Dietary intake of fatty acids and fish in relation to cognitive performance at middle age

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Abstract—*Objective:* To examine the associations of fatty acid and fish intake with cognitive function. *Methods:* Data are from a cross-sectional population-based study among 1,613 subjects ranging from 45 to 70 years old. From 1995 until 2000, an extensive cognitive battery was administered and compound scores were constructed for memory, psychomotor speed, cognitive flexibility (i.e., higher order information processing), and overall cognition. A self-administered food-frequency questionnaire was used to assess habitual food consumption. The risk of impaired cognitive function (lowest 10% of the compound score) according to the energy adjusted intake of fatty acids was assessed with logistic regression, adjusting for age, sex, education, smoking, alcohol consumption, and energy intake. *Results:* Marine omega-3 polyunsaturated fatty acids (PUFA) (eicosapentaenoic acid and docosahexaenoic acid) were inversely related to the risk of impaired overall cognitive function and speed (per SD increase: OR = 0.81, 95% CI 0.66 to 1.00 and OR = 0.72, 95% CI 0.57 to 0.90). Results for fatty fish consumption were similarly inverse. Higher dietary cholesterol intake was significantly associated with an increased risk of impaired memory and flexibility (per SD increase: OR = 1.27, 95% CI 1.02 to 1.57 and OR = 1.26, 95% CI 1.01 to 1.57). Per SD increase in saturated fat intake, the risk of impaired memory, speed, and flexibility was also increased, although not significantly. *Conclusions:* Fatty fish and marine omega-3 PUFA consumption was associated with a reduced risk and intake of cholesterol and saturated fat with an increased risk of impaired cognitive function in this middle-aged population.

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The notion that dietary factors influence cognitive function and subsequently the risk of dementia is growing. Besides the observation that antioxidant intake is associated with a lower risk of dementia,[1] saturated fat and cholesterol intake were found to be associated with a higher risk of dementia.[2-4] However, in a recent prospective study no association between the intake of any fatty acid and dementia or its subtypes was observed.[5] The findings on dietary cholesterol and saturated fat are consistent with some recent studies showing a protective effect of cholesterol-lowering drugs on dementia[6] and with the observed influence of cholesterol on amyloid precursor protein (APP) processing.[7] Furthermore, moderate fish consumption, as a proxy for omega-3 polyunsaturated fatty acid (PUFA) intake, was related to a reduced risk of dementia, in particular Alzheimer disease (AD).[2,8,9] This association may be attributable to several mechanisms, such as an anti-inflammatory effect of omega-3 PUFA, a decrease in the risk of cardiovascular disease, or an increase in the neuroplasticity of nerve membranes.[2,10,11]

Because a preclinical or subclinical phase of declining cognitive function precedes clinically apparent AD by decades,[12] it is important to examine the effect of diet on cognitive impairment at middle age. Population-based studies on dietary fat intake and cognitive function are scarce, especially among the middle aged.[13-17] Here, we examined the relationship between dietary intake of fatty acids and multiple cognitive domains in a cross-sectional population-based study among middle-aged men and women living in the Netherlands.

Materials and methods. *Study population.* Data are from men and women ranging from 45 to 70 years old who participated in the Doetinchem Cohort Study (DCS). The baseline measurements for this study were carried out between 1987 and 1991, and were part of a monitoring project on cardiovascular disease risk factors.[18,19] Each year a random sample (stratified by 5-year age classes and sex) was drawn from the municipal registry and invited for the study. A total of over 12,000 men and women were examined, and response rate for the age group of 45 years and older was 68%. In 1993–1997 and 1998–2002, there was a re-examination of a random sample of the 1987–1991 participants (response rate 75%). Nonrespondents more often had a low socio-

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economic status and more often smoked at baseline, but the associations between lifestyle factors and health status were not influenced by differential response.[20] Between 1995 and 2000, cognitive function was measured once in each participant aged 45 years or older. The study was approved by the Medical Ethics Committee of TNO Zeist. All participants signed an informed consent.

Dietary assessment. Concurrent to the cognitive testing, a self-administered food frequency questionnaire was administered to assess the habitual consumption of 178 food items during the previous year.[21] Briefly, frequency of consumption could be indicated as times per day, per week, per month, per year, or as never. For 28 food items, questions referred to portion sizes in color photographs. For other foods, commonly used units or portion sizes were specified. The questionnaire also included open-ended questions on brand names of fats used on bread and for cooking, and closed questions on the use of special diets and supplements. The validity of the food frequency questionnaire was examined among 121 participants with 12 monthly 24-hour recalls as reference method.[21] The Pearson correlation coefficients (energy-adjusted and corrected for intraindividual variation in 24-hour recalls) were 0.61 for fat and 0.32 for fish among men, and 0.63 for fat and 0.37 for fish among women. In general, the food frequency questionnaire was valid and adequate for ranking subjects according to energy and macronutrient intake.[21] Nutrient intake was calculated by multiplying the frequency of a certain food consumption by the portion size and the nutrient content per gram. Information on nutrient content of foods was derived from an extended version of the 1996 Dutch Food Composition Table (NEVO), supplemented with information from the 2001 Dutch Food Composition Table (NEVO) for omega-3 and omega-6 PUFA.

For the present study we used data on intake of fatty fish, total fat, saturated fat, cholesterol, monounsaturated fatty acids (MUFA), PUFA, the most important omega-6 PUFA (linoleic acid), and the three most important omega-3 PUFA (docosahexaenoic acid [DHA], eicosapentaenoic acid [EPA], and α-linolenic acid). Important sources of saturated fat are meat, dairy products, and baked goods; cholesterol is only present in animal products; MUFA is present in margarines, olive oil, dairy products, and meat; linoleic acid is particularly found in vegetable oils; the marine omega-3 PUFA are present in fatty fish, such as salmon, tuna, and mackerel; and α-linolenic acid is present in margarines, some oils and nuts, and green leafy vegetables. Total fat and MUFA intake were most highly correlated (Spearman correlation coefficient 0.89) and total fat and MUFA were both correlated to saturated fat intake ($r = 0.76$ and $r = 0.59$). All other correlation coefficients between fatty acids were below 0.50.

Assessment of cognitive function. Cognitive function was assessed using a neuropsychological test battery measuring global cognitive function and specific cognitive domains, such as memory function, speed of cognitive processes, and cognitive flexibility, which consisted of higher order information processing and complex speed tasks.[22-24] The tests used were the (Visual) Verbal Learning Test, the Concept Shifting Task, an abbreviated Stroop Color Word Test consisting of three subtasks, the Letter Digit Substitution Test, and a Category Fluency Test, in which as many animals as possible had to be named within 60 seconds. A detailed description of these tests can be found elsewhere.[22] These tests are sensitive to subcortical dysfunction and robust in detecting age-related impairment, even at middle age, because they have no ceiling effect.[25] They have been used in other large-scale studies on cognitive function.[24,26] Cognitive tests were carried out by trained investigators and took about 20 minutes to complete. In total, 1,667 subjects performed all cognitive tests.

The scores on the timed tests (Stroop and Concept Shifting Task) were log transformed first, because they were not normally distributed. Raw data were made comparable by transforming them into a standardized Z-score (the difference between each test score and the average score, divided by the SD of that score). Compound scores were computed to reduce the number of psychometric variables and improve the robustness of the underlying test construct. Tests were combined based on their conceptual coherence derived from neuropsychological practice in performance testing. We calculated compound scores for psychomotor or simple speed, by averaging the Z-scores of the 0, A, and B versions of the Concept Shifting Task and subtask I of the Stroop. To calculate a compound score for memory function the Z-scores of the total, maximal, and delayed recall scores of the Verbal Learning Test were averaged. For cognitive flexibility the average of the Z-scores of the C-version of the Concept Shifting Task and subtask III of the Stroop was calculated. As a reflection of global cognitive function the average of the Z-scores of the subtask III of the Stroop, the Letter Digit Substitution Task, the Word Fluency test, and the total and the delayed recall score of the Verbal Learning Test was calculated.

Other measurements. In all examinations, participants received a self-administered questionnaire at home and were invited to come to the research center for medical examinations. The self-administered questionnaire contained questions on demographic variables, lifestyle factors, (family) history of diseases, and medication use. The questionnaire was checked at the research center by trained staff. Level of education was assessed as the highest level achieved and classified into five categories: primary school, junior (vocational) education, secondary (vocational) education, vocational colleges, and university. Smoking status was assessed with a standard questionnaire and classified as current, former, and never smoking.[22] Alcohol consumption was measured with a standardized questionnaire as the number of drinks per day.

Self-reported history of myocardial infarction, cerebrovascular accident, and diabetes was recorded. During a physical examination at the research center, height and weight were measured. Body mass index (BMI) was calculated as weight (kg) divided by height squared (m^2). Blood pressure was measured twice at the left arm with a random-zero sphygmomanometer while the subject was seated. For the analyses the average of the two blood pressure measurements was taken.

Nonfasting blood samples were obtained using a standardized protocol. Plasma total and high density lipoprotein (HDL) cholesterol were determined at the Clinical Chemistry Laboratory of the University Hospital 'Dijkzigt' in Rotterdam, which is the Lipid Reference Laboratory for standardized cholesterol determinations in the Netherlands. Total cholesterol was determined enzymatically, using a Boehringer test kit.[27] HDL lipoproteins were determined after precipitation of apo B containing lipoproteins with magnesium phosphotungstate.[28]

Statistical analysis. Complete data on cognitive function, dietary intake, and confounders were available for 1,613 subjects. Impairment in overall cognitive function, speed, flexibility, and memory was defined as the lowest 10% of the compound Z-score. To obtain dietary factors that were uncorrelated with total energy intake, we calculated the energy-adjusted values according to the residual method for total, saturated, monounsaturated, and polyunsaturated fat intake.[29] Multivariable logistic regression was used with cognitive impairment as dependent variable and the dietary fatty acids as independent variables. Confounders that were taken into account were age (continuous), sex, education (five categories), smoking (current, former, never), alcohol consumption (glasses/day), and total energy intake. To examine possible nonlinearity the quadratic term of daily nutrient intake was entered into the model.

We additionally adjusted for other possible confounders, such as vitamin E, vitamin C, and beta-carotene intake, and for possible mediating variables, i.e., BMI, total and HDL cholesterol level, and systolic blood pressure. A history of cardiovascular disease, including diabetes mellitus, was also entered into the model as possible mediating factor. Furthermore, we excluded subjects who scored in the lowest 5% of the memory score, to examine whether an impaired memory influenced the report of the diet and thereby the results. We repeated the analyses after excluding non-fish consumers to investigate whether unknown confounders associated with consuming fish influenced the results. We also excluded subjects on a cholesterol-lowering diet and adjusted for the use of cholesterol-lowering drugs to examine whether this influenced our findings. We checked whether age (dichotomized above and below 65 years), sex, or a history of cardiovascular disease modified the associations, by putting interaction terms in the models. Finally, we tested for interaction between vitamin E intake and the omega-3 and omega-6 PUFA, because vitamin E can reduce the unfavorable oxidation of unsaturated fatty acids. The SAS computer package (version 8.1) was used for all statistical analyses (SAS Institute Inc., Cary, NC).

Table 1 *Adjusted* levels of baseline characteristics according to normal or impaired (lowest 10%) cognitive functioning*

Characteristics	Overall cognition		
	Normal, n = 1,450	Impaired, n = 163	*p* Value for difference
Age, y	56.2 (55.9–56.6)	59.4 (58.3–60.5)	<0.001
Men	46.9	58.6	0.006
Higher education	20.8	4.5	<0.001
Alcohol consumption, units/day	1.3 (1.2–1.4)	1.1 (0.8–1.3)	0.09
Current smokers	25.2	21.2	0.28
Systolic blood pressure, mm Hg	132.6 (131.7–133.6)	132.0 (129.3–134.7)	0.66
BMI, kg/m^2	26.4 (26.2–26.6)	25.9 (25.3–26.5)	0.13
Serum cholesterol, mmol/L	5.9 (5.9–6.0)	5.9 (5.8–6.1)	0.86
History of cardiovascular disease	4.3	8.1	0.04

Values are % or adjusted mean (95% CI).

* Adjusted for age, sex, and education where applicable.

BMI = body mass index.

Results. Mean age of the participants was 56.3 (SD = 7.1) years; 48.0% were men, and 11.7% had primary education only. Subjects with the highest total fat and cholesterol intake were slightly younger (56.0 [SD = 6.9] in the highest versus 56.9 [SD = 7.3] in the lowest fat intake quartile, $p = 0.04$). The proportion of men was lower among those with the highest energy-adjusted total and saturated fat intake (48% in highest versus 61% in lowest fat intake quartile, $p < 0.001$), but higher among those with the highest cholesterol intake ($p < 0.001$). Subjects with a high total fat, saturated fat, and cholesterol intake more often had primary education only, whereas those with a high fatty fish consumption less often had primary education only (6.0% in the highest versus 22.4% in the lowest fish consumption category, $p = 0.003$). After adjustment for age, sex, and education (where applicable), subjects with impaired cognitive function were older and more often men, they more often had a history of cardiovascular disease, and were less often highly educated (table 1). The adjusted mean daily intake of fatty fish and the marine omega-3 PUFA (EPA and DHA) was lower among subjects with impairment in overall cognition (table 2).

To examine whether subjects with cognitive impairment had changed their (report of their) diet in the 6 years prior to cognitive testing as a result of their impairment, we analyzed the previous change in dietary intake in those who were cognitively impaired and those who were not, adjusting for age, sex, and education (table 3). Information on change in dietary intake and cognitive function was available for 1,209 subjects. Overall, these subjects had increased their intake of total fat, saturated fat, MUFA, PUFA, and fatty fish and reduced their cholesterol intake

Table 2 *Adjusted* mean levels of daily nutrient intake according to normal or impaired (lowest 10%) cognitive functioning*

Mean daily intake	Overall cognition		*p* Value for difference
	Normal, n = 1,450	Impaired, n = 163	
Total fat, g†	84.0 (83.4–84.7)	84.8 (83.0–86.7)	0.43
Saturated fat, g†	35.2 (34.8–35.5)	35.3 (34.4–36.3)	0.71
MUFA, g†	31.5 (31.3–31.8)	31.6 (30.8–32.4)	0.91
PUFA, g†	16.7 (16.4–16.9)	17.2 (16.6–17.9)	0.12
Linoleic acid, g†	13.2 (13.0–13.5)	13.8 (13.2–14.5)	0.09
EPA and DHA, mg‡	167 (160–175)	145 (124–166)	0.05
α-Linolenic acid, mg‡	1137 (1114–1160)	1103 (1036–1171)	0.35
Cholesterol, mg	234 (230–238)	235 (222–247)	0.94
Fish, g	11.01 (10.45–11.57)	9.84 (8.19–11.49)	0.19
Fatty fish, g	3.06 (2.85–3.28)	2.30 (1.68–2.93)	0.03

Values are adjusted mean (95% CI).

* Adjusted for age, sex, and education.
† Energy adjusted according to the residual method.
‡ Omega-3 polyunsaturated fatty acid (PUFA).

MUFA = monounsaturated fatty acid; EPA = eicosapentaenoic acid; DHA = docosahexaenoic acid.

Table 3 *Adjusted* mean change in daily intake of selected nutrients in the 6 years prior to measuring cognitive function in a subsample*

	Overall cognition	
6-Year change in intake/day	Normal, n = 1,087	Impaired,† n = 122
Total fat, g‡	2.15 (1.39; 2.92)	0.99 (−1.28; 3.25)
Saturated fat, g‡	1.0 (0.65; 1.41)	0.17 (−0.95; 1.28)
MUFA, g‡	0.87 (0.53; 1.21)	0.39 (−0.61; 1.39)
PUFA, g‡	0.50 (0.22; 0.79)	0.93 (0.10; 1.76)
Cholesterol, mg	−7.3 (−11.8; −2.9)	−5.8 (−18.9; 7.3)
Fatty fish, g	0.12 (0.10; 0.14)	0.13 (0.07; 0.19)

Values are adjusted mean change (95% CI).

* Adjusted for age, sex, and education.
† Lowest 10% in the overall cognitive score; there were no significant differences in dietary change between subjects with normal and impaired cognition.
‡ Energy adjusted according to the residual method.

in the 6 years prior to cognitive testing, but the changes were not significantly different for subjects with and without cognitive impairment.

Logistic regression analyses after adjustment for age, sex, education, alcohol consumption, smoking, and energy intake showed that per SD increase in saturated fat intake the risk of impairment in memory, speed, and flexibility was increased by 15% to 19%, although this was not significant (table 4). Higher dietary cholesterol intake was significantly associated with an increased risk of impaired memory and flexibility (OR = 1.27 and 1.26). Per SD increase in marine omega-3 PUFA (EPA and DHA) intake, the risk of impaired overall cognitive function and speed was decreased by 19% and 28% (OR = 0.81, 95% CI 0.66 to 1.00 and OR = 0.72, 95% CI 0.57 to 0.90). Results for fatty fish consumption were inverse as well. There was no clear association between the intake of total PUFA, linoleic acid, α-linolenic acid, and MUFA and cognitive function.

The quadratic term of cholesterol was significant for the relation between cholesterol intake and overall cognition, speed, and flexibility. When we categorized cholesterol intake into quartiles there was a slight J-shaped association with a tendency to a lower risk in the second and third compared to the first quartile, and an increased risk in the highest quartile (results not shown).

Additional adjustment for possible intermediate cardiovascular risk factors, i.e., serum (HDL) cholesterol, systolic blood pressure, and BMI, did not attenuate the observed associations. Adjustment for a history of cardiovascular disease did not change the associations either. When we excluded subjects who scored in the lowest 5% of the memory domain results were similar or even stronger. Exclusion of people who did not eat fish (n = 116) or who were on a cholesterol lowering diet or adjustment for the use of cholesterol lowering drugs did not change the findings. We also adjusted for weight loss as indicator of underlying disease, which did not alter the results. Finally, age, sex, vitamin E, or a history of cardiovascular diseases did not clearly modify the above associations.

Discussion. This population-based study among middle-aged men and women showed that dietary cholesterol and to a lesser extent saturated fatty acid intake were associated with an increased risk of impaired cognitive function, whereas fatty fish and EPA and DHA consumption were associated with a decreased risk of cognitive impairment. These associations were independent of differences in age, sex, education, smoking, total energy intake, and cardiovascular risk factors. MUFA, total PUFA, linoleic acid, α-linolenic acid, and total fat intakes were not clearly related to cognitive function.

Measurement error is always an issue in studies using dietary assessments. Nonetheless, this mea-

Table 4 *Adjusted OR for the risk of impaired cognitive function (lowest 10%) according to one SD increase in fatty fish and fatty acid intake (n = 1,613)*

		Risk of impairment in:			
Intake/d	SD	Overall cognition	Speed	Memory	Flexibility
Total fat, g	11.6	1.04 (0.87–1.25)*	1.06 (0.88–1.27)	1.18 (0.99–1.41)	1.06 (0.89–1.27)
Saturated fat, g	5.9	1.01 (0.84–1.20)	1.18 (0.98–1.41)	1.15 (0.97–1.37)	1.19 (0.99–1.42)
MUFA, g	5.2	1.00 (0.84–1.20)	0.97 (0.81–1.17)	1.16 (0.98–1.38)	0.97 (0.81–1.16)
PUFA, g	4.2	1.10 (0.93–1.29)	0.98 (0.83–1.16)	1.07 (0.91–1.25)	0.97 (0.82–1.14)
Linoleic acid, g	4.0	1.10 (0.94–1.29)	0.96 (0.81–1.13)	1.04 (0.89–1.22)	0.97 (0.82–1.14)
EPA and DHA, mg†	134	0.81 (0.66–1.00)‡	0.72 (0.57–0.90)‡	1.01 (0.85–1.20)	0.86 (0.71–1.05)
α-Linolenic acid, mg†	445	0.82 (0.64–1.05)	1.13 (0.90–1.43)	1.00 (0.79–1.25)	0.96 (0.76–1.22)
Cholesterol, mg	79.8	1.00 (0.80–1.26)	1.14 (0.91–1.43)	1.27 (1.02–1.57)‡	1.26 (1.01–1.57)‡
Fatty fish, g	4.0	0.77 (0.60–0.97)‡	0.71 (0.55–0.92)‡	0.95 (0.80–1.13)	0.93 (0.77–1.12)

* OR (95% CI), adjusted for age, sex, education (five categories), alcohol consumption, smoking (current, former, never), and total energy intake.
† Omega-3 PUFA.
‡ $p < 0.05$.

MUFA = monounsaturated fatty acid; PUFA = polyunsaturated fatty acid; EPA = eicosapentaenoic acid; DHA = docosahexaenoic acid.

surement error is most likely random, which would result in regression dilution bias, suggesting the true association would only be stronger than the observed association.[30]

One of the major limitations of this study is that it is cross-sectional. A methodologic problem when studying the relationship between diet and cognitive impairment is that dietary data collected from subjects who are cognitively impaired or demented may be less reliable. Furthermore, subjects with cognitive impairment or dementia may have altered their diet as a consequence of the disease. This is especially an issue in cross-sectional studies. When we redid the analyses after exclusion of subjects who scored in the lowest 5% of the memory score results were similar and even slightly stronger. Furthermore, subjects with cognitive impairment (lowest 10% of the Z-score) did not change their (report of their) diet in a different way than those with normal cognitive function in the 6 years prior to cognitive testing. Finally, the majority of our study population was <65 years and their cognitive function was still relatively preserved, which makes a change in (the report of) diet due to cognitive impairment less likely. Nonetheless, a causal relationship cannot be inferred and the possibility of information bias is present.

We had no information on some possibly interesting factors. It would have been valuable to have plasma levels of fatty acids as well, because this can be regarded as an integrated measure of medium-term dietary intake, absorption, and individual biologic response and therefore may better reflect the overall impact of the different fatty acids, especially when used in combination with dietary intake.[31] Furthermore, we could not examine modification by the apolipoprotein E gene, which may have been interesting because responsiveness to dietary fat may differ per allele.[3,32]

One of the strengths of our study is that we used an extensive cognitive battery including tests that are sensitive to small cognitive changes at middle age. We investigated the association with scoring in the lowest decile of the cognitive function distribution. This cut-off point has been used in previous studies as well and yielded more power than a cut-off of, e.g., 1.5 SD. Besides, because the scores were not normally distributed, a percentual cut-off is more appropriate. The observed association will probably have no functional significance yet, because participants were middle aged and had only subtle impairments. However, the effect of eating 80 mg more cholesterol/day on cognitive flexibility for example was similar to the effect of being approximately 3 years older. In addition, these impairments are likely to represent the prodromes of dementia in at least a part of the study population.[12] Various studies showed that subjects with mild cognitive impairment progressed to dementia or AD at a rate of 10 to 15% per year, and that the risk of dementia was higher when rate of decline was higher.[33] Therefore the association with fatty acids is expected to become clinically important at old age, which is indeed suggested by some previous studies on fatty acids and dementia.[2,8,9] Furthermore, this study contained information on most specific fatty acids, such as the marine omega-3 PUFA, α-linolenic acid, and the omega-6 PUFA, linoleic acid, and on important confounders.

Few epidemiologic studies have reported on the relation between the consumption of fatty acids and fish and cognition. Previous cross-sectional studies showed inconsistent findings for MUFA and (saturated) fat intake, but a positive association between dietary cholesterol and cognitive impairment.[14-17] Prospective data from the Zutphen Elderly Study showed that moderate fish consumption was associated with a decreased risk of cognitive decline.[13] Recently, a few prospective population-based studies have examined this issue in relation to dementia.[2-5,8,9] Overall, a number of these studies found that fish consumption was inversely related to the risk of incident dementia or AD,[2,8,9] whereas a high intake of total fat, saturated fat, or cholesterol was found to be associated with a decreased risk.[2-4]

The most consistent findings from epidemiologic and clinical studies so far seem to be that cholesterol and (saturated) fat are positively and fish and marine omega-3 PUFA inversely associated with dementia and cognitive impairment. The results of the present study, which is the only one among primarily middle-aged subjects, are in line with these findings.

Cardiovascular diseases have been related to an increased risk of cognitive impairment.[34] A high dietary intake of cholesterol and saturated fat increases the risk of cardiovascular diseases and atherosclerosis, and thus possibly also of cognitive impairment, whereas omega-3 PUFA may be inversely associated with impaired cognitive function because they lower the risk of cardiovascular disease, including stroke.[10,11,35] Adjustment for a history of cardiovascular disease or cardiovascular risk factors, however, did not attenuate the observed associations.

Fish and the marine omega-3 PUFA were predominantly associated with processing speed, which has been found to be one of the early preclinical signs of AD.[36] Marine omega-3 PUFA may affect speed and cognition through inflammation, because they act as anti-inflammatory agents by inhibiting the synthesis of cytokines and mitogens.[37] Neuropathologic and epidemiologic evidence is accumulating that inflammatory processes, perhaps induced by β-amyloid peptides, are involved in the pathogenesis of cognitive decline[38] and AD.[39] Further hypotheses on the effect of marine omega-3 PUFA concern membrane fluidity, neurotransmission, and synaptic plasticity.[40]

Our finding that high cholesterol was associated with impaired cognitive function is in accord with the results of animal studies showing that a high cholesterol diet leads to accumulation of β-amyloid in the brain, which consequently leads to the formation

of the amyloid plaques that are pathognomonic for AD.[7,41] It has been suggested, however, that cholesterol is synthesized locally in the brain and only little is taken up from the plasma.[7] In contradiction, a population-based autopsy study found a linear positive relationship of plasma HDL cholesterol levels to neocortical neuritic plaques and neurofibrillary tangles, another pathologic hallmark of AD.[42]

Although cognitive impairment in this population was mild, it may represent a prodromal phase of dementia.[12] Whether dietary changes are not only able to reduce the risk of cardiovascular disease, but also of neurodegenerative disorders, such as dementia, remains to be determined.

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