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Fish, omega-3 fatty acids, cognition and dementia risk: Not just a fishy tale

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Shortened title: Fish, DHA and cognition

Keywords: Eicosapentaenoic acid (EPA), Docosahexaenoic acid (DHA), Alzheimer's disease, neuroinflammation and oxylipins

1. ABSTRACT

With growing and ageing populations, the incidence of dementia is expected to triple globally by 2050. In the absence of effective drugs to treat or reverse the syndrome, dietary approaches which prevent, or delay disease onset have enormous population health potential. Prospective epidemiological studies and mechanistic insight from experiment models strongly support a positive effect of a high fish and long chain omega-3 fatty acid (eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) intake on a range of cognitive outcomes and dementia risk, with effect sizes equivalent to several years of ageing between the highest and lowest consumers. As reviewed here an effect of EPA and DHA on neuroinflammation and oxylipin production is likely to in part mediate the neurophysiological benefits. However randomised controlled (RCTs) with EPA and DHA supplementation have produced mixed findings. Insight into the likely modulators of response to intervention and factors which should be considered for future RCTs are given. Furthermore, the impact of *APOE* genotype on disease risk and response to EPA and DHA supplementation is summarised. The prevalence of dementia is several-fold higher in *APOE4* females (~13% Caucasian populations) relative to the general population, who are emerging as subgroup who may particularly benefits from DHA intervention, prior to the development of significant pathology.

1. INTRODUCTION

Cognition refers to the mental process of acquiring knowledge and processing information. It includes such functions as attention, memory, problem solving, decision making, planning, inhibition, judgment and evaluation, reasoning, comprehension and production of language, and orientation/visuospatial skills. Dementia is a general term for a loss of one or more of these functions that is severe enough to interfere with daily life. There are now over 100 recognised forms of dementia, with Alzheimer's disease (AD) being the most prevalent and responsible for about two thirds of dementia cases.

Globally there are 50 million living with dementia [1], occurring in 5-8% of those aged over 60 years, with the prevalence increasing exponentially with age [2, 3](Figure1)

Figure 1: Dementia prevalence (%) by age group in the UK [3]

With growing and ageing populations, and more widespread diagnostic services, a diagnosed dementia rates are predicted to triple by 2050 [1]. Dementia is the second leading cause of

death globally after ischaemic heart disease [2] and in England and Wales dementia is now the single greatest cause of death in women, responsible for 16.5% of total mortality (versus 8.7% in men) [4]. This sex differences in dementia associated death rates, are reflective of the fact that two thirds of dementia patients are females [2], the physiological and molecular basis of which is only partially elucidated [5-7]. Accelerated neuropathology and cognitive decline evident during the menopausal transition in females and the higher penetrance of the at risk *APOE4* allele in female carriers are likely to be major contributing factors [8-11]. However, encouragingly age-standardised rates are decreasing in many high incomes countries. Between 1990 and 2016, a 6.8%, 10.3% and 8.4% reduction in dementia associated death, prevalence and Disability Adjusted Life Years (DALYs) rates respectively was observed in the UK [2]. These reductions have been attributed to greater education attainment (creating cognitive reserve), better cardiovascular health, and improved nutrition.

2. OVERVIEW OF INTERVENTIONS FOR DEMENTIA TREATMENT AND PREVENTION

There are currently few effective drugs to prevent or treat dementias. In the UK there are four licensed drugs available (*Donepezil, Rivastigmine, Galantamine*, and *Memantine*) which temporality treat symptoms by targeting synaptic function and neurotransmission. In 2021, the Food and Drug Administration (FDA) granted accelerated approval to *Aducanumab*, the first drug in 18 years for AD [12]. It is a monoclonal antibody which targets amyloid clearance and is currently undergoing regulatory review in Europe. Its purported efficacy is controversial with the benefits thought to be marginal in most patients [12].

In the absence of effective pharmaceutical options to prevent, reverse or treat dementia there is a widespread interest in lifestyle behaviour approaches including nutrition to prevent or delay neurophysiological and cognitive decline. In the 2020 *Dementia prevention, intervention, and care: 2020 report of the Lancet Commission* it was estimated 'that 12 modifiable risk factors account for around 40% of worldwide dementias, which consequently could theoretically be prevented or delayed' [13]. Many of these are nutrition dependent (hypertension, obesity, diabetes, depression and recovery from traumatic brain injury) and likely mediate the emerging role of nutrition in brain health.

Research into the role of nutrition in age-related cognitive decline is in its relative infancy compared with other chronic conditions such as cardiovascular disease and osteoporosis, with research evidence largely derived from prospective cohort studies or experimental models.

Although not fully consistent, a growing body of prospective cohort evidence shows that plant based dietary patterns and individual dietary bioactives such as selenium, vitamin D, B-vitamins, polyphenols and long chain omega-3 fatty acids improve cognition and reduce dementia risk, conversion of mild cognitive impairment to AD, and brain atrophy [14-20]. A Mediterranean dietary pattern (MDP) and the Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND) diet have emerged are particularly effective with high versus low adherence associated with up to a 40% reduced dementia rate [17, 21-23]. The potential of the protective role of a MDP was highlighted in the 2017 *Lancet Commission Dementia prevention*, *intervention, and care*, report [24], with a MDP being the only specific dietary approach for which the WHO 2019 *Risk Reduction of Cognitive Decline and Dementia* guidelines [25] recommended to adults with normal cognition to reduce the risk of cognitive decline and dementia. A defining component of an MDP is a high fish and omega-3 fatty acid intake. Here we focus on the role of the long chain omega-3 fatty acids (LC omega-3 PUFA), docosahexaenoic acid (DHA) in brain function and on the available evidence for a protective role of higher fish and DHA and eicosapentaenoic acid (EPA) intake and status in cognitive health. We critique the apparent inconsistencies between the, protective associations observed in prospective cohort and biological effects in experimental models, versus the inconsistent and often null or marginal effects seen in RCTs.

3. BRAIN FATTY ACID UPTAKE

DHA is a 22-carbon omega-3 fatty acid, with multifaceted structural and functional roles in the central nervous system. Although DHA can be synthesised in the liver from the plant precursor omega-3 fatty acid α-linolenic acid, bioconversion is less than 0.2% [26]. Within the brain, the synthesis of DHA from α-linolenic acid is negligible. Therefore, DHA uptake via the highly selective blood brain barrier (BBB) is required to replace the DHA consumed in metabolic reactions. A dietary supply of DHA as either oily fish or supplements is recommended to meaningfully enrich brain levels. DHA is the predominant PUFA in the brain, accounting for 15% of the total fatty acid which is several fold-higher than most other tissues such as the heart and the liver where it constitutes around 2% [27]. Grey matter including synaptic membranes, synaptic vesicles, and mitochondria are particularly enriched [28].

The BBB is formed of tightly connected endothelial cells, embedded within a network of pericytes and astrocytes foot processes that support its function [29]. Fatty acids cross the BBB is by two known mechanisms, either facilitated transport by several transmembrane proteins or

by passive diffusion [30]. BBB uptake of plasma fatty acids was historically thought to be only from non-esterified/ (NEFAs), which originate from lipoproteins or are bound to plasma protein mainly albumin [31]. More than 99% of NE-DHA is protein bound. NEFAs are transported through the endothelial cell membranes and cytoplasm via a group of fatty acid transport proteins (FATP) and fatty acid binding proteins (FABP). FATP1 and FATP4 are highly expressed in both the vascular and the parenchymal regions of the brain [32]. Recent studies show that FATP1 participates in 60% of DHA uptake [33]. Interestingly, in a cell culture model, amyloid β, the hallmark of AD pathology, induced a 96% reduction in FATP1 protein expression and an associated 45% reduction in DHA efflux [34]. More recently Acyl-CoA synthetase 6 (Acsl6) has been identified as essential for enriching the brain with DHA [35, 36]

Besides the NEFA form, DHA is also taken up into the brain in the form of lysophosphatidylcholine (LPC-DHA)[37]. The major facilitator superfamily domain-containing protein 2a (MFSD2A) is considered the major route of LPC-DHA uptake [38-40]. Indeed, *Mfsd2a* knockout mice showed 50% lower DHA levels compared to wildtype animals, with consequent cognitive deficits, anxiety and microcephaly [38]. Along with its emerging role in LPC-FAs transport and the regulation of BBB permeability [41], MFSD2A is emerging as having more far reaching functions in neuroinflammation and other physiological and pathophysiological brain processes [42]. Overall, although the uptake and partitioning co-efficient is higher for LPC-DHA relative to NEFA-DHA following intravenous injections, NEFA DHA is thought to be the main source of DHA for the brain due to its higher circulating concentrations [31, 43].

Although currently largely unknown it is emerging that variables such as age, menopause, neuropathology and *APOE* genotype status [44], may impact on the brain DHA uptake processes, and has implications for the recommended DHA dose in population subgroups, and the optimal intervention 'window of opportunity' when DHA supplementation is most likely to bring about cognitive benefits. Furthermore, defective brain DHA uptake could underpin the lack of benefit of DHA observed in several RCT, particularly in *APOE4* carriers (see section 9).

4. *APOE* GENOTYPE; IMPACT ON DEMNTIA/ ALZHEIMERS DISEASE RISK AND AGE OF ONSET

Apolipoprotein E (ApoE) produced mainly in the brain by glial cells, is the principal lipid transporter within the brain and cerebrospinal fluid (CSF), but also has numerous other roles in regulated neuroinflammation and neuronal function. Two missense mutations in *APOE* gene (rs429358 and rs7412), produce three allele variants ε2, ε3 and ε4. These alleles have different amino acids (cysteine or arginine) in positions 112 and 158, resulting in ApoE2 (Cys112, Cys158), ApoE3 (Cys112, Arg158), and ApoE4 (Arg112, Arg158) [45]. These amino acids differences lead to conformational changes in ApoE structure which affects binding to lipoprotein receptors and also the stability and tissue concentrations of the protein [46]. The global frequency of the ε2, ε3 and ε4 alleles are approximately 8.4%, 77.9% and 13.7% respectively [47]. *APOE* genotype is the most important common genetic determinant of cognitive decline and AD risk, with a 3-fold increased prevalence of the ε4 allele in AD versus the general population and the *APOE3/E4* and *APOE4/E4* genotypes having a 2-3 and 12-15 fold increased risk of AD compared to the wild-type APOE3/E3 genotype [48, 49]. In addition, *APOE4* is associated with an average lower age of AD onset [49]. It falls from 84 years in *APOE4* non-carriers to 76 years in *APOE3/E4 to 68* years in *APOE4/E4* [49, 50]. The aetiology of the increased risk in *APOE4* carriers is multi-faceted and can be attributed to defective β-amyloid clearance, a loss of neuronal synaptic plasticity and dendrite outgrowth, neuroinflammation, cerebrovascular and BBB dysfunction, and lower brain DHA status [51]. In a transgenic rodent model, the uptake of [14C]-DHA using in situ cerebral perfusion were significantly lower in *APOE4* versus *APOE2* animals, which was exacerbated by age [52]. This observation of a greater effect of age on brain DHA is consistent with our more recent rodent study, where the effect of age was more evident in females [53] and following induction of menopause [54]. In humans, DHA supplementation resulted in lower circulating DHA levels [55, 56], higher systemic β-oxidation [56] and lower CSF DHA following 18 months of supplementation [57]. Defective BBB transfer, brain lipid transport and increased oxidation of DHA following upregulated release by PhospholipaseA2, are all likely contributors to a lower DHA brain status in *APOE4* [44]. As will be discussed below, *APOE* genotype has also emerged as an important mediator of the effect of DHA status and intervention on incident dementia and cognitive outcomes, but the effect is inconsistent and likely to dependent on age, sex and brain health stage.

5. THE ROLE OF DHA IN THE BRAIN

Since first being identified in the brain by Klenk and Bongard in 1952 [58], many neurophysiological roles have been identified for DHA in experimental models, including membrane structural roles (fluidity and modulation of membrane protein function) and the modulation of neurogenesis and neuronal cell growth and cell survival, β-amyloid clearance, vascular function and brain perfusion, BBB permeability, oxidative status, neuroinflammation, synaptic function and neurotransmission, [9, 31, 59-67]. Synaptosomal membranes are particularly enriched in DHA, where it constitutes up to 40% of PUFA in select lipid species and modulates neurotransmitter levels and membrane dynamics [68]. Loss of synaptic plasticity is a major contributor to the pathogenesis of cognitive decline, mediated in part through reduced levels of brain-derived neurotrophic factor (BDNF) and its related signalling pathways [69]. DHA is known to increase the level of BDNF and consequently activates AkT and ERK signalling pathways leading to improved synaptic plasticity [70]. We have recently shown reduced recognition memory in menopausal *APOE4* mice models fed with high fat diet. This memory deficit was associated with a 13% reduction in cortical DHA, reduced BDNF expression and compromised Akt, mTOR and ERK signalling pathways, highlighting the mechanistic role of DHA, interacting with menopause and *APOE4*, in cognitive decline via modulation of synaptic plasticity-related pathways [54].

A systematic review on the effects of relatively long-term ω-3 intervention in animal AD models included data from 15 studies and reported significant reductions in amyloid levels, plaque burden and neuronal loss and improved cognition following DHA only or EPA+DHA supplementation [71].

Once released from membrane phospholipids via phospholipase A2, DHA regulates inflammation through modulation of cytokine production and as a precursor for a host of bioactive oxylipins [72-77](see section 7).

6. NEUROINFLAMMATION, OXYLIPINS AND BRAIN HEALTH

Amyloid plaque deposition is one of the hall mark of AD pathology. Risk factors such as *APOE4* carrier status, vascular pathologies and neuroinflammation play interactive roles in the cascade of synthesis of amyloid-β (Aβ) and the progression of cognitive decline [78]. Indeed, proinflammatory cytokines such as IL6 and TNFα are increased in the blood and brain of patients with AD [79, 80]. Brain microglia, the brain resident immune cells, are the major regulator of brain inflammatory status via the release of inflammatory cytokines such as IL1β, TNFα and inducible nitric oxide synthase (iNOS) [81]. Activated microglia surround amyloid

plaques in the cerebral cortex of AD patients, which suggests that Aβ deposition can trigger microglial activation and subsequent release of inflammatory cytokines [82, 83].

However, recent studies suggest that neuroinflammation also plays an Aβ independent role in the pathogenesis of cognitive decline [84, 85]. Imaging studies have observed microglial activation in patients with mild cognitive impairment (MCI) even before the appearance of amyloid deposits [86, 87] which increases with disease progression [88, 89].

PUFAs have been extensively studied as a modulator of the systemic inflammatory in chronic diseases such as atherosclerosis, diabetes and rheumatoid arthritis. These conditions are consistently associated with higher CRPs, TNFs, IL6, thromboxane A2 (TXA2) and leukotrienes B4 (LTB4)[90, 91], which are affected by tissue PUFA status. [92](Figure 2). Similar to its systemic anti-inflammatory role, n-3 PUFAs are considered effective modulators of the brain inflammatory status [93, 94]. Higher DHA intake was associated with lower IL6 in the mouse hippocampus [95] and inhibition of the NFk-β inflammatory pathway [96]. DHA reduced Aβ deposition in an AD mouse model [63] through reduction of IL12/IL23 signalling pathway [97].

Figure (2): Main oxidative products (oxylipins) of arachidonic acid (AA), eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) metabolism. Adapted from *Schulze et al,* 2020 [98].

The biological actions of PUFAs in controlling neuroinflammation are in part mediated through their enzymatically and non-enzymatically oxidized metabolites, called oxylipins [99] (Figure 2). These lipid-derived oxygenated metabolites of PUFA are synthesised by three groups of enzymes; cyclooxygenases (COXs), lipoxygenases (LOXs) and cytochrome P450 enzymes [98], which produce hydroxy-, dihydroxy- or epoxy- fatty acids (FAs). Due to their highly unsaturated nature, PUFAs are also non-enzymatically oxidised (i.e. autooxidation) by reactive oxygen and nitrogen species [100]. Oxylipins are precursors for specialized pro-resolving mediators (SPMs; resolvins, protectins, maresins and lipoxins) which have anti-inflammatory and pro-resolving roles [101]. N-6 PUFA-derived oxylipins are generally pro-inflammatory relative to EPA/DHA derived species. The enzymatic action of COXs on AA produces the pro-inflammatory prostaglandin H2 (PGH2), TXA2 and 5-, 12- and 15- hydroxy-eicosatetraenoic

246 acid (HETEs) [102]. It is worth mentioning that AA is also a precursor of the anti-inflammatory
247 and pro-resolving lipoxins A4 and B4 [99].

248 N-3 PUFA-derived oxylipins generally have anti-inflammatory and pro-resolving properties.
249 EPA produces less inflammatory prostaglandins (PGs), TXAs (3-series) and LTs (5-
250 series)[103] relative to AA derived oxylipins. Epoxy-EPA oxylipins (EpETEs) produces anti-
251 inflammatory responses [104] partly through the inhibition of NFk-β pathway and through
252 antagonising inflammation induced by PGE2 [105, 106]. RvE1 reduces proinflammatory
253 cytokine production [107], neutrophil infiltration and reduces proinflammatory gene
254 expression in peripheral blood mononuclear cells (PBMC)s and microglia through binding to
255 ChemR23 receptor [108, 109].

256 The role of oxylipins and SPMs in the protection against neuroinflammation and the
257 development of AD is gaining research attention [75, 110, 111]. The resolution of the
258 inflammatory process is disrupted with ageing and cognitive decline [112]. In murine models,
259 increased n-6 PUFA derived oxylipins and decreased n-3 derived oxylipins and SPMs are
260 generally observed in neuroinflammatory brain disorders [78]. We previously showed a
261 significant reduction in cortical 14- and 17-HDHA and hippocampal NPD1 with age [53].
262 Brain LXA4 was also found to decline with age, with the reduction more pronounced in an
263 AD- mouse model [113]. Interestingly, administration of LXA4 in this AD- mouse model [113]
264 and RvD1 in a post-operative cognitive impairment model [114] reduced cognitive decline in
265 both conditions. Protectin D1 was first detected in murine blood and neuroprotectin D1 (NPD1)
266 is present in the brain [115]. NPD1 level greatly increased in the hippocampus after LPS
267 stimulation [76]. It binds to the GPR37 receptor [116] to inhibit NFk-β and pro-inflammatory
268 gene expression [117]. NPD1 showed protective function in neurodegeneration through
269 modulating synaptic plasticity and microglial activity [118]. In human studies, LXA4 was
270 lower in patients with AD compared to MCI or subjective cognitive impairment (SCI) patients.
271 Similarly, LXA4 and MaR1 were reduced in post mortem hippocampi of AD patients
272 compared to controls, while the n-6 PUFA oxylipins 5-HETE, 15-HETE, TXB2 and PGs
273 increased [119].

274 Being precursors to oxylipins and SPMs, several studies have explored the potential benefits
275 of n-3 PUFA in preventing cognitive decline via modulating the levels of brain oxylipins and
276 SPMs. In aged rats, EPA and DHA supplementation increased cortical 5-HEPE, 7-, 10-, and
277 17-HDHA, PD1, RvD1, and RvD2 [120]. AA-derived PGE_2, PGD_2, and $PGF_{2\alpha}$ significantly

decreased with consequent improvement in reference memory. In response to LPS stimulation, n-3 PUFA supplemented mice showed an increase in hippocampal n-3 oxylipins compared to non-supplemented mice who showed an increase in the n-6 pro-inflammatory oxylipins [121]. In AD patients, EPA and DHA supplementation increased peripheral blood mononuclear cell (PBMC) RvD1 levels compared to controls [119].

Significant inter-individual variability in the response of oxylipins to n-3 PUFA supplementation has been reported [122]. We showed that select EPA- and DHA- derived brain oxylipins and SPMs were lower in *APOE4* compared to *APOE3* mice [53]. In addition, we recently reported that the plasma oxylipins response to EPA+DHA supplementation is influenced by *APOE* genotype in healthy individuals with a greater production of a number of EPA- and DHA- derived species in *APOE4* carriers [123]. Genetic variation in enzymes involved in PUFA metabolism have been implicated as possible modulator of oxylipin production from PUFAs. Genetic variation in LTA_4H, an enzyme in the pathway of leukotriene synthesis, significantly interacted with dietary n-3 and n-6 fatty acid intake to determine intima-media thickness [124]. Variants in *ALOX5* gene were associated with a differential oxylipin response to fish oil supplementation in healthy African American adults [125].

Given the central role of neuroinflammation in cognitive decline, the modulation of cytokine, oxylipin and SPM production is a tractable target to prevent and delay neuropathology by increasing EPA and DHA status and intake.

7. FISH AND DHA INTAKE AND STATUS AND COGNITION: PROSPECTIVE COHORT EVIDENCE

There is a substantial and a relatively consistent body of research from prospective cohorts, of an inverse association between fish and EPA and DHA intake and status (measured in a number of blood lipid fractions), and dementia and AD risk, brain atrophy and cognitive decline. In the earliest report from the Rotterdam Cohort study (n=5386), with an incident case rate of 1.1% (n=58) over the 2.1y, total fat, saturated fat and fish intake were inversely related to incident dementia [126]. However, in the 9.6y follow up of this cohort, with 465 dementia cases, total fish, EPA or DHA intake was not associated with either total dementia or AD risk [127]. This lack of association is in contrast to the findings of the largest prospective analysis conducted to date on fish, omega-3 fatty acids and dementia, namely the NIH-AARP study in 421,309 adults followed up for 16y, with 85,112 deaths [128]. Quintile 5

(Q5) vs Q1 of total fish intake was associated with a Hazard Ratio (HR) of AD death of 0.76 (95% CI: 0.61, 0.95) with an even stronger association evident when fried fish was removed. Considered LC omega-3 PUFA intake, a HR of AD death of 0.70 (95% CI: 0.54, 0.89) was observed in Q5 vs Q1 in males, with an even greater benefit in females (HR, 0.59 (95% CI: 0.43, 0.80)[128]. Q5 represented a mean intake of > 180mg and 160mg per day in males and females of long chain omega-3 PUFA, mainly EPA+DHA. This intake is modest compared to the typical UK and global recommended intakes of 450-500mg per day EPA+DHA minimum recommended intake [129, 130], which is mainly targeted towards cardiovascular health.

In an analysis of post-mortem brains, seafood consumption (≥ 1 meal[s]/week), measured on average 4.5 years before death was correlated with less AD pathology including lower neuritic plaques, less severe and widespread neurofibrillary tangles, and lower neuropathologically defined AD but only among apolipoprotein E (APOE ε4) carriers [131].

A number of analysis have reported positive associations between DHA or EPA+DHA status in blood lipids fractions and cognitive outcomes [132-134]. In the Framingham Cohort, high versus low (Quartile 4 vs Quartile 1) phosphatidylcholine (PC)- DHA was associated with a 47% reduction in all cause dementia [132]. In the Women's Health Initiative Memory Study (WHIMS), the HR of probable dementia in the 9.8y follow up was 0.92 (95%: 0.84, 1.00) per SD of red blood cell (RBC) EPA+DHA (omega-3 index) with a similar HR when EPA and DHA were considered separately [133]. The 15-year cumulative incidence of probable dementia was estimated to be 12.1% with high EPA+DHA exposure compared to 14.2% with low EPA+DHA exposure (absolute risk difference =2.05%).

Ageing and dementia progression are underpinned by total brain atrophy (loss of volume) and in AD the hippocampus is particularly affected. In the WHIMS study, a 1 SD greater RBC EPA+DHA level was correlated with 2.1 cm^3 larger brain volume and greater hippocampal volume (50 mm^3), with the effect size purported to be equivalent to one to two years of ageing [16]. An association between RBC EPA+DHA and medial temporal lobe volume trajectories assessed over a maximum of 10.8 years (median follow-up 4.0 years) was observed in the Three-City (3C) study, along with improved global cognition and memory and a 60% increased risk of dementia in Q1 vs Q5 of EPA+DHA status [135].

The findings from prospective cohort studies have been synthesised into four meta-analysis which focus on fish intake [136, 137], or both fish and LC omega-3 PUFA intake [138, 139] on a variety of cognitive outcomes, which are further summarised in an umbrella review of meta-analyses [15]. Samieri et al., pooled the French Three-City study and 4 US cohorts and included data from n=23,688 (88% female) with median follow-ups of 3.9–9.1y [137].

Higher fish intake was associated with slower decline in both global cognition and episodic memory. The effect of consuming ≥4 servings/week versus <1 serving/week of fish on episodic memory decline was estimated to be equivalent to four years of ageing. Although the Bakre et al., (n=9 studies) analysis does not provide information on actual fish portion consumption per category, a dose-dependent effect was observed with a RR (95% CI) of dementia of 0·84 (0·72, 0·98), 0·78 (0·68, 0·90) and 0·77 (0·61, 0·98) in those with low, middle and high consumption of fish versus those with no or lowest consumption of fish, with corresponding RRs of 0·88 (0·74, 1·04), 0·79 (0·65, 0·96) and 0·67 (0·58, 0·78), respectively for AD [136]. In the most comprehensive and granular meta-analysis Zhang et al., combine data from 21 individual studies (181,580 participants) with 4438 cases, during follow-up periods ranging from 2.1–21y to examine associations between fish, total PUFA and individual PUFA intakes and total dementia and dementia sub-types [139]. The main findings is that an increase in fish of one serving per week is associated with a lower RR (95% CI) of dementia and AD of 0.95 (0.90, 0.99) and 0.93 (0.90, 0.95), with equivalent RR for a 0.1-g/d increment of dietary DHA intake (but not EPA) of 0.86 (0.76, 0.96) and 0.63 (0.51, 0.76) respectively. This effect size for one portion of fish and AD is relatively consistent with the Wu et al., analysis who reported that an increment of 100 g per week of fish intake (UK portion is 140g) was associated with an 11% lower risk of AD (RR = 0.89, 95% CI: 0.79, 0.99)[138].

There is conflicting evidence that associations may be influenced by *APOE* genotype status, with some prospective cohorts reporting no influence [133, 135, 137], some no benefits of fish or EPA/DHA intake in *APOE4* carriers [140-142] and some reporting a beneficial association only in *APOE4* [131]. These apparent inconsistencies are likely attributable to a lack of a granular understanding of influencers of brain DHA metabolism in *APOE4.* It is possible that due to a defective brain DHA uptake and metabolism there is a greater DHA need throughout life in *APOE4.* However, with variables such as age, menopause and significant pathology potentially having a greater impact on brain DHA uptake in *APOE4*, beyond a certain physiological stage an increased DHA intake or blood status may have a lower or negligible cognitive benefit in *APOE4* as it will not translate into higher brain DHA levels. More research is needed to identify the optimal DHA intake and supplementation 'window' in *APOE4*.

Therefore overall, in prospective cohort studies high vs low/no fish and LC omega-3 PUFA consumption is associated with an up to 40% reduced risk of total dementia, and in particular AD, with effect-sizes equivalent to several years of ageing. It is likely the benefits of fish

consumption extend beyond the provision of LC omega-3 PUFA, with fish also being a rich sources of selenium, B12 and vitamin D, all of which may enhance cognition [18]. For a dietary component such as DHA/fish which is considered a signature of affluence and an overall healthy diet and lifestyle [135] the possibility of residual confounding should be considered, with some of the cognitive benefits seen in prospective cohorts, due to as yet unknown factors which are not fully corrected for in the statistical models.

8. FISH AND DHA INTAKE AND STATUS AND COGNITION: RCT EVIDENCE

To the best of our knowledge there is currently no RCT which has investigated the impact of fish intake in isolation (i.e. not as part of a multi-food or whole diet intervention) on cognitive outcomes. Prospective cohort evidence where EPA and DHA are predominantly derived from fish, have examined the impact on dementia risk and cognition over follow up periods up to 20y. In contrast RCTs have intervened with a mixed LC omega-3 PUFA or DHA-rich supplement for up to three years, but typically 6 months, which have produced mixed and often null findings (Table 1).

Cognitive benefits of EPA+DHA supplementation have not been observed in AD patients [143]. In the Alzheimer's Disease Cooperative study (ADCS), supplementation with 2.0g DHA for 18 months in those with mild to moderate AD, did not affect the co-primary outcome measures, the cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-cog) and the Clinical Dementia Rating (CDR) sum of boxes [143]. An effect of intervention on the ADAS-cog and the mini-mental state examination (MMSE) was however observed in *APOE4* non-carriers. In a 2008 RCT in 302 cognitively healthy individuals, no effect of doses of 400 or 1900mg EPA+DHA per day on a range of cognitive outcomes was evident [144]. This is in contrast to the findings of Stonehouse and colleagues who observed a significant impact of 1160mg DHA + 170mg EPA per day on the speed of episodic and working memory and episodic memory performance in women, over 6 months in young adults, with low habitual EPA and DHA intake at baseline (<200mg per week)[145] with Yurko-Mauro et al., also observing improvements in a number of cognitive outcomes supplementing with 900mg per day in those with subjective memory complaints for 6 months [146]. This is in contrast to the MAPT trial (3y, n=1680)[147] and a more recent RCT (18m, n=403)[148] who observed no impact of 800mg DHA plus 225mg EPA per day or 1720mg DHA plus 600mg EPA respectively on cognitive performance. The MAPT intervention highlights the importance of participant selection, with a much higher mean education

attainment in the study group relative to a general French population, which may provide cognitive reserve and have contributed to the lower than expected decline in cognitive function in the MAPT control group [147] and also a number of other RCTs [149, 150], which will have impacted the study power. A secondary analysis in MAPT in the control group showed the greatest cognitive decline in participants with the lowest quartile (Q1) vs. Q2-4 of baseline RBC EPA+DHA omega-3 index (EPA+DHA), with the optimal omega-3 index cut-off for predicting notable cognitive decline calculated as 5.3% [151]. Using this cut-off there was a consistent but non-significant difference in 3-year cognitive decline between EPA+DHA treated and placebo subjects with "low" baseline omega-3 index. The authors concluded that those with an omega-3 index below approximately 5% are at increased risk of cognitive decline and could be a good target for recruiting a responsive population subgroup.

Intervention studies which target cognition have predominately fed DHA-rich or DHA-only supplements as the bioactive LC omega-3 PUFA, based on the observation that brain DHA levels are >250 higher than EPA [152]. EPA does enter the brain with uptake efficiencies equivalent to DHA, but is thought to be rapidly metabolised following entry, although concentrations of EPA are higher than DHA in microglial [152]. The impact of EPA in cognition and depression is being increasingly recognised [152-154]. In a recent intervention Patan and colleagues observed a significant effect of an EPA-rich oil on cognitive global accuracy and speed relative to a DHA-rich or placebo oil fed for 6 months (Table 1). Future interventions should not only consider what dose, but also what DHA:EPA ratio of the supplement and its chemical form (ethyl ester, triglyceride, phospholipid LPC)[155].

The prodrome of AD is thought to be 20–30 years or potentially longer [156]. Therefore, cognitive assessment or brain volume and atrophy (assessed by MRI) rather than incident disease have to date been exclusively used as primary RCT outcomes. Cognitive questionnaires and other assessments tools historically may not have been fully fit for purpose, lacking the specificity and sensitivity to detect subtle effect of intervention on specific cognitive domains. The variability and lack of a standard battery of cognitive tests employed in cognitive RCTs is likely to be a large contributory to the heterogeneity in finding, between trials.

Furthermore, due attention is not given to the length of the intervention period. As brain DHA half-life is estimated to be 2.5 years [157], supplementation periods of at least one year are likely to be needed to detect the cognitive benefits associated with DHA enrichment of neuronal cells, such as effects on dendrite outgrowth and spine density, synaptic function and

β- amyloid processing. The impact of intervention period on the study conclusions is evidenced by comparing the 24 month and 36 month findings from the LipiDiDiet study which fed the Souvenaid (Fortasyn Connect) medicinal food, which combines 1200mg DHA and 300mg EPA with phospholipids, uridine monophosphate, choline, vitamins B12, B6, folic acid, C, E, and selenium. At 24 months, although an effect of Souvenaid on secondary outcomes was observed (hippocampal volume and CDR score) no effect of the intervention on the primary outcome, the neurocognitive test battery (NTB) performance, was evident. By 36 months the intervention had significantly increased the NTB test score by 60% relative to the control group, with the greatest cognitive benefits (based on the CDR score) evident in those with the highest cognitive status at baseline (MMSE ≥ 29).

There is a strong justification and need to conduct a future RCT in 'at-risk' cognitively healthy participants with incident dementia or AD as the primary outcome. Such a trial is likely to require at least a 5-year intervention period and several thousand per intervention arm, given the long prodrome and AD incident rates. Careful enrichment of the trial with an at-risk responsive population based on such factors at *APOE* genotype status, cardiovascular risk profile, baseline EPA+DHA status, education attainment, brain imaging and blood biomarker profiles is key to success. Consideration should also be given not only to the LC omega-3 PUFA dose, but the EPA:DHA ratio and chemical form.

9. FINAL THOUGHTS

The prospective and experimental evidence for the role of DHA in brain function and the cognitive benefits of increased fish, and LC n-3 PUFA intakes are convincing with large effect sizes. It is likely that EPA and DHA have complementary neurophysiological benefits, which includes an effect on oxylipin production, and should be co-supplemented or ideally consumed as oily-rich fish. Confirmation of the cognitive benefits is needed from well-designed RCTs which include large population subgroups who are likely to be most responsive and gain most benefit. Accumulating evidence suggests that *APOE4* carriers have a lower brain uptake and status and would particularly benefits from DHA intervention prior to any significant neuropathology, which affects brain DHA uptake.

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11. CONFLICTS OF INTEREST

The authors have no conflicts of interest to report.

Table 1: Select randomised controlled trials of nutrition interventions to improve cognition

Study	Population	Intervention	Duration	Outcome	Comment
van de Rest et al., (2008)**[144]**	Cognitively Healthy (n=302, 70y)	High dose: 847mg DHA + 1,093mg EPA per day Low dose: 176mg DHA + 226mg EPA per day	6 months	No effect on a range of range of cognitive domains	Plasma concentrations of EPA+DHA increased by 238% in the high-dose and 51% in the low-dose groups compared with placebo
Dangour et al., (2010)**[149]**	Cognitively Healthy (n=867, 74y)	500mg DHA + 200mg EPA per day	24 months	No effect on the California Verbal Learning Test (CVLT)	No effect on global cognitive function, Memory, Processing, Executive and Global delay z scores. High fish intake at baseline in some (Table 1) Lack of expected cognitive decline in the control arm
Quinn et al., (2010)**[143]**	Mild to moderate AD (n=402, 76y)	2g DHA per day	18 months	No effect on the Alzheimer's Disease Assessment-cognition Scale (ADAS-cog) No effect on CDR	Supplementation did not slow cognitive decline in patients with AD MMSE and ADAS-cog improved in *APOE4* non-carriers
Yurko-Mauro et al., (2010)**[146]**	SMC (n=485, 70y)	900mg DHA per day	6 months	Improved CANTAB Paired Associate Learning (PAL), a visuospatial learning and episodic memory test	DHA also improved immediate and delayed Verbal Recognition Memory scores but not working memory or executive function
Stonehouse et al., (2013)**[145]**	Healthy adults (n=228, 33y)	1160mg DHA + 170mg EPA per day	6 months	Effect on memory accuracy and reaction time (RT)	Screening process only recruited those with a low habitual intake of EPA + DHA of < 200mg/week

Andrieu et al., (2017)**[147]**	SMC (n=1680, 70y)	Multi-domain intervention with 800 mg DHA and 225 mg EPA per day or EPA+DHA alone	36 months	No effect of the multi-domain intervention and DHA+EPA alone	Cognitive tests included a composite score on the Free and Cued Selective Reminding test, ten Mini-Mental State Examination orientation items, Digit Symbol Substitution Test, and Category Naming Test.
Soininen et al., (2017 and 2020)**[150, 158]**	Prodromal AD (n=311, 71y)	1200mg DHA, 300mg EPA + phospholipids, uridine monophosphate, choline, vitamins B12, B6, folic acid, C, E, and selenium	24 months 36 months	No effect on the Neurocognitive Test Battery (NTB) primary outcome Effect on clinical dementia rating (CDR) Effect on hippocampal volume Effect on NTB Effect on CDR and memory Effect on hippocampal and whole brain volume	Unexpectedly lower rate of cognitive decline in the control group No effect on whole brain volume, memory or executive function No effect on Executive function
Zhang et al., (2018)**[159]**	MCI (n=240, 74y)	2g DHA per day	24 months	Effect on IQ, and information and digit span Effect on Aβ-42 level	Daily DHA may improve cognition and change Aβ-mediated autophagy
Danthiir et al., (2020)**[148]**	Cognitively healthy, (n=403, 73y)	1720mg DHA and 600 mg EPA per day	18 months	No effect of treatment on reasoning, working memory, short-term memory, retrieval fluency, and cognitive speed-related constructs.	A negative main effect was found on psychomotor speed Some sex and *APOE* genotype interactions evident
Jackson et al., (2021)**[153]**	Healthy adults (n=310, 36y)	900mg DHA and 270mg EPA per day (DHA-rich oil), 360mg DHA and 900mg EPA per day (EPA-rich oil)	6 months	Both global accuracy and speed improved with EPA-rich oil compared with placebo and DHA-rich oil	Accuracy of memory was improved with EPA- compared with DHA- rich oil Both EPA- and DHA-rich oils showed trends towards reduced prefrontal cortex oxygenated haemoglobin

This table is by no means exhaustive. The RCTs included were > 6 months in duration and were selected to demonstrate the discordance between individual study findings

AD- Alzheimer's Disease, DHA- docosahexaenoic acid, EPA- eicosapentaenoic acid, MCI- mild cognitive impairment, SMC- subjective memory complaints,

Figure legends:

Figure (1): Dementia prevalence (%) by age group in the UK [3]

Figure (2): Main oxidative products (oxylipins) of arachidonic acid (AA), eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) metabolism. Adapted from *Schulze et al,* 2020 [98].

2-PGs: 2 series prostaglandins, 3-PGs: 3 series prostaglandins, 4-LTs: 4 series leukotrienes, 5-LTs: 5 series leukotrienes, ALOXs: Arachidonate Lipoxygenases, ALOX5AP: 5-Lipoxygenase Activating Protein, COX-2: cylcloxygenase-2, CYP-450: cytochrome-P450, DHEQs: dihydroxyeicosatetraenoic acids, DHET: dihydroxyeicosatrienoic acid, DiHDPA: dihydroxydocosapentaenoic acid, EDP: epoxydocosapentaenoic acid, EEQ: epoxyeicosatetraenoic acid, EETs: epoxyeicosatrienoic acid, HDHA: hydroxydocosahexaenoic acid, HEPE: hydroxyeicosapentaenoic acid, HETE: hydroxy-eicosatetraenoic acid, HpDHA: hydroperoxide intermediate of DHA, sEH: serum epoxide hydrolase enzyme, TX: thromboxanes.

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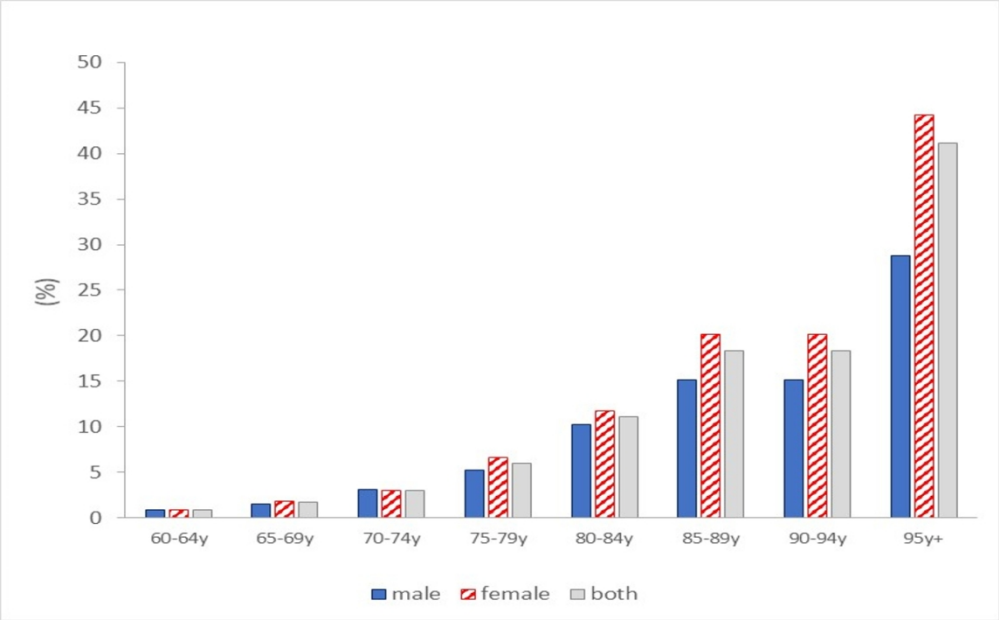

Figure (1): Dementia prevalence (%) by age group in the UK [3]

288x178mm (120 x 120 DPI)

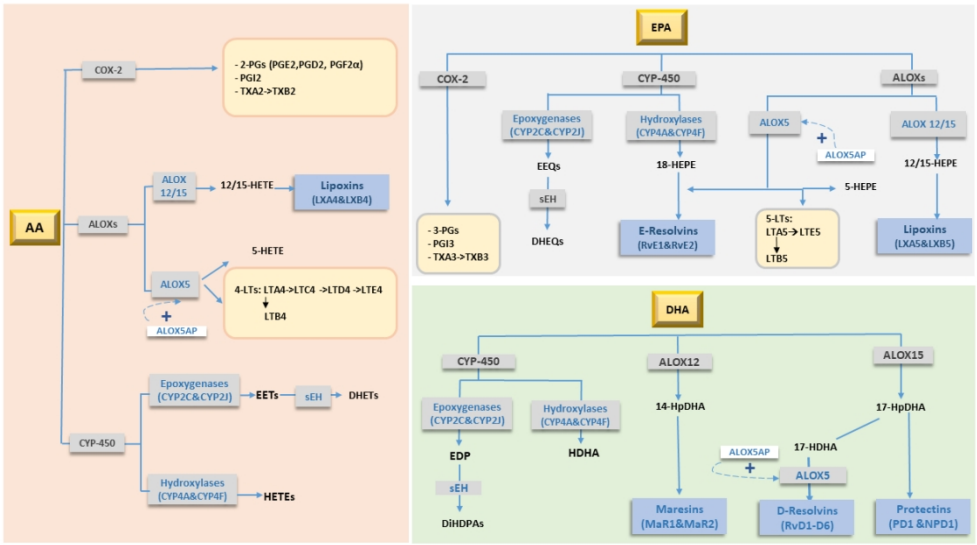

Figure (2): Main oxidative products (oxylipins) of arachidonic acid (AA), eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) metabolism. Adapted from Schulze et al, 2020 [98].

338x190mm (96 x 96 DPI)