ω-3 Fatty Acid Treatment in 174 Patients With Mild to Moderate Alzheimer Disease: OmegAD Study

A Randomized Double-blind Trial

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Background: Epidemiologic and animal studies have suggested that dietary fish or fish oil rich in ω-3 fatty acids, for example, docosahexaenoic acid and eicosapentaenoic acid, may prevent Alzheimer disease (AD).

Objective: To determine effects of dietary ω-3 fatty acid supplementation on cognitive functions in patients with mild to moderate AD.

Design: Randomized, double-blind, placebo-controlled clinical trial.

Participants: Two hundred four patients with AD (age range [mean±SD], 74±9 years) whose conditions were stable while receiving acetylcholine esterase inhibitor treatment and who had a Mini-Mental State Examination (MMSE) score of 15 points or more were randomized to daily intake of 1.7 g of docosahexaenoic acid and 0.6 g of eicosapentaenoic acid (ω-3 fatty acid–treated group) or placebo for 6 months, after which all received ω-3 fatty acid supplementation for 6 months more.

Main Outcome Measures: The primary outcome was cognition measured with the MMSE and the cognitive portion of the Alzheimer Disease Assessment Scale. The secondary outcome was global function as assessed with the Clinical Dementia Rating Scale; safety and tolerability of ω-3 fatty acid supplementation; and blood pressure determinations.

Results: One hundred seventy-four patients fulfilled the trial. At baseline, mean values for the Clinical Dementia Rating Scale, MMSE, and cognitive portion of the Alzheimer Disease Assessment Scale in the 2 randomized groups were similar. At 6 months, the decline in cognitive functions as assessed by the latter 2 scales did not differ between the groups. However, in a subgroup (n=32) with very mild cognitive dysfunction (MMSE >27 points), a significant ($P<.05$) reduction in MMSE decline rate was observed in the ω-3 fatty acid–treated group compared with the placebo group. A similar arrest in decline rate was observed between 6 and 12 months in this placebo subgroup when receiving ω-3 fatty acid supplementation. The ω-3 fatty acid treatment was safe and well tolerated.

Conclusions: Administration of ω-3 fatty acid in patients with mild to moderate AD did not delay the rate of cognitive decline according to the MMSE or the cognitive portion of the Alzheimer Disease Assessment Scale. However, positive effects were observed in a small group of patients with very mild AD (MMSE >27 points).

Trial Registration: clinicaltrials.gov Identifier: NCT00211159

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ALZHEIMER DISEASE (AD) IS severely debilitating. The onset is insidious, with loss of episodic memory as an early indicator of the disease. The currently approved drugs have a small but statistically significant symptomatic effect on cognition, behavior, and activities of daily living, but they do not affect the underlying disease process.

Increased intake of the ω-3 polyunsaturated fatty acids (primarily eicosapentaenoic acid [EPA], 20:5ω-3, and docosahexaenoic acid [DHA], 22:6ω-3) may be beneficial in reducing risk for AD. Several epidemiologic studies show a protective effect associated with increased fish consumption.[1-3] Cognitive performance is affected when animals are fed ω-3-depleted diets, but learning abilities are restored when they are given diets supplemented with the ω-3 fatty acid DHA.[4-8] Recently, in the APPsw (Tg2576) transgenic mouse model of AD, DHA-enriched diets significantly reduced total β-amyloid by 70% when compared with diets low in DHA or control chow diets.[9,10]

Since epidemiologic and experimental data indicated a beneficial effect of ω-3 fatty acids on preservation of cognition in AD, we conducted a randomized, double-blind, placebo-controlled study to evalu-

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ate the cognitive effects and safety of dietary supplementation with ω-3 fatty acids for 1 year in patients with mild to moderate AD. We chose a product rich in DHA because of the deficiency of this acid in brains affected by AD.[11-13]

METHODS

PATIENTS

In this study, which was conducted between December 31, 2000, and March 24, 2004, 204 patients were enrolled (**Figure 1**) from specialist memory clinics in the Stockholm, Sweden, catchment area. The inclusion criteria were as follows: AD according to *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (*DSM-IV*) criteria[14]; Mini-Mental State Examination (MMSE)[15] score between 15 and 30 points; patient living in his or her own home; treatment with a stable dose of acetylcholine esterase inhibitors for at least 3 months before the start of the study; and plan to continue acetylcholine esterase inhibitors for the duration of the study. Patients were excluded if treated with nonsteroidal anti-inflammatory agents (low-dose acetylsalicylic acid was accepted), ω-3 preparations, or anticoagulant agents; abused alcohol; had a concomitant serious disease; or did not have a caregiver. The recruitment process is shown in Figure 1.

PROCEDURES AND STUDY DESIGN

All 204 patients had undergone medical examination at the memory clinics. Information about history was provided by a close informant, and somatic, neurologic, and psychiatric status was assessed. Computed tomography or magnetic resonance imaging of the brain, psychometric testing of cognition, and routine blood sampling including apolipoprotein E testing were performed. Based on this information, a diagnosis of AD was made.

The study was designed as a randomized, double-blind, placebo-controlled study. Patients were randomized to receive four 1-g capsules daily, each containing either a combination of 430 mg of DHA and 150 mg of EPA (EPAX1050TG; Pronova Biocare A/S, Lysaker, Norway) or an isocaloric placebo oil (1 g of corn oil, including 0.6 g of linoleic acid) for 6 months, followed by 6 months of open treatment with ω-3 fatty acid supplementation in all patients (Figure 1). EPAX1050TG is a 60% ω-3 fatty acid concentrate in triglyceride form produced according to good manufacturing practice. Four milligrams of vitamin E (tocopherol) was added to each EPAX1050TG and placebo capsule.

Included patients underwent the following evaluations at baseline and at 6 and 12 months: routine blood and urine analyses, blood pressure assessments, global function using the Clinical Dementia Rating Scale,[16] and cognitive function using the MMSE[17] and the modified cognitive portion of the Alzheimer Disease Assessment Scale (ADAS-COG).[18]

Blood samples for analyses of serum fatty acid levels were also obtained to assess compliance with the ω-3 fatty acid therapy. These were analyzed by gas chromatography (TR-Fame column [30 m × 0.32 mm inner diameter × 0.25-μm film gas chromatography column]; Thermo Electron Corp, Waltham, Mass); results are given as the relative abundance of individual fatty acids.[19]

OUTCOME MEASURES

Primary efficacy variables were cognitive functions assessed by MMSE and ADAS-COG. Secondary outcomes were safety and tolerability, blood pressure, and global function as assessed by the Clinical Dementia Rating Scale (global, 0-3) and summary of boxes. With a statistical significance level of .05 and 80% power, 200 patients were required to detect a difference of more than 2.5 points between ω-3 fatty acid and placebo using the ADAS-COG.

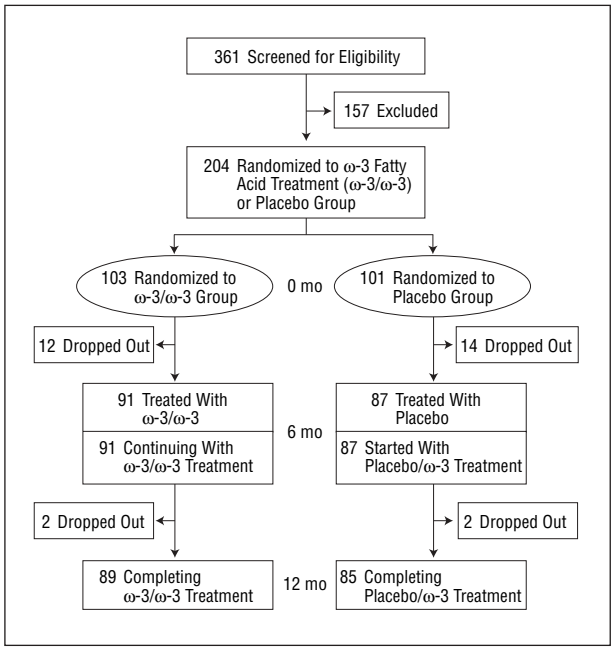

Figure 1. Design of study and trial profile.

Both intention-to-treat and per-protocol analyses were performed. In the intention-to-treat analyses, the last observation was carried forward to the subsequent registration. Since no differences in outcomes between the 2 methods were found, we have chosen to show these data using the per-protocol mode.

Longitudinal changes in MMSE and ADAS-COG were assessed using repeated-measures analysis of variance. The Fisher least significant difference test was used for post hoc analyses. For variations in cognitive decline rates between the 2 groups at 6 and 12 months, *t* tests were performed. Data are given as mean and 95% confidence interval unless otherwise stated.

ETHICAL CONSIDERATIONS

The study was conducted according to good clinical practice and ethical principles of the Declaration of Helsinki. Both patient and caregiver gave written informed consent before enrollment in the study. The local Ethics Committee of Karolinska Institutet, Stockholm, Sweden, approved the study.

RESULTS

Two hundred four patients (110 women and 94 men) completed the baseline assessments and were randomized to either treatment with the ω-3 fatty acid preparation or placebo for 6 months followed by 6 months with ω-3 fatty acid treatment in both groups (Figure 1). The characteristics of these groups, that is, ω-3/ω-3 and placebo/ω-3, respectively, at randomization are given in **Table 1**. One hundred seventy-four patients completed the entire study. There were no differences in age, sex, blood pressure, or body mass index (calculated as weight in kilograms divided by height in meters squared) between the ω-3/ω-3– and the placebo/ω-3–treated groups (Table 1) at inclusion. All patients continued to receive a stable dosage of acetylcholine esterase inhibitors.

Table 1. Baseline Characteristics of the ω-3/ω-3 Fatty Acid– and the Placebo/ω-3 Fatty Acid–Treated Groups and the Dropouts From the Study*

Characteristic	Study Group		Dropouts	
	ω-3/ω-3 (n = 89)	Placebo/ω-3 (n = 85)	ω-3/ω-3 (n = 14)	Placebo/ω-3 (n = 16)
Female sex, No. (%)	51 (57)	39 (46)	10 (71)	10 (63)
Age, y	72.6 ± 9.0	72.9 ± 8.6	77.0 ± 8.2	78.2 ± 7.5
Diabetes, No. (%)	10 (13)	4 (6)	1 (8)	0
Smoking, No. (%)	7 (10)	6 (9)	NA	NA
APOE4, No. (%)				
0	21 (24)	28 (33)	9 (57)	5 (31)
1	46 (52)	39 (46)	4 (22)	6 (31)
2	22 (25)	18 (21)	1 (7)	5 (31)
AChE inhibitor, No. (%)				
Donepezil	33 (37)	33 (39)	10 (71)	11 (69)
Galantamine	18 (20)	21 (25)	3 (21)	3 (19)
Rivastigmine	38 (43)	31 (36)	1 (7)	2 (13)
Acetylsalicylic acid	21 (24)	18 (21)	5 (36)	4 (25)
Antidepressant agents	40 (45)	32 (38)	6 (43)	4 (25)
Neuroleptic agents	9 (10)	5 (6)	1 (7)	0
Statin drugs	11 (12)	14 (16)	0	2 (13)
Herbal medication	5 (6)	10 (12)	1 (7)	1 (6)
Blood pressure, mm Hg				
Systolic	137 ± 17	137 ± 16	137 ± 18	133 ± 21
Diastolic	75 ± 9	76 ± 9	76 ± 11	74 ± 10
BMI	24.5 ± 3.1	24.1 ± 3.0	26.1 ± 2.3	23.5 ± 3.1
>25, No. (%)	35 (39.3)	29 (32.6)	8 (57.1)	5 (31.2)
<20, No. (%)	5 (5.6)	9 (10.1)	0	2 (12.5)

Abbreviations: AChE, acetylcholinesterase; *APOE4*, allele producing the ε4 type of apolipoprotein E; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); NA, data missing.

*Data are given as mean ± SD unless otherwise indicated. The ω-3/ω-3–treated group received 1.7 g of docosahexaenoic acid and 0.6 g of eicosapentaenoic acid; the placebo/ω-3–treated group received a placebo containing 1 g of corn oil, including 0.6 g of linoleic acid and between 6 and 12 months of the ω-3 fatty acid supplement.

SERUM FATTY ACID CONCENTRATION

The patients in the ω-3–treated group showed mean 2.4- and 3.6-fold increases in the ratios of DHA and EPA, respectively, in serum after the first 6 months (**Figure 2**). Corresponding mean values for the placebo-treated patients were 0.95 and 0.96, respectively. At 12 months, the placebo/ω-3–treated group attained similar levels of DHA and EPA in serum as in the ω-3/ω-3–treated group, which maintained elevated serum EPA and DHA ratios throughout the study (Figure 2). The placebo group exhibited a small increase in the level of serum linoleic acid at the first 6-month follow-up visit (Figure 2).

PRIMARY OUTCOME

There was no statistically significant difference during 6 and 12 months between the ω-3/ω-3– and the placebo/ω-3–treated groups on the MMSE or ADAS-COG (**Table 2**). Based on the assumption that ω-3 fatty acids might be acting primarily on early events in the brain in AD,[1-3] we performed post hoc analyses of subgroups. First, we dichotomized the patient group according to the MMSE median value of 24 points. In the group with MMSE 24 or greater (ie, those with the mildest disease), the decline in MMSE during the first 6 months was –1.0 and –1.4 points, respectively, in the ω-3–treated and placebo-treated control groups ($P=.40$) (Table 2), whereas in patients with more advanced AD, the decline rate tended to be more rapid in the ω-3–treated group than in the placebo-treated control group, that is, –0.9 vs 0 points, respectively ($P=.15$).

Given these results, we assessed whether any subgroup with mild dementia might benefit from ω-3 fatty acid treatment. Study of a subgroup of 32 patients with very mild AD (MMSE >27 points and global Clinical Dementia Rating Scale score of 0.5-1) revealed a statistically significant ($P=.02$) treatment effect in the MMSE scores over time between the 2 groups (**Figure 3**A). The placebo group exhibited a significant decline in mean MMSE scores between baseline and 6 months (–2.6 points; $P<.001$), while there was no change in MMSE over time within the ω-3/ω-3–treated group, either between baseline and 6 months (–0.5 points) or between 6 and 12 months (–0.6 points). The difference in decline rate between the 2 groups was statistically significant at the 6-month-follow-up ($P=.01$). When the placebo group received active ω-3 fatty acid treatment, the decline rate seemed to halt; there was no difference in the MMSE scores between 6 and 12 months (–0.83 points; $P=.23$; Figure 3A). All other results are given in Table 2.

When analyzing each subitem of the MMSE, significant treatment effects were found over time in the MMSE subitems "Delayed word recall" ($P=.04$; Figure 3B) and "Attention" ($P=.047$; Figure 3C), where the placebo/ω-3–treated group showed a significant reduction between baseline and 6 months for both items ($P=.003$ and $P=.002$, respectively) and stabilized between 6 and 12

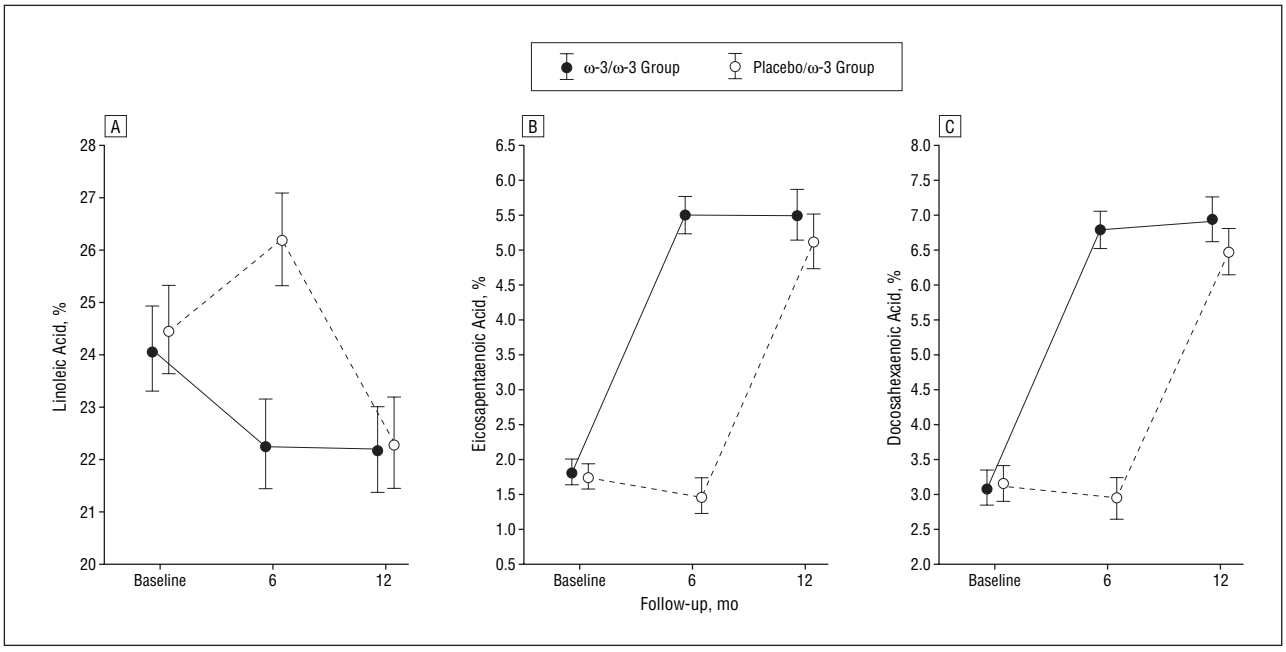

Figure 2. Serum fatty acids. Relative proportions of linoleic acid (placebo preparation; A), eicosapentaenoic acid (B), and docosahexaenoic acid (C). The ω-3/ω-3 group received 1.7 g of docosahexaenoic acid and 0.6 g of eicosapentaenoic acid; the placebo/ω-3 group received a placebo containing 1 g of corn oil, including 0.6 g of linoleic acid and between 6 and 12 months of the ω-3 fatty acid supplement.

months, whereas the ω-3/ω-3–treated group showed no significant decline at all. There was a statistically significant difference in decline rate for "Attention" (1 point) between the groups at the 6-month follow-up ($P=.02$) (available in **eTable 1 [http://www.archneurol.com]**).

Among patients with more than 27 points on the MMSE, there was no significant ($P=.96$) treatment effect for the ADAS-COG scores over time between the 2 groups. However, when analyzing the subitems of the ADAS-COG, the placebo/ω-3–treated group showed a significant worsening in "Delayed word recall" between baseline and 6 months ($P=.007$) but stabilized between 6 and 12 months. The ω-3/ω-3–treated group showed no deterioration in "Delayed word recall" scores (available in **eTable 2 [http://www.archneurol.com]**).

The subgroup with MMSE scores greater than 27 points received concomitant treatment with low-dose acetylsalicylic acid, statin drugs, neuroleptic agents, antidepressant drugs, and herbal medications to the same extent as in the entire study group (data not shown). No other demographic or pharmacologic features (eg, age, smoking habits, presence of diabetes, and alleles producing the ε4 type of apolipoprotein E) distinguished it from the rest, but for the MMSE score. Likewise, there was no difference in mean duration of acetylcholine esterase inhibitor treatment before initiation of ω-3 fatty acid or placebo treatments between the groups.

Since there was a weak trend toward more rapid decline of cognitive functions in the ω-3–treated group than in the placebo-treated control group for those with MMSE scores of fewer than 24 points during the first 6 months, we performed additional post hoc analyses. In a subgroup with the most advanced AD in this study (MMSE scores <22; n=52, mirroring the subgroup with MMSE scores >27 as described earlier), we did not observe any significant changes in MMSE or ADAS-COG scores, or subitems thereof, that indicated that the ω-3 fatty acid preparation conferred a deterioration in cognition (data not shown).

SECONDARY OUTCOME

The ω-3 fatty acid preparation was well tolerated and safe. The dropout rate was 15% (14 patients in the ω-3/ω-3–treatment arm and 16 patients in the placebo/ω-3–treatment arm) (Figure 1). The reasons for leaving the study were gastrointestinal tract symptoms such as diarrhea (n=9), dysphagia owing to the size of the capsules (n=9), new serious somatic disease (n=10), noncompliance (n=1), and withdrawal of informed consent (n=1).

No differences in global or total Clinical Dementia Rating Scale scores between the 2 groups were noted (Table 2). There were no significant changes in routine blood and urine test results. Blood pressure remained unaltered during the study. Table 1 gives the starting values. At 6 months, the ω-3–treated group had a mean systolic pressure of 138 mm Hg and diastolic pressure of 74 mm Hg, whereas the corresponding figures for the placebo group were 137 mm Hg and 76 mm Hg, respectively. At 12 months, the ω-3–treated group had a mean systolic pressure of 134 mm Hg and diastolic pressure of 74 mm Hg, whereas the corresponding figures for the placebo group were 134 mm Hg and 75 mm Hg, respectively.

COMMENT

To our knowledge, this randomized, double-blind, placebo-controlled study is the first to be published on the effects of ω-3 fatty acid supplementation, mainly DHA, as treatment for AD. It did not document any effect in patients with mild to moderate AD for 6 months. The findings from our study are consistent with the results of a

Table 2. Data for Cognitive and Global Scales at Baseline and at 6- and 12- Month Follow-up*

Patient Group	Baseline	Follow-up, mo	
		6	12
MMSE Score (0-30 Points)			
All patients			
ω-3/ω-3	23.6 (22.8-24.4)	22.8 (21.9-23.7)	22.1 (21.1-23.1)
Placebo/ω-3	23.2 (22.4-24.0)	22.4 (21.5-23.4)	21.9 (20.8-22.9)
Patients with MMSE score >27 points			
ω-3/ω-3	28.4 (28.1-28.7)	27.9 (27.1-28.7)	27.3 (26.1-28.4)
Placebo/ω-3	28.5 (28.2-28.9)	26.0 (24.2-27.8)	25.4 (23.3-27.5)
Patients with MMSE score >23 points			
ω-3/ω-3	26.6 (26.0-27.1)	25.7 (24.9-26.5)	25.1 (24.1-26.1)
Placebo/ω-3	26.1 (25.6-26.7)	24.6 (23.6-25.6)	24.7 (23.7-25.6)
Patients with MMSE score <24 points			
ω-3/ω-3	20.1 (19.3-20.8)	19.3 (18.3-20.2)	18.4 (17.1-19.6)
Placebo/ω-3	19.8 (19.0-20.6)	19.9 (18.6-21.1)	18.7 (17.3-20.1)
ADAS-COG Score (0-85 Points)			
All patients			
ω-3/ω-3	25.7 (23.6-27.8)	27.7 (25.4-30.0)	31.2 (28.3-34.2)
Placebo/ω-3	27.2 (25.1-29.4)	28.3 (26.0-30.6)	32.8 (29.8-35.9)
Patients with MMSE score >27 points			
ω-3/ω-3	14.2 (11.6-16.8)	15.7 (13.0-18.4)	17.3 (14.2-20.4)
Placebo/ω-3	19.0 (16.0-22.0)	20.5 (17.1-23.9)	22.5 (18.7-24.3)
Patients with MMSE score >23 points			
ω-3/ω-3	19.1 (17.3-21.0)	20.8 (18.8-22.8)	23.3 (20.8-25.7)
Placebo/ω-3	22.2 (20.1-24.2)	22.8 (20.6-25.0)	25.1 (22.5-27.7)
Patients with MMSE score <24 points			
ω-3/ω-3	33.9 (30.8-37.0)	36.2 (33.1-39.3)	41.0 (37.5-44.6)
Placebo/ω-3	33.1 (30.6-35.5)	34.6 (31.2-38.0)	41.9 (36.6-47.2)
CDR Scale, Global Score (0-3 Points)			
All patients			
ω-3/ω-3	1.0 (0.9-1.1)	1.1 (1.0-1.2)	1.2 (1.0-1.3)
Placebo/ω-3	1.1 (1.0-1.2)	1.1 (1.0-1.3)	1.3 (1.1-1.4)
Patients with MMSE score >27 points			
ω3/ω3	0.6 (0.5-0.8)	0.8 (0.5-1.0)	0.7 (0.5-0.9)
Placebo/ω3	0.6 (0.5-0.7)	0.6 (0.4-0.8)	0.7 (0.5-1.0)
Patients with MMSE score >23 points			
ω3/ω3	0.7 (0.6-0.8)	0.8 (0.7-0.9)	0.8 (0.7-0.9)
Placebo/ω3	0.8 (0.7-1.0)	0.8 (0.7-1.0)	1.0 (0.8-1.1)
Patients with MMSE score <24 points			
ω3/ω3	1.3 (1.1-1.5)	1.5 (1.3-1.7)	1.6 (1.4-1.8)
Placebo/ω3	1.4 (1.2-1.6)	1.4 (1.2-1.7)	1.6 (1.4-1.9)
CDR Scale Sum of Boxes (0-18 Points)			
All patients			
ω3/ω3	5.8 (5.1-6.5)	6.2 (5.4-6.9)	6.7 (5.9-7.5)
Placebo/ω3	6.0 (5.4-6.7)	6.5 (5.7-7.3)	7.1 (6.3-7.9)
Patients with MMSE score >27 points			
ω3/ω3	3.3 (2.4-4.1)	3.5 (2.2-4.7)	3.6 (2.5-4.7)
Placebo/ω3	3.1 (2.0-4.2)	3.9 (2.7-5.0)	4.0 (2.8-5.3)
Patients with MMSE score >23 points			
ω3/ω3	4.1 (3.5-4.7)	4.2 (3.5-5.0)	4.5 (3.7-7.2)
Placebo/ω3	4.6 (3.8-5.4)	4.7 (3.9-5.5)	5.2 (4.3-6.2)
Patients with MMSE score <24 points			
ω3/ω3	7.9 (7.1-8.7)	8.5 (7.6-9.5)	9.4 (8.4-10.5)
Placebo/ω3	7.7 (6.6-8.8)	8.6 (7.4-9.7)	9.3 (8.1-10.6)

Abbreviations: ADAS-COG, cognitive portion of the Alzheimer Disease Assessment Scale; CDR, Clinical Dementia Rating; MMSE, Mini-Mental State Examination.

*Data are given as mean (95% confidence interval). Low scores on the MMSE and high scores on the ADAS-COG and CDR Scale indicate more severe disease. The ω-3/ω-3–treated group received 1.7 g of docosahexaenoic acid and 0.6 g of eicosapentaenoic acid; the placebo/ω-3–treated received a placebo containing 1 g of corn oil, including 0.6 g of linoleic acid and between 6 and 12 months of the ω-3 fatty acid supplement. The ω-3/ω-3–treated group consisted of 89 patients and the placebo/ω-3–treated group consisted of 85.

recent pilot study that addressed the possibility of treating AD with EPA for a short time but failed to find effects.[20] A 4-week controlled intervention study suggested, however, that ω-3 fatty acids might be associated with improved quality of life in patients with AD.[21]

The total daily dose of ω-3 fatty acids used in our study (2.3 g) is similar to or lower than that shown to confer clinical benefits in previous trials of rheumatoid diseases (often, 3-4 g/d)[22,23] but twice as high as used in the GISSI-2 study (Gruppo Italiano per lo Studio della So-

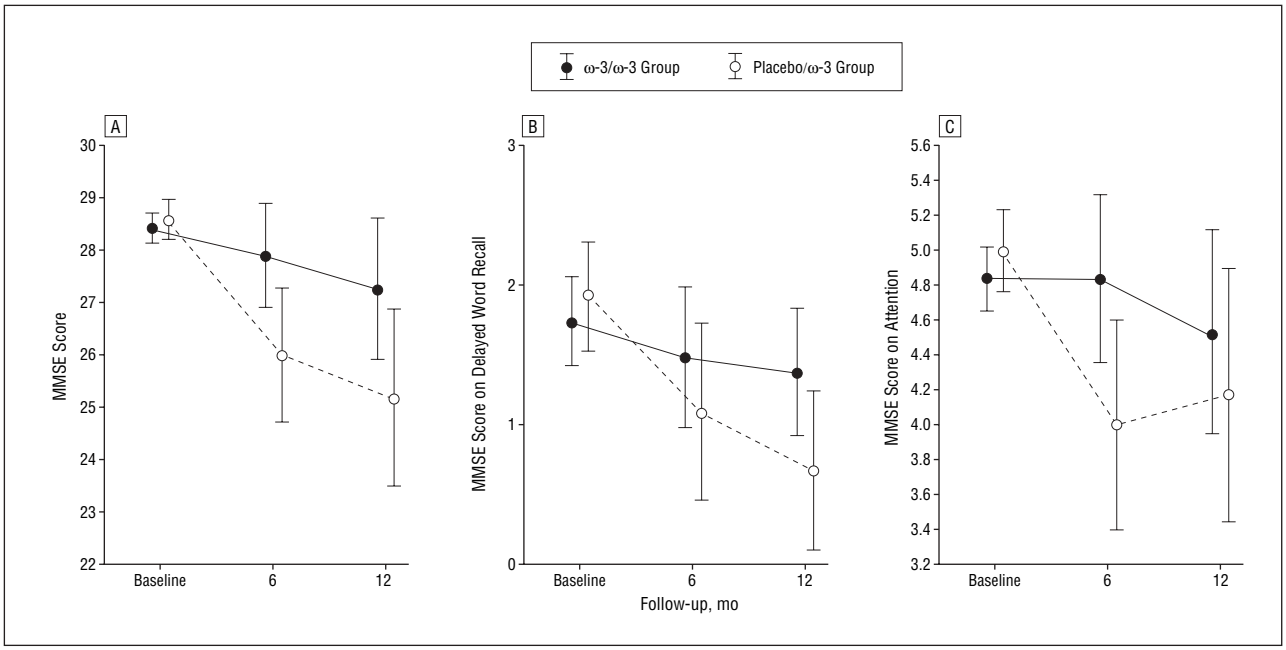

Figure 3. Cognitive tests in patients with very mild Alzheimer disease (Mini-Mental State Examination [MMSE] score >27 points). A, Changes in MMSE score. B and C, Results for the MMSE subitems "Delayed word recall" and "Attention," respectively. The ω-3/ω-3 group received 1.7 g of docosahexaenoic acid and 0.6 g of eicosapentaenoic acid; the placebo/ω-3 group received a placebo containing 1 g of corn oil, including 0.6 g of linoleic acid and between 6 and 12 months of the ω-3 fatty acid supplement.

pravvivenza nell'Infarto Miocardico)[24] for prevention of cardiovascular disease. However, it is many times higher than the estimated intake of ω-3 fatty acids in fish products in the epidemiologic studies of prevention of AD.[3-5]

In many trials of supplementation with purified ω-3 fatty acids, EPA has been the predominant acid (over DHA). In our study, 2.8-fold more DHA than EPA was given. The reason for this was data on deficiency of DHA in AD-affected brains[11-13] and data from DHA-treated APPsw Tg2576 transgenic mice, in which dietary DHA reduced brain total amyloid in a dose-dependent way, particularly in hippocampi and parietal cortices.[9,10] These areas are also the earliest to be affected by AD in human beings,[17] disturbing, for example, verbal episodic memory.[25,26] The neuropathologic findings in this mouse model of AD may mimic a very early stage of AD.

The lack of effect of ω-3 fatty acids on cognitive functions in patients with AD who had MMSE scores of 15 to 30, in combination with the positive effect on those subjects who had the most preserved cognitive functioning, are in agreement with findings from epidemiologic studies. These studies suggest that a high intake of DHA-rich fish prevents development of AD.[1-3] In a 7-year follow-up study, the risk for developing dementia was 0.66 (95% confidence interval, 0.47-0.93) in elderly subjects who consumed at least 1 fish meal per week compared with those who seldom or never consumed fish.[2] Combined data from the epidemiologic studies point to preventive effects from long-term fish intake. Those results and the results from the present study support the idea that ω-3 fatty acids have a role in primary prevention of AD but not in treatment of manifest disease.

Notwithstanding the negative results in the entire group of patients, our study indicated that the ω-3 fatty acid preparation conferred a slower decline of cognition in those with the mildest impairment (MMSE >27 points) compared with placebo-treated control subjects with a similar degree of cognitive dysfunction at the start of the study. This was also observed in the second part of the trial, when all patients were given the ω-3 fatty acid preparation, since the decline rate in the previously placebo-treated patients was reduced to become similar to that in those given the ω-3 fatty acid preparation during the entire trial. These findings, found in post hoc analyses, were based on a few patients with very mild AD and need to be confirmed in large patient cohorts. It is important to emphasize the similarities found in our post hoc analyses of patients with very mild AD. Both on the MMSE and ADAS-COG, the improvement was found in the memory component, reflecting a key symptom in AD, the episodic memory. Also, the latter 6 months of the study was not placebo controlled, which suggests the possibility that better cognitive performance could be due to practice effects (or other factors) rather than to the ω-3 fatty acid supplements.

The mechanisms by which ω-3 fatty acids could interfere in AD pathophysiologic features are not clear, but since anti-inflammatory effects are an important part of the profile of fish oils, they are conceivable also for AD. Similarly, as in previous studies with anti-inflammatory agents in patients, our findings were negative. It is possible that when the disease is clinically apparent, the neuropathologic involvement is too advanced to be substantially attenuated by anti-inflammatory treatment.

Recent epidemiologic evidence indicates that there may be a critical period, 2 or more years before the onset of dementia, during which inflammatory mediators are elevated in the brain mildly to moderately affected by AD.[27] Little is known about the pathologic progression from an at-risk state to clinical disease and whether a differ-

ent set of processes takes over at some point to cause progression of clinical disease.

These findings cannot serve as a basis for general recommendations for treatment of AD with dietary DHA-rich fish oil preparations. However, studies in larger cohorts with mild cognitive impairment, including those at risk for AD, are needed to further explore the possibility that ω-3 fatty acids might be beneficial in halting initial progression of the disease.

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eTable 1. Absolute Data on Subitems of the MMSE in Patients With MMSE>27 Points at Baseline*

MMSE Subitems	Treatment Group	Baseline	Follow-up, mo		*P* Value at Follow-up, mo	
			6	12	0-6	6-12
Orientation, time (maximum of 5 points)	ω-3/ω-3	4.74 (4.52-4.95)	4.37 (3.97-4.77)	4.26 (3.62-4.90)	.19	.71
	Placebo/ω-3	4.87 (4.51-5.18)	4.33 (3.71-4.96)	4.31 (3.68-4.93)	.16	.99
Orientation, place (maximum, 5 points)	ω-3/ω-3	5.00 (NA)	4.90 (4.74-5.05)	4.84 (4.66-5.02)	NS	NS
	Placebo/ω-3	5.00 (NA)	5.00 (NA)	4.92 (4.76-5.09)	NS	NS
Registration (maximum, 3 points)	ω-3/ω-3	3.00 (NA)	3.00 (NA)	3.00 (NA)	NS	NS
	Placebo/ω-3	3.00 (NA)	3.00 (NA)	3.00 (NA)	NS	NS
Attention (maximum, 5 points)	ω-3/ω-3	4.84 (4.60-5.08)	4.84 (4.66-5.02)	4.53 (4.03-5.02)	.99	.20
	Placebo/ω-3	5.00 (NA)	4.00 (2.99-5.01)	4.23 (3.33-5.13)	.002	.59
Delayed word recall (maximum, 3 points)	ω-3/ω-3	1.74 (1.47-2.01)	1.47 (0.98-1.97)	1.37 (0.86-1.88)	.21	.62
	Placebo/ω-3	1.85 (1.36-2.33)	1.08 (0.34-1.82)	0.77 (0.27-1.27)	.003	.12
Language (maximum, 2 points)	ω-3/ω-3	2.00 (NA)	2.00 (NA)	2.00 (NA)	NS	NS
	Placebo/ω-3	2.00 (NA)	2.00 (NA)	2.00 (NA)	NS	NS
Repetition (maximum, 1 point)	ω-3/ω-3	1.00 (NA)	0.95 (0.84-1.06)	0.89 (0.74-1.05)	NS	NS
	Placebo/ω-3	1.00 (NA)	0.92 (0.73-1.10)	0.77 (0.50-1.03)	NS	NS
3-Steps (maximum, 3 points)	ω-3/ω-3	3.00 (NA)	3.00 (NA)	3.00 (NA)	NS	NS
	Placebo/ω-3	3.00 (NA)	3.00 (NA)	3.00 (NA)	NS	NS
Reading (maximum, 1 point)	ω-3/ω-3	1.00 (NA)	1.00 (NA)	1.00 (NA)	NS	NS
	Placebo/ω-3	1.00 (NA)	1.00 (NA)	1.00 (NA)	NS	NS
Writing (maximum, 1 point)	ω-3/ω-3	1.00 (NA)	1.00 (NA)	1.00 (NA)	NS	NS
	Placebo/ω-3	1.00 (NA)	1.00 (NA)	1.00 (NA)	NS	NS
Copying (maximum, 1 point)	ω-3/ω-3	0.90 (0.74-1.05)	0.90 (0.74-1.05)	0.90 (0.74-1.05)	.99	.99
	Placebo/ω-3	0.92 (0.76-1.09)	0.92 (0.73-1.1)	0.92 (0.76-1.09)	.99	.99

Abbreviations: MMSE, Mini-Mental Status Examination; NA, no confidence intervals obtained; NS, no significance values obtained.

*Data are given as mean (95% confidence interval). The ω-3/ω-3–treated group received 1.7 g of docosahexaenoic acid and 0.6 g of eicosapentaenoic acid; the placebo/ω-3–treated received a placebo containing 1 g of corn oil, including 0.6 g of linoleic acid and between 6 and 12 mo of the ω-3 fatty acid supplement.

eTable 2. Absolute Data on ADAS-Cog Subscales in Patients With MMSE>27 Points at Baseline*

ADAS-COG Subscales	Treatment Group	Baseline	Follow-up, mo		*P* Value at Follow-up, mo	
			6	12	0-6	6-12
Word recall task (maximum, 10 points)	ω-3/ω-3	4.26 (3.71-4.82)	4.32 (3.53-5.10)	5.16 (4.51-5.81)	.90	.01
	Placebo/ω-3	5.54 (4.95-6.12)	5.54 (4.66-6.41)	6.38 (5.66-7.11)	.99	.03
Naming objects and fingers (maximum, 5 points)	ω-3/ω-3	0.05 (–0.06-0.16)	0.05 (–0.06-0.16)	0.11 (–0.05-0.26)	.99	.40
	Placebo/ω-3	0.15 (–0.07-0.38)	0.15 (–0.07-0.38)	0.23 (–0.03-0.5)	.99	.30
Delayed word recall (maximum, 10 points)	ω-3/ω-3	5.21 (4.24-6.8)	5.68 (4.8-6.56)	6.26 (5.14-7.39)	.20	.10
	Placebo/ω-3	7.00 (5.72-8.28)	8.31 (7.11-9.50)	8.00 (7.11-8.89)	.007	.51
Commands (maximum, 5 points)	ω-3/ω-3	0.21 (0.01-0.41)	0.11 (–0.05-0.26)	0.11 (–0.05-0.26)	.45	.99
	Placebo/ω-3	0.46 (–0.22-1.14)	0.54 (0.14-0.94)	0.46 (0.06-0.86)	.65	.65
Constructional praxis (maximum, 5 points)	ω-3/ω-3	0.58 (0.18-0.98)	0.79 (0.24-1.34)	0.58 (0.18-0.98)	.28	.28
	Placebo/ω-3	0.69 (0.24-1.15)	0.38 (0.08-0.69)	0.62 (0.31-0.92)	.19	.33
Ideational praxis (maximum, 5 points)	ω-3/ω-3	NA	NA	0.05 (–0.06-0.16)	NS	NS
	Placebo/ω-3	NA	NA	0.08 (–0.09-0.24)	NS	NS
Orientation (maximum, 8 points)	ω-3/ω-3	0.53 (0.03-1.02)	0.58 (0.14-1.01)	0.84 (0.17-1.51)	.85	.34
	Placebo/ω-3	0.46 (0.15-0.78)	1.08 (0.32-1.84)	1.69 (0.47-2.91)	.07	.07
Word recognition (maximum, 12 points)	ω-3/ω-3	2.84 (1.67-4.01)	4.05 (2.75-5.35)	3.95 (2.72-5.18)	.02	.84
	Placebo/ω-3	4.23 (2.95-5.52)	3.85 (2.62-5.08)	3.92 (2.33-5.51)	.54	.90
Remembering test instruction (maximum, 5 points)	ω-3/ω-3	0.11 (–0.05-0.26)	0.00 (NA)	0.05 (–0.06-1.16)	NS	NS
	Placebo/ω-3	NA	NA	0.31 (–0.15-0.76)	NS	NS
Spoken language ability (maximum, 5 points)	ω-3/ω-3	NA	0.05 (–0.06-0.16)	0.00 (NA)	.12	.12
	Placebo/ω-3	0.08 (–0.09-0.24)	0.08 (–0.09-0.24)	0.08 (–0.09-0.24)	.99	.99
Word-finding difficulty (maximum, 5 points)	ω-3/ω-3	0.11 (–0.05-0.26)	0.05 (–0.06-0.16)	0.05 (–0.06-0.16)	.60	.99
	Placebo/ω-3	NA	0.15 (–0.07-0.38)	0.38 (–0.01-0.78)	.21	.06
Comprehension of spoken language (maximum, 5 points)	ω-3/ω-3	0.26 (0.05-0.48)	NA	0.11 (–0.05-0.26)	.06	.44
	Placebo/ω-3	0.23 (–0.13-0.5)	0.38 (–0.01-0.78)	0.31 (0.02-0.6)	.35	.64
Concentration/ distractibility (maximum, 5 points)	ω-3/ω-3	NA	0.06 (–0.06-0.17)	0.05 (–0.06-0.16)	.36	.99
	Placebo/ω3	0.08 (–0.09-0.24)	NA	NA	.29	.99

Abbreviations: ADAS-COG, cognitive portion of the Alzheimer disease Assessment Scale; NA, no confidence intervals obtained; NS, no significance values obtained.

*Data are given as mean (95% confidence interval). The ω-3/ω-3–treated group received 1.7 g of docosahexaenoic acid and 0.6 g of eicosapentaenoic acid; the placebo/ω-3–treated received a placebo containing 1 g of corn oil, including 0.6 g of linoleic acid and between 6 and 12 mo of the ω-3 fatty acid supplement.