Published in final edited form as:
Prostaglandins Leukot Essent Fatty Acids. 2009 ; 81(0): 213–221. doi:10.1016/j.plefa.2009.05.015.

Omega-3 fatty acids and dementia

Greg M. Cole, Ph.D.,
Departments of Medicine and Neurology at University of California, Los Angeles, CA, USA; Geriatric Research, Education and Clinical Center, Greater Los Angeles Veterans Affairs Healthcare System, VA Medical Center, North Hills, CA, USA

Qiu-Lan Ma, M.D., Ph.D., and
Departments of Medicine, at University of California, Los Angeles, CA, USA; Geriatric Research, Education and Clinical Center, Greater Los Angeles Veterans Affairs Healthcare System, VA Medical Center, North Hills, CA, USA

Sally A. Frautschy, Ph.D.
Departments of Medicine and Neurology at University of California, Los Angeles, CA, USA; Geriatric Research, Education and Clinical Center, Greater Los Angeles Veterans Affairs Healthcare System, VA Medical Center, North Hills, CA, USA

Abstract

More than a dozen epidemiological studies have reported that reduced levels or intake of omega-3 fatty acids or fish consumption is associated with increased risk for age-related cognitive decline or dementia such as Alzheimer's disease (AD). Increased dietary consumption or blood levels of docosahexaenoic acid (DHA) appear protective for AD and other dementia in multiple epidemiological studies; however, three studies suggest that the ApoE4 genotype limits protection. DHA is broadly neuroprotective via multiple mechanisms that include neuroprotective DHA metabolites, reduced arachidonic acid metabolites, and increased trophic factors or downstream trophic signal transduction. DHA is also protective against several risk factors for dementia including head trauma, diabetes, and cardiovascular disease. DHA is specifically protective against AD via additional mechanisms: It limits the production and accumulation of the amyloid β peptide toxin that is widely believed to drive the disease; and it also suppresses several signal transduction pathways induced by Aβ, including two major kinases that phosphorylate the microtubule associated protein tau and promote neurofibrillary tangle pathology. Based on the epidemiological and basic research data, expert panels have recommended the need for clinical trials with omega-3 fatty acids, notably DHA, for the prevention or treatment of age-related cognitive decline—with a focus on the most prevalent cause, AD. Clinical trials are underway to prevent and treat AD. Results to-date suggest that DHA may be more effective if it is begun early or used in conjunction with antioxidants.

Address correspondence and request for reprints to: Greg M. Cole, PhD, GRECC Veterans Affairs, Greater Los Angeles Healthcare System, Research-151, Bldg 7, Rm A101, 16111 Plummer Street, North Hills, CA 91343, Tel: (818) 891-7711, ext 9949, Fax: (818) 895-5835, gmcole@ucla.edu.

Keywords

Alzheimer's disease; dementia; omega-3 fatty acid (n-3); docsahexaenoic acid (DHA); amyloid

Introduction

Alzheimer's Disease (AD) and other late life dementias double every five years after age 65. Some 80 million baby boomers are rapidly approaching this age in the U.S., and similar demographic shifts toward aging populations are occurring throughout the world. Until methods of preventing AD are found, it is not only the tens of millions of disease victims and their families that will suffer, but also our nation, our Medicare system, and our economy as whole. While genetics plays the major role in risk for familial AD with early onset, the majority of AD is late onset and appears to involve the interplay of multiple genetic and environmental risk factors (1). These interact to modulate the pathogenesis and risk of onset AD, but are not sufficiently powerful to act alone to determine outcomes. Among the environmental risk factors, increased consumption of fish/omega-3 fatty acids (this review), antioxidants (2), and non-steroidal anti-inflammatory drugs (3) are associated with reduced risk for AD. Based on this, our group and others have tested supplementation with the omega-3 fatty acid DHA, antioxidants, and NSAIDs in animal models for the treatment of AD. NSAIDs reduce amyloid accumulation in multiple models, but have toxicity issues, including GI bleeds and increased risk of cardiovascular events, that limit use for prevention (4). In contrast, omega-3 fatty acids are not only relatively inexpensive, but have an excellent safety profile and are proven to reduce cardiovascular disease mortality by 37% (5, 6). If omega-3 fatty acids can be proven to slow pathogenesis of AD and reduce AD risk, they would be an ideal intervention approach. Here we review the evidence for their efficacy.

Omega-3 Fatty Acids/DHA Reduce Risk for Alzheimer's Disease and Other Dementia

Omega- 3 fatty acids exert pleiotropic effects on the cardiovascular and central nervous systems (CNS) that may be protective against age-related cognitive decline, where the causes are either vascular or Alzheimer dementia or a mix of both. Low omega-3 fatty acid intake is one of many overlapping risk factors for both cardiovascular disease (CVD) and AD that correlate with diabetes, hypercholesterolemia, hypertension, hyperhomocysteinemia, dietary saturated fats, cholesterol, antioxidants, alcohol consumption, smoking, physical activity, the presence of atrial fibrillation, and atherosclerotic disease (7). Although low omega-3 fatty acid intake is only one of many risk factors, it matters. For example, recent meta-analysis indicates that omega-3 fatty acids from fish can provide a 36% reduction in an unambiguous, endpoint-death from coronary artery disease (8). The cardiovascular protective effects of omega-3 fatty acids are backed by repeated positive clinical trial results, which lead to practical recommendations for dietary supplementation (9), but clinical trials for dementia prevention have not been concluded. Nevertheless, a 2005 literature evidence-based meta-analysis on omega-3 fatty acids and dementia, requested by the U.S. Department of Health and Human Services, concluded that

there was sufficient evidence to merit clinical trials for the treatment and prevention of AD (10). Since then, the results of a number of new studies have been reported. Nine epidemiological studies now support that increased dietary intake of fish is associated with reduced risk for cognitive decline or dementia (Table 1). Several of the studies show a 40–50% reduced risk of dementia. Curiously, two results found no effect in subjects with a major AD genetic risk factor, the ApoE4 allele of apolipoprotein E. Because ApoE4 is found in ~40–50% of AD patients, a lack of response in ApoE4 cases would account for many of the apparent “non-responders” in epidemiological studies approaching 50% risk reduction. However, not all reports show the same ApoE genotype effect on omega-3 fatty acid response.

One potential confounding factor in epidemiology study might be limited reliability in dietary survey data. However, there have been another eight studies in which high blood levels of omega-6 (relative to omega-3) fatty acids were associated with AD and/ or increased cognitive decline (Table 2). In general, these studies show protection from omega-3 fatty acids, confirming the results based on dietary intake estimates. The prospective Framingham study from Schaefer et al. 2006 (11) is notable in that blood levels taken at ~10 years prior to assessment of cognitive status showed protection from dementia or AD (average age 76 years) in the group with the upper 25% quartile blood DHA levels. No other lipid was predictive of risk. The authors estimated a daily intake of 180 mg per day of DHA in the protected group and plasma DHA levels correlated with fish intake. However, estimated daily intakes of DHA from fish accounted for only half the variance suggesting that genetic factors or other n-3, notably alpha linolenic acid (ALA). In an atherosclerosis risk study from Minnesota that followed cognitive decline in younger patients with less AD risk (age 50–65 years), Beydoun et al. 2008 (12) found that higher plasma omega-3 fatty acid levels were associated with less decline in verbal fluency, particularly in hypertensive and dyslipidemic patients. They reported these patients as having more oxidative stress, which might deplete the highly peroxidizable long chain omega-3 fatty acids (omega-3 or n-3). Alternatively, because of the overlap between AD and CVD risk factors, protection against decline in midlife may involve reduction in both incipient vascular and Alzheimer dementia accelerated by hypertension and elevated blood lipids. In the same study and in others, high blood levels of omega-6 fatty acids (n-6) were associated with increased risk, consistent with the protective value of a low n-6/n-3 ratio. Supporting a possible association between omega-3 fatty acid levels and oxidative stress, Wang et al. 2008 (13) (Table 2) found an association between a high RBC n-3 index and levels of several lipid soluble antioxidants. The prospective blood level study of Whalley et al. 2008 (14) again reported less protection from high omega-3 fatty acid in ApoE4 carriers. ApoE4 carriers show evidence of increased oxidative stress, including lipid peroxidation products (15, 16), consistent with a large literature showing that ApoE4 increases susceptibility to oxidative stress in animal and cell culture experiments (reviewed in (17)). Thus, one logical explanation for a possible interaction between omega-3 fatty acids and ApoE4 genotype would be increased lipid peroxidation.

In summary, in the three years since the 2005 evidence-based review of the omega-3 fatty acid and dementia-related literature, the results of eight new studies have added further support to the 2005 conclusions, which called for randomized clinical trials that are 1)

sufficiently powered, 2) of an adequate length (e.g., three to five years of follow-up), 3) early intervention during “the lengthy presymptomatic latency period” as well as 4) in populations of cognitively-impaired adults, prior to a dementia diagnosis, such as individuals with various sub-types of mild cognitive impairment (MCI) (10).

The Western Diet is Omega-3 Deficient

The dietary intake and blood level studies in Tables 1 and 2 suggest a consistent reduction in risk for cognitive decline, AD, or other dementia for those in the upper quartiles or quintiles of omega-3 intake or levels. To be in this protected group based on epidemiology would require ~200 mg DHA daily intake. Consistent with these studies, this is much higher than the average U.S. daily intake, which is generally estimated to be closer to ~80 mg—or less than half that in the low-dementia risk groups. Because the risk factors are shared, these numbers are similar to those arising from the epidemiology for reducing CVD risk; however, the explanation for DHA-reduced dementia and AD risk likely involves more than that for reduced CVD and multiple effects, including neuroprotection and more specific effects on AD pathogenesis.

Alzheimer (AD) Pathogenesis

AD is believed to be caused by increased amyloid β (Aβ1-42) protein, which is derived from a larger β amyloid precursor protein, by sequential endoproteolysis catalyzed by enzymes called β- and γ- secretase. Aβ 1-42 aggregates to form neurotoxic oligomers and fibrils (1). These oligomers and fibrils of Aβ can cause oxidative damage, neuroinflammation, and synaptic dysfunction; as well as loss and activation of different kinases that phosphorylate tau protein and promote its aggregation into toxic species, including soluble tau oligomers and intraneuronal neurofibrillary tangles. While Aβ may initiate pathogenesis, tau pathology is a better correlate of neurodegeneration and progression, and synapse loss is the best correlate of cognitive decline (18).

DHA is Neuroprotective via Multiple Mechanisms

1. Reducing arachidonic acid and its metabolites

The omega-3 fatty acid DHA is preferentially taken up by the brain, where it is highly enriched in neurons and synapses, and esterified at the second position of phospholipids. While many effects relevant to CNS function have been reported (19), a subset of these shown in Table 3 would be predicted to be neuroprotective and relevant to Alzheimer and other dementia diseases. For example, because DHA and arachidonic acid (AA) compete for esterification into phospholipids at the most labile sites, higher ratios of n-3/n-6 intake reduce the flux of AA released by phospholipases, which are activated during glial or synaptic signaling, notably by calcium influx. In AD, there is both an overall pattern of chronic low level inflammation (20) and excitotoxic activity (21), resulting in elevated COX-2 (22, 23), increased AA products including cyclooxygenase products like PGE2 (24), and lipoxygenase products (25, 26). Increased DHA influx has the potential to reduce AA availability, particularly in compartments with higher lipid metabolism that contribute to both glial and neuronal hyperactivation. Reduced AA has been observed in brains of DHA-

fed AD model mice with a positive response (27-29). Thus, DHA should share some neuroprotective mechanisms with NSAIDs, for example, COX-2 (30) and lipoxygenase (26) inhibitors. If a significant part of DHA's protective activity stems in part from NSAID-like activity, this is noteworthy because, while NSAIDs reduce Alzheimer risk in most epidemiology, the protective effects are not seen with use in the two to three years prior to assessment and are much clearer when there is five or more years duration of use (31). This “lagging” or delayed protection is obviously a problem for clinical trials, where duration is a major expense.

2. Trophic factor signaling

A second mechanism for neuroprotective activity for DHA involves potentiating the activation of one branch of classical neurotrophic factor (BDNF, NGF, bFGF) or insulin signaling via the phosphatidylinositol-3 kinase (PI3-K) > Akt pathway. DHA increases neuronal phosphatidylserine (PS) and the rate of a critical activation step: Akt membrane docking, which occurs through a plecstrin homology domain pocket that binds the PI3-K product PIP3 and PS (32). The net effect is to increase neurotrophic signaling to down-regulate pro-apoptotic regulators of caspases like Bad that control cell death. Some evidence for this activity was found with elevated inactivation of Bad and reduced caspase activation in AD model mice fed DHA (27, 33).

3. BDNF

A third reported neuroprotective effect of DHA is simply to increase the production of brain-derived neurotrophic factor (BDNF) (34), which is depleted in AD hippocampus and believed to be responsible for many of the positive effects of exercise on cognition (35).

4. Antioxidant defenses

A fourth class of neuroprotective effect comes from antioxidant activity, which may be direct as discussed by Yavin et al. 2002, or indirect by induction of antioxidant defense enzymes (Table 3). Because omega-3 fatty acids are highly unsaturated fatty acids and subject to oxidative attack via autocatalytic feed–forward lipid peroxidation reactions, they need additional protection and appear to induce antioxidant defenses enzymes. This may occur via transcriptional regulation by the Nrf2>Keap>antioxidant response element pathway that is known to be regulated by PI3-K>Akt signaling (36). Thus, DHA potentiation of Akt may promote antioxidant defenses. Whatever the mechanism, omega-3 fatty acids can reduce oxidative damage in AD model mice (33) and in humans (37). This is significant because oxidative damage is clearly elevated in AD, including oxidative damage products of DHA itself (38-40).

5. Neuroprotection D1 (NPD1)

A fifth type of neuroprotective effect of DHA is mediated by a lipoxygenase metabolite of DHA, neuroprotectin D1 (NPD1) (41). This metabolite has a variety of effects including up-regulation of anti-apoptotic and down-regulation of pro-apoptotic mediators that regulate caspases involved in cell death. It appears to be a very potent neuroprotective agent with multiple activities.

6–11. Other neuroprotective functions

Other potentially neuroprotective activities listed in Table 3 include 6) promoting neurogenesis, 7) increasing a glucose transporter, 8) coupling of blood flow to glucose utilization, 9) improving synaptic membrane fluidity, 10) G-protein coupling that is involved in many signal transduction pathways and 11) directly binding to lipid-related transcription factors including forms of LXR, RxR, and PPAR. It is unclear whether these direct transcriptional effects occur *in vivo* with DHA itself, because the EC50 for this type of mechanism may require higher levels of free DHA than other pathways (42); however, these are possible targets for DHA metabolites. It is interesting to note that the insulin sensitizing PPAR agonist rosaglitazone has been in clinical trials for AD and, reminiscent of fish epidemiology discussed above, showed protection in non-ApoE4 carriers (43).

These mechanistic studies in preclinical models suggest neuroprotective mechanisms. Some direct evidence for neuroprotection in people is suggested by a recent German study that showed improved survival and recovery from severe head injury when brain trauma patients received fish oil supplements through their parental feeding tubes (44).

Disease-Specific Mechanisms of DHA Protection in Alzheimer Disease

Most of the neuroprotective mechanisms discussed above are potentially relevant to AD and other neurodegenerative diseases or CNS damage. However, since AD is believed to be initiated by Aβ peptide, many potential AD treatments are aimed at inhibiting Aβ production, for example: secretase inhibitors and modulators. DHA's efficacy in reducing Aβ production/ amyloid accumulation *in vitro* and in animal models has now been observed by eight out of nine studies (Table 4). In the one study that did not see a reduction in Aβ, the supplemented diet also failed to change brain DHA or AA levels (45).

DHA appears to reduce Aβ production by several mechanisms, including the induction of increased neuronal expression of SorLa/LR11 in multiple model systems *in vitro* and *in vivo* (46). SorLa is an amyloid precursor sorting protein with diminished expression levels in surviving neurons at early stages of late onset AD, but not early onset familial AD (47). Because SorLa (also called LR11) is known to limit Aβ production by trafficking amyloid precursor proteins away from the secretases that make Aβ, reduced levels of LR11 would be predicted to play a causal role to increase AD risk. There is some genetic evidence to support this hypothesis (48-51)

Whether or not genetic variants that limit expression of LR11 contribute to late onset AD, the majority of patients have reductions in expression. Omega-3 fatty acids appear to be one known environmental risk factor that can up-regulate SorLA/LR11 expression in animal models. We have recently found that soluble forms of LR11 can be detected in human CSF, and that deficits occur in AD patients (52). It will be worth evaluating CSF LR11 levels in clinical trials with DHA treatment.

There are several other candidate mechanisms for DHA reducing amyloid. DHA may also be able to lower Aβ by reducing expression of presenilin 1 and γ-secretase activity (28). Omega-3 fatty acids in fish oil are also reported to increase expression of an Aβ-clearing

transport protein, transthyretin (TTR) (53). Finally, because expression of a major Aβ-degrading enzyme, the insulin degrading enzyme (IDE), is regulated by the PI3-K> Akt pathway, DHA may increase IDE expression and Aβ clearance (54).

DHA Protects from Aβ oligomer Toxicity to Synapses

Consistent with DHA's many neuroprotective mechanisms, it can protect against Aβ oligomer toxicity and caspase activation *in vitro* (55). Lower doses of Aβ oligomers also cause loss of synapses without killing neurons. Recently, our group reported evidence for an Aβ oligomer-mediated defect in a pathway involving components implicated by different labs that were looking at Aβ oligomers *in vitro*. These included NMDA receptors, the tyrosine kinase fyn, Tiam1, rac, PAK, LIMK1, and, downstream, the actin-severing protein cofilin. This pathway is dysregulated in AD brain and regulates the oligomer-induced loss of dendritic spines in excitatory synapses *in vitro*, including the spine actin binding protein drebrin (56). Drebrin shows massive losses in AD temporal cortex and hippocampus, and DHA protects against this loss in a transgenic mouse model of AD (33). We now have evidence that DHA is remarkably effective in protecting against oligomer-induced synaptic marker loss in primary neurons *in vitro*, by blocking this synaptotoxic signal transduction pathway regulating dendritic spines and synapse formation (Q.L. Ma, F. Yang, E. Rosario, O.J. Ubeda, P.P. Chen, W. Beech, B. Hudspeth, S.A. Frautschy, G. M. Cole, manuscript in preparation). In our view, drebrin loss can be taken as an index of dysregulation of this pathway, and drebrin shows a precipitous loss in temporal cortex of AD brain as mild cognitive impairment emerges (MMSE >27) (57). After that, it shows no further reduction. Since drebrin loss was the most DHA-sensitive endpoint in our AD animal model studies, these results suggest that DHA intervention will be most effective at the earliest stages of cognitive decline.

DHA limits Tau Kinases that Promote Tau Pathology/Neurofibrillary Tangles

Neurofibrillary tangles are an AD pathology featuring intraneuronal accumulation of filamentous aggregates of the microtubule protein tau. This pathology is promoted by Aβ aggregate-induced induction of “tau kinases” that phosphorylate tau to keep it off microtubules, and to promote exposure of β conformation stable regions that bind to each other to make proteolytically stable tau amyloid fibrils. Two of the major tau kinases that are induced by Aβ are GSK3β and JNK. Since GSK3β is negatively regulated by the PI3-K> Akt pathway that DHA potentiates as discussed above. Thus, it is not surprising that in our amyloid plaque-forming AD model mice, on DHA-depleting high safflower oil diets, this inhibitory GSK3β phosphorylation is suppressed, and this is reversed by DHA treatment restoring inhibitory control of GSK3β (Ma et al., unpublished). While this effect would be predicted to limit tangle formation, those AD model mice lack a human tau transgene that is required for tangles to develop. Using triple transgenic AD model mice with two genes that increase Aβ and a mutant human tau, LaFerla's group has shown that DHA not only slows the accumulation of the intraneuronal Aβ implicated in the model, it also suppresses the activity of JNK and the accumulation of abnormally phosphorylated tau (28). Thus, DHA has multiple mechanisms for reducing both the amyloid peptide (Aβ) that initiates AD and

the tau kinases and tau pathology that appear to perpetuate neurodegeneration. Coupled with more than 10 other neuroprotective effects listed in Table 3, DHA is very well-positioned to play a causal role in preventing AD that can explain the positive epidemiology studies.

DHA Protection is Incomplete and Should be Combined with Antioxidants

Nevertheless, despite profound anti-Alzheimer effects *in vitro* and in multiple AD animal models, DHA protection is incomplete. For example, in our late intervention model where it protected drebrin and CamKII alpha as it does with Aβ oligomer toxicity *in vitro*, DHA failed to protect NMDA receptor loss (27) and the ERK> CREB signal transduction pathway (Ma et al., unpublished). These results suggest that DHA treatment alone will likely have some benefits, but may work best in combination with other treatments. We have previously argued that oxidative damage in AD brains may be depleting DHA, suggesting a combination with an antioxidant treatment (33). Anyone who has worked with DHA *in vitro*, knows that it needs to be protected by antioxidants, particularly at higher doses. While this is much less clear *in vivo*, where antioxidant defenses are usually sufficient, oxidation of supplemented DHA may be a problem in pathological environments (58). DHA is better protected *in vivo*, but clearly not adequately protected in AD brain because, as reviewed above, its F-4 isoprostane products are elevated. DHA's lipid peroxidation products like bifunctional aldehydes can cross-link proteins, including tau proteins (59). Further, specific toxic oxidized forms of DHA have recently been identified (60). One might predict lipid peroxidation to be an issue in AD because Aβ aggregates are known to increase oxidative damage, and AD has increased mitochondrial defects and elevation of most known oxidative damage markers (reviewed in (33)). Since Aβ aggregates accumulate in synapses (61), and this is where peroxidizable DHA is concentrated in areas of high metabolism and even in the mitochondria (62), there is every reason to expect the observed increase in DHA oxidation products in AD brain and CSF. Given that DHA is so readily oxidized, there is a very strong rationale suggesting that it be combined with antioxidant interventions like the classical vitamin E plus C or the more brain permeable and mitochondrial-protective alpha lipoic acid. Our group has also advocated that it be combined with the polyphenolic antioxidant curcumin, because it has additional anti-amyloid and AD protective activities (63).

Clinical Trials

Collectively, the strong positive epidemiology and preclinical data have led to multiple clinical trials for the treatment or prevention of AD with omega-3 fatty acids, notably DHA (Table 5).

Results to-date suggest that DHA alone may produce some benefits, but may not work well by itself in cases of established AD with MMSE <26; however, it may be effective with early intervention by itself (MCI), or even in established AD in combination with an antioxidant. For example, in a small Japanese trial from Kotani (64) as well as in the completed Swedish trial from Freund-Levi (65) and in a similar small 6 month Taiwanese trial from Chiu (66), DHA or fish oil appeared to stabilize MMSE in the MCI patients, but not in those with established AD. It is encouraging that the only example of a DHA/ antioxidant combination treatment approach, a pilot alpha lipoate/ fish oil trial from Shinto

and colleagues at OHSU (NCT000904029), MMSE was significantly stabilized over a 12-month period (67). If this level of efficacy is confirmed in larger trials, this will be a remarkable and cost-effective treatment. While these are the first trials to report, they are encouraging; additional trials are registered at clinical.trials.gov and ongoing (Table 6).

From the perspective of this review, it is unfortunate that none of the ongoing trials combine DHA with an antioxidant. The ADCS trial with DHA includes AD patients with MMSE 26 or below and is for an 18-month duration. It is larger and longer than the completed six-month Freund-Levi et al. treatment trial in Sweden, which failed to show clear cognitive benefit in similarly advanced AD patients, but the ADCS trial excludes MCI patients who are the most likely to benefit. Nevertheless, some 68% of the patients in the Freund-Levi trial were ApoE4 positive, and some of the epidemiology suggests that they may respond poorly. Therefore, there is hope for some positive results in the larger ADCS trial that may either take longer to manifest, or are ApoE genotype-dependent and require the larger patient pool. Further, since EPA can competitively reduce DHA incorporation, there may or may not be benefits from enhancing DHA delivery by using a slightly higher dose of algal DHA, rather than a fish oil product, and not having EPA in the formulation. We must await the trial result.

We would strongly advocate a combination approach in future planned trials with AD patients. We have argued for this on a theoretical basis and based on our preclinical results, but the positive data from the small OHSU pilot make this approach much more plausible. Despite these concerns, there is sufficient evidence to expect some significant protective effects, particularly with the early intervention efforts in three of the ongoing trials. Is DHA an essential nutrient? The counterargument is that dietary ALA provides sufficient DHA. As reviewed here, the epidemiology of fish and to a lesser extent DHA intake provide a strong case for protection from cognitive decline and dementia by higher intakes of marine omega 3 fatty acids than much of the population is achieving from other dietary n-3. The hypothesis that conversion from dietary ALA provides adequate DHA or EPA, does not explain the epidemiology showing protection from higher marine sources. Further, DHA rather than EPA is markedly enriched in the brain and the preclinical model data clearly implicate DHA as an effective protection against Alzheimer pathogenesis. That said, to date there are only a handful of small randomized clinical trials with fish oil showing protection and only in early stages of disease. More definitive, longer and larger, adequately powered trials with DHA are needed to examine DHA efficacy against cognitive decline due to Alzheimer. Fortunately, several trials are already currently underway. However, age-related cognitive decline is also caused by vascular disease and there, the clinical trial data are fairly compelling. Large clinical trials have shown that fish oil supplements reduce death from cardiovascular disease (CVD) in patients with substantial risk (6). Further, meta-analysis of the epidemiology of EPA +DHA intake shows similar protection from CVD death in healthy adults (68). In contrast, we lack similar evidence to conclude that merely lowering the n-6/n-3 ratio with ALA protects from CVD (69). This is very strong evidence that CVD protective levels of EPA/ DHA levels are not being derived from dietary ALA in the general population. While the relative roles for EPA and DHA in CVD and protection against stroke remain controversial (5), lowering the CVD death rate in our aging population is a

compelling argument for an essential role for combined EPA + DHA, but neither n-3 fatty acid on its own.

Conclusions

The combination of a strong rationale from both positive epidemiology and preclinical trials have propelled omega-3 fatty acid supplements into multiple clinical trials for age-related cognitive decline and dementia, notably AD. Because dementia risk doubles with every five years over age 65, the caseload of AD and vascular dementia will more than double as the baby boomers age. Dementia is amongst the chronic age-related diseases that is the most disabling, demanding the most intensive and expensive care and frequent institutionalization. Dementia alone can be predicted to drive the cost of Medicare and private health insurance up to the point where it becomes an unsustainable economic burden. Compared with most new medications, omega-3 fatty acids would be an outstanding intervention from long-term safety, side-effect, and cost perspectives. The evidence to-date from the small completed trials suggests possible efficacy both with early intervention and, in combination with antioxidants, in more established AD. Because of their outstanding safety profile, low cost, and proven efficacy in reducing mortality from cardiovascular disease, omega-3 fatty acids, and DHA in particular, are particularly attractive for prevention. This is particularly true in populations with typical Western diets like the U.S., where the average dietary intake of DHA is less than half that required in the epidemiology to reduce risk for either CVD or AD. The evidence for CVD alone is sufficient to begin to take steps to get our population out of the low omega-3 fatty acid intake, high-risk groups for these major diseases. For established AD, we are just beginning to learn how to use DHA supplements for treatment. They may not work well alone at late-stage AD, particularly in groups with high oxidative stress like ApoE4, so we can expect to combine DHA with other treatments, including antioxidants.

Acknowledgments

Martek Biosciences provided travel expenses and an honorarium for attendance at the workshop and drafting of this paper for Dr. Cole. Author roles. The authors have no financial interests to declare. Dr. Cole wrote various drafts and helped to organize tables; Dr. Ma provided data; Dr. Frautschy assisted in the writing and editing of the manuscript and prepared tables and figures.

Sources of support: This work was supported by NCCAM R01AT3008 and NIA R01AG13471.

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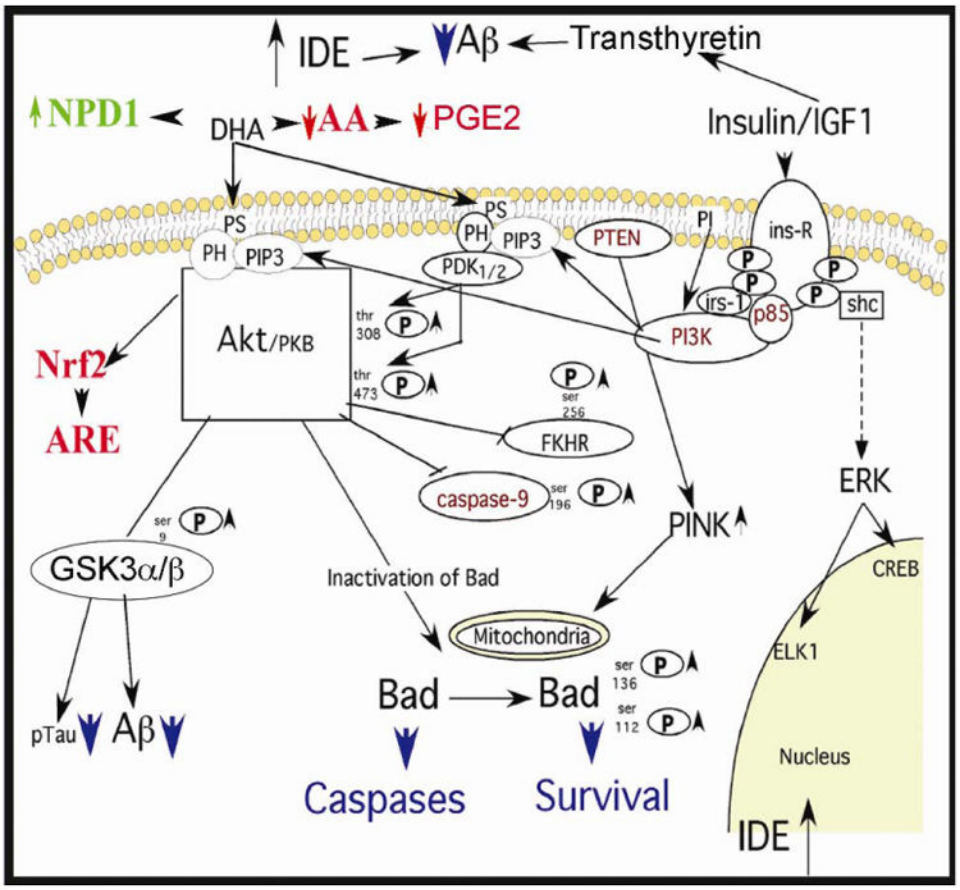

Figure 1. Summary of mechanisms of Anti-Alzheimer Effects of DHA

As reviewed in Tables 3 and 4, DHA has multiple-reported neuroprotective and anti-Aβ effects. These include reducing Aβ production by increasing SorLA/ LR11, and non-amyloidogenic processing of amyloid precursor and decreasing γ-secretase. Aβ clearance may be improved by induction of transthyretin or IDE. The DHA metabolite NPD1 can also be neuroprotective by reducing pro-apoptotic proteins such as Bad. Further, DHA increases in PS and PDK/AKT docking will potentiate neuroprotective trophic factor signaling through insulin, IGF1, BDNF, and other trophic factors. BDNF itself is induced by DHA. Downstream from AKT, there are anti-apoptotic effects on Bad and caspases, and up-regulation of the Nrf2 pathway to ARE and antioxidant defense enzymes. Further, the major tau kinase GSK3 will be inhibited, limiting tau/ tangles, which may also contribute to reduced Aβ production. Finally, one *in vivo* report found DHA limited activation of another tau kinase (JNK) and accumulation of tau pathology

Table 1

Dietary Fish Reduces AD Risk (9 positive studies).

Study	Population	Methods	Findings	Other
Kalmijn et al. 1997 (70)	Zutphen N=476 men, 64-89 yrs	Diet history, MMSE	Fish intake reduced in 153 impaired men, but n-3 not associated with 3 yr cognitive decline	Fish intake inversely correlated with cognitive decline (adjusted OR = 0.45, p = 0.09); Linoleic Acid raised risk.
Kalmijn et al. 1997 (71)	Rotterdam, N=5,386, 55+ yrs	Diet history, dementia	High fish, RR (D)=0.4; RR (AD)=0.3	Saturated fat and cholesterol increased risk
Morris et al., 2003 (72)	Chicago, N=815 unimpaired, 65-94 yrs	Diet history, 2.3 yr follow-up test for AD	131/ 815 developed AD, 60% less risk of AD with fish	DHA but not EPA associated with low AD risk
Kalmijn et al., 2004 (73)	Zutphen N=1,613, 45-70 yrs,	Diet history, Cog testing	High n-3 reduces risk of cognitive impairment	Cholesterol and sat. fat increased risk
Morris et al., 2005 (74)	Chicago, N=3,718 65+, mean 74 yrs	Diet history, Cog testing	Fish consumption associated with reduced cognitive decline over 6 yrs	No clear association with n-3 intake
Huang et al., 2005 (75)	Boston	Diet history, Dementia/ AD	Fish consumption reduces AD risk by 41%, dementia by 28%	Risk reduction only in non-ApoE4
Nurk et al., 2007 (76)	Norway, N=2031, 70-74 yrs	Diet history, Cog testing	Less than 10 g/ day fish intake predicts poor Cog performance	Most Cog function improved dose-dependently up to 75 g/ d fish
Barberger-Gateauet al. 2007 (77)	France, 3-City, n=8,085, Non-demented, 65+	Diet history, 4 yr follow-up, Dementia/AD	281 dementia (183 AD) Fish reduced dementia (HR=0.46) and AD (HR=0.65)	Fish only protective for AD in non-ApoE4 (HR=0.60)
van Gelder et al. 2007 (78)	Zutphen, (N=210, men 70-89 yrs)	Diet history, 5 yr follow-up, MMSE	~400 mg/day DHA+EPA associates with reduced decline	Dose-dependent effect

Abbreviations: Cognitive, Cog; DHA, docosahexaenoic acid; eicosapentanoic acid, EPA; hazard ratio, HR; Mini-mental status examination, MMSE; OR, Odds Ratio. Sat., saturated.

Table 2
Blood Omega-3 Fatty Acids and Cognitive Decline (8/10 Positive Studies)

Study	Population	Methods	Findings	Other
Conquer et al. 2000 (79)	Canada, N=55 77-83 yrs	Plasma PL, Cog testing	Low plasma n-3 in AD and Cog-impaired aged	Higher n-6 and lower n-3/n-6 in AD or impaired
Heude et al., 2003 (80)	France-EVA, N=246 63-74 yrs baseline	RBC, 4 yrs follow-up, MMSE	High n-3 predicts reduced decline (OR=0.59)	High n-6, n-6/n-3 predicts more decline
Laurin et al., 2003 (81)	Canada, 65+ yrs	Plasma PL	Higher DHA in dementia cases	Unchanged n-3 in AD
Schaefer et al 2006 (11)	Framingham, N=899 unimpaired, Median 76 yrs, prospective	Plasma PL, 9.1 yr follow-up Dementia/AD	99 /899 got dementia, 71 AD, high quartile DHA, RR=0.53 dementia 0.61 AD	3 servings/ week in high DHA quartile
Dullemeijer et al., 2007 (82)	Holland FACIT (folic acid) trial, N=807, 50-70 yrs cross-section	Plasma PL, Cog testing	High n-3 predicts less decline in sensorimoter and complex speed over 3 yrs.	Plasma n-3 did not predict 3-yr changes in memory, information-processing speed, or word fluency.
Beydoun et al., 2007 (12, 83)	Minneapolis, (n=2251, 50-65 yrs)	Plasma PL/ chol. Esters. Cog testing, 6 yr follow-up	140 decline, Higher n-3 reduces risk of decline in verbal fluency	Effects stronger w/ hypertension/ dyslipid-emia, important in middle age
Cherubini et al. 2007 (84)	Chianti, Italy, N=935, Mean age 75.6	Plasma, MMSE	n-3 levels reduced with cognitive deficits	(low n-3/n-6 trend, p=0.09)
Tully et al., 2003 (85)	Dublin, N=148 AD (76.5 yrs), 45 (70 yrs) controls	Serum cholesterolester DHA	DHA significantly reduced in all AD	DHA levels reduced with dementia severity
Wang et al., 2008 (13)	Oregon, N=46, AD + controls	RBC DHA	MMSE directly correlates with RBC n-3 index	Lower DHA and antioxidants associate
Whalley et al., 2008 (14)	England, N=120, born in 1936, age 64-68	RBC DHA	High RBC DHA associated w/ better cognitive function	Significant only in non-Apo E4

Abbreviations: cholesterol, chol; Cognitive, Cog; Etude sur le Vieillissement Arteriel, EVA; Folic Acid and Carotid Intima-Media Thickness, FACIT; phospholipids, PL; relative risk, RR; red blood cells, RBC.

Table 3

Neuroprotective effects of DHA

Neuroprotective Effect	References
(1) Anti-inflammatory. Reducing AA and metabolites via COX and lipoxygenase (PG, HETES, etc)	Tassoni et al., 2008; Rao et al. and Cao et al., 2007 (86-88)
(2) Insulin/trophic factor potentiation via Akt	Akbar et al., 2005 (32)
(3) Increased brain-derived neurotrophic factor	Rao et al., 2007; Wu et al., 2004 (34, 89)
(4) Antioxidant. Direct (?). Increasing AO enzymes (catalase, GSH peroxidase)	Yavin et al., 2002; Hashimoto et al., 2005; Hossain et al., 1999 (90-92)
(5) Anti-apoptotic. Increasing NPD1, anti-apoptotic& reducing pro-apoptotic proteins	Lukiw et al., 2005; Bazan et al., 2005 (41, 93)
(6) Promotes Neurogenesis	Innis et al., 2007 (94)
(7) Increasing a glucose transporter	Tsukada et al., 2000; Pifferi et al., 2007 (95, 96)
(8) Coupling blood flow to glucose utilization	Tsukada et al., 2000; Pifferi et al., 2007 (95, 96)
(9) Improving synaptic membrane fluidity	Hashimoto et al., 2006 (97)
(10) Increasing G-protein coupling	Litman et al., 2001 (98)
(11) PPAR or RXR agonists	Gani et al., 2008; Calderon, et al., 2007 (42, 99)

Abbreviations: antioxidant (AO); arachidonic acid, (AA); cyclooxygenase (COX); reduced glutathione (GSH); hydroxyeicosatetraenoic acids (HETE); prostaglandins (PG); neuroprotectin D1 (NPD1); peroxisome proliferators-activated receptor (PPAR); retinoid X receptor (RXR).

Table 4

DHA reduces production of the amyloid β protein that is believed to cause AD. (8/9 studies)

Effect of Omega-3 on Aβ/ Amyloid	Reference
(1) Reduced Aβ production -human neurons	Lukiw et al., 2005 (93)
(2) Reduced Aβ pathway products	Sahlin et al., 2007 (100)
(3) Reduced Aβ production –cell lines	Oksman et al., 2006 (29)
(4) Reduced amyloid accumulation in vivo	Lim et al., 2005 (101)
(5) Reduced amyloid accumulation in vivo	Oksman et al., 2006 (29)
(6) Reduced amyloid accumulation in vivo	Hooijmans et al., 2007 (102)
(7) Reduced intraneuronal Aβ in vivo	Green et al., 2007 (28)
(8) Reduced amyloid in vivo	Berg et al., 2007 (103)
(9) No effect on amyloid (or brain DHA)	Arendash et al., 2007 (45)

Table 5

Omega-3 Fatty Acids in Clinical Trials For AD Treatment or Prevention.

Clinical Trials-completed	Reference
240 mg/ day DHA + AA (3 mos) improved memory and attention in amnestic MCI (n=12) (but not AD (N=8))	Kotani et al., 2006 (64)
4 g fish oil (1.7 g DHA for 6 months, n=174) ; no sig. effect for MMSE<27, but improved delayed recall, attention; MMSE >27 stabilized with w-3 (n=32)	Freund-Levi et al. 2006 (65)
Memo trial, normal or MMSE >21 (n=302, 65+ yrs, 1800 vs 400 mg EPA+DHA vs placebo for 26 wks)- increases in attention, especially in E4+ and men, but no change in cognition	Van de Rest et al., 2008 (104)
6 months 1.8 g/day total n-3 g showed improvement in ADAS-cog compared to olive oil with MCI (p=0.03), No effect in AD; NCT00628017	Chiu et al., 2008 (66)
OHSU pilot, MMSE 15-26 (n=39, Fish oil (750mg DHA, 1050 EPA +/- 600mg alpha lipoate vs placebo)- FO+ lipoate stabilized MMSE, ADLs (p=0.02), NCT00090402	Shinto et al., 2008 (67)

Abbreviations: activities of daily living (ADLs); arachidonic acid (AA); fish oil (FO); mild cognitive impairment (MCI); Oregon Health State University (OHSU).

Table 6

Ongoing Clinical Trials (2008)

Ongoing Trials	PI.
OPAL trial, cognitive decline, age 70-79 MMSE>24, 500 mg DHA + 200 mg EPA (n=800): UK identifier: ISRCTN72331636	Dangour, et al., 2006 (UK) (105)
ADCS trial, mild to mod AD -2 g algal DHA/day for 18 months (n=400), NCT00440050	J. Quinn, OHSU (NIA/ADCS/ Martek)
MIDAS Early memory deficits, 900 mg/d, 6 months (n=465); NCT00278135	K. Yurko-Mauro (Martek Biosciences)
Primary Prevention of cognitive decline in frail elderly, MMSE>24, n=1200, omega 3 (VO137), 800 mg DHA /d 3 years BCT00672685	B. Vellas, University Hospital, Toulouse

Abbreviations: AD Cooperative studies (ADCS); Older People and n-3 Long-chain polyunsaturated fatty acids (OPAL). Mini-mental state examination (MMSE). Memory Improvement with Docosahexaenoic Acid study (MIDAS).