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COGNITIVE CHANGES WITH OMEGA-3 POLYUNSATURATED FATTY ACIDS IN NON-DEMENTED OLDER ADULTS WITH LOW OMEGA-3 INDEX

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Abstract: *Objectives:* To investigate the changes in specific domains of cognitive function in older adults reporting subjective memory complaints with a low omega-3 index receiving omega 3 polyunsaturated fatty acid (n-3 PUFA) supplementation or placebo. *Design:* This is a secondary exploratory analysis of the Multidomain Alzheimer Preventive Trial (MAPT) using subjects randomized to the n-3 PUFA supplementation or placebo group. *Setting:* French community dwellers aged 70 or over reporting subjective memory complaints, but free from clinical dementia. *Participants:* A subgroup of MAPT subjects in the lowest quartile of omega-3 index distribution with baseline values ≤ 4.83 % (n = 183). *Intervention:* The n-3 PUFA supplementation group consumed a daily dose of DHA (800 mg) and EPA (a maximum amount of 225 mg) for 3 years. The placebo group received identical capsules comprising liquid paraffin oil. *Measurements:* Linear mixed-model repeated-measures analyses were used including baseline, 6, 12, 24 and 36-month follow-up data to assess between-group differences in the change in eight cognitive tests over 36 months. *Results:* There was less decline on the Controlled Oral Word Association Test (COWAT) in the n-3 PUFA supplementation group compared to placebo (p = 0.009; between group mean difference over 36 months, 2.3; 95% CI, 0.6,4.0). No significant differences for any of the other cognitive tests were found, including other tests of executive functioning, although, numerically all results were in favour of the n-3 PUFA supplementation. *Conclusions:* We found some evidence that n-3 PUFAs might be beneficial for the maintenance of executive functioning in older adults at risk of dementia with low omega-3 index, but this exploratory finding requires further confirmation. A larger specifically designed randomised controlled trial could be merited.

Key words: Omega 3 polyunsaturated fatty acids, executive functioning; cognition.

Abbreviations: AD: Alzheimer's disease; ApoE: apolipoprotein E; Aβ: β- amyloid; CDR: clinical dementia rating; CDR-SB: clinical dementia rating sum of boxes; COWAT: Controlled Oral Word Association Test; DHA: docosahexaenoic acid; DSST: Digit Symbol Substitution Test; EPA: eicosapentaenoic acid; FAME: Fatty acid methyl esters; FCSRT: Free and Cued Selective Reminding test; PUFAs: polyunsaturated fatty acids; MAPT: Multidomain Alzheimer Preventive Trial; MCI: mild cognitive impairment; MMSE: Mini Mental State Examination; n-3: omega 3; RCT: randomised controlled trial; TMT: Trail Making Test; WAIS-R: Wechsler Adult Intelligence Scale-Revised.

Introduction

Intervention trials investigating the effects of omega 3 polyunsaturated fatty acids (n-3 PUFAs) for improving/maintaining cognitive function during ageing have provided mixed results (1–7). However, a meta-analysis of ten randomised controlled trials (RCTs) has highlighted that n-3 PUFAs could be beneficial in terms of immediate recall, attention and processing speed in subjects with mild cognitive impairment (MCI), whilst having no effect on global cognition (8). Thus, n-3 PUFAs might be useful in prodromal AD specifically improving certain cognitive domains and we hypothesise only in those exhibiting low n-3 PUFA levels.

Our hypothesis is based on data from the Multidomain Alzheimer Preventive Trial (MAPT), in which participants on n-3 PUFA supplementation with a low omega-3 index (≤ 4.83 %: lowest quartile of omega 3 index distribution) at baseline, showed a trend towards less cognitive decline over 36 months in comparison to subjects on placebo with low baseline omega-3 index (p for interaction = 0.065) (9). Furthermore, participants on placebo with a low omega-3 index at baseline declined by 0.236 points on a cognitive composite score over 36 months (SE 0.072, p = 0.001), whereas those on placebo with a higher omega-3 index remained stable (mean change -0.0011, SE, 0.037, p = 0.776) (9). Here we sought to extend our findings by exploring the effects of n-3 PUFA supplementation on a number of cognitive tests in subjects exhibiting a low omega-3 index in order to obtain preliminary information on which cognitive domains might be affected by n-3 PUFA treatment in individuals with sub-optimal levels.

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Methods

The Multidomain Alzheimer Preventive Trial (MAPT): standard protocol approvals, registrations and patient consents.

MAPT was a large phase III, 36 month, multicentre, randomized, placebo-controlled trial (registration: NCT00672685). The trial had a four arm design comprising a placebo group and three treatment groups; n-3 PUFA supplementation, multidomain intervention (involving nutritional and exercise counselling and cognitive training) and n-3 PUFA supplementation plus multidomain intervention. The trial was designed to assess the efficacy of the interventions in slowing cognitive decline in older adults at risk of dementia (n=1680) (10). The primary efficacy outcome of MAPT was change from baseline to 36 months in a composite cognitive score combining four cognitive tests: the free and total recall of the Free and Cued Selective Reminding test (FCSRT), the Mini Mental State Examination (MMSE) Orientation subset, the Digit Symbol Substitution Test (DSST), and the Category Naming Test (CNT) (9). In the main analysis of MAPT, no significant effects of any of the interventions were found on the composite cognitive score compared to placebo after adjustment for multiple testing (9). The MAPT protocol was approved by the French Ethics Committee located in Toulouse (CPP SOOM II) and was authorised by the French Health Authority (Ministry of Health). Written consent was obtained from all participants.

Participants

MAPT participants were community-dwelling, men and women without dementia, aged ≥ 70 who met at least one of the following criteria: subjective memory complaints, limitation in executing ≥ 1 Instrumental Activity of Daily Living, or slow gait speed (≤ 0.8 meters/sec) (10). To rule out possible effects of the multidomain intervention on cognitive changes, only subjects randomized to the placebo or n-3 PUFA treated arms of MAPT categorized as having a low omega-3 index (those present in the lowest quartile of omega-3 index distribution ie, ≤ 4.83 %) were analyzed in this study. This amounted to 85 subjects from the placebo group and 98 subjects from the n-3 PUFA supplemented group.

Randomization and masking

Subjects were randomised to one of the four MAPT groups (1:1:1:1 ratio) using computer-generated randomisation procedures stratified by centre. The trial was double-blind for all subjects for n-3 PUFA supplementation or placebo allocation.

Intervention

Subjects allocated to the n-3 PUFA supplementation arm were asked to consume two soft capsules daily as a single dose, containing 400 mg per capsule of docosahexaenoic acid (DHA) and a maximum amount of 112.5 mg per capsule of eicosapentaenoic acid (EPA) for 3 years (10). This amounted to 800 mg of DHA per day and a maximum amount of 225 mg of EPA per day. The placebo group consumed two identical soft capsules per day for 3 years comprising flavoured paraffin oil. Blinding was ensured by the identical appearance (size, color, smell and shape) of the placebo and active capsules. Unused capsules were returned at each visit, and compliance was assessed by tablet count.

Fatty acid assessment

Lipids were extracted from red blood cells (RBC) with a mixture of hexane and isopropanol after acidification as previously described using gas chromotography (10, 11). Omega-3 index was calculated as the sum of % DHA + % EPA expressed as a % of total RBC fatty acids.

Cognitive tests

The following cognitive tests were used to evaluate cognitive changes over 36 months: the free and total recall of the FCSRT (score range 0-96) (12), the Clinical Dementia Rating Sum of Boxes (CDR-SB; score range 0-18) (13), the Controlled Oral Word Association Test (COWAT; number of words/ 2 minutes) (14), the MMSE orientation subset (score range 0-10), since the time domain has been shown to be a strong independent predictor of cognitive decline in the elderly (15), the MMSE total test (score range 0-30) (16), the Trail Making Test (TMT) part A and B (time to complete in seconds) (17), the DSST (symbols/90 seconds) from the Wechsler Adult Intelligence Scale-Revised (WAIS-R) (18) and the CNT (number of words/2 minutes) (14). Data from cognitive tests conducted at study baseline, then at 6, 12, 24 and 36 months were used in this study. Outcome assessors were blinded to participants' group allocation.

Statistical analysis

For the baseline characteristics, data is expressed as mean ± standard deviation (SD) or as frequencies/percentages. Baseline characteristics were compared between the n-3 PUFA supplemented group and the placebo group using chi squared tests for categorical variables and t-tests or Kruskal Wallis tests for continuous variables. The effects of n-3 PUFA supplementation on cognitive decline in subjects with low omega 3 index (≤ 4.83 %) was not an a priori hypothesis of the MAPT study. After completing analysis of the primary hypotheses in MAPT (9), we performed additional post-hoc analyses using a linear mixed-model repeated-measures (MMRM) model including baseline, 6, 12, 24 and 36-month follow-up data to assess between-group differences in the change in cognitive test scores from baseline to 36 months. For tests demonstrating a significant between group difference in change from baseline to 36 months ($P < 0.05$) we undertook a further sensitivity analysis in which the data were stratified according to compliance. Participants in the n-3 PUFA supplementation group were categorized as compliant

Table 1

Baseline characteristics of participants. Participants were in the lowest quartile of omega-3 index distribution allocated to either the placebo or omega 3 polyunsaturated fatty acid (n-3 PUFA) supplemented group of the Multidomain Alzheimer Preventive Trial (MAPT). Data is expressed as mean ± standard deviation or as frequencies/percentages

Variables	Placebo (n = 85)	n-3 PUFA (n = 98)	p value
Age (y)	76.0 ± 4.4	75.9 ± 4.7	0.886
Sex, women (%)	52 (61.2 %)	68 (69.4 %)	0.244
Education (%):			0.130
No diploma or primary school certificate	24 (28.6 %)	32 (33.3 %)	
Secondary education	26 (31.0 %)	39 (40.6 %)	
High school diploma	10 (11.9 %)	11 (11.5 %)	
University level	24 (28.6 %)	14 (14.6 %)	
Apolipoprotein E ε4 carriers (%)	16 (26.2 %)	15 (20.8 %)	0.463
Omega-3 index	4.0 ± 0.6	4.1 ± 0.6	0.135
Body mass index	26.6 ± 3.4	26.0 ± 3.5	0.193
Weight (Kg)	69.5 ± 11.8	67.3 ± 12.4	0.230
Gait speed (metres/second)	1.1 ± 0.3	1.1 ± 0.3	0.300
Free and total recall FCSRT [a]	71.5 ± 11.2	73.9 ± 9.3	0.123
DSST [b]	36.1 ± 10.2	36.5 ± 10.3	0.781
COWAT [c]	19.0 ± 6.3	18.6 ± 6.4	0.672
CNT [d]	24.9 ± 7.6	25.1 ± 7.5	0.872
Orientation MMSE [e]	9.8 ± 0.5	9.8 ± 0.5	0.460
MMSE [f]	27.9 ± 1.4	28.2 ± 1.7	0.237
CDR 0.5 [g]	39 (45.9 %)	44 (45.4 %)	0.944
CDR-SB [h]	0.3 ± 0.4	0.3 ± 0.4	0.880
TMT A [i]	48.6 ± 16.8	47.4 ± 17.8	0.689
TMT B [j]	137.2 ± 63.8	126.4 ± 67.0	0.150

a. FCSRT, Free and Cued Selective Reminding test (score range 0-96), b. DSST, Digit Symbol Substitution Test (symbols/90 seconds), c. COWAT, Controlled Oral Word Association Test (number of words/ 2 minutes), d. CNT, Category Naming Test (number of words/2 minutes), e. orientation MMSE, orientation Mini Mental State Examination (score range 0-10), f. MMSE (score range 0-30), g. CDR, Clinical Dementia Rating (range 0-3), h. CDR- SB, Clinical Dementia Rating Sum of Boxes (score range 0-18), i. and j. TMT part A and B, Trail Making Test part A and B (time to complete in seconds). n-3 PUFA = omega 3 polyunsaturated fatty acids; p = probability.

if they had taken ≥ 75 % of the supplementation capsules at 36 months otherwise they were deemed noncompliant (n = 70 ≥ 75 % compliance; n = 21 < 75 % compliance). P < 0.05 was considered statistically significant. Since this was an exploratory analysis, there was no correction for multiple comparisons. All analyses were performed using SAS software version 9.4 (SAS Institute Inc, Cary, NC).

Results

Baseline demographic and clinical characteristics of the participants included in this study are shown in Table 1. No significant differences between groups were found at baseline. The mean age of the participants was approximately 76 years and around 65 % of the population were female. Participants exhibited a moderately high level of education and almost half of the participants had a CDR score of 0.5. About one quarter of the subjects carried at least one ApoE ε4 allele and the mean omega-3 index was around 4.0 % before intervention. After 12 months of intervention the mean (± SE) increase in omega 3 index of the n-3 PUFA supplemented group was 4.71 % (± 0.21: p < 0.0001). The mean difference in omega 3 index (± SE) between the placebo group and the n-3 PUFA supplemented group at 12 months was 3.53 % (0.3: p < 0.0001). The mean (± SD) overall compliance to intervention at 36 months according to capsules taken was 83.8 % ± 21.0.

Table 2 shows changes in cognitive test scores over 36 months in the n-3 PUFA supplementation and placebo groups. Subjects in the n-3 PUFA supplementation group improved by 1.7 points on the COWAT over 36 months, whilst those in the placebo group declined by 0.6 points (p = 0.009; between group mean difference over 36 months, n-3 PUFA vs placebo, 2.3;

Table 2

Linear mixed model repeated measures (MMRM) analyses demonstrating the effects of omega 3 polyunsaturated fatty acid (n-3 PUFA) supplementation on change in cognitive test scores. Change in cognitive test score was assessed over 36 months (n-3 PUFA supplemented vs placebo). All subjects were in the lowest quartile of omega-3 index distribution at baseline (≤ 4.83 %)

	Change from baseline to 36M		Difference in change from baseline to 36M	
Cognitive Test [a]	**Placebo**	**n-3 PUFA**	**n-3 PUFA vs placebo [b]**	**n-3 PUFA vs placebo**
	Mean (95% CI)	**Mean (95% CI)**	**Mean (95% CI)**	**p value**
Free and total recall FCSRT	-0.8 (-2.8,1.1)	-0.3 (-2.1,1.4)	0.5 (-2.1,3.1)	0.691
DSST	-0.2 (-1.9,1.4)	0.9 (-0.6,2.4)	1.1 (-1.1,3.3)	0.325
COWAT	-0.6 (-1.9,0.7)	1.7 (0.6,2.8)	2.3 (0.6,4.0)	0.009
CNT	-1.3 (-2.9,0.3)	-0.7 (-2.1,0.8)	0.7 (-1.5,2.8)	0.544
Orientation MMSE	-0.2 (-0.4,-0.1)	-0.1 (-0.2,0.0)	0.1 (-0.1,0.3)	0.226
MMSE	-0.6 (-1.1,-0.1)	-0.5 (-0.9,-0.1)	0.1 (-0.5,0.8)	0.636
CDR-SB	0.8 (0.4,1.2)	0.3 (-0.1,0.6)	-0.5 (-1.0,0.0)	0.060
TMT A	0.4 (-3.0,3.8)	-1.8 (-4.8,1.2)	-2.2 (-6.7,2.4)	0.346
TMT B	6.1 (-8.3,20.4)	-7.9 (-20.8,4.9)	-14.0 (-33.3,5.2)	0.152

a. FCSRT, Free and Cued Selective Reminding test (score range 0-96), DSST, Digit Symbol Substitution Test (symbols/90 seconds), COWAT, Controlled Oral Word Association Test (number of words/ 2 minutes), CNT, Category Naming Test (number of words/2 minutes), orientation MMSE, orientation Mini Mental State Examination (score range 0-10), MMSE (score range 0-30), CDR- SB, Clinical Dementia Rating Sum of Boxes, (score range 0-18), TMT A, B, Trail Making Test part A and B (time to complete in seconds); b. A positive value for the "difference in change from baseline to 36M" reflects positive effects of the intervention (n-3 PUFA group) except for the CDR-SB and TMT part A and B for which a negative value reflects positive effects of the intervention (due to differences in test scoring). CI = confidence interval; m= month; n-3 PUFA = omega 3 polyunsaturated fatty acids; p = probability.

95% CI, 0.6,4.0). Although statistically non-significant, the n-3 PUFA supplemented group exhibited less cognitive decline as measured on all other cognitive tests compared to placebo.

Sensitivity analysis stratified according to compliance showed similar results as the main analysis for those compliant to medication. Subjects in the n-3 PUFA supplementation group deemed to be compliant improved by 2.1 points on the COWAT over 36 months, whilst those in the placebo group declined by 0.6 points (p = 0.003; between group mean difference over 36 months, n-3 PUFA vs placebo, 2.7; 95% CI, 0.9,4.5). In contrast, subjects in the n-3 PUFA supplementation group noncompliant to medication only improved by 1.3 points on the COWAT over 36 months, whilst those in the placebo group declined by 0.6 points (p = 0.221; between group mean difference over 36 months, n-3 PUFA vs placebo, 1.9; 95% CI, -1.2,5.1).

Discussion

In this exploratory analysis of a sub-group of MAPT participants we observed that there was less cognitive decline over 36 months on the COWAT, a test of executive functioning, in the n-3 PUFA supplementation group compared to placebo in subjects reporting subjective memory complaints with low omega-3 index. Stratification of the n-3 PUFA data according to compliance supported our main finding inasmuch as less cognitive decline was observed on the COWAT in compliant subjects over 36 months, but not in non-compliant subjects over the same time period. However, no other significant differences between groups were found on any of the other cognitive tests, even though subjects in the n-3 PUFA supplemented group exhibited numerically less cognitive decline compared to subjects on placebo on all eight cognitive tests employed here.

Several RCTs have investigated the effects of n-3 PUFAs on cognition in the elderly and mixed results have been reported, although it seems that n-3 PUFAs might be beneficial in non-demented subjects with memory complaints before the onset of clinical AD (2, 4, 8, 19, 20). It could be that differences in baseline n-3 PUFA levels might at least in part account for the mixed results observed with n-3 PUFA supplementation for the prevention of cognitive decline in past trials. In line with this, here we provide some evidence that executive functioning might be maintained with n-3 PUFA supplementation in older adults with subjective memory complaints and low omega-3 index, but this exploratory result requires validation. However on a cautionary note, we found no evidence of beneficial effects of n-3 PUFA treatment over placebo on other tests of executive functioning used in this study such as the TMT part A and B and the CNT (21). A number of other studies have also shown no effect of n-3 PUFA supplementation on executive functioning in healthy older adults with memory problems (3, 20, 22). Thus, our findings warrant further investigation in a larger sample with low omega 3 index before conclusions can be drawn.

There are a number of mechanisms through which n-3 PUFAs might act at a molecular level to prevent cognitive

decline in the elderly. n-3 PUFAs, particularly DHA which is the major fatty acid in the brain (23), form an integral part of neural membrane phospholipids and thereby impact upon multiple inter-related brain functions including cell membrane fluidity, signal transduction and neurotransmission (24–26). n-3 PUFAs also exert an anti-inflammatory action through the production of altered lipid mediators (27), which in turn is thought to influence the progression of neuropathology (28) . Thus, it seems likely that sub-optimal n-3 PUFA levels might modulate certain aspects of cognition either directly or indirectly through the alteration of the inflammatory milieu. This is an area of research that warrants further attention in relation to clinical cognitive outcomes.

The strengths of this study are the long duration of the intervention period, the focus on a population with low RBC levels of n-3 PUFA - indicative of low dietary intake, and the repeated assessments of cognitive function in elderly subjects at risk of dementia. The main limitation of this study is related to the fact that it is a post-hoc analysis of a larger RCT, meaning that the sample size was small and that the study was not specifically powered to detect a significant difference between groups. Furthermore, due to the exploratory nature of the study we analyzed n-3 PUFA treatment effects on a relatively large number of cognitive tests without correction for multiple comparisons, meaning that it is possible that the significant effect on the COWAT may have arisen due to chance alone. It is also possible that confounding factors, such as poor cardiovascular health and inflammatory conditions, that are associated with a low omega 3 index might drive the cognitive changes observed.

In conclusion, we provide preliminary evidence that n-3 PUFA supplementation might prevent decline in executive functioning in older adults at risk of dementia with a low omega-3 index. A larger and well-powered RCT designed to examine the effects of n-3 PUFA supplementation on cognitive function in older adults with a low omega 3 index, would provide further evidence as to which cognitive domains n-3 PUFAs specifically modulate. Of particular interest, an RCT looking at both the molecular and clinical effects of n-3 PUFA supplementation in the same population might bring new insight on the therapeutic potential of n-3 PUFAs from both a mechanistic and clinical perspective.

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