day of the examination and filled out later at home by the participants and then mailed to the HUSK Project Centre in Bergen. The questionnaire included 169 food items that were grouped according to Norwegian meal patterns. It was designed to obtain information on usual food intake during the past year. The frequency of consumption was given per day, week, or month. The portion sizes were given as household measures or units such as slices or pieces.

Fish intake included sandwich spread and fish intake as a part of a main meal. Questions related to sandwich spread were as follows: How many slices of bread with the following spreads do you eat per week: tinned mackerel in tomato paste, smoked mackerel, pilchard, pickled herring, anchovies or similar fish, salmon, or trout? All these questions had 11 categories (0, 0.5, 1, 2–3, 4–5, 6–7, 8–14, 15–21, 22–28, 29–35, and ≥ 36 slices/wk). Questions related to fish intake as a main meal were 2-fold, related to frequency of intake and to the typical amount of intake per meal. The frequency of fish intake included 9 categories (0, <1, 1, 2, 3, 4, 5–6, 7–8, and ≥ 9 times/mo). The amount of fish intake was categorized into 5 categories that differed according to type of product: fishcakes, fish pudding, and fish balls (from 1 to ≥ 5 units); fish fingers (from 1–2 to ≥ 10 pieces); boiled cod, coalfish, and haddock (from 1 to ≥ 5 pieces); fried cod, coalfish, or haddock (from 1 to ≥ 5 pieces); fresh, salt-cured, or smoked herring (from 1 to ≥ 5 fillets); fresh or smoked mackerel (from 0.5 to ≥ 3 fillets); salmon or trout (both wild and farmed) (from 1 to ≥ 5 steaks); and fish stew, fish soup, and fish au gratin (from 1–2 to ≥ 9 dl). In the data analyses, the main meal was divided into 3 different categories: fatty fish (herring, mackerel, salmon, and trout), lean fish (cod, coalfish, and haddock), and processed fish (fish cakes, fish pudding, fish balls, fish fingers, fish stew, fish soup, and fish au gratin). The last category, “processed fish,” is imprecise in terms of nutritional value.

The questionnaire also included questions about dietary supplement intake, in which the product names of the most used supplements in Norway were considered. Use of cod liver oil and fish oil was reported as “seasonal use” (during the whole year or only winter half of the year), frequency per week, and amount per time.

Dichotomous variables were created for different types of fish and fish products. Individuals who reported use of certain products in the abovementioned categories were considered as users, whereas all those who reported that they never ate that product were considered nonusers. To identify the individuals who never ate any fish and fish products (including fish either as sandwich spread or as part of main meals, cod liver oil, and other fish oils), all dichotomous variables were combined. The amount of fish and fish products in grams per day was calculated by using a food database and software system developed at the Department of Nutrition, University of Oslo (Kostberegningssystem, version 3.2; University of Oslo, Oslo, Norway). Calculations of total intake of fish and fish products also included intake of cod liver

oil and other fish oils. For convenience, we use the term *seafood* to include all the fish and fish products described above.

Other variables

Self-reported information on history of myocardial infarction, angina pectoris, stroke, thrombosis, phlebitis, and hypertension was recorded in 1992–1993 and in 1997–1999. On the basis of information from both surveys, the subjects were categorized as with or without a history of cardiovascular disease (CVD), including the diseases and conditions mentioned above. About four-fifths (79.3%) of self-reported CVD cases and noncases were validated on the basis of hospitalizations records used in our earlier study (26), whereas the remaining 20% of CVD cases were presumably less severe and did not require hospitalization or occurred before 1992.

Educational level was self-reported and recorded in 5 categories: primary school (≤ 9 y), vocational secondary school (10–12 y), theoretical secondary school (10–12 y), college or university < 4 y, and university of ≥ 4 y.

Nonfasting EDTA blood samples were collected for the measurement of total homocysteine (tHcy) and gene polymorphisms. The EDTA sample was kept cool until centrifuged. The blood samples were stored at -80°C . The duration of storage ranged from a few days to 18 mo. Plasma tHcy was measured by using a fully automated HPLC assay (27, 28). Apolipoprotein E genotypes were determined in the packed cell fraction of blood samples by using a one-stage polymerase chain reaction method (29).

Statistical analysis

Cutoff points for poor cognitive test scores were set at about the 10th percentile of the cognitive test score, except for TMT-A, for which the 90th percentile was used. Preliminary analyses showed that cognitive test performance was most frequently associated with education (all test scores were significantly associated). Three of 6 cognitive test scores were significantly associated with tHcy, the KOLT and m-DST were significantly associated with sex and *ApoE* $\epsilon 4$ variant allele, and the KOLT score was the only test that was significantly associated with some important CVD variables referred to above. Intake of fish or fish products was significantly associated with sex, education, and tHcy. Body mass index, total cholesterol, and HDL cholesterol were not associated with cognitive test scores or with fish and fish product intakes, and inclusion of these variables in the statistical models did not change the results and were therefore excluded from final models. We also adjusted for depression score using a 7-item self-administered subscale for depression from the Hospital Anxiety and Depression Scale (30), which focuses mainly on the reduced pleasure response aspect (anhedonia) of depression, but also psychomotor retardation and impaired mood. Although the depression score was significantly associated with intake of seafood and with most cognitive test scores, it made little difference when introduced in the statistical models. Because inclusion of the depression score significantly reduced the numbers of subjects because of missing data, the results are not shown. The participants of the cognitive substudy were homogeneous in age (born 1925–1927); therefore, age was not included as a cofactor in the statistical models. Throughout the article, we analyzed the results using 2 different models: a simple model, in which we only adjusted for sex, and a multiple adjusted model, in which sex, *ApoE* $\epsilon 4$ variant allele, education,

history of CVD (limited to some important CVD variables), and tHcy were cofactors.

For comparison between the groups of fish and fish product intake, the chi-square test or the univariate analysis of variance was used. Adjusted mean cognitive scores by intake of various types of seafood were obtained from the univariate analysis of variance. Multinomial logistic regression analysis (adjusted for the same variables) with fish and fish products intake as the independent variable, and the number of tests with poor results as the dependent variable, was applied to find risk ratios for poor cognitive performance by using subjects without poor test performance as the reference group. Gaussian generalized additive regression models, as implemented in S-PLUS 6.2 for WINDOWS (Insightful Corporation, Seattle, WA), were used to generate graphic representations of the dose-response relations, with the use of both models. On the y axis, the model generated a reference value of zero that approximately corresponds to the value of cognitive test score associated with the mean of the average total fish intake in grams per day for all subjects. Multiple linear regression analyses were used to examine significant associations between the cognitive test scores and average of total fish intake. Except for generalized additive models, all statistical analyses were performed by using the STATISTICAL PACKAGE FOR THE SOCIAL SCIENCES 12.0 for WINDOWS (SPSS Inc, Chicago, IL). *P* values < 0.05 were considered significant.

RESULTS

Our study population had an overall high fish intake. Only 2% reported that they never ate fish and fish products (Table 1). The mean total intake of fish and fish products among consumers was

TABLE 1
Prevalence and mean intakes of different types of seafood (fish and fish products)

Type of fish and fish product	Prevalence (<i>n</i> = 2031)	Mean intake (95% CI)
	<i>n</i> (%)	<i>g/d</i>
Fish sandwich ¹	1314 (64.7)	16.0 (14.9, 17.1)
Main meal		
Fatty fish ²	1579 (77.7)	18.6 (17.7, 19.6)
Lean fish ³	1852 (91.2)	39.3 (38.0, 40.6)
Processed fish ⁴	1893 (93.2)	16.9 (16.4, 17.5)
Any type of fish as part of a main meal		
Never	65 (3.2)	—
≤ 1 time/mo	8 (0.4)	—
2–3 times/mo	51 (2.4)	—
1 time/wk	45 (2.2)	—
> 1 time/wk	1862 (91.8)	—
Cod liver oil and fish oil		
Winter half year	397 (19.5)	2.6 (2.4, 2.8)
All year round	436 (21.5)	5.6 (5.2, 5.9)
All fish and fish products combined	1990 (98.0)	85.4 (83.0, 87.8)

¹ Mackerel, pilchard, pickled herring, anchovies, salmon, or trout as a sandwich spread.

² Herring, mackerel, salmon, or trout as part of a main meal.

³ Cod, coalfish, or haddock as part of a main meal.

⁴ Fish balls, fish cakes, fish fingers, fish stew, fish soup, or fish au gratin as part of a main meal.

≈85 g/d. About four-fifths of the population ate fatty fish as part of a main course, whereas even more reported having lean fish and processed fish for a main course. Nearly 2 of 3 subjects consumed fish as a sandwich spread, and >2 of 5 reported intake of cod liver oil or other fish oils.

Comparison of subjects who reported consumption of seafood with those who did not

Because the number of subjects who never ate fish and fish products was small ($n = 41$), we also included those with a low total intake (<10 g/d) in the group defined as “nonconsumers.” Characteristics of the study population by intake of any type of fish and fish products are presented in **Table 2**. The proportions of women and subjects with low education (≤ 9 y) were significantly higher among subjects who consumed <10 g/d of any type of fish or fish product. The mean scores on all 6 cognitive tests were significantly better for those who ate any type of fish or fish product. The prevalence of poor cognitive performance was 2–3 times lower in those who reported eating seafood than in those who did not report eating seafood, independent of the cognitive test used. The proportion of subjects with poor scores on more than one cognitive test was greater in subjects who did not eat fish and fish products (27%) than in those who did (11%; $P < 0.001$).

In multivariate models including adjustments for sex, *ApoE* $\epsilon 4$ variant allele, education, history of some important CVD variables, and tHcy, the overall results changed moderately (data not shown), but because of missing data the significance was reduced for mean test scores (Table 2).

Compared with users of fish and fish products, the nonusers had a somewhat poorer health status. The prevalence of several diseases was significantly higher among those who did not eat

fish and fish products than among those who did (epilepsy: 5.5% compared with 0.8%, $P = 0.015$; asthma: 19.5% compared with 9.1%, $P = 0.005$; chronic bronchitis: 14.5% compared with 6.7%, $P = 0.036$; and osteoporosis: 20.3% compared with 11.0%, $P = 0.034$). We found no significant differences in the prevalence of history of some important CVD variables, diabetes, renal diseases, liver diseases, arthritis, thyroiditis, depression, psoriasis, or some other skin diseases between those who reported eating and those not eating fish and fish products (data not shown).

Cognitive scores in relation to type of fish and fish products

We studied the associations between cognitive performance and the main types of consumed seafood, ie, fatty fish, lean fish, processed fish, fish sandwich, and fish or cod liver oil. The adjusted mean cognitive test scores by different types of fish and fish products intake are presented in **Table 3**. Subjects who ate fatty fish or lean fish as their main meal performed significantly better in 5 of the 6 tests than did those who did not eat fatty fish or lean fish. Intake of processed fish as part of a main meal was associated with significantly better mean scores in 3 cognitive tests: KOLT, m-BD, and m-MMSE. Similarly, those who ate fish sandwiches performed better on 3 tests (m-DST, m-BD, and S-task). In contrast, those who ate fish oils performed better only in the S-task.

Dose-response relations between intake of seafood and cognitive function

In this population there were very few subjects who did not eat any type of fish or fish products. However, there was a considerable range in the amounts of fish eaten, which allowed us to

TABLE 2
Characteristics of the participants by intake of any type of seafood (fish and fish products)¹

	Intake of any type of seafood				P^3	P^4
	Yes		Never or <10 g/d			
	Total n	Value ²	Total n	Value ²		
Sex (male)	1951	902 (46.2) ⁵	80	16 (20.0)	<0.001	
Education ≤ 9 y	1923	763 (39.7)	74	39 (52.7)	0.029	
KOLT score	1947	35.4 (35.1, 35.8) ⁶	80	33.3 (31.6, 35.1)	0.020	0.15
Poor test score, $\leq 25^7$	1947	188 (9.7)	80	16 (20.0)	0.007	
TMT-A score	1944	55.7 (54.2, 57.2)	80	66.9 (59.7, 74.2)	0.003	0.029
Poor test score, $\geq 111^7$	1944	174 (9.0)	80	13 (16.3)	0.045	
m-DST score	1942	10.4 (10.2, 10.6)	80	9.1 (8.1, 10.0)	0.006	0.034
Poor test score, $\leq 5^7$	1942	156 (8.0)	80	14 (17.5)	0.006	
m-BD score	1939	15.1 (15.0, 15.2)	79	14.3 (13.8, 14.8)	0.005	0.013
Poor test score, $\leq 10^7$	1939	98 (5.1)	79	9 (11.4)	0.034	
m-MMSE score	1931	11.5 (11.5, 11.6)	79	11.2 (11.0, 11.4)	<0.001	0.002
Poor test score, $\leq 10^7$	1931	159 (8.2)	79	16 (20.3)	0.001	
S-task score	1944	15.3 (15.0, 15.5)	80	13.2 (12.0, 14.4)	0.001	0.017
Poor test score, $\leq 8^7$	1944	193 (9.9)	80	17 (21.3)	0.004	

¹ KOLT, Kendrick Object Learning Test; m-BD, modified version of Block Design; m-DST, modified version of Digit Symbol Test; m-MMSE, modified version of Mini-Mental State Examination; S-task, from the Controlled Oral Word Association Test; TMT-A, part A of the Trail Making Test.

² Adjusted for sex.

³ Pearson's chi-square or univariate ANOVA adjusted for sex.

⁴ Univariate ANOVA adjusted for sex, apolipoprotein E $\epsilon 4$ variant allele, education, history of cardiovascular disease, and plasma total homocysteine.

⁵ n ; % in parentheses (all such values).

⁶ \bar{x} ; 95% CIs in parentheses (all such values).

⁷ Cutoff points for poor cognitive score were set at approximately the 10th percentile, except for TMT-A, for which the 90th percentile was used.

TABLE 3

Mean cognitive test scores by intake of different types of seafood¹

Food and cognitive test	Intake of fish or fish product				P
	Yes		Never or <10 g/d		
	n	Mean (95% CI)	n	Mean (95% CI)	
Fatty fish²					
KOLT	1494	35.7 (35.3, 36.1)	429	34.3 (33.7, 35.0)	0.001
TMT-A	1490	54.8 (53.1, 56.4)	430	59.7 (56.7, 62.8)	0.005
m-DST	1489	10.5 (10.3, 10.7)	429	10.1 (9.7, 10.4)	0.030
m-BD	1488	15.1 (15.0, 15.2)	427	14.8 (14.6, 15.0)	0.012
m-MMSE	1482	11.5 (11.5, 11.6)	426	11.5 (11.4, 11.6)	0.34
S-task	1490	15.4 (15.2, 15.7)	430	14.5 (14.0, 15.0)	0.001
Lean fish³					
KOLT	1751	35.6 (35.2, 35.9)	172	33.3 (32.1, 34.5)	<0.001
TMT-A	1748	55.1 (53.6, 56.6)	172	64.4 (58.5, 68.2)	0.001
m-DST	1746	10.5 (10.3, 10.7)	172	9.7 (9.1, 10.3)	0.011
m-BD	1744	15.1 (15.0, 15.2)	171	14.6 (14.3, 14.9)	0.005
m-MMSE	1738	11.5 (11.5, 11.6)	170	11.4 (11.3, 11.5)	0.07
S-task	1748	15.3 (15.1, 15.6)	172	14.3 (13.5, 15.0)	0.009
Processed fish⁴					
KOLT	1779	35.5 (35.1, 35.9)	144	34.1 (32.8, 35.3)	0.033
TMT-A	1775	55.5 (54.0, 57.0)	145	60.3 (55.1, 65.6)	0.08
m-DST	1773	10.5 (10.3, 10.7)	145	9.9 (9.2, 10.5)	0.07
m-BD	1770	15.1 (15.0, 15.2)	145	14.5 (14.1, 14.8)	0.001
m-MMSE	1765	11.5 (11.5, 11.6)	143	11.4 (11.3, 11.5)	0.034
S-task	1775	15.2 (15.0, 15.5)	145	15.4 (14.6, 16.3)	0.66
Fish sandwich⁵					
KOLT	1252	35.6 (35.2, 36.1)	671	34.9 (34.3, 35.5)	0.06
TMT-A	1248	55.1 (53.3, 56.9)	672	57.3 (54.8, 59.7)	0.17
m-DST	1247	10.6 (10.4, 10.8)	671	10.1 (9.8, 10.4)	0.013
m-BD	1245	15.1 (15.0, 15.3)	670	14.9 (14.7, 15.1)	0.023
m-MMSE	1243	11.6 (11.5, 11.6)	665	11.5 (11.4, 11.5)	0.06
S-task	1248	15.5 (15.2, 15.8)	672	14.7 (14.3, 15.1)	0.002
Cod liver oil and fish oil					
KOLT	785	35.8 (35.2, 36.3)	1138	35.1 (34.7, 35.6)	0.07
TMT-A	785	54.7 (52.5, 57.0)	1135	56.7 (54.8, 58.6)	0.20
m-DST	784	10.5 (10.2, 10.8)	1134	10.4 (10.1, 10.6)	0.40
m-BD	783	15.1 (14.9, 15.2)	1132	15.0 (14.9, 15.2)	0.62
m-MMSE	783	11.6 (11.5, 11.6)	1125	11.5 (11.5, 11.6)	0.09
S-task	785	15.7 (15.4, 16.1)	1135	14.9 (14.6, 15.2)	0.001

¹ KOLT, Kendrick Object Learning Test; m-BD, modified version of Block Design; m-DST, modified version of Digit Symbol Test; m-MMSE, modified version of Mini-Mental State Examination; S-task, from the Controlled Oral Word Association Test; TMT-A, part A of the Trail Making Test. The univariate ANOVA was adjusted for sex, apolipoprotein E $\epsilon 4$ variant allele, education, history of cardiovascular disease, and plasma total homocysteine.

² Herring, mackerel, salmon, or trout as part of a main meal.

³ Cod, coalfish, or haddock as part of a main meal.

⁴ Fish balls, fish cakes, fish fingers, fish stew, fish soup, or fish au gratin as part of a main meal.

⁵ Mackerel, pilchard, pickled herring, anchovies, salmon, or trout as a sandwich spread.

investigate the dose-response relation between total intake of any type of fish and fish products and cognitive function. The results of all the cognitive tests improved with increasing intake of seafood up to 70–80 g/d and then leveled off (Figure 1). Linear regression analyses adjusted only for sex indicated that dose-response associations were significant for all cognitive tests. In the multiple-adjusted analyses, most of the relations remained significant (KOLT, m-DST, m-BD, and m-MMSE).

Number of poor test scores in relation to fish intake

The association between intake of different types of seafood and the number of tests yielding poor scores in an individual participant is presented in Table 4. A diet including fish or fish

products was associated with a low risk of having ≥ 4 tests with poor scores. The risk decreased by as much as 80% when all types of fish and fish products were combined.

DISCUSSION

In a large population-based study of elderly people, we found that consumers of fish and fish products had better cognitive function than did nonconsumers and, notably, that the associations between fish and fish product intake and cognition were dose-dependent. We also observed that the effect of fish on cognition differed according to the type of fish and fish product consumed.

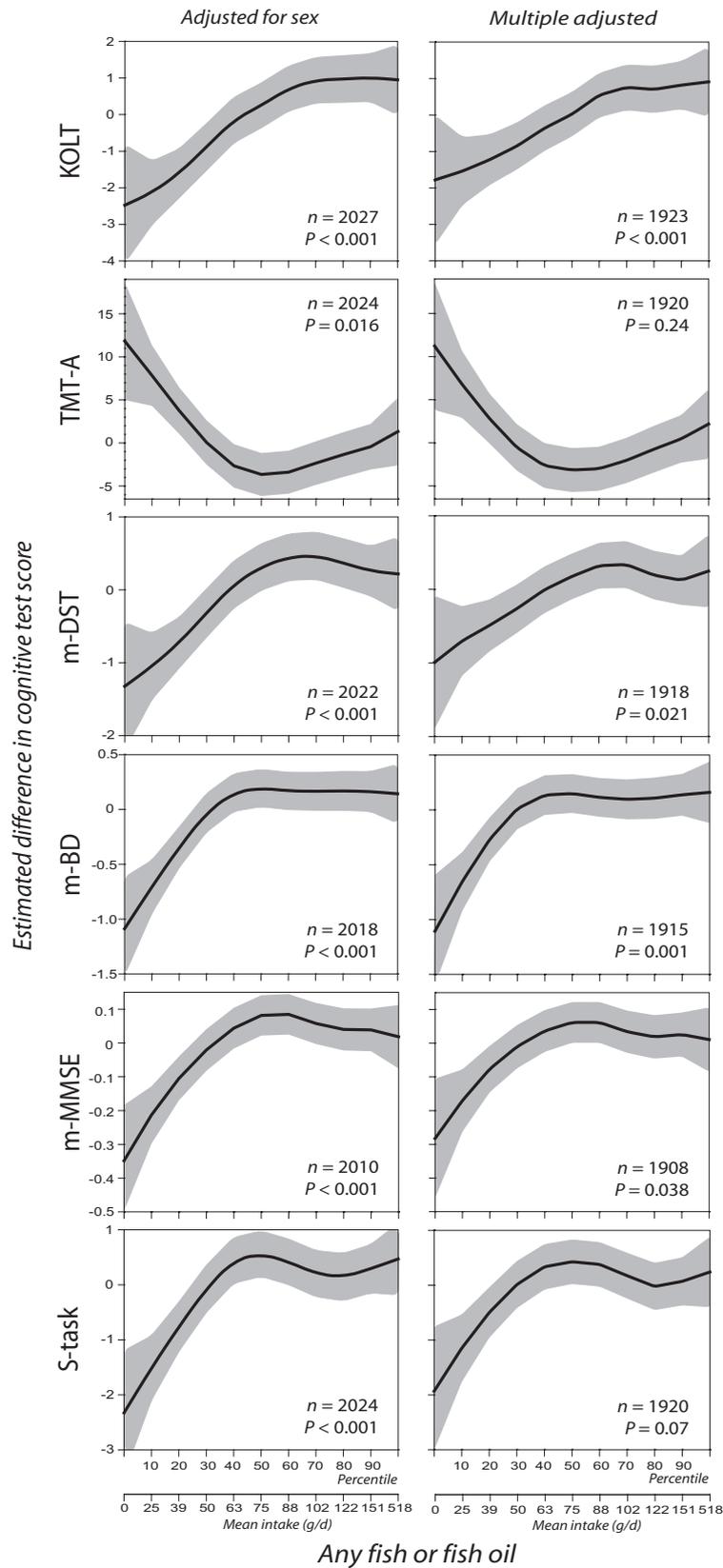


FIGURE 1. Associations between different cognitive tests scores and intake of any type of fish or fish product (including fish oils) obtained by Gaussian generalized additive regression models. The solid lines represent the estimated dose-response curves; the shaded areas represent the 95% CIs. Multiple adjustments included sex, apolipoprotein E $\epsilon 4$ variant allele, education, history of cardiovascular disease, and plasma total homocysteine. *P* values are from corresponding multiple linear regression analyses. KOLT, Kendrick Object Learning Test; m-BD, modified version of Block Design; m-DST, modified version of Digit Symbol Test; m-MMSE, modified version of Mini-Mental State Examination; S-task, from the Controlled Oral Word Association Test; TMT-A, part A of the Trail Making Test.

TABLE 4

Cross-sectional associations between habitual intake of different types of seafood (fish and fish products) during the previous year and the number of cognitive tests with poor scores¹

Daily intake of ≥ 10 g/d seafood	Number of cognitive tests with poor scores					Overall P^3
	0 ($n = 1318$)	1–3 ($n = 534$)		≥ 4 ($n = 39$)		
	OR	OR (95% CI)	P^2	OR (95% CI)	P^2	
Fatty fish ⁴	1.00	0.79 (0.62, 1.00)	0.053	0.44 (0.23, 0.87)	0.017	0.004
Lean fish ⁵	1.00	0.75 (0.52, 1.06)	0.11	0.28 (0.13, 0.61)	0.001	0.002
Processed fish ⁶	1.00	0.71 (0.49, 1.05)	0.08	0.26 (0.12, 0.59)	0.001	0.015
Fish sandwich ⁷	1.00	0.72 (0.58, 0.89)	0.003	0.44 (0.23, 0.85)	0.014	<0.001
Cod liver oil and fish oil	1.00	0.83 (0.67, 1.03)	0.08	0.41 (0.18, 0.90)	0.027	0.034
Any type of fish or fish oil	1.00	0.63 (0.36, 1.09)	0.10	0.19 (0.07, 0.50)	0.001	<0.001

¹ All values were adjusted for sex, apolipoprotein E $\epsilon 4$ variant allele, education, history of cardiovascular disease, and plasma total homocysteine.

² Multinomial logistic regression (intake of fish product as dichotomous variable).

³ Across all categories, univariate ANOVA.

⁴ Herring, mackerel, salmon, or trout as part of a main meal.

⁵ Cod, coalfish, or haddock as part of a main meal.

⁶ Fish balls, fish cakes, fish fingers, fish stew, fish soup, or fish au gratin as part of a main meal.

⁷ Mackerel, pilchard, pickled herring, anchovies, salmon, or trout as a sandwich spread.

Prevalence of participants who reported eating seafood

The proportion of participants who reported eating fish and fish products and the mean daily fish intake were higher in our population than in populations in previous studies (5, 11, 12). Despite the relatively low fish intake in previous studies, all suggested that fish eaters exhibit better cognitive performance than do noneaters (5, 11, 12). Our study, in a population who reported eating a lot of fish, allowed us to investigate the associations between fish intake and cognition variables in more detail.

Intake of seafood and cognitive test performance

We found that fish eaters had significantly better results on all cognitive tests than did nonconsumers. Most of these associations remained significant after adjustment for several nonnutritional factors (sex, *ApoE* $\epsilon 4$ variant allele, education, history of some important CVD variables, and tHcy) with a proven association with cognition. Moreover, the prevalence of poor scores, independent of the cognitive test used, was significantly lower among those who reported eating than in those who reported not eating fish and fish products.

The population-based Rotterdam Study was one of the first large prospective studies to show that fish consumption is associated with a reduced risk of dementia, particularly of AD (4). The favorable effect of fish consumption was observed at a relatively low intake (from ≈ 20 g/d) (4, 5). Other prospective studies (6–8) showed that subjects who consumed seafood at least once a week had a significantly lower risk of developing dementia or AD in the following 4–7 y. In contrast, an evidence-based study (31) focusing on the role of n–3 fatty acids reported that fish consumption was only weakly associated with a reduced risk of cognitive impairment and had no association with cognitive decline.

The associations between different types of fish and impaired cognitive outcome have been little studied. Huang et al (9) observed that the consumption of fatty fish was associated with a greater reduction in risk of dementia and AD than was eating lean fish. In the present study, the effects of fatty and lean fish intake

on cognitive test performance were comparable. However, when the significance level was restricted to $P < 0.001$ in the multiple-adjusted model, only the association between lean fish intake and the KOLT remained.

In contrast with another study (32), we observed that intake of fish oils had a beneficial effect only on the S-task. In the groups who reported consuming processed fish and fish sandwiches, the associations were inconsistent, possibly because cooking and preparation methods influence the nutritive value of the meal (9). Thus, our most consistent finding was related to total intake of fish and fish products. In line with this, we found that those who reported consuming ≥ 10 g seafood/d were protected against having multiple tests with poor scores. A reduction of up to 80% in the risk of having poor scores on ≥ 4 tests was found in those who reported eating ≥ 10 g seafood/d compared with those who reported eating less or no seafood.

Dose-response relation

Although few subjects never ate seafood, there was a wide span in intake. Using dose-response curves, we observed that the performance on all 6 of the cognitive tests, adjusted for sex, improved with increasing total fish intake up to 70–80 g/d and reached a plateau thereafter. The dose-response relations remained significant in all except the TMT-A and S-task after multiple adjustments, which indicated the robustness of these associations. A dose-response relation was suggested in an earlier study (9), in which the hazard ratio for dementia decreased with the number of servings per week of fatty fish.

Cognitive test abilities

The protective effect of eating fish and fish products extended to almost all of the tested cognitive abilities. Notably, the test of global cognitive ability, the m-MMSE, was frequently not affected by individual types of seafood. However, as with the other tests, a strong dose-response relation was found with the combined intake of any type of fish or fish oil. Few other studies have examined fish intake in relation to specific cognitive abilities in the elderly, but one report described a positive effect of eating

fatty fish on processing speed, but not on tests of memory or flexibility (11). Another study found that the BD and the DST scores were higher in consumers of fish oil (32).

Strengths and limitations of the study

The strengths of this study included a large population-based sample with a relatively high consumption of fish and fish products and inclusion of 6 different tests to study cognitive performance. The food-frequency questionnaire used was validated in several studies, including the correlation between self-reported dietary intake of fish and essential n-3 fatty acids in plasma phospholipids among 579 men and women (25) and 14-d weighed diet records with the intakes calculated from the food-frequency questionnaire in a group of 38 elderly women (24).

One limitation of dietary studies is errors in estimates of nutrients (11, 14, 31). Thus, it is possible to over- or underestimate true associations with outcomes. In addition, lack of a uniform quantification of fish intake makes comparisons between different studies difficult.

Because 77.3% of the study participant volunteered for cognitive testing, recruitment bias may have been an issue. Several differences between those who underwent and who did not undergo cognitive testing were reported earlier (33). However, the dietary habits were similar, and the difference in total fish intake was only 0.3 g/d ($P = 0.91$).

Cognition in the elderly is shaped by long-term exposures (34, 35). Thus, an important limitation of this study was its cross-sectional design. Furthermore, subjects with impaired cognition may have altered their diet as a consequence of a change in their cognitive status, although the direction of such a change is not predictable. In addition, self-reported dietary data collected from subjects who are cognitively impaired or demented may be less reliable. However, participants in the present study were not seriously impaired, and we do not believe this to have a major effect on our findings. Last but not least, foods are not consumed individually but as part of a diet; therefore, confounding by other food items is always an issue in studies using dietary assessments.

Conclusion

In a population-based study, we showed that intake of fish and fish products is associated with better performance across several cognitive abilities and that the associations are strongly dose-dependent. We also observed that the effect depends on the type of fish consumed. Our data indicate the need for additional studies in which more details about the type or species of fish and methods of preparation should be taken into account. Nevertheless, because this and earlier studies have shown that fish intake is associated with better cognition, the next question is what component of fish makes it good for the brain? Studies of n-3 fatty acids (36), niacin (37), and any other factor known to be enriched in fish are needed to answer this question.

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results and contributed to the study design and the writing of the paper. None of the authors had any financial conflicts of interest.

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