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Effect of fish-oil supplementation on mental well-being in older subjects: a randomized, double-blind, placebo-controlled trial[1–3]

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ABSTRACT

Background: It is suggested that a low intake of fish and/or n−3 PUFA is associated with depressed mood. However, results from epidemiologic studies are mixed, and randomized trials have mainly been performed in depressed patients, yielding conflicting results.

Objective: We investigated the effect of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) on mental well-being in a double-blind, placebo-controlled trial.

Design: Independently living individuals (n = 302) aged ≥65 y were randomly assigned to consume 1800 mg/d EPA+DHA, 400 mg/d EPA+DHA, or placebo capsules for 26 wk. Changes in mental well-being were assessed as the primary outcome with the Center for Epidemiologic Studies Depression Scale (CES-D), Montgomery-Åsberg Rating Scale (MADRS), Geriatric Depression Scale (GDS-15), and Hospital Anxiety and Depression Scale (HADS-A).

Results: Plasma concentrations of EPA+DHA increased by 238% in the high-dose and 51% in the low-dose fish-oil group compared with the placebo group, reflecting excellent compliance. Baseline CES-D scores ranged from 5.9 to 6.8 in the 3 groups and were not significantly different between groups. Mean changes in CES-D scores after 26 wk were −0.2, 0.2, and −0.4 (P = 0.87) in the high-dose fish oil, low-dose fish oil, and placebo groups, respectively. Treatment with neither 1800 mg nor 400 mg EPA+DHA differentially affected any of the measures of mental well-being after 13 or 26 wk of intervention compared with placebo.

Conclusions: In this randomized, double-blind, placebo-controlled trial we observed no effect of EPA+DHA supplementation for 26 wk on mental well-being in the general older population studied. This trial was registered at clinicaltrials.gov as NCT00124852. *Am J Clin Nutr* 2008;88:706–13.

INTRODUCTION

Depression is a common mental disorder with a complex etiology. Depressive disorders affect 121 million people worldwide (1) and are the third leading cause of burden of disease in high-income countries (2). Depression can be diagnosed reliably in primary care, but not all treatments are effective. According to a World Health Organization report, 36–50% of serious cases in developed countries and 76–85% of serious cases in less-developed countries do not receive treatment (3). Therefore, it is important to focus on factors that may help to prevent the development of depressive disorders.

Several studies showed depletions in n−3 polyunsaturated fatty acids (PUFAs) in blood or adipose tissue to be associated with depression (4–10). PUFAs are very-long-chain fatty acids found in plants and marine sources. The marine-based n−3 PUFAs primarily consist of eicosapentaenoic acid (EPA, C20:5n−3) and docosahexaenoic acid (DHA, C22:6n−3). Because n−3 PUFAs are a major component of neural membranes and act as precursors of compounds involved in immune and inflammatory responses, it is biologically plausible that they could play a role in mood and behavioral disorders (11).

Most observational studies showed an inverse association of fish intake with prevalence of depression (12–15). Three epidemiologic studies with 3204, 5689, and 29 133 subjects, respectively, have been performed in the general Finnish population (12, 13, 16), and 1 has been performed in 332 Dutch elderly men (15). Tanskanen al (12) and Timonen et al (13) found effects only in women (12, 13), which could explain why Hakkarainen et al(16), who studied a male population, found no association. However, this is contradictory to the findings of Kamphuis et al (15), who found an association in a male population. The age of this population (70–79 y) could explain the difference in results found. Hibbeln (14) made a cross-national comparison of 13 countries including 35 000 subjects and showed a negative association between fish intake and prevalence of major depression. Studies using n−3 PUFA concentrations in the blood also found higher concentrations to be associated with less depression (4–8), as was the case for n−3 PUFAs in adipose tissue (9, 10).

Until now, 19 randomized trials investigating the effects of n−3 PUFAs on depressed mood have been performed. Twelve studies, most of them performed in depressed patients, were included in a recent meta-analysis by Appleton et al (17), who stated that the evidence available provided little support. Fontani et al (18) performed the only trial in healthy subjects (n = 33) with a mean age of 33 y, who experienced an improvement in mood during daily supplementation with 1.6 g EPA and 0.8 g DHA for 35 d. Recently, Rogers et al (19) performed a trial in

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Received December 7, 2007.

Accepted for publication March 18, 2008.

mild to moderately depressed individuals from the general population and did not observe an effect after 3 mo of supplementation with 1.5 g EPA+DHA/d.

The aim of the present study was to investigate whether supplementation with n−3 PUFAs would be beneficial in improving the mental well-being of nondepressed, older individuals. We conducted a double-blind, randomized, placebo-controlled trial in 302 Dutch individuals who were administered a high dose (1.8 g/d) or a low dose (400 mg/d) of EPA+DHA or placebo capsules for 26 wk.

SUBJECTS AND METHODS

Subjects

The subjects were screened between November 2005 and February 2006, and the intervention took place between February 2006 and November 2006. The subjects were aged ≥65 y, and were mainly recruited through an existing database of volunteers with interest in participating in studies of Wageningen University, Netherlands. The exclusion criteria were as follows: *1*) score of >16 on the Center for Epidemiologic Studies Depression Scale (CES-D) (20), *2*) score of <21 points on the Mini-Mental State Examination (MMSE) (21), *3*) current or recent (<4 wk) use of fish-oil supplements, *4*) current use of antidepressant medication, *5*) current use of medication for dementia, *6*) serious liver disease, *7*) consumption of >4 glasses of alcohol/d, *8*) inability to participate as judged by the responsible medical doctor, *9*) allergy to fish, *10*) swallowing problems, *11*) current or recent (ie, <2 mo) participation in another clinical trial, or *12*) intake of fish >4 times/wk or >800 mg EPA+DHA/d from fish, as estimated from a fish consumption questionnaire. Additionally, compliance with capsule use during the 2-wk placebo run-in period had to be ≥80% on the basis of self-report. The study was approved by the Medical Ethical Committee of Wageningen University and all subjects gave written informed consent.

Study design

An independent person randomized subjects by means of computer-generated random numbers in stratified permuted blocks of size 6. Stratification factors included age (< and ≥69 y), sex, MMSE (< and ≥28), and CES-D screening test score (<5 and ≥5). Individuals were randomly allocated to receive a daily dose of fish oil containing either a low dose (≈400 mg) of EPA+DHA, a high dose (≈1800 mg) of EPA+DHA, or a placebo oil (sunflower oil high in oleic acid) for 26 wk (Lipid Nutrition/Loders Croklaan, Wormerveer, Netherlands). The oils were administered in 6 soft gelatin capsules daily, each containing 900 mg oil and 2.7 mg tocopherol as antioxidant (Banner Pharmacaps Europe BV, Tilburg, Netherlands). Fish oil capsules provided a mean (±SD) daily intake of 1093 ± 17 mg EPA and 847 ± 23 mg DHA in the high-dose group and 226 ± 3 mg EPA and 176 ± 4 mg DHA in the low-dose group, as estimated from 20 random samples taken at regular times during the study. The placebo capsules contained mainly oleic acid (18:1n−9). The capsules were individually packaged in foil pill strips containing the daily dose of 6 pills per strip to facilitate compliance and recording of capsule use (Medipack, Gorredijk, Netherlands). The capsules with fish oil or placebo oil were indistinguishable in appearance. Staff members and participants were blinded toward treatment allocation until completion of the trial and after completion of data analysis. Participants visited the research center at baseline and after 13 and 26 wk of intervention. At baseline and at 13 wk, participants received a 14-wk supply of capsules (1 wk extra as reserve). Compliance was judged by calculating the unused capsules in the returned foil strips and by reviewing a diary in which participants registered the number of capsules that were not consumed.

Sample size was calculated on the basis of the CES-D; a difference of 3 points was considered clinically relevant. With a mean (±SD) value of 9 ± 7 for Dutch elderly (22), a minimum sample size of 85 subjects per group would be required to detect a difference (power = 80%, 2-sided $\alpha = 0.05$). Taking into account a dropout rate of 15%, a sample size of 100 subjects per treatment group was considered adequate.

Assessment of mental well-being

Trained research assistants performed mental well-being tests at baseline and after 13 and 26 wk of intervention under supervision of a neuropsychologist. The participants were tested by the same research assistant, whenever possible, using a standard protocol. To assess mental well-being, 4 questionnaires were used:

1) CES-D: a 20-item scale developed to measure depressive symptoms experienced in the past week (20). The scale generates a total score ranging from 0 to 60; higher scores reflect more depressive symptoms. Adequate reliability and validity with elderly people was previously established (23–25).
2) Montgomery-Åsberg Depression Rating Scale (MADRS): a 10-item, observer-rated scale that is explicitly designed to measure changes in depressive symptoms (26). This scale generates a total score, which can range from 0 to 60; higher scores reflect more depressive symptoms. Adequate validity was established previously (27).
3) Short version of the Geriatric Depression Rating Scale (GDS-15): a 15-item test with yes and no answers designed specifically for rating depression in the elderly. The total score ranges from 0 to 15, and the list has been tested and used extensively in the older population (28). This scale is easy to administer and has been well validated in both home and clinical settings. The GDS has been used only at baseline and after 26 wk of intervention.
4) Subscale of the Hospital Anxiety and Depression Scale (HADS-A): used to identify anxiety symptoms; possible scores range from 0 to 21 (29).

Additionally, in a subgroup of 104 subjects, the Dutch version of the Profile of Mood States short form (s-POMS) (30) was administered and the CES-D was repeated. These additional measurements were performed at weeks 17 and 21 of the study by telephone interview. The s-POMS is a 32-item questionnaire with good psychometric properties that assesses 5 components of mood: depression, fatigue, anger, tension, and loss of vigor. Total scores range from 0 to 128.

Other measurements

Fasting venous blood samples were collected at baseline and after 13 and 26 wk of intervention. A blood sample for measurement of n−3 PUFAs was collected into 10-mL EDTA-containing evacuated tubes and then immediately placed in ice

water, centrifuged at 2000 × *g* at a temperature of 4 °C, and then stored at −80 °C until analyzed. Plasma cholesteryl ester n−3 PUFAs were measured as described previously (31).

Information on medical history, drug use, alcohol consumption, smoking habits, educational level, and marital status was obtained by questionnaire and reviewed for completeness by a research assistant. Education was categorized into 3 categories according to criteria of Statistics Netherlands. The level of physical activity was estimated by means of a previously described questionnaire based on the duration and intensity of sport, household, and leisure-time activities (32).

A food-frequency questionnaire was administered at screening, at baseline, and after 13 and 26 wk of intervention to estimate fish intake in the previous 3 mo. Research assistants, who were all trained by the same dietitian, interviewed the subjects. After answering a single general question about their average frequency of fish consumption per month, participants had to indicate on a 60-item list which kinds of fish they had consumed and how often. These 60 items were categorized into 3 groups on the basis of the amount of fat in the different types of fish, ie, lean, medium-fat, and fatty fish. Furthermore, information was obtained on how the fish was consumed: as a main meal component during dinner, as a snack, or on toast or with a bread meal. EPA+DHA intake was calculated by multiplying the frequencies of portions of fish consumed per month from each group by using an EPA+DHA conversion factor (33).

Body height was measured at baseline with a wall-mounted stadiometer to the nearest 0.1 cm. Body weight and waist circumference were measured at each center visit while the subjects were in a standing position and wearing light clothing and no shoes. Body weight was measured to the nearest 0.1 kg with a calibrated digital scale. Waist circumference was measured in duplicate to the nearest 0.1 cm at the midpoint between the lowest rib and the top of the iliac crest with a nonelastic tape.

Statistical analyses

Data analysis was performed on an intention-to-treat basis and according to a predefined data analysis plan using SPSS 12.0.1 (SPSS Inc, Chicago, IL). A 2-sided P value <0.05 was considered statistically significant.

Baseline characteristics of the treatment groups were compared by one-factor analysis of variance or with a Kruskal-Wallis test for continuous variables and a chi-square test for categorical variables. Because the mental well-being outcome measures were not normally distributed, differential changes between the 3 intervention groups were tested by using a Kruskal-Wallis test. These analyses were performed for effect after 13 and 26 wk. The 6 repeated CES-D measurements performed in a subgroup were also compared by using a Kruskal-Wallis test, as were the 2 s-POMS measurements performed in the same subgroup at weeks 17 and 21. Secondary analysis involved a per-protocol analysis and exploratory post hoc analyses in a subgroup of individuals in the tertile with the highest CES-D scores at baseline.

RESULTS

Randomization and attrition

Of 528 individuals who expressed an interest in participating, 302 subjects who fulfilled the inclusion criteria were randomly assigned to receive 1800 mg/d EPA+DHA ($n = 96$), 400 mg EPA+DHA ($n = 100$), or placebo ($n = 106$) (**Figure 1**). During the study, 9 subjects discontinued the use of capsules: 5 because of gastrointestinal complaints, 2 because participation became too burdensome, and 2 because they died before the end of the intervention. Of those subjects lost to drop-out, 7 subjects were still tested after 13 wk and 6 subjects after 26 wk to be able to include them in the intention-to-treat analyses ($n = 300$ at week 13 and $n = 299$ at week 26).

Participants' characteristics and compliance

The mean age of the participants was 70 y, and 55% of the population was male. At baseline, treatment groups were equally distributed with regard to demographic, anthropometric, and lifestyle factors (**Table 1**).

Apart from the individuals who stopped treatment prematurely, the average adherence to treatments based on counts of returned capsules was high (96%; <80% for only 3 subjects) and did not differ between the treatment groups. Compliance was confirmed by a change in the proportion of EPA+DHA in plasma cholesteryl esters of 51% in the low-dose fish-oil group (from 1.88 ± 1.12 to 2.83 ± 1.03 g/100 g fatty acids), 236% in the high-dose fish-oil group (from 1.90 ± 0.86 to 6.40 ± 1.53 g/100 g fatty acids), and by a small change of −2% in the placebo group (from 1.91 ± 1.15 to 1.87 ± 1.11 g/100 g fatty acids). The supplements were well tolerated; the main complaints concerned mild gastrointestinal discomfort. In the high-dose fish-oil group, 14% of the subjects reported adverse events, including gastrointestinal problems ($n = 10$), poly urination, restlessness, and weight gain. In the low-dose fish-oil group, 13% of the subjects reported adverse events, including gastrointestinal problems ($n = 9$), feelings of lifelessness, blurred vision, sore throat, and muscle pain. In the placebo group, 15% of the subjects reported adverse events, including gastrointestinal problems ($n = 12$), skin irritation, blurred vision, transient ischemic attack, and muscle pain. At the end of the study, blinding of subjects toward treatment allocation (fish oil, placebo, or "no idea") was evaluated. The proportion of participants who thought they had received fish oil or placebo did not differ between the groups ($P = 0.15$). In the high-dose fish-oil group, 25% correctly thought that they had received fish oil and 54% had no idea. In the low-dose group, 19% correctly thought that they had received fish oil and 64% had no idea. In the placebo group 25% correctly thought that they had received placebo and 60% had no idea.

Primary and secondary outcomes

Baseline scores on the depression questionnaires were comparable between the 3 groups. Mean CES-D scores ranged from 5.9 to 6.8, mean MADRS scores ranged from 3.8 to 3.9, mean GDS scores ranged from 0.8 to 1.1, and mean HADS-A scores ranged from 2.1 to 2.7 (Table 1). After 13 and 26 wk of supplementation, there were no significant differential changes in the fish oil groups compared with the placebo group for any of the measures of mental well-being. Mean changes after 26 wk were −0.2, 0.2, and −0.4 for the CES-D ($P = 0.87$); −1.0, −0.8, and −0.8 for the MADRS ($P = 0.73$); −0.1, 0.0, and −0.1 for the GDS ($P = 0.90$), and 0.1, 0.5, and −0.1 for the HADS-A ($P = 0.26$) in the high-dose fish-oil, low-dose fish-oil, and placebo groups, respectively (**Table 2**).

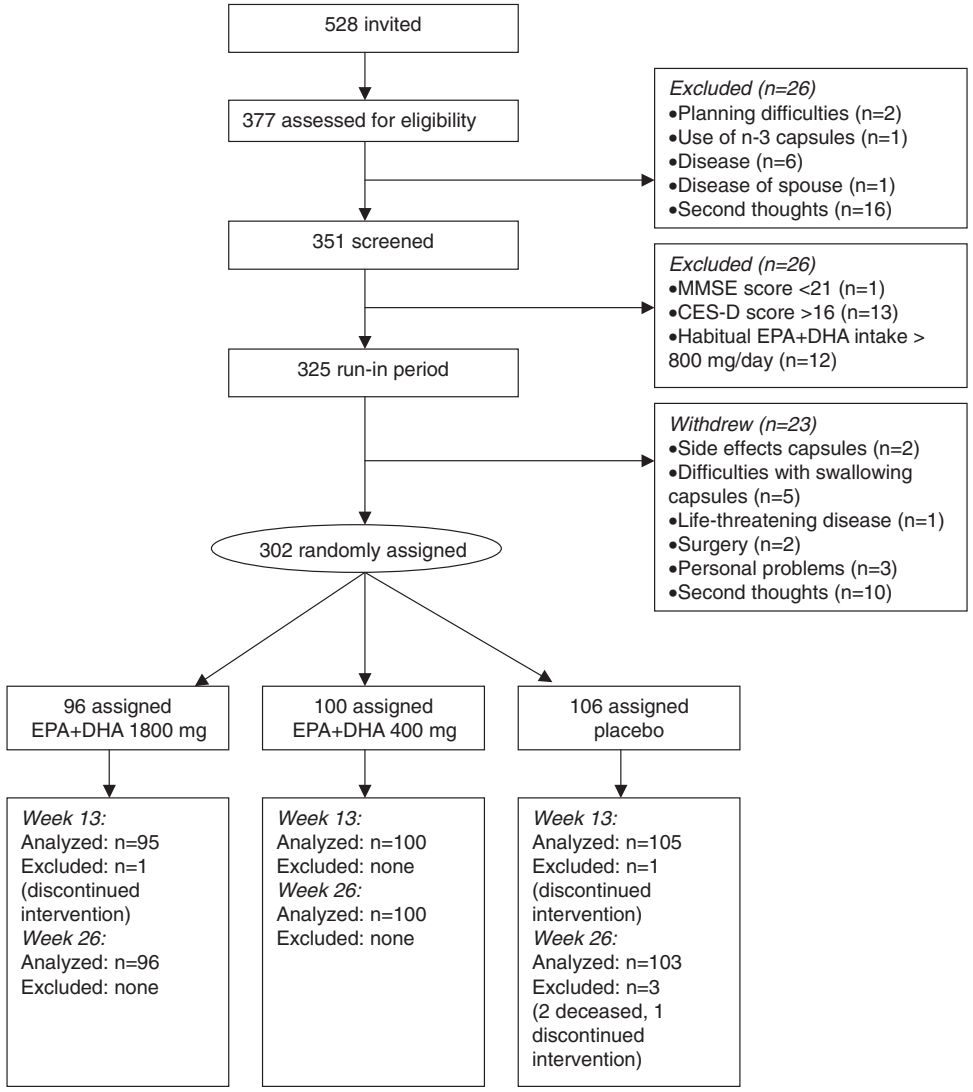

FIGURE 1. Flow diagram of participants throughout the study. EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid; CES-D, Center for Epidemiologic Studies Depression Scale; MMSE, Mini-Mental State Examination.

When we performed per-protocol analyses excluding the drop-outs and noncompliant subjects, the results were not different from those of the intention-to-treat analyses. Exploratory analyses in a subgroup of individuals in the tertile with the highest CES-D scores (cutoff CES-D at baseline: ≥8) showed that mean changes were generally larger than changes in the total group, but changes were not significant between the intervention groups (**Table 3**). Mean changes after 26 wk were -2.3 ± 6.7, -0.1 ± 5.4, and -2.4 ± 5.7 ($P = 0.23$) in the high-dose fish-oil, low-dose fish-oil, and placebo groups, respectively.

The course of CES-D scores in the subgroup of 104 subjects in whom the CES-D was administered 5 times, including the telephone interviews at weeks 17 and 21, is shown in **Figure 2**. The course of CES-D scores was not significantly different between the intervention groups.

Total scores and scores for the s-POMS components *depression*, *fatigue*, and *loss of vigor* at weeks 17 and 21 were not significantly different between the intervention groups. At week 21, scores for the mood component *anger* were significantly lower ($P = 0.01$) in the low-dose fish-oil group than in the placebo group (**Table 4**).

DISCUSSION

The present intervention study in older Dutch subjects showed no effect of daily supplementation with low or high doses of EPA+DHA on mental well-being as assessed by depression and anxiety questionnaires.

To the best of our knowledge, this is the first randomized, double-blind, placebo-controlled trial of fish-oil supplementation and mental well-being in a nondepressed population of older adults. Compliance in our study was excellent and did not differ between treatment groups, which indicated that most subjects tolerated taking 6 daily capsules for 26 wk. The drop-out rate in this study was 3%, and 7 of 9 subjects who discontinued capsule use were willing to undergo follow-up measurements.

We examined the effect of both a high (1800 mg) and a low (400 mg) dose of EPA+DHA on mental well-being. The high

TABLE 1
Characteristics of 302 subjects participating in a randomized, placebo-controlled trial, by treatment group[1]

	1800 mg EPA+DHA (n = 96)	400 mg EPA+DHA (n = 100)	Placebo (n = 106)
Age (y)	69.9 ± 3.4	69.5 ± 3.2	70.1 ± 3.7
Sex, male (%)	55	55	56
Married, living together (%)	80	81	77
Education (%)			
Low	10	11	5
Middle	54	49	59
High	35	40	37
BMI (kg/m^2)	26.1 ± 3.0	26.2 ± 3.4	26.5 ± 3.9
Waist circumference (cm)	94.5 ± 11.4	94.2 ± 10.6	95.9 ± 12.1
Physical activity score	11.5 ± 6.4	11.1 ± 6.2	11.4 ± 6.2
Smoking status (%)			
Smoker	8	8	10
Ex-smoker	64	54	56
Never-smoker	28	38	34
Alcohol consumers (%)	80	87	88
Median alcohol consumption (glasses/wk)[2]	10 (6–14)	8 (4–14)	8 (4–14)
Fish consumption (times/mo)	7 (4–9)	5 (3–9)	6 (4–8)
EPA+DHA intake (mg/d)	306 (131–592)	278 (103–487)	316 (166–584)
Plasma EPA-DHA (mass%)	1.9 ± 0.9	1.9 ± 1.1	1.9 ± 1.1
Mini-Mental State Examination Score	28 (27–29)	28 (27–29)	28 (27–29)
CES-D score[3]	5.9 ± 5.5, 5.0 (2.0–8.8)	6.1 ± 4.9, 5.0 (2.0–8.8)	6.8 ± 5.2, 6.0 (2.0–10.0)
MADRS score[3]	3.9 ± 4.4, 3.0 (0.0–6.0)	3.8 ± 4.2, 3.0 (0.0–5.0)	3.8 ± 3.5, 3.0 (1.0–7.0)
GDS-15 score[3]	0.8 ± 1.2, 0.0 (0.0–1.0)	0.9 ± 1.1, 0.5 (0.0–1.0)	0.9 ± 1.2, 1.0 (0.0–1.0)
HADS-A score[4]	2.1 ± 2.3, 1.0 (0.0–3.0)	2.1 ± 2.1, 2.0 (0.0–3.0)	2.7 ± 2.7, 2.0 (1.0–4.0)

[1] Values are $\bar{x}$ ± SD and/or median (quartiles 1–3), depending on the distribution. EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid; CES-D, Center for Epidemiologic Studies Depression Score (possible score: 0–60); MADRS, Montgomery-Åsberg Rating Scale (possible score: 0–60); GDS-15, Geriatric Depression Scale (possible score: 0–15); HADS-A, Hospital Anxiety and Depression Scale (possible score: 0–21). No significant differences between the 3 treatment groups were observed. $P < 0.05$ (one-factor ANOVA and Kruskal-Wallis for continuous variables and chi-square analysis for categorical variables).

[2] Mean consumption in consumers only.

[3] Higher scores indicate a poorer mental well-being.

[4] Higher scores indicate a higher anxiety level.

TABLE 2
Changes in scores on depression and anxiety questionnaires in Dutch elderly people after 13 and 26 wk of supplementation, by treatment group[1]

	1800 mg EPA+DHA[2]	400 mg EPA+DHA[3]	Placebo[4]
Depression			
CES-D[5]			
13 wk − baseline	−0.67 ± 3.57	0.74 ± 4.08	−0.54 ± 5.07
26 wk − baseline	−0.18 ± 4.81	0.20 ± 4.28	−0.43 ± 4.68
MADRS[5]			
13 wk − baseline	−0.96 ± 3.52	−0.23 ± 3.65	−0.84 ± 3.50
26 wk − baseline	−1.03 ± 3.44	−0.82 ± 3.70	−0.83 ± 3.39
GDS-15[5,6]			
26 wk − baseline	−0.05 ± 1.08	0.01 ± 1.12	−0.12 ± 0.96
Anxiety			
HADS-A[7]			
13 wk − baseline	−0.16 ± 1.59	0.30 ± 1.57	−0.30 ± 1.98
26 wk − baseline	0.10 ± 1.75	0.50 ± 2.48	−0.14 ± 1.89

[1] All values are $\bar{x}$ ± SD. No significant differences between the 3 treatment groups were observed, $P > 0.05$ (Kruskal-Wallis test). EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid; CES-D, Center for Epidemiologic Studies Depression Score (possible score: 0–60); MADRS, Montgomery-Åsberg Rating Scale (possible score: 0–60); GDS-15, Geriatric Depression Scale (possible score: 0–15); HADS-A, Hospital Anxiety and Depression Scale (possible score: 0–21).

[2] For treatment group 1, n = 96 at baseline, n = 95 after 13 wk, and n = 96 after 26 wk.

[3] For treatment group 2, n = 100 at baseline and after 13 and 26 wk.

[4] For treatment group 3, n = 106 at baseline, n = 105 after 13 wk, and n = 103 after 26 wk.

[5] Higher scores indicate a poorer mental well-being.

[6] The GDS-15 has been used only at baseline and after 26 wk of intervention.

[7] Higher scores indicate a higher anxiety level.

TABLE 3
Changes in scores on depression and anxiety questionnaires in the highest CES-D score tertile (CES-D ≥ 8) at baseline and after 13 and 26 wk of supplementation, by treatment group[1]

	1800 mg EPA + DHA[2]	400 mg EPA+DHA[3]	Placebo[4]
Depression			
CES-D[5]			
13 wk − baseline	−2.52 ± 4.81	−0.28 ± 3.89	−1.70 ± 7.11
26 wk − baseline	−2.26 ± 6.72	−0.11 ± 5.36	−2.40 ± 5.69
MADRS[5]			
13 wk − baseline	−2.66 ± 4.69	−0.92 ± 4.68	−0.98 ± 4.77
26 wk − baseline	−1.99 ± 5.05	−1.91 ± 5.19	−1.88 ± 3.76
GDS-15[5]			
26 wk − baseline	−0.04 ± 1.29	0.21 ± 1.67	−0.29 ± 1.17
Anxiety			
HADS-A[6]			
13 wk − baseline	−0.44 ± 1.89	0.48 ± 1.73	−0.37 ± 2.54
26 wk − baseline	0.44 ± 2.61	0.91 ± 3.21	−0.37 ± 2.07

[1] All values are $\bar{x}$ ± SD. No significant differences between the 3 treatment groups were observed, $P > 0.05$ (Kruskal-Wallis test). EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid; CES-D, Center for Epidemiologic Studies Depression Score (possible score: 0–60); MADRS, Montgomery-Åsberg Rating Scale (possible score: 0–60); GDS-15, Geriatric Depression Scale (possible score: 0–15); HADS-A, Hospital Anxiety and Depression Scale (possible score: 0–21).
[2] For treatment group 1, $n = 27$.
[3] For treatment group 2, $n = 33$.
[4] For treatment group 3, $n = 43$ after 13 wk and $n = 41$ after 26 wk of intervention.
[5] Higher scores indicate a poorer mental well-being.
[6] Higher scores indicate a higher anxiety level.

"pharmacologic" dose, which corresponds to eating ≈8 portions of fish per week, was chosen to ensure maximum contrast between the groups to detect an effect, if present. The low dose corresponds to the recommended intake in the Netherlands of 450 mg EPA+DHA/d (34). Such a dose is roughly equivalent to eating 2 portions of fish per week (one of which is oily fish) and can be more easily translated into dietary advice. Furthermore, Kamphuis et al (15) found that an intake of 400 mg n−3 PUFAs was associated with fewer depressive symptoms in an observational study of 332 older Dutch men. Yet, it is not clear which dose would be sufficiently high and most effective to influence mental well-being, especially in nonpatient populations. Moreover, because the causal mechanisms have not yet been elucidated, it is not clear whether either EPA or DHA or the combination of the 2 may influence mood.

The state of mental well-being of the subjects was assessed by a series of questionnaires that have been validated and used frequently in this field and in nondepressed community-dwelling populations (25, 35–38). However, because the questionnaires were designed to primarily assess depressive symptoms, rather than mental well-being, we may not have been able to demonstrate an effect of our intervention in this nondepressive population.

We selected a population of individuals aged ≥65 y, because depressive symptoms are highly prevalent in the elderly population and increase with age (39). Our target group was a nondepressed population (CES-D score < 16), because we aimed to investigate whether n−3 PUFA treatment could improve the state of mental well-being of older individuals in the general population. It was shown in a population-based study in the Netherlands that the distribution of CES-D scores in the general elderly population varied greatly, allowing room for improvement even among the nondepressed (40). However, to be able to study a group of subjects more sensitive to change, it would have been sensible to use not only an exclusion criterion of a CES-D score >16, but possibly a CES-D score <5 to exclude subjects with already optimal CES-D scores.

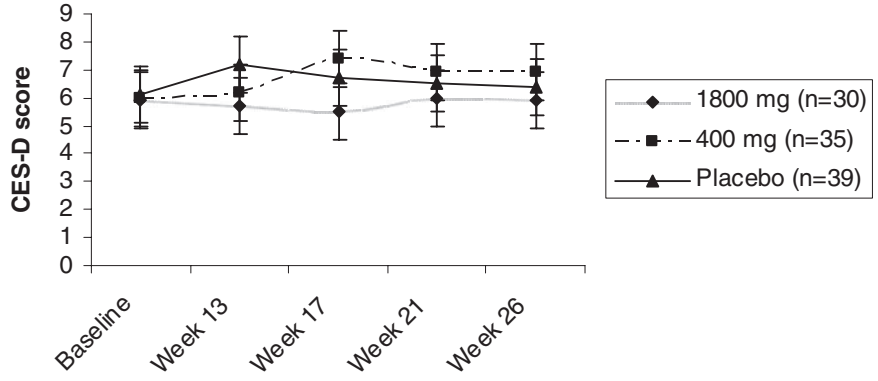

FIGURE 2. Course of mean Center for Epidemiologic Studies Depression Scale (CES-D) scores in Dutch elderly ($n = 104$) during the 26-wk intervention, by treatment group. No significant differences between interventions were observed ($P > 0.05$, Kruskal-Wallis test).

TABLE 4
Profile of Mood States scores at weeks 17 and 21 of intervention in Dutch community-dwelling elderly, by treatment group[1]

	1800 mg (n = 30)	400 mg (n = 35)	Placebo (n = 39)
Total score			
Week 17	14.5 ± 11.2	19.6 ± 20.6	19.7 ± 14.2
Week 21	17.5 ± 16.5	15.9 ± 12.8	18.7 ± 13.3
Depression			
Week 17	1.7 ± 3.0	4.1 ± 6.0	2.6 ± 3.5
Week 21	2.4 ± 4.1	3.0 ± 4.0	2.3 ± 3.1
Fatigue			
Week 17	2.4 ± 3.4	3.0 ± 4.1	3.7 ± 3.8
Week 21	2.5 ± 3.9	2.9 ± 3.8	3.8 ± 4.3
Anger			
Week 17	3.4 ± 3.6	3.8 ± 6.1	3.6 ± 3.5
Week 21	4.2 ± 5.2	1.8 ± 3.1[2]	3.9 ± 3.8
Tension			
Week 17	1.5 ± 2.0	2.7 ± 4.4	3.3 ± 3.4
Week 21	2.1 ± 3.3	2.1 ± 2.9	2.9 ± 3.1
Loss of vigor			
Week 17	5.5 ± 3.1	6.0 ± 3.7	6.5 ± 3.4
Week 21	6.3 ± 3.8	6.1 ± 3.8	5.8 ± 3.0

[1] All values are $\bar{x}$ ± SD.
[2] Significantly different from 1800 mg, $P < 0.05$ (Kruskal-Wallis test).

Our results contrast with those of another study that examined the effect of n−3 PUFA supplementation in younger, healthy, nondepressed subjects, in which 33 subjects with a mean age of 33 y received a daily dose of 1.6 g EPA and 0.8 g DHA for 35 d. This intervention resulted in an increased mental well-being as measured with a POMS questionnaire (18). On the basis of the fact that we had a larger number of subjects in our study, who were older and were supplemented for a longer period, we expected an effect in our study. Power calculations performed by Appleton et al (17) suggest that a sample size of ≈100 participants per group should be enough to show a clinically meaningful change in depressed mood, as indicated by a difference of 3–4 points on depression questionnaires.

In an exploratory post hoc analysis in subjects within the tertile with the highest CES-D scores (CES-D: ≥8), ie, impaired mood, we observed that scores on the depression questionnaires changed more during intervention, although not significantly so. From this finding it may be concluded that subjects with an impaired mental well-being may indeed benefit more from n−3 PUFA supplementation and emphasizes that the relatively optimal CES-D scores measured in our study population may be a limitation of this study. However, Rogers et al (19), who performed a trial in mildly to moderately depressed individuals from the general population, neither observed an effect on mood assessed with the HADS-A after a shorter period of supplementation with 1.5 g EPA+DHA/d.

Other double-blind randomized controlled trials of fish oil and depressive mood were mainly performed in patients with depressive disorders (17). The supplemental doses and contents varied, ranging from 0.2 g to 9.6 g PUFAs and consisted of EPA alone, DHA alone, or EPA plus DHA. The overall study duration ranged from 28 to 180 d, and beneficial effects appeared between 2 and 8 wk, which is considerably sooner than in our study. In conclusion, in this randomized, double-blind, placebo-controlled trial, we observed no effect of EPA+DHA supplementation for 26 wk on different measures of mental well-being in older individuals from the general population.

The authors' responsibilities were as follows—OvdR: planned and coordinated the study, collected and managed the data, performed the statistical analyses, interpreted the results, and drafted the manuscript. JMG, WAvS, and LCPGMdG: designed and initiated the trial; and FJK, ATFB, and WHH: provided advice on the study design and measurements. All authors helped interpret the results, critically reviewed the manuscript, and approved the final draft. None of the authors had any financial or personal conflicts of interest to disclose.

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