Docosahexaenoic Acid Supplementation and Cognitive Decline in Alzheimer Disease: A Randomized Trial

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**Context**
Docosahexaenoic acid (DHA) is the most abundant long-chain polyunsaturated fatty acid in the brain. Epidemiological studies suggest that consumption of DHA is associated with a reduced incidence of Alzheimer disease. Animal studies demonstrate that oral intake of DHA reduces Alzheimer-like brain pathology.

**Objective**
To determine if supplementation with DHA slows cognitive and functional decline in individuals with Alzheimer disease.

**Design, Setting, and Patients**
A randomized, double-blind, placebo-controlled trial of DHA supplementation in individuals with mild to moderate Alzheimer disease (Mini-Mental State Examination scores, 14-26) was conducted between November 2007 and May 2009 at 51 US clinical research sites of the Alzheimer’s Disease Cooperative Study.

**Intervention**
Participants were randomly assigned to algal DHA at a dose of 2 g/d or to identical placebo (60% were assigned to DHA and 40% were assigned to placebo). Duration of treatment was 18 months.

**Main Outcome Measures**
Change in the cognitive subscale of the Alzheimer’s Disease Assessment Scale (ADAS-cog) and change in the Clinical Dementia Rating (CDR) sum of boxes. Rate of brain atrophy was also determined by volumetric magnetic resonance imaging in a subsample of participants (n=102).

**Results**
A total of 402 individuals were randomized and a total of 295 participants completed the trial while taking study medication (DHA: 171; placebo: 124). Supplementation with DHA had no beneficial effect on rate of change on ADAS-cog score, which increased by a mean of 7.98 points (95% confidence interval [CI], 6.51-9.45 points) for the DHA group during 18 months vs 8.27 points (95% CI, 6.72-9.82 points) for the placebo group (linear mixed-effects model: P = .41). The CDR sum of boxes score increased by 2.87 points (95% CI, 2.44-3.30 points) for the DHA group during 18 months compared with 2.93 points (95% CI, 2.44-3.42 points) for the placebo group (linear mixed-effects model: P = .68). In the subpopulation of participants (DHA: 53; placebo: 49), the rate of brain atrophy was not affected by treatment with DHA. Individuals in the DHA group had a mean decline in total brain volume of 24.7 cm³ (95% CI, 21.4-28.0 cm³) during 18 months and a 1.32% (95% CI, 1.14%-1.50%) volume decline per year compared with 24.0 cm³ (95% CI, 20.28 cm³) for the placebo group during 18 months and a 1.29% (95% CI, 1.07%-1.51%) volume decline per year (P = .79).

**Conclusion**
Supplementation with DHA compared with placebo did not slow the rate of cognitive and functional decline in patients with mild to moderate Alzheimer disease.

**Trial Registration**
clinicaltrials.gov Identifier: NCT00440050

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(Reprinted) JAMA, November 3, 2010—Vol 304, No. 17 1903
chain polyunsaturated fatty acid in the brain, DHA is enriched in synaptic fractions and is reduced in the brains of patients with Alzheimer disease.9,10 The other major omega-3 fatty acid found in fish, eicosapentaenoic acid, is virtually absent from the brain.

These findings motivated researchers to conduct animal studies that used DHA, rather than mixed omega-3 fatty acids, for intervention studies aimed at reducing Alzheimer disease brain pathology in transgenic mouse models. In mutant amyloid precursor protein (APP) Tg2576 mice, DHA supplementation reduced amyloid β pathology11 as well as the neuritic damage associated with amyloid β plaques.12 In mice carrying 3 mutant transgenes (App, Ps1, Tau) associated with Alzheimer disease pathology, DHA supplementation reduced both amyloid β and tau pathology.13

The plausibility of effective intervention with DHA in humans is further supported by evidence that brain levels of DHA vary with dietary intake, and that the average daily intake of DHA in the US diet is approximately 70 mg,14 which is considerably below the levels noted to be protective in epidemiological studies. Based on all of these considerations, we hypothesized that DHA supplementation would slow the rate of cognitive and functional decline in individuals with Alzheimer disease.

METHODS

This randomized, double-blind, placebo-controlled trial was conducted by the Alzheimer’s Disease Cooperative Study (ADCS), a consortium of academic medical centers and private Alzheimer disease clinics funded by the National Institute on Aging to conduct clinical trials on Alzheimer disease. Fifty-one US centers participated in this trial after obtaining approval from their local institutional review boards. Written informed consent was obtained from study participants, legally authorized representatives, or both, according to local guidelines.

Individuals with probable Alzheimer disease, recruited from the sites’ clinic populations, were eligible if (1) their Mini-Mental State Examination (MMSE) score was between 14 and 26, (2) they were medically stable, (3) they consumed on average no more than 200 mg/d of DHA (as assessed by a brief 7-item food frequency questionnaire), and (4) they were not taking DHA or omega-3 fatty acid supplements. Individuals excluded were if they were taking drugs with central anticholinergic effects or sedatives or were receiving any investigational treatment for Alzheimer disease. Stable use (≥3 months) of cholinesterase inhibitors or memantine was permitted.

Randomization was achieved with a centralized interactive voice response system, using a block design with a block size of 3 (in the DHA group and 2 in the placebo group). The disproportionate enrollment in the treatment group was intended to enhance recruitment. The treatment period was 18 months. Visits were scheduled every 3 months, with adverse event assessments and pill counts to assess adherence at every visit.

Study Medication, Assignments, and Masking

The study drug was an algal-derived DHA (Martek Biosciences, Columbia, Maryland) administered as capsules, dosed as 1 g twice per day for a total daily dose of 2 g. Algal DHA contains approximately 45% to 55% of DHA by weight and does not contain eicosapentaenoic acid. The DHA dose was selected based on evidence that plasma levels increase in a dose-dependent manner up to approximately 2 g/d, while at higher doses no further increase in plasma DHA is seen.15 Placebo capsules (made up of corn or soy oil) were identical in appearance. The adequacy of blinding was assessed by questionnaires completed by caregivers, study coordinators, and site physicians.

Outcome Measures

The 2 co-primary outcome measures were the rate of change over 18 months on the cognitive subscale of the Alzheimer’s Disease Assessment Scale (ADAS-cog)16 and on the Clinical Dementia Rating (CDR) sum of boxes.17 The ADAS-cog is a 70-point scale that evaluates memory, attention, language, orientation, and praxis, with higher scores indicating greater impairment. The CDR sum of boxes is a global measure assessing memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care.

Secondary outcome measures included change in scores on the MMSE,18 the ADCS’s activities of daily living (ADCS-ADL) scale,19 the Neuropsychiatric Inventory (NPI),20 and the Quality of Life Alzheimer’s Disease scale.21 All outcome measures were obtained at baseline, 6 months, 12 months, and 18 months with the exception of the MMSE, which was obtained at baseline and at 18 months.

Subpopulations participated in studies of brain imaging (DHA: 53; placebo: 49) and cerebrospinal fluid (DHA: 29; placebo: 15) markers. In those participants, brain magnetic resonance imaging (MRI) or cerebrospinal fluid collection occurred at baseline and at the 18-month visit. The subpopulation was selected as follows: all participants without contraindication to MRI (eg, pacemaker) who were enrolled at trial sites that were also certified Alzheimer’s Disease Neuroimaging Initiative (ADNI) sites were invited (but not required) to participate in the MRI substudy. The MRI sequence, as well as methods for across-site standardization and quality control, were those used in the ADNI study.22 The methods of the ADNI study were used to generate brain volumes at baseline and 18 months, which were then used to generate rates of total brain atrophy, hippocampal atrophy, and ventricular enlargement. All participants without contraindication to cerebrospinal fluid examination (eg, anticoagulation) were invited to participate in the cerebrospinal fluid study. In these individuals, lumbar puncture was performed in the morning after an overnight fast.

In the fatty acid analysis for plasma and cerebrospinal fluid, plasma phospholipid fatty acid levels were determined using established methods,23,24 with modifications for cerebrospinal
fluid analysis. The fatty acid profiles were expressed as a percentage of the total micrograms of fatty acid (weight percentage).

**Statistical Analysis**

The primary aim of the statistical analysis was to determine if the rate of cognitive and functional decline differed between participants treated with DHA and participants randomized to placebo. The primary analysis was conducted using linear mixed-effects regression models to assess group differences in rate of change on ADAS-cog and CDR sum of boxes over 18 months. In addition, generalized estimating equations and analysis of covariance (ANCOVA) models were used in sensitivity analyses.

Power calculations were based in part on analysis of ADAS-cog total score data from the ADCS non-steroidal anti-inflammatory drugs trial (ADCS-NSAID). An estimated decline of 3.8 ADAS-cog points per year in the placebo group (ie, 66% of the observed rate in the ADCS-NSAID) was used for the power analysis. Assuming a 20% annual attrition rate and a 10% annual drop-in rate even dispersed along an 18-month treatment period, and an α level of .05, a sample size of 240 for active treatment and 160 for placebo provides 80% power to detect a 33% reduction in the rate of ADAS-cog decline. Power analysis was also performed for the co-primary outcome measure, the CDR sum of boxes, and was also based on the rates of change seen in the ADCS-NSAID trial. Assuming an annual rate of change of 1.47 points per year on the CDR sum of boxes (66% of that seen in the ADCS-NSAID), a sample size of 240 for active treatment and 160 for placebo provides 80% power to detect a 32% or larger reduction in the rate of change seen in the ADCS-NSAID trial. Power analysis was also performed for the co-primary outcome measure of cognitive and functional decline differed between participants treated with DHA and participants randomized to placebo. The primary analysis was conducted using linear mixed-effects regression models to assess group differences in rate of change on ADAS-cog and CDR sum of boxes over 18 months. In addition, generalized estimating equations and analysis of covariance (ANCOVA) models were used in sensitivity analyses.

Power calculations were based in part on analysis of ADAS-cog total score data from the ADCS non-steroidal anti-inflammatory drugs trial (ADCS-NSAID). An estimated decline of 3.8 ADAS-cog points per year in the placebo group (ie, 66% of the observed rate in the ADCS-NSAID) was used for the power analysis. Assuming a 20% annual attrition rate and a 10% annual drop-in rate even dispersed along an 18-month treatment period, and an α level of .05, a sample size of 240 for active treatment and 160 for placebo provides 80% power to detect a 33% reduction in the rate of ADAS-cog decline. Power analysis was also performed for the co-primary outcome measure, the CDR sum of boxes, and was also based on the rates of change seen in the ADCS-NSAID trial. Assuming an annual rate of change of 1.47 points per year on the CDR sum of boxes (66% of that seen in the ADCS-NSAID), a sample size of 240 for active treatment and 160 for placebo provides 80% power to detect a 32% or larger reduction in the rate of change seen in the CDR sum of boxes.

The primary analysis was an intent-to-treat analysis including all randomized participants. That is, participants were analyzed in the group to which they were randomized, regardless of medication adherence. All available assessments for ADAS-cog and CDR sum of boxes were used in the analysis for individuals who discontinued medication. A secondary per-protocol analysis was also performed on all randomized individuals who completed the study (18 months) and ingested at least 80% of the protocol-prescribed study medication as measured by pill count. The linear mixed-effects and generalized estimating equation models do not require imputation of missing data. Multiple imputation was used to impute 18-month values for the ANCOVA analyses.

A list of covariates anticipated to be associated with rate of decline on ADAS-cog score, CDR sum of boxes, or both was compiled before study initiation. This list consisted of baseline age, baseline MMSE score, baseline plasma phospholipid DHA level, duration of Alzheimer disease, education level, and apolipoprotein E (APOE) genotype. Each variable was to be included as a covariate in the linear mixed-effects model if both a univariate 2-sample test showed a significant difference in the variable between treatment groups at the α level of .10, and a bivariate measure of association showed a significant association between the variable and the rate of change on the outcome measure at the α level of .15. For the primary analysis, baseline MMSE score was found to be unbalanced between groups and associated with the rates of change in scores on the ADAS-cog and CDR sum of boxes, and was therefore included in the model as a covariate in the analysis of these co-primary outcome measures. Although it was not prespecified as a candidate covariate,
sex was also found to be both unbalanced between groups and associated with rate of change on the primary outcome measures, prompting an ad hoc analysis including both sex and MMSE score as covariates.

Several exploratory analyses were specified in the analysis plan prior to study initiation. One was an analysis of the effect of DHA on rate of progression in participants with higher and lower baseline MMSE scores, with the groups divided at the median MMSE score. The second was an analysis of the effect of DHA supplementation on rate of progression among APOE ε4 allele carriers and noncarriers. These exploratory analyses also used linear mixed-effects modeling in both intent-to-treat and per-protocol populations, with the same rules for including covariates.

Statistical software R version 2.7.027 was used for all statistical analyses. For the primary hypothesis, the analysis was duplicated by using SAS version 9 (SAS Institute Inc, Cary, North Carolina) for verification purposes. The significance level was set at a value of less than .05. All statistical testing was 2-sided.

### RESULTS

Participants were recruited between February and November 2007. Clinical activity was completed in May 2009 and the database was locked in June 2009. The flow of study participants is shown in Figure 1. Of 555 individuals screened, 402 met the study criteria and were randomized, 238 to DHA and 164 to placebo. Only sex and baseline MMSE differed between the DHA and placebo-treated populations at a P value of less than .10 (Table 1). Over the course of 18 months, 67 participants in the DHA group (28%) and 40 participants in the placebo group (24%) discontinued taking the study drug, with the minority discontinuing due to adverse events (Figure 1).

#### Plasma and Cerebrospinal Fluid Fatty Acid Levels

As expected, plasma phospholipid DHA increased in the DHA treatment group from 3.18 weight percentage at baseline to 9.80 weight percentage at 6 months, 10.20 weight percentage at 12 months, and 9.82 weight percentage at 18 months (207% increase, P < .001) with no significant change in plasma phospholipid DHA in the placebo group (3.13 weight percentage at baseline and 3.12 weight percentage at 18 months).

In a subgroup of 44 participants volunteering for cerebrospinal fluid collection at baseline and 18 months (DHA group: 29; placebo group: 15), a significant 38% increase in cerebrospinal fluid DHA was observed in the DHA group (2.53 weight percentage at baseline and 3.46 weight percentage at 18 months; P < .001) but not in the placebo group (2.50 weight percentage at baseline and 2.17 weight percentage at 18 months; P = .79). Seventy-three participants provided cerebrospinal fluid at baseline but 24 declined or had dropped out by 18 months.

#### Co-primary Outcome Measures

The effect of DHA treatment on the primary and secondary clinical outcome measures is shown in Figure 2. For the primary linear mixed-effects analysis of the rate of change of ADAS-cog and CDR sum of boxes, baseline MMSE score was the only covariate qualifying for inclusion in the model. The rate of mean change in ADAS-cog score over 18 months was 8.27 points (95% confidence interval 3.46 to 13.09) greater in the DHA group than in the placebo group (P = .001). The effect of DHA treatment on the primary linear mixed-effects analysis of the rate of change of ADAS-cog and CDR sum of boxes, baseline MMSE score was the only covariate qualifying for inclusion in the model. The rate of mean change in ADAS-cog score over 18 months was 8.27 points (95% confidence interval 3.46 to 13.09) greater in the DHA group than in the placebo group (P = .001). The rate of mean change in ADAS-cog score over 18 months was 8.27 points (95% confidence interval 3.46 to 13.09) greater in the DHA group than in the placebo group (P = .001).

### Table 1. Baseline Characteristics of Study Population

<table>
<thead>
<tr>
<th>Measure</th>
<th>All Participants (N = 402)</th>
<th>DHA (n = 238)</th>
<th>Placebo (n = 164)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>76 (8.7)</td>
<td>76 (8.3)</td>
<td>76 (7.8)</td>
<td>.49</td>
</tr>
<tr>
<td>Female sex, No. (%)</td>
<td>210 (52.2)</td>
<td>112 (47.1)</td>
<td>98 (60.8)</td>
<td>.02</td>
</tr>
<tr>
<td>Education, mean (SD), y^a</td>
<td>14 (2.8)</td>
<td>14 (2.9)</td>
<td>14 (2.7)</td>
<td>.57</td>
</tr>
<tr>
<td>APOE ε4 carriers, No. (%)</td>
<td>232 (57.7)</td>
<td>137 (57.6)</td>
<td>95 (57.9)</td>
<td>.83</td>
</tr>
<tr>
<td>Body mass index^b</td>
<td>26 (4)</td>
<td>26 (4)</td>
<td>26 (4)</td>
<td>.33</td>
</tr>
<tr>
<td>Modified Hachinski ischemia scale, mean (SD)^c</td>
<td>0.77 (0.78)</td>
<td>0.79 (0.78)</td>
<td>0.74 (0.78)</td>
<td>.46</td>
</tr>
<tr>
<td>Smokers, No. (%)</td>
<td>94 (23.4)</td>
<td>58 (24.4)</td>
<td>36 (21.9)</td>
<td>.63</td>
</tr>
<tr>
<td>Blood pressure, mean (SD), mm Hg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>134 (18)</td>
<td>134 (19)</td>
<td>134 (18)</td>
<td>.98</td>
</tr>
<tr>
<td>Diastolic</td>
<td>73 (10)</td>
<td>73 (10)</td>
<td>73 (10)</td>
<td>.54</td>
</tr>
<tr>
<td>Mini-Mental State Examination, mean (SD)^d</td>
<td>20.7 (3.6)</td>
<td>20.9 (3.6)</td>
<td>20.3 (3.7)</td>
<td>.10</td>
</tr>
<tr>
<td>Cognitive subscale on Alzheimer’s Disease Assessment Scale, mean (SD)^e</td>
<td>23.85 (9.0)</td>
<td>23.77 (8.9)</td>
<td>23.96 (9.2)</td>
<td>.87</td>
</tr>
<tr>
<td>Clinical Dementia Rating sum of boxes, mean (SD)^f</td>
<td>5.68 (2.61)</td>
<td>5.61 (2.62)</td>
<td>5.77 (2.61)</td>
<td>.73</td>
</tr>
<tr>
<td>DHA intake on food frequency questionnaire, mean (SD), mg/d</td>
<td>89 (53)</td>
<td>88 (51)</td>
<td>90 (57)</td>
<td>.96</td>
</tr>
<tr>
<td>Plasma DHA, mean (SD) weight, %</td>
<td>3.16 (1.12)</td>
<td>3.18 (1.21)</td>
<td>3.13 (0.96)</td>
<td>.86</td>
</tr>
<tr>
<td>Cholinesterase inhibitor use at baseline, No. (%)</td>
<td>345 (85.8)</td>
<td>208 (87.4)</td>
<td>137 (83.5)</td>
<td>.31</td>
</tr>
<tr>
<td>Memantine use at baseline, No. (%)</td>
<td>243 (60.4)</td>
<td>139 (58.4)</td>
<td>104 (63.4)</td>
<td>.25</td>
</tr>
</tbody>
</table>

Abbreviations: APOE, apolipoprotein E gene; DHA, docosahexaenoic acid.
^aExpressed as total years of formal education and was determined by report of the participant and caregiver.
^bCalculated as weight in kilograms divided by height in meters squared.
^cThe range of possible scores is 0 to 12.
^dA 30-point scale of cognitive function in which higher scores indicate less cognitive impairment.
^eA 70-point scale of cognitive function in which higher scores indicate more cognitive impairment.
^fA global measure of dementia severity with a range from 0 to 18, with higher scores indicating greater impairment.
Confidence interval [CI], 6.72-9.82 points) for the placebo group compared with 7.98 points (95% CI, 6.51-9.45 points) for the DHA group (linear mixed-effects model: \(P = .41\); Figure 2A). The rate of points change on CDR sum of boxes over 18 months was 2.93 (95% CI, 2.44-3.42) for the placebo group compared with 2.87 (95% CI, 2.44-3.30) for the DHA group (linear mixed-effects model: \(P = .68\); Figure 2B). The ad hoc linear mixed-effects analyses including both sex and baseline MMSE score as covariates also did not show a benefit of treatment with DHA on the ADAS-cog (\(P = .61\), CDR sum of boxes (\(P = .69\)), or ADCS-ADL (\(P = .38\)). Confirmatory generalized estimating equations and ANCOVA analyses did not show a benefit of treatment with DHA.

Secondary Outcome Measures

The linear mixed-effects analysis revealed a rate of decline on the ADCS-ADL of 11.51 (95% CI, 9.57 to 13.45) points change over 18 months for the placebo group (linear mixed-effects model: \(P = .38\); Figure 2C). The NPI changed by 2.93 points (95% CI, 0.92 to 4.94 points) over 18 months for the DHA group compared with 5.09 points (95% CI, 2.49 to 7.69 points) for the placebo group (linear mixed-effects model: \(P = .11\); Figure 2D). An ANCOVA analysis showed no change in MMSE score from baseline to 18 months (−3.70 [95% CI, −4.44 to −2.96] points change over 18 months for the DHA group compared with −4.04 [95% CI, −4.85 to −3.23] points change for the placebo group; \(P = .88\)).

Among the individuals participating in the MRI substudy (170 had an MRI at baseline and 102 had MRIs at baseline and 18 months [DHA group: 53; placebo group: 49]), an ANCOVA analysis showed no evidence of an effect of DHA treatment on the absolute amount of volume change during 18 months for total brain volume decline (24.7 cm\(^3\) [95% CI, 21.4-28.0 cm\(^3\)] and volume decline of 1.32% [95% CI, 1.14%-1.50%]) for the DHA group vs 24.0 cm\(^3\) [95% CI, 20.28 cm\(^3\)] and volume decline of 1.29% [95% CI, 1.07%-1.51%] in the placebo group; \(P = .79\), left hippocampus (141 mm\(^3\) [95% CI, 112-170 mm\(^3\)]) in the DHA group vs 175 mm\(^3\) [95% CI, 134-216 mm\(^3\)]) in the placebo group; \(P = .17\), right hippocampus (176 mm\(^3\) [95% CI, 139-211 mm\(^3\)]) in the DHA group vs 148 mm\(^3\) [95% CI, 115-181 mm\(^3\)]) in the placebo group; \(P = .29\), or in total ventricular volume (9.1 cm\(^3\) [95% CI, 7.7-10.4 cm\(^3\)]) in the DHA group vs 8.1 cm\(^3\) [95% CI, 6.4-9.8 cm\(^3\)]) in the placebo group; \(P = .55\).

In a per-protocol analysis, an identical analysis was performed on only randomized participants who completed the study and ingested at least 80% of study medication. Per-protocol results did not significantly differ from the intent-to-treat results (eTable 1 at http://www.jama.com).

### Adverse Events

The proportion of individuals with at least 1 adverse event, serious adverse event, hospitalization, and death were similar in the active and placebo groups (Table 2). During the blinded phase of the trial, the data and safety monitoring board noted that 3 individuals taking warfarin (of a total of 32 participants taking warfarin at the time of randomization) reported subtherapeutic international normalized ratio (INR) after initiating study drug, and the protocol was revised to require monthly...
INR testing, which was reported to the medical monitor for all participants taking warfarin for the duration of the trial. No further cases of study drug-associated INR instability were noted. After unblinding, all 3 participants with an adverse event of decreased INR were found to be receiving active DHA. There was also a single adverse event of increased INR in the placebo group.

The data and safety monitoring board also noted during the blinded phase of the trial that thrombotic events were occurring at a rate higher than expected overall, and such events were monitored closely during the trial. After unblinding, there was no significant difference between treatment and placebo in the incidence of thrombotic events (Table 2).

### Table 2. Adverse Events in Docosahexaenoic Acid (DHA) and Placebo Groups

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>DHA Group (n = 238)</th>
<th>Placebo Group (n = 164)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any adverse event</td>
<td>214 (89.9)</td>
<td>144 (78.8)</td>
<td>.52</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>18 (7.6)</td>
<td>10 (6.1)</td>
<td>.69</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>23 (9.7)</td>
<td>12 (7.3)</td>
<td>.47</td>
</tr>
<tr>
<td>Fall</td>
<td>42 (17.6)</td>
<td>33 (20.1)</td>
<td>.60</td>
</tr>
<tr>
<td>Dizziness</td>
<td>12 (5.0)</td>
<td>9 (5.5)</td>
<td>.82</td>
</tr>
<tr>
<td>Agitation</td>
<td>24 (10.1)</td>
<td>12 (7.3)</td>
<td>.38</td>
</tr>
<tr>
<td>International normalized ratio</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased</td>
<td>3 (1.3)</td>
<td>0</td>
<td>NA</td>
</tr>
<tr>
<td>Increased</td>
<td>0</td>
<td>1 (0.6)</td>
<td>NA</td>
</tr>
<tr>
<td>Serious adverse events</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>76 (31.9)</td>
<td>50 (30.5)</td>
<td>.83</td>
</tr>
<tr>
<td>Hospitalization</td>
<td>67 (28.2)</td>
<td>43 (26.2)</td>
<td>.73</td>
</tr>
<tr>
<td>Death</td>
<td>11 (4.6)</td>
<td>4 (2.4)</td>
<td>.29</td>
</tr>
<tr>
<td>Deep venous thrombosis or pulmonary embolus</td>
<td>8 (3.4)</td>
<td>2 (1.2)</td>
<td>.32</td>
</tr>
</tbody>
</table>

aIncludes adverse events occurring in at least 5% of participants, warfarin-associated adverse events of interest, all serious adverse events, and thrombosis-associated adverse events of interest.
bUnable to calculate because of zero value.
cDefined as events that result in death, hospitalization, prolongation of hospitalization, or are life threatening (based on the judgment of the study physician).

**Blinding Analysis**

When asked to guess treatment assignment for each participant at the final study visit, the majority of study partners (48.5%), study coordinators (50%), and site physicians (59.2%) responded “do not know.” The proportion correctly guessing the active DHA group was not significantly different for the study partner (22.3% for DHA and 26.4% for placebo; \( P = .49 \)) or study coordinator (27.1% for DHA and 18.4% for placebo; \( P = .13 \)), but site physicians were more likely to guess that participants in the DHA group were receiving treatment (21.9% for DHA and 11.3% for placebo; \( P = .02 \)). The reasons for the ratings (adverse events, perceived efficacy, etc) were not captured.

**Subgroup Analyses**

The planned subgroup analyses were intent-to-treat analyses. Based on a hypothesis that the individuals with the mildest dementia severity at baseline would benefit the most from DHA supplementation, a prespecified analysis of 2 subgroups divided by baseline dementia severity, using the median MMSE score of 21 as the cut point, found no effect of DHA treatment on rate of progression in either the high score (>21) or low score (≤21) MMSE group. Analysis of subgroups of participants divided by global CDR also failed to show evidence of DHA treatment effects in the most mildly impaired participants (eTable 2 at http://www.jama.com).

The statistical analysis plan also called for subgroup analyses of populations with and without the APOE e4 allele. While there was no DHA treatment effect on any outcome measure in the APOE e4–positive group (eTable 2 at http://www.jama.com), those receiving DHA in the APOE e4–negative group had a significantly lower decline in mean change in ADAS-cog score over 18 months (6.23 points [95% CI, 4.08 to 8.38 points] for 61 participants in the DHA group vs 10.11 points [95% CI, 7.12 to 13.10 points] for 48 participants in the placebo group; linear mixed-effects model: \( P = .03 \)) (Figure 3). This differential DHA effect...
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was also evident for the MMSE score
(−3.36 [95% CI, 2.16 to 4.56] in the
DHA group vs −5.12 [95% CI, 3.70 to
6.54] in the placebo group; P = .03), but
was not present on the CDR sum of
boxes, the ADCS-ADL, or the NPI
eTable 2). An effect of DHA was not
seen on rates of brain atrophy among
individuals who were APOE ε4−
negative and participating in the MRI
substudy (DHA group: 21; placebo
group: 17).

COMMENT

This study was designed to determine
if supplementation with DHA would
slow the rate of cognitive and func-
tional decline in patients with mild to
moderate Alzheimer disease. Despite en-
rollment of the target population of in-
dividuals with low baseline DHA, in-
crease of plasma phospholipid and
cerebrospinal fluid DHA in the group
treated with DHA, and ample progress-
ion of randomized participants on the
primary outcome measures, there was
no evidence of benefit of DHA supple-
mentation in this population. In the sub-
group of participants with paired MRI
scans, DHA had no effect on change in
volume of hippocampus, whole brain,
or ventricles. The hypothesis that DHA
slows the progression of mild to mod-
erate Alzheimer disease was not sup-
ported, so there is no basis for recom-
mending DHA supplementation for
patients with Alzheimer disease.

A large proportion of randomized
participants (28% of the DHA group
and 24% of the placebo group) did not
complete the study. This attrition rate
is within the spectrum seen in recent
18-month trials for Alzheimer dis-
ease, higher than seen in a study of ho-
mocysteine-lowering B vitamins,28 but
lower than reported with tarenflur-
bil.29 Because a minority of partici-
pants cited adverse events as the rea-
son for dropping out, we hypothesize
that the dropout rate was driven by the
perception of lack of efficacy. For fu-
ture studies of similar therapies in-
tended to slow the rate of decline rather
than result in perceptible symppto-
matic effects, it may be important to
temper the expectations of partici-
pants or run the risk of a dropout rate
that may limit the ability to generalize
study results.

However, because the dropout rate
was only modestly greater than antici-
pated in the statistical analysis plan, and
because the rate was not significantly
different between the 2 groups in this
study, the findings in the overall study
population appear to be reliable. Some
cautions must be exercised, however, in
interpreting the parallel results from the
MRI substudy. This subpopulation rep-
resents a convenience sample, relying
on participant volunteerism and site ex-
pertise rather than random selection to
guide enrollment. A previous analysis
has shown that this MRI subpopula-
tion at baseline did not significantly dif-
fer from the total study population,30
and the MRI outcomes are consistent
with the clinical outcomes of the trial,
but it is still important to note that the
MRI study population is not a statisti-
cal sample of the overall study popu-
lation.

Because part of the rationale for the
trial was epidemiological evidence that
DHA use before disease onset modifies
the risk of Alzheimer disease, it re-
 mains possible that an intervention with
DHA might be more effective if initi-
at ed earlier in the course of the dis-
 ease in patients who do not have overt
dementia. Although the analysis in this
study of the subpopulation of partici-
ants with baseline MMSE scores of
higher than 20 failed to provide sup-
port for this hypothesis, other studies
have reported post hoc analyses show-
 ing positive omega-3 fatty acid treat-
ment effects in less impaired individu-
als, with MMSE scores of 27 through
30.31 However, clinical trials of omega-3
fatty acids in healthy elderly individu-
als have failed to show cognitive ben-
efits within 6 months (Mental Health
in Elderly Maintained with Omega-3
[MEMO] study, n = 302)22 to 2 years
(Older People and n-3 Long-Chain
Polyunsaturated Fatty Acids [OPAL]
study, n = 867)31 of treatment. Because
these healthy elderly individuals do not
experience significant cognitive de-
cline in this time frame, however, the
absence of a cognitive effect does not
exclude the possibility of a neuropro-
tective effect of DHA in individuals at
risk of decline. Individuals intermedi-
ate between healthy aging and demen-
tia, such as those with mild cognitive
impairment, might derive benefit from
DHA supplementation, although fur-
ther study will be necessary to test this
hypothesis.

The propensity of DHA to be oxi-
dized may also be considered in inter-
preting these results. Some have sug-
gested that increased oxidative burden
is a risk in DHA supplementation stud-
ies34 but most studies have not sup-
ported this theoretical risk,35,36 and there
is no evidence that DHA treatment had
an adverse effect in this trial. How-
ever, in one small study of DHA with
and without a co-administered antioxi-
dant (lutein), unimpaired elderly par-
ticipants randomized to combined DHA
plus antioxidant derived greater ben-
efit on selected cognitive outcome mea-
sures than participants receiving DHA
alone or placebo,37 providing support
for the hypothesis that the clinical ben-
efit of DHA supplementation may de-
pend on the availability of circulating
antioxidants to protect the DHA from
oxidation after ingestion.

In an exploratory analysis, we found
that APOE ε4−negative participants who
received DHA supplementation showed
a benefit on the ADAS-cog and MMSE.
However, the significance testing was
not adjusted for multiple compari-
sions. Furthermore, the apparent treat-
ment effect in APOE ε4−negative partici-
pants was not seen on the CDR sum of
boxes, ADCS-ADL, NPI, or brain at-
rophy, weakening the interpretation
that this effect is clinically mean-
ful. On the other hand, several epide-
miological studies indicate that a pro-
tective effect of omega-3 fatty acids with
respect to dementia may be confined to
APOE ε4−negative individuals,38-40 so an
APOE genotype–specific effect is plau-
sible. Confirmation of our explor-
atory findings in an independent ran-
momized controlled study would be
necessary to infer a beneficial effect of

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(Reprinted) JAMA, November 3, 2010—Vol 304, No. 17 1909

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DHA supplementation is not useful for Alzheimer disease.

In summary, these results indicate that DHA supplementation is not useful for the population of individuals with mild to moderate Alzheimer disease.

Author Contributions: Dr Quinn had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Study supervision: Quinn, van Dyck, Asien.

Financial Disclosures: Drs Yurko-Mauro and Nelson reported being employees of Martek Biosciences, manufacturers of docosahexaenoic acid (DHA). Drs Quinn and Asien reported being named as co-inventors on a patent for DHA for the treatment of Alzheimer disease in apolipoprotein E epsilon-4-negative individuals, which was filed in July 2009 with Dr Yurko-Mauro as the inventor. Data lock for this trial was completed June 2009, the primary analysis was completed and results presented in July 2009. The patent was filed by Martek Biosciences in July 2009. Drs Quinn and Asien were added as co-inventors in February 2010. Drs Quinn and Asien have waived personal rights to royalties related to this patent. No other authors reported disclosures.

Funding/Support: This study was supported by grant U01 AG027720 from the National Institutes of Aging. The placebo and DHA study drugs were provided by Martek Biosciences. Martek also provided plasma and cerebrospinal fluid measurements of fatty acids, which were used as ancillary support for the magnetic resonance imaging subsitudy.

Role of the Sponsor: The study design was approved by an oversight committee of the National Institute on Aging. Representatives from the National Institute on Aging participated in meetings of the steering committee of the Alzheimer’s Disease Cooperative Study during the course of the trial. The National Institute on Aging was not otherwise involved in the design and conduct of the study, or in the analysis of data or preparation of the manuscript. Martek employees participated in design of the study and in revision of the manuscript, but were not involved in data management or data analysis.

Independent Statistical Analysis: The statistical analysis was conducted by the Alzheimer’s Disease Cooperative Study Data Core. Martek employees did not participate in the statistical analysis and did not have access to the data prior to the completion of data analysis.

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Online-Only Material: eTable 1 and eTable 2 are available at http://www.jama.com.

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It is not the critic who counts; not the man who points out how the strong man stumbled, or whether the doer of deeds could have done them better. The credit belongs to the man who is actually in the arena, whose face is marred by dust and sweat and blood; who strivers valiantly, who errs and comes short again and again; who knows the greatest enthusiasms, the great devo- tions; who spends himself in a worthy cause; who, at the best, knows in the end the triumph of high achievement, and who, at the worst, if he fails, at least fails while daring greatly, so that his place shall never be with those timid souls who know neither victory nor defeat.

—Theodore Roosevelt (1858-1919)