Effect of long-term omega 3 polyunsaturated fatty acid supplementation with or without multidomain intervention on cognitive function in elderly adults with memory complaints (MAPT): a randomised, placebo-controlled trial

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Summary

Background No large trials have been done to investigate the efficacy of an intervention combining a specific compound and several lifestyle interventions compared with placebo for the prevention of cognitive decline. We tested the effect of omega 3 polyunsaturated fatty acid supplementation and a multidomain intervention (physical activity, cognitive training, and nutritional advice), alone or in combination, compared with placebo, on cognitive decline.

Methods The Multidomain Alzheimer Preventive Trial was a 3-year, multicentre, randomised, placebo-controlled superiority trial with four parallel groups at 13 memory centres in France and Monaco. Participants were non-demented, aged 70 years or older, and community-dwelling, and had either relayed a spontaneous memory complaint to their physician, limitations in one instrumental activity of daily living, or slow gait speed. They were randomly assigned (1:1:1:1) to either the multidomain intervention (43 group sessions integrating cognitive training, physical activity, and nutrition, and three preventive consultations) plus omega 3 polyunsaturated fatty acids (ie, two capsules a day providing a total daily dose of 800 mg docosahexaenoic acid and 225 mg eicosapentaenoic acid), the multidomain intervention plus placebo, omega 3 polyunsaturated fatty acids alone, or placebo alone. A computer-generated randomisation procedure was used to stratify patients by centre. All participants and study staff were blinded to polyunsaturated fatty acid or placebo assignment, but were unblinded to the multidomain intervention component. Assessment of cognitive outcomes was done by independent neuropsychologists blinded to group assignment. The primary outcome was change from baseline to 36 months on a composite *Z* score combining four cognitive tests (free and total recall of the Free and Cued Selective Reminding test, ten Mini-Mental State Examination orientation items, Digit Symbol Substitution Test, and Category Naming Test) in the modified intention-to-treat population. The trial was registered with ClinicalTrials.gov (NCT00672685).

Findings 1680 participants were enrolled and randomly allocated between May 30, 2008, and Feb 24, 2011. In the modified intention-to-treat population (n=1525), there were no significant differences in 3-year cognitive decline between any of the three intervention groups and the placebo group. Between-group differences compared with placebo were 0·093 (95% CI 0·001 to 0·184; adjusted p=0·142) for the combined intervention group, 0·079 (–0·012 to 0·170; 0·179) for the multidomain intervention plus placebo group, and 0·011 (–0·081 to 0·103; 0·812) for the omega 3 polyunsaturated fatty acids group. 146 (36%) participants in the multidomain plus polyunsaturated fatty acids group, 142 (34%) in the multidomain plus placebo group, 134 (33%) in the polyunsaturated fatty acids group, and 133 (32%) in the placebo group had at least one serious emerging adverse event. Four treatment-related deaths were recorded (two in the multidomain plus placebo group and two in the placebo group). The interventions did not raise any safety concerns and there were no differences between groups in serious or other adverse events.

Interpretation The multidomain intervention and polyunsaturated fatty acids, either alone or in combination, had no significant effects on cognitive decline over 3 years in elderly people with memory complaints. An effective multidomain intervention strategy to prevent or delay cognitive impairment and the target population remain to be determined, particularly in real-world settings.

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Research in context

Evidence before this study

We searched PubMed and clinical trials registries (such as ClinicalTrials.gov, Current Controlled Trials, and the WHO International Clinical Trials Registry Platform) with the terms "(Alzheimer* OR dementia OR memory OR cognit*) AND prevent*" for articles published in English until May 11, 2015 (the date of our final search). We selected only trials that were specifically designed to assess efficacy on cognition, dementia, or a relevant biomarker (ie, those reporting an a-priori sample size calculation for cognitive outcomes, and assessing such outcomes at baseline). The results of this search up to May 11, 2015, were analysed in a published literature review.

Most prevention trials tested a single drug or intervention. The results of several trials suggested a protective effect of some interventions (antihypertensives, nutritional supplements, cognitive training, or physical activity) on cognitive decline, but these results have rarely been replicated in large samples. Several large multidomain trials of lifestyle factors have been designed in Europe in the past 12 years. The Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) study showed positive results on cognitive performance for a 2 year multidomain intervention (consisting of diet, exercise, cognitive training, and vascular risk monitoring) compared with general health advice. In addition to our trial, one other European preventive trial combined lifestyle intervention and supplementation: the ongoing Do-Health trial (for the prevention of age-related disease). In the USA, the focus has mainly been on pharmacological prevention trials, notably testing of anti-amyloid treatments, and several large trials have been implemented or designed, including A4 (Anti-Amyloid Treatment in Asymptomatic Alzheimer's), DIAN (Dominantly Inherited Alzheimer Network), API (Alzheimer's Prevention Initiative), and TOMMORROW.

Added value of the study

We tested supplementation with omega 3 polyunsaturated fatty acids and a multidomain intervention (integrating physical activity, cognitive training, and nutritional advice), either alone or in combination. To our knowledge, ours is the first trial to test the efficacy of a specific compound (ie, omega 3 polyunsaturated fatty acids) combined with multidomain lifestyle intervention versus placebo in a large sample and long-term. Our study is also the longest and largest randomised controlled trial so far testing the efficacy of omega 3 polyunsaturated fatty acids on cognitive decline in elderly adults, and the first to use a composite cognitive primary outcome measure recommended by regulatory authorities. Although results for the primary outcome did not reach significance in primary analysis, our study provides new data for the effect of a multidomain intervention and of its combination with polyunsaturated fatty acids.

Implications of all the available evidence

Taken together, the results of our study and previous studies offer new approaches for the prevention of age-related cognitive decline and Alzheimer's disease. Other preventive approaches with anti-amyloid drugs are expensive and difficult to implement in clinical practice. The interventions tested in our trial were safe and inexpensive, and exploratory analyses show the potential for slowing cognitive decline in people most at risk. However, an effective multidomain intervention strategy and target population remain to be determined, particularly in real-world settings.

Introduction

In the absence of a cure for dementia, interest in prevention and cognitive decline, the surrogate marker for dementia, is increasing.[1] So far, the aim of most trials has been to show efficacy of a single drug or intervention. The results of several trials have suggested that some single-domain interventions—such as antihypertensives, nutritional supplements, cognitive training, and physical activity[2]—have protective effects on cognitive decline, but these results have seldom been replicated in large samples. Supplementation with omega 3 polyunsaturated fatty acids, which have anti-inflammatory effects, might protect against cognitive decline and Alzheimer's disease: results from some cohort studies[3–5] examining the relationship between polyunsaturated fatty acids and cognitive decline or incident dementia are encouraging, but those from randomised controlled trials of up to 2 years' duration are conflicting.[2] Although the results of several trials of non-pharmacological multidomain interventions were positive, the efficacy of a specific compound in combination with lifestyle interventions compared with that of placebo has not been shown.[2]

We designed the Multidomain Alzheimer Preventive Trial (MAPT) to test the effect of supplementation with polyunsaturated fatty acids and a multidomain intervention (physical activity, cognitive training, and nutritional advice), alone or in combination, compared with placebo on cognitive decline in adults aged 70 years or older. We postulated that multidomain intervention plus placebo or supplementation with polyunsaturated fatty acids would have a protective effect on cognitive decline, and that the combined intervention would have a synergistic effect.

Methods

Study design and participants

Full methods have been described elsewhere previously.[6] Briefly, our study was a 3-year, multicentre, randomised, placebo-controlled superiority trial with four parallel groups, including three intervention groups (ie, one group with a multidomain intervention plus placebo, one group with polyunsaturated fatty acids and one

group with a multidomain intervention plus polyunsaturated fatty acids and one placebo group. Our trial was done at 13 memory centres in France and Monaco with expertise in the diagnosis and management of cognitive impairment and dementia.

Participants were aged 70 years or older and community-dwelling, and met at least one of three criteria: spontaneous memory complaint expressed to their physician, limitation in one instrumental activity of daily living,[7] or slow gait speed (≤0·8 m/s, or more than 5 s to walk 4 m).[8–10] Participants with a Mini Mental State Examination[11] (MMSE) score lower than 24, those in whom dementia was diagnosed, and those with any difficulty in basic activities of daily living[12] were excluded, as were those taking polyunsaturated fatty acid supplements at baseline. Full inclusion and exclusion criteria are listed in the appendix.

Participants were informed about the trial through diverse strategies based on site-specific resources, including investigating physicians' patient databases and advertisements (in local media and at conferences, which provided patients with a telephone number to call for more information). All participants were recruited by the investigating physicians, who verified inclusion and exclusion criteria and obtained written informed consent. The trial protocol was approved by the French Ethical Committee located in Toulouse (CPP SOOM II) and was authorised by the French Health Authority.

Randomisation and masking

Participants were randomly assigned (1:1:1:1) to the combined intervention (ie, the multidomain intervention plus polyunsaturated fatty acids), the multidomain intervention plus placebo, polyunsaturated fatty acids only, or placebo only. A computer-generated randomisation procedure (done by ClinInfo, a subcontractor) 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.

All participants and study staff were blinded to polyunsaturated fatty acid or placebo assignment—both sets of capsules looked and tasted identical. In view of the nature of the multidomain intervention, the study was unblinded for this component, but the independent neuropsychologists who were trained to assess cognitive outcomes were blinded to group assignment. Data analysts were not blinded to group assignment, but two data managers, one statistician (CC) and two physicians (SA and BV) did a blinded data review.

Procedures

Participants took two capsules of either placebo or polyunsaturated fatty acids daily. 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 total dose per capsule was 400 mg DHA and no more than 112·5 mg EPA. The total daily dose was fixed at a level that was high enough to exceed the daily recommended intake (ie, 250 mg DHA and 250 mg EPA), without exceeding the maximum daily intake limit of 2 g per day (as per the recommendations of l'Agence Française de Sécurité Sanitaire des Aliments, the French food safety authority) to avoid supplement-related adverse events. The study's scientific committee decided to use a dose that was higher than could be obtained through diet alone, to ensure that there was a true difference in intake of polyunsaturated fatty acids between the groups receiving the supplement and those receiving placebo (all participants could continue to consume fish during the trial). All capsules were supplied by Pierre Fabre Médicament (Castres, France). The placebo capsules contained flavoured paraffin oil.

See Online for appendix

The multidomain intervention consisted of 2 h group sessions focusing on three domains (cognitive stimulation, physical activity, and nutrition) and a preventive consultation (at baseline, 12 months, and 24 months) with a physician to optimise management of cardiovascular risk factors and detect functional impairments.[13] 12 small group sessions of the multidomain intervention were done in the first 2 months of the trial (two sessions per week in the first month, and one session per week in the second). Each session included 60 min of cognitive training (reasoning and memory training), 45 min of advice about and demonstrations of physical activity (participants were given advice during sessions and were encouraged to increase their physical activity in their daily life to the equivalent of at least 30 min walking per day, 5 days a week, and were provided with a home-based programme designed during individual interviews), and 15 min of nutritional advice (based on guidelines established by Programme National Nutrition Santé, the French National Nutrition and Health Programme).[14] For the remainder of the 3-year study, participants in the multidomain intervention groups attended a 1 h session each month to reinforce the key messages. Furthermore, two 2 h reinforcement sessions were held at 12 and 24 months (appendix).

Adherence to study interventions was assessed every 6 months. For supplementation, adherence was assessed by counting the number of capsules returned by participants (or based on treatment dates if the number of capsules was missing). Furthermore, biological samples were obtained at baseline and after 12 months to assess concentrations of DHA and EPA in red blood cell membranes, which has been detailed previously (results are expressed as a percentage of total fatty acids). For the multidomain intervention, adherence was calculated as the percentage of intervention sessions attended. Participants were deemed adherent if they attended at least 75% of the

multidomain group sessions (if applicable) and took at least 75% of the prescribed capsules. Self-reported physical activity was also measured as part of the frailty assessment, by using the Minnesota Leisure Time Physical Activity Questionnaire.

Outcomes

The primary efficacy outcome was change from baseline to 36 months in a composite *Z* score combining four cognitive tests (free and total recall of the Free and Cued Selective Reminding Test,[15] ten MMSE orientation items, the Digit Symbol Substitution Test score from the Wechsler Adult Intelligence Scale—Revised,[16] and the Category Naming Test[17] [ie, 2 min category fluency in animals]). Because of advances in the field since our trial was designed in 2007,[2] we decided to modify the primary outcome from one cognitive test to a composite cognitive score, which is now thought to be a better endpoint.[18] This protocol amendment was submitted to the local ethical committee on Feb 2, 2015, and was subsequently approved. Two different word lists were used at alternating visits for the Free and Cued Selective Reminding Test, to avoid learning effects. For all other tests or sub-tests, the same version was used at each visit.

Secondary outcomes were the individual components of the composite score, scores on other cognitive tests—ie, MMSE score, Trail Making Test A and B,[19] Controlled Oral Word Association Test,[17] and visual analogue scales measuring memory functioning and consequences in everyday life[20]—and scores on the Short Physical Performance Battery[21] and the Alzheimer's disease Cooperative Study—Activities of Daily Living Prevention Instrument.[22] Additional outcomes were Clinical Dementia Rating—Sum of Boxes,[23] Fried's frailty criteria,[24] and the Geriatric Depression Scale.[25]

All clinical and functional outcomes were assessed at baseline and at 6, 12, 24, and 36 months. Amyloid PET scans were done at five sites either at baseline or during follow-up (up to 36 months). Regional ^{18}F-florbetapir standardised uptake volume ratios were obtained via semi-automated quantitative analysis, in which the cerebellum was the reference region (further details have been published previously[26]). All adverse events and concomitant diseases and medications were recorded at 6, 12, 18, 24, 30, and 36 month follow-up visits during a consultation with a physician that included a physical examination. Blood sample analysis was also done at 6, 12, 24, and 36 months. Death and any other reasons for premature discontinuation of follow-up were recorded during follow-up and reported on a special form.

Statistical analysis

Before the primary outcome was changed from a single cognitive test to a composite cognitive score, the study was designed to detect a difference of 0·334 SD in the Free and Cued Selective Reminding Test score between any intervention group and the placebo group. To detect this difference, with an α risk of 1·25% and 80% power, 201 individuals were required in each group. To take into account the estimated attrition rate (30%) during the 3-year trial, a sample size of 1148 (ie, 287 participants per group) would be needed. A review of the first 480 recruited participants suggested that the dropout rate would be higher than initially expected (ie, 13–20% per year rather than 10% per year). A new sample size calculation was done for the Free and Cued Selective Reminding Test outcome, and it was subsequently decided to increase the sample size to 1680 (ie, 420 per group). No follow-up outcome data were analysed when this decision was taken. Furthermore, the baseline demographic data of the first participants suggested the presence of selection bias during recruitment because the level of education was higher than expected in the study sample, meaning that the rate of cognitive decline in 3 years would probably be lower than initially expected.[27]

The amendment to the protocol for the modification of the primary outcome to a composite cognitive score and statistical analysis plan was approved by the relevant local ethical and regulatory authorities before the masked data review and locking of the database. No follow-up data were analysed before this amendment. The composite score was the average of four *Z* scores. It was calculated by summing the *Z* scores (standardised with baseline means and SDs for each test from the intention-to-treat population) of each component and dividing the total by four. A *Z* score of –1, for example, represents a score that is 1 SD below the baseline mean. A one-point decrease on the composite score indicates an average decline of 1 SD across the four components.

The primary efficacy analysis was done on a modified intention-to-treat basis (ie, it included all randomly assigned participants with a composite score at baseline who completed at least one post-baseline visit) according to a predefined statistical analysis plan. Baseline characteristics of participants who were included in the intention-to-treat population were compared with those of excluded participants with *t* tests (in some cases after transforming the variable of interest), or with Wilcoxon rank sum tests for quantitative variables and χ^2 tests for qualitative variables. For participants diagnosed with dementia during follow-up, only cognitive scores before the diagnosis were taken into account. Further analyses were done in the per-protocol population, which excluded all major protocol violations—ie, participants who didn't fulfil the inclusion or exclusion criteria, didn't receive at least one dose of polyunsaturated fatty acids supplement or who didn't attend at least one multidomain intervention session, didn't receive the intervention they were allocated to, changed treatment arm during the trial (ie, crossover), or took non-study polyunsaturated fatty acids supplements during follow-up. Finally, we did two post-hoc factorial-style analyses, in which we compared 3-year cognitive decline in all participants receiving the multidomain intervention

with that in participants who did not receive the multidomain intervention, and in which we compared all participants receiving polyunsaturated fatty acids to all subjects taking placebo.

Two prespecified subgroup analyses were done according to baseline clinical dementia rating (CDR; CDR=0 *vs* CRD=0·5) and MMSE (MMSE=30 *vs* MMSE<30) scores. Other subgroup analyses were exploratory, such as red blood cell DHA and EPA concentrations (low level was defined by the lowest quartile—ie, ≤4·83%), Fried criteria (none *vs* at least one frailty criteria), and Cardiovascular Risk Factors, Aging, and Incidence of Dementia (CAIDE) risk score (≥6 [ie, at risk] *vs* <6).[28] Additional post-hoc subgroup analyses were also done according to *APOE* ε4 genotype, and the presence of brain amyloid deposition, in a subsample of the population who underwent a florbetapir PET scan, which was judged to be positive when standardised uptake value was 1·17 or greater.[29]

Efficacy analyses for the primary and secondary outcome measures were done with mixed-model repeated-measures analyses. We estimated trajectories with scores from all available study visits (baseline, and 6, 12, 24, and 36 month follow-up visits). Missing data were not imputed. Mixed models included all available data, including those from participants with incomplete follow-up; missing data were assumed to be missing at random. Even though the model can be used to estimate the overall effect of interventions on change with time, the prespecified primary comparison was the estimated between-group difference in change from baseline to 36 months. Time was used as a continuous variable, and we used maximum likelihood tests to assess the linearity of trajectories by testing terms for $(time)^2$ and $(time)^3$. We used restricted maximum likelihood tests to assess centre-specific random intercepts, participant-specific random intercepts, and participant-specific random slopes for all models; these random effects were retained in the model if they were significant.

In the primary analysis, the fixed effects included in the model were randomisation group, time, $(time)^2$, $(time)^3$, and the interactions between randomisation group and each time term. Additionally, participant-specific and centre-specific random intercepts, and participant-specific random slopes for all time terms were included in this model. An unstructured covariance matrix was used for the random effects. We did a post-hoc sensitivity analysis of the primary outcome, in which time was a categorical variable. The model specification for the secondary outcomes is detailed in the appendix. For the subgroup analyses, additional interaction terms were included in the fixed effects to test for between-subgroup differences in intervention effects. All analyses presented were unadjusted for covariates. We assessed model fit by verifying the normality of the residuals and the random distribution of the studentised residuals.

Safety analyses were done for all participants who received at least one dose of study drug or attended at least one multidomain intervention session. All adverse events, including those that were not necessarily related to the study intervention, were recorded and coded with Medical Dictionary for Regulatory Activities terminology in a centralised datacentre and reported by system organ class. Between-group comparisons were assessed with χ^2 tests.

All 95% CIs were two-sided and unadjusted. All p values are presented before and after adjustment for multiple comparisons (based on the Hochberg procedure)[30] at the two-tailed 5% significance level. This procedure was used to control for type I error, taking into account that, in each analysis, three intervention groups were compared with the placebo group. Statistical analyses were done in SAS (version 9.4). Safety analyses were done in STATA (version 11.2). Analyses were done by an academic team at Toulouse University Hospital, with input from an independent statistician for the safety analysis (Catherine Gentil).

Role of the funding source

The funders had no role in study design; data collection, analysis, or interpretation; or writing of the Article. The corresponding author and the statistician (CC) had full access to all data in the study. The corresponding author and the principal investigator (BV) had final responsibility for the decision to submit for publication.

Results

The first study centre opened on April 30, 2008, and the final 3-year follow-up visit was done on April 10, 2014. 2591 people were assessed for eligibility, and 1680 participants were enrolled and randomly allocated between May 30, 2008, and Feb 24, 2011 (figure). The final study visit was completed by 1286 participants (77%); completion rates were similar between groups (figure). The main reasons for early discontinuation were: participants' decision, adverse events, death, and loss to follow-up (figure). Reasons for early discontinuation did not differ significantly between groups at 36 months (p=0·79).

155 participants were excluded from the modified intention-to-treat efficacy analysis: no cognitive assessment was available after baseline for 154, and one participant in the polyunsaturated fatty acid group withdrew consent. Excluded participants were older (mean age 76·2 years [SD 4·8] *vs* 75·3 years [4·4]; p=0·014) and had lower cognitive function (mean MMSE score 27·7 [SD 1·7] *vs* 28·1 [1·6]; p=0.003) than participants who were included in the analysis. The number of participants excluded did not differ significantly between groups (figure; p=0·40). Baseline characteristics of the 1525 participants included in the modified intention-to-treat analysis were well balanced at baseline (table 1), with no substantial differences in any demographic or clinical characteristics.

The intervention effects on primary and secondary outcome measures in the modified intention-to-treat and per-protocol analyses are presented in table 2 and the appendix. In the primary efficacy analysis, the composite *Z* score of participants in the multidomain plus polyunsaturated fatty acids group improved by a mean of 0·024 points in 36 months, whereas the *Z* score of those in the placebo group fell by a mean of 0·069 points (between-group difference 0·093 [95% CI 0·001–0·184]), but this difference was not significant after correction for multiple comparisons (adjusted p=0·142; table 2). The mean differences in 3-year change from baseline on the composite *Z* score between the multidomain plus placebo group and the placebo group, and between the polyunsaturated fatty acid group and the placebo group were not significant (table 2). Post-hoc sensitivity analyses, in which time was a categorical variable in the mixed-effects model, did not significantly affect results (appendix). The impact of the combined intervention on the composite *Z* score was not significant in the per-protocol analysis compared with placebo (appendix).

In a post-hoc analysis, in which all participants who received the multidomain intervention were pooled, cognitive decline from baseline to 36 months, as measured with the composite *Z* score, was significantly less in those who had received the multidomain intervention than in those who did not receive this intervention (data not shown; p=0·015) in the modified intention-to-treat population. In a separate analysis in which all participants who received polyunsaturated fatty acids were pooled, cognitive decline did not differ significantly between those who received polyunsaturated fatty acids and those who did not (data not shown; p=0·715) in the modified intention-to-treat population.

In the modified intention-to-treat analysis of secondary outcomes, at 36 months, participants in the multidomain intervention groups showed less decline in the ten MMSE orientation items than those not in multidomain intervention groups, but the difference was only significant for the combined intervention group compared with the placebo group (mean difference 0·131 [95% CI 0·029–0·233]; adjusted p=0·036; table 2). Findings were similar in per-protocol analysis (appendix). The interventions did not significantly affect other secondary cognitive outcomes, depression, autonomy, or physical performance compared with the placebo group in either modified intention-to-treat or per-protocol analyses (table 2; appendix).

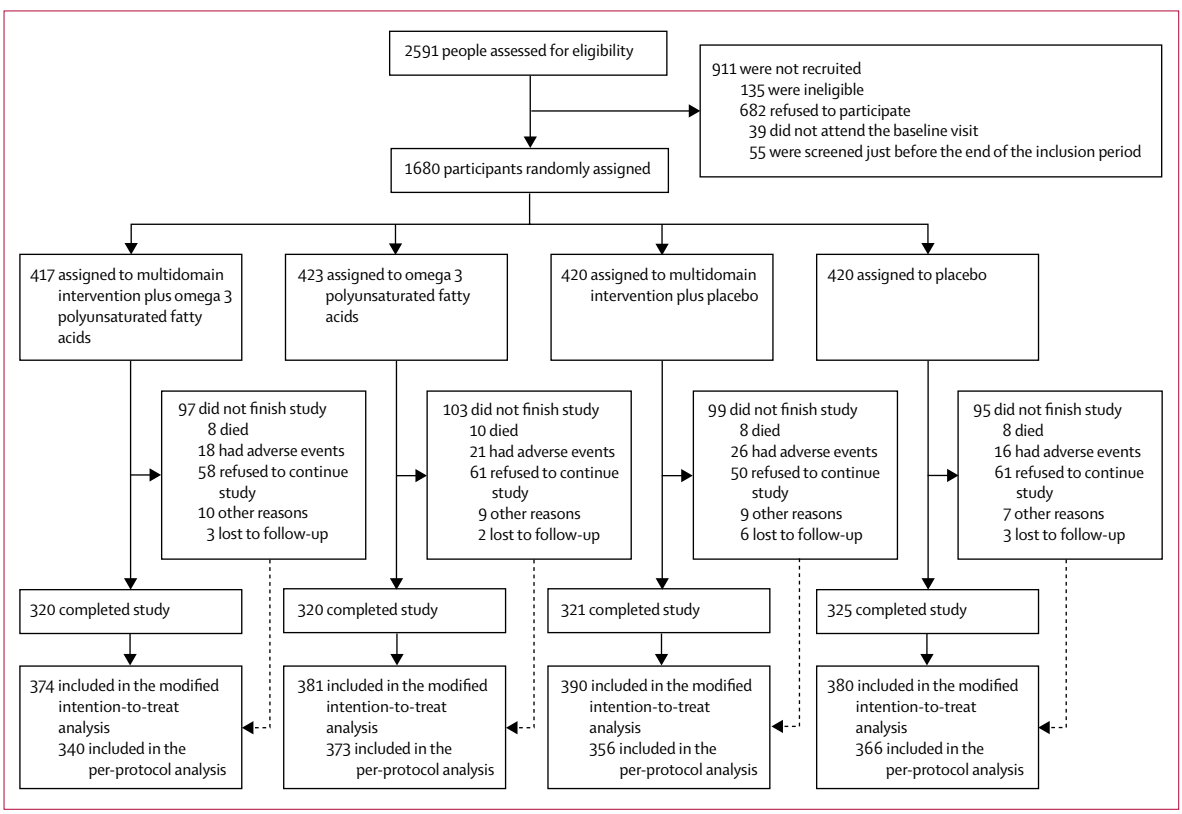

Figure: **Trial profile**
The modified intention-to-treat analysis included all randomly assigned participants with a composite score at baseline who completed at least one post-baseline visit. The per-protocol analysis excluded all major protocol violations—ie, participants who didn't fulfil the inclusion or exclusion criteria, didn't receive at least one dose of polyunsaturated fatty acids supplement or who didn't attend at least one multidomain intervention session, didn't receive the intervention they were allocated, changed treatment arm during the trial (ie, crossover), or took non-study polyunsaturated fatty acids supplements during follow-up.

In subgroup analyses, the effects of the interventions did not differ between groups according to *APOE* ε4 status (p=0·109; table 3). Cognitive decline in participants with a CAIDE score of 6 or greater at baseline was less in the combined intervention group than in the placebo group (p=0·023; table 3).

Table 4 summarises all adverse events. 1414 (86%) of 1652 subjects reported at least one adverse event and

	Multidomain plus polyunsaturated fatty acids (n=374)	Multidomain plus placebo (n=390)	Polyunsaturated fatty acids (n=381)	Placebo (n=380)	Overall (n=1525)
Age, years	75·4 (4·4)	75·0 (4·1)	75·6 (4·7)	75·1 (4·3)	75·3 (4·4)
Female sex	229 (61%)	252 (65%)	245 (64%)	252 (66%)	978 (64%)
Education					
No diploma or primary school certificate	75 (20%)	81 (21%)	96 (26%)	82 (22%)	334 (22%)
Secondary education	145 (39%)	129 (33%)	120 (33%)	117 (31%)	511 (34%)
High school diploma	52 (14%)	56 (15%)	43 (12%)	67 (18%)	218 (15%)
University level	100 (27%)	120 (31%)	108 (29%)	110 (29%)	438 (29%)
APOE ε4	71 (23%)	76 (24%)	64 (21%)	76 (24%)	287 (23%)
Composite score (mean *Z* score)	–0·04 (0·68)	0·00 (0·71)	0·03 (0·63)	0·02 (0·66)	0·00 (0·67)
Mini Mental State Examination	28·15 (1·57)	28·05 (1·62)	28·14 (1·60)	28·10 (1·53)	28·11 (1·58)
Clinical dementia rating					
0	223 (60%)	224 (57%)	220 (58%)	220 (58%)	887 (58%)
0·5	151 (40%)	166 (43%)	160 (42%)	160 (42%)	637 (42%)
Free and Cued Selective Reminding Test					
Free recall*	27·33 (6·49)	27·41 (6·86)	28·24 (6·55)	27·55 (6·80)	27·63 (6·68)
Total recall*	45·18 (3·55)	45·33 (3·87)	45·62 (3·19)	45·04 (4·37)	45·29 (3·78)
Delayed free recall†	10·51 (2·90)	10·62 (2·81)	10·94 (2·80)	10·76 (2·99)	10·71 (2·88)
Delayed total recall†	15·40 (1·23)	15·43 (1·24)	15·48 (1·13)	15·37 (1·53)	15·42 (1·29)
Trail Making Test					
Part A	47·13 (16·53)	46·38 (17·19)	46·15 (16·15)	46·08 (17·58)	46·43 (16·86)
Part B	121·09 (59·89)	118·64 (57·51)	125·96 (68·78)	120·25 (58·80)	121·45 (61·37)
Verbal fluency					
Category Naming Test	25·45 (7·08)	26·26 (7·53)	26·01 (7·53)	26·29 (7·55)	26·00 (7·43)
Controlled Oral Word Association Test	19·35 (6·28)	19·88 (6·60)	19·56 (6·59)	20·21 (6·56)	19·75 (6·51)
DSST (WAIS—R coding)	37·42 (9·70)	38·57 (10·51)	37·18 (9·74)	38·36 (9·87)	37·89 (9·97)
Memory functioning‡	49·97 (16·44)	49·53 (16·56)	49·40 (17·12)	50·28 (17·35)	49·79 (16·86)
Consequences of everyday life‡	39·18 (22·73)	41·19 (23·38)	38·90 (22·92)	40·22 (23·02)	39·88 (23·01)
Geriatric Depression Scale	3·17 (2·47)	3·20 (2·58)	3·27 (2·67)	3·21 (2·70)	3·21 (2·60)
ADCSADLPI	39·49 (4·85)	39·58 (4·93)	39·80 (4·59)	39·95 (4·82)	39·70 (4·80)
Fried Frailty Criteria—gait speed	1·10 (0·26)	1·09 (0·27)	1·09 (0·26)	1·10 (0·26)	1·09 (0·26)
Short Physical Performance Battery	10·55 (1·72)	10·66 (1·72)	10·57 (1·52)	10·66 (1·55)	10·61 (1·63)
Fried Frailty Criteria					
Involuntary weight loss	15 (4%)	19 (5%)	23 (6%)	12 (3%)	69 (5%)
Exhaustion	60 (16%)	55 (14%)	59 (16%)	59 (16%)	233 (15%)
Weakness (handgrip strength)	81 (22%)	82 (22%)	92 (25%)	78 (21%)	333 (23%)
Slow gait speed	18 (5%)	20 (5%)	13 (3%)	9 (2%)	60 (4%)
Low physical activity	53 (14%)	49 (13%)	57 (15%)	48 (13%)	207 (14%)
Presence of ≥1 criteria	160 (45%)	165 (44%)	180 (49%)	160 (44%)	665 (45%)
Blood pressure (mm Hg)					
Systolic	142·79 (20·28)	141·16 (18·88)	140·42 (19·51)	139·74 (19·93)	141·02 (19·66)
Diastolic	79·83 (11·95)	78·18 (11·28)	78·27 (11·40)	79·00 (11·37)	78·81 (11·50)
Body-mass index	26·19 (4·34)	26·04 (3·92)	26·32 (4·07)	25·99 (3·84)	26·13 (4·04)

Data are mean (SD), or n (%), unless otherwise specified. Percentages were calculated on the basis of the number of participants for whom data were available for each criterion. DSST=Digit Symbol Substitution Test. WAIS—R=Wechsler Adult Intelligence Scale—Revised. ADCSADLPI=Alzheimer's Disease Cooperative Study Activities of Daily Living Prevention Instrument. *48 is the total possible score. †16 is the total possible score. ‡Measured on a visual analogue scale.

***Table 1*: Baseline characteristics of the modified intention-to-treat population**

	Estimated mean within-group 3-year change from baseline (95% CI)				Estimated mean 3-year between-group difference in change from baseline (95%CI)								
	Multidomain plus polyunsaturated fatty acids (n=374)	Multidomain plus placebo (n=390)	Polyunsaturated fatty acids (n=381)	Placebo (n=380)	Multidomain plus polyunsaturated fatty acids *vs* placebo	Raw p value	Adjusted p value*	Multidomain plus placebo *vs* placebo	Raw p value	Adjusted p value*	Polyunsaturated fatty acids *vs* placebo	Raw p value	Adjusted p value*
Composite Z score	0·024 (0·041 to 0·089)	0·010 (−0·054 to 0·075)	−0·058 (−0·123 to 0·007)	−0·069 (−0·133 to −0·004)	0·093 (0·001 to 0·184)	0·047	0·142	0·079 (−0·012 to 0·170)	0·090	0·179	0·011 (−0·081 to 0·103)	0·812	0·812
Free and Cued Selective Reminding Test (free and total)	1·543 (0·672 to 2·414)	1·393 (0·531 to 2·255)	0·718 (−0·149 to 1·584)	1·794 (0·923 to 2·664)	−0·250 (−1·482 to 0·981)	0·690	0·690	−0·400 (−1·625 to 0·824)	0·521	0·690	−1·076 (−2·304 to 0·152)	0·086	0·258
DSST (WAIS—R coding)	0·457 (−0·194 to 1·109)	0·985 (0·340 to 1·630)	0·610 (−0·043 to 1·262)	0·501 (−0·144 to 1·146)	−0·044 (−0·961 to 0·873)	0·926	0·926	0·484 (−0·428 to 1·396)	0·298	0·894	0·109 (−0·809 to 1·027)	0·816	0·926
Category Naming Test	−0·574 (−1·235 to 0·088)	−0·537 (−1·196 to 0·122)	−0·837 (−1·498 to −0·175)	−0·678 (−1·335 to −0·021)	0·104 (−0·828 to 1·037)	0·826	0·826	0·141 (−0·790 to 1·072)	0·767	0·826	−0·159 (−1·091 to 0·774)	0·739	0·826
Ten MMSE orientation items	−0·027 (−0·099 to 0·045)	−0·056 (−0·128 to 0·016)	−0·148 (−0·221 to −0·076)	−0·158 (−0·230 to −0·086)	0·131 (0·029 to 0·233)	0·012	0·036	0·102 (0·000 to 0·204)	0·050	0·099	0·009 (−0·093 to 0·111)	0·861	0·861
Lexical Fluency Test (COWAT)	0·410 (−0·139 to 0·959)	0·938 (0·391 to 1·485)	0·634 (0·084 to 1·184)	0·251 (−0·295 to 0·797)	0·159 (−0·616 to 0·933)	0·688	0·688	0·687 (−0·086 to 1·460)	0·081	0·244	0·383 (−0·392 to 1·157)	0·333	0·665
MMSE	−0·180 (−0·368 to 0·008)	−0·183 (−0·370 to 0·004)	−0·305 (−0·494 to −0·116)	−0·299 (−0·486 to −0·112)	0·119 (−0·146 to 0·384)	0·379	0·775	0·117 (−0·148 to 0·381)	0·387	0·775	−0·006 (−0·272 to 0·260)	0·965	0·965
Trail Making Test (part A)	−3·154 (−4·762 to −1·546)	0·322 (−1·273 to 1·917)	0·079 (−1·528 to 1·687)	−2·270 (−3·862 to −0·678)	−0·885 (−3·148 to 1·378)	0·443	0·443	2·592 (0·338 to 4·846)	0·024	0·073	2·349 (0·087 to 4·611)	0·042	0·084
Trail Making Test (part B)	−2·495 (−7·599 to 2·609)	2·316 (−2·753 to 7·385)	−1·020 (−6·150 to 4·109)	−0·030 (−5·085 to 5·025)	−2·465 (−9·649 to 4·719)	0·501	0·787	2·346 (−4·813 to 9·505)	0·520	0·787	−0·990 (−8·192 to 6·211)	0·787	0·787
Memory functioning†	−2·620 (−4·263 to 0·976)	−0·230 (−1·861 to 1·400)	−0·080 (−1·721 to 1·561)	−0·871 (−2·501 to 0·759)	−1·749 (−4·063 to 0·566)	0·139	0·416	0·641 (−1·665 to 2·946)	0·586	0·586	0·791 (−1·522 to 3·104)	0·502	0·586
Consequences of everyday life†	−4·490 (−7·061 to −1·918)	−3·803 (−6·333 to −1·273)	−2·058 (−4·606 to 0·489)	−1·212 (−3·766 to 1·343)	−3·278 (−6·902 to 0·346)	0·076	0·229	−2·591 (−6·187 to 1·004)	0·158	0·315	−0·847 (−4·454 to 2·761)	0·645	0·645
Clinical Dementia Rating (sum of boxes)	0·304 (0·194 to 0·415)	0·363 (0·254 to 0·472)	0·284 (0·173 to 0·394)	0·297 (0·187 to 0·407)	0·008 (−0·148 to 0·163)	0·924	0·924	0·066 (−0·089 to 0·221)	0·404	0·924	−0·013 (−0·169 to 0·142)	0·867	0·924
Geriatric Depression Scale	0·280 (0·010 to 0·549)	0·126 (−0·143 to 0·394)	0·444 (0·174 to 0·715)	0·295 (0·027 to 0·562)	−0·015 (−0·394 to 0·365)	0·939	0·939	−0·169 (−0·548 to 0·210)	0·382	0·879	0·150 (−0·230 to 0·530)	0·439	0·879
ADCSADLPI	0·409 (−0·125 to 0·943)	0·349 (−0·177 to 0·875)	−0·592 (−1·123 to −0·061)	−0·008 (−0·539 to 0·523)	0·417 (−0·337 to 1·170)	0·278	0·349	0·356 (−0·391 to 1·104)	0·349	0·349	−0·584 (−1·335 to 0·167)	0·127	0·349
Fried Frailty Criteria—gait speed	−0·089 (−0·116 to −0·061)	−0·070 (−0·098 to −0·043)	−0·099 (−0·126 to −0·071)	−0·080 (−0·107 to −0·052)	−0·009 (−0·048 to 0·030)	0·655	0·655	0·009 (−0·029 to 0·048)	0·633	0·655	−0·019 (−0·058 to 0·020)	0·338	0·655
Short Physical Performance Battery	−0·325 (−0·509 to −0·141)	−0·189 (−0·372 to −0·006)	−0·378 (−0·563 to −0·193)	−0·260 (−0·443 to −0·077)	−0·065 (−0·325 to 0·195)	0·624	0·624	0·071 (−0·188 to 0·330)	0·591	0·624	−0·118 (−0·379 to 0·142)	0·374	0·624

DSST=Digit Symbol Substitution Test. WAIS—R =Wechsler Adult Intelligence Scale—Revised. COWAT=Controlled Oral Word Association Test. MMSE=Mini-Mental State Examination. ADCSADLPI=Alzheimer's Disease Cooperative Study Activities of Daily Living Prevention Instrument. *Adjusted for multiple comparisons with the Hochberg procedure to account for the fact that three intervention groups were compared with the placebo group in each analysis. †Measured on a visual analogue scale.

***Table 2*: Primary and secondary outcome measures in the modified intention-to-treat population**

	Multidomain plus polyunsaturated fatty acids *vs* placebo (n; 95% CI)	Raw p value (within-subgroup intervention *vs* placebo)	Adjusted p value* (within-subgroup intervention *vs* placebo)	p value (between-subgroup intervention *vs* placebo)	Multidomain plus placebo *vs* placebo (n; 95% CI)	Raw p value (within-subgroup intervention *vs* placebo)	Adjusted p value* (within-subgroup intervention *vs* placebo)	p value (between-subgroup intervention *vs* placebo)	Polyunsaturated fatty acids *vs* placebo (n; 95% CI)	Raw p value (within-subgroup intervention *vs* placebo)	Adjusted p value* (within-subgroup intervention *vs* placebo)	p value (between-subgroup intervention *vs* placebo)	p value (between-subgroup any intervention *vs* placebo)
Prespecified subgroups													
CDR 0·5	0·183 (151; 0·038 to 0·329)	0·014	0·041	0·117	0·113 (166; −0·028 to 0·255)	0·117	0·234	0·587	0·066 (160; −0·079 to 0·210)	0·371	0·371	0·346	0·453
CDR 0	0·034 (223; −0·083 to 0·151)	0·568	0·692	..	0·062 (224; −0·057 to 0·181)	0·305	0·692	..	−0·024 (220; −0·142 to 0·094)	0·692	0·692	..	..
MMSE <30	0·122 (292; 0·018 to 0·226)	0·022	0·066	0·245	0·084 (318; −0·019 to 0·187)	0·111	0·221	0·812	0·022 (309; −0·081 to 0·125)	0·679	0·679	0·710	0·681
MMSE=30	−0·008 (82; −0·201 to 0·185)	0·935	0·935	..	0·057 (72; −0·140 to 0·254)	0·569	0·935	..	−0·021 (72; −0·222 to 0·180	0·837	0·935	..	..
Exploratory subgroups (based on biomarkers)													
APOE ε4 carrier	0·240 (71; 0·042 to 0·439)	0·018	0·053	0·109	0·201 (76; 0·003 to 0·400)	0·047	0·094	0·189	0·176 (64; −0·034 to 0·385)	0·101	0·101	0·099	0·295
APOE ε4 non-carrier	0·053 (233; −0·060 to 0·167)	0·356	0·669	..	0·048 (242; −0·064 to 0·161)	0·397	0·669	..	−0·024 (243; −0·136 to 0·087)	0·669	0·669	..	..
Low DHA and EPA in red blood cells†	0·205 (96; 0·016 to 0·395)	0·034	0·102	0·191	0·157 (83; −0·039 to 0·353)	0·117	0·117	0·406	0·187 (98; −0·003 to 0·377)	0·054	0·109	0·065	0·303
Normal DHA and EPA in red blood cells†	0·061 (263; −0·043 to 0·165)	0·253	0·505	..	0·063 (283; −0·041 to 0·166)	0·234	0·505	..	−0·018 (264; −0·123 to 0·087)	0·739	0·739	..	..
No frailty criteria	0·098 (199; −0·027 to 0·223)	0·125	0·375	0·744	0·076 (212; −0·048 to 0·200)	0·232	0·384	0·913	0·057 (188; −0·071 to 0·185)	0·384	0·384	0·440	0·814
At least one frailty criteria	0·066 (160; −0·077 to 0·209)	0·364	0·729	..	0·086 (165; −0·057 to 0·229)	0·237	0·712	..	−0·017 (180; −0·156 to 0·121)	0·805	0·805	..	..
High dementia risk (CAIDE score ≥6)	0·131 (327; 0·031 to 0·230)	0·010	0·031	0·023	0·108 (329; 0·007 to 0·209)	0·036	0·071	0·115	−0·002 (326; −0·102 to 0·098)	0·967	0·967	0·678	0·032
Low dementia risk (CAIDE score <6)	−0·201 (35; −0·468 to 0·066)	0·139	0·418	..	−0·097 (56; −0·330 to 0·137)	0·416	0·667	..	0·056 (40; −0·201 to 0·315)	0·667	0·667	..	..
SUV positive‡	0·708 (16; 0·375 to 1·041)	<0·0001	<0·0001	0·0002	0·471 (23; 0·179 to 0·763)	0·002	0·003	0·0033	0·184 (28; −0·093 to 0·461)	0·191	0·191	0·2012	0·001
SUV negative‡	−0·075 (56; −0·309 to 0·160)	0·531	0·631	..	−0·104 (45; −0·350 to 0·142	0·406	0·631	..	−0·064 (32; −0·328 to 0·199)	0·631	0·631	..	..

A positive value of change is in favour of the intervention, whereas a negative value is in favour of the placebo. CDR=Clinical Dementia Rating. MMSE=Mini-Mental State Examination. DHA=docosahexaenoic acid. EPA=eicosapentaenoic acid. CAIDE=Cardiovascular Risk Factors, Aging, and Incidence of Dementia. SUV=standardised uptake value. *Adjusted for multiple comparisons with the Hochberg procedure to account for the fact that three intervention groups were compared with the placebo group in each analysis. †Low concentrations of DHA and EPA were defined by the lowest quartile of DHA plus EPA percentage at baseline in the intention-to-treat population (ie, 4·83). ‡SUV positive was determined by a cortical SUV of greater than 1·17.

***Table 3*: Estimated mean difference in 3-year change from baseline on composite *Z* score in the three intervention groups compared with the control group**

555 (34%) reported at least one serious adverse event. Adverse events occurred at a similar frequency in all groups (table 4). The proportion of participants with one or more adverse events associated with the study treatment did not differ significantly between groups (p=0·35). Among participants who discontinued the study medication because of an adverse event, gastrointestinal disorders (abdominal pain and nausea) were the most often reported, and occurred with similar frequency across groups (data not shown). Ten cases of bleeding led participants to discontinue study medication: three in the polyunsaturated fatty acids supplementation group (one haemorrhagic stroke, two haematomas), five in the multidomain intervention plus placebo group (one each of haemorrhagic stroke, intracerebral haemorrhage, haematuria, haemoptysis, and epistaxis) and two in the placebo group (one haemorrhagic stroke, one subarachnoid haemorrhage).

During 36 months' follow-up in the modified intention-to-treat population, 201 (55%) of 366 participants were adherent in the combined intervention group, 204 (53%) of 387 were adherent in the multidomain intervention plus placebo group, 276 (79%) of 350 were adherent in the polyunsaturated fatty acid group, and 296 (85%) of 350 were adherent in the placebo group (p<0·0001 between groups). Attendance to group sessions decreased with time: between 30 and 36 months, 130 (17%) of the 764 participants allocated to the multidomain intervention attended the session, whereas 980 (69%) of the 1417 participants assigned to supplementation or placebo groups were still taking their allocated medication. The concentrations of DHA and EPA in red blood cells, an indicator of adherence, were significantly higher in the two groups receiving active supplementation (mean increase of 3·52% [SE 0·11] and 3·29% [0·11] in the multidomain intervention plus polyunsaturated fatty acids and polyunsaturated fatty acids alone groups, respectively) than in the two groups receiving placebo (mean change –0·02% [0·11] in the placebo group and 0·06% [0·11] in the multidomain intervention plus placebo group) at 12 months (p<0·0001). In the groups receiving placebo or polyunsaturated fatty acid only, duration of weekly physical activity between baseline and 36 months significantly decreased by 107 min (p=0·0004) and 94 min (p=0·002), respectively. Weekly duration of physical activity did not change significantly from

	Multidomain plus polyunsaturated fatty acids (n=411)	Multidomain plus placebo (n=417)	Polyunsaturated fatty acids (n=409)	Placebo (n=415)	Overall (n=1652)
Total emerging adverse events	1507	1442	1480	1382	5811
At least one emerging adverse event	347 (84%)	358 (86%)	355 (87%)	354 (85%)	1414 (86%)
At least one serious emerging adverse event	146 (36%)	142 (34%)	134 (33%)	133 (32%)	555 (34%)
At least one serious emerging adverse event leading to treatment discontinuation	36 (9%)	44 (11%)	49 (12%)	41 (10%)	170 (10%)
At least one adverse event leading to study discontinuation	24 (6%)	31 (7%)	24 (6%)	20 (5%)	99 (6%)
At least one adverse event leading to death	9 (2%)	8 (2%)	11 (3%)	12 (3%)	40 (2%)
Most frequently reported emerging adverse events*					
Surgical and medical procedures	123 (35%)	135 (38%)	110 (31%)	118 (33%)	486 (34%)
Infections and infestations	113 (33%)	100 (28%)	118 (33%)	135 (38%)	466 (33%)
Musculoskeletal and connective tissue disorders	108 (31%)	108 (30%)	104 (29%)	102 (29%)	422 (30%)
Injury, poisoning, and procedural complications	105 (30%)	82 (23%)	87 (25%)	96 (27%)	370 (26%)
Nervous system disorders	86 (25%)	100 (28%)	88 (25%)	88 (25%)	362 (26%)
Cardiac and vascular disorders	109 (31%)	84 (24%)	83 (23%)	80 (23%)	356 (25%)
Gastrointestinal disorders	81 (23%)	88 (25%)	94 (26%)	76 (21%)	339 (24%)
Vision and hearing disorders	74 (21%)	70 (20%)	58 (16%)	60 (17%)	262 (19%)
General disorders (congenital, endocrinology, and haematology disorders)	61 (18%)	62 (17%)	83 (23%)	53 (15%)	259 (18%)
Metabolism and nutrition disorders	63 (18%)	69 (19%)	48 (14%)	51 (14%)	231 (16%)
Psychiatric disorders	48 (14%)	40 (11%)	43 (12%)	42 (12%)	173 (12%)
Respiratory, thoracic, and mediastinal disorders	46 (13%)	40 (11%)	47 (13%)	37 (10%)	170 (12%)
Investigations (eg, coronarography, check-up)	33 (10%)	42 (12%)	49 (14%)	39 (11%)	163 (12%)
Renal and urinary disorders, reproductive system and breast disorders	31 (9%)	42 (12%)	45 (13%)	40 (11%)	158 (11%)

Emerging adverse events—ie, adverse events that occurred in 10% or more of participants in any study arm are shown. *The denominator for these percentages is the number of participants in each arm who experienced at least one emerging adverse event.

***Table 4*: Adverse events in all participants who received at least one dose of polyunsaturated fatty acids or placebo, or who attended at least one multidomain intervention session**

baseline to 36 months in either the multidomain intervention plus polyunsaturated fatty acid group (–24 minutes; p=0·422) or the multidomain intervention plus placebo group (3 min; p=0·914).

In post-hoc analyses, we assessed whether low concentrations of DHA and EPA in red blood cells modified the efficacy of any intervention on cognitive performance. Cognitive performance in 85 participants with low DHA and EPA concentrations at baseline in the placebo group declined by 0·236 points on the composite score (SE 0·072; p=0·001) during 36 months' follow-up, whereas in 277 participants with higher DHA and EPA concentrations at baseline, cognitive performance remained stable (mean change –0·011 [SE 0·037]; p=0·776). The primary outcome did not differ significantly between the intervention groups in this subgroup analysis.

Additional post-hoc subgroup analyses were done according to the presence of brain amyloid in a subsample of 269 participants who underwent amyloid PET scans, as shown by the standardised uptake value data in table 3. Less cognitive decline during follow-up was noted in the combined intervention group (adjusted p<0·0001) and in the multidomain intervention plus placebo group (p=0·003) than in the placebo group in amyloid-positive participants (table 3).

Discussion

In this trial, a multidomain lifestyle intervention and omega 3 polyunsaturated fatty acid, either individually or in combination, did not significantly reduce cognitive decline over 3 years compared with placebo. The results of exploratory subgroup analyses suggested that the combined polyunsaturated fatty acid and multidomain intervention or the multidomain intervention alone might help to slow cognitive decline in people most likely to undergo decline—ie, those with a CAIDE dementia risk score of 6 or greater at baseline, and those with a positive amyloid PET scan. Our study was not designed to test intervention effects in subgroups, and so all subgroup results should be considered exploratory and need to be confirmed. Another limitation of all the subgroup analyses was that the populations were not completely independent.

Studies published in the past 2–3 years have shown beneficial effects of multidomain interventions.[2] The largest[31] of these studies was done in participants aged 60–77 years, and showed that cognitive performance over 24 months improved more in those with a CAIDE risk score of 6 or higher who received a multidomain lifestyle intervention than in those in the control group. In our study, participants were older, and the placebo group underwent cognitive decline. Two previous trials[32,33] also showed that supplementation with DHA and EPA had no effect on cognitive function in cognitively healthy older adults (ie, >65 years at least) after 6 and 24 months, respectively. In another 6-month trial[34] in participants with age-related cognitive decline, DHA supplementation had beneficial effects on visuospatial learning, episodic memory, and verbal recognition memory compared with placebo, but not on working memory or executive function.

The strengths of our study are the randomised, controlled design, the novel approach of testing a combined intervention involving both a nutritional supplement and a lifestyle intervention, the long duration of the intervention period, and the repeated and objective assessments of cognitive function in memory centres. Furthermore, all centres were trained in how to administer the multidomain intervention and how to assess outcomes, and none of the centres involved in this trial had previously used the intervention before the study. Finally, we strictly recorded all adverse events during the 36 months, and thoroughly assessed safety.

Our primary outcome was designed to be similar to the Alzheimer's Disease Cooperative Study-Preclinical Alzheimer Cognitive Composite. A previous study[18] showed that this score can reliably measure the first signs of cognitive decline in at-risk populations, and the score is recommended by regulatory agencies for secondary prevention trials in Alzheimer's disease.[35] Composite scores enable testing of the effect of an intervention on several cognitive domains simultaneously, and can be more sensitive to change than the individual tests used to calculate them.[36,37] Our trial is the first preventive trial to use a composite score that consists of four tests.

Understanding the clinical relevance of changes in composite scores is one of the challenges associated with the use of a composite score as primary outcome measures. An initial estimate of the Minimal Clinically Important Difference of this score—which was obtained by using a change from a CDR of 0 to a CDR of 0.5 as an anchor measure in a secondary analysis of data from a previous prevention trial—was –0·3 points in a year.[38] In our trial, as expected, participants with the usual risk factors for cognitive decline (*APOE* ε4, CDR 0·5, amyloid-positive scans) showed greater cognitive decline on this composite score than those without these risk factors (data not shown). These results support the potential use of this score as an outcome in preventive trials. Moreover, we showed that 36 month decline in the composite score was 0·24 points for those with low DHA and EPA concentrations in red blood cells at baseline, which is similar to the worsening noted in patients with CDRs of 0·5 subjects, whereas those with normal DHA and EPA concentrations showed no change in the composite cognitive score during the trial (data not shown). This result is consistent with the association between low DHA and EPA concentrations and brain atrophy reported in the Framingham cohort and the Women's Health Initiative Memory Study—Magnetic Resonance Imaging (WHIMS-MRI) study.[5,39] Several trials are assessing the efficacy of supplementation with polyunsaturated fatty acids on cognitive function or on biomarkers.[2] However, only one trial is focusing on individuals with low DHA and EPA concentrations (NCT01953705).

Our study has several limitations. Although all outcome assessors were blinded, and the nutritional supplementation component was double-blind, by design, participants were not blinded to the multidomain intervention component. Also, PET scan subgroup results should be interpreted with caution because most scans were done after baseline, and therefore amyloid positivity could have been affected by the interventions. Other limitations of our intervention are also the low intensity of the multidomain intervention and the decreasing adherence with time, particularly for the multidomain component, despite the fact that we designed a pragmatic intervention with reducing intensity over time. Furthermore, we did not use a food frequency questionnaire to assess fish intake, but we measured DHA and EPA concentrations in all participants at baseline and 12 months, which better shows long-term fatty acid intake because this measure is less sensitive to recent changes than plasma fatty acids.[40] Furthermore, this study was not designed to test the individual contributions of dietary changes, increased physical activity, and increased cognitive stimulation for the prevention of cognitive decline, and the individual effects of each component, as well as the optimal content, remain to be determined. Finally, our volunteer sample was particularly well educated, and the high level of cognitive reserve might have minimised cognitive decline in this sample compared with that in representative population-based samples.[41]

In summary, even though the primary analysis did not reach significance, our trial provides new data for the effect of a multidomain intervention with or without polyunsaturated fatty acid supplementation. An effective multidomain intervention strategy and target population remain to be determined, particularly in real-world settings. Additional research should also further assess the benefits of polyunsaturated fatty acid supplementation on cognitive decline in individuals who are deficient for these nutrients.

Contributors

SA, SG, J-FD, JT, PR, J-PC, MW, PJ-O, and BV conceived and designed the study. SG, MB, SB, LB, MN-C, TD, J-FD, FD, AG, YG, AP, KS, JT, PR, OR, PL, PP, IC, P-JO, and BV gathered data, which were analysed and interpreted by SA, NC, CC, and BV. SA, NC, CC, and BV wrote the Article, which was critically reviewed by all authors.

Declaration of interests

SA has received grants from Europe, Ipsen, and France Alzheimer, 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 support from the AMPA Association. J-FD reports grants from Ipsen and Roche. J-PC has a patent (WO 2007/071670) issued, and has submitted, on behalf of Pierre Fabre Research Institute and Pierre Fabre Médicament, an application for a Health Claim according to article 13.5 of European Regulation 1924/2006. MW receives research-support grants from the US National Institutes of Health, National Institute on Aging, and 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-Centred Outcomes Research Institute (PPRN-1501-26817); the Global Alzheimer's Platform Foundation, and the Monell Chemical Senses Center. The Brain Health Registry, of 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; provided consulting to Synarc, Pfizer, Janssen, the Alzheimer's Drug Discovery Foundation, Avid Radiopharmaceuticals, Araclon, Merck, Biogen Idec, BioClinica, and Genentech; holds stock options with Alzheon; and been provided with funding for academic travel by Pfizer, Kenes, University of California, San Diego, Alzheimer's Disease Cooperative Study, University Center Hospital 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, Rockafeller University, Memorial Sloan-Kettering Cancer Center, and Biogen Idec. BV reports grants from Pierre Fabre, Avid, Exonhit, AbbVie, Lilly, Lundbeck, MSD, Otsuka, Regenron, 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 other authors declare no competing interests.

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