



The importance of fish and docosahexaenoic acid in Alzheimer disease^{1,2}

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Alzheimer disease is devastating both to the afflicted person and to that person's family. Capable persons become helpless and must be cared for by the family and by the community. This common problem of aging will expand in the near future because people are living longer. It is estimated that 20–40% of the population now over the age of 85 y may have Alzheimer disease (1). A further daunting statistic is that, once Alzheimer disease is identified as the cause of cognitive decline, the patient may live for many years with a high yearly cost of care. Are there potential and safe measures that would prevent this slide into cognitive failure? Fish and fish oil contain 2 fatty acids, docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), that may have promise. The major dietary sources of these 2 fatty acids are fish and shellfish, from both salt water and fresh water. DHA can also be synthesized in the body from the *n*–3 fatty acid α -linolenic acid (18:3), which is present in some vegetable oils and some nuts and seeds. However, this synthetic step is relatively inefficient.

DHA is 22 carbons long and has 6 double bonds with the *n*–3 configuration. It is the most prominent fatty acid in the brain, retina, and spermatozoa (2) and is necessary for vision, cognition, and sperm motility. DHA is especially rich in the neurons and synaptosomes of the cerebral cortex, where it occupies the no. 2 position of membrane phospholipids. In premature infants whose formula contained DHA balanced with *n*–6 arachidonic acid, vocabulary and motor performance increased and vision improved (3). Monkeys deficient in dietary *n*–3 fatty acids have reduced vision, abnormal electroretinograms, and greater amounts of stereotypic behavior and polydipsia. Of interest also is the fact that dietary DHA can be incorporated into monkey brain phospholipids later in life as well as during development (4). However, the brains of Alzheimer disease patients have a lower content of DHA in the gray matter of the frontal lobe and hippocampus than do the brains of persons without Alzheimer disease (5). The brains of persons with Alzheimer disease have an amyloid protein complex and an inflammatory component.

With this background, a logical question is: "Would fish consumption retard the decline in cognitive function that might otherwise occur in an elderly population, which is subject to Alzheimer disease?" Fish and fish oil have a high content of DHA and its 20-carbon precursor EPA. Studies to answer this question were begun in the 1990s. In a typical study, the investigators estimated the amount of fish in the diet or measured the composition of the plasma fatty acids at baseline, which provided an index of fish consumption. Cognition was estimated at baseline

with a follow-up years later to correlate any change in cognition with the baseline fish consumption, plasma fatty acids, or both. In the past, some studies were positive and some were negative. A recent report from the Framingham Heart Study showed that persons with plasma phosphatidylcholine DHA in the top quartile of values had a significantly (47%) lower risk of developing all-cause dementia than did those in the bottom quartile (6). Significantly ($P = 0.04$) greater protection was obtained from consuming 2.9 fish meals per week than from consuming 1.3 fish meals per week. Two additional positive studies are described in this issue of the Journal (7, 8).

In the Zutphen Elderly Study (7), initial data were obtained from 210 men aged 70–89 y. Fish consumption and cognitive function were measured in 1990 and 1995, and fish consumers had less cognitive decline than did fish nonconsumers. A linear relation was found between the estimated intake of DHA and EPA (DHA+EPA) and the prevention of cognitive decline. A DHA+EPA intake of ≈ 380 mg/d seemed to prevent cognitive decline. This amount of DHA+EPA would be found in 20 g Chinook salmon or in 100 g cod. Two to three meals of fish per week would supply ≈ 380 mg EPA+DHA/d.


The Minneapolis study of 2251 white men and women began in 1987–89 with analyses of plasma fatty acids in cholesterol esters and phospholipids (8). Three neuropsychological tests were given at baseline and again between 1990 and 1992 and between 1996 and 1998. The risk of decreased global cognition was greater with higher concentrations of palmitic acid and arachidonic acid (20:4 n –6) in both cholesterol esters and phospholipids. In contrast, the risk of cognitive decline was lower with a higher concentration of linoleic acid (18:2 n –6). Cognitive decline was associated with lower plasma *n*–3 fatty acids (DHA+EPA) in the subgroup of subjects with hypertension and dyslipidemia, but this association was not found for the entire group.

In each of these studies, the *n*–3 fatty acids retarded the decline in cognition over time. One mechanism for the positive

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effect could be the antithrombotic and antiinflammatory properties of EPA (9). Moreover, the entrance of DHA into the brain could correct DHA deficiency in membrane phospholipids in the cerebral cortex in patients with Alzheimer disease (5), and EPA would counter the proinflammatory action of arachidonic acid, which is a precursor of cytokine and proinflammatory eicosanoids that may be associated with greater cognitive decline. The association of palmitic acid in the plasma cholesterol esters and phospholipids is of interest. This 16-carbon saturate is associated with thrombosis and the elevation of plasma LDL cholesterol that can lead to atherosclerotic obstruction. Both of these conditions could increase the tendency to develop dementia.

Along with numerous previous studies, the Zutphen and Minneapolis studies provide the rationale for a future clinical trial of fish, fish oil, or both in elderly patients prone to the development of Alzheimer disease. Such a trial would involve blood measurements of fatty acids in the plasma and in the red blood cells (red blood cells are more representative of tissue fatty acid composition than is plasma) and tests of cognition at baseline and at a future time, perhaps after 5 y. Because there may be a vascular component to Alzheimer disease, the background diet of any fish-oil trial also should be low in saturated fat and cholesterol (10). Alzheimer disease is so prevalent and so disastrous that definitive clinical trials to delay or prevent it must be carried out. In the meantime, because evidence exists that n-3 fatty acids prevent episodes of sudden death, the American Heart Association has already recommended that all adults consume 2 fish meals per week (11). For people who are allergic to fish or who cannot obtain fish, we suggest the consumption of one fish-oil capsule (1000 mg) per day. The possibility that the fatty acids DHA and EPA in fish and fish oil may delay the ravages of Alzheimer disease is of great interest. 

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