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## Depression and cardiovascular mortality: a role for n-3 fatty acids? 1,2,3,4

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### ABSTRACT

**Background:** Recent studies indicate that depression plays an important role in the occurrence of cardiovascular diseases (CVDs). The underlying mechanisms are not well understood.

**Objective:** We investigated whether dietary intake of the n-3 fatty acids (FAs) eicosapentaenoic acid and docosahexaenoic acid could explain the relation between depressive symptoms and cardiovascular mortality.

**Design:** The Zutphen Elderly Study is a prospective cohort study conducted in the Netherlands. Depressive symptoms were measured in 1990 with the Zung Self-rating Depression Scale in 332 men aged 70–90 y and free from CVD and diabetes. Dietary factors were assessed with a cross-check dietary history method in 1990. Mortality data were collected between 1990 and 2000. Logistic and Cox regression analyses were performed, with adjustment for demographics and CVD risk factors.

**Results:** Compared with a low intake ( $\bar{x}$ : 21 mg/d), a high intake ( $\bar{x}$ : 407 mg/d) of n-3 FAs was associated with fewer depressive symptoms [odds ratio: 0.46; 95% CI: 0.22, 0.95; *P* for trend = 0.04] at baseline and no significant reduced risk of 10-y CVD mortality [hazard ratio (HR): 0.88; 95% CI: 0.51, 1.50]. The adjusted HR for an increase in depressive symptoms with 1 SD for CVD mortality was 1.28 (95% CI: 1.03, 1.57) and did not change after additional adjustment for the intake of n-3 FAs.

**Conclusion:** An average intake of  $\approx$ 400 mg n-3 FA/d may reduce the risk of depression. Our results, however, do not support the hypothesis that the intake of n-3 FAs explains the relation between depression and CVD.

## INTRODUCTION

By the year 2020, ischemic heart disease and cerebrovascular disease will be the leading causes of death in the world. Moreover, ischemic heart disease and depression are also projected to be the top 2 contributors of the global burden of disease (1). Studies indicate that depression plays an important role in the occurrence of cardiovascular disease (CVD), both in patients with CVD and in the general population without CVD (2, 3). Several mechanisms to explain the association have been proposed but remain insufficiently understood. These mechanisms may act directly through pathophysiologically linked pathways or indirectly through shared cardiovascular risk factors, lifestyle factors, and diet (4, 5).

One of the explanations for the association between depression and CVD is a low intake of the n-3 fatty acids (FAs) eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), of which the main source is fish consumption. Low consumption of fish is a well-established risk factor for CVD mortality (6, 7) and may also predispose to depression (8, 9). Although there is indirect support for a low intake of n-3 FAs as a common cause for depression and CVD, it has not been investigated whether this could also explain the increased risk of depression for CVD. This requires the examination of intake of n-3 FAs in relation to both the risk of depression and CVD.

We determined, first, whether intake of the n-3 FAs EPA and DHA was related to the risk of depressive symptoms, and, second, whether intake of these n-3 FAs could explain the increased risk of depressive symptoms on 10-y cardiovascular mortality. Data from the Zutphen Elderly Study, a population-based prospective cohort study of healthy elderly men in the Netherlands, were used.

## SUBJECTS AND METHODS

### Zutphen Elderly Study

The Zutphen Elderly Study is a population-based prospective cohort study on diet, risk factors for CVD, and health in elderly men. The study design and measurements have been described in detail elsewhere (10). In brief, the study started in 1985 as a continuation of the Zutphen Study, the Dutch contribution to the Seven Countries Study (11). In 1985, the 555 survivors of the original cohort were invited for the examinations. In addition, a random sample of 711 men of the same age, living in Zutphen but not belonging to the original cohort, was invited to participate. Of these 1266 men, 887 (70%) gave informed consent and participated in the baseline examinations. Data collection followed the international protocol used in previous surveys of the Seven Countries Study (11), extended with gerontologic variables. In 1990, the second round of the Zutphen Elderly Study took place. In that round, information on depression, functional status, cognitive function, and self-reported health were added. In 1995 and 2000, the third and fourth rounds of examinations were carried out. Mortality data were collected until the year 2000.

### Depressive symptoms

Depressive symptoms were measured in 1990 with the use of the Self-rating Depression Scale (SDS), developed by Zung (12). This scale was developed to assess depression among patients admitted to a psychiatric hospital, has frequently been used in noninstitutionalized elderly persons (13), and was highly comparable among different countries (14). The reproducibility of the SDS is good in elderly men (Cronbach  $\alpha$ : 0.75) (15) and has been validated repeatedly with other questionnaires on depressive symptoms such as the Centers for Epidemiologic Studies Depression ( $r = 0.69$ ) (16), the Geriatric Depression Scale ( $r = 0.59$ ) (17), and the Hamilton Depression scale ( $r = 0.80$ ) (18). The questionnaire contains 20 items either positively or negatively formulated, based on clinical diagnostic criteria commonly used to diagnose depressive disorders. The answers on those items are coded on a 4-point Likert-type scale that varied from "none or sometimes" to "most or always." Positive items were converted into negative ones with total scores ranging from 20 to 80. Men with >2 missing items were excluded from the analysis. If 1 or 2 items were missing, a mean score of the present items of the subject was calculated to replace the missing items. An index for the SDS was derived by dividing the sum of the answers by 80 multiplied by 100 (range: 25–100), with

a higher score indicating more depressive symptoms. The original clinical cutoffs are no depressive symptoms (SDS score < 50) and mild-to-severe depressive symptoms (SDS score  $\geq$ 50) (13).

### **Dietary factors**

Information on habitual food consumption was obtained in 1990 with the cross-check dietary history method, adapted to the Dutch situation (19) and has been described in detail elsewhere (20). In brief, each participant, and if possible in the presence of the person who prepared the hot meal, was interviewed by a trained dietitian about his average food consumption pattern in the 2 wk before the interview. A checklist of foods and quantities of food bought per week was used to calculate and verify the participant's food consumption pattern. Total fish consumption was computed by adding the number of grams of all fish consumed per day. Fish is the main source (71%) of the n-3 FAs EPA and DHA. Other sources of n-3 FAs are meat, eggs, and plant foods such as leek (21). Nutrient intake, including the intake of EPA and DHA, was calculated with the Dutch food table.

### **Cardiovascular endpoints**

Mortality data were collected during 10 y of follow-up (1990–2000), obtained through general practitioners, and verified with information from hospital registries. No persons were lost to follow-up. Coding of causes of death was done by one clinical epidemiologist who was blinded to the risk factor status of the subjects. Mortality from CVD was coded according to the International Classification of Diseases, 9th revision (ICD-9 codes: 390–459). In the analyses, both primary ( $n = 78$ ) and secondary ( $n = 44$ ) causes of death were used. The number of patients with at least one cardiovascular cause of death was 92. Men who died from causes other than CVD were censored at date of death. Men who were still alive at the end of the study were censored at the date of the last examination in 2000.

### **Other variables**

The self-administered questionnaire contained questions on demographic characteristics, educational level, and lifestyle habits. Marital status was classified as living alone (unmarried, separated, or widowed) or together. Alcohol intake was assessed in the dietary survey and expressed in absolute grams of alcohol per day. Participants were classified as current, past, or never smokers according to their smoking habits. Body mass index (BMI; in  $\text{kg}/\text{m}^2$ ) was calculated from weight and height, which were measured while the participant was standing in light clothing without shoes. Physical activity was assessed with a self-administered validated questionnaire designed for retired men (22). All types of activity with an intensity of  $>2$  kcal energy expended/kg body weight during 1 h were summed and expressed as minutes of total physical activity per week (in min/wk).

Arterial blood pressure was measured twice on the right arm after 5 min of rest with a random zero sphygmomanometer, with the participant in a supine position. The average of 2 readings of both systolic and diastolic blood pressure (fifth Korotkhoff phase) was calculated.

Nonfasting venous blood samples were taken, and total and HDL cholesterol (in mmol/L) were measured with the use of standardized procedures according to the criteria of the World Health Organization's Lipid Reference Laboratory in Atlanta, GA (23). History of myocardial infarction was obtained with the use of the Rose questionnaire (24) and verified by information from general practitioners, hospital registries, or both. A clinical history of stroke, heart failure, and diabetes was based on the doctor's conclusion with the use of questionnaire information and the results of the physical examination and verified by information from general practitioners or hospital registries.

### **Study sample**

Depressive symptoms were measured for the first time between March and June 1990, when 556 (77%) of the 718 men still alive since the start of the study in 1985 participated. Of them, 380 (68%) were free of CVD and diabetes. We excluded 43 men with  $>2$  missing items on the SDS as well as 5 men with missing values in covariates. Thus, a study sample of 332 men remained for statistical analysis.

### Data analysis

The intake of n-3 FAs was adjusted for energy intake with the use of the regression residual method (25). Means and SDs were computed for continuous baseline variables, and medians and 10–90 percentiles were computed for continuous variables with a skewed distribution. Frequency distributions were given for categorical variables according to categories of depressive symptoms [no depressive symptoms (SDS < 50) and mild-to-severe depressive symptoms (SDS  $\geq$ 50)]. Differences between categories of depressive symptoms were tested with analysis of variance, Kruskal-Wallis test (in case of skewed distribution), or chi-square test.

Cross-sectional associations between intake of n-3 FAs and depressive symptoms in 1990 were examined with logistic regression analysis. Depression was the dependent variable, and daily intake of n-3 FAs (middle compared with low and high compared with low) was the independent variable. In the first model we adjusted for age. In the second model we also adjusted for years of education, BMI, smoking (past compared with never and current compared with never), alcohol consumption (1–29 g/d compared with 0 g/d and  $\geq$ 30 g/d compared with 0 g/d), systolic blood pressure (in mm Hg), physical activity (in min/wk), living alone (yes compared with no), and energy intake (in kcal).

The prospective associations between daily intake of n-3 FAs (middle compared with low and high compared with low) and CVD mortality was estimated with Cox proportional hazard models. With a log compared with log minus log plot the assumptions of proportional hazards were checked. The assumptions of proportionality were not violated. In the first model we adjusted for age. In the second model we also adjusted for years of education, BMI, smoking, alcohol consumption, systolic blood pressure, total and HDL-cholesterol concentrations, physical activity, living alone, and energy intake.

Finally, we investigated with Cox proportional hazard models whether the daily intake of n-3 FAs could explain the relation between depressive symptoms and CVD mortality. Tertiles of n-3 FAs were added to the model containing depressive symptoms (per SD), with age and classical CVD risk factors as independent variables and CVD mortality as dependent variable.

All analysis were performed with the SAS statistical software package, version 9.1.2 (26). Point estimates are given with corresponding 95% CIs.

### RESULTS

At baseline, the average depression score was 42.6 ( $\pm$ 10), which is low in comparison with the clinical cutoff for mild depression (50–59). About 22% of the elderly men had mild-to-severe depressive symptoms. The baseline characteristics of the study sample by categories of depressive symptoms are shown in **Table 1**. Men with mild-to-severe depressive symptoms (SDS  $\geq$ 50) were less educated, less physically active, had a higher BMI, and were more likely to live alone than were men with no depressive symptoms.

**TABLE 1** Baseline characteristics of the study sample according to depressive symptoms measured in 1990<sup>1</sup>

Characteristic	No depression <sup>2</sup> (n = 260)	Mild to severe depression <sup>3</sup> (n = 72)
Age (y)	75 ± 4 <sup>4</sup>	76 ± 5
Education (y)	11.0 ± 4.4	8.7 ± 2.7 <sup>5</sup>
Physical activity (min/wk)	540 (115–1223) <sup>6</sup>	420 (32–900) <sup>5,6</sup>
Alcohol consumption (%)	74	79
Smoking (%)	23	24
Living alone (%)	18	31 <sup>5</sup>
BMI (kg/m <sup>2</sup> )	25.4 ± 2.9	26.2 ± 2.9 <sup>5</sup>
SBP (mm Hg)	149 ± 20	151 ± 20
DBP (mm Hg)	82 ± 11	84 ± 12
Total cholesterol (mmol/L)	6.1 ± 1.1	6.0 ± 1.1
HDL cholesterol (mmol/L)	1.2 ± 0.3	1.1 ± 0.2
Daily intake		
Energy (kcal)	2150 ± 457	2123 ± 472
n-3 FAs (mg) <sup>7</sup>	105.0 (8–463) <sup>6</sup>	87 (6–355) <sup>6</sup>

<sup>1</sup> SBP, systolic blood pressure; DBP, diastolic blood pressure; FA, fatty acid.

<sup>2</sup> No depressive symptoms was a Self-rating Depression Scale (SDS) score <50.

<sup>3</sup> Mild-to-severe depressive symptoms was a SDS score ≥ 50.

<sup>4</sup>  $\bar{x}$  ± SD (all such values).

<sup>5</sup> Differences determined with ANOVA, Kruskal-Wallis (in case of skewed distribution), or chi-square test; *P* < 0.05.

<sup>6</sup> Median; 10th–90th percentiles in parentheses.

<sup>7</sup> n – 3 FAs included eicosapentaenoic acid and docosahexaenoic acid.

Cross-sectional analyses showed that men in the highest tertile of n–3 FAs (mean daily intake: 407 mg) had a 54% (OR: 0.46; 95% CI: 0.22; 0.95) lower risk of depressive symptoms than did men in the lowest tertile of n–3 FAs (mean daily intake: 21 mg) (**Table 2**). In addition, an increase of 50 mg in daily intake of n–3 FAs was associated with a 7% (OR: 0.93; 95% CI: 0.87, 1.01) reduction in risk of depressive symptoms. Compared with no fish consumption, consumption of ≥20 g fish/d was associated with a 37% lower risk of depressive symptoms (OR: 0.63; 95% CI: 0.30, 1.34).

**TABLE 2** Odds ratios (95% CIs) of depressive symptoms measured in 1990 for intake of n–3 fatty acids (FAs) measured in 1990 (n = 332)<sup>1</sup>

	Model 1 <sup>2</sup>	Model 2 <sup>3</sup>
n–3 FAs		
Low (<59 mg/d)	1	1
Middle (59–156 mg/d)	0.86 (0.47, 1.58)	0.84 (0.43, 1.64)
High (≥156 mg/d)	0.52 (0.27, 1.03)	0.46 (0.22, 0.95)
<i>P</i> for trend	0.06	0.04

<sup>1</sup> Depressive symptoms was a Self-rating Depression Scale score ≥50. n – 3 FAs included eicosapentaenoic acid and docosahexaenoic acid. Odds ratios with accompanying CIs were assessed with logistic regression models.

<sup>2</sup> Model 1 was adjusted for age.

<sup>3</sup> Model 2 was additionally adjusted for years of education, BMI (in kg/m<sup>2</sup>), smoking [never (reference), past, and current], alcohol consumption [0 g/d (reference), 1–19 g/d, and ≥30 g/d], systolic blood pressure (in mm Hg), physical activity (in min/wk), living alone (yes compared with no), and energy intake (in kcal).

After 10 y of follow-up, 170 (51%) of the 332 men had died, of whom 92 (28%) had died of CVD. The total number of person-years was 2574, and the mean follow-up period was 7.8 y ( $\pm 3.1$  y). The prospective association for daily intake of n-3 FAs for CVD mortality is given in **Table 3**. The fully adjusted hazard ratios (HRs) of CVD mortality associated with medium and high daily intake of n-3 FAs were 0.85 (95% CI: 0.51, 1.42) and 0.88 (95% CI: 0.51, 1.50), respectively.

**TABLE 3** Adjusted hazard ratios (95% CIs) for 10-y cardiovascular mortality and intake of n-3 fatty acids (FAs) at baseline ( $n = 332$ )<sup>1</sup>

	Cases/PY	Model 1 <sup>2</sup>	Model 2 <sup>3</sup>
n-3 FAs			
Low (<59 mg/d)	32/820	Reference	Reference
Middle (59–156 mg/d)	32/897	0.94 (0.58, 1.54)	0.85 (0.51, 1.42)
High ( $\geq 156$ mg/d)	28/857	0.91 (0.54, 1.51)	0.88 (0.51, 1.50)
<i>P</i> for trend		0.71	0.63

<sup>1</sup> PY, person-year. n-3 FAs included eicosapentaenoic acid and docosahexaenoic acid. Hazard ratios with accompanying CIs were estimated with Cox proportional hazard models.

<sup>2</sup> Model 1 was adjusted for age.

<sup>3</sup> Model 2 was additionally adjusted for years of education, BMI (in kg/m<sup>2</sup>), smoking [never (reference), past, and current], alcohol consumption [0 g/d (reference), 1–29 g/d, and  $\geq 30$  g/d], systolic blood pressure (in mm Hg), total and HDL-cholesterol concentrations (in mmol/L), physical activity (in min/wk), living alone (yes compared with no), and energy intake (in kcal).

The adjusted HR for an increase in the SDS index with 1 SD for CVD mortality was 1.28 (95% CI: 1.03, 1.57) and did not change (HR: 1.28; 95% CI: 1.03, 1.58) after additional adjustment for n-3 FAs. Analyses with CVD as primary cause of death showed similar results.

## DISCUSSION

Lack of n-3 FAs in the diet has been suggested to explain the relation between depression and CVD. The results of our study, however, although confirming that a high intake of n-3 FAs was associated with fewer depressive symptoms, do not support the view that intake of n-3 FAs explains the relation between depression and the occurrence of CVD.

To interpret the findings, different aspects of the present study need to be addressed. The main strengths of the present study are its prospective design with a long follow-up period and the study sample of elderly men who were free of CVDs and diabetes at baseline. Second, selective loss to follow-up could not have disturbed our results, because the mortality follow-up was complete. Third, food consumption was obtained with a dietary history method. This extensive method estimates the habitual food consumption and reduces random misclassification.

The present study has also methodologic limitations that need to be considered. First, selective participation of healthier respondents and exclusion of men with missing values from the baseline sample who had a worse health profile and higher mortality rates (results not shown) may have diluted the associations. Moreover, the present study population consisted of older white men, and the results may not be generalizable to women and nonwhite populations. Second, in an observational study the possibility of residual confounding cannot be ruled out. We tried to minimize this possibility by adjusting for several known risk factors for depression and CVD in the analyses, including education, physical activity, BMI, and living status. Unfortunately, we did not have information on depression treatment. Note that the average SDS score was below the clinical cutoff for mild depression ( $>50$ ). Only 2 men had a SDS score that was indicative of major depression (SDS score  $> 70$ ). Therefore, treatment for depression is not an issue in our study. In addition, we did not collect data on supplemental

use of n-3 FAs. However, use of n-3 FA supplements was nonexistent in 1990 in the Netherlands. Third, the association between the intake of n-3 FAs and depressive symptoms was observed in a cross-sectional analysis and is not necessarily causal. Reversed causality is an alternative explanation, because the presence of depressive symptoms may cause a low intake of n-3 FAs resulting from loss of appetite and decreased food consumption. However, energy intake was not materially lower in depressed subjects; moreover, we adjusted for energy intake. Finally, it can be argued that depressive symptoms are markers of subclinical CVD, therefore reflecting reversed causality. We tried to minimize this possibility by excluding men with prevalent CVD. Furthermore, in a previous article we made a plausible argument against reversed causality (27).

A low intake of n-3 FAs may predispose to depression through several biological mechanisms (8, 9). High concentrations of n-3 FAs in neuronal membranes are hypothesized to play a role in synaptic neurotransmission through mechanisms involving the metabolism, release, uptake, and receptor functioning of neurotransmitters (8). For instance, low concentrations of the essential n-3 FAs are associated with reduced production of 5-hydroxy-indolacetic acid that is the main metabolite of serotonin and an indicator of reduced serotonin turnover (28). Neurotransmission is thought to be impaired in depressed patients. Second, low concentrations of n-3 FAs are associated with elevated concentrations of inflammatory markers (29), which are associated with both depression (30, 31) and atherosclerosis (32).

Our results agree with previous observational studies that showed an inverse association between intake of fish and depression (33-35), blood concentrations of n-3 FAs and depression (36, 37), and n-3 FAs in adipose tissue and depression (38), although 2 studies did not find an association between intake of n-3 FAs and depression (39, 40). To our knowledge, thus far no prospective studies have investigated the association between intake of n-3 FAs and the incidence of depression. However, preliminary results of randomized controlled trials suggest that an additional intake of n-3 FAs (0.5-9.6 g/d) leads to a greater reduction in depressive symptoms compared with standard treatment in depressed patients (41, 42).

Two meta-analyses calculated relative risks of the incidence of stroke and mortality from coronary heart disease for weekly consumption of fish, the main source of n-3 FAs, compared with consumption <1 time/mo. The risk of the incidence of stroke and mortality from coronary heart disease were 0.87 (95% CI: 0.72, 0.94) and 0.85 (95% CI: 0.76, 0.96), respectively (6, 7). These estimates are comparable with our results of 0.85 and 0.88 for total cardiovascular mortality, which may not have been statistically significant because of lack of power. Although we did show an association between intake of n-3 FAs and depressive symptoms, and to lesser extent with CVD mortality, intake of n-3 FAs did not explain the increased risk of depressive symptoms on CVD mortality in elderly men.

If lack of consumption of n-3 FAs cannot explain the increased risk of CVD mortality associated with depression in elderly men, what other explanations are possible? An alternative mechanism is that dysregulation of the hypothalamic-pituitary-adrenocortical axis, often present in depression, promotes atherosclerosis through injury of vascular endothelial cells, hypertension, and inflammation (4). Depression has also been associated with autonomic dysfunction (43). In patients with myocardial infarction depression was associated with decreased heart rate variability, which contributed to their increased risk of mortality compared with patients who were not depressed (44). In conclusion, although a low intake of n-3 FAs may increase the risk of depression, the results of the present study do not support the view that a low intake of n-3 FAs explains the relation between depression and CVD in elderly men.

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