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To cite this version:
Julien Delrieu, Pierre Payoux, Isabelle Carrié, Christelle Cantet, Michael Weiner, et al.. Multidomain intervention and/or omega-3 in nondemented elderly subjects according to amyloid status. Alzheimer’s & Dementia: the Journal of the Alzheimer’s Association, 2019, 15, pp.1392 - 1401. 10.1016/j.jalz.2019.07.008 . hal-03489075

HAL Id: hal-03489075
https://hal.science/hal-03489075
Submitted on 21 Jul 2022

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Multidomain intervention and/or omega-3 in non-demented elderly subjects

according to amyloid status

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Word count: 3716.
ABSTRACT

Introduction

The Multidomain Alzheimer Preventive Trial (MAPT) assessed the efficacy of omega-3 fatty acid supplementation, a multidomain intervention (MI), or a combination of both on cognition. Impact according to cerebral amyloid status was evaluated by PET scan.

Methods

Participants were non-demented and had memory complaints, limitation in one instrumental activity of daily living, or slow gait. The primary outcome was a change from baseline in 36 months measured with a cognitive composite Z score.

Results

No effect was observed on cognition in the negative amyloid group (n = 167). In the positive amyloid group (n = 102), we observed a difference of 0.708 and 0.47 in the cognitive composite score between the MI plus omega-3 fatty acids group, the MI alone group and the placebo group, respectively.

Discussion

MI alone or in combination with omega-3 fatty acids was associated with improved primary cognitive outcome in subjects with positive amyloid status.

Keywords: MAPT; Multidomain intervention; Omega-3; PET; Amyloid; Prevention; Alzheimer

TRIAL REGISTRATION: ClinicalTrials.gov Identifier: NCT01513252.
1. Background

Multidomain intervention (MI) trials designed to prevent cognitive decline or dementia have very diverse target populations, although all trials excluded individuals with dementia at baseline. Three main types of target populations can be identified on the basis of the inclusion criteria of these trials: 1) elderly participants not selected on the basis of specific risk factors, 2) persons at risk (subjective cognitive decline, vascular risk and metabolic factors, sedentary lifestyle), and 3) cognitively impaired elderly subjects [1]. Therefore, in MI trials the potential target population is heterogeneous and no Alzheimer’s disease (AD) biomarkers are currently used to enhance inclusive population criteria. The use of AD biomarkers could identify a target population that is more responsive to MI.

The negative results of bapineuzumab [2] and solanezumab [3] phase III trials were an important methodological turning point in AD therapeutic trials. It was demonstrated that approximately 20 to 25% of the participants included in these trials showed no cerebral amyloid pathology. Evidence of an amyloid signature is therefore now essential to include participants in therapeutic “disease-modifying” trials [4]. Recent results of a phase Ib study evaluating the impact of aducanumab on brain amyloid burden and cognitive parameters (Mini-Mental State Examination (MMSE) and Clinical Dementia Rating (CDR)) are promising and appear to validate the use of amyloid biomarker assessment in preventive therapy trials [5].

The Multidomain Alzheimer Preventive Trial (MAPT) is a large and long-term trial designed to test whether a MI in combination with omega-3 fatty acid supplementation is effective in slowing cognitive decline in older at-risk adults. In the MAPT study, MI and polyunsaturated fatty acids, either alone or in combination, had no significant effects on cognitive decline in elderly subjects with memory complaints over a 3-year period [6]. In this ancillary amyloid
positron emission tomography (PET) MAPT study, amyloid PET scans were performed in a subgroup and the effects of the MAPT interventions were assessed according to patients’ amyloid status. Our hypothesis was that the impact of an intervention on primary cognitive outcome in the MAPT study differs according to amyloid status. Therefore, the main objective of this study was to determine the efficacy of MI and/or omega-3 fatty acid supplementation on cognitive composite scores according to amyloid status, based on a population of older adults from the ancillary amyloid PET MAPT study.

2. Methods

2.1 Study design and participants

All subjects enrolled in the ancillary amyloid PET study were participants in the MAPT study, a multicenter, randomized, placebo-controlled study. The MAPT protocol is registered on a public-access clinical trial database (www.clinicaltrials.gov, no. NCT01513252). The ancillary amyloid PET study protocol was approved by the French Ethics Committee in Toulouse in December 2007.

Subjects who were included were 70 years old and over and fulfilled at least one of the following three clinical criteria: spontaneous memory complaint, limitation in one instrumental activity of daily living [6], or slow gait. The ancillary amyloid PET study, using florbetapir radiotracer, was proposed to subjects enrolled in 10 centers close to nuclear medicine departments with amyloid PET imaging facilities (Bordeaux, Limoges, Montpellier, Nice and Toulouse). Subjects with dementia were not included in the trial. Written informed consent was obtained from all participants.

2.2 Randomization and masking

Participants were randomly assigned (1:1:1:1) to the combined intervention, MI plus placebo, polyunsaturated fatty acids only, or placebo only group. A computer-generated randomisation
procedure was used with block sizes of eight and stratification by centre A clinical research assistant, who was not involved in the assessment of participants, used a centralised interactive voice response system to identify which group to allocate the participant to, and which lot number to administer. This procedure was used in MAPT trial, inclusion in the amyloid PET MAPT study was realized after the randomization during the clinical follow-up. All participants and research staff were blinded to polyunsaturated fatty acid or placebo assignment and to amyloid status. Independent neuropsychologists were blinded to group assignment and to amyloid status.

2.3. Procedures

Participants took two capsules of either the placebo or polyunsaturated fatty acids daily (in a single dose, preferably at the same time each day and with food). The active supplement used was V0137, an oil mixture containing natural fish oil with a minimum of 65% docosahexaenoic acid (DHA) and a maximum of 15% eicosapentaenoic acid (EPA). The placebo capsules contained flavoured paraffin oil. The MI consisted of 2-hour group sessions focusing on three domains (cognitive stimulation, physical activity, and nutrition) and a preventive consultation at baseline and at 12 and 24 months. Each session included 60 min of cognitive training (reasoning and memory training), 45 min of advice about and demonstrations of physical activity, and 15 min of nutritional advice. The frequency and number of MI sessions have been described previously (12 sessions of 2-hours in the first two months, 1 session of 1-hour per month to reinforce the key messages, 2 sessions of 2-hours at 12 and 24 months) [6].

Clinical visits were scheduled every 6 months to assess physical condition (frailty assessment and self-reported physical activity), corresponding treatments, and adherence. Neuropsychological tests included the Free and Cued Selective Reminding Test (FCSRT,
episodic memory/recall) [7], the Controlled Oral Word Association Test and Category Naming Test (COWAT and CNT, verbal fluency) [8], the Digit Symbol Substitution Subtest of the Wechsler Adult Intelligence Scale–Revised (attention and executive function) [9], the Trail-Making Test (TMT, switching) [10], the MMSE [11] and the CDR [12].

PET scans were performed as close as possible to a clinical visit during the 3 years of follow up for each patient. However, we considered in our analysis that all the scans were carried out at the baseline visit by collecting them cross-sectionally. Subjects were examined using five different hybrid PET/CT scanners: one PET/CT 690 (GE Healthcare), one Discovery RX VCT (GE Healthcare), two TruePoint HI-REZ (Siemens Medical Solutions) and one Biograph 4 Emission Duo LSO (Siemens Medical Solutions) [13]. All tomographs operated in 3D detection mode. All PET sinograms were reconstructed with an iterative algorithm, with corrections for randomness, scatter, photon attenuation and decay, which produced images with an isotropic voxel of 2 × 2 × 2 mm and a spatial resolution of approximately 5 mm full-width at a half-maximum at the center of the field of view. The acquisition data were processed using the standard package delivered with each acquisition system. All cerebral emission scans were begun 50 min after injection of a mean of 4 MBq/kg weight of 18F-AV45. In each subject, 10-min or 15-min frames were acquired to ensure movement-free image acquisition.

2.4. Adherence

For supplementation, adherence was assessed by counting the number of capsules returned by participants. For MI, adherence was calculated as the percentage of intervention sessions attended. Participants were deemed adherent if they attended at least 75% of the MI group sessions (if applicable) and returned less than 25% of the prescribed capsules. Given the limitation in assessing omega-3 supplementation by counting the number of capsules returned
by participants, adherence was also evaluated by concentrations of DHA and EPA in red blood cell membranes with biological samples obtained at baseline and after 12 months.

2.5. Primary outcome

The primary outcome measure was the change in cognitive composite score after a 3-year follow-up. Based on a review of the literature on preclinical AD [14], we used a composite of four measures that were established to show sensitivity to decline in the early stages of AD. The MAPT cognitive composite score was calculated by combining the standardized Z score (using baseline means and standard deviations) of the following four cognitive tests and dividing the sum by 4, for baseline, 6, 12, 24 and 36 months respectively:

- Total recall score + free recall score (0-96 words),
- CNT (animals in 2 minutes),
- Digit Symbol Substitution Test score (0-93 symbols), and
- MMSE orientation score (0-10 points).

2.6. Classification of amyloid PET scans

Semi-automated quantitative analysis (cortical to cerebellar regional mean standardized uptake values, SUVr) was applied using the mean signal of six predefined anatomically relevant cortical regions of interest (frontal, temporal, parietal, precuneus, anterior cingulate and posterior cingulate) with the whole cerebellum used as the reference region. For this procedure, the 18F-AV45 PET images were coregistered to the 18 F-AV45 template provided by Avid Radiopharmaceuticals and previously published [15]. Quality control based on a semiquantification process was also provided by Avid. Based on the literature, the positivity threshold for amyloid PET was set at SUVr >1.17 [16,17].

2.7. Statistical analysis
Analysis was conducted in the intention-to-treat (ITT, n = 269), per-protocol (n = 256), and per-protocol with adherence ≥ 75% (n = 192) populations for the sample of subjects who had an amyloid PET scan (n = 271). Efficacy in subgroups according to the presence of brain amyloid (defined by cortical SUVr >1.17) was assessed by post-hoc analysis.

Intention-to-treat included all randomly assigned participants with a composite score at baseline who completed at least one post-baseline visit. The per-protocol population excluded all major protocol violations (participants who did not meet the inclusion or exclusion criteria, did not receive at least one dose of polyunsaturated fatty acid supplement or did not attend at least one MI session, did not receive the intervention to which they were allocated, changed treatment arm during the trial, or took non-study polyunsaturated fatty acid supplements during follow-up. In the per-protocol with adherence population, participants were deemed adherent if they attended at least 75% of MI group sessions (if applicable) and took at least 75% of the prescribed capsules.

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 composite score from baseline to 36 months. Time was used as a continuous variable. All confidence intervals (CIs) were two-sided with a 95% confidence level. All P values were presented before and after adjustment for multiple comparisons (using the Hochberg procedure) and the statistical significance was set at a P value < .05. All the models were completed with and without adjustments for gender, age, level of education, global CDR score, apo-E4 genotype and time of PET (period between baseline visit and PET scan).

All statistical analyses were performed using SAS software version 9.4 (SAS Institute Inc, Cary, NC). For each linear mixed model, we included subject-specific random effects to take into account the intra-subject correlation: a random intercept to take into account the
heterogeneity of the composite score at baseline and a random slope to take into account the heterogeneity of the slopes between subjects. In the unadjusted linear mixed models, we included the following fixed effects: intervention group according to their amyloid status (8 categories), time, and interaction between group and time. Then, to test the difference of the effect of the intervention between the negative and positive amyloid groups, we used the estimates of the interaction term parameters with the ESTIMATE command in the SAS MIXED procedure.

3. Results

3.1. Enrollment and rates of study completion

Among the 1,680 participants in the MAPT study, 271 amyloid PET scans were performed in this ancillary study at baseline (10 subjects) and at 6 months (52 subjects), 12 months (92 subjects), 24 months (108 subjects) and 36 months (9 subjects). Subjects were enrolled between July 12, 2010, and November 12, 2012. Initially, participation in the ancillary study was proposed only during baseline, 6-month and 12-month visits, and from October 2011 it was proposed during all visits. The flow chart of participants in the ancillary amyloid study is shown in Fig. 1. At baseline, spontaneous memory complaint was present in 266 (98.88%) of the 269 participants, limitation in one IADL in 18 (6.69%) and slow walking speed in 31 (11.61%). Thirty-eight (14.23%) participants reported two of these factors and 4 (1.5%) reported all three factors.

The ITT population included 269 subjects (102 positive and 167 negative amyloid PET subjects). In the positive amyloid ITT sample, 89 (87.3%) subjects completed follow-up. In the negative amyloid ITT sample, 153 (91.6%) subjects completed follow-up.

FIG. 1

3.2. Baseline characteristics
At baseline, subjects who participated in this ancillary study were significantly younger (on average 74.74 ± 4.26 vs. 75.46 ± 4.44 years, \( P = .010 \)), had a slightly higher MMSE score (28.28 ± 1.50 vs. 28.03 ± 1.61, \( P = .018 \)) and a lower TMT B test score (112.93 ± 42.95 vs. 124.56 ± 66.53, \( P = .017 \)) than subjects included in the MAPT study who did not participate in this ancillary study.

Baseline characteristics of the 269 participants included in the ITT analysis are presented in Table 1. In positive amyloid participants, the ITT population included 102 subjects. The four groups differed for free recall (\( P = .0334 \)) and delayed free recall (\( P = .0115 \)) on the FCSRT and global CDR score (\( P = .0096 \)), but did not differ for free recall and total recall on the FCSRT (\( P = .0632 \)), apo-E4 status (\( P = .3995 \)), MMSE orientation score (\( P = .4678 \)), intervention compliance (\( P = .0151 \)) and cognitive composite score (\( P = .6186 \), Table 1).

In negative amyloid participants, the ITT population included 167 subjects. The four groups differed in level of education (\( P = .0144 \)) and intervention compliance (\( P = .0032 \)), but did not differ in terms of cognitive composite score (\( P = .9099 \), Table 1).

MI and polyunsaturated fatty acids adherences are presented in the table 1. In positive amyloid subjects, the concentrations of DHA and EPA in red blood cells, as indicator of adherence, were higher in the two groups receiving active supplementation (mean increase of 3.57% [SD 2.07] and 3.62% [1.61] in the MI plus omega-3 polyunsaturated fatty acids and polyunsaturated fatty acids alone groups, respectively) than in the two groups receiving placebo (mean change -0.09% [0.11] in the placebo group and +0.33% [2.07] in the MI alone group) at 12 months. In negative amyloid subjects, this concentration was higher in MI plus omega-3 polyunsaturated fatty acids (+3.92% [2.14]) and polyunsaturated fatty acids alone groups (+2.96% [2.26]) than in MI alone (+0.24% [1.74]) and placebo groups (-0.03% [1.92]).
3.3. Primary analysis

The results of the primary analysis are presented in Fig. 2 and table 2.

Negative amyloid group

In the three populations (intention-to-treat, per-protocol and per-protocol with adherence ≥ 75%), no intervention effect was observed on cognitive composite score change at 36 months in the negative amyloid group for any of the three interventions (MI plus omega-3 polyunsaturated fatty acids, omega-3 polyunsaturated fatty acids alone, MI alone).

Positive amyloid group

In the three populations with positive amyloid PET, we observed a significant positive effect of the intervention on the change in composite score in 36 months for the MI plus omega-3 polyunsaturated fatty acids group and the MI alone group.

In the ITT population, the composite score for the MI plus omega-3 polyunsaturated fatty acids group improved in 36 months (0.290, 95% CI = [0.015 to 0.564]) and was stable for the MI alone group (0.053, 95% CI = [-0.171 to 0.276]), whereas for the placebo group the composite score declined (-0.418, 95% CI = [-0.606 to -0.231]). Therefore, we observed a difference over the 36-month period of 0.708 (Hochberg \( P < .0001, 95\% \text{ CI} = [0.375 to 1.041] \)) in the cognitive composite criteria between the MI plus omega-3 polyunsaturated fatty acids group and the placebo group, and 0.471 (Hochberg \( P < .0034, 95\% \text{ CI} = [0.179 to 0.763] \)) between the MI alone group and the placebo group. The effect of the intervention on change in composite scores at 36 months for the MI plus omega-3 polyunsaturated fatty acids
and MI alone groups persisted after adjustment. The intervention had no effect on the composite score at 36 months for the omega-3 polyunsaturated fatty acids group (Hochberg $P = 0.1911$ without adjustment, Hochberg $P = 0.1356$ after adjustments).

Lastly, the effect of the intervention on the composite score at 36 months differed in the negative and positive amyloid groups with MI plus omega-3 polyunsaturated fatty acids and MI alone in the ITT population ($P = 0.0002$ and $P = 0.0033$ without adjustment, $P = 0.0040$ and $P = 0.0543$ with adjustments, respectively).

**TABLE 2 AND FIG. 2**

### 4. Discussion

In the positive PET subjects, significant differences in favor of the MI plus omega-3 polyunsaturated fatty acids group and the MI group were noted at 36 months. In the negative amyloid subjects, no significant differences in the primary outcome were observed. The negative amyloid placebo group showed no significant cognitive decline during the three years of clinical follow-up. This negative result is probably related to lack of power to detect a treatment effect in this group. However, this population does not appear to be a good target for an interventional trial. This result is consistent with the data in the literature which indicate that non-demented subjects with negative amyloid biomarkers show very slight cognitive decline [18].

With regard to cognition, the population in this ancillary study was heterogeneous. In the positive amyloid group, 57 subjects with CDR = 0 and 45 subjects with CDR = 0.5 were included. Therefore, the effects of MI plus omega-3 polyunsaturated fatty acids and MI alone were positive in early stages of AD [19, 20], probably in preclinical AD and in milder cognitive impairment due to AD because subjects with dementia due to AD were not included in the MAPT study.
If AD represents the effects of a chronic imbalance between Aβ production and Aβ clearance and this imbalance can be caused by numerous distinct factors, different strategies can be proposed in association to treat or prevent AD [21]. In MAPT, interventions appear to act in synergy, with a greater effect in the MI plus omega-3 polyunsaturated fatty acids group. MI has a probable symptomatic impact of increasing cognitive reserve with an initial cognitive effect that tends to dissipate over time. This symptomatic effect is potentially related to an effect on brain connectivity (better balance between local processing and global integration) and/or neuroplasticity [22]. Indeed, exercise and cognitive interventions could improve neuroplasticity through mental and physical skills linked to cognitive-associative brain circuits [23]. The mechanism of action of MAPT interventions among positive amyloid subjects is probably not exclusively symptomatic, MI alone or in combination could modify also potentially amyloid pathology. Some data in the literature could support this hypothesis. In FINGER trial, lifestyle intervention may be beneficial for cognition in older at-risk individuals even in the presence of APOE-related genetic susceptibility to AD [24]. In DIAN study, mutation carriers with high physical activity showed significantly better cognitive and significantly less AD-like pathology in cerebrospinal fluid than individuals with low physical activity [25]. Omega-3 polyunsaturated fatty acid supplementation may have also an effect on amyloid pathology. This has been demonstrated in vitro and in animal models of AD. In vitro studies have revealed that DHA substantially inhibits Aβ fibrillation and reduces amyloid-induced toxicity [26]. In animal models, DHA reduces amyloidogenic processing by decreasing β- and γ-secretase activity, whereas the expression and protein levels of BACE1 (β-site APP-cleaving enzyme, β-secretase) and presenilin-1 remain unchanged. DHA increases protein stability of α-secretase resulting in an increase in non-amyloidogenic processing [27]. In addition, human in vivo tests have shown that there is a link between omega-3 polyunsaturated fatty acids and amyloid pathology. Gu et al. found that in 1,219
cognitively healthy elderly subjects, a higher dietary intake of omega-3 polyunsaturated fatty acids was associated with lower plasma levels of Aβ42 [28]. A higher intake of vitamin B12, vitamin D and omega-3 polyunsaturated fatty acids was associated with a lower Aβ load in AD regions [29]. Higher serum DHA levels were inversely associated with AD-related biomarkers as brain amyloid load and medial temporal atrophy [30]. Targeted prevention can be achieved by classifying individuals into subpopulations that differ in their susceptibility to a particular disease. So, in MAPT, subpopulation with amyloid pathology seems to be a good subpopulation for targeted prevention with MI and omega-3 supplementation.

The strengths of our ancillary study were the long duration of the intervention period and the novel approach of testing a combined intervention involving both a nutritional supplement and a lifestyle intervention in non-demented subjects according to their amyloid status. Furthermore, our primary outcome was designed to be as similar as possible to the Alzheimer’s Disease Cooperative Study - Preclinical Alzheimer Cognitive Composite (ADCS-PACC). A previous study demonstrated that this can reliably measure the first signs of cognitive decline in populations at risk, and it is recommended by regulatory agencies for secondary prevention AD trials.

Our study has several limitations. The majority of amyloid PET scans were not completed at the baseline visit, but rather at 12 months (n = 94) and 24 months (n = 111). In this study, we hypothesized that amyloid status does not change during follow-up. Baseline amyloid status was defined by an amyloid PET scan, regardless of when it was performed. The literature shows that amyloid burden and status (positive or negative) change little over several years. In a study by Villemagne et al. of healthy controls followed for 75 months (n = 145), four negative amyloid PET scans became positive and no positive amyloid scans became negative. The change in amyloid status was even less in subjects with minimal cognitive impairment [31]. Therefore, the risk of amyloid status misclassification is marginal in our work. We also
mentioned the presence of some differences between groups at baseline. However, the effect of the intervention persisted after making adjustments for these differences. All participants were blinded to polyunsaturated fatty acids or placebo assignment but not to MI. It is thus possible that some of the differences between MI and placebo was simply attributable to the fact that individuals knew whether or not they were receiving MI. However, given the nature of this intervention, it would have been virtually impossible for the multidomain component of our intervention to be double-blind [32]. We also note that analysis of subjects according to their amyloid status was not pre-specified and was exploratory.

In summary, the ancillary amyloid MAPT study provides new data on the effects of MI in combination with DHA and EPA in non-demented amyloid subjects in maintaining cognitive function compared with the cognitive decline observed in the placebo group. This analysis was exploratory and the results require further confirmation. An ongoing trial is currently assessing the feasibility and impact of a multimodal lifestyle intervention in association with nutritional intervention in individuals with prodromal AD (NCT03249688, MIND-ADmini).
References


Contributors

JD, SA, and BV conceived and designed the study. Data were analyzed and interpreted by CC, JD, SA, IC, PP and BV. JD, SA, CC, and BV wrote the article, which was critically reviewed by all authors.

Acknowledgements/Conflicts/Funding Sources
Acknowledgments

The MAPT study was supported by grants from the Gérontopôle of Toulouse, the French Ministry of Health (PHRC 2008, 2009), the Pierre Fabre Research Institute (manufacturer of the polyunsaturated fatty acid supplement), Exonhit Therapeutics, and Avid Radiopharmaceuticals. This study was supported by the University Hospital Center of Toulouse. We are indebted to the investigators from the University Hospital of Toulouse, Hôpital de Tarbes, Hôpital de Foix, Hôpital de Castres, the University Hospital of Limoges, the University Hospital of Bordeaux, Hôpital de Lavaur, the University Hospital of Montpellier, Hôpital de Montauban, and the University Hospital of Nice for their participation in this study.

Members of the MAPT Study Group

Bruno Vellas, Sophie Guyonnet, Isabelle Carrié, Lauréane Brigitte, Catherine Faisant, Françoise Lala, Julien Delrieu, Hélène Villars, Emeline Combrouze, Carole Badufle, Audrey Zueras, Sandrine Andrieu, Christelle Cantet, Christophe Morin, Gabor Abellan Van Kan, Charlotte Dupuy, Yves Rolland, Céline Caillaud, Pierre-Jean Ousset, Bertrand Fougère, Sherry Willis, Sylvie Belleville, Brigitte Gilbert, Francine Fontaine, Jean-François Dartigues, Isabelle Marcet, Fleur Delva, Alexandra Foubert, Sandrine Cerda, Marie-Noëlle Cuffi, Corinne Costes, Olivier Rouaud, Patrick Manckoundia, Valérie Quipourt, Sophie Marilier, Evelyne Franon, Lawrence Bories, Marie-Laure Pader, Marie-France Basset, Bruno Lapoujade, Valérie Faure, Michael Li Yung Tong, Christine Malick-Loiseau, Evelyne Cazaban-Campistron, Françoise Desclaux, Colette Blatge, Thierry Dantoine, Cécile Laubarie-Mouret, Isabelle Saulnier, Jean-Pierre Clément, Marie-Agnès Picat, Laurence Bernard-Bourzeix, Stéphanie Willebois, Iléana Désormais, Noëlle Cardinaud, Marc Bonnefoy, Pierre Livet, Pascale Rebaudet, Claire Gédéon, Catherine Burdet, Flavien Terracol, Alain Pesce,

Declaration of interests

SA has received grants from Europe, Ipsen, and France Alzheimer’s, served as a consultant for Ipsen, Pierre Fabre, Lilly, Nestlé, Sanofi, and Servier, and received non-financial support from Biogen, Nutrition Santé, Pfizer, and Icon, and other forms of support from the AMPA Association. MW receives research-support grants from the US National Institutes of Health, the National Institute on Aging, and the National Institute of Mental Health (U19AG024904, P01AG19724, R01 MH098062, P50 AG23501, and R01MH101472), the US Department of Defense (W81XWH-12-2-0012, W81XWH-13-1-0259, W81XWH-14-1-0462, and W81XWH-14-2-0176), the Alzheimer’s Association (BHR-16-459161), the California Department of Public Health (13-12004 and 16-10054), the Alzheimer’s Drug Discovery Foundation (20150802), the Larry L. Hillblom Foundation (A-011-NET), the Patient-Centered Outcomes Research Institute (PPRN-1501-26817), the Global Alzheimer’s Platform Foundation, and the Monell Chemical Senses Center. The Brain Health Registry, for which he
is the principal investigator, receives support from the Rosenberg Alzheimer’s Project, the Ray and Dagmar Dolby Family Fund, Connie and Kevin Shanahan, Global Alzheimer’s Platform Foundation, Patient-Centered Outcomes Research Institute, General Electric, Monell Chemical Senses Center, the Stroke Foundation, Johnson & Johnson, Cogstate, and the Drew Foundation. He has served on scientific advisory boards for Pfizer, Alzheon, Eli Lilly and the Alzheimer’s Disease Neuroimaging Initiative, was a consultant for Synarc, Pfizer, Janssen, the Alzheimer’s Drug Discovery Foundation, Avid Radiopharmaceuticals, Araclon, Merck, Biogen Idec, BioClinica, and Genentech, holds stock options with Alzheon and has been provided with funding for academic travel by Pfizer, Kenes, the University of California, San Diego, Alzheimer’s Disease Cooperative Study, the University Hospital Center of Toulouse, Araclon, AC Immune, Nutricia, Eli Lilly, New York Academy of Sciences, the Alzheimer’s Association, Merck, the Alzheimer’s Drug Discovery Foundation, Tokyo University, Kyoto University, Weill-Cornell University, Rockefeller University, Memorial Sloan-Kettering Cancer Center, and Biogen Idec. BV receives grants from Pierre Fabre, Avid, Exonhit, AbbVie, Lilly, Lundbeck, MSD, Otsuka, Regeneron, Sanofi, Roche, AstraZeneca, LPG Systems, Nestlé, and Alzheon, and personal fees from Lilly, Lundbeck, MSD, Otsuka, Roche, Sanofi, Biogen, Nestlé, Transition Therapeutics, and Takeda. All the other authors declare no competing interests.
Table 1
Baseline characteristics of the intention-to-treat ancillary amyloid MAPT study population (n = 269)

<table>
<thead>
<tr>
<th>Subject characteristics</th>
<th>Negative (n = 167)</th>
<th>Positive (n = 102)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Omega-3 + MI</td>
<td>MI</td>
</tr>
<tr>
<td></td>
<td>(n = 56)</td>
<td>(n = 45)</td>
</tr>
<tr>
<td>Male gender, N (%)</td>
<td>23 (41.07)</td>
<td>17 (37.78)</td>
</tr>
<tr>
<td>Age in years, mean (SD)</td>
<td>74.75 (4.42)</td>
<td>74.35 (3.92)</td>
</tr>
<tr>
<td>Education, N (%)</td>
<td>8 (14.55)</td>
<td>9 (26.47)</td>
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<tr>
<td>No diploma or primary school certificate</td>
<td>15 (34.09)</td>
<td>3 (18.75)</td>
</tr>
<tr>
<td>High-school diploma</td>
<td>11 (32.33)</td>
<td>8 (21.62)</td>
</tr>
<tr>
<td>University level</td>
<td>12 (35.71)</td>
<td>12 (35.71)</td>
</tr>
<tr>
<td>ApoE4 carrier, N (%)</td>
<td>8 (35.48)</td>
<td>5 (17.86)</td>
</tr>
<tr>
<td>DHA (µg/g RBC), mean (SD)</td>
<td>30.20 (9.32)</td>
<td>29.44 (8.47)</td>
</tr>
<tr>
<td>SUV, mean (SD)</td>
<td>1.06 (0.07)</td>
<td>1.05 (0.08)</td>
</tr>
<tr>
<td>CDR score, N (%)</td>
<td>36 (64.29)</td>
<td>21 (46.67)</td>
</tr>
<tr>
<td>CDR = 0</td>
<td>20 (35.71)</td>
<td>9 (26.47)</td>
</tr>
<tr>
<td>CDR = 0.5</td>
<td>39.32 (4.12)</td>
<td>38.74 (6.04)</td>
</tr>
<tr>
<td>Code test score, mean (SD)</td>
<td>40.25 (4.05)</td>
<td>40.38 (4.07)</td>
</tr>
<tr>
<td>TMT A, mean (SD)</td>
<td>45.44 (15.17)</td>
<td>40.74 (8.36)</td>
</tr>
<tr>
<td>TMT B, mean (SD)</td>
<td>46.53 (15.97)</td>
<td>42.25 (13.63)</td>
</tr>
<tr>
<td>CNT score, mean (SD)</td>
<td>26.21 (6.54)</td>
<td>27.07 (7.10)</td>
</tr>
<tr>
<td>Other measures</td>
<td>39.32 (4.12)</td>
<td>38.74 (6.04)</td>
</tr>
<tr>
<td>ADCS-ADL PI/45, mean (SD)</td>
<td>40.25 (4.05)</td>
<td>40.38 (4.07)</td>
</tr>
<tr>
<td>GDS, mean (SD)</td>
<td>39.32 (4.12)</td>
<td>38.74 (6.04)</td>
</tr>
<tr>
<td>SPPB, mean (SD)</td>
<td>39.32 (4.12)</td>
<td>38.74 (6.04)</td>
</tr>
<tr>
<td>MLTPAQ (physical activity, min/week), mean (SD)</td>
<td>39.32 (4.12)</td>
<td>38.74 (6.04)</td>
</tr>
<tr>
<td>Adherence ≥75%, N (%)</td>
<td>32 (57.14)</td>
<td>24 (75.00)</td>
</tr>
</tbody>
</table>

Abbreviations: ADCS-ADL, Alzheimer’s Disease Cooperative Study–activities of daily living; CDR, Clinical Dementia Rating score; CNT, Category Naming Test; COWAT, Controlled Oral Word Association Test; DHA, docosahexaenoic acid; FCSRT, Free and Cued Selective Reminding Test; GDS, Geriatric Depression Scale; MLTPAQ, Minnesota Leisure Time Physical Activity Questionnaire (self report physical activity); MMSE,
Mini-Mental State Examination; SPPB, Short Physical Performance Battery; SUV, standardized uptake value; TMT, Trail Making Test.
### Table 2

Estimated mean difference in 3-year change from baseline on composite Z score for the three intervention groups compared with the placebo group

<table>
<thead>
<tr>
<th>Groups</th>
<th>n</th>
<th>Estimated mean within-group 3-year change from baseline (95% CI)</th>
<th>Estimated mean between-group difference in change from baseline (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>vs. placebo Hochberg $P$</td>
<td>Adjusted $P^*$</td>
</tr>
<tr>
<td></td>
<td></td>
<td>n</td>
<td>Hochberg $P$</td>
</tr>
<tr>
<td>ITT analysis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive amyloid PET</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multidomain plus polyunsaturated fatty acids</td>
<td>16</td>
<td>0.290 (0.015 to 0.564)</td>
<td>0.708 (0.375 to 1.041)</td>
</tr>
<tr>
<td>Polyunsaturated fatty acids</td>
<td>28</td>
<td>-0.234 (-0.438 to -0.030)</td>
<td>0.184 (-0.093 to 0.461)</td>
</tr>
<tr>
<td>Multidomain plus placebo</td>
<td>23</td>
<td>0.053 (0.0171 to 0.276)</td>
<td>0.471 (0.179 to 0.763)</td>
</tr>
<tr>
<td>Placebo</td>
<td>35</td>
<td>-0.418 (-0.606 to -0.231)</td>
<td>-</td>
</tr>
<tr>
<td>Negative amyloid PET</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multidomain plus polyunsaturated fatty acids</td>
<td>56</td>
<td>0.065 (-0.080 to 0.210)</td>
<td>-0.075 (-0.309 to 0.160)</td>
</tr>
<tr>
<td>Polyunsaturated fatty acids</td>
<td>32</td>
<td>0.075 (-0.114 to 0.264)</td>
<td>-0.064 (-0.328 to 0.199)</td>
</tr>
<tr>
<td>Multidomain plus placebo</td>
<td>45</td>
<td>0.036 (-0.128 to 0.199)</td>
<td>-0.104 (-0.350 to 0.142)</td>
</tr>
<tr>
<td>Placebo</td>
<td>35</td>
<td>0.140 (-0.044 to 0.324)</td>
<td>-</td>
</tr>
<tr>
<td>Per-protocol analysis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive amyloid PET</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multidomain plus polyunsaturated fatty acids</td>
<td>15</td>
<td>0.299 (0.100 to 0.588)</td>
<td>0.718 (0.372 to 1.064)</td>
</tr>
<tr>
<td>Polyunsaturated fatty acids</td>
<td>28</td>
<td>-0.235 (-0.442 to -0.028)</td>
<td>0.185 (-0.096 to 0.466)</td>
</tr>
<tr>
<td>Multidomain plus placebo</td>
<td>19</td>
<td>0.059 (-0.189 to 0.307)</td>
<td>0.478 (0.166 to 0.791)</td>
</tr>
<tr>
<td>Placebo</td>
<td>35</td>
<td>-0.419 (-0.610 to -0.229)</td>
<td>-</td>
</tr>
<tr>
<td>Negative amyloid PET</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multidomain plus polyunsaturated fatty acids</td>
<td>52</td>
<td>0.103 (-0.049 to 0.255)</td>
<td>-0.034 (-0.277 to 0.209)</td>
</tr>
<tr>
<td>Polyunsaturated fatty acids</td>
<td>32</td>
<td>0.074 (-0.118 to 0.266)</td>
<td>-0.063 (-0.333 to 0.207)</td>
</tr>
<tr>
<td>Multidomain plus placebo</td>
<td>42</td>
<td>0.024 (-0.148 to 0.196)</td>
<td>-0.113 (-0.369 to 0.143)</td>
</tr>
<tr>
<td>Placebo</td>
<td>33</td>
<td>0.137 (-0.053 to 0.327)</td>
<td>-</td>
</tr>
<tr>
<td>Per-protocol adherence analysis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive amyloid PET</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Multidomain plus polyunsaturated fatty acids</td>
<td>11</td>
<td>0.293 (-0.033 to 0.619)</td>
<td>0.709 (0.322 to 1.095)</td>
</tr>
<tr>
<td>Polyunsaturated fatty acids</td>
<td>24</td>
<td>-0.181 (-1.0403 to 0.042)</td>
<td>0.235 (-0.069 to 0.539)</td>
</tr>
<tr>
<td>Multidomain plus placebo</td>
<td>14</td>
<td>0.197 (-0.092 to 0.486)</td>
<td>0.612 (0.257 to 0.968)</td>
</tr>
<tr>
<td>Placebo</td>
<td>29</td>
<td>-0.416 (-0.623 to -0.209)</td>
<td>-</td>
</tr>
<tr>
<td>Negative amyloid PET</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multidomain plus polyunsaturated fatty acids</td>
<td>32</td>
<td>0.131 (-0.060 to 0.322)</td>
<td>0.036 (-0.242 to 0.314)</td>
</tr>
<tr>
<td>Polyunsaturated fatty acids</td>
<td>24</td>
<td>0.065 (-0.158 to 0.288)</td>
<td>-0.030 (-0.331 to 0.270)</td>
</tr>
<tr>
<td>Multidomain plus placebo</td>
<td>29</td>
<td>0.096 (-0.107 to 0.299)</td>
<td>0.001 (-0.286 to 0.287)</td>
</tr>
<tr>
<td>Placebo</td>
<td>29</td>
<td>0.095 (-0.107 to 0.297)</td>
<td>-</td>
</tr>
</tbody>
</table>

Abbreviations: ITT, intention-to-treat; PET, positron emission tomography
*Analysis adjusted for age, sex, level of education, APO ε4 genotype, clinical dementia rating global score, and time of positon emission tomography.
Fig. 1. Trial profile for the ancillary amyloid MAPT study.

1,680 participants randomly assigned in MAPT study

417 assigned to combined intervention (omega-3 + multidomain intervention)

423 assigned to omega-3 intervention

420 assigned to multidomain intervention

420 assigned to placebo

During the clinical follow-up: 1,539 subjects assessed for eligibility in one of the centers with PET imaging facilities

1,268 subjects not included in the ancillary amyloid MAPT study:
- 705 subjects not eligible (out of time, early discontinuation)
- 414 subjects refused to participate
- 81 subjects did not attend the PET visit (technical problem, personal reason)
- 68 subjects included in the MAPT-NI (FDG-PET)

271 amyloid PET scans performed

2 subjects were excluded because no post-baseline cognitive assessment was available

269 subjects included in the intention-to-treat analysis

72 subjects received combined intervention (omega-3 + multidomain intervention)

60 subjects received omega-3 intervention

68 subjects received a multidomain intervention

69 subjects received a placebo

16 positive amyloid PET scans

56 negative amyloid PET scans

28 positive amyloid PET scans

32 negative amyloid PET scans

23 positive amyloid PET scans

45 negative amyloid PET scans

35 positive amyloid PET scans

34 negative amyloid PET scans

14 completed study

51 completed study

25 completed study

30 completed study

21 completed study

40 completed study

29 completed study

32 completed study

MAPT: Multidomain Alzheimer’s Preventive Trial; PET: Positron Emission Tomography; MI: Multidomain Intervention; MAPT-NI: MAPT-NeuroImaging
Fig. 2. Mean change from baseline in composite cognitive score over 36 months (intention-to-treat population, n=269).

MI : Multidomaine intervention; A+ : positive amyloid status ; A- : negative amyloid status
RESEARCH IN CONTEXT

**Systematic review:** In multidomain intervention (MI) trials, the potential target population is heterogeneous and no Alzheimer’s disease (AD) biomarkers are currently used to enhance inclusive population criteria. The use of AD biomarkers could help to identify a target population that is more responsive to MI.

**Interpretation:** A significant cognitive difference in favor of the combined intervention group and the MI alone group was observed over 36 months in subjects with a positive amyloid PET scan compared with the placebo group.

**Future directions:** This analysis was exploratory and these results need to be validated in further trials. Future research should also assess the impact of multidomain intervention on cerebral amyloid burden.