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ORIGINAL INVESTIGATION

Docosahexaenoic acid-concentrated fish oil supplementation in subjects with mild cognitive impairment (MCI): a 12-month randomised, double-blind, placebo-controlled trial

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Abstract
Rationale Epidemiological studies have suggested a beneficial effect of fish oil supplementation in halting the initial progression of Alzheimer's disease. However, it remains unclear whether fish oil affects cognitive function in older people with mild cognitive impairment (MCI).
Objectives This study investigated the effects of fish oil supplementation on cognitive function in elderly person with MCI.
Methods This was a 12-month, randomised, double-blind, placebo-controlled study using fish oil supplementation with concentrated docosahexaenoic acid (DHA). Thirty six low-socioeconomic-status elderly subjects with MCI were randomly assigned to receive either concentrated DHA fish oil (n=18) or placebo (n=18) capsules. The changes of memory, psychomotor speed, executive function and attention, and visual-constructive skills were assessed using cognitive tests. Secondary outcomes were safety and tolerability of the DHA concentrate.
Results The fish oil group showed significant improvement in short-term and working memory (F=9.890; ηp^2=0.254; p<0.0001), immediate verbal memory (F=3.715; ηp^2= 0.114; p<0.05) and delayed recall capability (F=3.986; ηp^2=0.121; p<0.05). The 12-month change in memory (p<0.01) was significantly better in the fish oil group. Fish oil consumption was well tolerated, and the side effects were minimal and self-limiting.
Conclusions This study suggested the potential role of fish oil to improve memory function in MCI subjects. Studies with larger sample sizes, longer intervention periods, different fish oil dosages and genetic determinations should be investigated before definite recommendations can be made.

Keywords Fish oil · Mild cognitive impairment · Docosahexaenoic acid · Cognitive function · Memory

Abbreviations

AD	Alzheimer's disease
ADAS-cog	Cognitive section of the AD Assessment Scale
ANCOVA	Analysis of covariance
CDT	Clock drawing test
DHA	Docosahexaenoic acid

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EPA	Eicosapentaenoic acid
GDS	Geriatric depression scale
MCI	Mild cognitive impairment
MMSE	Mini-mental state examination
PUFAs	Polyunsaturated fatty acids
RAVLT	Rey Auditory Verbal Learning Test

Introduction

Mild cognitive impairment (MCI) is an emerging diagnosis that represents a transitional state between the cognitive changes of normal ageing and the fully developed clinical features of dementia (Petersen 2007). MCI has been the subject of continuous attention in the scientific community. Subsequently, an intensive approach has been conducted to investigate the potential of alternative agents to combat cognitive decline during ageing (Scholey et al. 2010; Cropley et al. 2012; Fagherazzi et al. 2012; Lee et al. 2012b; Lu et al. 2012; Macpherson et al. 2012), or at least reducing the progression from MCI to dementia, such as Alzheimer's disease (AD).

To date, studies of the effects of dietary omega-3 polyunsaturated fatty acids (PUFAs) on cognitive function have been receiving great attention. There is convincing evidence from epidemiological studies that marine omega-3 PUFAs may help to reduce the risk of developing dementia in late life (Sonobe et al. 2011). A decline in sensorimotor and complex speed was found in patients presenting with lower levels of eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA) and total omega-3 PUFAs (Schaefer et al. 2006; Dullemeijer et al. 2007; Milte et al. 2011). Studies from Japan and the USA suggested that supplementation with EPA or a combination of omega-3 and omega-6 fatty acids improved mini-mental state examination (MMSE) scores (Yehuda et al. 1996; Otsuka 2000) and improved cognitive dysfunction caused by organic brain damage or ageing (Kotani et al. 2006), while two other studies found no significant changes after an ethyl-EPA (Boston et al. 2004) or DHA supplement (Quinn et al. 2010) in delaying cognitive decline.

MCI is an increasing geriatric health problem in Asia, at least among elderly people with low socioeconomic status (Lee et al. 2012a). Recently, the Nakayama study found that the risk of progression from mild memory impairment to clinically diagnosable AD in a Japanese community was 10.6 % after 5 years' follow-up (Sonobe et al. 2011). There is a need to examine whether supplementation with these essential fatty acids among MCI (a pre-demented stage of AD) subjects would yield better outcomes. Therefore, the objectives of the present study was to conduct a 12-month, randomised, double-blind, placebo-controlled trial in order to determine the effectiveness of DHA-enriched fish oil supplementation on cognitive function, as well as its safety and tolerability among Malay and Chinese subjects with MCI.

Materials and methods

Subjects

Between December 2008 and May 2009, a total of 399 elderly people aged 60 years and above, no known physical or mental illness and ability to communicate, were successfully recruited from middle to low socioeconomic households in Cheras, Kuala Lumpur, Malaysia, to diagnose MCI. Subjects were recruited with the help of the Housing Management Officer, and residential representatives, as well as using posters, banners, invitation letters, informational lectures and word-of-mouth invitation. Briefly, the subjects were diagnosed as having MCI if they met the following conditions: (1) memory complaints, (2) preserved global cognitive function, (3) intact ADL and instrumental activities of daily living (IADL), (4) not demented, (5) not depressed and (6) abnormal cognitive impairments for age. Neuropsychological assessments were conducted by clinical psychologists, of which a prevalence of 21.1 % was reported elsewhere (Lee et al. 2012a).

Prior to the trial, all 67 MCI subjects were invited, visited and re-visited using a door-to-door approach in order to ensure optimum participation in the supplementation trial. The inclusion criteria were those diagnosed with MCI and staying in their own home and not currently living alone or on a waiting list for a nursing home. Those with any type of newly diagnosed neurodegenerative disease, psychiatric disease or mental disorder, taking omega-3 preparations, vitamin supplements/drinks/injections with doses of vitamin B6, folate or vitamin B12, vitamin E and ginkgo biloba for the past year; suffering from alcohol abuse or from a concomitant disease, such as uncontrolled diabetes, cancer and kidney failure; were not eligible for this trial. At baseline, 36 MCI subjects were enrolled in the trial, as shown in Fig. 1.

The study had obtained ethical approval from the Medical Research Ethics Committee, Universiti Kebangsaan Malaysia Medical Centre, and written informed consent for the study was obtained from all subjects.

Randomisation, assignment and masking

A 12-month, randomised, double-blind, placebo-controlled trial comparing fish oil supplementation high in DHA with placebo in subjects with MCI was conducted. Randomisation was achieved using computer-generated random numbers in stratified permuted blocks of size four. Stratification factors considered were age 60–74 years and ≥75 years, and gender. All subjects were randomly assigned to receive three

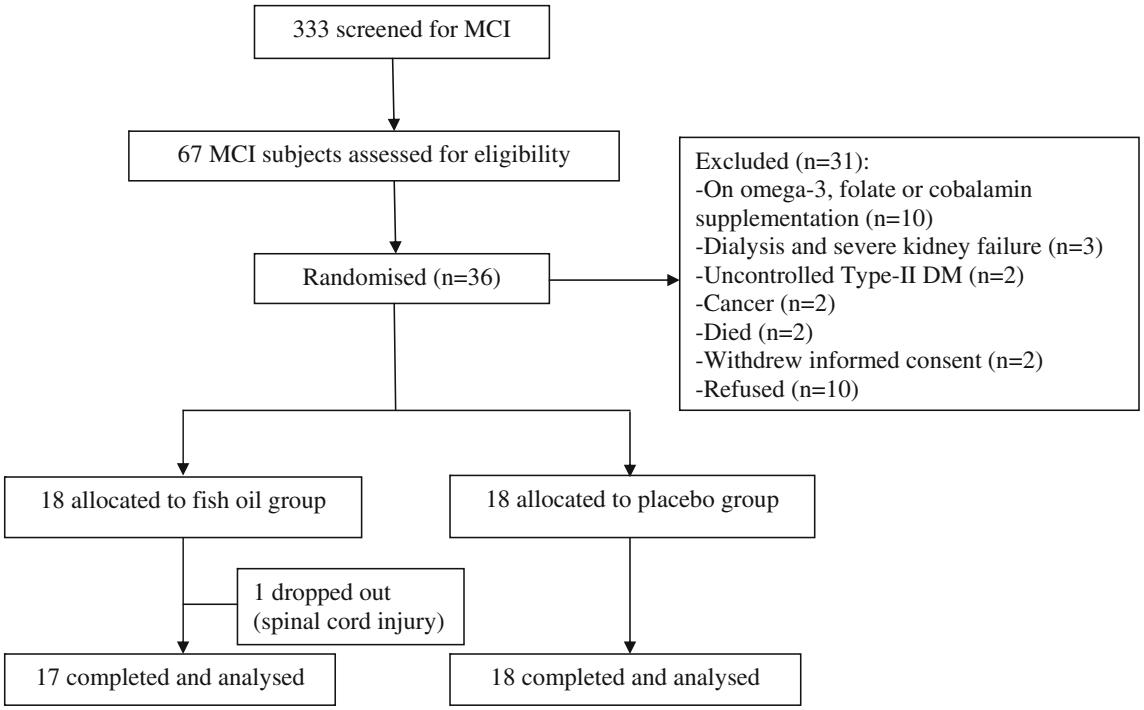

Fig. 1 Subjects recruitment and trial design

1-g soft gelatine capsules each day, each containing 430 mg of DHA and 150 mg of EPA (EPAX 1050TG; EPAX AS, Lysaker, Norway), or an isocaloric placebo corn oil (0.6 g linoleic acid) (Fig. 1). Both the EPAX 1050TG and placebo were visually identical and odourless. The total dosage for the fish oil group was approximately 1.3 g DHA and 0.45 mg EPA daily. The dose was decided on the basis of available literature on previous fish oil trials.

Intervention and follow-up

The trial was conducted at clinical trial ward, Universiti Kebangsaan Malaysia Medical Centre from March 2011 and completed in February 2012. All subjects were scheduled for a monthly appointment to ensure adherence to the study protocol. Compliance with the trial was assessed by capsule counts during the last week of each month, together with the replenishment of capsules for the following month. Subjects with low capsule consumption were reminded to take the capsules regularly as previously instructed.

Laboratory assay

Fasting venous blood samples were collected at baseline and after 6 and 12 months' intervention in order to measure trial compliance. The procedures involved the extraction of total lipid from plasma following the procedures described by Folch et al. (1957), transesterification of fatty acids methyl esters and quantification of the plasma fatty acid composition using gas chromatography. The fatty acid composition was expressed as a relative percentage of the total amount of fatty acids reported (%).

Outcome measures

Primary outcome measure was changes in cognition as assessed using selected neuropsychological tests. The battery comprised the following tests pertaining to different cognitive domains: memory [Visual reproduction I and II subtests from Wechsler Memory Scale–Revised (WMS-R) (Wechsler 1984), Rey Auditory Verbal Learning Test (RAVLT) (Rey 1964) and Digit span backward from Wechsler Adult Intelligent Scale–Revised (WAIS-R) (Wechsler 1997)], executive function and attention [Clock drawing test (CDT) (Sunderland et al. 1989) and Digit span forward (WAIS-R) (Wechsler 1997)], psychomotor speed [Digit symbol substitution test from WAIS-III (Wechsler 1997)], and visuospatial skills [Matrix reasoning and Block design from WAIS-III (Wechsler 1997)]. Geriatric depression scale (GDS) (Sheikh and Yesavage 1986) was used to measure depressive symptomatology. MMSE (Folstein et al. 1975) was used as a screening test for dementia and global cognitive function.

Safety and tolerability were monitored using a questionnaire, where subjects were asked to report any adverse effects or intolerance due to capsule consumption.

Other measurements

Information was obtained about socio-demography (chronological age, marital status and education level), lifestyle practices (such as smoking and exercise), past and current medical history, drug prescription and alcohol consumption. The completeness of the data was checked by a research assistant.

Statistical analysis

Data analysis of completers was performed. The differences between fish oil and placebo groups were examined with independent Student's *t* tests, paired *t* test and chi-square tests. Longitudinal changes in all neuropsychological assessments were assessed using repeated measures analysis of covariance. Bonferroni's test was used for multiple comparisons in post hoc analyses (all neuropsychological tests). A list of covariates was included to investigate the effects of fish oil supplementation on cognitive function due to the significance of mean difference at baseline. They included baseline age, baseline systolic and diastolic blood pressure. Years of schooling was considered as a potential covariate because education level may affect overall cognitive function as well. In addition, the cognitive domains were constructed with Z-scores, and the performance of memory, executive function and attention, psychomotor speed and visuospatial skills were evaluated. The treatment code was released once data analyses have been completed. Statistical analyses were conducted using the SPSS statistical software package (version 17.0; SPSS Inc., Chicago, IL, USA).

Results

Subjects

A total of 36 subjects were randomised to receive either fish oil supplementation or placebo for 12 months (Fig. 1). The remaining 31 MCI subjects were excluded because they were on omega-3 PUFAs or folate supplementation (n=10), dialysis and severe kidney failure (n=3), had uncontrolled DM (n=2), cancer (n=2), passed away (n=2), refused to participate (n=10) and withdrew informed consent (n=2).

At 3 months, one female participant from the fish oil group suffered a spinal cord injury and left the study. Thus, a total of 35 MCI subjects were included in the final analysis. As shown in Table 1, at baseline, the fish oil group was older (p=0.044) and had higher systolic (p=0.027) and diastolic blood pressure (p=0.003) than the placebo group.

Primary outcome measures

The effect of 12 months of fish oil supplementation versus a placebo on cognitive function in MCI subjects is summarised in Table 2. There were statistically significant treatment (time by group interaction) effects, with the fish oil group showing score improvements in digit span (F=9.890; ηp^2=0.254; p<0.0001), visual reproduction I (F=3.715; ηp^2=0.114; p<0.05), and RAVLT delayed recall (F=3.986; ηp^2=0.121; p<0.05) performance compared with the placebo group after controlling for age, education, and baseline systolic and diastolic blood pressure. However, no significant effects were observed either in the fish oil or placebo group with respect to MMSE, visual reproduction II, RAVLT total immediate recall, block design, digit symbol substitution, matrix reasoning, and CDT and GDS scores.

Memory and executive and attention functions improved significantly during the 1-year study in the fish oil group (Table 3). The 1-year change in cognitive function was significantly better in the fish oil group (p<0.01) than in the placebo group in terms of memory. Fish oil supplementation did not affect executive and attention, psychomotor speed and visuospatial skills (Table 3). Performance on MMSE (p=0.814) and GDS (p=0.068) were not affected by fish oil group.

Table 1 Baseline characteristics of fish oil and placebo groups

Characteristic	Fish oil group (n=17)	Placebo group (n=18)
Age[a]	66.4±5.1*	63.5±3.0
Malays[b]	12 (70.6)	12 (66.7)
Female sex[b]	14 (82.4)	13 (72.2)
Years of schooling[a]	5.9±3.0	5.8±3.3
Smoking[b]	2 (11.8)	3 (16.7)
Type II DM[b]	8 (47.1)	7 (38.9)
BMI (kg/m^2)[a]	28.2±4.5	27.7±3.5
Systolic BP (mmHg)[a]	142.3±21.8*	126.8±17.9
Diastolic BP (mmHg)[a]	79.6±10.3**	69.4±8.9
LA (%)[a]	0.15±0.30	0.22±0.32
EPA (%)[a]	0.37±0.52	0.58±1.08
DHA (%)[a]	2.09±1.38	2.02±1.31

*P<0.05, **P<0.01

[a] Data are given as mean±SD. The levels of omega-3 polyunsaturated fatty acids are expressed as percent total plasma lipid

[b] Values are the frequency with percentage in parentheses

[c] *LA* linoleic acid, *BMI* body mass index, *BP* blood pressure, *DHA* docosahexaenoic acid, *EPA* eicosapentaenoic acid

Secondary outcome measures

Plasma omega-3 PUFAs fatty acid composition

Subjects in the fish oil group showed an increase in the DHA and EPA content of 83.7 % and 121.6 %, respectively,

Table 2 Cognitive scores at baseline and after 6 and 12 months according to treatment group

Trial group	Baseline[a]	6 months[a]	12 months[a]
	MMSE scores (0–30 points)		
Fish oil	26.4 (25.096–27.658)	26.8 (25.783–27.818)	26.6 (25.668–27.550)
Placebo	26.4 (25.127–27.605)	26.6 (25.648–27.617)	26.5 (25.570–27.391)
	Digit span (1–19 points)		
Fish oil**	8.0 (6.994–9.036)	8.2 (7.058–9.363)	9.6 (8.437–10.749)
Placebo	8.5 (7.554–9.529)	8.4 (7.242–9.472)	8.0 (6.877–9.113)
	VR I (0–41 points)		
Fish oil*	20.0 (15.234–24.820)	27.6 (23.456–31.786)	29.2 (25.207–33.269)
Placebo	21.0 (16.394–25.666)	23.0 (18.941–26.997)	23.1 (19.154–26.952)
	VR II (0–41 points)		
Fish oil	13.3 (8.297–18.362)	19.7 (14.256–25.228)	20.8 (15.564–26.110)
Placebo	12.6 (7.710–17.445)	20.1 (14.827–25.438)	18.0 (12.943–23.143)
	RAVLT total immediate recall (0–75 points)		
Fish oil	35.1 (30.646–39.550)	39.3 (35.981–42. 594)	45.5 (42.706–48.291)
Placebo	32.7 (28.435–37.047)	37.4 (34.197–40.593)	40.1 (37.384–42.785)
	RAVLT delayed recall (0–15 points)		
Fish oil*	6.7 (4.897–8.442)	6.1 (4.399–7.878)	8.1 (6.645–9.462)
Placebo	6.1 (4.431–7.860)	6.4 (4.687–8.052)	5.0 (3.587–6.312)
	Block design (1–19 points)		
Fish oil	6.7 (5.347–8.102)	6.5 (5.189–7.787)	7.2 (5.908–8.489)
Placebo	7.7 (6.372–9.037)	7.3 (6.005–8.518)	8.2 (6.953–9.449)
	Digit symbol substitution (1–19 points)		
Fish oil	5.5 (3.723–7.218)	5.5 (3.723–7.218)	5.5 (3.723–7.218)
Placebo	4.9 (3.254–6.634)	4.9 (3.254–6.634)	4.9 (3.254–6.634)
	Matrix reasoning (1–19 points)		
Fish oil	7.6 (6.373–8.747)	6.8 (5.765–7.836)	7.1 (6.271–7.961)
Placebo	7.3 (6.156–8.453)	8.0 (6.964–8.968)	7.9 (7.073–8.708)
	CDT (0–10 points)		
Fish oil	7.3 (6.810–7.880)	7.9 (7.315–8.474)	7.8 (7.142–8.477)
Placebo	7.5 (6.935–7.969)	7.8 (7.261–8.383)	7.8 (7.145–8.436)
	GDS (0–12 points)		
Fish oil	2.5 (1.320–3.678)	2.3 (1.488–3.138)	1.9 (1.245–2.575)
Placebo	3.0 (1.888–4.169)	2.4 (1.573–3.169)	2.5 (1.887–3.172)

CDT clock drawing test, *GDS* geriatric depression scale, *MMSE* mini-mental state examination, *RAVLT* Rey Auditory Verbal Learning Test, *VR* visual reproduction

*$P<0.05$, indicates significant treatment effect compared with placebo; **$P<0.0001$, indicates extremely significant treatment effect compared with placebo

[a]Data are given as mean (95 % CI). Data are controlled for covariates: baseline age, total years of education, baseline systolic and diastolic blood pressure

in the plasma after the trial while no changes were observed for the placebo group.

Safety, tolerability and capsules compliance

Most subjects tolerated the supplementation. The main complaints were difficulty in swallowing the capsules (one subject each for fish oil and placebo groups), constipation (two subjects each for fish oil and placebo groups) and mild gastrointestinal discomfort (one subject each for fish oil group and placebo group). Compliance with the trial was high, with a capsule consumption rate for the fish oil and placebo groups of 94.5 % and 93.8 %, respectively.

Discussion

This study is the first randomised, double-blind, placebo-controlled trial to investigate the supplementation of DHA-concentrated fish oil for 12 months in improving cognitive function in elderly individuals with MCI. Compliance with the trial was excellent, with approximately two-fold increase in DHA and EPA for those treated with fish oil capsules. The dropout rate was only 2.8 %. There were no severe adverse events, and the side effects were minimal and self-limiting.

The present study used two distinct substances as the supplementation agents. However, there appears to be some doubtful blindness between the fish oil and placebo due to the fishy taste after consumption. Nevertheless, this fact alone did

Table 3 Change in cognitive domain mean Z-scores by groups over 12 months

	Fish oil (n=17)				Placebo (n=18)				Fish oil vs. placebo	
	Baseline	12 months	Change in cognitive performance	p	Baseline	12 months	Change in cognitive performance	p	Cognitive change attributed to fish oil[b]	p
Memory[a]	0.000 (0.692)	0.958 (0.711)	0.958 (0.764)	<0.0001***	−0.001 (0.627)	0.160 (0.625)	0.160 (0.587)	0.263	0.799 (0.339–1.258)	0.001**
Executive function/attention[a]	−0.003 (0.677)	0.519 (0.958)	0.522 (0.869)	0.025*	−0.003 (0.873)	−0.027 (0.981)	−0.238 (0.683)	0.884	0.545 (−0.122–1.213)	0.106
Psychomotor speed[a]	−0.001 (0.999)	0.085 (0.591)	0.086 (1.085)	0.748	−0.001 (0.999)	0.014 (0.442)	0.149 (1.048)	0.953	0.071 (−0.287–0.428)	0.690
Visuospatial skills[a]	−0.001 (0.809)	0.185 (0.618)	0.186 (0.841)	0.375	0.000 (0.799)	0.044 (0.820)	0.044 (0.600)	0.761	0.141 (−0.361–0.643)	0.571

Construction of cognitive domains using Z-scores:

$\text{Memory} = \left(Z_{\text{VisualreproductionI}} + Z_{\text{VisualreproductionII}} + Z_{\text{Reyauditoryverballearningtestimmediaterecall}} + Z_{\text{Reyauditoryverballearningtestdelayedrecall}} + Z_{\text{Digitspanbackward}}\right)/5$

$\text{Executivefunction/attention} = \left(Z_{\text{Clockdrawingtest}} + Z_{\text{Digitspanforward}}\right)/2$

$\text{Psychomotor speed} = Z_{\text{Digit symbol substitution test}}$

$\text{Visuospatialskills} = \left(Z_{\text{Blockdesign}} + Z_{\text{Matrixreasoning}}\right)/2$

*P<0.05, indicates significant treatment effect within group; **P<0.01, indicates significant treatment effect between groups; ***P<0.0001, indicates extremely significant treatment effect within group

[a] Data are given as mean (SD)

[b] Data are given as mean (95 % CI)

not appear to influence the outcome. Future studies should consider using a more effective blinding such as citrus flavouring to mask the fishy taste of the fish oil capsules.

Daily oral fish oil supplementation for 12 months in subjects with MCI beneficially affected memory function, particularly short-term and working memory, immediate visual memory and delayed recall capability. This indicated that MCI might be an intermediate and reversible phase if subjects were to receive fish oil. Nevertheless, the positive changes over time might be due to the augmentation of practice effect in subjects who are supplemented rather than an actual increase in cognitive abilities because the same sensitive tests were used in parallel sessions. Our findings were in agreement with other trials which reported a protective effect of fish oil supplementation on cognitive function in patients with normal cognition, MCI or mild stage AD (Freund-Levi et al. 2006; Chiu et al. 2008; Ng et al. 2011; Sinn et al. 2012). However, controversial findings have been reported to support the cognitive benefits of fish oil supplementation in patients with AD (Boston et al. 2004; Kotani et al. 2006; Shinto et al. 2008; Van de rest et al. 2008; Dangour et al. 2010; Quinn et al. 2010). We believe that the discrepancies in findings are mainly attributable to the extent of cognitive impairment. The subjects involved in this study were mildly impaired with respect to cognition, whereas many of the previous studies involved patients in a more progressive stage of the condition.

The mechanisms by which the beneficial effects of fish oil supplementation may enhance memory function in MCI subjects are not fully understood. DHA is abundant in the hippocampus of the human brain, which is involved in memory and spatial orientation (Pomponi 2008). DHA is important for neuronal functioning, maintaining membrane integrity, attenuation of amyloid β, and reducing inflammation and oxidative stress (Cunnane et al. 2009). The incorporation of DHA increases neuronal membrane fluidity and improves neurotransmission, which could be important in cognitive development and memory-related learning by increasing the neuroplasticity of nerve membranes, synaptogenesis and improve synaptic transmission (Fontani et al. 2005). EPA and DHA have been shown to potently modulate neuroinflammation by decreasing the production of eicosanoids from arachidonic acid, while DHA and its derivative metabolites inhibit the secretion of pro-inflammatory cytokines (Parker et al. 2006) while at the same time being substrate for the production of anti-inflammatory docosanoids (Calviello et al. 2008).

Previous epidemiological studies have found that a protective effect of omega-3 fatty acids with respect to dementia may be confined to apolipoprotein E (APOE) ε4 negative individuals (Huang et al. 2005; Barberger-Gateau et al. 2007; Whalley et al. 2008). Specifically, APOE ε4 negative participants who received DHA supplementation showed an

improving result on the ADAS-cog and MMSE scores (Quinn et al. 2010). As such, the beneficial effect of omega-3 fatty acids in APOE ε4 negative subjects and the absence of effect in APOE ε4 positive subjects may suggest that the adverse genetic effect of APOE ε4 allele on cognitive deficits is not easily reversible or negated by supplementation of omega-3 fatty acids. Due to the lack of available data, the gene–diet interaction of omega-3 fatty acids and APOE ε4 allele (both in Asian and non-Asian populations) on cognitive function needs to be further explored.

It is important to be highlighted that the subjects in this study were recruited from a low socioeconomic background, where the consumption of foods high in omega-3 PUFAs was inadequate due to financial constraints. The result suggested that fish oil supplementation in populations with a lower intake of seafood is beneficial since they may be more susceptible to memory dysfunction than populations with a more adequate intake of nutritious food. In addition, other dietary (such as folate and cobalamin intake) or non-dietary (such as environmental exposure) factors could have contributed to failure to observe the differences for other cognitive domains in this specific population. Future trials should consider a higher dose of fish oil supplementation to demonstrate a greater benefit across the test outcome.

The strength of this trial was its double-blind, randomised, placebo-controlled design. Besides, its low dropout rate increases the reliability of the presented data. Third, this study assessed cognitive changes with detailed and sensitive tests to detect the subtle effects of fish oil supplementation on cognitive function. A limitation of this study was that a majority of subjects had to be excluded, which may influence the trial outcomes. Additionally, it would be more valuable to obtain the APOE genetic profile to distinguish the possibility of this genetic polymorphism in affecting the roles of fish oil in modulating cognitive function.

In summary, the study presented encouraging results on the possible role of DHA-concentrated fish oil supplementation on memory function in subjects with MCI. However, no firm recommendation can be drawn from this data. Future studies should replicate this research in a different population with a larger sample size and longer follow-up period, and consider the effect of supplementation of DHA alone or with combination dosage of DHA and EPA before definite statements can be made. Comparative studies on the fish oil supplementation trial in different MCI subtypes are relevant to determine the most beneficial MCI subtypes.

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