DHA May Prevent Age-Related Dementia[1–3]

Greg M. Cole* and Sally A. Frautschy

Departments of Medicine and Neurology, University of California, Los Angeles, CA 90095; and Geriatric Research, Education, and Clinical Center, Greater Los Angeles Veterans Affairs Healthcare System, VA Medical Center, North Hills, CA 91343

Abstract

The risk for dementia, a major contributor to incapacitation and institutionalization, rises rapidly as we age, doubling every 5 y after age 65. Tens of millions of new Alzheimer's disease (AD) and other dementia cases are projected as elderly populations increase around the world, creating a projected dementia epidemic for which most nations are not prepared. Thus, there is an urgent need for prevention approaches that are safe, effective, and affordable. This review addresses the potential of one promising candidate, the (n-3) fatty acid docosahexaenoic acid (DHA), which appears to slow pathogenesis of AD and possibly vascular dementia. DHA is pleiotropic, acting at multiple steps to reduce the production of the β-amyloid peptide, widely believed to initiate AD. DHA moderates some of the kinases that hyperphosphorylate the τ-protein, a component of the neurofibrillary tangle. DHA may help suppress insulin/neurotrophic factor signaling deficits, neuroinflammation, and oxidative damage that contribute to synaptic loss and neuronal dysfunction in dementia. Finally, DHA increases brain levels of neuroprotective brain-derived neurotrophic factor and reduces the (n-6) fatty acid arachidonate and its prostaglandin metabolites that have been implicated in promoting AD. Clinical trials suggest that DHA or fish oil alone can slow early stages of progression, but these effects may be apolipoprotein E genotype specific, and larger trials with very early stages are required to prove efficacy. We advocate early intervention in a prodromal period with nutrigenomically defined subjects with an appropriately designed nutritional supplement, including DHA and antioxidants.   J. Nutr. 140: 869–874, 2010.

Introduction

There are no cures in sight for chronic diseases of aging, only increasingly expensive chronic treatments. A major shift from costly disease management toward prevention is now mandated because the U.S. and other developed and developing nations with aging populations face projections of unsustainable health care costs to pay for the health care of aging populations. Many of the most costly and debilitating conditions are neurodegenerative. The most prevalent forms of these diseases have polygenic influences interacting with aging and environmental risk factors: notably, stroke and vascular dementia, Parkinson's disease, and Alzheimer's disease (AD).[4] These conditions develop slowly, with a prolonged prodromal pathological buildup of pathological lesions generally driven by combined risk factors. Intervention to prevent AD, the focus of this review, should ideally begin well before disease onset, during an insidious decade-long presymptomatic phase.

The most successful prevention approach is to block the factors initiating lesion pathogenesis, which can be accomplished in animal models, but that approach would be extremely difficult to test in the clinic because it would require very early intervention decades before clinical outcomes. Therefore, the best interventions will be those that are cheap, safe, pleiotropic, and with multiple potential benefits; for example, they may apply to common features of the chronic diseases of aging that we seek to prevent. While they may be less specific than novel drug and antibody approaches that are under intensive study for treatment, prevention interventions with diet and/or exercise may be more effective and are more practical with respect to costs and safety concerns.

AD pathogenesis

From the genetics of early onset AD, we have learned that it can be initiated by aggregates of the 42–amino acid β-amyloid (Aβ42) peptide derived from its amyloid precursor protein (APP). Aβ42 peptide is normally produced and cleared, but when this is out of balance because of genetics or aging, small increases in Aβ42 result in elevated small neurotoxic and synaptotoxic oligomer assemblies leading to massive accumulations of larger fibrillar amyloid plaque and vascular deposits. In

[4] Abbreviations used: AA, arachidonic acid; Aβ-42, amyloid β-protein 42; AD, Alzheimer's disease; ADAScog, Alzheimer's Disease Assessment Scale-cognitive subscale; ADCS, Alzheimer Disease Cooperative Studies; Apo, apolipoprotein; APP, amyloid precursor protein; CDR, clinical dementia rating; COX, cyclooxygenase; CVD, cardiovascular disease; DHA, docosahexaenoic acid; EPA, eicosopentaenoic acid; GSK3, glycogen synthase kinase 3; IRS, insulin receptor substrate; JNK, c-jun N-terminal kinase; MMSE, minimental state examination; NSAID, nonsteroidal antiinflammatory drugs; PAL, Paired Associate Learning; PC, phosphatidylcholine.
* To whom correspondence should be addressed. E-mail: gmcole@ucla.edu.

the amyloid cascade hypothesis, pathological Aβ assemblies can cause excitotoxicity, oxidative damage, mitochondrial dysfunction, inflammation, and microglial activation, as well as activation of kinases that hyperphosphorylate the microtubule protein τ, leading to τ aggregates (1). The resultant τ oligomers further aggregate to form fibrils or paired helical filaments, which accumulate as β-sheet stabilized intraneuronal neurofibrillary tangles, a lesion correlated with AD progression and neuron loss. Animal model studies demonstrate that Aβ and τ pathology can both cause synaptic and neuronal dysfunction and loss. The relative contributions of these different pathological species to the prolonged and complex pathogenesis leading to regional neurodegeneration and a range of emerging symptoms remain controversial. Part of the controversy may arise from variation between regions and individuals with different risk factors and versions of the AD syndrome, but it is also likely that contributions of these lesions to the cascade are simply complex and regionally stage dependent. Whatever their individual contributions are at different stages, inflammation, oxidative damage, and protein aggregate accumulation are common features that occur early and accompany many of the neurodegenerative diseases of aging. Inflammation, oxidative damage, and lipid profiles have epidemiological evidence as factors modifying dementia risk, suggesting that they represent useful targets to explore for prevention.

Our group and many others have tested potential prevention strategies using transgenic mouse models that express familial AD mutations and induce mild cognitive deficits that correlate with Aβ oligomerization and, unlike in AD, precede the plaque pathology (2,3). The first interventions examined using these models, amyloid vaccine (4) and the nonsteroidal antiinflammatory drugs (NSAIDs) (5), were effective against amyloid plaque pathogenesis, but both have had safety and efficacy issues. This has led to safer passive immunization approaches already in clinical trials, but it is unlikely to be widely used for prevention because of cost and safety issues. We have looked for safer pleiotropic alternatives to NSAID prevention approaches and explored both the polyphenolic NSAID/antioxidant curcumin and the (n-3) fatty acid docosahexaenoic acid (DHA) that we and others observed has neuroprotective, antioxidant, antiinflammatory, and Aβ42-reducing activities in vitro and in animal models.

DHA

Two major essential PUFA series, the (n-6) PUFA, with double bonds beginning at carbon number 6, and (n-3) PUFA, with double bonds beginning at carbon number 3, are regulated by dietary intake. Linoleic acid [18:2(n-6)] is obtained predominantly from plants and serves as a substrate of elongases and desaturases to produce the common animal tissue fat, arachidonic acid [AA; 20:4(n-6)]. AA is the (n-6) PUFA series substrate for the cyclooxygenases (COX) and lipoxygenases, which produce proinflammatory lipid mediators. Of the (n-3) PUFA series, a small percentage of α-linolenic acid [18:2(n-3)], common in plant sources like flaxseed, soy, nuts (e.g., walnuts), and other oily seeds, is elongated and desaturated to produce antiinflammatory long-chain (n-3) PUFA, including eicosapentaenoic acid [EPA; 20:5(n-3)] and DHA [22:6(n-3)]. The bulk of preformed intake of EPA + DHA is from fish, notably oily fish. Unlike EPA, DHA is in high concentration in brain and neuronal phospholipids where it may be as high as 35% of phosphatidylethanolamine (6). AA and DHA compete for esterification into the labile phospholipid SN-2 position, so that releasable SN-2 AA in brain membranes can be reduced by lowering the dietary (n-6):(n-3) PUFA ratio. Because of ubiquitous high intake of (n-6) fatty acids in Western diets, this is most readily accomplished by increasing the intake of preformed DHA from fish or supplements. The antiinflammatory effects of increasing (n-3) fatty acids intake are achieved by competitively reducing phospholipid incorporation of available AA and the (n-6):(n-3) fatty acid ratio in brain. For example, DHA reduces proinflammatory AA prostaglandin products from COX enzymes that are the targets of NSAID. The neuroinflammation that accompanies AD and NSAID has been repeatedly associated with reduced AD risk in epidemiological studies (7), indicating that the COX enzymes may be viable targets for AD interventions (8). However, results to date from studies using specific COX-2 inhibitors have suggested little efficacy with established AD or in initial results from a prevention trial that was halted due to safety concerns (9), although a long-term protective benefit in the Alzheimer's Disease Anti-Inflammatory Prevention Trial naproxen arm was reported (10).

DHA reduces epidemiological risk for cognitive decline and dementia

Our recent literature review found 9 epidemiological studies associating increased fish consumption with reduced risk for dementia, including AD. Furthermore, 8 out of 10 studies found that higher blood (n-3) fatty acids were associated with reduced cognitive decline (11).

The epidemiology is not entirely consistent. One report found that high fish consumption but not dietary (n-3) fatty acid intake appeared protective in the Chicago Health and Aging Project (12). Another study showed no risk reduction with increased RBC DHA but reduced dementia (4.3–5.1%) in those with high RBC PUFA and high whole blood mercury, a good correlate of higher long-term fish intake (13). One possible explanation for the lack of significant risk protection reported in the latter study with only small trends ($P = 0.19$) with RBC DHA levels (2.8–4.1% total PUFA) is that these DHA concentrations are lower than those reported in other studies showing significant risk reduction [e.g., DHA = 6.34 ± 1.1% with no decline vs. 5.89 ± 1.0% with decline ($P = 0.04$) (14) or DHA = 5.4 ± 1.2% in the protected fish oil group vs. 4.6 ± 1.0% without fish oil (15)]. It is also possible that measuring phosphatidylcholine (PC) DHA rather than total DHA may be a stronger predictor of risk reduction because, in the Framingham study, high plasma PC DHA corresponded to 47% risk reduction (16), and, in another study, only RBC PC DHA but not phosphatidylethanolamine DHA was lower in AD patients (400%) (17). Despite some inconsistencies in the epidemiology, metaanalysis assessing the quality of available epidemiology and preclinical studies concluded that clinical trials were warranted (18), and clinical trials are beginning to resolve the issue in favor of (n-3) fatty acid protection with some restrictions.

Clinical trials

Four small completed clinical trials with (n-3) fatty acids (typically from fish oil) suggested possible protection, but only in mild cognitive impairment patients, whereas 2 trials with (n-3) fatty acids plus antioxidants or other nutrients (α-lipoate, L. Shinto, Oregon Health and Science University) and B vitamins plus UMP, a putative enhancer of DHA incorporation (Souvenaid, P. Scheltens, The Netherlands) have suggested possible efficacy in established AD [reviewed in (11)]. A large 6-mo placebo-controlled trial with 900 mg/d algal DHA, the Memory Improvement with DHA Study trial (485 participants with mild memory complaints), recently reported that DHA improved

performance in participants with age-related cognitive decline, manifested as logical memory scores >1 SD below the younger adult mean using a computerized cognitive test, Cantab Paired Associate Learning or PAL, a visual-spatial episodic memory test (19). Error rates in the PAL were designed and reported to discriminate between probable early AD and depression, which had similar scores on the more established cognitive battery used for AD, the Alzheimer's Disease Assessment Scale-cognitive subscale (ADAScog) (20). DHA was reported to cut the error rate in half on the PAL ($P < 0.03$), and the response correlated with blood levels of DHA, consistent with an effect of DHA on early AD. There were no serious adverse events.

An 18-mo Alzheimer Disease Cooperative Studies (ADCS) trial with 2 g/d algal DHA versus placebo examined progression in 402 randomized mild- to moderate-AD participants [mean age of 76 $\pm$ 8.7 y, minimental state exam (MMSE) = 20.7 $\pm$ 3.6, 59% apolipoprotein E4 (ApoE4) positive and 41% ApoE4 negative] reported no effect on cognitive test scores (ADAScog and MMSE) in participants with ApoE4, but possible slowing of progression by the same measures in participants with ApoE3 (21). The ADCS trial result was significant for ADAScog scores only in the ApoE3 subgroup (a widely accepted measure of cognitive decline based on subject performance) of treated versus untreated non-ApoE4 carriers ($P = 0.0285$). The ApoE4 negative planned comparison subgroup analysis was an exploratory, secondary analysis with no adjustment for multiple comparisons and requires independent confirmation. Although MMSE, another standardized test measure of cognitive decline, showed that the DHA group was associated with a similar slowed progression in the non-ApoE4 group, it did not alter scores that included rater assessments of global severity (clinical dementia rating) and behavioral disturbances (neuropsychiatric inventory and activities of daily living). Whether the possible DHA benefit on cognitive performance in the ApoE3 group was a result of random variation or a real effect will require further study. Statistical nonsignificance seems less likely to reflect mere chance because the result echoes the epidemiology, where 3 of the more recent studies found that risk reduction as a result of fish intake was less or even absent in ApoE4 carriers (11). Additional large clinical trials are underway and should assess the issues of very early intervention and nutrigenomic interactions. For example, in addition to modulation of trial outcomes by genetic variance in the lipid transporter ApoE, one can anticipate a contribution to a variable response due to low activity variants of the desaturases that convert plant source (n-3) fatty acids to long-chain, bioactive EPA and DHA (22).

DHA: Multiple mechanisms for AD prevention

The (n-3) fatty acid DHA has the NSAID-like antiinflammatory effects of lowering AA, as discussed above. Our group and others have shown that DHA can reduce production of Aβ from APP and Aβ42 accumulation in AD model mice (23–26) and cultured human neurons (27). One group reported that (n-3) fatty acids did not modify amyloid levels in the cerebral cortex or behavior, but this negative result was from an experiment using bigenic mutant PS1$\times$ APP transgenic mice where, for whatever reason, the diet did not alter brain fatty acids levels (28). This lack of a diet effect on brain fatty acid composition is in contrast with the positive studies, including our own, where DHA supplementation increased DHA and markedly reduced the (n-6):(n-3) PUFA ratio in the frontal cortex (29). The Aβ42 reduction may be due to multiple effects of DHA incorporated into brain phospholipid, such as changes in membrane and lipid raft structure and fluidity (30), which influence APP processing (31); a repression of presenilin 1 and, therefore, gamma secretase (26); or the induction of anti-amyloidogenic chaperones for APP [SorLA (32)] and Aβ itself [transthyretin (33,34)]. A lipoxgenase product of DHA, neuroprotection D1, may mediate 1 or more of the effects to downregulate APP processing to Aβ (27).

In addition to reducing Aβ production, DHA is neuroprotective. Aging APP transgenic mice fed a diet high in (n-6) fatty acids, but deficient in (n-3) fatty acids, showed increased caspase activation, dramatic loss of the AD-sensitive dendritic spine marker drebrin, and other excitatory synaptic markers, whereas DHA supplements protected caspase, activation, drebrin, PSD-95, and CaMKII-α loss and cognitive deficits (29,35). Proposed mechanisms for DHA's neuroprotective effects include increasing survival signaling through the PI3-K/Akt pathway by increasing membrane docking through pleckstrin homology domains (36), increasing a neuroprotective DHA enzymatic metabolite, neuroprotectin D1 (27), and increasing brain-derived neurotrophic factor (37) and reducing oxidative damage (38) as well as multiple additional neuroprotective and cardiovascular protective activities (11).

Of particular interest, AD patients and AD animal models have synaptic and dendritic loss that may begin with a postsynaptic attack by Aβ oligomers (39), whereas DHA shows strong synaptic protection from preformed Aβ oligomers in vitro (40), consistent with protection of the dendritic spine marker drebrin in APP Tg mice (35). Perhaps surprisingly, the Aβ oligomer synaptic attack may be related to a seemingly disconnected target for nutritional treatment, type II diabetes. Classic insulin-resistant diabetes is a risk factor for developing AD, and insulin signaling defects in AD brain are a focus for treatment in AD (41). Insulin/neurotrophic factor signaling protects from Aβ oligomer toxicity, but the signal transduction pathways involved appear defective in AD and AD models (42,43) and may be blunted by Aβ aggregates in vitro (44). Thus, there is increasing evidence for an AD defect in insulin-like signaling that may limit glucose utilization, synaptic plasticity, and survival signaling. In fact, clinical trials with glitazone insulin sensitizing drugs (PPARγ agonists) have already had some clinical trial success in ApoE3 but not ApoE4 carriers (41,45). This is reminiscent of the apparent ApoE dependence of the ADCS clinical trial with DHA. DHA and its derivatives can be PPAR agonists, but whether this is physiological remains unclear (46). There are other pathways for DHA effects on insulin-like signaling. One relevant mechanism is hyperphosphorylation of insulin receptor substrate (IRS), an adaptor protein coupling insulin and other neurotrophic factor signaling to PI3-K/Akt survival signaling upstream of c-jun N-terminal kinase (JNK) and glycogen synthase kinase 3 beta (GSK3beta). Aβ oligomer–activated τ kinases JNK and GSK3β also cause hyperphosphorylation of IRS, resulting in resistance to insulin/neurotrophic factor signaling, but the (n-3) fatty acid DHA protects from the accumulation of both phospho-IRS and phospho-τ (similar to that seen in neurons in AD brain) in both oligomer-treated neurons and AD model triple transgenic mice (40). Because DHA increases neuroprotective brain-derived neurotrophic factor and also reduces Aβ and Aβ-induced insulin/trophic factor resistance, it should have a potent pleiotropic protective effect against Aβ's synaptotoxic and neurotoxic activities. **Figure 1** summarizes some of these anti-Alzheimer pathways.

Thus, DHA protects against AD by reducing the initiating Aβ42 toxin as well as suppressing synaptotoxicity via τ kinase activation and the impact of these kinases on at least 2 important

substrates, τ and IRS. Although in principal DHA should also reduce brain AA metabolites and inflammation, to date there is little or no evidence that the (n-3) fatty acid reduces biomarkers for neuroinflammation in cerebrospinal fluid of AD patients (47).

Pleiotropic activities needed for AD prevention

While DHA or fish oil have many potentially beneficial and potent effects, both clinical trial and animal model data suggest that the benefits are real but limited and may be improved by combining DHA with other nutrients. Because of its 6 double bonds, DHA is highly susceptible to lipid peroxidation, and lipid peroxidation products of DHA are elevated in brains of AD patients (48,49). Because DHA alone does not appear sufficient to control neuroinflammation in our models (G. M. Cole, G. P. Lim, and S. A. Frautschy, unpublished results) and it is readily oxidized, we advocate combining it with an antiinflammatory/antioxidant agent, such as curcumin (35). A small clinical trial has already produced positive results with fish oil plus lipoate (50). The Souvenaid trial with fish oil/DHA, UMP, B vitamins, and antioxidants represents another apparently successful approach (51)

Recognizing the need for an antioxidant and the limited efficacy of DHA as an NSAID, our group has focused on curcumin (diferulomethane), which was identified as the yellow pigment in the curry spice turmeric, a polyphenolic antioxidant consisting of 2 methoxyphenol groups linked by a β-diketone bridge. In turmeric, curcumin acts as good food preservative inhibitor of lipid peroxidation. It should protect DHA from lipid peroxidation, known to be elevated in AD and by Aβ aggregates. As a turmeric extract, curcumin has potent antiinflammatory activity contributing to a long history of use in traditional Asian and Ayruvedic medicine. It is the Indian version of vitamin E and aspirin, rolled into 1 molecule. In AD models, curcumin reduced pro-inflammatory cytokines, oxidative damage, and amyloid β protein and cognitive deficits (52). The limited bioavailability of curcumin in supplement preparations has stymied clinical trials (53), but this delivery problem has been solved with new lipidated formulations (54) that are already in clinical trials for cancer and AD. The combination of curcumin plus (n-3) fatty acids appears synergistic in reducing defects in a triple transgenic AD model (55) and in other AD models (our unpublished results). Many other combinations are possible, and we anticipate that cocktails combining DHA with other nutrients will prove useful for AD prevention.

Western diets, cardiovascular risk, and vascular dementia

While the most frequent cause of late onset dementia is AD, the second most frequent cause is vascular dementia. In fact, the risk factors for AD and cardiovascular disease (CVD) are generally shared (56), and CVD risk factors accelerate AD (57). One consequence is that varying with the population, perhaps one-third of all dementia cases is mixed dementia (58). Thus, any

FIGURE 1 AD pathways targeted by DHA. AD is initiated by increased levels of Aβ-42 derived from APP, which traffics to a membrane compartment where secretase enzymes, including a complex dependent on presenilin 1 (PS1) generate Aβ. The chaperone LR11 traffics APP away from the secretases. DHA reduces Aβ production, reportedly by increasing LR11 and reducing PS1, leading to less Aβ and, thus, fewer toxic Aβ oligomers (AβO). DHA also increases levels of neuroprotectin D1 (NPD1) and neuroprotective brain-derived neurotrophic factor (BDNF). It improves signaling of BDNF, insulin, and other neurotrophic factors (NTF) through their receptors [NTF-R and insulin receptor (ins-R)], which autophosphorylate (P) at Tyr residues to couple to protective signaling via adaptor proteins, such as IRS. For example, IRS binds the p85 subunit of phosphatidylinositol 3-kinase (PI3K) to generate PIP3 lipid, which promotes binding and activation of downstream PDK and Akt kinases through their pleckstrin homology (PH) domains. DHA facilitates this activation by increasing phosphatidylserine (PS), which accelerates PH domain membrane binding. Activated Akt increases the Aβ protease, insulin degrading enzyme (IDE), inhibits the τ kinase GSK3β, and acts on multiple survival signals to promote neuron growth and survival. AβO acts on unidentified receptors (N-methyl-d-aspartate, integrin, and Prp), which signal through fyn to rac to cause toxicity via another τ kinase, JNK. JNK serves a priming kinase for GSK3β, also a τ kinase. Together, they phosphorylate and inactivate IRS, which leads not only to its rapid degradation and insulin/neurotrophic factor resistance, but also to accumulation of τ oligomers and tangles. In summary, DHA protects against these toxic pathways, reducing pJNK, ptau, and pIRS. DHA also reduces brain AA levels to limit AβO-induced increases AA via cytosolic phospholipase A2 (cPLA2) activation. Less AA means less downstream prostaglandin (PG), leukotriene (LT), and hydroxyeicosatetraenoic acid (HETE) products of COX and lipoxygenase (LOX). These AA products are implicated in inflammation and excitotoxicity, which, together with τ pathology and trophic signaling deficits, contribute to synaptic and cognitive deficits.
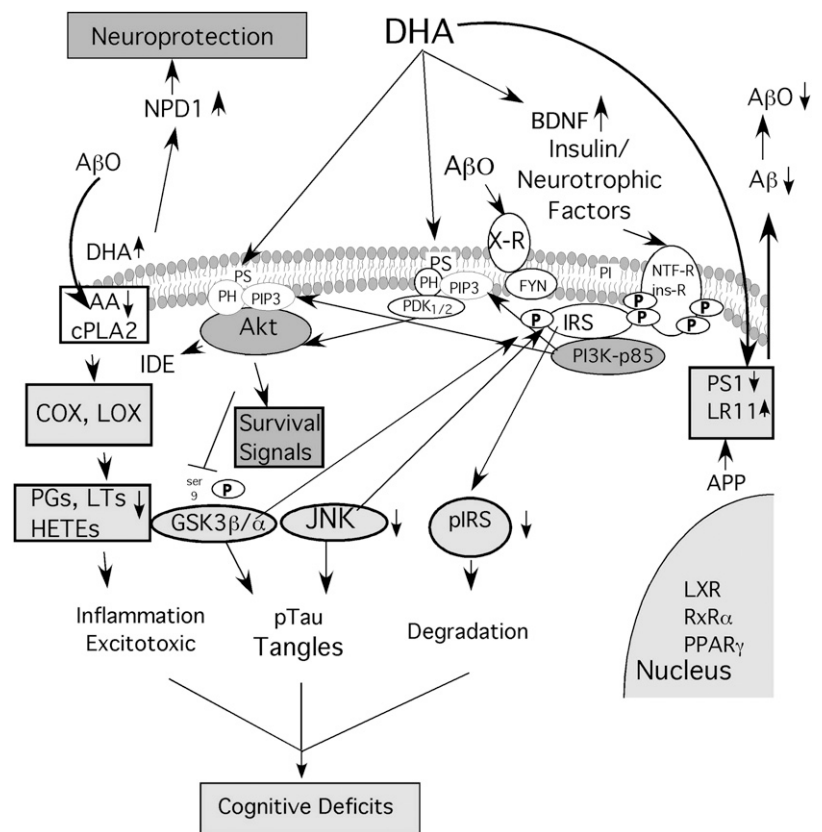
reasonable approach to reducing AD and dementia risk is to address the CVD risk factors. One of the most easily addressed risk factors for CVD is low intake of marine (n-3) fatty acids, which is typical of Western diets (59–61).

Conclusions

In conclusion, although there are many new AD treatment approaches under development, these are likely to be costly and have significant side effect issues. Prevention of dementia requires much greater safety and very few or no adverse side effects. Fish oil/DHA appears to be efficacious against AD with multiple pleiotropic activities in preclinical models and with some initial success in clinical trials with early (pre-AD) intervention. Larger trials in minimally cognitively impaired patients are warranted. The major advantages with DHA and related combined nutritional approaches with DHA and natural antioxidant (lipoate), polyphenolic (curcumin), or similar interventions are that individually these approaches have safety and side effect track records, broad spectrum utility in preclinical models, and low cost. There is a real opportunity to use them for prevention.

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