Benefits of fatty fish on dementia risk are stronger for those without *APOE* ε4

T.L. Huang, PhD; P.P. Zandi, PhD; K.L. Tucker, PhD; A.L Fitzpatrick, PhD; L.H. Kuller, MD, Dr PH; L.P. Fried, MD, MPH; G.L. Burke, MD, MS; and M.C. Carlson, PhD

Abstract—*Objective:* To compare associations of lean fish vs fatty fish (tuna or other fish) intake with dementia, Alzheimer disease (AD), and vascular dementia (VaD) and in relation to *APOE* ε4 status in the Cardiovascular Health Cognition Study (CHCS). *Methods:* Fish intake was assessed by food frequency questionnaires. Incident dementia, AD, and VaD were determined through a series of cognitive tests, physician's assessment, and committee consensus. We used Cox proportional hazards regression to calculate hazard ratios of dementia, AD, and VaD with lean fried fish, fatty fish, or total fish intake, which were then stratified by the presence of *APOE* ε4. *Results:* Although consumption of lean fried fish had no protective effect, consumption of fatty fish more than twice per week was associated with a reduction in risk of dementia by 28% (95% CI: 0.51 to 1.02), and AD by 41% (95% CI: 0.36 to 0.95) in comparison to those who ate fish less than once per month. Stratification by *APOE* ε4 showed this effect to be selective to those without the ε4 allele. Adjustment by education and income attenuated the effect. *Conclusion:* In the Cardiovascular Health Cognition Study, consumption of fatty fish was associated with a reduced risk of dementia and Alzheimer disease for those without the *APOE* ε4 allele.

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Eating fish has been associated with reduced risk of cognitive decline.[1-7] Although animal studies support the notion that the protective effect is due to the omega-3 fatty acids found in fish, epidemiologic studies fail to show this consistently. In the Zutphen Elderly Study, lower intake of fish, but not of dietary omega-3 fatty acids, was associated with cognitive impairment.[1] The Rotterdam study also showed an association of fish, but not omega-3 fatty acids, with dementia.[4,7] Conversely, Morris et al.[6] found that both intake of fish and docosahexaenoic acid (DHA) was associated with lower risk of Alzheimer disease (AD).

There are many reasons to believe that DHA and eicosapentaenoic acid (EPA) found in fish contribute to differences observed in cognitive status in the elderly. Omega-3 fatty acids reduce inflammation by inhibiting the release of arachidonic acid (AA) from membranes and inhibiting the action of cyclooxygenase-2, which converts AA to the proinflammatory series 2 prostaglandins.[8] DHA is also a ligand for the nuclear receptor peroxisome proliferator-activated receptor-γ (PPAR-γ). PPAR-γ agonists, such as DHA and nonsteroidal anti-inflammatory drugs, inhibit the β-amyloid–stimulated secretion of inflammatory molecules by microglia and monocytes.[9] DHA is involved in the synthesis of neurites by nerve growth factor, is involved in cell signaling, and is essential for optimal neural maturation of infants.[10] DHA protects AD-modeled rats from cognitive decline by increasing the DHA/AA molar ratio and by decreasing apoptosis and free radical formation.[11] Both EPA and DHA are also shown to reduce cholesterol and to lower the risk of death from cardiovascular disease and stroke.

Using data from the Cardiovascular Health Study (CHS), Mozaffarian et al. showed that people who consumed fatty fish had a lower risk of ischemic stroke[12] and death due to myocardial infarction vs those who ate leaner fried fish.[13] Fatty fish are rich sources of EPA and DHA and typically include salmon, sardines, herring, mackerel, trout, and tuna, whereas lean fish include cod, haddock, and halibut. In this study, we used methods similar to those outlined by Mozaffarian et al. to look at the frequency of

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For a full list of participating CHS investigators and institutions, see "About CHS: Principal Investigators and Study Sites" at http://www.chs-nhlbi.org.

From the Jean Mayer USDA Human Nutrition Research Center on Aging (Drs. Huang and Tucker), Tufts University, Boston, MA; Department of Mental Health (Drs. Zandi and Carlson), Johns Hopkins Bloomberg School of Public Health, Baltimore, MD; Department of Epidemiology (Dr. Fitzpatrick), University of Washington, Seattle, WA; University of Pittsburgh (Dr. Kuller), Pittsburgh, PA; Department of Medicine (Dr. Fried), Johns Hopkins University, Baltimore; Department of Public Health Sciences, (Dr. Burke), Wake Forest University School of Medicine, Winston-Salem, NC.

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Address correspondence and reprints requests to Tina L. Huang, PhD, Jean Mayer USDA Human Nutrition Research Center on Aging, Tufts University, Dietary Assessment & Epidemiology Research Program, 9th Floor, 711 Washington Street, Boston, MA 02111; e-mail: tina.huang@tufts.edu

consumption of fatty vs lean fish with incidence of dementia, AD, and vascular dementia (VaD) in the dementia substudy of the CHS.

Methods. *Population.* The goal of the CHS was to identify risk factors that lead to the development of heart disease in the elderly.[14] During its initial recruitment in 1989/90, 5,201 participants, aged 65 years and older, were enrolled from randomized Medicare eligibility lists in four U.S. communities: Forsyth County, NC, Washington County, MD, Sacramento, CA, and Pittsburgh, PA.[15] In 1992 to 1993, the study recruited 687 additional African Americans from Forsyth County, Sacramento, and Pittsburgh. In 1998, the CHS Cognition Study (CHCS) was launched to assess the 3,602 subjects who had brain MRI in 1992 to 1994 and concurrently completed the Modified Mini-Mental State Examination (3MSE).[16] The CHCS includes 227 subjects with prevalent dementia, 577 with mild cognitive impairment (MCI), 245 with incident pure AD, 62 with VaD, and 151 subjects with mixed AD and VaD. For the purposes of our analysis, subjects with prevalent dementia at baseline or with MCI were eliminated. Another 565 subjects who lacked sufficient information to derive energy intake, had extreme energy intake values (<600 and >4,000 kcal), were missing fish intake data, or responses from more than 12 food items on the Food Frequency Questionnaire (FFQ) were also eliminated, leaving 2,233 subjects. The length of follow-up from time of MRI to onset of AD, dementia, or death ranged between 0.1 and 8.4 years and averaged 5.4 years. The institutional review board at each center approved the study, and all participants signed an informed consent at entry and at specified intervals during the study.

Dietary assessment. In 1989, a modified National Cancer Institute (NCI) FFQ was administered.[17] There were 99 food items, and an additional 46 questions that addressed eating styles and habits. The 99 food questions were administered using the picture sort method, and subjects were asked to determine their frequency of consumption of each type of food. They had five choices ranging from never, 5 to 10 times per year, one to three times per month, one to four times per week, to almost every day. To validate the picture sort method in older adults, macronutrient intakes derived from each method were compared against six 24-hour recalls on different days of the week, approximately once per month. Questions asked about consumption of fish included "tuna fish/tuna salad or tuna casserole," "fried fish or fish sandwich," or "other fish (baked or broiled)." Fish intake was also compared against plasma phospholipid DHA and EPA levels in 56 subjects. Combined EPA and DHA levels correlated well with intake of tuna and other fish, but not of fried fish.[13] This was expected, as most fish served fried or in sandwiches in the United States tends to be from lean species like cod or haddock. Furthermore, the act of frying the fish may lead to loss of natural fatty acids in the fish and replacement with cooking oil.[18] Total energy intake was determined using NCI software. When compared with food records, the mean intake of total calories, fat, carbohydrates, and fiber from the FFQ were within 5 to 10% of those obtained from the food records, both overall and within gender-age groups.[17] More details of the dietary assessment methods can be found in Kumanyika et al.[17] Incidence rates of dementia in subjects who were not included due to insufficient dietary data did not differ from those who remained in the study.

Dementia/AD diagnosis. Each subject in the CHCS was administered the Mini-Mental State Examination (MMSE)[19] in 1989/1990, and in subsequent years, the expanded 100-point form of the MMSE, the 3MSE.[20] Other data collected prospectively through 2000 included the Digit Symbol Substitution Test,[21] Benton Visual Retention Test,[22] the Center for Epidemiological Studies of Depression Scale score,[23] activities of daily living (ADLs),[24] and instrumental ADLs (IADLs),[25] other measures of functionality, medications, onset of cardiovascular events including stroke, and all hospitalizations. The Telephone Interview for Cognitive Status (TICS)[26] was administered if a patient did not come into the clinic, and an Informant Questionnaire for Cognitive Decline in the Elderly (IQCoDE)[27] was administered to close relatives, caretakers, and physicians when the participant died. Subjects were then screened for high risk of dementia using an 80-point cutoff on the 3MSE, a decline of at least 5 points on the 3MSE from previous examinations, a TICS score of <28, an IQCoDE score of >3.6, a stroke, a medical record review with a diagnosis of dementia, or residence in a nursing home. All subjects who were at the Pittsburgh site, all minorities, and all subjects who were considered at high risk were then asked to complete an additional battery of neuropsychological tests. Subjects who failed tests of memory or more than one other cognitive domain (premorbid intelligence, language, visuoperceptual/visuoconstructional, executive function, or motor) were then seen by a neurologist. If a participant refused, was unable to come into the clinic, or was deceased, dementia was assessed using the prospectively collected data from the annual clinic examination, supplemented with data from medical records, physician questionnaires, and informant/proxy interviews (including the Dementia Questionnaire). At the Pittsburgh site, attempts were made to evaluate all living participants at the clinic to ascertain screening bias.

All information was reviewed by a committee of neurologists and psychiatrists to assess dementia status. A patient was classified with dementia if he or she had had a progressive or static cognitive deficit severe enough to affect ADLs, a previously normal level of intellectual functioning, impairment in two or more cognitive domains that did not necessarily include memory, and if they satisfied the *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition* criteria for dementia status.[16] The classification of specific types of dementia was completed after the review of the MRI. The National Institute of Neurological and Communicative Diseases and Stroke–Alzheimer's Disease and Related Disorders Association (ADRDA) criteria were used to classify AD, and the State of California Alzheimer's Disease Diagnostic and Treatment Center (ADDTC) criteria were used for VaD. For these analyses, we used National Institute of Neurological Disorders and Stroke-ADRDA probable or possible with no ADDTC VaD to identify "pure" AD or ADDTC probable or possible with no AD to identify "pure" VaD. More information on diagnosis and assessment of dementia and its subtypes can be found in Fitzpatrick et al.[28]

Other variables. Age at baseline, education, race, gender, body mass index (BMI), and most recent income were established at the baseline visit. Education referred to the number of years of traditional school, as going to vocational school showed no benefit for this population. Income referred to the income in the previous 12 months and was represented in eight categories ranging from less than $5,000 per year to greater than $50,000. An annual examination was administered in which vital signs, anthropometry, medical history and behaviors, physical function, and psychosocial interviews were assessed. *APOE* genotype was determined from the 91.5% of subjects who consented to DNA analysis.

Statistical analysis. We used analysis of variance, trend tests, and χ^2 tests to compare baseline characteristics of subjects who consumed different amounts of fish. Cox proportional hazards regression was used to compare risk ratios of three levels of fried fish intake across the years of follow-up. We combined other fish and tuna to generate a group of fatty fish by converting each to the number of servings consumed per week and summing them. For fatty fish, we compared four levels of intake. The category of total fish resulted from the addition of fatty fish and fried fish, again first converted to the number of servings per week, summed, and then converted back into four levels of intake. We tested possible confounders by adding them to the model and determining their significance using the likelihood ratio test. We also tested for interactions of the main covariate by gender or presence of *APOE* ε4. Our final models included variables that are commonly used in the assessment of AD, based on their significance in the models, and whether they remained in the model using stepwise regression analysis. Here we present two models: (1) a model including age at baseline, minority status, gender, presence of *APOE* ε4, energy intake, baseline BMI, and region and (2) a model to illustrate the attenuation of the hazard ratios (HRs) by education and income. Fried fish and tuna or other fish were analyzed separately and then together in the same models. Because the interaction between fish and *APOE* ε4 had $p < 0.10$, we subsequently stratified by presence of *APOE* ε4. All analyses were performed using Stata 8.0 (Statacorp, College Station, TX).

Results. During the follow-up period, 378 (16.9%) of the 2,233 subjects developed dementia, with 190 (8.5%) developing AD, and 50 (2.4%) developing pure VaD. This group reported a mean consumption of 0.65 servings of fried fish

Table 1 *Baseline characteristics by consumption of fatty and lean fried fish*

	Fatty fish				Lean, fried fish		
No. of servings per wk	<0.25	0.25–2	2–4	≥4	<0.25	0.25–2	≥2
n	281	798	705	449	1102	737	394
Age, y	72.4	71.8	71.9	70.9*	71.8	71.7	71.5
% Male	43.4	44.6	43.0	32.5†	35.8	44.9	51.0†
% White	96.4	97.2	96.4	97.8	97.5	97.8	93.9†
Education, y	11.6	12.5	13.1	13.3*	13.1	12.4	12.2*
% With at least one *APOE* ε4 allele‡	21.0	20.1	21.4	23.2	20.6	21.3	22.8
Avg income, %§							
<12K¶	17.2	37.4	29.7	15.6*	44.0	35.5	20.4*
12–25K	15.3	41.1	27.6	16.0	48.3	34.9	16.8
25–35K	10.5	38.1	33.0	18.5	44.5	34.6	20.9
35–50K	10.0	36.5	33.6	19.9	53.9	28.6	17.4
>50K	6.4	23.9	37.5	32.2	57.5	28.3	14.2
Energy, kcal/d	1537	1659	1857	2011*	1600	1840	2154*
BMI	25.8	26.4	26.2	26.7*	26.2	26.5	26.5*
Study region, %							
Wake Forest	20.9	43.6	27.6	7.9†	46.0	35.7	18.3†
UC Davis‖	10.4	37.8	32.6	19.2	59.0	31.0	10.0
Johns Hopkins	13.1	40.6	29.5	16.8	39.8	39.0	21.3
U. Pittsburgh	5.7	19.3	37.1	37.9	53.8	25.1	21.0

* Trend test, $p < 0.05$
† Significant difference, χ^2, $p < 0.001$.
‡ The *APOE* allele type information is missing for 189 patients.
§ Income data are missing for 125 patients.
¶ K = $1000.
‖ University of California, Davis.

and 2.3 servings of tuna or other fish per week. Baseline characteristics by consumption of fatty fish vs lean fish are presented in table 1. Although consumption of fried fish did not differ by age, younger subjects tended to consume more tuna or other fish than older subjects. Subjects who were more educated or had higher incomes consumed more fatty fish and less lean fish (using trend tests, each analysis was significant at $p < 0.001$) relative to those with less education or of lower socioeconomic status. Those who ate more fish, regardless of the type, also had higher overall energy intake (trend test, $p < 0.001$). There was a trend toward higher consumption of fried fish with greater BMI ($p < 0.001$), and the association between higher fatty fish intake and greater BMI approached significance ($p = 0.07$). Men consumed more fried fish than women, and women consumed more fatty fish than men ($p < 0.001$ for each). Consumption patterns of both types of fish also varied by study region, with subjects from California consuming the least lean fish and subjects in Pittsburgh consuming the most fatty fish. Minorities also tended to eat more fried fish than whites.

We compared HRs of fried fish vs tuna or other fish and total fish consumption of dementia and AD using COX proportional hazards regression. Modeling fried fish consumption and tuna or other fish consumption separately or in the same models did not have a substantial impact on the HRs. There was no significant difference in risk of dementia or AD with greater servings per week of fried fish either before or after controlling for fatty fish, age at baseline, minority status, gender, presence of *APOE* ε4, energy, BMI, region, education, or income (table 2 (for more details, also see tables E-1 and E-2 on the *Neurology* Web site at www.neurology.org). Conversely, univariate models showed that eating tuna or other nonfried fish once per month to two times per week, compared to very low or no consumption, was associated with a nonsignificant 25% lower rate of dementia (95% CI: 0.55 to 1.03) and a 31% nonsignificant lower rate for AD (95% CI: 0.45 to 1.06), and consumption of these fish four times per week or more was significantly associated with protection against incident dementia (HR 0.63, 95% CI: 0.44 to 0.90) and AD (HR 0.56, 95% CI: 0.34 to 0.91) (see tables E-1 and E-2). These associations were not significantly affected by further controlling for intake of fried fish, age at baseline, minority status, sex, presence of *APOE* ε4, energy, BMI, and region. However, after adjusting for education and income, HRs were attenuated (table 2). Total fish intake tended to have lower HRs with dementia and AD, but these were not significant. In the full model, consumption of more than one serving per month to two servings per week of total fish showed HRs of 0.87 (95% CI: 0.62 to 1.23) for dementia and 0.78 (95% CI: 0.48 to 1.28) for AD (see tables E-1 and E-2). With univariate analysis, consuming 0.25 to two servings of fried fish increased the risk of pure VaD (HR

Table 2 *Hazard ratios of dementia and Alzheimer disease by consumption of fried fish and tuna or other fish*

	Dementia			AD		
No. servings/wk	Events/ person-yr	M1† HR (95% CI)	M2‡ HR (95% CI)	Events/ person-yr	M1† HR (95% CI)	M2‡ HR (95% CI)
Fried fish*						
<0.25	178/5970	1	1	91/5709	1	
0.25–2	133/3929	1.18 (0.92–1.52)	1.12 (0.87–1.44)	66/3735	1.07 (0.74–1.54)	0.97 (0.67–1.40)
≥2	67/2128	1.11 (0.76–1.47)	0.97 (0.69–1.35)	33/2035	1.06 (0.66–1.69)	0.95 (0.60–1.52)
Tuna and other fish*						
<0.25	57/1423	1	1	32/1367	1	1
0.25–2	134/4250	0.76 (0.55–1.06)	0.85 (0.61–1.19)	68/4051	0.72 (0.46–1.12)	0.85 (0.54–1.33)
2–4	122/3846	0.72 (0.51–1.02)	0.83 (0.59–1.18)	58/3656	0.59 (0.36–0.95)§	0.72 (0.44–1.17)
≥4	65/2509	0.65 (0.43–0.98)§	0.79 (0.53–1.20)	32/2405	0.54 (0.31–0.95)§	0.69 (0.91–1.22)

* Fried fish and tuna or other fish are in the same model.
† Model 1: controlling for age at baseline, minority status, sex, presence of *APOE* ε4, energy, body mass index, region.
‡ Model 2: controlling also for education and income.
§ $p < 0.05$

HR = hazard ratio.

2.6, 95% CI: 1.39 to 4.96), but the risk associated with eating two to four servings of fried fish per week was not significant (HR 1.68, 95% CI: 0.74 to 3.84). Adjustment for other variables produced similar results. The HRs associated with consumption of fatty fish for VaD were similar to those of dementia but were not significant (data not shown).

We tested for interactions between the presence of the *APOE* ε4 allele and intake of either fried fish, fatty fish, or total fish on the outcome of dementia and found borderline significance with fatty fish (0.25 to two servings per week, $p = 0.08$; two to four servings per week, $p = 0.28$; more than four servings per week, $p = 0.09$ relative to less than once per month). Results stratified by *APOE* ε4 differed between those who possessed vs those who lacked the allele (table 3; for more detail, see table E-3). Fatty fish appeared to have little or no association for individuals with *APOE* ε4 (HR for two to four servings per week 0.91, 95% CI: 0.48 to 1.71), but was associated with significantly lower hazard ratios for those without the allele (HR for two to four servings per week 0.60, 95% CI: 0.40 to 0.89). After controlling for age at baseline, minority status, sex, energy, BMI, and region, the association remained significant for *APOE* ε4–negative individuals. However, adding education and income to the models attenuated the association (see table 3). Although only a small number of cases consumed fewer than 0.25 servings of fish per week in our *APOE* ε4–positive group, the differences in HR and CIs between *APOE* ε4–negative and the total population were large (compare tables 2 and 3), suggesting that the effect of stratifying by *APOE* ε4 was unlikely to be spurious. Only those without *APOE* ε4 had lower HRs with total fish consumption, but the association was not significant unless four or more servings of fish had been consumed per

Table 3 *Hazard ratios of dementia by consumption of tuna or other fish stratified by APOE ε4*

			Model 1*		Model 2†	
No. of servings/wk	n	Events/person-yr	HR	95% CI	HR	95% CI
APOE ε4 positive						
<0.25	59	14/311	1		1	
0.25–2	160	40/775	1.07	0.58–1.98	1.23	0.66–2.30
2–4	151	34/805	0.99	0.52–1.89	1.06	0.55–2.05
≥4	104	23/553	0.91	0.44–1.88	1.03	0.49–2.16
APOE ε4 negative						
<0.25	206	41/1022	1		1	
0.25–2	561	76/3064	0.72	0.46–1.12	0.85	0.54–1.33
2–4	490	69/2691	0.59‡	0.36–0.95	0.72	0.44–1.17
≥4	313	33/1791	0.54‡	0.31–0.95	0.69	0.91–1.22

* Model 1: controlling for age at baseline, minority status, sex, presence of *APOE* ε4, energy, BMI, region, fried fish.
† Model 2: controlling also for education and income.
‡ $p < 0.05$.

week (HR 0.64, 95% CI: 0.45 to 0.92) (see table E-3). Stratification by *APOE* ε4 revealed a similar pattern for AD, in that a significant reduction in hazards was associated with fatty fish for those without, but not with, *APOE* ε4. Controlling for the same variables mentioned above had very little effect on HRs or significance. However, as with dementia, significance was lost after adding income and education to the models (data not shown). There was insufficient power to examine VaD by stratification of *APOE* ε4.

Discussion. Eating fatty fish, such as tuna or "other fish" was associated with a lower risk of developing dementia and AD, whereas lean, fried fish was not. The HR decreased with the number of servings per week of fatty fish, suggesting a dose-response relationship. However, the findings were attenuated after adjusting for education and income. There was a lower reduction in risk with total fish than fatty fish, thus supporting our hypothesis that benefits of fish are derived primarily from its DHA. There were significant differences in the association of fatty fish with dementia and AD for *APOE* ε4–negative vs *APOE* ε4–positive individuals on the outcome of dementia. Those without an *APOE* ε4 allele had a 35 to 45% lower risk with consumption of fatty fish, whereas there was little or no difference for *APOE* ε4–positive individuals.

Because it is thought that omega-3 fatty acids in fish are protective against cardiovascular mortality, presumably through lowering blood pressure and inflammation and increasing endothelial relaxation,[29] we also examined the relationship between fatty fish and VaD. Although the HRs were similar to those of dementia, they were not significant due to lack of power. We did find a greater risk of pure VaD for those who consumed 0.25 to 2 servings of fried fish per week vs little or none. Because there were only 50 subjects with VaD and the association was diminished with greater consumption of fried fish, the source of this effect remains unclear. Given the biologic plausibility, future studies are warranted.

Although the differences in the associations of fatty fish vs lean fish with incidence of dementia and AD are most likely due to the inherent natural content of the DHA in the fish before preparation, they may have also been influenced by preparation methods. Fried fish is typically lean fish, whereas fish that is baked or broiled is usually higher in fat. Interestingly, the total amount of omega-3 fatty acids and the omega-6–to–omega-3 ratio can vary significantly depending on the preparation method. Studies of sardines and mackerel show that frying reduces the DHA portion of fat to one-third of its original content.[18] However, that study and others show that cooking does not modify the amount of DHA in herring[30] or salmon.[31] Thus, cooking methods as well as species of fish are probably likely determinants of whether consumption is protective against dementia.

Several case-control studies and shorter term longitudinal studies find fish intake to be associated with a lower risk of dementia even after controlling for education. In our population, there were significant and opposite trends with intake of fried lean fish (negative association) and of fatty fish (positive association) with education and income. Because the CHS population is derived from four different counties across the United States, we expected that education and income would be more heterogeneous than in most population studies. These patterns raise the possibility that education and income determine opportunities for exposure to fatty fish and omega-3 fatty acids. Specifically, fatty fish is generally more costly and less widely available than fried fish. To the extent that education and income allow greater fish consumption, which was then associated with a lower risk of dementia and AD, adjustment may be over control, as it is in the causal pathway. However, it is important to note that there may be other aspects of these socioeconomic status factors (such as other dietary habits, physical exercise, or access to medical care) that may be true confounders of the association, and further work is needed to separate these effects.

This study is the first to report differences in the association of fish with *APOE* ε4, a genetic risk factor for AD. Given that *APOE* ε4 polymorphisms do influence lipid profile response to consumption of fats[32,33] and play a significant role in AD, we hypothesized that each genotype would have a different response to omega-3 fatty acids in fish. One previous study has shown that the distribution of polyunsaturated phospholipid species in synaptic plasma membranes differed in mice that were *APOE* deficient.[34] Thus, the absorption and transport of polyunsaturated fats are probably different depending on genotype, which may influence the risk of dementia. More studies are needed to determine whether the *APOE* genotype modifies the risk or protective effects of all fat types on dementia and AD.

Results from this study have several potential limitations. The FFQ used did not contain portion sizes and frequency of consumption was limited to five categories. Our aim was to compare the risk of dementia by level of lean and fatty fish consumption. Although tuna fish plus other fish correlated with DHA plasma phospholipid levels in a subsample of subjects in the CHS,[13] the "other fish" group may have included some lean fish as well, thus reducing precision in measurement of fatty fish. Therefore, our findings may have underestimated the true association between fatty fish and dementia or AD. Limitations in our data precluded us from being able to control for vitamin E, which is found in fish and has been shown have a protective effect against dementia in clinical trials.[35] Vitamin E may also protect polyunsaturated fatty acids from oxidation.[36,37] However, a previous study that tested for interactions with vitamin E observed no modification of fish's relationship to DHA and cognitive decline.[2] Another limitation to our study was that 565 subjects with either incomplete FFQs or improbable energy intake

were excluded from analysis. These subjects, however, did not have a greater risk of dementia than those with complete data.

Although several studies have suggested that fish and DHA are protective against dementia and AD, we are aware of no previous study that has compared the consumption of different types of fish to the outcome of dementia. The findings from our study, that fatty fish appeared to be associated with a greater reduction in dementia and AD than leaner fish, support the hypothesis that DHA is the primary protective nutrient in fish. This study is also unique in that it presents findings stratified by *APOE* ε4, suggesting that the presence of the ε4 allele may modify the relationship of fatty fish to dementia and AD. Several studies have now found that fish and DHA are associated with a lower incidence of dementia, and there are multiple neurobiologic pathways by which DHA could be protective, suggesting that clinical trials are warranted to confirm the potentially protective effects of fish and omega-3 fatty acid intake, particularly among individuals at risk of AD.

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