Consumption of Fish and n-3 Fatty Acids and Risk of Incident Alzheimer Disease

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Background: Dietary n-3 polyunsaturated fatty acids improve brain functioning in animal studies, but there is limited study of whether this type of fat protects against Alzheimer disease.

Objective: To examine whether fish consumption and intake of different types of n-3 fatty acids protect against Alzheimer disease.

Design: Prospective study conducted from 1993 through 2000, of a stratified random sample from a geographically defined community. Participants were followed up for an average of 3.9 years for the development of Alzheimer disease.

Patients: A total of 815 residents, aged 65 to 94 years, who were initially unaffected by Alzheimer disease and completed a dietary questionnaire on average 2.3 years before clinical evaluation of incident disease.

Main Outcome Measure: Incident Alzheimer disease diagnosed in a structured neurologic examination by means of standardized criteria.

Results: A total of 131 sample participants developed Alzheimer disease. Participants who consumed fish once per week or more had 60% less risk of Alzheimer disease compared with those who rarely or never ate fish (relative risk, 0.4; 95% confidence interval, 0.2-0.9) in a model adjusted for age and other risk factors. Total intake of n-3 polyunsaturated fatty acids was associated with reduced risk of Alzheimer disease, as was intake of docosahexaenoic acid (22:6n-3). Eicosapentaenoic acid (20:5n-3) was not associated with Alzheimer disease. The associations remained unchanged with additional adjustment for intakes of other dietary fats and of vitamin E and for cardiovascular conditions.

Conclusion: Dietary intake of n-3 fatty acids and weekly consumption of fish may reduce the risk of incident Alzheimer disease.

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A primary component of membrane phospholipids in the brain is the n-3 polyunsaturated fatty acid, docosahexaenoic acid (DHA; 22:6n-3). High levels of DHA are found in the more metabolically active areas of the brain, including the cerebral cortex, mitochondria, synaptosomes, and synaptic vesicles. Fish is a direct dietary source of preformed DHA. In addition, DHA is synthesized endogenously through a process of desaturation and elongation of its precursor n-3 fatty acids, α-linolenic acid (18:3n-3) and eicosapentaenoic acid (EPA; 20:5n-3).

In laboratory studies, animals fed diets enriched with n-3 polyunsaturated fatty acids had better regulation of neuronal membrane excitability, increased levels of neurotransmitters and higher density of neurotransmitter membrane receptors, increased hippocampal nerve growth, greater fluidity of synaptic membranes, higher levels of antioxidant enzymes, decreased levels of lipid peroxides, reduced ischemic damage to neurons, and increased cerebral blood flow. In behavioral models, animals fed diets enriched with n-3 fatty acids had superior learning acquisition and memory performance over animals fed control diets.

Epidemiologic investigation of dietary n-3 fatty acids and Alzheimer disease is limited. One case-control study reported that n-3 fatty acid levels in plasma phospholipids of patients with Alzheimer disease were 60% to 70% of levels found in age-matched control subjects. Two prospective studies found that fish consumption was inversely associated with...
risk of incident Alzheimer disease.33,34 We examined whether fish consumption and intake of DHA and other n-3 fatty acids were associated with protection against Alzheimer disease in a biracial community.

METHODS

POPULATION

Participants were from the Chicago Health and Aging Project, a population-based study of risk factors for incident Alzheimer disease.35 In a 1993 to 1997 census of a south-side Chicago, Ill, community, 8501 residents 65 years and older were identified, of whom 6138 (78.8% of 7813 surviving residents) participated in 90-minute interviews that included the administration of 4 cognitive tests.36-39 The study population was 62% black, 38% white, and 61% female, with a mean educational level of 11.8 years.

Subsequent to the population interview, 1056 participants were randomly selected for clinical evaluation of prevalent Alzheimer disease, and 729 of them were evaluated (76% of 961 surviving residents). Sample selection was within strata defined by age, sex, race, and cognitive performance (good, intermediate, or poor). This phase of the study identified a cohort of 3838 unaffected persons to follow up for incident disease. The disease-free cohort consisted of 3352 persons who had good performance on the baseline cognitive tests, and 486 whose cognitive performance was intermediate or poor but who were unaffected by Alzheimer disease at the baseline clinical evaluation.

Three years after the baseline interview, all participants were recontacted for follow-up interviews, and 4320 participated (86.7% response among 4983 survivors). A second random sample stratified by age, sex, race, and decline in cognitive performance (no, small, or large decline) was selected from the disease-free cohort for clinical evaluation of incident Alzheimer disease. Random selection occurred with different sampling probabilities within the strata to ensure that persons most likely to have Alzheimer disease were sampled and that a sufficient number of comparable persons who were unaffected were also selected. Of the 1249 selected, 842 persons agreed to participate (73.9% of 1140 survivors), and 815 had complete data for the analysis of fish consumption and incident disease.

The institutional review board of Rush-Presbyterian-St Luke’s Medical Center approved the study, and all participants (or legal guardian) gave written consent. Descriptions of the population interviews40 and clinical evaluations39 have been published previously.

DIETARY ASSESSMENT

Diet was assessed on average 1.9 years after baseline (or 2.3 years before the clinical evaluations) by means of a modified Harvard self-administered food frequency questionnaire (FFQ).41 The FFQ was distributed to participants along with a self-addressed envelope for its return. The 154-question FFQ (139 food items) included 4 seafood items (tuna fish sandwich, fish sticks/fish cakes/fish sandwich, fresh fish as a main dish, and shrimp/lobster/crab). Other questions inquired about use of vitamin supplements, specific brand names of cereals and margarines, type of cooking oil, and fat preferences for milk and meat products that were used in the computation of nutrient intake. Nutrient intake was obtained by multiplying the nutrient content of individual food items by the frequency of consumption and summing over all items. Nutrient content of individual food items was based on the Harvard University Nutrient Composition Database, which is continually updated through the US Department of Agriculture sources,42 along with selected individual publications. For analysis, estimated intake levels of all nutrients and fats were energy-adjusted by means of the regression residual method.43 Total n-3 fatty acid intake was based on the sum of 18:3n-3 (α-linolenic acid), 20:5n-3 (EPA), 22:5n-3, and 22:6n-3 (DHA). Weekly consumption of fish was computed by summing the responses to frequency of intake for the 3 fish items.

In a reproducibility and validity study of randomly selected Chicago Health and Aging Project participants, Spearman rank correlation coefficients between 2 FFQs completed approximately 1 year apart for 139 persons were 0.55 for total intake of n-3 fatty acids, 0.58 for DHA intake, and 0.44 for EPA intake (all P < .001). Pearson correlation coefficient was 0.33 (P = .01) between plasma levels of marine n-3 fatty acids and the FFQ in 56 participants.

CLINICAL EVALUATION FOR INCIDENT ALZHEIMER DISEASE

Alzheimer disease was diagnosed on the basis of structured neuropsychological clinical evaluations that were conducted in participants’ homes by a team consisting of a neurologist, a nurse practitioner, a phlebotomist, and a neuropsychological technician. The evaluations included a complete medical history and neuropsychological examination, medication use, neuropsychological testing (using the tests of the Consortium Established for Research on Alzheimer’s Disease44 and others36,45-51), informant interviews for cognitively impaired individuals, and laboratory testing. Diagnostic use of magnetic resonance imaging was restricted to persons with evidence of dementia and uncertainty as to whether a stroke had occurred or was related to the dementia. A board-certified neurologist, blinded to participants’ dietary information, reexamined each patient and reviewed all clinical data. The diagnosis of probable Alzheimer disease was based on criteria of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer’s Disease and Associated Disorders Association.52 For analyses, the definition included all cases of Alzheimer disease, including 14 cases with a coexisting dementing condition. Demented persons without Alzheimer disease (n = 11) were analyzed as noncases. Apolipoprotein E genotyping was conducted by methods of Hixson and Vernier53 and the primers described by Wenham et al.54

COVARIATES

Race questions and categories were those used by the 1990 US census. Age was computed from self-reported birth date and date of disease-free status. All nondietary variables except clinical stroke were obtained at the baseline population interview, which included interviewer inspection of all medications taken within the previous 2 weeks. Level of education was computed from self-reported highest grade or years of formal education. History of hypertension was defined as antihypertensive medication use or participant report of high blood pressure. Heart disease was defined as self-reported history of heart attack, use of digitalis, or evidence of angina pectoris based on participant responses to a standardized questionnaire.55 History of stroke was defined as probable or possible stroke as diagnosed at the clinical evaluation by a neurologist on the basis of a uniform, structured examination, medical history, and magnetic resonance imaging diagnostic testing.

STATISTICAL METHODS

We used logistic regression programmed in SAS56 to generate odds ratios as estimates of the relative risk of incident Alzheimer disease. All statistics and models were weighted for the strati-
FISH CONSUMPTION

Fish consumption was inversely associated with the risk of incident Alzheimer disease. The age-adjusted relative risks for at least weekly fish consumption were in the protective direction but not statistically significant. These became stronger and statistically significant with additional control for other risk factors, including sex, race, education, presence of the APOE-ε4 allele, and total energy intake (Table 2). Persons who consumed 1 fish meal per week or more than 1 fish meal per week had 60% less risk of Alzheimer disease than did persons who reported eating fish rarely or never (for both groups, relative risk, 0.4; 95% confidence interval, 0.2-0.9). Because of the possibility that persons with cardiovascular conditions increased their fish intake as a preventive measure (see Table 1), we reanalyzed the data after excluding weekly fish consumers who reported that they ate more fish now than 10 years previously. The association was more protective in this restricted group (n=641). In the multivariable model with additional adjustment for histories of stroke, heart disease, and hypertension, the relative risk was 0.4 (95% confidence interval, 0.2-0.9) for 1 fish meal per week and 0.3 (95% confidence interval, 0.1-0.6) for 2 or more per week when compared with nonconsumers.

n-3 FATTY ACID INTAKE

Total intake of the n-3 polyunsaturated fatty acids was inversely and linearly associated with risk of incident Alzheimer disease in both the age- and multivariable-adjusted models (in each model, P for linear trend = .01) (Table 3). Persons in the top fifth of intake had a statistically significant 70% reduction in risk compared with persons in the lowest fifth of intake with adjustment for age. The relative risk was slightly modified in the multivariable model but remained statistically significant.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>n-3 Fatty acid, range, g/d</td>
<td>0.37-1.05</td>
<td>1.06-1.22</td>
<td>1.23-1.39</td>
<td>1.40-1.60</td>
<td>1.61-4.10</td>
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<td>Age, mean, y</td>
<td>73.0</td>
<td>73.6</td>
<td>72.6</td>
<td>73.5</td>
<td>72.7</td>
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<td>Sex, % F</td>
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<td>59.2</td>
<td>61.2</td>
<td>62.8</td>
<td>48.0</td>
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<td>52.3</td>
<td>53.5</td>
<td>52.4</td>
<td>50.3</td>
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<td>Education, mean, y</td>
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<td>12.3</td>
<td>12.6</td>
<td>12.7</td>
<td>13.2</td>
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<td>APOE-ε4 allele, % with ≥1 allele</td>
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<td>34.0</td>
<td>37.0</td>
<td>44.9</td>
<td>27.6</td>
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<td>Vitamin E, mean, IU/d†</td>
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<td>65</td>
<td>75</td>
<td>60</td>
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<td>18.7</td>
<td>19.0</td>
<td>19.2</td>
<td>19.9</td>
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<td>Monounsaturated fat, mean, g/d†</td>
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<td>21.2</td>
<td>21.8</td>
<td>22.8</td>
<td>24.7</td>
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<td>n-6 Polyunsaturated fat, mean, g/d†</td>
<td>7.4</td>
<td>10.0</td>
<td>10.9</td>
<td>12.2</td>
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<td>trans-Unsaturated fat, mean, g/d†</td>
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<td>2.9</td>
<td>3.1</td>
<td>3.2</td>
<td>3.8</td>
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<td>Hypertension, %</td>
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<td>65.1</td>
<td>58.0</td>
<td>67.2</td>
<td>68.0</td>
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<tr>
<td>Heart disease, %</td>
<td>21.4</td>
<td>12.5</td>
<td>18.2</td>
<td>14.4</td>
<td>20.7</td>
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<tr>
<td>Stroke, %</td>
<td>10.0</td>
<td>8.3</td>
<td>8.6</td>
<td>6.2</td>
<td>6.7</td>
</tr>
</tbody>
</table>

Abbreviation: APOE, apolipoprotein E.

*All but age are age standardized to the total sample by 5-year age groups (65-74 years, 75-79 years, 80-84 years, 85+ years). Means and percentages are weighted for the stratified sampling design.

†Energy-adjusted by means of the regression-residual method separately within sex.
There was also a linear protective association with intake of DHA (22:6n-3). The inverse relative risks were more protective than for total n-3 fatty acid intake, with statistically significant 60% to 80% reductions in risk for the upper 3 quintiles in the multivariable model. The range of intake of EPA (20:5n-3) was low, with 40% of participants consuming 0 g/d. Therefore, we compared the risk of Alzheimer disease for persons in each of the top three quintiles of intake for DHA, EPA, and Linolenic (18:3n-3) against the lowest intake quintile. The relative risk of Alzheimer disease was lowest in the highest intake quintile of all three n-3 fatty acids.

### Table 2. Relative Risk of Incident Alzheimer Disease (AD) by Frequency of Fish Consumption Among 815 Participants With 3.9 Years of Follow-up, Chicago Health and Aging Project, 1993-2000

<table>
<thead>
<tr>
<th>Frequency of Intake</th>
<th>P Value for Trend*</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of subjects</td>
<td></td>
</tr>
<tr>
<td>Incident AD cases</td>
<td></td>
</tr>
<tr>
<td>Weighted %‡</td>
<td></td>
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<tr>
<td>Relative risk (95% confidence interval)</td>
<td></td>
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<tr>
<td>Age adjusted‡</td>
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<tr>
<td>Multivariable‡</td>
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</table>

Abbreviation: APOE, apolipoprotein E.

*P value for linear trend is based on a logistic regression model with fish consumption modeled as a continuous variable with all persons in a category assigned a fraction of weekly consumption: 0 (never), 0.56 (1-3 times per month), 1.54 (once per week), and 3.01 (2+ times per week).

†Weighted percentages of AD cases adjusted for the stratified sampling design.

‡Age-adjusted models include terms for age (years), period of observation (years), and indicator variables for fish consumption 1 to 3 times per month, once per week, and 2 or more times per week. Multivariable relative risks are based on logistic regression models with terms from the age-adjusted model plus sex, race (black or white), education (years), total energy intake, APOE-ε (any ε4 vs none), and race × APOE-ε4 interaction.

### Table 3. Relative Risks for Incident Alzheimer Disease (AD) by Quintile of Intake of n-3 Fatty Acids, Docosahexaenoic Acid (DHA), and Eicosapentaenoic Acid (EPA) Among 815 Persons After 3.9 Years of Follow-up, Chicago Health and Aging Project, 1993-2000

<table>
<thead>
<tr>
<th>Quintiles of Intake</th>
<th>P Value for Trend*</th>
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<tbody>
<tr>
<td>Total n-3 fatty acids</td>
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</tr>
<tr>
<td>Median, g/d</td>
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<tr>
<td>Incident AD cases</td>
<td></td>
</tr>
<tr>
<td>Weighted %†</td>
<td></td>
</tr>
<tr>
<td>Relative risk (95% confidence interval)</td>
<td></td>
</tr>
<tr>
<td>Age adjusted‡</td>
<td></td>
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<td>Multivariable‡</td>
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<tr>
<td>DHA (22:6n-3)</td>
<td></td>
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<tr>
<td>Median, g/d</td>
<td></td>
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<tr>
<td>Incident AD cases</td>
<td></td>
</tr>
<tr>
<td>Weighted %†</td>
<td></td>
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<tr>
<td>Relative risk (95% confidence interval)</td>
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<tr>
<td>Age adjusted‡</td>
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<td>Multivariable‡</td>
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<tr>
<td>EPA (20:5n-3)</td>
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<td>Median, g/d</td>
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<td>Incident AD cases</td>
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<td>Weighted %†</td>
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<td>Relative risk (95% confidence interval)</td>
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<td>Age adjusted‡</td>
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<td>Multivariable‡</td>
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<tr>
<td>Linolenic (18:3n-3)</td>
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<tr>
<td>Median, g/d</td>
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<td>Incident AD cases</td>
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<td>Multivariable‡</td>
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</table>

Abbreviation: APOE, apolipoprotein E.

*P value for linear trend is based on logistic regression models with the energy-adjusted nutrient variable modeled as a continuous variable with persons in each quintile assigned the weighted median value for that quintile.

†Weighted percentages of AD cases adjust for the stratified sampling design.

‡Multivariable models are adjusted for age (years), sex, race, education (years), APOE-ε4, the interaction between race and APOE-ε4, and period of observation (years).

§For this analysis, quintile 2 was combined with quintile 1 because the intake level was 0 g/d for 40% of participants.
The multivariable relative risks for intake of DHA (22:6n-3), EPA (20:5n-3), or total n-3 fatty acids did not change materially when we controlled for intake of di- 
(22:6n-3), EPA (20:5n-3), or total n-3 fatty acids did not change materially when we controlled for intake of dietary vitamin E, other types of fat (n-6 polyunsaturated, monounsaturated, saturated, trans-unsaturated), or cardiovascular diseases (stroke, heart disease, hypertension). The multivariable relative risks for intake of α-linolenic acid were approximately 1.0 with adjustment for vitamin E intake, but were unchanged when adjusted for cardiovascular disease.

In further analyses, we examined each n-3 fatty acid and fish consumption for evidence of effect modification. Intake of α-linolenic acid was strongly protective among persons with the APOE-ε4 allele (multivariate relative risk, 0.08 per natural log [milligram] increase in linolenic acid; P = .02), but there was no apparent association among persons who were ε4 negative. The interaction remained statistically significant with additional control for intake of vitamin E or other types of fat. In addition, total intake of n-3 fatty acids was protective only among women (P for interaction = .02). Otherwise, there was no evidence that age, sex, race, education, or APOE-ε4 genotype modified the effects.

To examine the possibility that the observed associations may be due to dietary changes or inaccurate reporting among persons with cognitive impairment, we reanalyzed the data after deleting data for persons whose baseline cognitive scores ranked in the lowest 10% of the distribution. The protective association with intake of total n-3 fatty acids became stronger (the multivariable relative risks [95% confidence intervals] for quintiles 2 through 5 were 0.4 [0.1-1.0], 0.4 [0.1-1.3], 0.4 [0.1-0.8], and 0.3 [0.1-0.8]). The multivariable relative risks for quintiles of DHA intake did not change appreciably except for the highest quintile, in which the relative risk was modified, to 0.5 from 0.3 in the total sample. Adjustment for the timing of the dietary assessment had little influence on the estimated relative risks.

**COMMENT**

Consumption of the n-3 polyunsaturated fatty acids and fish was associated with reduced risk of incident Alzheimer disease in this large prospective study. Persons who consumed at least 1 fish meal per week had 60% less risk of Alzheimer disease than did persons who rarely or never ate fish. Of the marine n-3 fatty acids, only DHA (22:6n-3) was protective against the development of Alzheimer disease. Intake of α-linolenic acid was also protective, but only among persons with the APOE-ε4 genotype.

The study has a number of strengths that support the validity of the findings. Protective associations were observed for DHA, a major component of brain phospholipids, with fish, its primary food source, and with α-linolenic acid, which is largely obtained from vegetable oils. The strength of these associations makes it unlikely that the findings are due to chance. These associations held even after adjustment for education and other important risk factors, including cardiovascular conditions that could potentially account for the observed relative risks. The study participants were randomly selected from the general population, and all underwent structured clinical evaluation for incident disease, thus minimizing bias due to participant selection or case detection. The examiners were blinded to participants' dietary habits, and the dietary assessments were completed before clinical evaluation for incident disease. A limitation of the study is that, for a large number of participants, the dietary assessments were not obtained at baseline. This could have biased the results if some of these participants had already developed disease when their diet was assessed, and also changed their diet. For several reasons, this alternative explanation of the protective associations appears unlikely. The results did not change when we eliminated persons with low cognitive scores at baseline, or when we controlled for the timing of the dietary assessments. Furthermore, in a previous analysis of 2953 participants of the larger study, we found significantly less cognitive decline among persons who consumed fish at least weekly.

We did not observe a protective benefit from EPA (20:5n-3); however, the range of intake was low, and we cannot rule out an effect at higher dose levels obtained from cold-water fatty fish or fish oil supplements. The EPA levels in most low-fat fresh fish are negligible. In a random sample of 232 persons from the study population, more than 90% of the fresh fish that was reported in 24-hour dietary recalls was very low in fat.

This study supports the protective associations found by the 2 other epidemiologic studies that examined the relationship between fish consumption and incident Alzheimer disease.35,34 Numerous animal models provide evidence of a biological basis for the association. The n-3 fatty acids have been studied extensively for their antiatherosclerotic properties.3 Notably, it was DHA that had the strongest protective effect against Alzheimer disease. Docosahexaenoic acid is the most abundant fatty acid in the phospholipids of the cerebral gray matter and represents 45% to 65% of total phosphatidylserine in the mitochondria, which plays a role in neuronal signaling.2 Docosahexaenoic acid is selectively accumulated in the brain during fetal and infant brain growth.5 However, several studies have shown that it is possible to increase n-3 fatty acids in the brain through diet well after the period of early brain development.7,19,20 There is a high turnover of phospholipid fatty acids in the brain.1 In one study, consumption of preformed DHA was 7 times more likely to result in uptake by the brain than DHA derived through consumption of linolenic acid.80 Several prospective studies found decreased risk of stroke with increased fish consumption56,66 and intake of n-3 fatty acids.44

The n-3 polyunsaturated fatty acids have been shown to have profound effects on membrane functions, leading to change in nerve conduction, neurotransmitter release, neurotransmitter reuptake, and postsynaptic trans-
mitter effects. A large number of animal studies have demonstrated that dietary n-3 fatty acids increased learning acquisition and memory performance,4,18,24-31 and 2 epidemiologic studies found decreased risk of Alzheimer disease with increased fish consumption.33,34 These studies, together with our finding that consumption of fish and n-3 fatty acids was associated with reduced risk of Alzheimer disease, provide a strong basis for further study through epidemiologic investigations and clinical trials. Our findings suggest that consumption of fish (at least weekly), oil-based salad dressings, and nuts may reduce the risk of Alzheimer disease.

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Author contributions: Study concept and design (Drs Morris, Evans, and Bennett); acquisition of data (Drs Morris, Evans, Bengtsson, Tangney, Bennett, Aggarwal, and Schneider); analysis and interpretation of data (Drs Morris, Evans, Bengtsson, Tangney, Bennett, and Wilson); drafting of the manuscript (Dr Morris); critical revision of the manuscript for important intellectual content (Drs Morris, Evans, Bengtsson, Tangney, Bennett, Wilson, Aggarwal, and Schneider); statistical expertise (Drs Morris and Bengtsson); obtained funding (Drs Morris, Evans, and Bennett); administrative, technical, and material support (Drs Morris, Evans, Wilson, Aggarwal, and Schneider); study supervision (Drs Morris, Evans, Tangney, and Bennett).

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