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Association of fish oil supplement use with preservation of brain volume and cognitive function

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Abstract

Objective—The aim of this study was to investigate whether the use of fish oil supplements (FOSs) is associated with concomitant reduction in cognitive decline and brain atrophy in older adults.

Methods—We conducted a retrospective cohort study to examine the relationship between FOS use during the Alzheimer's Disease Neuroimaging Initiative and indicators of cognitive decline. Older adults (229 cognitively normal individuals, 397 patients with mild cognitive impairment, and 193 patients with Alzheimer's disease) were assessed with neuropsychological tests and brain magnetic resonance imaging every 6 months. Primary outcomes included (1) global cognitive status and (2) cerebral cortex gray matter and hippocampus and ventricular volumes.

Results—FOS use during follow-up was associated with significantly lower mean cognitive subscale of the Alzheimer's Disease Assessment Scale and higher Mini-Mental State Examination scores among those with normal cognition. Associations between FOS use and the outcomes were observed only in *APOE* ε4–negative participants. FOS use during the study was also associated with less atrophy in one or more brain regions of interest.

Keywords

Alzheimer's disease; Brain atrophy; Cognition; Docosahexaenoic acid; Omega-3

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1. Introduction

Fish oil is a rich source of eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), and long-chain polyunsaturated omega-3 fatty acids (n-3 PUFAs). For increasing numbers seeking to augment their diets for cognitive health, factors such as convenience, cost, and concerns about long-term effects of methyl mercury may motivate the use of fish oil supplements (FOSs) to replace or augment dietary consumption of marine sources of n-3 PUFAs [1].

Although observational studies have generally reported better cognitive functioning or lower rates of incident Alzheimer's disease (AD) in populations reporting greater dietary intake of fatty fish, but with few exceptions [2–8], the results of placebo-controlled trials of 3- to 24-month treatment with DHA or DHA + EPA have not supported these findings [9–12]. Treatment with n-3 PUFAs has been ineffective in controlled trials of mild-to-moderate AD [13–16]; however, there is some evidence that intervening in very mild AD or mild cognitive impairment (MCI) may be beneficial [8,14,17,18].

By the time that AD is clinically evident, years of cumulative neuropathology has already occurred, so it is not surprising that n-3 PUFA supplements do not benefit cognition in established dementia. If neuroprotective roles exist for DHA and EPA, then biological markers of neuro-degeneration such as cognitive performance and volumetric magnetic resonance imaging (MRI) measures should be relatively preserved in FOS users [19], particularly in those taking them prophylactically or early in the neuropathologic process.

The primary objective of this study was to examine the relationship between the use of FOSs and concomitant longitudinal brain structural changes, as well as cognition across the spectrum of aging and age-related neurodegeneration. Second, we sought to investigate associations between duration of FOS use and these outcomes. To accomplish these aims, we examined repeated standardized measurements of brain volume (BV) and cognition from the Alzheimer's Disease Neuroimaging Initiative (ADNI) cohort [20,21].

2. Methods

2.1. Design

We conducted a retrospective cohort study of participants recruited into the ADNI from inception to August 2010. ADNI is a 5-year multicenter study launched in 2003 to assess changes of cognition, brain structure, and biomarkers in three groups of elderly individuals: normal controls, MCI, and AD [21]. Study methods are available at www.adniinfo.org.

Written consent was obtained from subjects before participation in the ADNI. This study protocol was reviewed and designated as exempt for human subjects research by the Rhode Island Hospital Institutional Review Board.

2.2. Participants

A total of 819 elderly participants (229 with normal cognition [NC], 397 MCI, and 193 AD), aged 55 to 90 years, were recruited into the ADNI from 50 clinical centers in the United

States [22]. After screening and baseline visits, follow-up evaluations were conducted at 6-month intervals for up to 48 months for NC and MCI subgroups; AD participants were assessed at 6-month intervals for up to 24 months and at month 36. Results of comprehensive neuropsychological testing and brain MRI were documented for all participants at 6- to 12-month intervals. Ninety-five percent of the ADNI participants attended at least one postbaseline study visit, and 80% of the cohort had four or more follow-up assessments.

The analysis cohort consisted of 117 participants reporting FOS use at the initial study visit and during follow-up and 682 who did not report FOS use during the study. Eleven participants initiated FOS use during follow-up; this group was excluded from the analysis cohort because the duration of FOS use was brief (≤6 months) or supplements were initiated too late in the study to allow adequate time for follow-up. The unexposed cohort (n = 691) included participants who did not report FOS use during the study; nine were subsequently excluded because of missing outcome data.

2.3. Exposure classification

Information on FOS use was extracted from the ADNI concomitant medication file, a longitudinal record of medication use within the cohort. According to the protocol, subjects were queried about prescription and nonprescription drug uses at screening and subsequent study visits. For those with memory impairment, study partners assisted research staff with medication reconciliation. For each participant, we constructed the primary exposure variable, FOS use, defined as the presence or absence of any form of FOSs reported during the study visit. The FOS user status was ascertained at each visit, and the participant-reported date of initiation was designated as the first day of FOS exposure in the data set. Those using FOSs at consecutive visits were considered to be continuously exposed between visits. The duration of FOS exposure for each subject was estimated by subtracting the discontinuation date from the start date; for those who did not discontinue FOSs during the study, the date of the last visit was considered the final day of FOS exposure.

2.4. Outcomes

The primary outcome measures were the total scores at each visit for (1) the cognitive subscale of the 70-point Alzheimer's Disease Assessment Scale (ADAS-cog) and the Mini-Mental State Examination (MMSE) and (2) cerebral cortex gray matter, ventricle, and hippocampus volumes from serial MRI. The secondary outcome measure was the estimated duration of FOS use.

2.5. Brain imaging acquisition and processing

All participants received high-resolution structural brain MRI scans on 1.5-T scanners as specified by the ADNI protocol [23]. Multiple procedures to minimize cross-site variation were used during the study, including standardized MRI protocols and acquisition parameters and systematic phantom-based monitoring of instruments. Raw three-dimensional T1-weighted magnetization-prepared rapid acquisition gradient echo images were preprocessed (gradient warping, scaling, B1 correction, and N3 inhomogeneity correction). Acquisition, quality control, and preprocessing of ADNI MRI data are described

at http://adni.loni.ucla.edu/research/protocols/mri-protocols. Segmentation of brain regions was performed on T1-weighted images using an automated set of algorithms implemented in FreeSurfer (https://surfer.nmr.mgh.harvard.edu). Specifically, raw imaging data were downloaded from ADNI by Dr. Anders Dale and colleagues at the Departments of Neurosciences and Radiology, University of California, San Diego. Phantom scans were used to correct for gradient nonlinearities, followed by image intensity normalization. Neuroanatomic labels are assigned to each voxel based on probabilistic information estimated from an atlas. Accuracy of this procedure has been shown to be comparable with that of manual labeling and sensitive to subtle changes in AD and normal aging. The volumes so acquired were uploaded to the ADNI Web site for access by investigators. For this study, volumetric measures in millimeter [2] were downloaded from ADNI for the cerebral cortex gray matter, ventricles, and hippocampus. These regions were selected based on their relevance to neuropathology of AD. Overall ventricular volume was derived by combining volumes for all ventricles for each brain. Likewise, bilateral hippocampal volumes were combined. Total intracranial volumes were used in accounting for variation in head sizes in all volumetric analyses.

2.6. Cognitive evaluation

The ADAS-cog consists of 11 items measuring memory, language, praxis, attention, and other aspects of cognitive functioning. Total scores range from 0 to 70, with higher scores indicating greater levels of impairment. The MMSE assesses seven cognitive domains, including attention, memory, and visual construction. Total scores range from 0 to 30 points, with higher scores indicating better cognitive function.

2.7. Potential confounders

Confounders were chosen a priori and represent the participant-level characteristics available in the data set that could be associated with the exposure and outcomes. Cognitive models controlled for age, gender, education, race, vascular risk factors, *APOE* ε4 carrier status, cholinesterase inhibitor (CHEI) use, and baseline cognitive diagnosis and cognitive test scores. BV models controlled for age, gender, vascular risk factors, education, *APOE* ε4 carrier status, CHEI use, intracranial volume, and baseline cognitive diagnosis and region of interest volumes (cerebral cortex gray matter/ventricle/hippocampus).

The potential effects of vascular risk factors on cognition and BV were summarized in the models with a cardiovascular (CV) risk score using the method by Carmichael et al. [24] for ADNI data. One point is assigned for a baseline diagnosis of CV disease, current tobacco use, hypertension, diabetes, and cerebrovascular accident or stroke; the CV risk score (range, 0–5) is the sum of these scores.

2.8. Statistical analysis

Baseline sociodemographics, duration of FOS use, and subgroup means for the outcomes (cognitive test scores and BVs) were compared using χ^2 tests and one-way analyses of variance (ANOVAs). Using a series of longitudinal regression models implemented with generalized estimating equations (GEEs) [25,26] with robust standard errors (SEs), longitudinal changes for each outcome measure were assessed, as well as associations

between time-varying FOS exposure (users vs. nonusers at each visit) and the outcomes in the analysis cohort and the cognitive subgroups. The effect of duration of FOS exposure on the outcomes was assessed similarly.

GEE models do not require a distributional form of the response variable (cognition and BVs in this study) and have been shown to provide unbiased estimates of the model parameters even in the case when the within-subject correlation structure is incorrectly specified [25,26]. A working autoregressive correlation structure was chosen to accommodate within-subject correlation. GEEs are used to model incomplete longitudinal data and assume the missing data are missing completely at random, an assumption that cannot be directly tested. No imputation of missing values was performed. Analyses were performed using Stata, version 10.0 (StataCorp, College Station, TX, USA), and SAS, version 9.2 (SAS Institute Inc, Cary, NC, USA), and the significance level was set a priori to $\alpha = 0.05$.

2.9. Relationship between FOSs and the study outcomes

2.9.1. Primary analyses—In the analysis cohort, we simultaneously regressed the cognitive and BV outcomes at time t ($t = 6, \ldots, 48$ months) on time and the use of FOSs at time t, while controlling for confounders (Section 2.7).

2.9.2. Secondary analyses—To further investigate associations between FOS use during follow-up and the cognitive and brain structural outcomes, we conducted several secondary analyses. All models controlled for cognitive group membership (except the within-group analyses of cognitive diagnosis) and other potential confounders as in the previous analyses.

2.9.3. *APOE* ε4 genotype—After stratifying the analysis cohort by the *APOE* ε4 carrier status, associations between FOS use and change over time in cognition and BV were evaluated.

2.9.4. Cognitive diagnosis—The analysis cohort was stratified by diagnostic group membership at study entry (NC, MCI, and AD), and the cognitive and BV analyses were repeated.

2.9.5. Duration of exposure—The effect of duration of FOS exposure was investigated using longitudinal models to regress cognitive and BV outcomes on participant-reported time on FOSs within the analysis cohort. Time on FOSs was defined as (1) duration of supplement use at baseline and (2) cumulative time on FOSs (duration of exposure at baseline + follow-up) in months. Duration variables were entered into the models as continuous variables, then in quartiles. All duration models were evaluated with and without the FOS use indicator variable.

2.9.6. Sensitivity analysis—Lifestyle factors (e.g., diet, exercise, and other health habits) are potential confounders of the association between FOSs and the outcomes; however, this information was not collected during ADNI. As such, we considered multivitamin use at baseline as a proxy for this information and repeated the previous analyses, controlling for use of multivitamin supplements.

3. Results

3.1. Participant characteristics

Baseline characteristics of the cohort are presented in (Table 1). The three cognitive subgroups were similar in age, gender distribution, and race/ethnicity. In comparison with participants without dementia at baseline, the MCI and AD groups were more cognitively impaired (lower MMSE scores and higher ADAS-cog scores) and had a higher proportion of *APOE* ε4 carriers. Mean cerebral cortex gray matter volume was not significantly different between the groups at baseline; however, NC subjects had smaller ventricles ($P < .05$) than those with AD and smaller hippocampus volumes than those observed in the MCI ($P < .001$) and AD ($P < .001$) groups.

Within the ADNI cohort, 14.3% (n = 117) reported regular use of FOSs (NC, 13.5%; MCI, 8.2%; and AD, 30%) at the initial study visits. The proportion of ADNI participants using FOSs at baseline and at one or more subsequent study visits during follow-up was 95.7% (n = 112) at 12 months, 87.2% (n = 102) at 24 months, 64.9% (n = 76) at 36 months, 32.5% (n = 38) at 42 months, and 11.1% (n = 13) at the 48-month study visit. The number of FOS users assessed at each time point during the ADNI is shown in Table 2.

Most reported long-term FOS use before enrollment in the ADNI study; 11.1% reported FOS use exceeding 10-year duration and 59.8% reported 1 to 10 years of use. The remainder (29.8%) used FOSs for less than 12 months on entering the study. Those with NC at baseline reported the longest mean duration of use (6.0 years [standard deviation {SD}, 9.5 years]), followed by the MCI (4.7 years [SD, 7.6 years]) and AD (2.7 years [SD, 2.5 years]) groups. Duration of FOS use at study entry differed significantly between diagnostic groups [$F(2, 816) = 10.87$, $P = .001$]. Bonferroni post hoc comparisons indicated that FOS duration of use for the NC and MCI groups exceeded that reported by those with AD (NC vs. AD, $M = 3.30$, 95% CI, 1.57–5.03, $P < .001$; MCI vs. AD, $M = 2.00$, 95% CI, 0.443–3.56, $P < .01$). There was a trend toward statistical significance for greater years of FOS use in the NC versus MCI comparison (NC vs. MCI, $M = 1.30$, 95% CI, −0.1725 to 2.773, $P = .06$).

The majority (88.9%) of ADNI participants using FOSs at enrollment reported that supplements were primarily used for “general health,” whereas 2.7% cited “joint protection/arthritis” reasons. Few (4.3%) endorsed the use of FOSs for “memory/brain protection”; all had been diagnosed with a memory disorder at baseline (MCI, n = 3; AD, n = 2).

3.2. Primary analyses

3.2.1. Associations between FOS use and cognitive/BV outcomes in the ADNI cohort—In general, ADAS-cog scores increased over time (β = 0.05; SE, 0.01; $P < .01$) and MMSE scores decreased over time (β = −0.05; SE, 0.01; $P = .02$); however, significant associations between FOS use and both cognitive outcome measures were observed at follow-up (6–48 months; Table 3). Compared with nonusers, reported use of FOSs during follow-up was associated with lower mean ADAS-cog scores (β = −3.86; SE, 1.59; $P = .02$) and higher mean MMSE scores (β = 0.96; SE, 0.43; $P = .02$) at any given time in the study.

Overall, mean hippocampus volume decreased significantly over time (β = −12.69; SE, 0.55; P <.01), as did cerebral cortex gray matter volume (β = −305.02; SE, 23.21; P <.01), whereas mean ventricular volume increased over time (β = 234.77; SE, 9.61; P <.01). Use of FOSs at any given time (t) during the study was associated with brain structural differences compared with those not reporting use of FOSs during follow-up: increased hippocampal volume at month t (β = 160.80; SE, 70.65; P =.02), decreased ventricular volume (β = −2330.46; SE, 1085.19; P =.03), and increased cerebral cortex gray matter volume (β = 11904.12; SE, 4477.22; P <.01).

3.3. Secondary analyses

3.3.1. Associations between FOS use and the *APOE* ε4 carrier status— Stratifying the analysis cohort by the *APOE* ε4 carrier status revealed that the association between FOSs and better cognitive scores (ADAS-cog and MMSE) remained significant only in the *APOE* ε4 (−) group. FOS use during the study was also associated with significantly higher mean hippocampus (β =232.15; SE, 39.62; P <.01) and cerebral cortex gray matter volumes (β = 14988.00; SE, 4980.90; P < .01) in *APOE* ε4 noncarriers; however, no association was found between FOS use and ventricular volume in the stratified sample.

3.3.2. Associations between FOS use and cognitive/BV outcomes in the cognitive subgroups—When the cohort was stratified by groups (NC, MCI, and AD), significant associations between FOS use during the study and cognition (ADAS-cog and MMSE) were observed only in those with baseline normal cognitive function (Table 4). In the fully adjusted model, mean ADAS-cog scores were lower at any given time t for FOS users at time t compared with nonusers (β = −7.01; SE, 1.56; P < .01). In addition, the mean MMSE score was higher among FOS users compared with nonusers (β = 1.94; SE, 0.28; P < .01). In the NC group, FOS use during follow-up was also associated with higher mean hippocampus (β = 299.39; SE, 46.97; P <.01) and cerebral cortex gray matter volumes (β = 18255.70; SE, 2561.43; P < .01) at any point in the study (Table 4). Brain imaging analyses within the MCI and AD groups revealed a significant positive association between FOS use during the study and mean cerebral cortex gray matter volumes in the MCI cohort and mean hippocampal volumes in the AD subgroup compared with FOS nonusers.

3.3.3. Associations between duration of FOS use and cognitive/BV volume outcomes in the ADNI cohort—Estimated participant-reported time on FOSs (duration of supplement use before baseline and total time on FOSs [duration of exposure before study entry + follow-up]), in months, was entered into the cognitive and BV models, first with duration before baseline, then using total time on FOSs. No associations between duration of FOS exposure and any of the cognitive or BV outcomes were observed (data not shown).

3.4. Sensitivity analysis

Controlling for documented use of multivitamins at baseline in the cohort in analyses for the primary and secondary outcomes did not significantly change the parameter estimates in any of the cognitive and BV models.

4. Discussion

This retrospective cohort study is the first to examine the potential association of ongoing FOS use with conservation of BV and cognition across the spectrum of normal aging and neurodegeneration. After adjusting for potential confounders, use of FOSs during the ADNI was associated with less cerebral cortex gray matter and hippocampal atrophy and better performance on the ADAS-cog and MMSE, on average, compared with nonusers; these results were observed in the entire ADNI cohort, for those without a dementia diagnosis at baseline, and in the *APOE* ε4 (−) group.

Our findings in the cognitively normal group complement those of other recent observational studies that have investigated the relationship between cognitive function, brain atrophy, and n-3 PUFA levels in nondemented elderly. Bowman et al. [27] used principal component analysis to identify associations between plasma nutrient biomarker patterns and cognition, as well as total cerebral volume and percentage of white matter hyperintensities (WMHs) in the Oregon Brain Aging Study cohort. Another cross-sectional study contrasted quartiles of red blood cell n-3 PUFA concentrations for middle-aged and elderly participants in the Framingham study [28] and reported that the lowest levels of DHA and DHA + EPA were associated with lower total brain and greater WMH volumes, as well as greater cognitive deficits in multiple domains. Samieri et al. [29] reported that higher baseline plasma levels of EPA, but not DHA, were associated with less regional gray matter atrophy in the right amygdala and sections of the right hippocampal and parahippocampal areas over 4 years in a subgroup of elders participating in the French Three-City Study.

Not surprisingly, we did not find support for cognitive benefits associated with FOS use during the study in the AD subgroup in this observational study; these results are consistent with outcomes of well-designed randomized controlled trials of DHA in dementia populations. The null association for FOS use during follow-up and the cognitive outcomes in the MCI subgroup is discordant with results of controlled trials of DHA in this at-risk population [8,14,17,18]. The relationships of FOS use with preserved cerebral cortex gray matter volume in MCI and hippocampus volume in AD have not been previously reported. In contrast, an 18-month clinical trial of DHA in AD patients failed to show any effect on MRI volumes [13]. We may have been able to demonstrate hippocampal volume differences in FOS users with AD if the exposure overlapped a critical period for neuroprotection, including the prodromal phase, when FOS use may have its greatest effects. However, these analyses must be interpreted cautiously because of the potential influence of reverse causation because participants may have initiated FOS use to treat clinical symptoms of neurodegeneration.

Currently, there is limited understanding of how certain factors, such as timing and duration of exposure, might moderate n-3 PUFAs' neuroprotective and cognitive effects. Although a number of prospective cohort studies have identified positive associations between consumption of fatty fish and better cognitive health in long-term follow-up, the effects of supplemented fish oils or DHA have been studied in controlled trials for much shorter periods, up to 18 months in populations with dementia or MCI and 24 months in the cognitively normal elderly [9,16]. The predominance of ADNI participants using FOSs for

unusually long periods was unexpected but provided a unique opportunity to study multiple clinical outcomes during long periods of exposure to supplemented n-3 PUFAs. Those reporting 10 or more years of FOS use would have initiated the supplements during midlife, a potentially important time for interventions aimed at preventing age-related cognitive decline. Of note, surrogate markers of preclinical AD (e.g., memory deficits, smaller whole brain and regional BVs, and cerebrospinal fluid and brain amyloid imaging) are observed in *APOE* ε4 carriers, as early as midlife [30,31].

Middle age may be a particularly significant period for the potential role of n-3 PUFA in cognitive aging. Two recent observational studies support this theory [32,33]; both reported positive associations between higher concentrations of DHA or total n-3 PUFAs + DHA and better cognitive function in subjects aged 44 to 64 years. One of the studies [32] examined the effect of *APOE* ε4 and determined that the association between the n-3 PUFA status and cognitive performance over 4 years of follow-up was significant only in the *APOE* ε4 (−) group. It is unclear whether n-3 PUFAs are ineffective in counteracting the deleterious effects of *APOE* ε4 in the brain or if adequate levels of long-chain fatty acids before, or during middle age, might mitigate early neurodegenerative processes in at-risk individuals. Intervening with DHA supplements in nondemented *APOE* ε4 carriers in late life may have questionable benefits, based on recent studies that indicate significant impairment of DHA homeostasis in this group [34,35]. Compared with noncarriers, those who are *APOE* ε4 (+) achieve lower than expected plasma levels in response to an oral dose of DHA and have marked decrements in whole-body clearance [36].

Thus, accumulating evidence points to *APOE* as the most important moderator of n-3 PUFA effectiveness in the aging brain [4,13,32,34,35,37]. The relationship between *APOE* genotype and PUFA-mediated neuroprotection has been investigated in a number of epidemiologic studies of older adult populations; most have reported associations of better cognitive effectiveness in *APOE* ε4 non-carriers [4,32,37,38]. We found similar results in the subgroup analysis of the entire study cohort, stratified by the *APOE* ε4 carrier status.

This study is the first to report an association between FOS use and brain structural changes in all three cognitive diagnostic groups; these findings may suggest a potential role for FOSs by reducing neurodegeneration over time. The neuroprotective activities of n-3 PUFAs may be largely mediated through vascular effects; however, other mechanisms have been proposed, including the activities of neuroprotectin D1 (NPD1), a potent lipid mediator synthesized from DHA during periods of oxidative stress [39]. In animal models, NPD1 mitigates AD-related neurodegeneration through downregulation of inflammatory signaling pathways, modulation of amyloid precursor protein cleavage, and removal of apoptotic cells and may play an important role in preventing or slowing progression of dementia [40,41].

Our inability to demonstrate a significant association between duration of FOS use with the cognitive or BV outcomes contradicts the results of the analyses in which exposure was characterized as time-varying FOS use. Although one explanation might be a true lack of a biologic relationship between the length of the exposure and study outcomes, this reasoning seems unlikely given the putative neuroprotective mechanisms ascribed to DHA and the lengthy duration of FOS exposure, particularly among those with NC at baseline. However,

it seems more plausible that the null association may be related to the presence of unmeasured confounding. Because the ADNI data set lacked data on factors such as lifestyle and nutrition (fatty fish consumption) or a biologic measure of the n-3 PUFA status, we were unable to consider this information in the analyses [42]. Those who were FOSs exposed for shorter durations may have had long-term exposures to other forms of n-3 PUFAs. In this scenario, the short- and long-term users may have similar levels of exposure, leading to attenuated differences between the two groups. Because individuals who routinely use nutritional supplements generally report better health habits, we conducted sensitivity analyses, controlling for use of vitamin supplements in the models for the primary and secondary outcomes; however, the results were not informative of between-group differences.

In addition, misclassification bias is an important consideration in observational studies that rely on self-reported exposures. Inaccurate recall of details of remote exposures is not an infrequent occurrence; in this study, nondifferential misclassification of exposure duration in the cognitively impaired subgroups may have contributed to the lack of association between FOS duration and the outcomes. ADNI procedures did not require verification of medication use beyond self-report, so these possibilities cannot be eliminated.

Our findings should be evaluated within the context of several other limitations. The first, and the most important, is the possibility that the associations between FOS exposure during the study and the outcomes might be explained by reverse causation (also known as protopathic bias). Because the study population included prevalent users of FOSs, including those with MCI and AD, it is possible that preclinical or subtle cognitive changes were determinants of FOS exposure in these subgroups. Compared with the NC group, AD participants were more than twice as likely to report FOS use, and the duration of exposure (mean, 2.7 years) suggests initiation of supplements could have been coincident with established neurodegenerative processes.

We investigated participant-reported reasons for FOS use and found that few endorsed using FOSs for cognitive benefits. The majority used FOSs for “general health”; however, these participants may have initiated FOSs to treat or prevent multiple conditions, including cognition.

Second, unique aspects of this study cohort may limit the generalizability of our results; ADNI participants are better educated, have higher premorbid intelligent quotients, and are less racially and ethnically diverse than the general elderly population [22].

5. Conclusion

Effective and safe interventions to prevent or delay the onset and treat AD are urgently needed. At present, increasing numbers of older adults use FOSs for cognitive health, without evidence for effectiveness. Although a causal effect of FOS use on cognition and brain atrophy cannot be concluded from our results, they highlight the need for future research on the effects of long-term FOS use on cognitive aging and dementia prevention in middle-aged and older adults.

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RESEARCH IN CONTEXT

1. Systematic review: Although observational studies have generally reported positive associations between higher quantities of fish consumption and lower rates of cognitive decline or incident Alzheimer's disease (AD) in nondemented elderly, with few exceptions, the results of randomized, double-blind, placebo-controlled trials of 3- to 24-month treatment with docosahexaenoic acid (DHA) have not supported these findings. Additionally, DHA as a treatment for cognitive impairment in dementia has been shown to be generally ineffective in placebo-controlled trials in mild-to-moderate AD; however, there is some evidence that intervening in very mild AD or in mild cognitive impairment (MCI) may be beneficial.
2. Interpretation: This retrospective cohort study examines relationships between reported use of DHA (in the form of fish oil supplements [FOSs]) during ADNI and longitudinal changes in cognitive performance and brain volume in normal controls, MCI, and AD subjects. The innovation of this report is the (1) investigation of cognitive and brain structural outcomes associated with FOS use for durations exceeding those used in randomized clinical trials and (2) analysis of longitudinal outcomes in the population stratified by *APOE* ε4 genotype—a potential moderator of DHA cognitive effects that has not been available in a number of previous observational studies and controlled trials.
3. Future directions: The effects of long-term FOS use on sensitive biomarkers of cognitive aging should be studied in randomized controlled trials of middle-aged or older adults.

Table 1

Population characteristics at baseline

Characteristics	All (n = 819)	NC (n = 229)	MCI (n = 397)	AD (n = 193)	*P* value*
Age, y, mean ± SD	75.3 ± 6.9	76.0 ± 5.0	74.9 ± 7.5	75.5 ± 7.5	.14
APOE ε4 status, % (N)					
Carrier (+)	48.4 (400)	26.6 (61)	53.4 (212)	65.8 (127)	<.0001
Noncarrier (−)	51.2 (419)	73.4 (168)	46.6 (185)	34.2 (66)	<.0001
Gender, %					
Female	41.8	48.0	35.5	47.2	.36
Race, % (N)					
Caucasian	93.0 (762)	91.7 (210)	93.5 (371)	93.8 (181)	.94
CV risk score, mean ± SD	1.75 ± 1.11	1.67 ± 1.1	1.78 ± 1.1	1.77 ± 1.1	.44
Fish oil supplement use, % (N)	14.3 (117)	13.5 (31)	8.1 (32)	28 (54)	<.0001
Duration of fish oil supplement use by cognitive subgroup, y, mean ± SD		6.0 ± 9.5	4.7 ± 7.6	2.7 ± 2.5	<.001
Cognition, mean ± SD					
MMSE	26.8 ± 2.7	27.8 ± 2.4	26.7 ± 2.4	25.7 ± 2.8	<.0001
ADAS-cog	11.7 ± 6.4	6.2 ± 2.9	11.5 ± 4.4	18.6 ± 6.3	<.001
MRI volumetric comparisons					
Hippocampus volume (mm^3)		6768.68 (1108.90)	6273.37 (1144.57)	6290.48 (1200.12)	<.0001
Ventricular volume (mm^3)		43262.19 (24182.39)	45502.06 (23143.11)	49274.90 (28633.18)	.04
Cerebral cortex volume (mm^3)		392689.40 (41706.61)	387538.93 (42602.97)	384431.73 (43391.82)	.13
Intracranial volume (mm^3)		1460204.18 (139330.04)	1472862.07 (148113.38)	1441954.67 (154518.06)	.07

Abbreviations: NC, cognitively normal controls; MCI, mild cognitive impairment; AD, Alzheimer's disease; SD, standard deviation; *APOE*, apolipoprotein E; CV, cardiovascular; MMSE, Mini-Mental State Examination; ADAS-cog, Alzheimer's Disease Assessment Scale—cognitive subscale.

*Cognitive subgroup comparisons.

Table 2

Numbers of participants using FOSs at baseline and during the ADNI

Study visit	Normal cognition, attended assessment (n)	Mild cognitive impairment, attended assessment (n)	Alzheimer's disease, attended assessment (n)
Baseline	31	32	54
Month 12	31	28	49
Month 24	28	24	42
Month 36	24	19	33
Month 42	10	16	12
Month 48	6	5	3

Abbreviations: FOS, fish oil supplement; ADNI, Alzheimer's Disease Neuroimaging Initiative.

Table 3

Covariate-adjusted parameter estimates for main effects of FOS use and time (ADNI analysis cohort)*

		Main effect of time			Main effect of FOS use		
Outcome variable	**Group**	**Value**	**SE**	***P* value**	**Value**	**SE**	***P* value**
Cognitive outcomes							
ADAS-cog	ADNI cohort	0.05	0.01	<.01	−3.86	1.59	.02
	APOE ε4 (+)	0.08	0.02	<.01	−1.40	4.27	.74
	APOE ε4 (−)	0.02	0.01	.07	−4.68	1.40	<.01
MMSE	ADNI cohort	−0.05	0.01	.02	0.96	0.43	.02
	APOE ε4 (+)	−0.07	0.01	<.01	0.16	0.53	.76
	APOE ε4 (−)	−0.04	0.01	<.01	1.12	0.44	.01
Brain volume outcomes							
Hippocampus volume	ADNI cohort	−12.69	0.55	<.01	160.80	70.65	.02
	APOE ε4 (+)	−13.80	0.81	<.01	−34.68	111.24	.76
	APOE ε4 (−)	−11.78	0.72	<.01	232.15	39.62	<.01
Ventricular volume	ADNI cohort	234.77	9.61	<.01	−2330.46	1085.19	.03
	APOE ε4 (+)	271.94	15.23	<.01	−2746.48	2105.34	.19
	APOE ε4 (−)	201.37	11.43	<.01	−1786.25	1134.96	.12
Cerebral cortex gray matter volume	ADNI cohort	−305.02	23.21	<.01	11904.12	4477.22	<.01
	APOE ε4 (+)	−357.89	32.72	<.01	5585.13	3131.46	.07
	APOE ε4 (−)	−258.52	32.08	<.01	14,988	4980.90	<.01

Abbreviations: FOS, Fish oil supplement; ADNI, Alzheimer's Disease Neuroimaging Initiative; SE, Standard error; ADAS-cog, Alzheimer's Disease Assessment Scale—cognitive subscale; *APOE*, Apolipoprotein E; MMSE, Mini-Mental State Examination; CVD, Cardiovascular disease.

*Cognition models controlled for age, gender, education, race, CVD risk score, *APOE* ε4 carrier status, cholinesterase inhibitor use, and baseline scores. Brain volume models controlled for age, gender, CVD risk score, education, *APOE* ε4 carrier status, cholinesterase inhibitor use, and baseline intracranial volume.

Table 4

Covariate-adjusted parameter estimates for main effects of FOS use and time (cognitive subgroups)*

		Main effect of time			Main effect of FOS use		
Outcome variable	**Group**	**Value**	**SE**	***P* value**	**Value**	**SE**	***P* value**
Cognitive outcomes							
ADAS-cog	NC	−0.01	0.01	.59	−7.01	1.56	<.01
	MCI	0.08	0.02	<.01	−3.29	2.57	.20
	AD	0.10	0.03	<.01	−4.58	3.04	.13
MMSE	NC	−0.01	0.01	.05	1.94	0.28	<.01
	MCI	−0.07	0.01	<.01	0.68	0.62	.28
	AD	−0.08	0.01	<.01	0.88	0.46	.06
Brain volume outcomes							
Hippocampus volume	NC	−10.31	0.79	<.01	299.39	46.97	<.01
	MCI	−14.49	0.81	<.01	88.16	143.71	.54
	AD	−11.95	1.31	<.01	195.02	64.78	<.01
Ventricular volume	NC	161.50	11.20	<.01	−1051.43	740.31	.16
	MCI	273.28	15.24	<.01	−2070.55	1621.73	.20
	AD	265.56	22.48	<.01	−2831.05	2042.54	.17
Cerebral cortex gray matter volume	NC	−218.29	35.51	<.01	18255.70	2561.43	<.01
	MCI	−350.57	34.98	<.01	17406.86	3994.45	<.01
	AD	−345.89	53.20	<.01	−1331.65	1675.79	.43

Abbreviations: FOS, Fish oil supplement; SE, Standard error; ADAS-cog, Alzheimer's Disease Assessment Scale—cognitive subscale; MMSE, Mini-Mental State Examination; NC, Cognitively normal controls; MCI, Mild cognitive impairment; AD, Alzheimer's disease.

*Cognition models controlled for age, gender, education, race, CVD risk score, *APOE* ε4 carrier status, cholinesterase inhibitor use, and baseline scores. Brain volume models controlled for age, gender, CVD risk score, education, *APOE* ε4 carrier status, cholinesterase inhibitor use, and baseline intracranial volume.

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