Nutritional
Neuroscience

Background: Why the Future of Prevention is Neuro-Prevention

Daniel T. Johnston, MD, MPH

Chief Medical Officer and
Co-founder

Omega-3 index testing and health outcomes

The Omega-3 Index is the sum of EPA+DHA in RBC membranes expressed as a percent of total fatty acids. Typical levels range from 3% to 9%, with a US average value of between 5%-6%. The Index is a marker of tissue EPA+DHA and therefore reflects an individual´s EPA+DHA status. The Omega-3 Index currently fulfills most of the criteria for a cardiovascular risk factor. In routine clinical practice, the Omega-3 Index can be used to assess baseline n-3 fatty acid status and to check for compliance with a recommendation to increase the n-3 fatty acid intake.

Although strongly correlated with the EPA+DHA intake, the exact value for the HS-Omega-3 Index cannot be just deduced from knowing the omega-3 intake. There is considerable person-to-person variability, and it is very difficult to know the actual amount of omega-3 consumed in the diet, particularly if relying on fish as the source. This is because omega-3 levels vary by season, by location of the catch, and by preparation method so that the specific amount in a particular serving of fish is unknown. As lipid levels are routinely measured when people are on lipid-lowering drugs; the same logic applies to omega-3 fatty acids and the need to know your index.

A biomarker, like the Omega-3 Index, is superior to diet-record-based estimates of omega-3 intake for individuals and can uncover disease-risk relationships with omega-3 status that could not be discerned using food frequency questionnaires. As the popular use of the HS-Omega-3 Index in major research projects helps to clarify the role(s) that these fatty acids play in human health, individuals can already take the same test and compare their personal values;

- to detect omega-3 “insufficiency”, and
- to rank individuals with respect to risk for disease, and
- to help individuals achieve omega-3 levels equivalent to a “protective zone”.

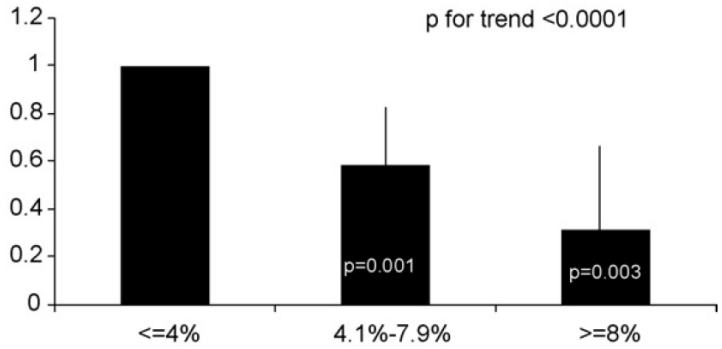
Implementation of the Omega-3 Index could ultimately reduce the economic burdens of cardiovascular, neuropsychiatric and some age-related cognitive decline.

The following are the effects seen on Surrogate Parameters in the literature as a result of increasing the HS-Omega-3 Index® as applied to cardiovascular health.

These were the effects while modifying the diet and increasing HS-Omega-3 Index®

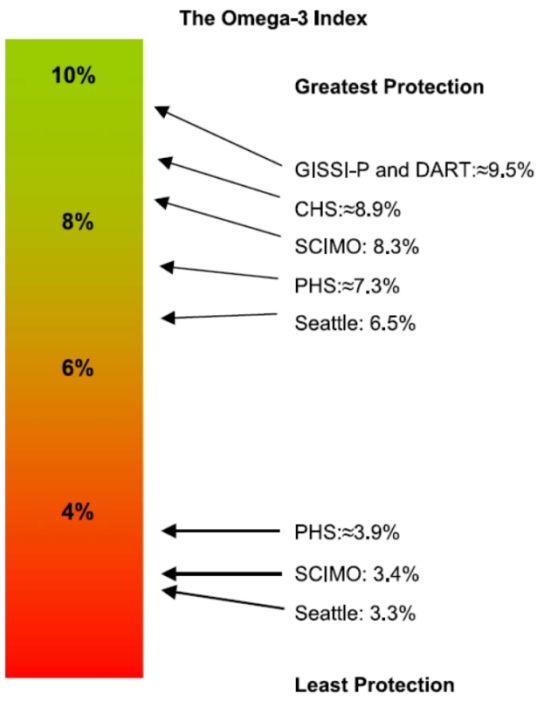
Heart Rate	↓		(Harris et al Am J Cardiol 2006; 98:1393-5)
Heart Rate Variability		↑	(Carney et al Psychosom Med 2010;72:748)
Blood Pressure		↓	(Dewell et al J Nutr Res 2011;141:2166; Skulas-Ray et al Ann Behav Med 2012;44:301)
Platelet Function	↓		(Larsson et al, Thromb Haemost 2008;100:634

Inflammator. Biomarker	↓		Harris et al, Lipids 2008;43:805) (Duda et al Cardiovasc Res 2009;81:319 Dewell et al J Nutrition 2011;141:2166 Blocket al World J Cardiovasc Dis2012;2:14
Triglycerides	↓		(Skulas-Ray Am J Clin Nutr 2011;93:243, Schuchardt et al PLEFA 2011;85:381 Shearer et al J Lipid Res. 2012;53:2429)
„Small dense“ LDL	↓		(Maki et al J Clin Lipidol 2011;5:483)
„Large bouyant“ LDL		↑	(Maki et al J Clin Lipidol 2011;5:483)



In a study of acute coronary syndromes (ACS), Omega-3 Index was determined in 768 ACS patients and 768 age-, sex- and race-matched controls. While the combined groups had a mean age of 61+/-12 years, 66% male, and 92% Caucasian . The subjects were grouped in to categories by omega-3 Index which low, <4%; intermediate 4.1-7.9%; and high, > or =8% The odds ratio for an ACS event was 0.58 for the middle group and 0.31 for the high omega-3 index group (Block 2008)

(Block RC, Harris WS, Reid KJ, Sands SA, Spertus JA. (2008) EPA and DHA in blood cell membranes from acute coronary syndrome patients and controls. Atherosclerosis. Apr;197(2):821-8)



These seven major studies have helped to define the target "protection zones", which individuals can use. [Nilsen. AJCN. 74:50, 2001; Marchioli. Circulation. 105:1897, 2002; Mozaffarian. Circulation.107:1372, 2003; Burr. Lancet. 2:757, 1989; von Schacky Ann Intern Med 130:554, 1999; Albert. NEJM. 346:1113, 2002; Siscovick. JAMA. 274:1363, 1995] These Protection zones would be expected to remain at the same ranges for both cardiovascular as cognitive or age related risks.

The target HS-Omega-3 Index proposed is 8% and above, a level that current research indicates is associated with the lowest risks (e.g. for death from CHD). On the other hand, an Index of 4% or less (which is common in the US) indicates the highest risk. At the present, there are no known sex- or age-specific values but these are likely to develop as more individual data is collected.

It is important to know that differing levels of risk associated with omega-3 fatty acids are independent of risks associated with other factors such as cholesterol, blood pressure, diabetes, family history of CHD, smoking, or other cardiac conditions; these are independent of and not influenced by omega-3 fatty acids. All risk factors – including the HS-Omega-3 Index—should be addressed as part of any global risk reduction strategy.

If the HS-Omega-3 Index is in the in the intermediate zone, (4% to 8%), it is suggested to increase the EPA+DHA intake by about 500 mg/day. But if in the high risk zone (<4%), it is important to increase intake of EPA+DHA by as much as possible (e.g.

1000mg/day); either of these can be accomplished by eating more oily fish or by taking good quality fish oil supplements. It is usual to wait some weeks after changing the omega-3 intake before re-testing the HS-Omega-3 Index in order to allow the body time to reach a new steady state.

The HS-Omega-3 Index is optimal between 8% and 11%. In many persons a substantially lower HS-Omega-3 Index can be found, e.g. below 4%. Compared with an HS-Omega-3 Index of 4%, a HS-Omega-3 Index between 8 and 11% means:

- a lower risk for and with cardiovascular disease, like myocardial infarction, cardiac arrhythmias, sudden cardiac death or congestive heart failure
- lower probability for psychiatric diseases like ADHD or depression
- lower probability for “age-related” and other cognitive impairments
- healthier pregnancy with better perinatal outcomes including post-partum depression, higher IQ in children
- possibly improved fertility
- higher childhood IQ scores including verbal fluency and writing
- improved symptoms from inflammatory diseases such as osteoarthritis and various skin conditions
- decreased cellular aging as shown by telomere attrition
- improved mental resilience to sleep loss/deprivation
- possibly improved neurocognitive function in areas such as cognitive flexibility, executive function, and processing speed

SECTION 3: Omega-3 EPA/DHA and Brain Health in Older Adults: Current Status

Fish oils, which are rich sources of the two omega-3 fatty acids, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), are closely associated with brain health. This association started by the early observation that DHA is one of the two most plentiful fatty acids in the brain, and it is particularly enriched in the retina of the eye. Studies in animals (Davis-Bruno, 2011) and in newborn infants (Rogers 2013) confirmed that visual function and certain learning behaviors were adversely affected by DHA deficiency, and more recently, anecdotal reports of very high dose fish oil being used to successfully treat traumatic brain injury (Lewis 2013), and animal experiments showing accelerated healing after spinal cord injury (Michael-Titus, 2013) have built the evidence for omega-3s playing a functional role in the central nervous system. When studies reporting a link between fish intake and dementia /cognitive function began to be published and biomarker-based studies showed lower plasma/erythrocyte omega-3 levels in patients with cognitive dysfunction, we could expect randomized trials to prospectively test whether higher omega-3 intakes could forestall the development of dementia (D) and Alzheimer's disease (AD). There is considerable research developing the application of fish oils in the prevention (and possibly treatment) of dementia and Alzheimer's disease and there are several reviews on this topic (Robinson, 2010; Denis, 2013; Lin, 2012; Luchtman, 2013; Cederholm, 2013).

Before examining the studies themselves, it is helpful to review how scientists study diet-disease relationships. There are two common epidemiological approaches, both of which look for associations between:
1) INTAKE of nutrient X and disease Y, and
2) BLOOD LEVELS of nutrient X (i.e., biomarkers) and disease Y.

Both of these can be studied "cross sectionally", that is, at one point in time (disease prevalence); or "prospectively" where intake/biomarker levels are determined at one time point and one tracks the development of the disease (incidence) longitudinally.

The strongest of these study designs is typically the prospective/biomarker approach, but even this cannot show that a deficiency of nutrient X CAUSES the disease – association never proves causation – but this is considered good evidence of possible causation. The way to study causation is with a randomized controlled trial (RCT) where nutrient X is given to one group of randomly selected people and a placebo to an identical group, and then they are both followed over years for the development of disease. This, however, is a "drug" model and it has limitations when studying nutrients (which, by definition, are already present in the body at some level in everyone, which is not the case for drugs). Thus, in nutrition research, RCTs and prospective/biomarker-based studies should both be viewed as providing strong evidence for diet-disease relationships. When it comes to omega-3 fatty acids and dementia, all of these research approaches have been utilized… and a consensus begun to form.

Fish and Omega-3 Intake Linked with Cognitive Function and Brain Anatomy

An example of a cross sectional/intake-based study was reported by Conklin et al in 2007. In a group of 55 men and women with a mean age 45 years, the highest tertile (highest 1/3) of EPA+DHA dietary intake was associated with larger hippocampal volume. This is important as hippocampal atrophy is commonly observed prior to symptomatic impairment, (Fjell, 2010) . Another example was the Cardiovascular Health Study (Virtanen, 2008). Here, in 2465 participants (59% women, average age 75 years) the reported intake of fatty, non-fried fish (those are the richest in EPA and DHA) was inversely associated with the presence of subclinical brain infarcts on magnetic resonance imaging (MRI) examination (i.e., defined as ischemic lesions ≥ 3mm diameter). The intake/prospective approach is exemplified by the Prospective Investigation of the Vasculature in Uppsala Seniors (PIVUS) study. Here the investigators tested the hypothesis that higher cognitive test scores and greater brain volume would be associated with higher (vs lower) dietary intake of omega-3 fatty acids (Titova, 2013). The dietary intake of EPA and DHA was determined by a 7-day food protocol in 252 cognitively healthy elderly subjects at the age 70. Five years later, the participants' global cognitive function was examined, and their brain volumes were measured by MRI. Intake of EPA and DHA at the age of 70 years was positively associated with global gray matter volume and with global cognitive performance score at age 75. Intake was not, however, significantly associated with total brain, global white matter, or regional gray matter volumes. In other words, people who ate more fish had fewer infarcts. These studies suggest that more fish in the diet helps preserve brain health, but they do not prove that fish (or the omega-3 fatty acids in fish) provide this benefit since another component of fish could also be beneficial, the foods people avoid in order to eat fish could be harmful, or people who eat fish might have other lifestyle habits that are protective.

The pattern of significantly reduced dementia risk has not been observed in all studies with elevated fish intake (Huang, 2010; Cunnane, 2009), but weekly fish consumption and higher DHA levels in the blood have generally been associated with a lower risk of developing dementia or specific signs of brain aging (Huang, 2010; Cunnane, 2013).

Wu et al. (2015) performed a meta-analysis of the literature reviewing omega-3 fatty acids intake and risks of dementia and Alzheimer's disease. They systematically reviewed and analyzed prospective cohort studies, as evidence from previous studies were inconsistent. This study reviewed relevant studies, up to June 2013, reporting on associations of dietary intake of long-chain omega-3 fatty acids or fish with the incidence of dementia and Alzheimer's disease. When comparing the highest to lowest category of long-chain omega-3 fatty acids intake and fish intake, the pooled relative risks (RRs) for dementia were 0.97 (95% CI 0.85-1.10) and 0.84 (95% CI 0.71-1.01), respectively. Evidence synthesis for AD risk did not show a statistically significant association with long-chain omega-3 fatty acids intake (RR=0.89, 95% CI 0.74-1.08). However, a higher intake of fish was associated with a 36% (95% CI 8-56%) lower risk

of AD. Dose-response meta-analysis showed that an increment of 100g per week of fish intake was associated with an 11% lower risk of AD (RR=0.89, 95% CI 0.79-0.99). Effectively, a higher intake of fish was associated with a lower risk of Alzheimer's disease.

In an observational study, those Americans who consumed more than the average (180 mg per day from 2 to 3 servings of fatty fish per week) were 47% less likely to develop dementia over the next 9 years (Schaefer, 2006).

In the elderly, omega-3 fatty acids could modulate physical performance by impacting neuro- muscular function. The cut-off value of 1.0 m/s for usual gait speed identifies slower older adults with a high risk of negative health outcomes, including hospitalization and death. In a pooled analysis of individual data from nine selected cohorts (from 34,485 community-dwelling older adults aged 65 years or older), gait speed was associated with survival in older adults. (Studenski, 2011).There are shared pathologies underlying cognitive and motor declines, even though specific executive cognitive deficits are not shown to account for slowing of usual gait in aging (Watson 2010). A cross-sectional association between an omega-3 index and gait speed was studied in a 982 subject study of French elderly community-dwellers. In this population 24.3% (n=239) had a low gait speed (<0.63 m/s) at baseline, which was associated with a higher omega-6 to omega-3 ratio. However, a high plasma concentration of omega-3 was associated with higher gait speed. These findings suggest a protective effect of EPA and DHA on physical performance decline with age (Frison 2015).

Omega-3 Biomarkers Linked with Cognitive Function and Brain Anatomy

The biomarker-based approach was also used in the Cardiovascular Health Study measuring both cross sectional and prospective endpoints. In this study, 3660 participants aged ≥65 had a brain MRI done and a blood sample taken at baseline. Five years later, 2313 had another MRI done. Baseline blood DHA levels were inversely related to the presence of subclinical infarct volume and white matter grade at baseline, and they were inversely associated with worsening white matter grade over time.

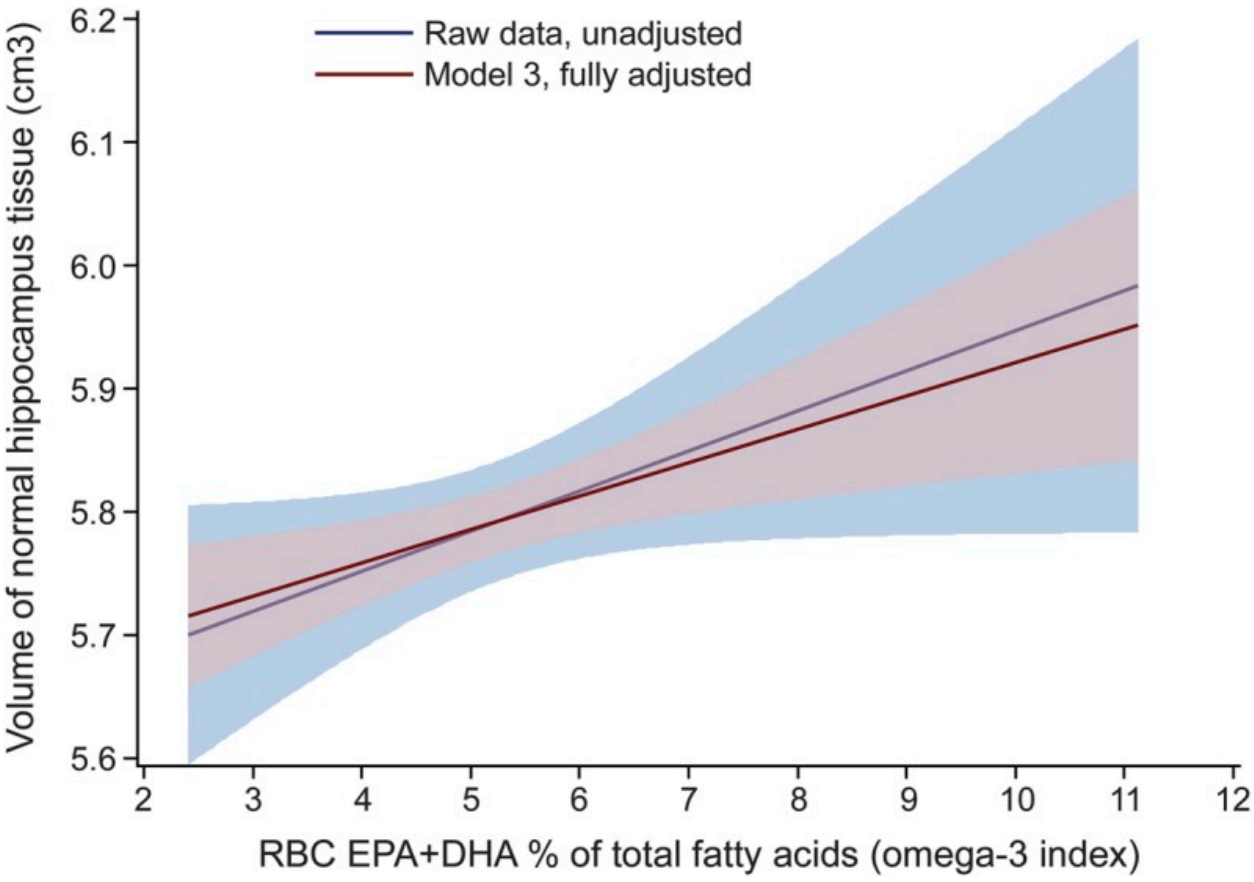
There have been two reports from the Framingham Heart Study linking omega-3 biomarker levels with brain health. The first was a prospective study looking at DHA levels in 899 participants in the original cohort in Framingham who were 76 years old on average when the blood was drawn (Schaefer, 2006). They were free of clinical dementia at that time. They were followed over the next 9 years for the development of dementia/AD. Here those in the highest quartile of DHA (levels associated with eating about 3 fish meals per week) were nearly half as likely to develop dementia/Alzheimer's disease over time compared to those with lower levels (see Exhibit A). In the Framingham Offspring cohort, a cross sectional study (in which the author was involved) compared RBC levels of DHA and EPA with MRI and cognitive markers of dementia risk in 1,575 dementia-free participants (67±9 years)(Tan, 2012). Participants

with RBC DHA levels in the lowest quartile when compared to the others had lower total brain and greater white matter hyperintensity volumes. A lower level of RBC DHA and of RBC DHA+EPA (the latter termed “the omega-3 index”, Harris and von Schacky, 2004) was also associated with lower scores on tests of visual memory, executive function and abstract thinking. Hence, lower RBC omega-3 levels were linked with smaller brain volumes and a ‘vascular’ pattern of cognitive impairment even in persons free of clinical dementia.

Another study using the omega-3 index as a biomarker of omega-3 fatty acid status used data from the Women’s Health Initiative Memory Study (Ammann, 2013). Here we examined the extent to which the omega-3 index had a protective association with domain-specific cognitive function. The cognitive domains examined were: fine motor speed, verbal memory, visual memory, spatial ability, verbal knowledge, verbal fluency, and working memory. Postmenopausal women (n=2157, mean age ~70) had blood drawn at baseline which was processed and frozen. Three years later they underwent the first cognitive testing panel and this was repeated for the next 6 years. A higher omega-3 index was associated with better fine motor speed, verbal knowledge, and verbal fluency. However, after statistical adjustment for nine other factors, the independent relationships were lost. No significant differences were found between the high and low omega-3 index tertiles in the rate of cognitive change over time. Therefore, in this cohort of women free of dementia at enrollment, while there were some connections between omega-3 status and deficits in certain cognitive function domains, these relationships were either mediated by or otherwise associated with other lifestyle/physiological factors.

Other examples of biomarker-based studies that found significant associations between MRI metrics and omega-3 levels are Bowman et al. 2012 and Samieri et al. 2012.

Pottala et al.(2014) conducted another analysis from the same cohort and found a significant direct relationship between the omega-3 index measured at baseline and total brain volume measured by MRI 8 years later. A higher omega-3 index was specifically correlated with greater hippocampal volume. They concluded that a lower omega-3 index may signal increased risk for hippocampal atrophy which is associated with hippocampal sclerosis and Alzheimer's disease .



Mean normal hippocampal brain volume in cubic centimeters by omega-3 index using linear regression with 95% confidence bands (Pottalia 2014). Omega-3 Index levels below 7% are likely to be indicative of lower brain volume, while above 7% hippocampal brain volume remains level or is greater.

Omega-3 Fatty Acids and Dementia: Intervention Studies

There are currently no published studies attempting to reverse the disease with omega-3 fatty acids – prevention appears to be the only hope. Because of the (typically) very slow development of dementia/Alzheimer's disease and the inability to really know when the process begins, performing intervention studies to forestall the development of disease requires a very long time and large numbers of subjects for adequate power. To date there have been several trials (Witte 2013; . van de Rest, 2008; Geleijnse, 2010; Geleijnse, 2013; Lee, 2013; Quinn, 2010) and only one that lasted more than 2 years (40 months; and this study used very low omega-3 doses and focused on patients with a history of coronary heart disease; Geleijnse, 2010).

A developing consensus of beneficial effects have been seen for some endpoints (e.g., executive function, attention, anxiety) for some subgroups (e.g., non-carriers of apoE4 allele, mild cognitive impairment; see review by Cederholm et al.(2013), so we already have reason for hope in the general population.

Recommendations as based on most recent reviews

Fish body consumption and omega-3 fatty acid supplements (EPA and DHA) may help prevent mild cognitive impairment and cognitive decline in otherwise healthy individuals, but also help patients with dementia and Alzheimer's disease.

Zhang et al. (2016) analyzed data from 21 studies on neuro-cognitive protection offered by eating fish, polyunsaturated fatty acids (PUFAs) and omega-3 PUFAs against dementia, Alzheimer's disease and Parkinson disease; they found consumption of fish and omega-3 PUFAs was protective against the diseases and related symptoms. With approximately one serving of fish per week as associated with 5% and 7% reduced risk for dementia and Alzheimer's disease, during the follow-up period (up to to 21 years). An incremental amount of 100mg DHA per day was associated with 14% lower risk for dementia and 37% reduced risk for Alzheimer's disease.

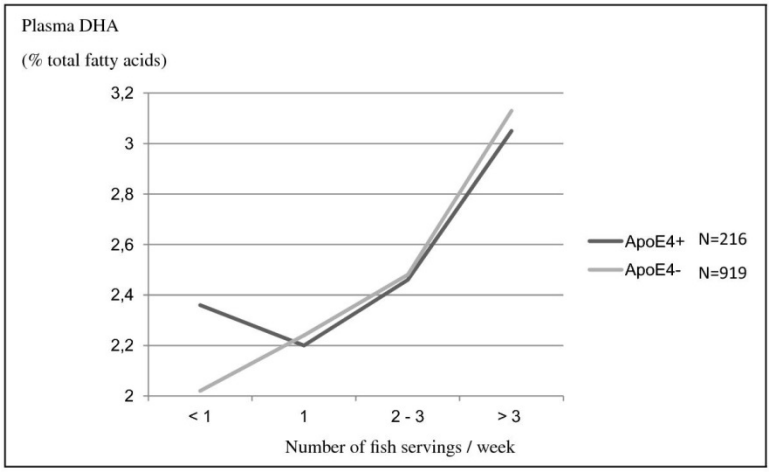
Americans are said to consume between 60 and 80 milligrams per day of DHA and between 20 and 30 mg per day of EPA (NHANES 2009-2010). At our present state of knowledge, there is virtually no risk associated with increasing the typically low (less than 120 mg/day) EPA+DHA intake in Americans to 200, 500 or even 1000 mg/day (see international recommendations in Flock et al. 2013) and this can be accomplished by eating more oily fish or with omega-3 supplements from algal or fish oils (Harris, 2013).

Across the many observational studies that have tracked dementia risk with fish or DHA intake, no specific dose has emerged as but there is clear indication that benefits are seen just in studies where higher levels were consumed. DHA and EPA levels, so the Omega-3 Index, is clearly linked to intake of fish itself, which we can now also be linked to brain health (Kim 2013). To demonstrate of benefits seen in clinical trials, DHA supplements various doses, up to 2000 milligrams per day have been tested with some success at improving cognitive function in older people (Dacks 2013), but no specific dose yielding a greater chance of improvement (Mazereeuw 2012). Here is where the Omega-3 index helps individuals find their status, and track their attempts to optimize their status.

ApoE4 genetic risk factor and Omega-3 metabolism.

As reviewed, epidemiological and experimental research suggest a protective effect of the omega-3 fatty acids, EPA and DHA against age-related cognitive decline, dementia

and Alzheimer's. However, in the elderly, some randomized controlled trials with omega-3 fatty acids supplements have given inconsistent results on cognitive outcomes. One explanation proposed has been an inadequate identification of potential beneficiaries according to their Apolipoprotein E (ApoE) genotype as some evidence suggested that the ApoE4 genotype modifies the metabolism of DHA. People who carry the ApoE4 genetic risk factor (e.g. for Alzheimer's disease), have been thought to be less likely to benefit from DHA. Several though not all observational studies report a protective association only in people who do not carry the ApoE4 allele (Cunnane 2009, Huang 2010). In a randomized trial, DHA only appeared to benefit Alzheimer's patients who do not carry the ApoE4 allele (Quinn 2010, Thifault 2013). The ApoE4 allele changes how the ageing human brain processes long-chain omega-3 fatty acids (Hennebelle 2014), and this may contribute to the inconsistent evidence seen in some studies of Omega-3 fatty acid in aging and dementia. Recently, a review cited five epidemiological studies and three intervention studies with omega-3 fatty acid supplements found possible explanations include different age groups (adults vs. more elderly), cognitive status (healthy vs. mild cognitive impairment), and even the measures of cognition (attention, working memory or global cognition) or the actual amounts of DHA intake within studies (Barberger-Gateau, 2016). However, such an imperfect metabolism of DHA should suggest that higher doses might be more beneficial in overcoming ApoE4-related effects.



Relationship between frequency of fish intake and plasma DHA according to APOE4 genotype. (Barberger-Gateau, 2016).

Within the Three-City study, Bordeaux, individuals eating very little fish (less than one serving per week) and carriers (the ApoE4+) had higher mean plasma DHA than non-carriers (ApoE4- , see figure). However, there was no significant difference in plasma DHA between carriers and non-carriers for higher frequency of fish intake. Plasma DHA

strongly increased with increasing fish intake in both groups. There was no interaction with ApoE genotype for plasma EPA (Barberger-Gateau, 2016).

Another recent study Morris et al. (2016) , looked at 554 Chicago residents who died over a ten-year period, within a long-term aging study. They conducted autopsies to look directly at the brain for physiological changes. They also used seafood intake information from food frequency questionnaires at a mean of 4.5 years before death. Here, eating fish regularly was clearly associated with a reduced risk of Alzheimer's disease. Despite the fact that people who ate more fish did have higher levels of mercury in the brain, the mercury levels were too low to cause harm, and the benefits of eating fish easily outweighed risks and benefits such as neuritic plaques (signs of Alzheimer's). Higher brain concentrations of mercury were not significantly correlated with increased levels of any brain neuropathology.

Subjects who ate seafood at least once per week had lower levels of physiological signs associated with Alzheimer's, and the benefits were particularly seen in ApoE4 carriers, which itself is an increased risk of Alzheimer's (Morris, 2016). However, fish oil supplementation had no statistically significant correlation with any neuropathological marker. This reassuring study suggests that despite the increased mercury caused by eating more fish, and even in ApoE4 carriers, the overall effect of fish consumption is beneficial (Shatenstein, 2015)

The US FDA already recommends that pregnant women and young children eat more fish for its nutritional benefits. Now we can accept that fish consumption also is beneficial with older age, so older people should eat fish regularly too.

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