Omega-3 Fatty Acid Supplementation Effects on Weight and Appetite in Patients with Alzheimer's Disease: The Omega-3 Alzheimer's Disease Study

Gerd Faxén Irving, PhD,* ** Yvonne Freund-Levi, MD,† ** Maria Eriksdotter-Jönhagen, MD, PhD,†
Hans Basun, MD, PhD,‡ Kerstin Brismar, MD, PhD,§ Erik Hjorth, MSc,† Jan Palmblad, MD, PhD,∥
Bengt Vessby, MD, PhD,# Inger Vedin, Msc,∥ Lars-Olof Wahlund, MD, PhD,† and
Tommy Cederholm, MD, PhD#

OBJECTIVES: To study the effects of omega (Ω)-3 fatty acid (FA) supplements on weight and appetite in patients with mild to moderate Alzheimer's disease (AD) in relation to inflammatory biomarkers and apolipoprotein E ε4 (APOEε4).

DESIGN: Randomized, double-blind, placebo-controlled trial.

SETTING: Specialist memory clinics in the Stockholm catchment area.

PARTICIPANTS: Two hundred four patients (aged 73 ± 9, 52% women) with mild to moderate AD.

INTERVENTION: Patients with AD received 1.7 g of docosahexaenoic acid (DHA) and 0.6 g of eicosapentaenoic acid (EPA) (Ω-3/Ω-3 group; n = 89, aged 73 ± 9, 57% women) or placebo 0.6 g of linoleic acid per day (placebo/Ω-3 group; n = 85, aged 73 ± 9, 46% women) for 6 months. After 6 months, all patients received DHA and EPA for another 6 months.

MEASUREMENTS: Anthropometry, biochemical nutritional and inflammatory markers, and appetite assessed by caregiver.

RESULTS: Mean weight and body mass index (kg/m²) at baseline were 70.0 ± 11.8 kg and 24.3 ± 3.0 kg/m², respectively. At 6- and 12-month follow-up, weight had increased 0.7 ± 2.5 kg (P =.02) and 1.4 ± 2.9 kg (P < .001) in the Ω-3/Ω-3 group. In the placebo group, weight was unchanged at 6 months but had increased (P =.01) at 12 months follow-up after Ω-3 supplementation was initiated. Appetite improved in the Ω-3/Ω-3 group over the treatment period (P =.01). In logistic regression analyses, not carrying the APOEε4 allele and high plasma DHA concentrations were independently related to weight gain in the combined group of patients at 6 months follow-up.

CONCLUSION: A DHA-enriched Ω-3 FA supplement may positively affect weight and appetite in patients with mild to moderate AD. Not carrying the APOEε4 allele and high DHA were independently associated with weight gain. J Am Geriatr Soc 57:11–17, 2009.

Key words: Ω-3 fatty acids; weight gain; Alzheimer's disease; dementia; appetite; nutrition; APOE

Cross-sectional studies show that patients with dementia weigh less and have lower body mass index than cognitively intact elderly.[1] Weight loss might precede the diagnosis of Alzheimer's disease (AD).[2,3] Even though weight loss is present in the early stages of the disease, it increases with the severity and progression of AD.[4] The etiology of the weight loss is probably multifactorial. Potential contributing factors are inflammatory components of the disease; impaired olfaction and taste;[5] and behavior problems like agitation, restlessness,[6] and wandering, which lead to increased energy expenditure.[7]

Although it has been suggested that inflammatory processes in the brain are of etiologic importance in AD,[8] only a few studies have reported high levels of proinflammatory cytokines in the plasma or cerebrospinal fluid of patients with AD.[9,10] Tumor necrosis factor alpha (TNF-α) derived from the local central nervous system (CNS) inflammatory reaction in AD may account for the AD-related anorexia and weight loss.[11] It has been reported that antiinflammatory

treatment that reduces TNF-α in geriatric patients might prevent cachexia.[12] Omega (Ω)-3 fatty acids (FAs) have been shown to have antiinflammatory effects through several mechanisms (e.g., they decrease levels of proinflammatory eicosanoids and cytokines and produce antiinflammatory resolvins). Such administration may have the potential to reduce anorexia and weight loss in patients with AD. Fish fat and fish oils are the most important sources of Ω-3 FAs in humans. Several prospective studies have reported protective associations between fish and the risk of incident AD.[13–15] The content of Ω-3 FAs in the brain, as well as in plasma, is low in patients with AD, and progression of the disease appears to aggravate this.[16]

One of the major risk factors for developing late-onset AD (LOAD) is the occurrence of the apolipoprotein E ε4 (APOEε4) genotype. APOE is the major lipoprotein in the brain and an important cholesterol-transporting protein.[17] Dietary interventions in midlife in individuals carrying the APOEε4 allele might modify the risk of dementia and AD.[18,19]

The primary aim of this study was to evaluate the effects of Ω-3 FA supplementation on weight, appetite, and other nutritional parameters. In addition, the importance of inflammation and APOEε4 on weight was evaluated.

METHODS

Patients

Two hundred four patients (aged 73 ± 9, 52% women) with mild to moderate AD were included in the Omega-3 Alzheimer's Disease (OmegAD) Study, previously described in detail.[20] The study was conducted between December 2001 and March 2004. All subjects were recruited from specialist memory clinics in the Stockholm catchment area.

The inclusion criteria required that patients have a diagnosis of AD according to the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*, criteria,[21] and a Mini-Mental State Examination (MMSE)[22] score between 15 and 30, be living in their own homes, be treated with a stable dose of acetylcholine esterase inhibitors (AChEIs) for at least 3 months before study start, and plan to remain on AChEI for the study period. Patients were excluded if they were being treated with nonsteroidal antiinflammatory drugs (low-dose acetylsalicylic acid was accepted), Ω-3 preparations, or anticoagulation agents; abused alcohol; suffered from a concomitant serious disease; or did not have a caregiver.

Procedures and Study Design

Before inclusion in the study, all 204 patients had undergone a medical examination at one of the memory clinics, including information about history from a close informant and assessment of somatic, neurological, and psychiatric status. Computerized brain tomography or magnetic resonance imaging and psychometric testing of cognition were performed, blood samples for APOE genoype analyses were extracted from peripheral blood cells using standard methods,[23] and APOE genotype was determined using a microsequencing method on microtiter plates (AffiGene APOE Sangtec Medical Bromma, Stockholm, Sweden). A member of the study team (YFL) reassessed the AD diagnosis.

Two hundred four patients (110 women and 94 men) completed the baseline assessments, and 174 patients completed the study. The study was designed as a double-blind randomized placebo-controlled study. Patients were randomized in blocks of four, using sealed envelopes and according to a computerized table of random numbers, to receive four 1-g capsules daily, each containing 430 mg DHA and 150 mg EPA (EPAX1050TGfrom Pronova Biocare A/S, Lysaker, Norway) or an isocaloric placebo oil (containing 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 for all patients. The two groups were denoted the Ω-3/Ω-3 and placebo/Ω-3 group, respectively. The dropout rate was 15% (14 in the Ω-3/Ω-3 group and 16 in the placebo/Ω-3 group). The reasons for leaving the study were mainly gastrointestinal symptoms, such as diarrhea (n = 9) and dysphagia (due to the size of the capsules; n = 9), intervening serious somatic disease (n = 10), nonadherence (n = 1), and withdrawn informed consent (n = 1). The Ω-3 preparation was well tolerated and safe.

EPAX1050TG is a 60% Ω-3 concentrate in triglyceride form produced according to Good Manufacturing Practices. Four mg of vitamin E (tocopherol) was added to each EPAX1050TG and placebo capsule.

Methods

Included patients underwent the following evaluations at baseline and 6 and 12 months described in detail previously:[20] routine blood and urine samples, blood pressure assessments, global function using the Clinical Dementia Rating Scale (CDR), and cognitive function using the MMSE and the modified cognitive subscale of the Alzheimer's Disease Cognitive Assessment (ADAS-Cog) Scale. Neuropsychiatric symptoms were analyzed using the Neuropsychiatric Inventory (NPI)[24] and are presented elsewhere.[25] The NPI covers 12 domains (e.g., apathy, depression, and appetite), and the caregiver rates the answers. The appetite domain was analyzed in this study. The caregiver rated the appetite of the study participant at three levels (decreased, unchanged, or increased) at baseline, assessed in comparison with habitual status and at 6- and 12-month follow-up from the previous assessments). Changes were categorized into four frequencies ranging from 1 (< 1/week) to 4 (daily or constantly). Thus, a score of 1 to 9 was constructed, with 1 corresponding to constantly or always decreased appetite, 5 indicated unchanged appetite, and 9 equaled constantly or always increased appetite compared with habitual status at baseline or previous assessments.

Nutritional assessment was performed using anthropometric and biochemical assessments at baseline and 6 and 12 months and included body mass index (BMI, kg/m^2), triceps skinfold (TSF, mm) measured using a Harpenden Skinfold caliper, and arm muscle circumference (AMC, cm) calculated according to Jelliffe.[26] The measurements were made between the acromiom and the olecranon on the nondominant arm.

Blood samples for analysis of plasma FA levels were assessed using gas chromatography (TR-Fame-column 30 m × 32 mm ID × 0.25 μm film gas chromatography columns; Thermo Electron Corp., Walheim, Beverly, MA). Results are given as the relative abundance of individual FAs.[27]

Plasma albumin was analyzed using the routine methods and reference range of the Laboratory of Clinical Chemistry at Karolinska University Hospital. To measure inflammation, high-sensitivity plasma C-reactive protein (hs-CRP) and plasma interleukin (IL)-6 were analyzed. Routine hs-CRP measurements were made using nephelometry at the Department of Clinical Chemistry at the hospital. Subclinical inflammation was defined as a hs-CRP level higher than 3mg/L.[28] IL-6 levels were analyzed in plasma samples according to enzyme-linked immunosorbent assay using commercially available kits (R&D Systems, Abingdon, Oxon, UK). The detection range was 0.156 to 10 pg/mL for IL-6. Insulin-like growth factor (IGF)-I was determined in plasma according to radioimmune assay after separation of IGFs from IGF binding proteins using acid ethanol extraction and cryoprecipitation.[29] The intra- and interassay coefficients of variation were 4% and 11%, respectively. Plasma levels of IGF-I decrease with age,[30] so IGF-I values were also expressed as standard deviation scores calculated from the regression of the values of 247 healthy adult subjects.[31]

Statistical Analyses

Before the start of the study, power analyses were performed as described previously.[20] Because cognition was the primary overall outcome of the study, no specific power analysis with weight as outcome measure was performed.

Data are presented as means ± standard deviations, 95% confidence intervals (Cis), and medians (25th–75th percentiles). To analyze the variations between two groups the Student t-test, the Mann Whitney U-test and the chi-square test were used in accordance with the type and distribution of the variables. Possible changes at 6- and 12-month follow-up were evaluated using the Student paired t-test or Wilcoxon matched pair test. To analyze longitudinal changes within and between the two groups, analysis of variance repeated measures was used. The Fisher least significant difference (LSD) test was used for post hoc analyses. For correlation analyses, Pearson and Spearman correlation coefficients were calculated depending on the type and distribution of the variables. Logistic regression was performed to evaluate the independent relationship between different relevant variables and weight gain. For the statistical analyses, APOEε4 was dichotomized into carriers and noncarriers of the APOEε4 allele, and appetite was dichotomized into increased or stable and decreased appetite, as assessed by caregivers and compared with earlier habitual status or previous assessments. The Statistica 7.0 software package (Statsoft, Tulsa, OK) was used for the statistical calculations.

Ethical Considerations

The study was conducted according to Good Clinical Practice guidelines and the ethical principles of the Declaration

Table 1. Apolipoprotein E ε4 (APOEε4) Allele, Mini-Mental State Examination (MMSE) Score, and Anthropometric Variables in Patients with Alzheimer's Disease at Baseline and at 6 and 12 Months

Variable	Ω-3/Ω-3 (n = 89)			Placebo/Ω-3 (n = 85)		
	Baseline	6 Months	12 Months	Baseline	6 Months	12 Months
Age, mean ± SD	72.6 ± 9			72.9 ± 8.6		
Female, %	57			46		
APOEε4, n (%)						
0	21 (24)			28 (33)		
1	46 (52)			39 (46)		
2	22 (25)			18 (21)		
MMSE, score, mean ± SD (range 0–30)	23.6 ± 3.8	22.8 ± 4.4	22.1 ± 5	23.2 ± 3.8	22.4 ± 4.2	21.9 ± 4.6
Weight, kg, mean ± SD	69.6 ± 12.2	70.2 ± 12.2*	71 ± 12.1†	70.5 ± 11.5	70.6 ± 11.8	71.6 ± 11.6*
Men	78.2 ± 10.9	79.1 ± 10.9	79.3 ± 10.8	76.1 ± 9.3	76.3 ± 9.5	77.2 ± 9.6*
Women	63.1 ± 8.5	63.7 ± 8.5	64.8 ± 8.9†	63.8 ± 10.4	63.9 ± 10.9	65 ± 10.4
Body mass index (kg/m²), mean ± SD	24.5 ± 3.1	24.8 ± 3.1*	25 ± 3.1†	24.1 ± 2.9	24.1 ± 2.9	24.4 ± 2.6*
Triceps skinfold thickness, mm, median (25th–75th percentile)						
Men (normal range >6)	10.2 (7.6–12)	8.9 (7.6–11.4)	9.4 (7.8–12.6)	9.6 (7–12.4)	9.2 (6.2–11.4)†	8.2 (6.2–10.4)
Women (normal range >10)	16.7 (13.8–19.4)	16.6 (13.8–19)	17.2 (13.8–19.8)	16.4 (12.8–20.2)	17.1 (12.4–19.8)	17.2 (12.4–20)
Arm muscle circumference, cm						
Men (normal range >21)	26.7 (24.5–28.7)	26.8 (24.5–27.9)	26.5 (24.8–28.4)	26 (24.5–27.1)	26 (25.1–27.5)	25.7 (24.8–27.7)
Women (normal range >19)	22.6 (21.3–23.9)	22.8 (21.6–24.1)	22.7 (21.3–24)	22.2 (21–23.3)	22.1 (20.9–23)	21.9 (21–23.6)
Appetite score (1–9)	4.8 ± 2	5.1 ± 2.3	5.6 ± 2.3	4.9 ± 2	4.8 ± 2.4	5.3 ± 2.3

* P < .05, † .01 indicate significance levels in changes over time within the groups at 0–6 and 0–12 months, respectively. No significant variations were noticed in changes between the groups at either 6 or 12 months.
Ω-3/Ω-3 = iatervention group (subjects who received Ω-3 fatty acids from baseline to 12 months; 38 men and 51 women); Placebo/Ω-3 = control group (subjects who received placebo oil from baseline to 6 months and Ω-3 fatty acids from 6 to 12 months; 46 men and 39 women).
SD = standard deviation.

Table 2. Biochemical Variables in Patients with Alzheimer's Disease at Baseline at 6 and 12 Months

Variable	Ω-3/Ω-3 (n = 89)			Placebo/Ω-3 (n = 85)		
	Baseline	6 Months	12 Months	Baseline	6 Months	12 Months
Percentage eicosapentaenoic acid 20:5, mean ± SD[‖]	1.8 ± 0.9	5.5 ± 1.5[‡]	5.5 ± 1.8	1.8 ± 0.8	1.5 ± 0.8[§]	5.1 ± 1.4[‡]
Percentage docosahexaenoic acid 22:6, mean ± SD[‖]	3.1 ± 1.3	6.7 ± 1.5[‡]	6.9 ± 1.6*	3.2 ± 1.2	3 ± 1[§]	6.5 ± 1.3[‡]
Plasma albumin, g/L (normal range 36–45)	38 ± 2.6	37.3 ± 2.8[†]	37.3 ± 2.4	37.7 ± 2.7	37.6 ± 2.7	36.8 ± 2.7[†]
Plasma IGF-I, μg/L (normal range 84–115[#])	141 ± 41	139 ± 46	—	138 ± 42	134 ± 42	—
IGF-I SD score**	0.4 ± 1.1	0.3 ± 1.1	—	0.3 ± 1.0	0.2 ± 1.1	—
Plasma interleukin-6, pg/mL	0.75 (0.5–1.2)	0.6 (0.5–1.4)	—	0.7 (0.5–1.2)	0.8 (0.5–1.4)	—
Plasma high-sensitivity C-reactive protein, mg/L	1 (0.4–1.6)	0.8 (0.5–1.5)	0.8 (0.4–1.9)	0.8 (0.4–2.0)	0.8 (0.4–2.1)	0.6 (0.5–2.0)

* $P < .05$; [†] .01; [‡] .001, significance levels in changes over time within the groups at 6 months and at 12 months; [§] .001, significance levels in difference in change from 0 to 6 months between the groups. No differences in changes were noticed from 6 to 12 months between the groups.
[‖] Fatty acids are given as the relative amount in percentage of all fatty acids analyzed in total plasma.
[#] Mean values in 171 healthy controls 70–96 years of age.[30]
** Number of standard deviations (SDs) from the mean in a reference population.[31]
Ω-3/Ω-3 = intervention group (subjects who received Ω-3 fatty acids from baseline to 12 months; 38 men and 51 women); Placebo/Ω-3 = control group (subjects who received placebo oil from baseline to 6 months and Ω-3 fatty acids from 6 to 12 months; 46 men and 39 women); IGF-I = insulin-like growth factor-I SD = standard deviation.

of Helsinki. Patients and caregivers gave written informed consent before study entry. The local ethics committee at Karolinska University Hospital Huddinge approved the study.

RESULTS

Baseline Characteristics

Baseline data were similar for the two groups and are shown in Tables 1 and 2. Almost one-third of the Ω-3/Ω-3 group and one-quarter of the placebo/Ω-3 group scored higher than 27 on the MMSE, indicating mild AD. Approximately two-thirds of the patients were carriers of the *APOEε4* allele (Table 1). Approximately one-third of each group had a BMI less than 23 (not significant between the groups). Median TSF and AMC were in the normal range in both groups. Mean plasma albumin (Table 2) was within the reference range, but approximately one-fifth of each group had values below this range. Six and eight subjects in Ω-3/Ω-3 group and placebo/Ω-3 group, respectively, had plasma IGF-1 levels below reference values for elderly healthy controls. A hs-CRP level greater than 3 mg/L was found in seven individuals in the Ω-3/Ω-3 group and 13 in the placebo/Ω-3 group.

Six- and 12-Month Follow-Up

Weight had increased significantly in the Ω-3/Ω-3 group at 6 months and even more at 12 months (Figure 1, Table 1). The weight of the placebo-treated patients remained the same at 6 months, whereas significant weight gain was seen after 6 months of active treatment with Ω-3 FAs. The difference between the groups was not significant at any time point. The weight gain associated with Ω-3 FA treatment was observed mainly in patients with BMI less than 23 at study start. Their weight increment was significant at 6 and 12 months, which contrasted with a nonsignificant weight increase in Ω-3 FA–treated patients with BMI of 23 or greater (data not shown). The variations were nonsignificant between the leaner and less-lean subjects.

Twenty-three individuals (26%) in the Ω-3/Ω-3 group and 23 (27%) in the placebo/Ω-3 group lost weight during the 12-month study period (mean 2.1 ± 1.9 kg (1.5%) and 3.3 ± 4.1 kg (2.5%), respectively).

Appetite as assessed by the caregiver seemed to improve with the intervention, and a significant increase was noticed after 12 months of treatment in the Ω-3/Ω-3 group ($P < .05$; Table 1). During placebo treatment the appetite score was unchanged but improved when Ω-3 FA treatment was initiated (Table 1). The variation was nonsignificant between the groups.

Table 2 lists biochemical changes over the observation period. The plasma levels of EPA and DHA increased after the Ω-3 FA treatment. Unexpectedly, plasma albumin
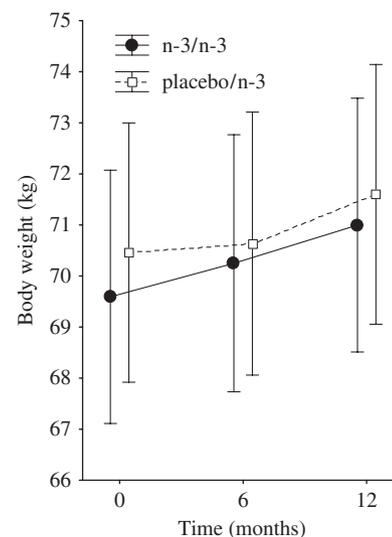
Figure 1. Change in weight in patients given Ω-3 fatty acids (FAs) for 6 and 12 months (Ω-3/Ω-3) and in patients given placebo for 6 months and Ω-3 FA between 6 and 12 months (placebo/Ω-3). The increase was significant at 6 and 12 months in the Ω-3/Ω-3 group and between 6 and 12 months in the placebo/Ω-3 group.

decreased in the Ω-3/Ω-3 group at 6 months but remained stable between 6 and 12 months (Table 2). A similar decrease in plasma albumin was seen in the placebo/Ω-3 group after the 6 months of Ω-3 treatment. No significant changes or differences were observed within or between the groups at 6 months in plasma IGF-I, IGF-I SD-score, plasma IL-6, or hs-CRP (Table 2). Nor were there any significant Ω-3 treatment effects related to carrying the APOEε4 allele over time in any of the examined variables (data not shown).

Correlations and Logistic Regressions

There was a univariate correlation between increase in weight and increase in appetite in the combined group of individuals at 6 (correlation coefficient $(r) = 0.33$, $P < .001$) and 12 ($r = 0.28$, $P < .001$) months. Weight gain and changes in CRP correlated inversely between 6 and 12 months in the combined group ($r = -0.18$, $P = .02$).

Logistic regression analyses were performed to evaluate the independent relationship between different relevant variables and weight gain. Not carrying the APOEε4 allele (OR = 2.19, 95% CI = 1.0–4.6) and increased DHA levels (OR = 3.3, 95% CI = 1.0–11.0) were positively associated with weight gain at 6 months (Table 3).

DISCUSSION

This is the first study to report nutritional effects of Ω-3 FA supplementation given to patients with mild to moderate AD. Weight gain was noted after supplementation with Ω-3 FA, although not significantly different from the placebo group. Likewise, Ω-3 FA treatment significantly improved appetite after 12 months of treatment in the Ω-3/Ω-3 group. An inverse correlation was found between weight gain and change in plasma hs-CRP. Higher plasma DHA levels during the treatment period and not carrying the APOEε4 allele were related to weight gain in logistic regression models in the combined group of patients.

The gain in weight was modest but increased steadily during active treatment in both groups. Appetite seemed to follow the same pattern.

EPA and DHA levels in plasma were measured and indicated good patient adherence to the supplementation throughout the study. EPA has been the predominant FA over DHA in supplementation trials of patients with somatic disorders (e.g., rheumatoid arthritis and cardiovascular disease). In this study, DHA and EPA were given at a

ratio of 3:1. More DHA than EPA was given, because previous data indicate a specific deficiency of DHA in the brains of people with AD.[32] Moreover, experimental data support the notion that DHA is of particular importance for cognitive function.[33]

The participants were diagnosed with AD of mild to moderate severity. Although mean BMI and median TSF and AMC were within the reference ranges in the combined group of patients, a mean BMI of 24, as found in this group, might be regarded as suboptimal, because a BMI less than 23 has been found to be related to poorer 7-year survival in AD patients.[34] Weight loss is one of the principal features of AD and indicates deterioration. Thus, it is important to monitor weight in order to monitor the condition of a patient with AD. The number of patients who lost weight during the study period was modest in comparison with some other 1-year follow-up studies in patients with mild to moderate dementia.

Inflammation (i.e., high plasma hs-CRP concentrations) has been associated with poor memory, vascular dementia, and AD in some population-based studies, whereas others have found no associations. One study reported that higher baseline hs-CRP in women was associated with poor memory at 12-year follow-up.[35] The present study found no such association. Hs-CRP was low (~1 mg/L in both groups of participants) and did not change significantly during the treatment period. The mild to moderate degree of disease probably explains why systemic inflammation was not detected in these patients, although there was a correlation between low hs-CRP and weight gain during the second part of the trial in the combined group. This finding may nevertheless indicate a role for inflammation in appetite regulation in people with AD, which would be in line with several reports on appetite in people with other chronic illnesses.[36,37] Further studies in this field are needed.

Unexpectedly, plasma albumin decreased after 6 months of Ω-3 treatment in the Ω-3/Ω-3 group and after 6 months of treatment in the Ω-3/placebo group at 12 months. The results of this study do not explain the reason or potential clinical significance related to this finding. Because Ω-3 FAs are known to regulate DNA transcription,[38] it might be that the Ω-3 FA treatment had effects on gene expression for albumin. More studies addressing this issue are needed.

Several studies have indicated negative long-term effects of the APOEε4 allele on nutrition-related functions. The APOEε4 allele is associated with weight loss in women with AD[39] as well as in women without dementia.[40] The result from the present study is in line with such results, because it was found that not carrying the APOEε4 allele was independently associated with weight gain. Subjects who did not carry the APOEε4 allele showed weight gain at 6 months. Some reports have suggested that the relationship between the APOEε4 allele and weight loss may converge in the medial temporal lobe (the earliest site of AD pathology). For example APOEε4 carriers seem more prone to suffering from impaired olfactory function before the onset of cognitive impairment.[41,42] In addition, the response in serum lipid profiles to dietary interventions varies between individuals with and without the APOEε4.[43] Furthermore, elderly individuals with the APOEε4 allele with a high intake of calories and fats are at higher risk of AD than

Table 3. Multiple Logistic Regression with Weight Gain as Dependent Variable and Various Relevant Covariates (Yes/No) at 6 Months

Variable	Odds Ratio	95% Confidence Interval	P-Value
Apolipoprotein Eε4 noncarrier	2.19	1.04–4.61	.04
Ω-3 fatty acid treatment	0.48	0.16–1.42	.18
Appetite increment	0.54	0.23–1.28	.16
Docosahexaenoic acid increment	3.34	1.01–11,00	.045
Eicosapentaenoic acid increment	0.89	0.26–2.98	.84
C-reactive protein decrease	1.17	0.59–2.31	.64

individuals without the *APOEε4* allele.[19] There were no clear relationships between the occurrence of the *APOEε4* allele and plasma levels of Ω-3 FAs and no clear Ω-3 FA treatment effects in the current study (data not shown).

One limitation of the study is the lack of food intake data. The patients and their caregivers were advised not to change their dietary habits during the study. Data from food frequency questionnaires were collected in a subsample of the patients and will be presented separately. Another limitation of the study is that power calculations were not performed with weight as the outcome variable, because the main purpose of the OmegAD Study was to evaluate cognitive effects of Ω-3 FA treatment.

In summary, patients with mild to moderate AD who received Ω-3 FA supplementation, especially enriched with DHA, gained weight over treatment periods of 6 to 12 months. However, no firm conclusions can be drawn because there was no significant difference between the treatment groups. It has been suggested that Ω-3 FAs reduce anorexia and cachexia in patients with malignant diseases, although this hypothesis is still not proven.[44] Supportive of the assumption that Ω-3 FAs may improve appetite and result in weight gain in patients with AD was the positive association between elevations in plasma DHA and gain in weight noticed in the logistic regression analyses.

REFERENCES

1. White H, Pieper C, Schmader K et al. Weight change in Alzheimer's disease. J Am Geriatr Soc 1996;44:265–272.
2. Cronin-Stubbs D, Beckett LA, Scherr PA et al. Weight loss in people with Alzheimer's disease: A prospective population based analysis. BMJ 1997;314:178.
3. Barrett-Connor E, Edelstein SL, Corey-Bloom J et al. Weight loss precedes dementia in community-dwelling older adults. J Am Geriatr Soc 1996;44:1147–1152.
4. White H, Pieper C, Schmader K. The association of weight change in Alzheimer's disease with severity of disease and mortality: A longitudinal analysis. J Am Geriatr Soc 1998;46:1223–1227.
5. Schiffman SS, Graham BG, Sattely-Miller EA et al. Taste, smell and neuropsychological performance of individuals at familial risk for Alzheimer's disease. Neurobiol Aging 2002;23:397–404.
6. Morris CH. Eating habits in dementia. A descriptive study. Br J Psychiatry 1989;154:801–806.
7. Rheaume Y, Riley ME, Volicer L. Meeting nutritional needs of Alzheimer patients who pace constantly. J Nutr Elderly 1987;7:43–52.
8. Engelhart MJ, Geerlings MI, Meijer J et al. Inflammatory proteins in plasma and the risk of dementia. The Rotterdam Study. Arch Neurol 2004;61:668–672.
9. Fillit H, Ding WH, Buee L et al. Elevated circulating tumor necrosis factor levels in Alzheimer's disease. Neurosci Letter 1991;129:318–320.
10. Tarkowski E, Blennow K, Wallin A et al. Intracerebral production of tumor necrosis factor-α, a local neuroprotective agent, in Alzheimer disease and vascular dementia. J Clin Immunol 1999;19:223–230.
11. Zuliani G, Ranzini M, Guerra G et al. Plasma cytokines profile in older subjects with late onset Alzheimer's disease or vascular dementia. J Psychiatr Res 2007;41:686–693.
12. Yeh SS, Blackwood K, Schuster MW. The cytokine basis of cachexia and its treatment: Are they ready for prime time? J Am Med Dir Assoc 2008;9:219–236.
13. Morris MC, Evans DA, Bienias JL et al. Consumption of fish and Ω-3 fatty acids and risk of incident Alzheimer disease. Arch Neurol 2003;60:940–946.
14. Barberger-Gateau P, Letenneur L, Deschamps V et al. Fish, meat, and risk of dementia: Cohort study. BMJ 2002;325:932–933.
15. Schaefer EJ, Bongard V, Beiser AS et al. Plasma phosphatidylcholine docosahexaenoic acid content and risk of dementia and Alzheimer disease: The Framingham heart study. Arch Neurol 2006;63:1545–1550.
16. McGahon BM, Martin DS, Horrobin DF et al. Age-related changes in synaptic function: Analysis of the effect of dietary supplementation with omega-3 fatty acids. Neuroscience 1999;94:305–314.
17. Lane RM, Farlow MR. Lipid homeostasis and apolipoprotein E in the development and progression of Alzheimer's disease. J Lipid Res 2005;46:949–968.
18. Laitinen MH, Ngandu T, Rovio S et al. Fat intake at midlife and risk of dementia and Alzheimer's disease. A population-based study. Dement Geriatr Cogn Disord 2006;22:99–107.
19. Luchsinger JA, Tang MX, Shea S et al. Caloric intake and the risk of Alzheimer disease. Arch Neurol 2002;59:1258–1263.
20. Freund-Levi Y, Eriksdotter-Jönhagen M, Cederholm T et al. Omega 3 fatty acid treatment in174 patients with mild to moderate Alzheimer's disease: OmegAD Study. Arch Neurol 2006;63:1402–1408.
21. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, 4th Ed. Washington, DC: American Psychiatric Association, 1994.
22. Folstein MF, Folstein SE, McHugh PR. "Mini mental state". A practical method for grading cognitive state of patients for the clinician. J Psychiatr Res 1975;12:189–198.
23. Hixson JE, Vernier DT. Restriction isotyping of human apolipoprotein E by gene amplification and cleavage with HhaI. J Lipid Res 1990;31:545–548.
24. Cummings JL, Mega M, Gray K et al. The neuropsychiatric inventory: Comprehensive assessment of psychopathology in dementia. Neurology 1994;44:2308–2314.
25. Freund-Levi Y, Eriksdotter-Jönhagen M, Cederholm T et al. Omega 3 supplementation in mild to moderate Alzheimer's disease: Effects on neuropsychiatric symptoms. Int J Geriatr Psychiatry 2007;22:1–9.
26. Jelliffe DB. The Assessment of the Nutritional Status of the Community. Geneva: WHO, 1966.
27. Boberg M, Croon LB, Gustafson IB et al. Platelet fatty acid composition in relation to fatty acid composition in plasma and to serum lipoprotein lipids in healthy subjects with special reference to the linoleic acid pathway. Clin Sci (Lond) 1985;68:581–587.
28. Pearson TA, Mensah GA, Alexander RW et al. Markers of inflammation and cardiovascular disease: Application to clinical and public health practice: A statement for healthcare professionals from the Centers for Disease Control

and Prevention and the American Heart Association. Circulation 2003;107: 499–511.

29. Bang P, Eriksson U, Sara V et al. Comparison of acid ethanol extraction and acid gel filtration prior to IGF-I and IGF-II radioimmunoassays: Improvement of determinations in acid ethanol extracts by the use of truncated IGF-I as radioligand. Acta Endocrinol (Copenhagen) 1991;124:620–629.

30. Hilding A, Hall K, Wivall-Hilleryd IL et al. Serum levels of insulin-like growth factor I (IGF-I) in 152 patients with growth hormone (GH) deficiency aged 19–82 years in relation to healthy subjects. J Clin Endocrinol Metab 1999;84: 2013–2019.

31. Hilding A, Brismar K, Degerblad M et al. Altered relation between circulating levels of insulin-like growth factor binding protein-1 and insulin in growth hormone deficient patients and insulin-dependent diabetic patients compared to that in healthy subjects. J Clin Endocrinol Metab 1995;80:2646–2652.

32. Tully AM, Roche HM, Doyle R et al. Low serum cholesteryl ester-doc-osahexaenoic acid levels in Alzheimer's disease: A case-control study. Br J Nutr 2003;89:483–489.

33. Lim GP, Calon F, Morihara T et al. A diet enriched with the omega-3 fatty acid docosoahexaenoic acid reduces amyloid burden in an aged Alzheimer mouse model. J. Neurosci 2005;25:3032–3040.

34. Faxén-Irving G, Basun H, Cederholm T. Nutritional and cognitive relation-ships and longterm mortality in patients with various dementia disorders. Age Ageing 2005;34:136–141.

35. Komulainen P, Lakka TA, Kivipelto M et al. Serum high sensitivity C-reactive protein and cognitive function in elderly women. Age Ageing 2007;36:443–448.

36. Koehler F, Doehner W, Hoernig S et al. Anorexia in chronic obstructive pul-monary disease—association to cachexia and hormonal derangement. Int J Cardiol 2007;119:83–89.

37. Carrero JJ, Quereshi AR, Axelsson J et al. Comparison of nutritional and inflammatory markers in dialysis patients with reduced appetite. Am J Clin Nutr 2007;85:695–701.

38. de Urquiza AM, Liu S, Sjoberg M et al. Docosahaxaenoic acid, a ligand for the retinoid X receptor in mouse brain. Science 2000;290:2140–2144.

39. Vanhanen M, Kivipelto M, Koivisto K et al. APOE-epsilon4 is associated with weight loss in women with AD. A population-based study. Neurology 2001;56:655–659.

40. Cauley JA, Zmuda JM, Yaffe K et al. Apolipoprotein E polymorphism. A new genetic marker of hip fracture risk- the study of osteoporotic fractures. J Bone Miner Res 1999;14:1175–1181.

41. Bacon AW, Bondi MW, Salmon DP et al. Very early changes in olfactory function due to Alzheimer's disease and the role of apolipoprotein E in olfac-tion. Ann NY Acad Sci 1998;855:723–731.

42. Borenstein GA, Bowen JD, Rajaram L et al. Impaired olfaction as a marker for cognitive decline. Interaction with apolipoprotein E ε4 status. Neurology 1999;53:1480–1487.

43. Berglund L. The APOE gene and diets: Food (and drink) for thought. Am J Clin Nutr 2001;73:669–670.

44. Fearon KCH, Barber MD, Moses AG et al. Double-blind, placebo-controlled, randomized study of eicosapentaenoic acid diester in patients with cancer cachexia. J Clin Oncol 2006;24:3401–3407.