



Cognitive Vitality Reports® are reports written by neuroscientists at the Alzheimer's Drug Discovery Foundation (ADDF). These scientific reports include analysis of drugs, drugs-in-development, drug targets, supplements, nutraceuticals, food/drink, non-pharmacologic interventions, and risk factors. Neuroscientists evaluate the potential benefit (or harm) for brain health, as well as for age-related health concerns that can affect brain health (e.g., cardiovascular diseases, cancers, diabetes/metabolic syndrome). In addition, these reports include evaluation of safety data, from clinical trials if available, and from preclinical models.

Omega-3 fatty acids (DHA, EPA, and fish)

Evidence Summary

Supplements do not improve cognition in most elderly people or Alzheimer's patients, but might help people with mild impairment or APOE4 non-carriers. Possible benefits against cardiovascular disease.

Neuroprotective Benefit: Up to 5 years of treatment does not protect against cognitive decline in healthy older adults but may benefit people with mild impairment at baseline as well as non-APOE4 carriers.

Aging and related health concerns: DHA or EPA might not slow the aging process, but they may help prevent or treat cardiovascular disease.

Safety: Few safety concerns noted in trials or observational studies at doses lower than 3 grams/day. Possible increased risk of bleeding at high doses.



What is it? Omega-3 fatty acids are essential for brain and body health. They are a family of polyunsaturated fatty acids sometimes referred to as n-3 fatty acids, a term that describes their shared chemical structure. The omega-3 fatty acids vary in length from the shorter alpha-linolenic acid (ALA) to the long-chain eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). Our bodies are not very good at converting short-chain to long-chain omega-3 fatty acids so eating ALA doesn't usually raise DHA levels ([Burdge Calder 2005](#)). We also cannot make omega-3 fatty acids from scratch – we have to consume them.

Omega-3 fatty acids are distinct from omega-6 polyunsaturated fatty acids. Some research suggests that diets with a high ratio of omega-6 to omega-3 fatty acids could lead to inflammation, disease, and dementia ([Simopoulos 2008](#)) ([Loef Walach 2012](#)). However, since omega-6 fatty acids are essential nutrients, reducing their intake is not necessarily a healthy choice ([Harris et al 2009](#)).

Neuroprotective Benefit: Up to 5 years of treatment does not protect against cognitive decline in healthy older adults but may benefit people with mild impairment at baseline as well as non-APOE4 carriers.

Clinical Evidence: No clinical trials have been sufficiently large and long enough to test whether DHA or fish oil supplements can reduce the risk of developing dementia per se. Supplementation does not appear to improve cognitive function in elderly people ([Sydenham 2012](#)), even with a 5 year treatment with daily 350 mg of DHA and 650 mg of EPA ([Chew 2015](#)). However, some improvement has been seen in randomized trials on people who have cognitive impairment that is not severe enough to be considered dementia ([Mazereeuw 2012](#)), for example with a 900 mg DHA supplement taken daily in older people with age-related memory impairment ([Yurko-Mauro 2010](#)).

People who eat fish every week or who have higher DHA levels in their blood have had a lower risk of developing dementia or specific signs of brain aging in many studies ([Cunnane et al 2012](#))([Huang 2010](#)). However, a pattern of reduced dementia risk has not been seen in all studies ([Huang 2010](#), [Cunnane 2009](#)).

According to a 2012 meta-analysis of 10 randomized trials, long-chain omega-3 fatty acid supplementation is not likely to benefit Alzheimer's patients but might yield some modest cognitive benefits in people with mild cognitive impairment ([Mazereeuw 2012](#)), a subset of whom may progress to Alzheimer's. Some scientists believe that this evidence suggests that Alzheimer's must be treated as early as possible.



More recent trials with various formulations have been mixed. A low dose daily treatment of 180 mg DHA plus 120 mg EPA had no benefit to elderly patients with either normal or impaired cognition ([Mahmoudi 2014](#)). A treatment of phosphatidylserine enriched with DHA (equivalent to roughly 100 mg per day) given to elderly people with mild memory impairment was reported to improve some aspects of their abilities (sustained attention and memory recognition) although other aspects of cognition and memory were not affected ([Vakhapova 2014](#)). A very small trial suggested that omega-3 fatty acids given in combination with alpha lipoic acid for a full year slowed cognitive and functional decline, a benefit to Alzheimer's patients ([Shinto 2014](#)). Souvenaid™, a medical food available in Europe that contains DHA and EPA plus a variety of other nutritional components, has improved some symptoms in patients with Alzheimer's disease or frontotemporal dementia in small trials but did not slow the cognitive decline in Alzheimer's patients in another larger study ([Shah 2013](#)).

APOE4 carriers: People who carry the ApoE4 genetic risk factor for Alzheimer's disease may 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 E4 allele (reviewed in [Huang 2010](#), [Cunnane 2009](#)). Similarly, in a clinical trial, DHA did not significantly help Alzheimer's patients overall but it did appear to benefit patients who do not carry the APOE4 allele ([Quinn 2010](#)). The E4 allele changes how the body and brain processes long-chain omega-3 fatty acids [18-20], which may partially contribute to the sometimes inconsistent evidence on whether these fats protect the brain from aging and dementia. Scientists are investigating if higher doses of DHA might have more benefit in E4 carriers.

Laboratory Evidence: DHA is a major building block of the brain that is critical for healthy development and function. Indeed, a woman's ability to create DHA from the shorter-chain omega-3 fatty acid ALA is increased during pregnancy ([Burdge Calder 2005](#)). In adults, researchers have identified a variety of potential ways in which DHA may protect or improve brain function. For example, DHA may reduce inflammation, increase the birth-rate of new neurons in the adult brain, generate other protective chemicals like neuroprotectin D1, increase the fluidity of cell membranes, alter signaling pathways inside cells, and protect against the beta-amyloid and tau pathways that are believed to drive Alzheimer's disease ([Cunnane 2009](#))([Cole Frautschy 2009](#)).

EPA is another long-chain omega-3 fatty acid that may also improve brain function, although its protective properties are far less established ([Huang 2010](#)). Both EPA and DHA could also protect the brain indirectly by protecting the cardiovascular system ([Mozaffarian 2012](#)). Vascular problems contribute to dementia in many older adults, suggesting that maintenance of cardiovascular health may help protect against dementia in old-age ([Roman 2012](#)).



A meta-analysis of randomized trials strongly suggests that omega-3 fatty acids can help treat depression and depressive symptoms in many people, particularly if more EPA than DHA is given ([Grosso 2014](#)). Treating depression might in turn protect the brain from dementia, although the evidence for this is not conclusive ([Diniz 2013](#)).

Fish contain nutrients beyond DHA and EPA that might benefit health. For example, it can be an excellent though varied source of lean protein, selenium, and vitamins A, D, and B12 ([Huang 2010](#)).

Aging and related health concerns: DHA or EPA might not slow the aging process, but they may help prevent or treat cardiovascular disease.

There is no consistent scientific evidence that raising DHA intake can slow the rate of aging per se ([Dacks et al 2013](#)). DHA concentration in cell membranes is suggested to contribute, not protect, from aging. However, omega-3 fatty acids might reduce inflammation ([Rangel-Huerta 2012](#)), a driving factor for age-related diseases. Omega-3 fatty acids can protect against vascular disease and possibly the risk of death from cardiovascular disease ([Kotwal 2012](#), [Casula 2013](#)) and some cancers ([Makarem 2013](#), [Szymanski 2010](#)), although the evidence is inconclusive. Earlier clinical trials were much more promising than latter ones, possibly because the use of statins has become more prevalent and might mitigate the cardiovascular protection from DHA/EPA ([Sethi 2014](#)). Higher DHA vs EPA content in the supplements might also yield more protective effects ([Sethi 2014](#)).

Safety: Few safety concerns noted in trials or observational studies at doses lower than 3 grams/day. Possible increased risk of bleeding at high doses.

Long-chain omega-3 fatty acids are well-tolerated and generally recognized as safe at doses below 3 grams per day. They are one of the most widely consumed nutraceuticals in the Western world and they have been studied extensively for cardiovascular health and depression. These compounds may improve aspects of health ranging from cardiovascular disease, risk of death from cancer, age-related macular degeneration, Crohn's disease, depression, and ADHD. However, doses higher than 3 grams per day may cause harm ([Tur et al 2012](#)). Prostate cancer risk has an inconsistent association with DHA and EPA or fish intake, with some reports of increased risk and others of decreased risk. For mortality related to prostate cancer, the 3 cohort studies available all reported a lower risk of death with higher fish intake ([Lovegrove 2014](#)).



A meta-analysis of randomized trials reported that omega-3 fatty acids are not associated with an increased risk of health problems, with the most likely side effect being gastrointestinal disturbances ([Villani 2013](#)). Omega-3 fatty acids were long-suspected to raise the risk of major bleeding, particularly in older adults. However, recent reviews of the clinical research argue that that concern may not be warranted and that omega-3 fatty acids will not raise the risk of bleeding, although people who have a high risk of bleeding have not generally been studied and some doctors may choose to err on the side of caution ([Villani 2013](#), [Wachira 2014](#)).

Sources and dosing:

Omega-3 fatty acids can be consumed through fish, supplements derived from fish or algae, foods enhanced with omega-3, and FDA-approved drugs.

Food: The most common food source of DHA is dark-meat fin-fish like tuna, salmon, mackerel, herring, and sardines. DHA and EPA are found in much lower levels in shellfish, tilapia, and fried fish ([Chung 2008](#)). The only vegetarian source of DHA is specific types of algae and related supplements. Some plants contain short-chain fatty acids like alpha-linolenic acid but not DHA or EPA. To substantially raise the levels of DHA in the blood, most people need to consume DHA directly ([Burdge Calder 2005](#)).

Although some studies report that better cognitive function in aging is associated with fatty but not lean fried fish or shellfish, other studies report that the intake of fish in general rather than fish specifically high in DHA has been most strongly associated with a decreased risk of dementia ([Kim et al 2013](#)) ([Huang 2010](#)). In other words, fish may exert a benefit independently from DHA.

Supplements and food with added supplements: DHA and/or EPA supplements from fish oil or algae are widely available, although their quality and content varies ([Zargar Ito 2011](#)). Currently, no substantial scientific evidence exists to show that different supplements are more or less effective to potentially protect the brain from disease.

It is important to note that not all supplements are reliable, as some may contain toxins or fail to contain the ingredients listed on their label. DHA is prone to oxidation, so some sources recommend that it be refrigerated or co-delivered with antioxidants. However, these different formulations have not been rigorously compared in well-conducted studies.

FDA-approved drugs: Doctors can prescribe pharmaceutical sources of DHA and EPA, like Lovaza™, Vascepa™, and Epanova™. These drugs are reliable high-dose sources that have been rigorously tested and purified. However, for the purposes of cognitive aging and dementia, there is no evidence yet that



these drugs are more or less likely to help the brain than other common sources. Vascepa contains only EPA while Lovaza and Epanova contain a combination of DHA and EPA in different chemical forms.

Dose: The dose of DHA that is most likely to benefit the brain is not known due to the diversity of results and design of available studies. Based on published studies, a therapeutic dose could fall within 180 to 2000 milligrams (mg) per day. However, a therapeutic dose for brain health has not been established, and may vary based on genetics, such as ApoE4 status.

In 2009, the average American consumed between 60 and 80 milligrams per day of DHA and between 20 and 30 mg per day of EPA (NHANES 2009-2010). In one well-conducted observational study, Americans who consumed slightly more than the average level (180 mg DHA 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](#)). However, across the many observational studies that have tracked dementia risk with fish and/or DHA intake, no specific ideal dose has emerged and, in general, the intake of DHA and EPA in general has been less often linked to brain health than the intake of fish itself ([Kim et al 2013](#)). In clinical trials, DHA supplements of 400 to 2000 milligrams per day have been tested, and showed only very limited benefits for improving cognitive function in older people ([Dacks 2013](#)), and no dose for optimal therapeutic benefit has been identified ([Mazereeuw 2012](#)).

Future research:

People may respond differently to omega-3 fatty acids based on their genetics, age and other factors. More research is needed to identify which people are more likely to benefit from consuming more omega-3 fatty acids and which type of omega-3 fatty acids.

Several [clinical trials](#) are underway to provide more information on whether long-chain omega-3 fatty acids may protect against [dementia](#) or [cognitive decline](#) in elderly people. These include:

- [EPOCH](#) trial in healthy older people (completed but not published as of August 2015)
- [VITAL](#) study in healthy people over 65 (scheduled completion in 2016)
- [MAPT](#) study in frail elders (scheduled completion in 2014)

Clinical trials are also testing whether long-chain omega-3 fatty acids can protect the brain from sports-related concussions in pediatric or college-level athletes ([NCT01903525](#), [NCT01814527](#)) and from post-traumatic stress disorder ([NCT00644423](#)) or traumatic brain injury ([NCT01515917](#)) in veterans.



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