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# The benefit of docosahexaenoic acid for the adult brain in aging and dementia

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A B S T R A C T

A brief overview of the evidence for omega-3 fatty acids and, in particular, of docosahexaenoic acid (DHA), involvement in cognition and in dementia is given. Two studies are presented in this regard in which the key intervention is a DHA supplement. The fist, the MIDAS Study demonstrated that DHA can be of benefit for episodic memory in healthy adults with a mild memory complaint. The second, the ADCS AD trial found no benefit of DHA in the primary outcomes but found an intriguing benefit for cognitive score in ApoE4 negative allele patients. This leads to a consideration of the mechanisms of action and role of ApoE and its modulation by DHA. Given the fundamental role of ApoE in cellular lipid transport and metabolism in the brain and periphery, it is no surprise that ApoE affects n-3 PUFA brain function as well. It remains to be seen to what extent ApoE4 deleterious effect in AD is associated with n-3 PUFA-related cellular mechanisms in the brain and, more specifically, whether ApoE4 directly impairs the transport of DHA into the brain, as has been suggested.



## 1. Introduction

A fairly substantial literature now underpins the positive relationship between long chain n-3 fatty acid intake and protection from cognitive decline as well as dementia. For example, a lower plasma concentration of docosahexaenoic acid (DHA, 22:6n-3) has been associated with cognitive decline in both healthy elderly people [1,2] as well as in patients with Alzheimer's disease (AD) [3,4]. The Framingham study related decreased plasma phosphatidylcholine DHA content to increased cognitive decline and rates of dementia [4]. Another aspect of the relationship between long chain n-3 fatty acids and cognition is the literature relating fish intake to cognitive decline. There have been many such epidemiological studies, some quite large with both positive results and some null studies. The VA Normative Aging Study found an association between fish intake and the Mini Mental State Examination (MMSE) in over 1000 healthy men of median age 68 [5]. The PAQUID Study observed a 35% reduction in risk of AD in 1600 French adults over 68 years of age who consumed only one fish meal a week or more [6]. Morris et al. have also shown an association of decreased AD risk with fish eating in Americans [7].

Intervention studies of fish oil or EPA/DHA supplementation have recently been reviewed [8]. A recent meta-analysis of 10 randomized, controlled trials that included studies of aging healthy adults as well as those with mild dementia or AD primarily with DHA as the intervention indicated positive results for patients with mild cognitive impairment [9]. Several epidemiological studies have suggested that ApoE4 allele negative patients benefit from DHA supplementation and that ApoE4 allele patients may not [10–12]. In addition, some recent imaging studies have shown an association of brain structural features with omega-3 intake. Raji et al. observed that weekly fish consumption was positively associated with gray matter volumes in several substructures including hippocampus and cingulate and orbitofrontal cortices [13]. The use of fish oil supplements was associated with higher mean hippocampal and cerebral cortex gray matter volumes as well as better cognitive scores (ADAS-cog and MMSE) in those with normal cognition [14]. Such cross-sectional studies are not conclusive but the associations that they suggest are then good candidates for interventional studies using randomized clinical trial methodology.

*Abbreviations:* DHA, docosahexaenoic acid; AD, Alzheimer's disease; ApoE, apolipoprotein E; CNS, central nervous system; LDLR, low-density lipoprotein receptor; VLDLR, very low-density lipoprotein receptor; LRPs, LDLR-related proteins; BBB, blood brain barrier; CSF, cerebrospinal fluid

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## 2. Results

One key study in the domain of benefits of DHA for brain function is the MIDAS study, an acronym for Memory Improvement after DHA Study [15]. This was a randomized, controlled, multi-center trial of cognitive outcome in 485 healthy elderly patients. The intervention was 900 mg of algal DHA/d vs. corn/soy oil placebo capsules over a 24 week period. The primary endpoint was the score in the Paired Associate Learning (PAL) test from CANTAB. This is a computer generated, objective test that is sensitive to early episodic memory changes. Secondary endpoints included various tests of cognitive function, Activity of Daily Living (ADL) skills, plasma fatty acid analysis, safety and tolerability. Subjects were $>55$ years of age and the population had a mean age of 70 years. The subjects had a subjective memory complaint and were screened for age related cognitive decline by means of the Logical Memory subtest of the Wechsler Memory Scale and also the MMSE. The cut offs for these tests were as follows: subjects had an immediate ($\leq 28$) or delayed ($\leq 15$) recall score that was $\geq 1$ standard deviation below the mean of younger subjects of 25–35 years, and also had an MMSE $>26$. Subjects were excluded who reported taking omega-3 supplements, consuming $>200$ mg/d DHA in their diets, used medications for AD, major anti-psychotic or anti-depressant medications, had major medical conditions or who abused alcohol or drugs.

There was a significant improvement in the primary outcome, the PAL test, in the DHA supplemented group (Table 1). After 24 weeks, there were 4.5 fewer errors made in the DHA group while the practice effect produced only 2.4 fewer errors in the placebo group. There were significant differences also in two of the measures of verbal recognition memory, the immediate and delayed recall, but not in the free recall (Table 1). No differences were detected between groups in tests for pattern recognition or spatial working memory nor in geriatric depression [15].

This was an impressive demonstration in a RCT of considerable size that DHA provided a benefit to the elderly for episodic memory and measures of visual recognition memory. When compared to normative data vs age, it could be estimated that the improvement in the PAL measure corresponded to that of being 7 years younger, whilst the controls appeared to be 3.6 years younger. In addition, the cognitive changes (PAL score) were significantly correlated with plasma DHA content which was increased from baseline values to the extent of 3.2 percentage points, expressed as a weight percent of total fatty acids. No erythrocyte data was obtained in this study.

Adverse events and serious adverse events were carefully monitored in this study and there were no significant differences between groups in this regard, nor were there differences in hematological or clinical chemistry measures. There was however a significant decrease in heart rate observed in the DHA group of $-3.2$ bpm (vs. $-1$ in the placebo group).

Since the MIDAS Study was published in 2010, there have been five studies of healthy adults involving memory related measures and with DHA/EPA as the key intervention and with the number of subjects greater than 100. Of these, three studied young adults of age 35 years or less [16–18]and two studied middle aged to elderly individuals [19,20]. Dangour et al. reported no changes in cognitive measure such as the California Verbal Learning Test in 70–79 year old adults after providing an experimental treatment of 700 mg/d of EPA/DHA [19]. However, as the authors noted, over the 24 months period of the study, the subjects experienced no decline in cognitive function; thus, it does not seem possible to measure a benefit of a supplement on declining cognitive function [21]. In a study of 176 healthy young adults of 18–45 years of age who were given 1.16 g/d of DHA or placebo, Stonehouse et al. that reaction times for both episodic and working memory improved and episodic memory improved in women and working memory in men [20]. In a rather large study of 285 young women, age 18–25, Benton et al. gave 400 mg/d of DHA and found no differences in a series of measures of mood and cognitive function [16]. Jackson et al. tested 1 g/d of EPA- or DHA- rich fish oils in 18–35 year old healthy adults on a series of cognitive tests and found effects in both directions on the Stroop test and some apparent benefit of the EPA-rich fish oil on subjective mental fatigue [17]. It is worth mentioning that Lee et al., when providing a larger dose of 1.74 g/d of EPA/DHA for 12 months found a benefit for several measures of memory function in a small group of 36 more elderly patients with mild cognitive impairment [22]. Also, Witte et al. studied executive functions and neuroimaging in a group of 65 healthy subjects age 50–75 years of age given 2.2 g/d of n-3 PUFA in a randomized, controlled trial design [23]. They observed a benefit in executive function including verbal fluency. They also observed changes in white matter microstructural integrity which they interpreted to be beneficial as well as increases in gray matter volume in the frontal, temporal, parietal and limbic areas primarily within the left hemisphere. These authors demonstrated an increase in the omega-3 index (erythrocyte EPA+DHA) as well as in the erythrocyte EPA content.

It appears that benefits of DHA are best observed during aging where there is some decrement in cognition, e.g., a mild cognitive impairment or memory complaint or perhaps when a person is exposed to certain chronic physical or mental stressors. A limitation of the these interventional studies is that they can only address limited aspects of memory. In the case of the MIDAS study, the PAL task is considered to be a measure of episodic memory, one of many different aspects of the clinical construct of memory.

There has also been a major trial of DHA in patients with AD as reported by Quinn et al. in 2010 [18]. This study was performed under the auspices of the National institutes of Health by the Alzheimer's Disease Cooperative Study group and so was a

**Table 1**
Positive results in cognitive testing in the MIDAS trial.

| Cognitive test | Baseline score mean ± SD | Wk 24 score mean ± SD | Wk 24, change from baseline mean ± SE | P value |
|---|---|---|---|---|
| **CANTAB PAL** | | | | |
| DHA | **13.4 ± 11.6** | **8.8 ± 9.9** | **−4.5 ± 0.64** | **0.032** |
| Placebo | **12.1 ± 10.9** | **9.7 ± 10.4** | **−2.4 ± 0.62** | |
| **Verbal recognition memory, immediate, (total correct)** | | | | |
| DHA | **10.8 ± 1.5** | **11.0 ± 1.4** | **0.2 ± 0.11** | **0.018** |
| Placebo | **10.9 ± 1.5** | **10.9 ± 0.0** | **0.4 ± 0.11** | |
| **Verbal recognition memory, delayed, (total correct)** | | | | |
| DHA | **10.4 ± 1.8** | **10.7 ± 1.5** | **0.3 ± 0.11** | **0.012** |
| Placebo | **10.5 ± 1.8** | **10.7 ± 1.8** | **0.1 ± 0.11** | |

Taken from Reference [13] ,Table 2.