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ORIGINAL CONTRIBUTION

Serum polyunsaturated fatty acids are not associated with the risk of severe depression in middle-aged Finnish men: Kuopio Ischaemic Heart Disease Risk Factor (KIHD) Study

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Abstract
Purpose The aim of this study is to investigate whether serum $n-3$ polyunsaturated fatty acids (PUFAs) or $n-6$ to $n-3$ ratio is associated with risk of severe depression in middle-aged Finnish men.
Methods The association between the serum concentrations of fatty acids and depression was investigated in 2077 men aged 42–60 years at baseline in a prospective follow-up setting. The population-based Kuopio Ischaemic Heart Disease Risk Factor (KIHD) Study cohort was recruited between 1984 and 1989 and followed until the end of 2007. The baseline levels of serum total $n-3$ PUFAs, $n-6$ PUFAs and individual fatty acids were determined. Data on hospital treatments due to major depressive disorder were derived from the national hospital discharge register.
Results During the average follow-up time of 18 years, 46 men received a discharge diagnosis of depression. When the Cox proportional hazards model was adjusted for age, examination year, baseline socioeconomic status, alcohol consumption, smoking, maximal oxygen uptake and body mass index, there was no association between serum total $n-3$ PUFAs and the risk of depression [relative risk (RR) in the highest compared to the lowest tertile 0.71, 95% confidence interval (CI): 0.38; 1.43]. Serum concentrations of $n-6$ PUFAs, $n6/n3$ PUFA ratio, or individual fatty acids were not associated with the risk of severe depression, either.
Conclusions We did not find evidence that serum $n-3$ PUFA concentration or $n-6/n-3$ ratio would be associated with risk of severe depression in middle-aged Finnish men.

Keywords Depression · Fatty acids · Polyunsaturated · EPA · DHA

Abbreviations

AA	Arachidonic acid, C20:4$n-6$
ALA	Alpha-linolenic acid, C18:3$n-3$
BMI	Body mass index
CES-D	Center for epidemiological studies depression scale
CI	Confidence interval
CV	Coefficient of variation
DHA	Docosahexaenoic acid, C22:6$n-3$
DPA	Docosapentaenoic acid, C22:5$n-3$
EPA	Eicosapentaenoic acid, C20:5$n-3$
HPL	Human population laboratory
LA	Linoleic acid, C18:2$n-6$
PUFA	Polyunsaturated fatty acid
RCT	Randomized controlled trial
RR	Relative risk

Introduction

Severe depression is a growing health challenge all over the world, and recent meta-analysis on randomized

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controlled trials (RCTs) [1] presented that long-chain $n-3$ polyunsaturated fatty acids ($n-3$ PUFAs) showed a significant antidepressant efficacy. In addition, several studies have revealed an association between the low intake of long-chain $n-3$ PUFAs and increased prevalence of depression [2] as well as a significant reduction in serum levels of $n-3$ PUFAs in depressed patients [3]. However, the association of the beneficial effects of $n-3$ PUFA intake with mental disorders has been suggested to be non-linear [4]. Some studies have also reported an inverse relationship between severity of depression and circulating levels of $n-3$ PUFAs [5, 6]. Severity associated inversely to concentrations of eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), alpha-linolenic acid (ALA) and total $n-3$ PUFAs [5, 6].

Few prospective cohort studies have been published on the relationship between $n-3$ PUFAs and depression [7, 8]. A previous longitudinal study in Finland [7] observed no association between intake of $n-3$ PUFAs and depression. In general, fish and seafood are the main sources of long-chain $n-3$ PUFAs in diet. In epidemiological studies non-existent, infrequent or minor consumption of fish has associated with greater prevalence or increased risk of depression [9–11]. Interestingly, this association has been observed especially in women [9, 10], while the Finnish study [7] where no association was detected, included men only.

The associations between depression and $n-3$ fatty acids might be explained by unfavourable ratio of $n-6$ to $n-3$ PUFAs [5, 12]. During the recent decades, the intake of $n-3$ PUFAs in Western diets has decreased while intake of $n-6$ PUFAs has increased [13]. These fatty acids have different physiological functions and it is suggested that the imbalance between these PUFAs has resulted in increasing incidence of different diseases [14]. Depression has been considered a disease with low-grade inflammation [15]. High $n-6$ to $n-3$ ratio enhances proinflammatory cytokine production, whereas $n-3$ PUFAs as such have anti-inflammatory properties [16] Thus, it has been assumed that diets with high ratios of $n-6$ to $n-3$ PUFAs may increase the risk of depression and other inflammatory diseases [16]. Interestingly, the blood $n-6$ to $n-3$ PUFA ratio [5, 17, 18] or concentrations of an $n-6$ PUFA, arachidonic acid (AA), has been found to be higher in depressed subjects compared to controls [5, 19]. In a large population-study [8], subjects with depressive disorders had a higher ratio of $n-6$ to $n-3$ PUFAs, but differences in individual PUFAs were mostly small.

Taken together, several studies suggest that $n-3$ PUFAs may be protective against depression, but only a few prospective studies have been published. The results have been inconsistent, and significance of a gender as a confounding factor is ambiguous. Moreover, there are only a few prospective studies on the association between the $n-6$ to $n-3$ PUFA ratio or the serum levels of individual fatty acids and the risk of depression. The aim of this study was to investigate whether serum $n-3$ PUFAs [sum of EPA + DPA (docosapentaenoic acid) + DHA] or $n-6$ to $n-3$ ratio is associated with lower risk of severe depression in middle-aged Finnish men.

Methods

Study population and design

The Kuopio Ischaemic Heart Disease Risk Factor (KIHD) Study is an ongoing population-based cohort study designed to investigate risk factors for cardiovascular diseases and other chronic diseases in middle-aged men living in eastern Finland [20]. The baseline examinations were conducted between 1984 and 1989 in a random sample of men living in the city of Kuopio and neighbouring rural communities. A total of 2682 men, who were 42, 48, 54 or 60 years old at baseline (82.9% of those eligible), were recruited in two cohorts. The first cohort consisted of 1166 men who were 54 years old, enrolled between 1984 and 1986, and the second cohort included 1516 men who were 42, 48, 54 or 60 years old, enrolled between 1986 and 1989. During the years 1998–2001, all men from the second cohort were invited to the 11-year re-examinations of the study, and 854 men (85.6%) participated.

For the present study, we excluded men without information on serum fatty acids ($n = 155$), men with missing dietary data ($n = 41$), those with significant depressive symptoms at baseline ($n = 321$) and a history of mental illness ($n = 88$), leaving 2077 men for the analyses. The average follow-up time of the study population was 18.3 years (range 0–24 years). The study protocol was approved by the Research Ethics Committee of the University of Kuopio and Kuopio University Hospital, and after complete description of the study to the subjects, written informed consent was obtained.

Assessment of depressive symptoms

At baseline, depressive symptoms were assessed with the 18-item Human Population Laboratory (HPL) Depression Scale [21]. The scale consists of items dealing with mood disturbance, negative self-concept, loss of energy, problems with eating and sleeping, trouble with concentration, and psychomotor retardation or agitation. It was developed especially for screening general population samples [21], and it also conceptually resembles other brief checklists of

symptoms such as the Center for Epidemiological Studies Depression Scale (CES-D) [22, 23]. The HPL Depression Score is generated by assessing one point for each true or false answer that is an indicative of depression. The cut-off score of five or more has earlier been used to define depression [21, 23, 24]. Those who scored five or more at baseline ($n = 321$, 12% of participants) were considered to have elevated depressive symptoms and were thus excluded from the analyses.

Outcome data

Outcome data was severe depression diagnosed by a physician. These data included participants who received a discharge diagnosis of depressive disorder during the follow-up period. The information was obtained by computer linkage to the national hospital discharge register, which covers every hospitalization in Finland. The participants who were hospitalized and had been diagnosed as having major depression (International Classification of Diseases (ICD-9: 2961-, ICD-10: F32.1-3, F33.1-3; $n = 27$), depressive disorder not otherwise specified (ICD-9: 2968A, ICD-10: F32.9, F33.9; $n = 14$), chronic depression (ICD-8: 300.41, ICD-9: 3004A, ICD-10: F34.1; $n = 3$) or adjustment disorder with depressive symptoms (ICD-9: 3090A; $n = 2$) during the follow-up period were categorized as having incident severe depression.

Serum fatty acids

As described previously [25], serum esterified and non-esterified fatty acids were determined at baseline and at 11-year examination in one gas chromatographic run without preseparation. Fatty acids [s-EPA, s-DHA, s-DPA, s-ALA, s-LA (linoleic acid), s-AA] were chromatographed in an NB-351 capillary column (HNU-Nordion, Helsinki, Finland) by a Hewlett-Packard 5890 Series II gas chromatograph (Hewlett-Packard, Avondale, Pa) with a flame ionization detector. The coefficient of variation (CV) for repeated measurements of major esterified fatty acids was about 5%. Because the relative degree of fatty acid saturation varies among the various types of esterified fatty acids (i.e., cholesterol esters, phospholipids, and triglycerides), the concentration of esterified fatty acids were adjusted for serum low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and triglyceride concentrations. The CV for major non-esterified fatty acids was about 15%. For non-esterified fatty acids, no adjustment was necessary. Based on serum fatty acid concentrations, we calculated the levels of $n - 3$ PUFAs (EPA + DPA + DHA), total $n - 6$ PUFAs (LA + AA) and $n - 6/n - 3$ PUFA ratio.

Other measurements

Dietary intake of foods, beverages and nutrients was quantitatively assessed by a 4-day food recording at the time of blood sampling during the baseline-examination phase of the KIHD study [26]. Participants completed questionnaires related to their background, current smoking habits, history of alcohol consumption, marital status and education at baseline, which have been described previously [25, 27]. A detailed description of the determination of maximal oxygen uptake has also been published previously [25]. The variable of adulthood socio-economic status was formed from a variety of indicators, including current income, current and previous occupations, highest level of education, perception of financial security, and housing tenure [28]. The variable "good appetite" used as a covariate was derived from the HPL depression score statement "I have a good appetite". The weight and height of the participants were measured by a study nurse, and the body mass index (BMI) was calculated as the ratio of weight in kilograms to the square of height in metres.

Statistical methods

Differences in baseline characteristics between those who received a discharge diagnosis of depression during the follow-up period and the rest of the cohort were examined using the Student's *t*-test or chi-squared test. When the distribution of the variables was skewed, the non-parametric Mann–Whitney U-test was utilized.

Altogether, 74 participants had a unipolar depressive disorder as a discharge diagnosis during the average follow-up period of 18.3 years. After exclusions, 46 participants with severe depression remained for the final analysis. To study the differences between serum fatty acid groups, we divided the study population into three groups according to the tertile values: $n - 3$ PUFA (EPA + DPA + DHA: <3.85%, 3.85–4.92% and >4.92% of all serum fatty acids), EPA (<1.21%, 1.21–1.76% and >1.76%), DPA (<0.50%, 0.50–0.58% and >0.58%), DHA (<2.09%, 2.09–2.63% and >2.63%), LA (<24.6%, 24.6–28.3% and >28.3%), ALA (<0.62%, 0.62–0.80% and >0.80%), AA (<4.3%, 4.3–5.2% and >5.2%), $n - 6/n - 3$ PUFA ratio (<5.3:1, 5.3:1–6.8:1, >6.8:1) and total $n - 6$ PUFA (<29.6%, 29.6–33.6% and >33.6%). Because of the relatively modest number of cases, in the stratified analyses dichotomous variables were used instead of tertiles; median values were used as the cut-off point. Tests of linear trend were conducted by assessing the median values for each category of exposure variable and treating those as a single continuous variable. For the tests of quadratic (non-linear) trend, the linear trend

Table 1 Baseline characteristics of the study population according to the diagnosis of severe depression

	Whole study population ($n = 2077$)	Subjects hospitalized due to depression ($n = 46$)	Subjects not hospitalized due to depression ($n = 2031$)	P value for difference
Serum values				
Serum $n-3$ (EPA + DHA + DPA, %)	4.7 (1.6)	4.5 (1.4)	4.7 (1.6)	0.34[a]
Serum total $n-3$ (%)	5.4 (1.6)	5.2 (1.4)	5.4 (1.6)	0.40[a]
Serum EPA (%)	1.7 (0.9)	1.5 (0.7)	1.68 (0.9)	0.34[a]
Serum DHA (%)	2.5 (0.7)	2.4 (0.7)	2.5 (0.7)	0.41[a]
Serum DPA (%)	0.55 (0.1)	0.54 (0.1)	0.55 (0.1)	0.60[a]
Serum total *n6*/*n3* ratio	6.2 (1.8)	6.6 (2.0)	6.2 (1.8)	0.25[a]
Dietary intake				
Energy intake (MJ/day)	9.9 (2.6)	11.3 (2.8)	9.9 (2.6)	<0.001[a]
Total fat (E%)	38.6 (6.3)	39.7 (6.5)	38.5 (6.3)	0.21[a]
Polyunsaturated fatty acids (E%)	4.5 (1.4)	4.7 (1.2)	4.5 (1.4)	0.58[a]
Saturated fatty acids (E%)	17.9 (4.3)	18.4 (4.2)	17.9 (4.3)	0.43[a]
EPA, dietary intake (mg/day)	111 (157)	94 (132)	112 (157)	0.44[a]
DHA, dietary intake (mg/day)	213 (288)	177 (216)	214 (289)	0.31[a]
Energy-adjusted folate (μg/day)	255 (57)	240 (65)	256 (56)	0.07[a]
Alcohol consumption (grams/week)	71 (126)	70 (82)	71 (127)	0.94[b]
Other factors				
Age (years)	52.9 (5.2)	51.7 (5.8)	53.0 (5.2)	0.11[a]
Maximal oxygen uptake (ml/kg/min)	31.1 (7.6)	32.3 (6.9)	31.0 (7.6)	0.26[a]
Marital status: living alone (%)	11.8	17.4	11.6	0.16[c]
Socio-economic status (points)	9.1 (4.6)	9.9 (3.9)	9.1 (4.6)	0.59[c]
Smoking (%)	31	33	31	0.45[d]
Body mass index (kg/m^2)	26.9 (3.4)	27.0 (3.5)	26.9 (3.4)	0.83[a]
HPL depression score	1.3 (1.3)	1.9 (1.5)	1.3 (1.3)	0.002[a]

All values are mean ± SD or percentages

SD standard deviation; *E%* per cent of energy; *EPA* eicosapentaenoic acid; *DHA* docosahexaenoic acid; *DPA* docosapentaenoic acid; *MJ* megajoule; *HPL* Human population laboratory

[a] Student's *t*-test

[b] Mann–Whitney U-test

[c] Chi-squared test

[d] Fishers' exact test

variable was squared after centring it at median serum fatty acid value.

The relative risk (RR) of depression was examined using the Cox proportional hazards model adjusted for age and examination years (Model 1) and further, for socio-economic status, maximal oxygen uptake, smoking, alcohol consumption and BMI (Model 2). The correlations between KIHD Study baseline and 11-year follow-up examinations were estimated by the Pearson's correlation coefficient. All P values were two-tailed ($\alpha = 0.05$). All statistical analyses were conducted using the statistical software package SPSS 14.0 for Windows (SPSS Inc., Chicago, IL, USA).

Results

The baseline characteristics of the study subjects are presented in Table 1. The men who were hospitalized because of depression during the follow-up had higher intake of energy and higher HPL depression scores than others. The correlation coefficient between the serum long-chain $n-3$ PUFAs at baseline and at 11-year follow-up was 0.42 ($P < 0.001$) and for the serum $n-6$ PUFAs 0.47 ($P < 0.001$).

Table 2 presents the RRs between serum fatty acids and risk of getting a discharge diagnosis of depression during the follow-up. We did not find any significant associations

Table 2 Relative risk (RR) and 95% confidence interval (CI) of severe depression during the average follow-up of 18.3 years in middle-aged men according to the tertiles of serum fatty acids

	Model 1[a]			Model 2[b]		
	RR	95% CI	*P for trend*	RR	95% CI	*P for trend*
$n-3$			0.29			0.33
(EPA + DHA + DPA)						
1	1			1		
2	0.41	0.19; 0.91		0.41	0.19; 0.91	
3	0.71	0.38; 1.38		0.71	0.38; 1.43	
$n-6$			0.76			0.55
1	1			1		
2	0.91	0.43; 1.91		0.96	0.45; 2.04	
3	1.10	0.55; 2.23		1.25	0.59; 2.65	
EPA			0.19			0.17
1	1			1		
2	0.57	0.28; 1.16		0.55	0.26; 1.12	
3	0.64	0.33; 1.32		0.62	0.31; 1.25	
DHA			0.79			0.98
1	1			1		
2	0.93	0.46; 1.87		0.96	0.47; 1.96	
3	0.91	0.45; 1.84		0.99	0.48; 2.04	
Linoleic acid			0.47			0.28
1	1					
2	0.62	0.28; 1.37		0.67	0.29; 1.51	
3	1.23	0.63; 2.39		1.43	0.70; 2.91	
Alpha-linolenic acid			0.35			0.22
1	1					
2	1.07	0.50; 2.28		1.16	0.54; 2.51	
3	1.41	0.67; 2.94		1.60	0.75; 3.43	
Arachidonic acid			0.21			0.20
1	1			1		
2	0.77	0.39; 1.53		0.77	0.39; 1.53	
3	0.64	0.31; 1.30		0.62	0.30; 1.29	
$n-6/n-3$ ratio			0.99			0.98
1	1			1		
2	0.79	0.38; 1.65		0.77	0.37; 1.62	
3	0.99	0.50; 1.96		0.97	0.49; 2.00	

EPA eicosapentaenoic acid; *DHA* docosahexaenoic acid; *DPA* docosapentaenoic acid

[a] RR, relative risk derived from Cox proportional hazards models. Model 1: adjusted for age and examination years

[b] RR, relative risk derived from Cox proportional hazards models. Model 2: adjusted for age, examination years, body mass index (kg/m^2), socioeconomic status in adulthood (points), cigarette smoking (years), alcohol consumption (g/week) and maximal oxygen uptake (ml/kg/min)

between the serum levels of total $n-3$ PUFAs, total $n-6$ PUFAs or any individual fatty acids (EPA, DHA, LA, ALA or AA) and the risk of depression. Further adjustments for the intake of energy-adjusted folate, intake of energy, education, good appetite and points of HPL depression scale did not change the association (RR change $< 5\%$). We also repeated the analyses after including men with history of mental illness in the study population, but this did not change the associations (data not shown).

We also evaluated the interaction between total $n-3$ and total $n-6$ PUFAs by using stratified analyses (both stratified by median). However, no evidence for effect modification by total $n-6$ PUFAs was found (P for interaction 0.72). We also examined the possible non-linear association between the fatty acids and the risk of

depression, but no such associations were found (P for non-linear trends > 0.10).

Discussion

This prospective cohort study of middle-aged Finnish men suggests that serum levels of total $n-3$ PUFAs or total $n-6$ PUFAs or individual fatty acids or the $n-6/n-3$ PUFA ratio are not associated with the risk of severe depression.

Previous studies

Two recent cross-sectional studies on patient samples have shown that in major depression there is a deficiency of $n-3$ PUFAs in serum and red cells [18, 29]. Nevertheless, low levels of these fatty acids may be due to decreased intake of $n-3$ PUFAs as a result of depression rather than supporting the hypothesis that low fatty acid intake actually causes depression. Our results are congruent with another prospective Finnish study [7], in which no association was found between $n-3$ PUFAs and the risk depression. Nevertheless, in our study, the average concentrations of serum $n-3$ PUFAs were relatively small (mean 4.7%), which may affect the results. In comparison, in a study by Tiemeier et al. [8], the concentration of total $n-3$ PUFAs in plasma phospholipids was approximately 5.8% in subjects with no depressive symptoms and 5.5% in subjects with depressive disorder. These are higher than the serum concentrations in our study population, where the concentrations were a sum of esterified (in cholesterol esters, phospholipids, and triglycerides) and non-esterified fatty acids. This indicates that our study population had relatively low levels of $n-3$ PUFAs. When the average levels are low, it might be difficult to detect an association between serum $n-3$ PUFA levels and risk of severe depression. In addition, while our results differ from the results of the RCTs [1], we could assume that the severity of disease is one reason affecting the association. Most of the participants in the RCTs are outpatients, while our study participants with severe depression were requiring hospital treatment. Moreover, the dosage of the long-chain $n-3$ PUFAs given in the RCTs is usually greater than the amount of long chain $n-3$ PUFAs obtained from diet.

Limitations

Our study has some limitations. First, the number of depressed subjects was relatively small. In Finland, there is no national register of outpatients with depression, and thus the study was limited to subjects with severe depression requiring hospitalization. Although we found no significant association between $n-3$ PUFAs and risk of depression, we cannot fully exclude the possibility that non-significance especially with $n-3$ PUFAs is due to the relatively small number of hospitalizations, or in other words, the lack of power in the study. On the other hand, severity of depression may influence the dietary intake of $n-3$ PUFAs.

Second, we had information about the serum fatty acid concentrations measured at baseline for the whole cohort and for the subgroup (31% of the study population) at 11-year examination. The intakes of fatty acids could have changed during the follow-up, and thus use of a single measurement of these fatty acids may underestimate the association between the risk of severe depression and serum fatty acids. Nevertheless, the fatty acid concentrations of the subgroup remained relatively similar to the baseline values, suggesting that the fatty acid concentrations are fairly stable even during longer follow-up periods.

Strengths

The main strength of our study is that we used a prospective follow-up setting with population-based recruitment. Compared to cross-sectional studies, prospective studies give more reliable information on the causal relationship as serum concentrations have been measured before observed depression. We were also able to exclude those who had history of mental illness or current depressive symptoms. This further adds to the reliability of evaluation of causal relationship. In addition, our study population was relatively large, and the controlling of confounding factors was possible due to numerous measurements carried out at baseline.

Another strength of the study is that we have measured serum long-chain PUFA concentrations, which is a proper method for assessing the status of these fatty acids in the body. Serum long-chain $n-3$ PUFAs correlate well with fish, fish oil and seafood intake [30] and reflect dietary intakes over several weeks [31]. Moreover, serum values reveal not only the actual intake of these fatty acids but also individual differences in fatty acid metabolism and storage.

Potential explaining factors: gender and energy intake

It has been reported previously that the association between $n-3$ PUFAs and depression has been found especially [9] or only [10] in women. Unfortunately, there are no separate analyses conducted according to gender in the RCTs [1]. However, a great majority of the participants in these studies have been women, which may explain the discrepancy between RCTs and the present study. Our study population consisted of men only, and no association was

found between $n-3$ PUFAs and depression. The gender difference might be explained by differences in neurotransmitter metabolism between the sexes [10]. On the other hand, it has been proposed that men usually eat more than women, get more energy from food and also more $n-3$ PUFAs than women do [10], which may affect the shown association. It has been discussed earlier that energy intake may also influence the relationship between $n-3$ PUFA status and depression [32]. Depressed individuals may eat less than non-depressed people, which may affect $n-3$ PUFA status and thus the results of studies. However, in our study those who became depressed during the follow-up actually obtained more energy from the diet than those who remained non-depressed. Nevertheless, we repeated the analyses adjusting with energy intake, and the results remained unaltered.

Ratio of $n-6$ to $n-3$ fatty acids

It has previously been assumed that high $n-6$ to $n-3$ PUFA ratio may increase the risk of depression, or at least depressed patients have increased ratios of $n-6$ to $n-3$ compared to controls [8, 17]. In contrast, in a study by Peet and colleagues [29] the ratio of $n-6$ to $n-3$ did not differ significantly between depressed and controls. In our study population, there was no statistically significant difference between the ratio of the subjects who received a discharge diagnosis and those who did not. The main dietary sources of $n-3$ PUFAs are fish and seafood, whereas the $n-6$ PUFAs are derived mainly from vegetable oils (linoleic acid), but also from animal products (arachidonic acid). In the early 1980s in Finland the consumption of vegetable oils was relatively low but has increased 3 fold during the recent decades [33]. Thus, it may be possible that the serum ratio of $n-6$ to $n-3$ has changed during the follow-up time. In addition, the ratio of $n-6$ to $n-3$ was relatively low in our study population at baseline (6.2:1). Moreover, the small variation in the fatty acid ratios between the study subjects may have affected our finding of no association between the ratio of these fatty acids and risk of severe depression.

Conclusions

In this prospective, population-based study among middle-aged Finnish men, serum $n-3$ or $n-6$ PUFAs were not associated with risk of severe depression. Further studies are required to clarify the effect of gender on the association between fatty acids and depression.

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