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Challenges to determining whether DHA can protect against age-related cognitive decline

DHA, an omega-3 fatty acid, is an important constituent of brain membranes and has a key role in brain development and function. This review aims to highlight recent research on DHA's role during age-related cognitive decline and Alzheimer's disease. Animal and *in vitro* studies have provided some interesting mechanistic leads, especially on brain glucose metabolism, that may be involved in neuroprotection by DHA. However, results from human studies are more mitigated, perhaps due to changing DHA metabolism during aging. Recent innovative tools such as ^{13}C-DHA for metabolic studies and ^{11}C-DHA for PET provide interesting opportunities to study factors that affect DHA homeostasis during aging and to better understand whether and how to use DHA to delay or treat Alzheimer's disease.

Keywords: aging • Alzheimer's disease • apoE • brain glucose metabolism • cognitive decline • docosahexaenoic acid • metabolism • omega-3 fatty acids

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Alzheimer's disease (AD) is the most common form of age-related cognitive decline in Western countries [1] and is characterized by a progressive loss of memory that affects daily living activities. The main neuropathological features of AD are the accumulation of senile plaques, the presence of neurofibrillary tangles, regional brain atrophy and a regional hypometabolism of glucose. In the absence of typical features of AD, individuals with cognitive decline greater than expected during normal aging are defined as having mild cognitive impairment (MCI) [2]. About 50% of MCI progress to AD within 5 years. With increasing life expectancy, age-related cognitive decline has become a major concern for healthcare policies and research. Age is the most important risk factor for AD, but the sporadic form of AD is also associated with genetic risk factors, especially carrying the *APOE4* allele [3], higher risk in women, comorbidities, such as diabetes, hypertension and cardiovascular disease [1] and poor lifestyle, including sedentarity, stress and poor nutrition [4,5].

No pharmacological treatment is currently available to cure AD. Modifying lifestyle habits to delay the onset of AD has attracted special attention, especially strategies that improve nutrition and physical activity. Due to their central position within the central nervous system, omega-3 polyunsaturated fatty acids (PUFA) may be good candidates to promote cognitive health during aging. Indeed, omega-3 PUFA, especially docosahexaenoic acid (DHA), are important components of all cell membranes [6] and play a critical role in optimal brain development and function [7]. This review aims to update the potential protective role of dietary DHA intake in age-related cognitive decline which has been intensively investigated over the past decade. First, we will describe a selection of the evidence from *in vitro* and animal studies highlighting the protective role of omega-3 PUFA against some neuropathological features of age-related cognitive decline, especially glucose hypometabolism. Then we will discuss the results obtained from human studies, especially the divergence of results obtained from epidemiological studies and randomized clinical trials (RCT). Finally, we will highlight some metabolic features that

Future Medicine part of fsg

may need to be taken into account in clinical trials to better understand the metabolism of omega-3 PUFA during aging and age-related cognitive decline and to adapt dietary recommendations in this population.

Omega-3 fatty acids & the neuropathology of Alzheimer's disease: evidence from *in vitro* & animal studies

Senile plaques

The most important neuropathological hallmark of age-related cognitive decline is the formation of senile plaques through the aggregation of β amyloid (Aβ) peptides, resulting from the amyloidogenic cleavage of amyloid precursor protein (APP) [1]. *In vitro* and animal studies have shown that providing DHA decreases Aβ accumulation and neurotoxicity [8–10] in cells implicated in the neurovascular unit, in other words, neurons, glial cells, endothelial cells and pericytes [11]. DHA inhibits β-secretase activity and promotes α-secretase stability, leading to the inhibition of amyloidogenic pathway in favor of the non-amyloidogenic pathway [12]. DHA also stimulates the phagocytosis of Aβ42 by microglia [13] and inhibits the oligomerization and fibrillation of Aβ peptides [14,15]. DHA regulation of the amyloidogenic pathway also implicates membrane lipid rafts. The immediate environment of lipid rafts is highly enriched in cholesterol and favors the interaction between APP and β-secretase and, hence, Aβ accumulation [16]. DHA reduces cholesterol biosynthesis and promotes a delocalization of cholesterol from lipid rafts to nonrafts membrane fractions [12]. Part of the protective effect of DHA against Aβ neurotoxicity seems also to be mediated through its hydroxyl-derivative, as shown *in vitro* with the natural derivative, neuroprotectin D1 (NPD1) [17,18] or synthetic forms of NPD1 [19].

Neurofibrillary tangles & Tau hyperphosphorylation

AD neuropathology is also characterized by the presence of neurofibrillary tangles, composed of abnormally hyperphophorylated Tau proteins [1]. Under physiological conditions, Tau proteins bind to microtubules to ensure their stability. The hyperphosphorylation of Tau proteins occurring during AD prevents them from binding to microtubules and so contributes to microtubule disassembly. Studies in mouse models of AD show that supplementation with DHA [20], hydroxyl-derivative of DHA [19], as well as endogenous conversion of n-6 PUFA to omega-3 PUFA in *fat-1* mouse model [21] all reduce Tau accumulation and phosphorylation. This effect may go through the inactivation of c-Jun N-terminal kinase, a kinase implicated in Tau phosphorylation [20,22]. Interestingly, DHA also promotes the expression of cytoskeletal proteins associated with stable and dynamic microtubules in primary rat hippocampal neurons [23].

Brain glucose hypometabolism

Regional brain glucose hypometabolism on the order of 10–15% occurs in healthy aging in the absence of any measurable cognitive decline [24–26]. In AD, brain glucose hypometabolism is more severe reaching upwards of 35% in some brain areas [27]. There is a positive association between glucose hypometabolism and the degree of cognitive decline in MCI or AD patients [28,29]. Brain glucose hypometabolism may be a consequence of neural degeneration and synaptic loss associated with AD. However, it is also clearly present in cognitively normal individuals with risk factors for AD, in other words, aging, family history of AD or prediabetes, so may also be contributing to the cause of AD [30].

We have recently shown in rats that a low DHA content in brain induced by feeding a diet deficient in omega-3 PUFA is associated with lower glucose uptake by the brain. ^{18}F-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography (PET) was used to determine glucose uptake expressed as standardized uptake values (SUVs). Two-month-old male Wistar rats received either an omega-3 PUFA deficient diet (1370 mg LA and 6 mg ALA/100 g of diet) or a control diet supplying adequate amount of omega-3 PUFA (1307 mg LA and 309 mg ALA/100 g of diet). The omega-3 PUFA deficiency was associated with a 60% reduction in brain phospholipid DHA and a significant decrease of glucose utilization in the brain corresponding to both a reduction of the rate of FDG input during the early phase (27% lower than in controls) and a lower plateau level of FDG incorporation (12% lower SUVmax) (Figure 1). Brain glucose uptake is highly dependent on glucose transporter activity, especially GLUT1, which is localized in both endothelial cells of the blood–brain barrier and astrocytes [31]. Interestingly, omega-3 PUFA deficiency in rats reduces gene and protein expression of GLUT1 [32,33], without changing other glucose transporters such as the neuronal GLUT3 isoform. *In vitro* studies on rat brain endothelial cells depleted of DHA show that the incorporation of DHA in cell membranes by its addition in the culture medium led to a 35% increase in glucose transport activity associated with an increase in GLUT1 density [34,35]. Altogether, these results suggest an important role of omega-3 PUFA in the regulation of brain glucose metabolism, in part due to the regulation of the endothelial and astroglial GLUT1. Modulating DHA dietary intakes may therefore help to prevent or correct the glucose hypometabolism observed during

age-related cognitive decline [36]. Nevertheless, a small, short-term pilot study showed that a 3-week fish oil supplementation providing daily 680 mg of DHA and 323 mg of EPA was not sufficient to alter brain FDG uptake in older persons despite them having mild glucose intolerance [37].

Omega-3 fatty acids & prevention of age-related cognitive decline in humans: epidemiological studies vs clinical trials

Fish & dietary docosahexaenoic acid intakes: results from cross-sectional & prospective studies

The endogenous synthesis of DHA from its dietary essential precursor, α-linolenic acid, is very low in humans [38]. Providing sufficient amount of DHA through dietary intakes, especially through the consumption of fatty fish, is therefore recommended to ensure the optimal bioavailability of DHA to the tissues, notably to the brain. A number of cross-sectional and prospective studies have highlighted a positive correlation between fish and/or DHA dietary consumption and cognitive performances in healthy elderly [39–42], as well as with lower accumulation of Aβ peptides [43] and lower brain atrophy [44,45]. Compared with individuals with MCI or AD, cognitively healthy elderly tend to consume higher amount of fatty acid and/or DHA [46–49], an observation that agrees with prospective studies showing an inverse correlation between fish consumption and the incidence of dementia, especially AD [50–54]. Consuming fatty fish at least once a week may therefore help reduce the risk to develop AD by more than 50% [52].

Although many epidemiological studies suggest a protective role of fish and/or DHA consumption on the incidence of age-related cognitive decline, three prospective studies do not show any significant association between higher fish consumption and risk of AD. The first study was based on a subsample of participants and may have a lack of statistical power, the association between fish consumption and a reduction of the risk of AD bordering on significant [55]. In the Rotterdam study, the 2-year follow-up reported a protective role of fish consumption against the risk of AD, but this result was no longer found in the 6- and 10- year follow-up of the same cohort [56,57]. In this study, the consumption of fish was quite low and consisted principally of lean fish that are not particularly rich in omega-3 PUFA. Moreover, the *APOE* polymorphisms may need to be considered in the statistical models since three studies have shown that the relationship between higher consumption of fish and lower risk of AD is reduced or absent in carriers of *APOE4* [53–54,58].

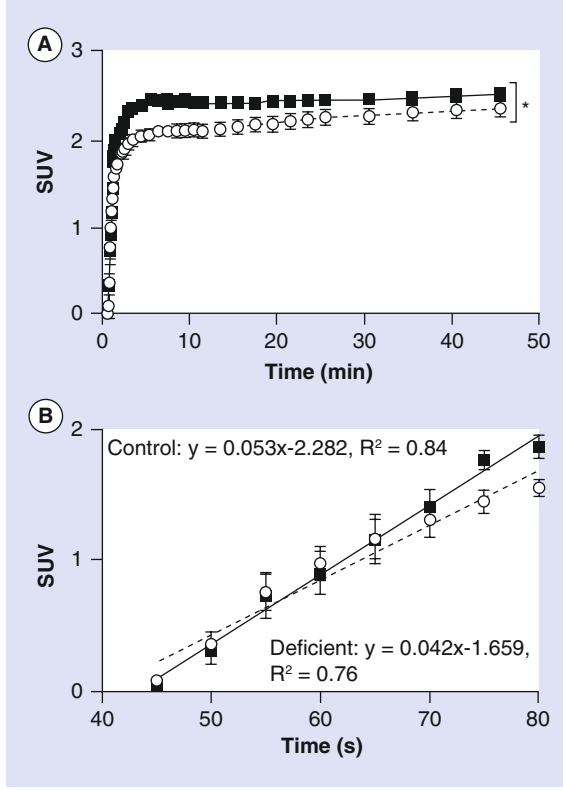

Figure 1. Omega-3 fatty acid dietary supply and brain glucose uptake. (A) ^{18}F-fluorodeoxyglucose (^{18}F-FDG) standardized uptake values (SUVs) were obtained by *in vivo* PET imaging of the whole brain of control (•; n = 5) and omega-3 PUFA deficient rats (○; n = 6). SUVs are expressed as measured activity/normalized dose (mean ± SEM). *Indicates SUV_{max} at 45 min was significantly different between the two groups. **(B)** A linearization of ^{18}F-FDG uptake during the first 80 s following ^{18}F-FDG infusion was used to calculate the rate of brain glucose uptake in the two groups (previously unpublished data).

Docosahexaenoic acid blood levels: is there a link with dietary intake?

Fish and DHA dietary intake are usually evaluated through the administration of food-frequency questionnaires. Measuring dietary DHA intake is a laborious measurement based on self-reported consumption and is subject to high day-to-day variability. Conversely, measuring DHA level in the plasma is a simple and reliable technique. Hence, it would be helpful if dietary DHA intake correlated linearly and significantly with plasma DHA. Most epidemiological studies have shown a positive association between fish consumption and lower risk of AD, yet the results from blood samples are more mitigated, as reviewed previously [39,59]. The discrepancy of the results may be partly explained by a lack of an established reference lipid class in the blood, because studies have been performed either on DHA in erythrocytes, plasma

phospholipid, cholesteryl esters, triglycerides, free fatty acids or plasma total lipids. In addition, several factors may modify DHA metabolism and hence the relationship between dietary and plasma DHA concentrations.

We speculate that lower DHA intake in AD patients could still be associated with similar plasma DHA concentrations as in the healthy elderly [46], because age-related cognitive decline may be accompanied by a shift in the diet-plasma relationship for DHA. It has recently been proposed that the relationship between diet and plasma DHA is disrupted in carriers of *APOE4*, but may also vary with age, sex or dietary habits [60]. These factors were also identified as modulating DHA concentrations in erythrocytes following omega-3 PUFA supplementation [61]. In this latter study [61], supplementation explained 66% of the variance in omega-3 PUFA content in the erythrocytes suggesting that other factors such as body weight, physical activity, age or sex contribute to about one third of the variance in DHA.

Post-mortem brain studies

Several studies have used postmortem samples of human brain to measure brain DHA concentration in AD patients (Figure 2) [59]. As expected due to lower DHA dietary intakes observed during age-related cognitive decline, some studies have shown that AD patients have lower DHA levels in the hippocampus, a brain structure implicated in memory and learning [62–64]. Similar results were observed in the frontal cortex, which is important for reasoning, attention, planning and emotions [63,65–69]. Nevertheless, other studies did not show any modification of DHA content of the frontal cortex [70–73] or in other brain regions that are also implicated in AD, such as the temporal or parietal lobes and the parahippocampus [62,66–67,70–71,74]. In accordance with animal studies, it has been recently proposed that an altered composition of lipid rafts in human frontal cortex, including a decrease in their DHA content, may be related to the neuropathology of AD, especially the formation of senile plaques [68,69].

Randomized clinical trials

A recent prospective study showed that daily consumption of an omega-3 PUFA supplement prevented cognitive impairment as measured by MMSE in elderly Chinese [75], but the type or concentration of the omega-3 PUFA supplement were not specified. Several other RCTs showed that DHA-enriched supplements delay cognitive decline in elderly with cognitive impairments (Table 1) [76–78]. Some of them have suggested that DHA supplementation improves cognitive performances in elderly with memory complaints [79,80], MCI [81,82] and AD [83]. However, other studies do not show any cognitive improvement due to DHA supplement in AD [84–86].

The discrepancy in the results from RCT may partly been explained by the highly heterogeneous protocols used, especially considering the dose, the type and the duration of the DHA supplementation (Table 1). For example, most studies used fish oil as a supplementation, providing both DHA and eicosapentaenoic acid (EPA), with the latter also potentially contributing to the preventive effect of fish oil against cognitive decline. Moreover, the protective role of DHA against age-related cognitive decline may depend on *APOE* genotype [84] and on the degree of cognitive decline at baseline, and may be stronger in those with the mildest cognitive impairment [85–86,88–91]. This suggests that DHA may be more efficient as a preventive intervention rather than as a curative treatment. As we will discuss in the following section, we hypothesized that age-relative cognitive decline may be accompanied by a shift in DHA metabolism in older persons with memory problems such that they may be less able to benefit from DHA-enriched supplements as cognitively healthy individuals.

Docosahexaenoic acid metabolism during age-related cognitive decline

To attempt to explain the divergent results between epidemiological studies and RCT and between various RCT, we hypothesized that DHA metabolism may be altered during age-related cognitive decline. The development of uniformly labelled tracers with stable isotopes constitutes a new approach to safely assess DHA metabolism in human clinical studies. A 1-month follow-up of a single dose of uniformly carbon-13 labelled DHA (^{13}C-DHA) showed that ^{13}C-DHA remained longer in the blood of elderly (mean age 76 years) compared with young adults (mean age 27 years) [92]. ^{13}C-DHA homeostasis also differed between the different plasma lipid classes: compared with young adults, plasma enrichment in ^{13}C-DHA in elderly was fourfold to fivefold higher in triglycerides and free fatty acids within hours and twice higher in PL and CE within days to weeks following the ingestion of the tracer.

Carrying *APOE4* also disrupts DHA metabolism [58,93–94]. The protective role of higher fish consumption or higher blood DHA against age-related cognitive decline may not be observed in carriers of *APOE4* [53–54,95]. Whole body half-life of DHA in the healthy elderly was 77% shorter in carriers of *APOE4* compared with the noncarriers [93], due to higher β-oxidation of DHA in the *APOE4* carriers as measured by expired ^{13}C-CO_2 after the ingestion of the tracer ^{13}C-DHA. The relationship between dietary

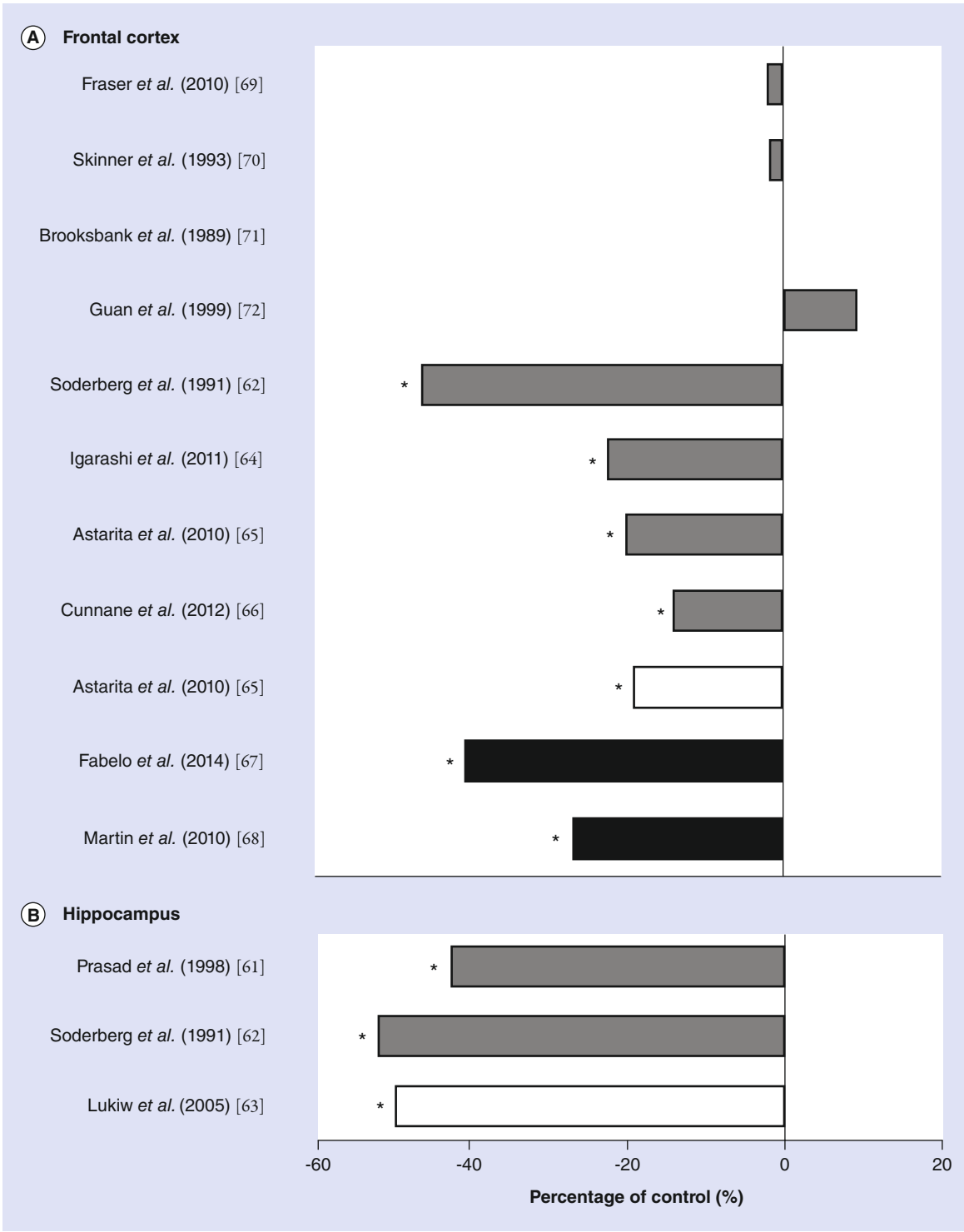

Figure 2. Summary of the published literature on docosahexaenoic acid content in (A) the frontal cortex and (B) the hippocampus during Alzheimer's disease. Bars show docosahexaenoic acid values as a percentage of age-matched healthy elderly groups for each study shown. Date were obtained from either brain phospholipids (gray bars), brain free fatty acids (white bars) or lipid raft fractions (black bars).
*Studies presenting a significant difference between control and Alzheimer's disease.

Table 1. Impact of docosahexaenoic acid supplementation in elderly with cognitive complaints, mild cognitive impairment or Alzheimer's disease.

Cognitive status	Age (years)	Duration (months)	n	Supplement	Results compared to placebo	Ref.
MCI	>60	12	18	Placebo		[87]
			17	1290 mg DHA + 450 mg EPA	↑ Memory improvement	
AD	>55	12	12	Placebo		[83]
			11	675 mg DHA + 975 EPA	Less ↓ in IADL	
			11	675 mg DHA + 975 mg EPA + 600 mg LA	Less ↓ in MMSE and IADL	
MC	50–90	4	62	Placebo		[88]
			60	300 mg PS + 79 mg DHA + EPA (DHA:EPA ratio of 3:1)	↑ Immediate recall compared to P; Greater ↑ in subgroup with higher baseline cognitive performances	
MC	50–90	4/4	60	Placebo / 100 mg PS + 26 mg DHA + EPA (DHA:EPA ratio of 3:1)	↑ Cognitive performances (sustained attention and memory recognition)	[79]
		4/4		300 mg PS + 79 mg DHA + EPA/100 mg PS + 26 mg DHA + EPA (DHA:EPA ratio of 3:1)	Maintained cognitive performances	
AD	Mean 76	18	112	Placebo		[84]
			152	2g Algal DHA containing 45–55% of DHA	No change on cognitive decline and brain atrophy	
C	>65	6	28	Placebo		[89]
			29	180 mg DHA + 120 mg EPA	Less ↓ in AMT scores	
MCI	>65	6	71	Placebo		
			71	180 mg DHA + 120 mg EPA	No change	
MCI	55–90	6	6	Placebo		[85]
			12	1080 mg EPA + 720 mg DHA	Significant ↑ in ADAS-Cog score	
AD	55–90	6	9	Placebo		
			8	1080 mg EPA + 720 mg DHA	No change	
MC	>55	6	218	Placebo		[80]
			219	900 mg DHA	↑ Cognitive performances in CANTAB	
AD	Mean 74	6/6	85	Placebo /1.7 g DHA +0.6 g EPA	Less ↓ in MMSE score in subgroup with very mild AD	[90]
		12	89	1.7 g DHA + 0.6 g EPA	Less 6-month ↓ in MMSE score in subgroup with very mild AD	
MCI	>65	6	11	Placebo		[82]
			16	1.55 g DHA + 0.4 g EPA	↑ GDS score and verbal fluency	
			13	1.67 g EPA + 0.16 g DHA	↑ GDS score	
MCI	Mean 70	3	9	Placebo		[86]
	Mean 67	3	12	240 mg DHA and ARA + antioxidant	↑ Immediate memory and attention	

AMT: Abbreviated Mental Test; AD: Alzheimer's disease; ADAS-Cog: Alzheimer's Disease Assessment Scale–Cognitive; C: Control; CANTAB: Cambridge Neuropsychological Test Automated Battery; D: Dementia; DHA: Docosahexaenoic acid; GDS: Geriatric depression scale; IADL: Instrumental activities of daily living; MC: Memory complaints; MCI: Mild cognitive impairment.

Table 1. Impact of docosahexaenoic acid supplementation in elderly with cognitive complaints, mild cognitive impairment or Alzheimer's disease (cont.).

Cognitive status	Age (years)	Duration (months)	n	Supplement	Results compared to placebo	Ref.
AD	Mean 67	3	8	240 mg DHA and ARA + antioxidant	No change	
C	67–92	6	8	600 mg DHA + 500 mg EPA	75% of the subjects had cognitive improvements	[91]
D	67–92	6	22	600 mg DHA + 500 mg EPA	55% of the subjects had cognitive improvements	

AMT: Abbreviated Mental Test; AD: Alzheimer's disease; ADAS-Cog: Alzheimer's Disease Assessment Scale–Cognitive; C: Control; CANTAB: Cambridge Neuropsychological Test Automated Battery; D: Dementia; DHA: Docosahexaenoic acid; GDS: Geriatric depression scale; IADL: Instrumental activities of daily living; MC: Memory complaints; MCI: Mild cognitive impairment.

and plasma DHA therefore seems to shift in carriers of *APOE4*, who need higher dietary fish intakes to increase plasma DHA concentration [60]. In carriers of *APOE4,* β-oxidation may preferentially affect omega-3 PUFA compared with monounsaturated or saturated fatty acids, explaining the modification of DHA metabolism occurring with *APOE4* [96,97].

Daily dietary intake of DHA has been estimated to be lower in many populations than the 250 mg/day recommended [98]. At the same time, a higher intake of DHA may also modify its own metabolism. In a recent study, the metabolism of ^{13}C-DHA in older adults (mean age 72 years) was followed before and in the last month of a 5-month supplementation providing 1.4 g of DHA and 1.8 g of EPA daily [99]. While on the supplement, DHA clearance from plasma was faster and β-oxidation of ^{13}C-DHA was 87% higher compared with before the supplement. However, the kinetics of ^{13}C-DHA in *APOE4* carriers while on the supplement was not the same [59]. *APOE4* carriers also present a lower plasma response to a 6-week supplementation with 3 g/day of DHA + EPA compared with noncarriers [94]. Aging alone also disrupts DHA homeostasis following short-term supplementation with fish oil; compared with young adult, plasma DHA concentration was indeed increased 42% more in elderly [100].

The PET tracer, ^{11}C-DHA, has permitted the estimation of brain DHA turnover of 4 mg/day and a brain DHA half-life of 2.5 years [101]. DHA kinetics in the brain are therefore clearly different from those of the whole-body, because the latter is estimated to be 32 days in carriers of *APOE4* and 140 days in noncarriers of *APOE4* [93]. The study of brain DHA homeostasis using PET imaging may therefore provide some useful information on genotype- and diet-related modifications to DHA during aging [102]. Postmortem studies of brain from AD patients show a linear relationship between apoE and DHA concentrations [103], suggesting a role of apoE protein and indirectly in *APOE4* genotype, in the maintenance of DHA concentrations within the brain. It was recently shown that omega-3 PUFA provided through the diet cross the blood–brain barrier and increase DHA content in the cerebrospinal fluid in AD [104]. Moreover, the recent finding of an efficient transporter for DHA into the brain [105] provides new field of investigation to better understand DHA homeostasis in the brain.

Hence, DHA metabolism is influenced by two important risk factors for AD – aging and *APOE4*. This may suggest that a shift in DHA homeostasis during age-related cognitive decline, especially AD, may contribute to the divergent results obtained in RCT studies. A modification of DHA metabolism during AD has been reported previously, especially an increase in peroxidation products [106], even in the early stages of age-related cognitive decline [107]. This effect was lower when participants had higher omega-3 PUFA dietary intakes [87]. Further studies are needed to better characterize the link between risk of AD and whole body and brain metabolism of DHA.

Conclusion

Animal and *in vitro* studies provide some promising results on the role played by DHA in the prevention of age-related cognitive decline. DHA may help prevent the formation of senile plaques and neurofibrillary tangles and may also help maintain brain glucose uptake during aging. Nevertheless, differences in DHA synthesis and metabolism have been observed between animals and humans. Humans have lower endogenous synthesis of DHA from ALA compared with animals. Moreover, the human brain strongly retains DHA in membrane phospholipids despite very low DHA dietary intakes. The promising protective effect of DHA observed in cellular and animal models has yet to be widely confirmed in clinical studies. The consumption of fatty fish and DHA has been mostly reported to have a protective role against cognitive decline and AD, but results obtained from blood or brain samples do not help explain this protective effect. The use of isotopically

labeled tracers highlights some modifications in DHA metabolism due to healthy aging, *APOE4* genotype and dietary intakes that should be considered in future clinical studies. Understanding the complexity of DHA metabolism during age-related cognitive decline such as AD is essential to improve and adapt dietary strategies to this large and vulnerable population.

Future perspective

The use of uniformly labeled tracers has allowed great advances in understanding DHA kinetics during aging. Recent studies have shown that ^{13}C-DHA metabolism differs depending on age, *APOE* genotype and dietary intake. Nevertheless, to fully understand the protective role of omega-3 PUFA against AD and adapt dietary recommendations in this population, several points remained to be clarified in the future:

- ^{13}C-DHA homeostasis should be evaluated in AD;
- Supplementation with omega-3 fatty acids are mainly done using fish oil, which is enriched in both DHA and EPA. The further study of EPA metabolism during aging and AD and its relationship with dietary intakes will provide useful information to understand whether protective role of fish oil against AD can be optimized and observed more consistently;
- The recent discovery of a brain DHA transporter [105] and the use of PET imaging will bring new information on DHA homeostasis in the brain and may be helpful to develop nutritional strategies adapted to favor DHA incorporation within the brain;
- The mechanisms associated with the protective role of DHA against cognitive decline and AD remained to be fully characterized in humans, especially the role of DHA in brain glucose metabolism. PET imaging tracers such as ^{18}F-FDG or ^{11}C-PIB, a marker of senile plaques, will help improve our understanding of the relationship between omega-3 dietary intake and brain glucose hypometabolism and amyloid deposition.

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Executive summary

Omega-3 fatty acids & the neuropathology of AD (Alzheimer's diesease): evidence from in vitro & animal studies

- DHA has a protective role against Aβ accumulation and toxicity.
- DHA reduces the hyperphosphorylation of Tau proteins, associated with the formation of neurofibrillary tangles.
- DHA play a key role in the regulation of brain glucose metabolism.

Omega-3 fatty acids & prevention of AD in humans: epidemiological studies vs clinical trials

- Epidemiological studies suggest that higher consumption of fatty fish enriched in docosahexaenoic acid (DHA) prevents age-related cognitive decline and the development of AD.
- The relationship between dietary and plasma DHA during AD is complex and influenced by several factors such as age, sex, *APOE4* genotype, body weight or physical activity.
- Postmortem brain studies show a reduced amount of DHA in the hippocampus but not necessarily in the cortex of AD patients compared with cognitively healthy control.
- Results from RCT are inconsistent but broadly suggest that DHA consumption may be more efficient as a preventive strategy against cognitive decline rather than as a curative strategy in AD.

DHA metabolism during age-related cognitive decline

- Healthy aging is associated with a slower clearance of plasma DHA.
- Carrying the *APOE4* allele is the main genetic factor of sporadic AD and is associated with higher β-oxidation of DHA and lower whole-body half-life of DHA compared with the noncarriers.
- DHA metabolism is influenced by omega-3 polyunsaturated fatty acids (PUFA) intake and the response to a supplementation in omega-3 PUFA differs between carriers and noncarriers of *APOE4.*
- Uniformly-labeled tracers of omega-3 PUFA are innovative and useful tools to better understand DHA metabolism during aging and AD.

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