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Fish consumption and risk of subclinical brain abnormalities on MRI in older adults

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ABSTRACT

Objective: To investigate the association between fish consumption and subclinical brain abnormalities.

Methods: In the population-based Cardiovascular Health Study, 3,660 participants age ≥65 underwent an MRI scan in 1992–1994. Five years later, 2,313 were scanned. Neuroradiologists assessed MRI scans in a standardized and blinded manner. Food frequency questionnaires were used to assess dietary intakes. Participants with known cerebrovascular disease were excluded from the analyses.

Results: After adjustment for multiple risk factors, the risk of having one or more prevalent subclinical infarcts was lower among those consuming tuna/other fish ≥3 times/week, compared to <1/month (relative risk 0.74, 95% CI = 0.54–1.01, $p = 0.06$, p trend = 0.03). Tuna/other fish consumption was also associated with trends toward lower incidence of subclinical infarcts. Additionally, tuna/other fish intake was associated with better white matter grade, but not with sulcal and ventricular grades, markers of brain atrophy. No significant associations were found between fried fish consumption and any subclinical brain abnormalities.

Conclusions: Among older adults, modest consumption of tuna/other fish, but not fried fish, was associated with lower prevalence of subclinical infarcts and white matter abnormalities on MRI examinations. Our results add to prior evidence that suggest that dietary intake of fish with higher eicosapentaenoic acid and docosahexaenoic acid content, and not fried fish intake, may have clinically important health benefits. *Neurology*® **2008;71:439–446**

GLOSSARY

ARR = absolute risk reduction; **BMI** = body mass index; **CHD** = coronary heart disease; **CHS** = Cardiovascular Health Study; **DHA** = docosahexaenoic acid; **EPA** = eicosapentaenoic acid; **FFQ** = food frequency questionnaire; **HDL-C** = high-density lipoprotein cholesterol; **LDL-C** = low-density lipoprotein cholesterol; **PUFA** = polyunsaturated fatty acid; **RR** = relative risk.

Clinically unrecognized or "silent" brain infarcts are very common, particularly with advancing age. Among adults age ≥65 without infarcts on initial brain MRI, nearly 20% had at least one new infarct when MRI was performed about 5 years later, but without recognized TIA or clinical stroke in nearly 90% of cases.[1] Persons with MRI-defined infarcts experience greater cognitive decline than persons without infarcts, and such individuals are also at higher risk of future clinical stroke.[1-3]

Fish consumption is associated with risk of clinically recognized stroke. Among older adults, consumption of tuna or other broiled or baked fish correlated with plasma phospholipid n-3 polyunsaturated fatty acid (PUFA) levels and was associated with lower stroke risk.[4] Consumption of fried fish did not correlate with n-3 PUFA levels and was associated with higher stroke

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risk.[4] Whether fish consumption affects the risk of subclinical infarcts or other subclinical brain abnormalities is unknown. Fish consumption is associated with decreased risk of dementia and cognitive decline,[5] for which major risk factors are subclinical brain abnormalities.[6] We hypothesized that, as with overt infarcts,[4] consumption of tuna/other fish would be associated with lower risk of subclinical infarcts among older adults, while fried fish consumption would be associated with higher risk. We also investigated associations of fish consumption with MRI-defined white matter abnormalities and ventricular and sulcal enlargement.[7,8]

METHODS

Study population. The Cardiovascular Health Study (CHS) is a prospective cohort study of 5,888 older adults. The design and recruitment experience have been described.[8,9] Briefly, 5,201 men and women age ≥65 at baseline were randomly selected and enrolled in 1989–1990 from Medicare eligibility lists in four United States communities. An additional 687 black participants were enrolled in 1992–1993. Each center's institutional review committee approved the study, and all subjects gave informed consent. All participants underwent extensive baseline evaluations including standard questionnaires, physical examination, performance measures, and laboratory testing.[8-10] Parts of the baseline evaluation were repeated during annual follow-up visits. Prevalent coronary heart disease (CHD), stroke, TIA, hypertension, and diabetes were defined using patients' reports and confirmed by centralized review of hospital and clinic records.[8,9]

Assessment of dietary intake. Usual dietary intakes were assessed in 1989–1990 using a picture-sort version of the National Cancer Institute food frequency questionnaire (FFQ).[11] Participants were asked to indicate how often, on average, they had consumed various specific foods during the past year, including tuna fish, other broiled or baked fish, and fried fish or fish sandwiches (fish burgers). Nutrient intakes were estimated from questionnaire responses and adjusted for total calories using regression analyses.[12,13] Dietary eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) intakes were calculated from questionnaire responses using estimated fish and shellfish serving sizes (3–5 oz [84–140 g])[14] and US commercial landings data.[15] Tuna or other broiled or baked fish correlated with combined plasma phospholipid EPA+DHA concentrations ($r = 0.51$), a biomarker of n-3 fatty acid intake, in a subsample of participants.[16] Phospholipid EPA+DHA concentrations did not correlate with fried fish consumption ($r = 0.04$), consistent with the lean types of fish that are typically fried (e.g., cod, pollock).[16]

Usual dietary intakes were assessed again in 1995–1996 using Willett's semiquantitative FFQ.[17] Participants were asked to indicate how often, on average, they had consumed given amounts of various specified foods during the past year, including canned tuna fish (3–4 oz [84–112 g]); dark-meat fish such as mackerel, salmon, sardines, bluefish, and swordfish (3–5 oz [84–140 g]); and other white fish (3–5 oz [84–140 g]). Consumption of fried fish was not specifically assessed. Nutrient intakes were calculated as frequency of intake multiplied by nutrient composition of the specified portion size. Nutrient estimates were based on US Department of Agriculture[14] and Harvard University food composition database sources, and adjusted for total energy by regression analyses.[13] Dietary EPA and DHA were calculated from questionnaire responses using estimates for each fish serving, as previously described,[18] and validated in other cohorts by comparisons with multiple weighted 1-week dietary records and against adipose stores of n-3 fatty acids[17,19]; the correlation between EPA+DHA intake and proportion in adipose tissue was 0.47.[19]

Brain imaging. CHS participants were invited to undergo MRI scanning between 1991 and 1994. A total of 3,660 (62%) underwent scanning and were slightly younger and healthier than those who did not undergo MRI.[20] All participants were again invited to undergo MRI scanning 5 years later, between 1997 and 1999, and 2,313 were scanned. A total of 2,116 participants underwent both scans and were healthier than the 1,544 who underwent only the initial scan, including a lower prevalence of cardiovascular disease, hypertension, and diabetes, and current smoking, and higher income and education.[1]

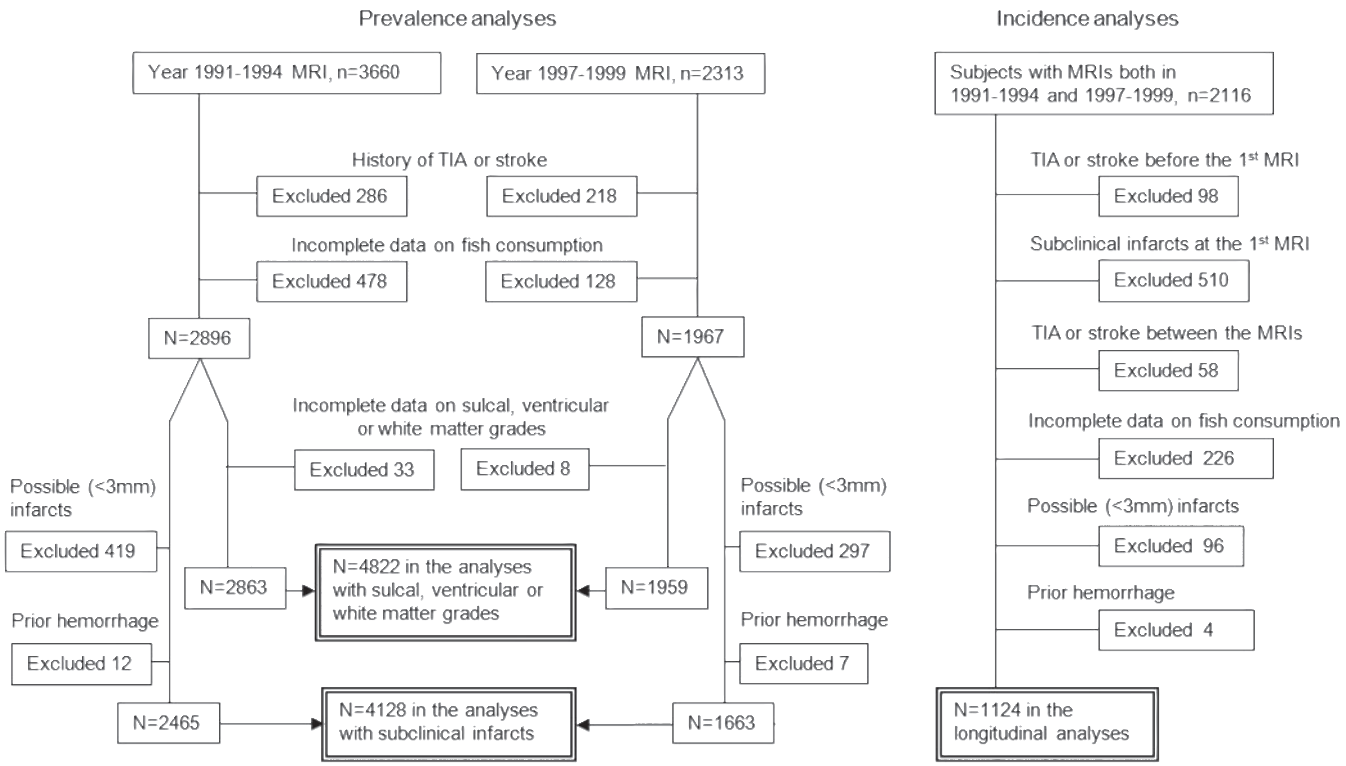
The cranial MRI scanning protocol included sagittal T1-weighted localizer images and axial T1, spin density, and T2-weighted images.[21] Without knowledge of participants' clinical information, neuroradiologists at the CHS reading center identified infarcts and estimated white matter, ventricular, and sulcal grades, as detailed previously.[10,20] Grades were defined using a semiquantitative 10-point scale from 0 to 9 (most abnormal), based on comparison templates.[10] As previously described,[22] ventricular and sulcal grades were grouped for analysis as ≤2, 3, 4, and ≥5, and white matter grade as ≤1, 2, 3, and ≥4. Brain infarct was defined as an area of abnormal signal intensity, ≥3 mm in size, in a vascular distribution that lacked mass effect.[10]

Statistical analysis. We used the prospectively collected repeated measures of dietary intake and MRI scans to perform both cross-sectional and longitudinal analyses. Relative risk (RR) of subclinical infarcts was evaluated using logistic regression. RR of number of subclinical infarcts (range 0 to 4) or abnormal sulcal, ventricular, and white matter grades (four levels) was evaluated using ordinal logistic regression. Absolute risk reduction (ARR) was calculated by multiplying the absolute risk in the reference group by the multivariable-adjusted RR reduction in the comparison group.

For cross-sectional analyses of prevalent subclinical neurologic abnormalities, dietary intake in 1989–1990 was related to MRI findings in 1991–1994, and dietary intake in 1995–1996 to MRI findings in 1997–1999. After confirming in preliminary analyses that the observed relationships were similar in the two periods evaluated separately, data were combined to assess the repeated measures. All analyses were clustered within-individual with robust variance estimates to assess both between- and within-individual covariance (specifying that observations were independent across individuals but not within individuals).

For each diet-MRI pairing, we excluded participants with history of prevalent TIA or stroke, incomplete data on fish consumption, or incomplete data on sulcal, ventricular, or white matter grades (figure 1). For evaluation of subclinical infarcts, we also excluded possible (<3 mm) infarcts or evidence of prior hemorrhage (figure 1). For longitudinal analyses of incident subclinical neurologic abnormalities, we excluded participants with any MRI-defined (clinical or subclinical) infarcts or prior hemorrhage at the first MRI (figure 1). We then related dietary intake from the first questionnaire to subclinical MRI findings on the second MRI, excluding participants with clinically diagnosed

Figure 1 **Exclusion criteria for the cross-sectional and longitudinal analyses**



TIA or stroke before the first MRI or between the two MRIs (figure 2).

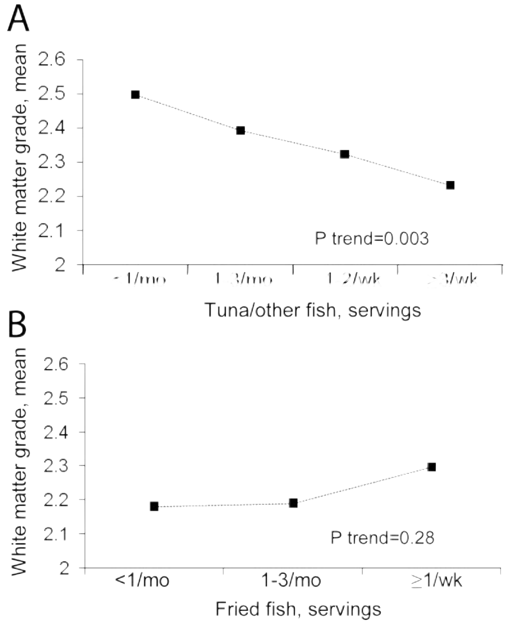
Multivariate models included possible confounders based upon clinical interest, previously published associations with MRI findings,[1,4,23] or associations with exposures or outcomes in the present analysis. Covariates were those from the examination closest in time to the brain imaging. The final models included tuna/other fish intake, fried fish intake, age, sex, race, enrollment center, diabetes, education, smoking, pack-years of smoking, body mass index, prevalent CHD, alcohol use, physical activity, energy intake, meat consumption, and vegetable consumption. Because the second dietary questionnaire did not include information on fried fish consumption, only data from the first MRI were used for analyses of relationships of fried fish intake with MRI abnormalities. For covariate adjustment only, fried fish values for the second questionnaire were imputed using responses on the 1989–1990 FFQ and age, sex, race, enrollment center, diabetes, education, smoking, pack-years of smoking, body mass index, prevalent CHD, alcohol use, physical activity, energy intake, meat consumption, and vegetable consumption. Further adjustments for systolic blood pressure, atrial fibrillation, exercise intensity, use of estrogen, aspirin, lipid-lowering or hypertension medication, LDL or HDL cholesterol, triglycerides, time between MRI scans, carotid intima-media thickness, forced expiratory volume, history of frequent falls, serum creatinine, serum c-reactive protein, fasting glucose, insulin, fibrinogen, factor VII, use of fish oil (<5% of participants), or consumption of saturated fat, fiber, or fruit did not appreciably alter (<5%) the risk estimates between fish or EPA+DHA intake and the MRI findings.

Likelihood ratio tests using multiplicative interaction terms were used to explore potential effect modification by age, sex, race, education, diabetes, prevalent CHD, hypertension, systolic blood pressure, alcohol intake, smoking, and use of aspirin, lipid lowering, or antihypertensive medications. All p values were two-tailed ($\alpha = 0.05$). Analyses were performed using Stata 8.0 (Stata Corp, College Station, TX).

RESULTS At baseline, higher tuna/other fish consumption was associated with younger age, female sex, higher education, lower systolic blood pressure, higher LDL and HDL cholesterol, and higher ankle-arm index, whereas higher fried fish consumption was associated with male sex, nonwhite race, lower education, higher prevalence of diabetes, higher BMI, and lower HDL cholesterol (table 1). Tuna/other fish consumption was also associated with higher energy intake, higher fruit and vegetable consumption, and lower saturated fat intake. Fried fish consumption was associated with higher energy intake, saturated fat intake, vegetable consumption, and beef or pork consumption, and lower alcohol intake.

A total of 567 of 2,465 participants (23.0%) had one or more subclinical infarcts on the first MRI. On the second MRI, 382 of 1,663 participants (23.1%) had one or more subclinical infarcts. In multivariable-adjusted analyses, the RR for having a subclinical infarct was 0.74 (95% CI = 0.54–1.01, $p = 0.06$; p trend = 0.03) in individuals consuming tuna/other fish ≥3 times/week, compared to consumption <1/month (table 2) (reference group absolute risk = 26.5%; ARR = 6.9%). In contrast, fried fish consumption was associated with nonsignificant trends toward higher prevalence of subclinical infarct (table 2). Evaluated

Figure 2 **White matter grades according to fish consumption**



Adjustments were made for fried fish or tuna/other fish consumption and age, sex, race, enrollment center, diabetes, education, smoking status, pack-years of smoking, body mass index, coronary heart disease at the time of MRI, alcohol use, physical activity, energy intake, meat consumption, and vegetable consumption.

continuously, each one serving/week of tuna/other fish was associated with 7% lower RR of having any prevalent subclinical infarct (95% CI = 0.6–12%, p = 0.03). Each one serving/week of tuna/other fish was also associated with 7% lower RR of each additional multiple infarct (95% CI = 0.8–12%, p = 0.03).

In the longitudinal analyses, 187 of 1,124 participants (16.6%) had one or more new subclinical infarcts between the two MRIs. Tuna/other fish consumption tended to be associated with lower incidence of subclinical infarct after adjustment for age, sex, race, and fried fish consumption (table 3). The RR in those consuming tuna/other fish ≥3 times/week was 0.56 (95% CI = 0.30–1.07, p = 0.08; p trend = 0.04; ARR = 9.6%), compared to <1/month. Each one serving/week of tuna/other fish was associated with trends toward 11% lower RR of any incident subclinical infarct (95% CI = −0.7–22%, p = 0.07) and 12% lower RR of each additional multiple infarct (95% CI = −0.1–22%, p = 0.05). Further adjustment for other risk factors attenuated these trends, although the directions of effect remained similar to findings seen for prevalent infarct. No associations were seen between fried fish consumption and incident subclinical infarcts (table 3).

Consumption of tuna/other fish was associated with better white matter grade (figure 1). Individuals consuming tuna/other fish ≥3 times/week had 10.6% better white matter grade scores, compared to <1/month (p trend = 0.003), after adjustment for other risk factors. Evaluated continuously, each one serving/week of tuna/other fish was associated with a 3.8% better white matter grade score (p = 0.06). Tuna/other fish consumption was not significantly associated with sulcal or ventricular grades ($p > 0.10$ for each). Conversely, in these models, strong associations with sulcal and ventricular grades were seen for male gender, white race, and higher age, consistent with previously reported findings.[24] Fried fish consumption was not associated with white matter grade (figure 1) or sulcal or ventricular grades ($p >$ 0.10 for each).

Findings for estimated consumption of dietary EPA+DHA were generally similar to those for consumption of tuna/other fish. For example, compared to the lowest quintile of EPA+DHA intake, individuals in the highest quintile had 23% lower risk of prevalent subclinical infarct (RR = 0.77, 95% CI = 0.59–1.00, p = 0.048; p trend = 0.03; corresponding ARR = 6.0%), and 8.7% better white matter grade score (p trend = 0.01).

Little evidence was present for significant effect modification (statistical interaction) by age, sex, race, education, diabetes, CHD at the time of MRI, hypertension, systolic blood pressure, alcohol intake, smoking, or use of aspirin, lipid lowering, or hypertension medications ($p > 0.05$).

DISCUSSION In this large cohort of older adults, higher consumption of tuna/other fish or dietary EPA+DHA was associated with lower prevalence of clinically unrecognized (MRI-defined) infarcts and better white matter grade but not with measures of brain atrophy (ventricular or sulcal grades) among individuals without known TIA or stroke. Tuna/other fish and EPA+DHA consumption were also associated with trends toward lower incidence of subclinical infarcts, although the associations were attenuated and no longer significant after multivariate adjustment, possibly related to limited power (only 187 incident subclinical infarcts). No associations were found between fried fish consumption and any subclinical neurologic abnormalities.

Both subclinical infarcts and white matter abnormalities are commonly observed on MRI scans in the elderly,[1,10,23,24] but most often do not cause acute symptoms or signs and are clinically unrecognized. However, these abnormalities are not benign. Both are associated with cognitive and neurobehavioral impairments and with higher risk of future overt stroke.[2,3,6,25] Recent articles from the Zutphen El-

Table 1 Participant characteristics at the time of the first MRI, according to fish consumption

Characteristic	Tuna or other fish, servings <1/mo (n = 254)	1–3/mo (n = 658)	1–2/wk (1,380)	≥3/wk (n = 571)	Fried fish, servings* <1/mo (n = 1,408)	1–3/mo (n = 915)	≥1/wk (n = 540)
Age, y	76.3 (5.9)	75.4 (5.0)	75.4 (4.9)	74.3 (4.5)†	75.3 (5.0)	75.1 (4.9)	75.3 (5.1)
Male, %	45	45	42	32†	36	44	49†
White race, %	94	96	95	96	97	96	92†
Current smoker, %	11	10	8	8†	9	8	9
Smoking, pack-years	16 (24)	19 (27)	16 (24)	16 (24)†	16 (24)	17 (25)	18 (28)
Education ≥ high school diploma, %	56	71	78	84†	82	73	66†
Coronary heart disease, %	20	19	19	22	19	19	21
Diabetes, %	11	13	13	11	10	14	14†
BMI, kg/m^2	26.0 (4.6)	26.4 (4.5)	26.3 (4.2)	26.8 (4.6)	26.1 (4.5)	26.6 (4.3)	26.6 (4.3)†
Systolic blood pressure, mm Hg	135 (20)	134 (21)	134 (20)	131 (21)†	134 (20)	134 (20)	134 (21)
LDL-C, mg/dL	124 (33)	125 (34)	127 (33)	131 (32)†	127 (34)	126 (32)	128 (33)
HDL-C, mg/dL	52 (14)	52 (14)	54 (15)	54 (14)†	55 (15)	53 (14)	51 (13)†
Triglycerides, mg/dL	145 (85)	147 (83)	143 (80)	143 (82)	141 (84)	148 (81)	146 (78)
Ankle-arm index	1.08 (0.16)	1.10 (0.17)	1.10 (0.17)	1.13 (0.17)†	1.10 (0.16)	1.10 (0.18)	1.09 (0.19)
Leisure-time activity, kcal/wk	1,833 (6,437)	1,532 (4,177)	2,079 (6,728)	1,817 (4,537)	1,816 (5,521)	2,006 (5,948)	1,933 (6,240)
Energy intake, kcal/d	1,630 (640)	1,570 (560)	1,840 (630)	2,050 (650)†	1,610 (530)	1,830 (600)	2,250 (740)†
Saturated fat, % from calories	13 (3)	12 (3)	12 (3)	11 (3)†	11 (3)	12 (3)	13 (3)†
Beef or pork, servings/d	0.9 (0.7)	0.8 (0.6)	0.8 (0.7)	0.8 (0.6)	0.6 (0.6)	0.9 (0.6)	1.2 (0.8)†
Fruits, servings/d	1.7 (1.0)	1.8 (1.0)	2.2 (1.1)	2.6 (1.1)†	2.2 (1.1)	2.1 (1.0)	2.1 (1.1)
Vegetables, servings/d	1.9 (1.3)	1.8 (1.1)	2.6 (1.2)	3.3 (1.4)†	2.5 (1.3)	2.4 (1.3)	2.8 (1.4)†
Alcohol, drinks/wk	1.6 (5.3)	2.1 (5.8)	2.4 (5.1)	2.2 (4.5)	2.4 (5.4)	2.0 (5.2)	1.9 (4.8)†
EPA+DHA, g/d	0.05 (0.03)	0.12 (0.06)	0.31 (0.15)	0.58 (0.28)†	0.29 (0.27)	0.26 (0.18)	0.37 (0.23)†

Values are means (SD) (continuous variables) or percents (categorical variables).
†$p < 0.05$ across categories of intake, adjusted for age.
*Because few persons consumed fried fish ≥5 times per week (n = 22), these participants were combined with those consuming fried fish 1–4 times per week.
BMI = body mass index; LDL-C = low-density lipoprotein cholesterol; HDL-C = high-density lipoprotein cholesterol; EPA = eicosapentaenoic acid; DHA = docosahexaenoic acid.

derly Study[26] and the Atherosclerosis Risk in Communities Study[27] demonstrated inverse associations between dietary or plasma EPA+DHA and cognitive decline among elderly participants. Similar results have been found in some other,[28] but not all,[29] studies. Fish or EPA+DHA consumption has also been associated with lower risk of dementia and Alzheimer disease,[5,30] which are characterized by progressive cognitive decline. Our findings suggest that prevention of subclinical infarcts and white matter abnormalities may be one mechanism whereby fish or EPA+DHA consumption may decrease the development of these debilitating conditions.

Subclinical infarcts and white matter abnormalities are considered to be of vascular origin, presumably resulting from occlusion of small arteries in the brain and subsequent ischemia.[31] Fish consumption has been associated with lower risk of clinical ischemic strokes.[4,32] This lower risk may be related to favorable effects of EPA+DHA on blood pressure, lipids, red blood cell deformability, inflammation, endothelial cell function, cerebral arteriolar reactivity, and platelet function[33-36] (although impact on platelets is very minor at dietary doses of EPA+DHA[37]). In contrast to large clinical strokes, small subclinical infarcts are not thought to be due to arterial stenosis or emboli from the heart or large arteries. Rather, disease of small cerebral vessels is regarded as the most important cause of lacunar infarcts and white matter abnormalities, although exact mechanisms are poorly understood.[38]

Tuna/other fish and EPA+DHA consumption were not associated with sulcal or ventricular grades, indicators of brain atrophy. Thus, the observed associations with subclinical infarcts and white matter abnormalities were relatively specific, rather than reflecting general associations of tuna/other fish or EPA+DHA intake with fewer brain abnormalities. The specificity of the findings suggests that fish consumption, and EPA+DHA, may affect mechanisms

Table 2 Fish consumption and risk of any prevalent subclinical infarct

	Tuna or other fish, servings*					Fried fish, servings†			
	<1/mo (n = 385)‡	1-3/mo (n = 804)‡	1-2/wk (n = 2,037)‡	≥3/wk (n = 902)‡	*p* Trend	<1/mo (n = 1,203)	1-3/mo (n = 801)	≥1/wk (n = 461)	*p* Trend
Age, sex, and race adjusted	1	0.97 (0.73-1.30)	0.85 (0.66-1.10)	0.70 (0.52-0.94)	0.004	1	1.09 (0.88-1.35)	1.12 (0.87-1.45)	0.33
Multivariate adjusted§	1	0.96 (0.72-1.28)	0.87 (0.67-1.15)	0.74 (0.54-1.01)	0.03	1	1.12 (0.89-1.40)	1.20 (0.90-1.60)	0.18

Values are OR (95% CI).
*Dietary intake in 1989-1990 was related to MRI findings in 1991-1994, and dietary intake in 1995-1996 was related to MRI findings in 1997-1999.
‡Numbers represent total MRIs performed, including 1,050 individuals with one MRI scan and 1,539 individuals with MRI scans in both time periods. Data were combined to assess the repeated measures while accounting for both between- and within-individual covariance (specifying that observations were independent across individuals but not within individuals).
§Model adjusted for tuna/other fish intake (four categories), fried fish intake (three categories), age (years), sex, race (white, nonwhite), enrollment center (four sites), diabetes (yes/no), education (<high school, high school, >high school), smoking status (never, former, current), smoking history (pack-years), body mass index (kg/m^2), CHD at the time of MRI (yes/no), alcohol use (beverages/wk), physical activity (kcal/wk), total energy intake (kcal/d), and meat consumption and vegetable consumption (quartiles).
†Based on the first food frequency questionnaire and MRI only.

related to ischemic injury, particularly related to small vessel disease.

Few prior studies have investigated the relationships between consumption of different types of fish meals and risk of stroke.[4,39] We did not find any beneficial associations between fried fish consumption and subclinical brain abnormalities, in accordance with previous studies of fried fish intake and risk of ischemic stroke and CHD.[4,16] In contrast to tuna or other broiled or baked fish meals, the types of fish used in fried fish meals, such as fish burgers or fish sticks, are typically low in EPA+DHA, as supported by the lack of association of fried fish intake with blood levels of these fatty acids.[16] Commercially prepared fried fish meals may also contain trans fatty acids or lipid oxidation products formed when frying oils are used repeatedly.[40] Although not all studies have found differences between types of fish meals consumed,[39] the results of the present article support the growing evidence that the type of fish meal consumed is important for obtaining the health benefits of fish consumption. The lower risk of subclinical brain abnormalities with estimated dietary EPA+DHA consumption suggests that the n-3 fatty acid content of the fish meal may be particularly important.

Our analysis has strengths, including the use of prospectively collected data on dietary intake and MRI findings, the population-based recruitment, the large numbers of participants enrolled, and the extensive standardized examinations of other risk factors. Potential limitations are also present. Participants who underwent MRI scans were somewhat healthier than those who did not, so results may not be fully applicable to the general elderly population. Although interreader reliabilities of white matter and ventricular grades are good, estimates of sulcal grade have greater interreader variability.[24] Information on fish preparation methods (e.g., frying) was unavailable from the second FFQ, limiting our ability to separately evaluate fried fish at the second MRI and possibly biasing results for overall fish consumption toward the null. The estimation of dietary fish and EPA+DHA consumption by FFQ is imperfect and would result in some exposure misclassification. Because this would largely be random with respect to the outcomes, such errors would diminish ability to detect relationships between dietary habits

Table 3 Fish consumption and risk of incident subclinical infarcts

	Tuna or other fish, servings*					Fried fish, servings			
	<1/mo (n = 87)	1-3/mo (n = 243)	1-2/wk (n = 541)	≥3/wk (n = 253)	*p* Trend	<1/mo (n = 569)	1-3/mo (n = 348)	≥1/wk (n = 207)	*p* Trend
Age, sex, and race adjusted	1	0.86 (0.47-1.58)	0.73 (0.41-1.28)	0.56 (0.30-1.07)	0.04	1	0.87 (0.60-1.26)	0.94 (0.60-1.46)	0.63
Multivariate adjusted*	1	0.86 (0.46-1.59)	0.75 (0.41-1.37)	0.65 (0.32-1.31)	0.20	1	0.88 (0.60-1.30)	0.99 (0.60-1.62)	0.80

Values are OR (95% CI).
*Model adjusted for tuna/other fish intake (four categories), fried fish intake (three categories), age (years), sex, race (white, nonwhite), enrollment center (four sites), diabetes (yes/no), education (<high school, high school, >high school), smoking status (never, former, current), smoking history (pack-years), body mass index (kg/m^2), CHD at the time of MRI (yes/no), alcohol use (beverages/wk), physical activity (kcal/wk), total energy intake (kcal/d), and meat consumption and vegetable consumption (quartiles).

and disease risk; thus, our results are likely to underestimate the true association between fish or EPA+DHA consumption and risk of subclinical brain abnormalities. The FFQs and MRI scans were not administered simultaneously; however, FFQs assess long-term habitual dietary intakes. Observed associations could be related to other differences related to fish consumption, such as a healthier lifestyle in general. However, we adjusted for a variety of other risk factors and lifestyle habits.

Our results support the need for randomized trials of fish or fish oil intake to reduce subclinical ischemic events, which would be feasible and important given the high incidence of such events in older adults.

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