

Plasma fatty acid composition and depression are associated in the elderly: the Rotterdam Study¹⁻³

Henning Tiemeier, H Ruud van Tuijl, Albert Hofman, Amanda J Kiliaan, and Monique MB Breteler

ABSTRACT

Background: It has been hypothesized that n-3 polyunsaturated fatty acids (PUFAs) are involved in mood regulation, but epidemiologic evidence for such a link in the general population is lacking.

Objective: This study examined whether community-dwelling elderly persons with depression have a fatty acid composition that is different from that of nondepressed persons.

Design: We screened 3884 adults aged ≥ 60 y for depressive symptoms as part of the Rotterdam Study. Subjects who screened positive had a psychiatric interview to diagnose depressive disorders. All eligible subjects had their blood drawn for measurement of plasma phospholipid concentrations. We compared percentages of n-3 and n-6 PUFAs and their ratios between 264 subjects with depressive symptoms, including 106 subjects with depressive disorders, and 461 randomly selected reference subjects. We also investigated whether atherosclerosis or the inflammatory response as measured by C-reactive protein underlies the relation between fatty acid composition and depression.

Results: Subjects with depressive disorders had a higher ratio of n-6 to n-3 PUFAs, but differences in individual PUFAs were mostly small. However, depressed subjects with normal CRP concentrations (< 1.5 mg/L) had a substantially altered fatty acid composition; percentages of n-3 PUFAs and ratios of n-6 to n-3 PUFAs were significantly lower and higher, respectively, in subjects with depressive disorders than in control subjects [5.2% compared with 5.9% ($P = 0.02$) and 7.2 compared with 6.6 ($P = 0.01$), respectively]. This relation was not due to atherosclerosis.

Conclusions: In community-dwelling persons, fatty acid composition is related to depression. Because this relation was not secondary to inflammation, atherosclerosis, or possible confounders, it suggests a direct effect of fatty acid composition on mood. *Am J Clin Nutr* 2003;78:40-6.

KEY WORDS Lipid composition, depression, polyunsaturated fatty acids, phospholipids, inflammatory response, population-based study, elderly, Rotterdam Study

INTRODUCTION

The long-chain polyunsaturated fatty acids (PUFAs) fall into 2 main families: n-3 and n-6. The n-3 PUFAs are derived from fish and some plants, whereas the n-6 PUFAs are derived mainly from vegetable oil. The principal precursors of the n-3 and n-6 PUFAs cannot be endogenously synthesized from carbohydrates. The specific concentrations of n-3 and n-6 PUFAs in blood or cell membranes thus reflect dietary intakes (1). Long-term

changes in the dietary habits of Western societies are believed to have altered the ratio of n-6 to n-3 PUFAs. In ecologic studies, the increase in the incidence of ischemic heart disease and depressive disorders in the past century has been postulated as being related to dietary changes, which are characterized by a slightly increased intake of total and saturated fats and a 2-3-fold increase in the intake of oils from seeds (2-5).

Different mechanisms may underlie this postulated relation. Fatty acid composition determines the biophysical properties of neuronal membranes and influences neurotransmission (6). Higher n-3 PUFA concentrations lead to higher membrane fluidity, which in turn increases serotonin transport (3, 7). These biochemical mechanisms connect fatty acids to the current receptor- and neurotransmitter-based hypothesis of depression. But other mechanisms are also discussed. For example, dietary intake of n-3 PUFAs decreases the risk of atherosclerosis (8), and increased n-6 PUFAs result in an overproduction of prostacyclins and inflammatory markers (9). Both inflammation and atherosclerosis have been associated with depression and could link fatty acids and depression (10-12).

A few small hospital studies investigated the relation between fatty acid composition and depressive disorders (10, 13-16). In these studies, n-3 PUFA concentrations were lower in subjects with depression than in healthy control subjects. However, because the studies performed thus far have been restricted to psychiatric patients, it is unknown whether fatty acid composition affects mood in the general, community-dwelling population. Various factors such as chronic diseases, cigarette smoking, and cholesterol concentrations are related to both depression and fatty acid composition (17). These confounders might explain the associations observed in earlier studies. The present population-based study investigated the relation between the

¹ From the Departments of Epidemiology & Biostatistics (HT, AH, and MMBB) and Psychiatry (HRvT), Erasmus Medical Centre, Rotterdam, Netherlands, and Numico Research, Wageningen, Netherlands (AJK).

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³ Reprints not available. Address correspondence to MMB Breteler, Department of Epidemiology & Biostatistics, Erasmus Medical Centre, PO Box 1738, 3000 DR Rotterdam, Netherlands. E-mail: breteler@epib.fgg.eur.nl.

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fatty acid composition of plasma phospholipids and depressive disorders in elderly persons, with control for a number of demographic and biological variables. Nutrient intakes in elderly persons usually show less day-to-day variation than do those in younger persons (18), and fatty acid concentrations presumably reflect long-term intakes under the assumption of fairly consistent dietary patterns.

SUBJECTS AND METHODS

Study population

This study is based on the Rotterdam Study, an ongoing, population-based cohort study in which all inhabitants of a suburb of Rotterdam who were aged ≥ 55 y in 1990–1993 were invited to participate (19). A total of 7983 men and women (78% percent of those eligible) entered the study. The Medical Ethics Committee of the Erasmus University approved the study, and written informed consent was obtained from all participants. In the third survey, we added assessment of depressive symptoms to the study protocol. Measurements took place between March 1997 and December 1999 and included a home interview and a visit to the research center. Of the 4703 persons who participated in the home interview, 3884 visited the research center and had venous blood samples drawn. On average, compared with the subjects who visited the research center, the 819 subjects who did not were older (77.5 compared with 72.3 y), were more likely to be female (70% compared with 58%), and had more depressive symptoms (12.2% compared with 6.8%; overall prevalence: 7.8%). In the present analysis, we compared fatty acid composition between all subjects with depressive symptoms and randomly selected reference subjects.

Depression assessment

Depressive disorders were assessed by using a two-step procedure. First, participants completed the Dutch version of the original Center for Epidemiologic Studies Depression scale (CES-D) during the home interview. The CES-D is a 20-item, self-reported measure of symptoms experienced in the past week. Each item is scored on a scale of 0–3 points. The criterion validity of the CES-D version is well established (20). We used a score of 16 as a cutoff, and this score had a very high sensitivity for major depression in a random sample of older subjects in the Netherlands (21). Moreover, previous studies verified that a score of ≥ 16 on the CES-D represents clinically significant depressive symptoms (22). Second, subjects who screened positive had a psychiatric work-up with the Dutch version of the Present State Examination (PSE-10), a semistructured psychiatric interview included in the Schedules for Clinical Assessment in Neuropsychiatry (SCAN) (23). The psychometric properties of the SCAN have been studied in Dutch patients. Excellent agreement on the syndrome level and substantial test-retest reliability were found (24). One or the other of 2 experienced clinicians conducted all interviews. Psychiatric disorders were classified according to criteria from the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (DSM-IV), with an algorithm based on the PSE-10 scores. The diagnostic categories include major depression and dysthymia in addition to minor depression (as defined in the appendix of the DSM-IV).

Of the 3884 subjects who visited the research center and had blood taken, 264 (6.8%) screened positive on the CES-D and were included in the analysis of depressive symptoms. Of those 264 subjects, 9 refused the subsequent psychiatric interview and 5 could not

be reached. Psychiatric disorders and duration of symptoms were thus defined in 250 (94.7%) participants according to DSM-IV criteria. Psychiatric work-up revealed that 106 subjects had a depressive disorder as defined by the DSM-IV. The remaining 144 subjects were diagnosed as having either an anxiety disorder ($n = 20$) or another psychiatric disorder ($n = 9$) or did not meet criteria for an Axis I psychiatric disorder ($n = 115$; subclinical depressive symptoms).

Selection of reference subjects

A sample of 461 participants ranging in age from 61 to 101 y served as the reference group. They were randomly selected from participants in the Rotterdam Study who screened negative for depression. Having many control subjects increases statistical efficiency, but financial constraints did not permit determination of fatty acid composition in all the subjects. The subjects with depressive symptoms were not matched with control subjects on the basis of possible confounding variables, and thus we were able to study the effect of several of these variables on the relation between fatty acids and depression.

Blood specimens

After the subjects had fasted overnight, blood was collected under standardized conditions in a 10-mL tube containing citrate anticoagulant. The anticoagulated blood was then put on ice immediately and centrifuged at $2000 \times g$ and 4°C for 10 min. Plasma was separated from the cells, divided into two 1.5-mL aliquots, and frozen within 3 h at -80°C until analyzed. The concentrations of fatty acids originating from the phospholipid fraction of plasma were measured. Total lipid extracts of plasma were prepared according to a standard method (25). Plasma lipids were extracted from 0.25 mL plasma with chloroform and methanol after addition of an internal standard (nonadecanoyl 1,2-diacyl-*sn*-glycero-3-phosphocholine; Avanti Polar Lipids Inc, Alabaster, AL). Thereafter, solid-phase extraction was used to separate the phospholipids from the other lipid classes in the extract by NH_2 columns (Bond Elut, 500 mg, 3 mL; Varian, Middelburg, Netherlands). After separation, the phospholipids were methylated via reaction with 14% (by wt) BF_3 in methanol at 100°C for 1 h. Butylated hydroxytoluene was added as an antioxidant to all organic solvents. Fatty acid methyl esters present in the phospholipid fraction were measured via high-resolution capillary gas-liquid chromatography (Shimadzu GC17A chromatograph; Shimadzu Benelux, 's-Hertogenbosch, Netherlands) with split injection (1:15), a flame ionization detector, and a 50-m fused silica column (CP-SIL 88 for fatty acid methyl esters, 0.25 mm inside diameter, 0.2- μm film; Varian). The temperature program was as follows: an initial temperature of 160°C for 10 min, followed by a temperature increase of $3.2^\circ\text{C}/\text{min}$ up to 190°C , a 15-min isotherm period, a temperature increase of $5.0^\circ\text{C}/\text{min}$ up to 230°C , and a 7-min isotherm period.

The amounts of fatty acids present in the phospholipid fraction were quantified on the basis of the amount of fatty acid methyl ester internal standard (19:0) that was recovered and were expressed as mg/L plasma and as percentages of total fatty acids (based on mg/L values). Total phospholipid fatty acid concentrations did not differ between the depressed and the reference subjects (1139 and 1140 mg/L, respectively). Therefore, a difference between the groups in percentages of individual fatty acids also reflected a difference in absolute amounts. The data were transferred electronically to minimize transcription errors.

TABLE 1
Selected characteristics of the study subjects¹

	Reference subjects without depressive symptoms (n = 461)	Subjects with subthreshold depressive symptoms ² (n = 115)		Subjects with depressive disorders (n = 106)	
		Value	P ³	Value	P ³
Age (y)	72.5 (61–101) ⁴	73.9 (61–93)	0.10	73.7 (61–97)	0.16
Women (%)	58.6	77.3	0.01	72.6	0.05
Primary education only (%)	48.8	58.2	0.44	56.6	0.52
MMSE score	27.6 ± 2.2 ⁵	27.2 ± 2.1	0.55	26.2 ± 3.7	0.001
History of stroke (%)	2.0	7.8	0.01	7.5	0.03
Smoking (%)					
Current smoker	15.0	17.3	0.21	20.8	0.06
Exsmoker	49.5	44.3	0.49	40.6	0.16
Blood pressure (mm Hg)					
Systolic	144 ± 21	141 ± 20	0.17	139 ± 24	0.03
Diastolic	75 ± 12	72.2 ± 11	0.06	73 ± 12	0.23
Total cholesterol (mmol/L)	5.9 ± 0.9	5.8 ± 1.0	0.37	5.8 ± 1.0	0.40
HDL cholesterol (mmol/L)	1.4 ± 0.4	1.4 ± 0.4	0.12	1.4 ± 0.4	0.88
Activities of daily living score ⁶	0.5 ± 0.5	0.7 ± 0.6	0.01	0.8 ± 0.6	0.001
C-reactive protein (mg/L)	3.1 ± 4.6 (1.5) ⁷	3.1 ± 5.2 (1.6)	0.95	3.8 ± 5.3 (1.6)	0.16

¹MMSE, Mini Mental State Examination.

²Subjects who screened positive on the Center for Epidemiologic Studies Depression scale but who did not fulfill the criteria from the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition, for depressive disorders or for any other psychiatric disease.

³Analysis of covariance or logistic regression adjusted for age and sex where appropriate.

⁴Unadjusted \bar{x} ; range in parentheses.

⁵Unadjusted $\bar{x} \pm$ SD.

⁶Higher scores indicate a higher degree of functional disability in the activities of daily living.

⁷Median in parentheses.

Other measurements

The following variables were considered as possible confounding variables: age, sex, level of education, history of stroke, cognitive function as measured by the Mini Mental State Examination, disabilities in the activities of daily living, and the cardiovascular disease risk factors cigarette smoking, blood pressure, and serum total and HDL cholesterol. Education was measured on an ordinal scale and was later dichotomized at the median of the baseline sample into low and high education. A history of stroke was obtained from all subjects through direct questioning and computerized linkage with medical records from general practitioners. We measured cholesterol concentrations in fasting blood samples by using an automated enzymatic procedure. Cigarette smoking was scored according to the following categories: current, former, and never smoker. Functional status was assessed by using the Disability Index of the Stanford Health Assessment Questionnaire (26). This measure reflects the consequences of disease in terms of functional performance and activities.

We also measured the inflammation marker C-reactive protein (CRP) by using a nephelometric method, and we measured intima-media thickness as an indicator of atherosclerosis. Intima-media thickness was assessed by recording ultrasonographic images of the common carotid artery; in the analyses, we used the average of measurements from the near and the far walls of both the left and the right sides.

Statistical analysis

We used the individual fatty acid percentages of total fatty acids in the analyses. Furthermore, we calculated the ratio of n–6 to n–3 PUFAs, as well as the ratios of arachidonic acid (AA) to eicosapentaenoic acid (EPA) and of AA to docosahexaenoic acid (DHA). Previous work focused on the ratio of AA to EPA, whereas DHA is

believed to be important in mental function (10, 15). The association of fatty acids with depressive symptoms, subclinical depressive symptoms, and depressive disorders was quantified with analysis of covariance. Fatty acid percentages and ratios were entered into separate models as continuous variables. Equal variance of fatty acid percentages in the subjects with depressive symptoms and in the reference subjects was tested with Levene's test for equality of variances. No significant differences in variance were found. Age (continuous) and sex were controlled for in all analyses. To check for confounding, we added potential confounders to the basic model. If this changed the effect estimate meaningfully (defined as >5%), the variables were included in further analyses (27). In the tables, we present unadjusted means and fully adjusted mean differences.

Finally, we investigated whether CRP and intima-media thickness were intermediates in or effect modifiers of the association between fatty acid ratios and depression. To study possible intermediates, we examined whether the associations changed when these variables were entered into the model as covariates and calculated the non-parametric (Spearman's) correlation of CRP and intima-media thickness with fatty acids. Effect modification was formally tested by putting the product terms into the model. Furthermore, we stratified the analyses by the median of the CRP concentrations. We used SPSS for WINDOWS (version 9.0; SPSS Inc, Chicago) in all our analyses.

RESULTS

The characteristics of the reference subjects and of the subjects with depressive disorders are shown in **Table 1**. The subjects with depressive disorders were significantly more likely to be female and to have had a stroke and had significantly lower activities of daily living scores and cognitive scores.

TABLE 2

Percentages and ratios of fatty acids in plasma phospholipids in reference subjects without depressive symptoms, in subjects with subthreshold depressive symptoms, and in subjects with depressive disorders¹

	No depressive symptoms ² (n = 461)	Subthreshold depressive symptoms ³ (n = 115)			Depressive disorders (n = 106)		
		Unadjusted \bar{x}	Adjusted difference (95% CI)	P ⁴	Unadjusted \bar{x}	Adjusted difference (95% CI)	P ⁴
SFAs (% of total fatty acids)	45.9	46.1	0.1 (-0.2, 0.4)	0.4	46.1	0.1 (-0.3, 0.4)	0.7
MUFAs (% of total fatty acids)	11.8	11.9	0 (-0.4, 0.4)	1.0	11.8	-0.1 (-0.5, 0.3)	0.7
PUFAs (% of total fatty acids)							
n-6							
Linoleic acid (18:2)	21.8	21.8	0.1 (-0.4, 0.7)	0.7	21.6	-0.1 (-0.7, 0.6)	0.7
Dihomogammalinolenic acid (20:3)	3.3	3.3	-0.1 (-0.2, 0.1)	0.4	3.3	0 (-0.2, 0.1)	0.7
AA (20:4)	9.0	8.7	-0.2 (-0.7, 0.2)	0.3	9.3	0.5 (0, 1.0)	0.05
Total	35.3	35.1	-0.2 (-0.7, 0.4)	0.6	35.6	0.4 (-0.2, 1.1)	0.2
n-3							
EPA (20:5)	0.9	0.9	0 (-0.1, 0.1)	0.6	0.8	0 (-0.2, 0.1)	0.4
Docosapentaenoic acid (22:5)	0.9	1.0	0 (-0.1, 0.1)	0.8	0.9	0 (-0.1, 0.1)	0.3
DHA (22:6)	3.7	3.7	0 (-0.3, 0.2)	0.9	3.5	-0.2 (-0.5, 0)	0.05
Total	5.8	5.9	0 (-0.3, 0.3)	0.9	5.5	-0.3 (-0.7, 0)	0.06
Ratios							
n-6:n-3 PUFAs	6.6	6.4	-0.1 (-0.7, 0.4)	0.7	6.9	0.4 (0, 0.8)	0.05
AA:EPA	13.0	11.7	-0.9 (-2.4, 0.7)	0.3	14.1	1.6 (0, 3.2)	0.06
AA:DHA	2.7	2.6	-0.1 (-0.3, 0.2)	0.5	2.9	0.3 (0, 0.5)	0.04

¹SFAs, saturated fatty acids; MUFAs, monounsaturated fatty acids; PUFAs, polyunsaturated fatty acids; AA, arachidonic acid; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid.

²Unadjusted \bar{x} .

³Subjects who screened positive on the Center for Epidemiologic Studies Depression scale but who did not fulfill the criteria from the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition, for depressive disorders or for any other psychiatric disease.

⁴Analyses of covariance with percentages of fatty acids entered as continuous variables and with adjustment for age, sex, smoking status, systolic blood pressure, and activities of daily living score.

We found no difference in plasma phospholipid fatty acid composition between the reference subjects and the 264 subjects who had depressive symptoms as determined by the CES-D (data not shown). Comparisons of the 115 subjects with subclinical depressive symptoms and the 106 subjects who fulfilled the criteria for a DSM-IV depressive disorder with the reference subjects are shown in **Table 2**. The percentages and ratios of phospholipid fatty acids did not differ significantly between the subjects with subclinical depressive symptoms and the reference subjects.

When the subjects with DSM-IV depressive disorders were compared with the reference subjects, moderate, borderline significant differences in mean percentages were observed for only 2 individual PUFAs. Percentages of AA and DHA were higher and lower, respectively, in the subjects with depressive disorders than in the reference subjects. However, we observed borderline significant differences in the ratios of n-6 to n-3 PUFAs, of AA to EPA, and of AA to DHA. These differences were due to the higher and lower percentages of n-6 and n-3 PUFAs, respectively, in the subjects with depressive disorders than in the reference subjects.

The results shown in **Table 2** were adjusted for age, sex, smoking status, blood pressure, and activities of daily living score. Neither adjustment for any of the other possible confounders that we measured nor adjustment for CRP concentration or intima-media thickness changed the results. Thus, there was no evidence that the inflammation marker CRP or atherosclerosis as measured by intima-media thickness mediates the relation between fatty acids and depressive disorders. Moreover, all Spearman's correlation coefficients for the relation of each variable to fatty acids were <0.01 except for the coefficient for percentage of saturated fatty acids. However, a formal test for interaction showed that the relation between the ratio of n-6 to n-3 PUFAs and depressive

disorders depended on the CRP concentration (interaction term included in analysis of covariance; $P = 0.02$). The difference in the ratio of n-6 to n-3 PUFAs between the depressed subjects and the reference subjects increased with lower concentrations of CRP. Therefore, we stratified the analysis of the relation between fatty acids and depressive disorders at the median of the CRP concentrations (1.5 mg/L). Among the subjects with a CRP concentration > 1.5 mg/L, we found no significant difference in fatty acid composition between the reference subjects and the depressed subjects (data not shown). The analysis of the subjects with a CRP concentration < 1.5 mg/L is shown in **Table 3**. Among these subjects, the depressed subjects had significantly lower percentages of n-3 PUFAs than did the reference subjects, and all 3 of the fatty acid ratios differed significantly between the depressed subjects and the reference subjects, indicating significantly different distributions of fatty acids.

To further investigate whether a substantially different fatty acid composition is seen in all depressed subjects with a normal CRP concentration (upper limit: 5 mg/L), we repeated the analyses and excluded all subjects (depressed and reference subjects) with a CRP concentration above the normal range. The depressed subjects with a normal CRP concentration had a significantly lower mean percentage of total n-3 PUFAs and a significantly higher mean ratio of n-6 to n-3 PUFAs in plasma phospholipids than did the reference subjects with a normal CRP concentration [5.2% compared with 5.9% ($P = 0.02$) and 7.2 compared with 6.6 ($P = 0.01$), respectively].

DISCUSSION

This population-based study showed that fatty acid composition is associated with depressive disorders in the elderly after

TABLE 3
Percentages and ratios of fatty acids in plasma phospholipids in subjects with low C-reactive protein concentrations (<1.5 mg/L)¹

	Reference subjects without depressive symptoms ² (<i>n</i> = 232)	Subjects with depressive disorders (<i>n</i> = 51)		
		\bar{x}	Adjusted difference (95% CI)	<i>P</i> ³
SFAs (% of total fatty acids)	45.8	46.1	0.3 (−0.2, 0.7)	0.2
MUFAs (% of total fatty acids)	11.6	11.5	−0.1 (−0.7, 0.5)	0.6
PUFAs (% of total fatty acids)				
n−6				
Linoleic acid (18:2)	22.1	22.4	0.3 (−0.6, 1.2)	0.6
Dihomogammalinolenic acid (20:3)	3.2	3.2	−0.1 (−0.3, 0.1)	0.5
AA (20:4)	9.0	9.3	0.3 (−0.4, 1.0)	0.4
Total	35.6	36.1	0.6 (−0.3, 1.4)	0.2
n−3				
EPA (20:5)	0.9	0.7	−0.2 (−0.4, 0)	0.05
Docosapentaenoic acid (22:5)	1.0	0.9	0 (−0.1, 0)	0.1
DHA (22:6)	3.7	3.2	−0.4 (−0.8, −0.1)	0.02
Total	5.9	5.2	−0.7 (−1.2, −0.1)	0.01
Ratios				
n−6:n−3 PUFAs	6.6	7.6	0.9 (0.3, 1.6)	0.006
AA:EPA	13.2	16.4	3.3 (0.9, 5.7)	0.007
AA:DHA	2.7	3.1	0.4 (0.1, 0.7)	0.02

¹SFAs, saturated fatty acids; MUFAs, monounsaturated fatty acids; PUFAs, polyunsaturated fatty acids; AA, arachidonic acid; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid.

²Unadjusted \bar{x} .

³Analyses of covariance with percentages of fatty acids entered as continuous variables and with adjustment for age, sex, smoking status, systolic blood pressure, and activities of daily living score.

adjustment for demographic and biological variables. The subjects with depressive disorders had moderately higher ratios of n−6 to n−3 PUFAs than did the reference subjects, but the differences in individual fatty acids were mostly small. However, the depressed subjects with a normal CRP concentration had a much more substantial shift in fatty acid composition. No difference in fatty acid composition was found between the subjects with subclinical depressive symptoms and the reference subjects.

Some methodologic issues of the present study need to be discussed before we can interpret the findings. First, it was a cross-sectional study and thus cannot show whether depression precedes or follows from altered fatty acid composition. Although depressed subjects generally have less appetite, our results probably do not reflect this. Dietary changes would have had to selectively affect percentages of n−3 PUFAs and the ratio of n−6 to n−3 PUFAs but leave percentages of saturated and monounsaturated fatty acids unaffected. However, the possibility that the intake of PUFAs changed after the onset of depression (eg, eating less oily fish) cannot be ruled out.

Second, the prevalence of subjects with depressive symptoms in this study (7.8%) was relatively low, but within the range (2.8–35%) reported in a recent review (28), and is also comparable to that in the United States (9.0%) (22). Furthermore, subjects with depressive disorders were slightly underrepresented in the analytic sample because they were less likely to visit the research center. However, we think that the observed relation between fatty acids and depression is unlikely to have been due to a selection effect.

The strengths of the present study were its size, the population base, and the psychiatric work-up in subjects who screened positive on the depression scale. We determined which depressive symptoms were due to depressive disorders. Therefore, misclassification of disease is unlikely to have influenced our results. In addition, we controlled for numerous confounders. Furthermore,


we were able to separate the effects of smoking and atherosclerosis. To our knowledge, only 3 hospital studies compared ratios of n−6 to n−3 PUFAs between depressed subjects and control subjects. Maes et al (10, 16) repeatedly found a shift in the ratio of n−6 to n−3 PUFAs, but in a study by Peet et al (13), the ratio of n−6 to n−3 PUFAs did not differ significantly between depressed subjects and control subjects. In the latter study, concentrations of both total n−3 and total n−6 PUFAs were higher in control subjects than in depressed subjects. Other studies examined fatty acid composition along a spectrum of worsening depressive disorders, compared depressed patients with other psychiatric inpatients, or focused on n−3 PUFAs only (14, 15, 29).

Several mechanisms may be responsible for the observed association between fatty acid composition and depression. There is a large body of evidence showing that fatty acid composition influences the biophysical properties of neuronal membranes (30). Via this pathway, fatty acids have an effect on receptor function, neurotransmitter reuptake, and signal transmission. In animal models of depression, diet has been shown to influence membrane properties, eg, n−3 PUFA-enriched food augments serotonin receptor sensitivity (3).

Furthermore, a low ratio of n−6 to n−3 PUFAs reduces the risk of vascular disease, presumably by affecting platelet aggregation or blood pressure or via direct atherogenic effects (8, 31, 32). According to the vascular depression model, vascular factors contribute significantly to the pathogenesis of depression. However, in the present study, we found no indication that atherosclerosis is an intermediate between fatty acid composition and depression. The same holds for immune activation. Our data suggest that acute phase proteins do not link fatty acids and depression, unless CRP is not specific enough to measure the immune process. Immune activation is associated with depression, and an unfavorable ratio of n−6 to n−3 PUFAs probably stimulates the production of proinflammatory cytokines and other signs of the

inflammatory response system (9). High concentrations of n-6 PUFAs (especially of AA) are assumed to increase the production of proinflammatory prostaglandins, whereas high concentrations of n-3 PUFAs (especially of EPA and DHA) may inhibit the formation of prostaglandin E₂ (10, 33). Indeed, the differences in PUFAs between the depressed and the reference subjects in our study were mainly due to the fatty acids associated with the immune response. However, if immune modulation underlies the relation, we should have found more subjects with depression among those with both a high ratio of n-6 to n-3 PUFAs and a high CRP concentration.

Rather, the association between fatty acids and depression became stronger with lower CRP concentrations. Different explanations for this interaction are possible. The acute phase response signaled by CRP is characterized by lipolysis (34). Fatty acids are mobilized from adipocytes and hepatocytes. Acute phase high-density lipoproteins have been shown to have a phospholipid composition that is different from that of normal ones (35). This suggests that the serum phospholipid fatty acid compositions in the present study may have been less informative with respect to long-term dietary intakes in the presence of high CRP concentrations. Another possible explanation is that high CRP concentrations identify a subpopulation with more health problems, which in turn are associated with depressive disorders in late life. Biological risk factors for depression, such as fatty acid composition, may be relatively less important. On the other hand, low CRP concentrations indicate healthier subjects, and in these subjects, the relation of depression with fatty acid composition may not be diluted by other health-related factors.

In summary, we showed that community-dwelling subjects with depressive disorders have a fatty acid composition that is different from that of nondepressed subjects. Our data suggest that this result was not secondary to smoking or cardiovascular disease risk factors and that fatty acid composition is not linked to depression by atherosclerosis or the inflammatory marker CRP. The findings make it more credible that relatively low concentrations of n-3 PUFAs have a direct effect on mood disorder. Specific diets might thus influence mood. Ultimately, clinical trials are necessary to prove whether dietary changes or fatty acid supplementation may play a role in the prevention or treatment of depressive disorders. So far, a positive effect of supplementation with the n-3 PUFAs has been shown only for the short-term course of bipolar and recurrent depression (36-39). 

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HT performed the statistical analyses and drafted the report. HRvT conducted most of the psychiatric interviews. AH is the guarantor of the Rotterdam Study. AJK supervised the laboratory measurements of fatty acids and CRP at Numico Research. MB supervised the study and, together with AJK, designed the study. All authors contributed to the interpretation of the data and the writing of the article. AJK is a full-time employee of Numico Research BV. None of the other authors had any financial or personal interests in Numico Research BV.

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