Effects of N-3 Polyunsaturated Fatty Acids on Dementia

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Abstract

N-3 polyunsaturated fatty acids (PUFAs) including α-linolenic acid (ALA), eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) have anti-inflammatory effects and neuronal protective functions and may benefit prevention of dementia; however, the epidemiological evidence is very limited. Therefore, the literature about the association between n-3 PUFA and dementia was searched, by using Pubmed. In the analyses of observational studies, n-3 PUFA has been reported to be beneficially associated with dementia in 17 studies; however, the beneficial association between n-3 PUFA and dementia was denied by three studies. In the analyses of intervention studies, n-3 PUFA supplementation was beneficially associated with dementia in eight studies; however, five studies reported the negligible effect of n-3 PUFA for dementia. N-3 PUFA may improve Alzheimer’s disease by increasing clearance of amyloid-β peptide, neurotrophic and neuroprotective factors, and by anti-inflammatory effects. In conclusion, patients with mild memory and/or cognitive impairment can be treated by a long-term and higher intake of n-3 PUFA.

Keywords: Alzheimer’s disease; Docosahexaenoic acid; Eicosapentaenoic acid; N-3 polyunsaturated fatty acids

Introduction

It has been considered that n-3 polyunsaturated fatty acids (PUFAs) including α-linolenic acid (ALA), eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) have anti-atherosclerotic and anti-inflammatory effects and also neuronal protective functions and may benefit prevention of dementia; however, the epidemiological evidence is limited. Furthermore, there is a lack of consensus on the benefits of EPA and DHA supplemenations on cognition in dementia and/or Alzheimer’s disease (AD) elderly. An National Institutes of Health (NIH) State of the Science Conference panel concluded in 2010 that insufficient evidence is available to recommend the use of any primary prevention therapy for AD or cognitive decline with age [1]. Therefore, the literatures were reviewed to find whether serum n-3 PUFAs are associated with risk of dementia.

The Search Strategy and the Results

The literature about the association between n-3 PUFA and dementia was searched, by using Pubmed. Eighty-nine, 206 and 398 articles were found by using “EPA and dementia”, “DHA and dementia” and “n-3 PUFA and dementia and human or omega-3 PUFA and dementia and human” as the keywords, respectively. After the review of the literatures, articles were divided into “observational studies”, “intervention studies” and “the underlying mechanisms for n-3 PUFA-mediated improvement or prevention of dementia”.

The Observational Studies Which Investigated the Association Between N-3 PUFA and Dementia

The observational studies which assessed the association between n-3 PUFA and dementia are shown in Table 1 [2-21]. Recently, Yamagishi et al performed an intra-cohort case-control study nested in a community-based cohort, involving 7,586 Japanese individuals aged 40 - 74 years. Serum ALA, EPA, and DHA were measured in 315 cases of incident disabling dementia. Serum ALA level was inversely associated with risk of disabling dementia. However, associations of EPA and DHA with disabling dementia were not statistically significant [2]. ALA, but not EPA and DHA, was also associated with reduction of the risk for mild dementia among the Korean elderly [3]. In the Invecchiare in Chianti study where plasma fatty acids (FAs) were measured by gas chromatography in 935 community-dwelling older persons from the population of two towns near Florence, Italy, dementia is associated with low plasma n-3 PUFA relative concentrations, especially low plasma ALA concentrations [4]. Recent studies demonstrated a significant association of ALA with dementia.

In the Mayo Clinic Study of Aging, the odds ratio of mild cognitive impairment (MCI) decreased with increasing n-3 PUFA intake [5]. The top quartile of plasma phosphatidylcholine DHA level was associated with a significant 47% reduction in the risk of developing all-cause dementia in the Framingham Heart Study [6]. In the Cardiovascular Health Cognition Study, consumption of fatty fish was associated
Table 1. The Observational Studies Which Assessed the Association Between N-3 PUFA and Dementia

| Authors                  | Study design          | Subjects                                      | Results/conclusions                                                                 |
|--------------------------|-----------------------|-----------------------------------------------|-------------------------------------------------------------------------------------|
| Yamagishi et al [2]      | Community-based nested case-control study | 315 cases of incident disabling dementia       | Serum ALA was inversely associated with risk of disabling dementia: the multivariate odds ratios (95% CI) were 0.57 (0.39 - 0.85), 0.51 (0.34 - 0.76), and 0.61 (0.41 - 0.90) for persons with the second, third, and highest quartiles of ALA, respectively, as compared with the lowest quartile (P for trend = 0.01). |
| Kim et al [3]            | Cross-sectional study | 57 elderly (age ≥ 65 years) patients           | Multivariate-adjusted regression analysis showed that a higher level of ALA significantly decreased the risk of mild dementia after adjusting for age, sex, and height. |
| Cherubini et al [4]      | Cross-sectional study | 935 community-dwelling older persons          | After adjustment for age, gender, education, body mass index, weight loss, smoking status, cholesterol and triglycerides levels, daily intake of alcohol, FA and total energy, cardiovascular disease, depression and other FA levels, participants with dementia had significantly lower n-3 PUFA levels (2.9% vs. 3.2%; P < 0.05), particularly ALA levels (0.34% vs. 0.39%; P < 0.05), than did participants with normal cognitive function. |
| Roberts et al [5]        | Cross-sectional study | 1,233 non-demented subjects aged ≥ 70 years   | Compared to the lowest tertile, the OR (95% CI) for the upper tertiles were 0.62 (0.42 - 0.91; P for trend = 0.012) for n-3 PUFA after adjustment for age, sex, number of years of education, and caloric intake. |
| Schaefer et al [6]       | Prospective follow-up study | 899 men and women who were free of dementia at baseline, had a median age of 76.0 years, and were followed up for a mean of 9.1 years | The top quartile of plasma phosphatidylcholine DHA level was associated with a significant 47% reduction in the risk of developing all-cause dementia. |
| Huang et al [7]          | Cross-sectional study | Subjects who participated in the Cardiovascular Health Cognition Study (CHCS) | 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 - 1.02), and AD by 41% (95% CI: 0.36 - 0.95) in comparison to those who ate fish less than once per month. Stratification by APOE epsilon4 showed this effect to be selective to those without the epsilon4 allele. |
| Morris et al [8]         | Prospective study conducted from 1993 through 2000, of a stratified random sample from a geographically defined community | 815 residents, aged 65 - 94 years, who were initially unaffected by AD | Participants who consumed fish once per week or more had 60% less risk of AD compared with those who rarely or never ate fish (RR: 0.4; 95% CI: 0.2 - 0.9) in a model adjusted for age and other risk factors. Total intake of n-3 PUFA was associated with reduced risk of AD, as was intake of DHA. EPA was not associated with AD. |
| Morris et al [9]         | Cross-sectional analyses of deceased participants in the Memory and Aging Project clinical neuropathological cohort study, 2004 - 2013 | 554 deceased participants (51.6%). The mean (SD) age at death was 89.9 (6.1) years, 67% (193) were women, and the mean (SD) educational attainment was 14.6 (2.7) years. | In models adjusted for age, sex, education, and total energy intake, seafood consumption (≥ 1 meal(s)/week) was significantly correlated with less AD pathology including lower density of neuritic plaques (β = -0.69 score units (95% CI: -1.34 to -0.04)), less severe and widespread neurofibrillary tangles (β = -0.77 score units (95% CI: -1.52 to -0.02)) and in multiple cognitive domains with weekly seafood consumption and with moderate to high n-3 PUFA intake from food. |
| van de Rest et al [10]   | Longitudinal, community-based epidemiologic study of aging and dementia (the Rush Memory and Aging Project) | 915 participants (age 81.4 ± 7.2 years, 25% men) who had completed at least one follow-up cognitive assessment and dietary data | Consumption of seafood was associated with slower decline in semantic memory (β = 0.024; P = 0.03) and perceptual speed (β = 0.020; P = 0.05) in separate models adjusted for age, sex, education, participation in cognitive activities, physical activity, alcohol consumption, smoking, and total energy intake. In secondary analyses, APOEε4 carriers demonstrated slower rates of decline in global cognition and in multiple cognitive domains with weekly seafood consumption and with moderate to high n-3 PUFA intake from food. |
| Lopez et al [11]         | Case-cohort study     | 266 community dwelling men and women aged 67 - 100 years (mean = 80.2) | Plasma DHA in the highest tertile was associated with a 65% reduced odds of all-cause dementia (95% CI: 0.17 - 0.92) and a 60% reduced odds of AD (95% CI: 0.15 - 1.10). Dietary DHA in the highest tertile was associated with a 73% reduced odds of all-cause dementia (95% CI: 0.09 - 0.79) and a 72% reduced odds of AD (95% CI: 0.09 - 0.93). |
| Tully et al [12]         | Case-control study    | The subjects (119 females and 29 males) aged 76.5 (SD 6.6) years had an MMSE score of 19.5 (SD 4.8). The control subjects (36 females and 9 males) aged 70 (SD 6.0) years were not cognitively impaired (MMSE score > 24) | Serum cholesteryl ester-EPA and DHA levels were significantly lower (P < 0.05 and P < 0.001, respectively) in all MMSE score quartiles of patients with AD compared with control values. Serum cholesteryl ester-DHA levels were progressively reduced with severity of clinical dementia. Step-wise multiple regression analysis showed that cholesteryl ester-DHA was the important determinants of MMSE score. |
with a reduced risk of dementia and AD for those without the APOE epsilon4 (APOEε4) allele [7]. In the prospective study conducted from 1993 through 2000, dietary intake of n-3 PUFA and weekly consumption of fish was associated with reduction of the risk of incident AD [8]. In cross-sectional analyses, moderate seafood consumption was correlated with lesser AD neuropathology [9]. An ongoing longitudinal, community-based epidemiological study of aging and dementia suggested protective relations of one meal per week of seafood and n-3 PUFA against decline in multiple cognitive domains [10].

In the case-cohort study, plasma and dietary DHA were associated with protection against dementia [11]. The case-control study showed that serum cholesteryl ester-DHA levels were progressively reduced with severity of clinical dementia and were the important determinants of mini-mental

Table 1. The Observational Studies Which Assessed the Association Between N-3 PUFA and Dementia - (continued)

| Authors          | Study design             | Subjects                                                                 | Results/conclusions                                                                 |
|------------------|--------------------------|--------------------------------------------------------------------------|--------------------------------------------------------------------------------------|
| Conquer et al    | Cross-sectional study    | Patients with AD, OD, or CIND and compared them with a group of elderly control subjects with normal cognitive functioning | Plasma phospholipid and PC levels of DHA, total n-3 PUFA, and the n-3/n-6 ratio were lower in the AD, OD, and CIND groups. In the plasma PE fraction, levels of DHA and the total n-3 PUFA levels were significantly lower in the AD, OD, and CIND groups. |
| Whalley et al    | Observational follow-up study | 120 volunteers, born in 1936, at approximate ages of 64, 66, and 68 years | Total n-3 PUFA and DHA concentrations were associated with benefits for cognition at approximately 64 years old and from approximately 64 to approximately 68 years old. After adjustment for sex, APOE epsilon4 status, and intelligence quotient at 11 years old, the effects associated with total n-3 PUFA remained significant. |
| Nishihira et al  | Cross-sectional study    | 185 participants (mean age 84.1 ± 3.4 years) assessed in 2011 who were free from frank dementia | Serum DHA levels decreased with increasing age (P = 0.04). Higher global cognitive function was associated with higher levels of serum EPA (P = 0.03) and DHA + EPA (P = 0.03) after controlling for confounders. |
| Ammann et al     | Retrospective cohort study | 2,157 women with normal cognition enrolled in a clinical trial of postmenopausal hormone therapy | No association between RBC DHA + EPA levels and age-associated cognitive decline was found, in a cohort of older, dementia-free women. |
| Phillips et al   | Cross-sectional study    | 135 individuals aged between 55 and 91 years (19 AD, 55 CIND, and 61 HV) | Across the whole sample, and after controlling for age, years of education, level of socio-economic deprivation, and gender, n-3 PUFA intake, plasma PC DHA, and plasma PC EPA were all significant positive predictors of memory functioning. |
| Feart et al      | Cross-sectional analysis of the association between plasma FA and a Mediterranean diet (MeDi) adherence was performed by multi-linear regression | The study population (mean age 75.9 years) consisted of 1,050 subjects from Bordeaux (France) included in the Three-City cohort | The protective effect of the MeDi on cognitive functions might be mediated by higher plasma DHA and lower n-6/n-3 PUFA ratios. |
| Kroger et al     | Cohort study of a representative sample of persons aged ≥ 65 years | 663 non-demented subjects, 149 incident cases of dementia, including 105 with AD. | In adjusted Cox regression models with age as the time scale, there were no associations between total n-3 PUFA, DHA, or EPA and dementia or AD. |
| Devore et al     | Age- and sex-adjusted Cox proportional hazard and multivariate-adjusted models to evaluate the relative risk of dementia and AD across categories of typical fish intake and fish type consumed | 5,395 participants aged ≥ 55 years in the Rotterdam Study who were free of dementia and reported dietary information at baseline | During an average follow-up of 9.6 years, dementia developed in 465 participants (365 with AD). In multivariate-adjusted models, total fish intake was unrelated to dementia risk (P for trend = 0.7). Compared with participants who typically ate no fish, those with a high fish intake had a similar dementia risk (HR: 0.95; 95% CI: 0.76 - 1.19), as did those who typically ate fatty fish (HR: 0.98; 95% CI: 0.77 - 1.24). Dietary intakes of n-3 PUFA were also not associated with dementia risk. |
| Samieri et al    | Of non-demented participants who were followed up for 4 years, 65 developed dementia. The association between the proportion of plasma FA at baseline and the risk of incident dementia was assessed by multivariate proportional hazard models, taking into account depressive status | 1,214 non-demented participants in the Three-City Study from Bordeaux (France) | A higher plasma EPA concentration was associated with a lower incidence of dementia (HR: 0.69; 95% CI: 0.48 - 0.98), independently of depressive status. The relations between DHA, total n-3 PUFA, and incident dementia did not remain significant in multivariate models. Higher ratios of AA to DHA of n-6 to n-3 FA were related to an increased risk of dementia, particularly in depressive subjects (n = 90): ratio of AA to DHA (HR: 2.65; 95% CI: 1.07 - 6.56) and ratio of n-6 to n-3 (HR: 1.61; 95% CI: 1.04 - 2.47). |
state examination (MMSE) score [12]. Plasma phospholipid, phosphatidylcholine and phosphatidylethanolamine levels of DHA, total n-3 PUFA, and the n-3/n-6 ratio were lower in the AD, other dementias, and cognitive impairment no dementia (CIND) groups [13]. In an observational follow-up study, total n-3 PUFA and DHA concentrations were associated with benefits for cognition at approximately 64 years old [14]. After adjustment for sex, APOEε4 status, and intelligence quotient at 11 years old, the effects associated with total n-3 PUFA remained significant.

In the cross-sectional study using the data from the Keys to Optimal Cognitive Aging (KOCOA) study, an ongoing cohort of relatively healthy volunteers aged over 80 years old, living in Okinawa, Japan, higher serum EPA and DHA + EPA levels were independently associated with better scores on global cognitive function among the oldest old, free from dementia [15]. In the retrospective cohort study, an association between red blood cell (RBC) DHA + EPA levels and age-associated cognitive decline was not observed in a cohort of older, dementia-free women [16]. The study which investigated differences in dietary intake and blood plasma content of EPA and DHA in individuals with CIND, AD and healthy volunteers (HVs), showed the possibility that n-3 PUFA has an impact on cognitive decline [17]. Higher adherence to a Mediterranean diet (MeDi) and n-3 PUFA may contribute to decreased dementia risk. In the study which investigated the relationship between plasma FA and MeDi adherence suggested that the protective effect of the MeDi on cognitive functions might be mediated by higher plasma DHA and lower n-6/n-3 PUFA ratio [18].

In a cohort study of a representative sample of persons aged ≥ 65 years, conducted from 1991 to 2002, no associations between n-3 PUFA and dementia or AD were found [19]. Devore et al studied the dietary consumption of fish and n-3 PUFA in relation to long-term (an average follow-up of 9.6 years) dementia risk, by using 5,395 participants aged ≥ 55 years in the Rotterdam Study who were free of dementia and reported dietary information at baseline. In this Dutch cohort, a moderate consumption of fish and n-3 PUFA do not appear to be associated with long-term dementia risk [20]. Of 1,214 nondemented participants in the Three-City Study from Bordeaux (France) who were followed up for 4 years, 65 participants developed dementia. The association between the proportion of plasma FA at baseline and the risk of incident dementia was assessed by multivariate proportional hazard models, taking into account depressive status. A high plasma EPA concentration may decrease the risk of dementia, whereas high ratios of n-6 to n-3 PUFA and of arachidonic acid (AA) to DHA may increase the risk of dementia, especially in depressed older persons [21].

In the analyses of observational studies, three studies reported a significant association between ALA and dementia. N-3 PUFA, DHA, DHA + EPA, and EPA have been reported to be significantly associated with dementia, in two, five, two, and one studies, respectively; however, the association between DHA + EPA and dementia was denied by one study. Fish or seafood intake was beneficially associated with dementia in four studies; however, one article challenged such association.

The Intervention Studies Which Investigated the Association Between N-3 PUFA and Dementia

The intervention studies which assessed the association between n-3 PUFA and dementia are shown in Table 2 [22-34]. In a randomized, double-blind, placebo-controlled trial (RCT), healthy older adults with subjective memory impairment were allocated to fish oil group or placebo group for 24 weeks. EPA and DHA supplementation increases RBC n-3 PUFA content, working memory performance, and blood oxygen level-dependent signal in the posterior cingulate cortex during greater working memory load in older adults with subjective memory impairment [22]. However, another RCT confirmed an overall negligible benefit of n-3 PUFA supplementation for individuals with CIND or AD [23]. Eriksdotter et al demonstrated the dose-response relationships between plasma levels of n-3 PUFA and preservation of cognition [24]. The large intervention study showed no effect of dietary doses of n-3 PUFA on global cognitive decline in coronary heart disease patients [25].

A 6-month RCT showed that increased intakes of DHA and EPA benefited mental health in older people with MCI, and increasing n-3 PUFA intakes may reduce depressive symptoms and the risk of progressing to dementia [26]. In RCT, patients with AD received 1.7 g of DHA and 0.6 g of EPA or placebo 0.6 g of linoleic acid per day for 6 months. After 6 months, all patients received DHA and EPA for another 6 months. A DHA-enriched n-3 PUFA supplement may positively affect weight and appetite in patients with mild to moderate AD. Not carrying the APOEε4 allele and high DHA were independently associated with weight gain [27].

An RCT involving 302 cognitively healthy (MMSE score > 21) individuals aged 65 years or older was performed to investigate the effect of EPA and DHA supplementation on cognitive performance. Participants were randomly assigned to 1,800 mg/day EPA-DHA, 400 mg/day EPA-DHA, or placebo capsules for 26 weeks. No overall effect of 26 weeks of EPA and DHA supplementation on cognitive performance was observed [28].

In an RCT where 204 AD patients (74 ± 9 years) with acetylcholine esterase inhibitor treatment and an MMSE > 15 points were randomized to daily intake of 1.7 g DHA and 0.6 g EPA or placebo for 6 months. Supplementation with n-3 PUFA in patients with mild to moderate AD did not result in marked effects on neuropsychiatric symptoms except for possible positive effects on depressive symptoms in non-APOEε4 carriers and agitation symptoms in APOEε4 carriers [29].

Recall of object locations was significantly better after n-3 PUFA (2,200 mg/day) supplementation compared with placebo [30]. A 24-week n-3 PUFA (1.8 g/day) treatment showed a significant improvement in AD assessment scale compared to the placebo group in participants with MCI, which was not observed in those with AD [31].

In Japan, participants in elderly care facilities and nursing homes were randomized in active and placebo groups [32]. This study suggested that DHA-enriched meals protect against age-related cognitive decline, and also improve apathy and
### Table 2. The Intervention Studies Which Assessed the Association Between N-3 PUFA and Dementia

| Authors               | Duration and dose of n-3 PUFA                                      | Subjects                                      | Severity of dementia                                      | Results/conclusions                                                                                                                                                                                                 |
|-----------------------|---------------------------------------------------------------|-----------------------------------------------|-----------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Boespflug et al [22]  | Fish oil (EPA + DHA: 2.4 g/day, n = 11) or placebo (corn oil, n = 10) for 24 weeks | Healthy older adults (62 - 80 years) with subjective memory impairment | Subjective memory impairment, but not meeting criteria for MCI or dementia | In the fish oil group, blood oxygen level-dependent (BOLD) increases at 24 weeks were observed in the right posterior cingulate and left superior frontal regions during memory loading. A region-of-interest analysis indicated that the baseline to endpoint change in posterior cingulate cortex BOLD activity signal was significantly greater in the fish oil group compared with the placebo group. |
| Phillips et al [23]   | N-3 PUFA (600 mg EPA and 625 mg DHA per day) or placebo (olive oil) over a 4-month period | 57 participants with CIND and 19 with AD | CIND and AD | There was no benefit of n-3 PUFA supplementation for subjects with cognitive impairment and dementia.                                                                                                               |
| Eriksdotter et al [24] | Daily intake of 2.3 g n-3 PUFA or placebo for 6 months; subsequently all received the n-3 PUFA for the next 6 months | 174 AD patients (74 ± 9 years) | AD | Preservation of cognitive functioning was significantly associated to increasing plasma n-3 PUFA levels over time.                                                                                                   |
| Geleijnse et al [25]  | 400 mg/day of EPA-DHA, 2 g/day of ALA, both EPA-DHA and ALA, or placebo for 40 months | 2,911 coronary patients (78% men) aged 60 - 80 years | MMSE score, 28.2 - 28.4 | Changes in MMSE score during intervention did not differ significantly between EPA-DHA and placebo (-0.65 vs. -0.69 points, P = 0.44). The risk of cognitive decline was 1.03 (95% CI: 0.84 - 1.26, P = 0.80) for EPA-DHA (vs. placebo). |
| Sinn et al [26]       | EPA (1.67 g EPA + 0.16 g DHA/day; n = 17), DHA (1.55 g DHA + 0.40 g EPA/day; n = 18) or the n-6 PUFA, LA (LA; 2.2 g/day; n = 15) for 6 months | 50 people aged > 65 years with MCI | MCI | Compared with LA group, GDS scores improved in the EPA (P = 0.04) and DHA (P = 0.01) groups and verbal fluency in DHA group (P = 0.04). Improved GDS scores were correlated with increased DHA + EPA (r = 0.39, P = 0.02). Improved self-reported physical health was associated with increased DHA. |
| Irving et al [27]     | 1.7 g of DHA and 0.6 g of EPA (n = 89) or placebo 0.6 g of LA per day (n = 85) for 6 months | 204 patients (aged 73 ± 9, 52% women) with AD | Mild to moderate AD | At 6- and 12-month follow-up, weight had increased 0.7 ± 2.5 kg (P = 0.02) and 1.4 ± 2.9 kg (P < 0.001) in the n-3/n-3 group. In the placebo group, weight was unchanged at 6 months but had increased (P = 0.01) at 12 months follow-up after n-3 PUFA supplementation was initiated. Appetite improved in the n-3/n-3 group over the treatment period (P = 0.01). In logistic regression analyses, not carrying the APOEε4 allele and high plasma DHA concentrations were independently related to weight gain in the combined group of patients at 6 months follow-up. |
| van de Rest et al [28] | 1,800 mg/day EPA-DHA, 400 mg/day EPA-DHA, or placebo capsules for 26 weeks | 302 cognitively healthy individuals aged 65 years or older | MMSE score > 21 | No overall effect of 26 weeks of EPA and DHA supplementation on cognitive performance was observed.                                                                                                           |
| Freund-Levi et al [29]| Daily intake of 1.7 g DHA and 0.6 g EPA or placebo for 6 months | 204 AD patients (74 ± 9 years) with acetylcholine esterase inhibitor treatment and an MMSE > 15 | AD with an MMSE > 15 | No significant overall treatment effects on neuropsychiatric symptoms, on activities of daily living or on caregiver’s burden were found. However, significant positive treatment effects on the scores in the agitation in APOEε4 carriers (P = 0.006) and in depression scores in non-APOEε4 carriers (P = 0.005) were found. |
| Kulzow et al [30]     | N-3 PUFA (2,200 mg/day, n = 22) or placebo (n = 22) for 26 weeks | 44 (20 female) cognitively healthy individuals aged 50 - 75 years | Cognitively healthy | Recall of object locations was significantly better after n-3 PUFA supplementation compared with placebo. Performance in the AVLT was not significantly affected by n-3 PUFA.                                                                 |

**Note:** MCI = Mild Cognitive Impairment; AD = Alzheimer’s disease; CIND = Cognitive Impairment Not Dementia; MMSE = Mini-Mental State Examination; A VLT = Auditory Verbal Learning Test; GDS = Global Deterioration Scale; APOEε4 = apolipoprotein E epsilon 4; LA = Linoleic acid; APOEε4 = apolipoprotein E epsilon 4.
Effects of N-3 PUFA on Dementia

The accumulation of neurototoxic amyloid-β peptide (Aβ) is a pathologically profound characteristic of AD [35-40]. Aβ is derived from amyloid precursor protein (APP) [41]. APP is cleaved by α-secretases within the Aβ domain to produce α-secretase-cleaved soluble APP (sAPPα). sAPPα is neurotrophic and neuroprotective and enhancing APP processing by α-secretases [42, 43]. EPA and DHA are able to increase membrane fluidity and

caregiver burden for the oldest-elderly Japanese with cognitive impairment. The 24-week supplementation with 900 mg/day DHA improved learning and memory function in age-related cognitive decline [33]. However, supplementation with algal DHA compared with placebo did not slow the rate of cognitive and functional decline in patients with MCI (P = 0.03), which was not observed in those with AD. Higher proportions of EPA on RBC membranes were also associated with better cognitive outcome (P = 0.003).

In the analyses of intervention studies, n-3 PUFAs have been reported to improve dementia in three studies. EPA + DHA supplementation was beneficially associated with dementia in three studies; however, four studies reported the negligible effects of EPA + DHA for dementia. DHA was favorably associated with dementia in two studies, however, which was challenged by one article.

The Underlying Mechanisms for N-3 PUFA-Mediated Improvement of Dementia

AD: Alzheimer’s disease; ALA: α-linolenic acid; AVLT: auditory verbal learning test; CIND: cognitive impairment no dementia; DHA: docosahexaenoic acid; EPA: eicosapentaenoic acid; GDS: geriatric depression scale; LA: linoleic acid; MCI: mild cognitive impairment; MMSE: mini-mental state examination (scores < 24 are indicative for impaired cognitive functioning, and the maximum possible score on the MMSE test is 30); PAL: paired associate learning; PUFA: polyunsaturated fatty acids; RBC: red blood cell.
lead to increase in sAPPα secretion [44]. Transthyretin (TTR) binds Aβ and may reduce brain Aβ. N-3 PUFA treatment appeared to increase plasma-TTR in patients with AD [45]. N-3 PUFA is associated with enhancing clearance of Aβ.

Hjorth et al. reported that DHA and EPA can be beneficial in AD by enhancing removal of Aβ, increasing neurotrophin production, and decreasing pro-inflammatory cytokine production [46].

AD is associated with brain inflammation and reduced levels of specialized proresolving mediators (SPMs) which are derivatives of n-3 and n-6 PUFA and induce resolution of inflammation. Supplementation with n-3 PUFA for 6 months prevented a reduction in SPMs released from peripheral blood mononuclear cells (PBMCs) of AD patients [47]. Serini et al. treated in vitro phytohemagglutinin (PHA)- or lipopolysaccharide (LPS)-stimulated PBMC from AD patients and age-matched healthy controls with EPA or DHA. The addition of both EPA and DHA markedly reduced the cytokine release [48].

Prostaglandin F-2α release from LPS-stimulated PBMC from AD patients was significantly diminished by a DHA-rich fish oil as compared with placebo. Prostaglandin F-2α changes were correlated inversely with changes in plasma DHA and EPA. Decreased IL-6 and IL-1β levels correlated with decreased prostaglandin F-2α levels [49].

Isoform-specific protein kinase C (PKC) activators may be useful as therapeutic agents for the treatment of AD. Three new epsilon-specific PKC activators (AA-CP4, EPA-CP5, and DHA-CP6), made by cyclopropanation (CP) of PUFA, have been developed. DHA-CP6 reduced the intracellular and secreted levels of Aβ by 60-70% [50]. AD patients treated with DHA-rich n-3 PUFA supplementation increased their plasma concentrations of DHA (and EPA), which were associated with reduced release of IL-1β, IL-6, and granulocyte colony-stimulating factor from PBMC [51].

N-3 PUFA may improve AD by increasing clearance of Aβ, neurotrophic and neuroprotective factors, and by anti-inflammatory effects.

**Limitation of Present Study**

Only one database (Pubmed) was searched for articles to be reviewed.

**Conclusion**

Characteristics of patients whose dementia can be improved or prevented by n-3 PUFA are shown in Table 3. Patients with mild memory and/or cognitive impairment can be treated by a long-term and higher intake of n-3 PUFA.

**Conflicts of Interest**

The author declares that he has no conflicts of interest concerning this article.

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**Table 3. Characteristics of Patients Whose Dementia Can Be Improved or Prevented by N-3 PUFA**

| 1. Mild memory and/or cognitive impairment |
|-----------------------------------------|
| a) Subjective memory impairment         |
| b) Mild cognitive impairment (MCI)      |
| c) Cognitive impairment no dementia (CIND) |
| d) Mild Alzheimer’s disease             |
| 2. Higher intake of fish                |
| 3. Additional daily n-3 PUFA intake > 2.0 g |
| 4. Additional daily DHA intake > 900 mg  |
| 5. Duration of treatment > 6 months     |
seafood and long-chain omega-3 fatty acids with cognitive decline. Neurology. 2016;86(22):2063-2070.

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