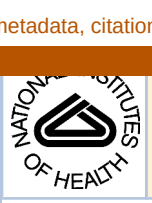



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# Long-chain omega-3 polyunsaturated fatty acids are inversely associated with depressive symptoms in women

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## Abstract

**Objective—**Experimental and observational data suggest higher dietary intake of long-chain omega-3 polyunsaturated acids may lead to decreased risk of depressive disorders. We assessed multivariable-adjusted associations of fish consumption and dietary intakes of eicosapentaenoic acid [EPA] and docosahexaenoic acid [DHA] with depressive symptoms in a population-based sample of 3,317 African American and Caucasian men and women from the Coronary Artery Risk Development in Young Adults study (CARDIA).

**Methods—**Diet was assessed in Year 7 (1992–93) and depressive symptoms were measured in Years 10 (1995–96), 15 (2000–01), and 20 (2005–06) by the 20-item Center for Epidemiological Studies Depression Scale (CES-D). Depressive symptoms were defined as CES-D score ≥ 16 or self-reported use of antidepressant medication.

**Results—**In the entire cohort, the highest quintiles of intakes of EPA (at least 0.03% energy), DHA (at least 0.05% energy), and EPA+DHA (at least 0.08% energy) were associated with lower risk of depressive symptoms at Year 10 (p-trends: 0.16, 0.10, 0.03, respectively). The observed inverse associations were more pronounced in women. For the total number of occasions with depressive symptoms, the multivariable adjusted odds ratios (95% confidence interval) in women were 0.75 (0.55–1.01) for fish intake; 0.66 (0.50–0.89), for EPA; 0.66 (0.49–0.89) for DHA; and 0.71 (0.52–0.95) for EPA+DHA, when comparing highest to lowest quintiles. Analyses of continuous CES-D scores revealed inverse associations with fourth root transformed omega-3 variables in women.

**Conclusions—**Our findings suggest that dietary intakes of fish and long-chain omega-3 fatty acids may be inversely associated with chronic depressive symptoms in women.

### Keywords

omega-3 fatty acids; depressive symptoms; EPA; DHA; fish



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## INTRODUCTION

Long-chain omega-3 polyunsaturated fatty acids (PUFA) including eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are important in the development of the central nervous system [1–4], with DHA being the major omega-3 PUFA in the mammalian nervous system [2]. A hypothesis has been proposed that intake of omega-3 fatty acids are of etiological importance in depression [5,6]. A growing body of research supports this hypothesis. Ecologic studies have found the prevalence of major depression and post-partum depression significantly associated with low fish consumption [7,8]. Clinical studies have found lower omega-3 fatty acid levels in the red blood cell membranes [9,10] or serum phospholipids [11] of depressed patients. Population-based epidemiologic studies have related fatty acid composition of plasma phospholipids to DSM-IV depressive disorders [12] or low fish consumption in women to depressive symptoms [13,14]. Randomized clinical trials found that treatment with omega-3 fatty acids improved depression [15–17]. However, several studies [18–21], which include randomized clinical trials [19,21], do not support this association. A recent meta-analysis [22], which included 12 randomized controlled trials that investigated effects of omega-3 fatty acids on depressed mood, cited considerable heterogeneity due to several factors: probable publication bias, a variety of different measures of depression being used, the nature of the intervention (e.g. EPA vs. DHA or combination, dosage, etc.), and trial population characteristics. Two other reviews [23,24] suggested that the evidence in favor of omega-3 fatty acids for mood disorders is preliminary and recommended avenues for further research. One [24] included the recommendation to examine which omega-3 fatty acid (EPA, DHA, or a combination) is optimal, although they indicated the support for EPA was somewhat stronger than for DHA.

In the human intervention studies which have been conducted, both those for depression [15–17,19,21,25] as well as for other conditions [26–29], omega-3 fatty acids have been found to be generally safe and well tolerated. Since most randomized clinical trials of omega-3 PUFAs for depression have had small sample sizes [22], further investigation of their relation with depression is warranted [22–24]. Furthermore, because two studies found the association between fish consumption and depression specific to women [13,14], a potential gender difference should be confirmed by other studies.

The Coronary Artery Risk Development in (Young) Adults (CARDIA) Study is a large cohort study of young African American (AA) and Caucasian men and women which has collected data on diet with the diet history method [30], and a measure of depressive symptoms using the Center for Epidemiologic Studies Depression Scale. The diet history included intake of fish and omega-3 fatty acids. We tested the hypothesis that higher intake of omega-3 fatty acids and fish are inversely associated with depressive symptoms measured at the single exam closest to the dietary assessment and with the total number of exams with depressive symptoms. Additionally, we tested whether this association would be modified by gender.

## METHODS

### Study Population

The CARDIA study is a multicenter, longitudinal study on lifestyle and evolution of cardiovascular disease risk factors in 5,115 young AA and Caucasian men and women aged 18 to 30 years at the baseline examination (1985–86). Participants were recruited from four geographic areas: Birmingham, Alabama; Chicago, Illinois; and Minneapolis, Minnesota; and Oakland, California. Six follow-up examinations were completed in 1987–88 (Year 2), 1990–91 (Year 5), 1992–93 (Year 7), 1995–96 (Year 10), 2000–01 (Year 15), and 2005–06 (Year

20). A detailed description of the design, recruitment, and methods of the CARDIA study has been published previously [31].

From the cohort of 5,115 participants, several exclusions from the analysis were made. Excluded were participants who did not attend both the Year 7 and Year 10 examination (n= 1472); those who were missing the CES-D score or covariate data from Year 10 (n= 153); those with extreme values for energy intake at Year 7 (< 800 kcal/day or > 8000 kcal/day for men and < 600 kcal/day or > 6000 kcal/day for women) (n=169); and those who self-reported being on medication for bipolar disorder (n=4). These minimum and maximum limits for energy intake were used because these data are potentially unreliable [32]. Participants with bipolar disorder were excluded because omega-3 fatty acids are potentially efficacious for this disorder [33] and including them might magnify the omega-3 effect. The final sample size used for analysis was 3317.

We compared the 3317 participants included in the study to the 1798 who were excluded on Year 0 characteristics. Those who were excluded were more likely to be younger, African American, to smoke, to consume more alcohol, and have less education. However, those excluded did not differ from those included on several health related characteristics at Year 0: previous physician or nurse diagnosis of a nervous, mental, or emotional disorder, systolic or diastolic blood pressure, body mass index, total cholesterol, physical activity, intake of EPA, DHA, or total servings of fish.

## Data Collection

Data were collected by centrally trained and certified technicians according to the CARDIA manual of operations. Throughout the study, quality of the data collection was monitored by the CARDIA Coordinating Center and the CARDIA Quality Control Committee. The study was approved by the Institutional Review Boards of each local center. Informed consent was obtained from each participant at each examination.

## Diet assessment

Predictor variables for this analysis were grams of EPA and DHA separately, the sum EPA + DHA, because the dose-response might be stronger for the sum, and servings of fish intake, because fish are the major source of omega-3 PUFAs. Diet data were collected at baseline, Year 7, and Year 20 based on a dietary history using an interviewer administered quantitative food frequency questionnaire [30]. Details regarding the development and implementation of this instrument are provided elsewhere [30]. Briefly, a certified nutritionist interviewed participants on frequency of food consumption in the past month from a list of approximately 100 foods. Participants reported on frequency, amount and method of food preparation for each food item reported during this period. Plastic food models and food estimation tools, such as measuring cups and spoons and a ruler, were used to assist in estimating usual amounts consumed. The University of Minnesota Nutrition Coordinating Center Nutrient database was used to estimate nutrient intake (NCC Nutrient Database, Version 20, October 1991, Nutrition Coordinating Center, University of Minnesota, Minneapolis). The database is a food composition table containing values for 94 nutrients, including omega-3 fatty acids, in over 2,490 food items. The CARDIA dietary history provides information about habitual nutrient intakes. The comparative validity and reliability of the CARDIA diet questionnaire have been reported previously [34,35]. Sex and energy-adjusted test-retest correlations for polyunsaturated fat were 0.27 and 0.57 in African Americans and Caucasians, respectively [35]. Validity correlations between daily intake of polyunsaturated fat from the CARDIA diet history and means from seven randomly scheduled 24-h recalls were 0.23, 0.67, 0.23, and 0.13 for AA men, Caucasian men, AA women, and Caucasian women, respectively [35]. The Year

7 history was used for this study since it was closest in time to the depressive symptoms assessment made at Year 10.

### Outcome variable assessment

Depressive symptoms were measured three times at the Years 10, 15, and 20 exams using the 20-item Center for Epidemiologic Studies Depression Scale (CES-D) [36] which has a maximum score of 60. Participants are asked to indicate how often they experienced each symptom in the past week (0, rarely or none of the time; 1, some of the time; 2, much of the time; 3, most or all of the time). Examples of questions included in the scale are: "During the past week, I felt that could not shake off the blues even with help from my family and friends", "I felt that everything I did was an effort", and "I had crying spells". A cutoff score of 16 or higher is suggested [36,37] in epidemiologic studies to indicate high level of depressive symptoms. Because treatment with an antidepressant medication will distort the underlying CES-D score, we used three approaches for analyzing this outcome [38]. The first modeled the CES-D score at Year 10 as a binary trait: we assumed a treated participant would have an untreated CES-D score at least as high as 16 and we classified participants as having a high level of depressive symptoms at a visit if they scored 16 or higher on the CES-D or if they self-reported using antidepressant medication specifically for depression. Hereafter this outcome will be referred to as "depressive symptoms". As a measure of chronicity, we also summed the number of exams from Years 10, 15, and 20 for which a participant had depressive symptoms. Second, we treated the CES-D score as a continuous variable but assumed right censoring on the observed scores for treated participants. Third, we treated the CES-D score as a continuous variable but added a constant to the observed CES-D score of participants who were treated. We used values ranging from 5 points to 25 points.

### Other participant characteristics

Other covariates used in this analysis were measured at Year 10 and Year 20. A dietary history was not obtained at Year 10. However, nutrient-intake in the CARDIA study has been shown to exhibit good seven-year tracking (that is, the degree to which individuals in the lowest or highest quintiles for dietary intake at Year 0 remain in the same or adjacent quintiles at Year 7) [39]. Thus, the Year 7 diet data could be viewed as a surrogate for data that would have been collected at Year 10.

Height and weight were measured with the participant wearing light clothing and no shoes and body mass index (BMI) was computed as weight (kg) divided by height squared ($m^2$). Age, race, years of education, income, marital and employment status, number of cigarettes smoked per day, and use of anti-depressant medication were self-reported. Alcohol intake (mL/d) was computed from the self-reported frequency of beer, wine, and liquor consumed per week [40]. A physical activity score was obtained from the CARDIA Physical Activity History, a modified version of the Minnesota Leisure Time Physical Activity Questionnaire [41].

### Statistical Analysis

Statistical analyses were conducted using SAS for Windows, release 9.2 (SAS Institute Inc., Cary, NC, USA). Sex group characteristics were compared using analysis of variance or Chi-square tests. Multiple logistic regression was used to assess the independent associations of omega-3 fatty acids intake or fish intake measured at year 7 with risk of depressive symptoms at year 10. The proportional odds model was used to assess associations of the dietary exposures with the total number of exams having depressive symptoms. The censored normal regression model was used to analyze the CES-D scores as a continuous outcome with the scores of treated participants right censored. The linear regression model was used to analyze the continuous CES-D scores with a constant added to the score of treated particpants. The exposure variables were analyzed as continuous after applying a fourth root transform to achieve a more symmetric

distribution. However, because transforming variables complicates interpretation of results, monthly fish intake and omega-3 fatty acids were also categorized into sex-specific quintiles. For EPA and DHA, we computed the nutrient density [42] and used this in the analysis. Analyses were conducted for the entire cohort with adjustment for sex and race, and also stratifying by sex. Tests for interactions between sex and dietary exposures were done to assess a potential gender difference. Trend tests were performed by assigning to each individual the median value of a dietary risk factor in its quintile and modeling this as a continuous variable. The year 10 covariates used in the analysis were age, education, BMI, physical activity, smoking, income, employment status, alcohol intake, and marital status. We also adjusted for year 7 intakes of linoleic acid and folic acid because the former may affect conversion of α-linolenic acid to EPA and DHA [43], and the latter has been found associated with omega-3 PUFA intake and with depression [44]. For the analysis of servings of fish intake we additionally adjusted for year 7 total energy intake. All p-values are two sided.

## RESULTS

Mean (SD) age of the 3317 participants in this study was 32.1 (3.6) years at year 10 with a range of 24 to 42 years. Overall, 22.4 percent of the study subjects (N=744) had a CES-D score of 16 or higher or were taking antidepressant medication at year 10. Table 1 shows characteristics of the cohort by sex. Women had higher mean CES-D scores and proportion scoring 16 or higher. They also had higher mean BMI, lower mean physical activity level, and were more likely than men to be separated or divorced, to be unemployed, and to have an income in the lowest category. Women had lower median fish intake.

Table 2 presents the results of the logistic regression analysis adjusted for potential confounders for the entire cohort and stratified by sex. In the entire cohort there were weak inverse associations for EPA and DHA, and a significant association for EPA + DHA (p-trends 0.16., 0.10, and 0.03, respectively). Comparing the highest quintile of omega-3 fatty acid (at least 0.03 %, 0.05%, and 0.08%, respectively for EPA, DHA, and EPA+DHA) intake to the lowest, the odds ratios were approximately 0.8 for EPA, DHA, and EPA+DHA. The test for interaction between sex and EPA+DHA was marginally statistically significant (p=0.06), indicating the associations differed between men and women. In the analysis stratifying by sex, there were significant, and stronger, inverse associations for EPA, DHA, and EPA + DHA in women (p-trends 0.07, 0.02, and 0.008, respectively). For women, the odds ratios for the highest quintiles compared to the lowest were all no greater than 0.78. There were no significant associations for these PUFAs in men. There were no associations for fish intake (Table 2).

Table 3 presents results of the multivariable adjusted proportional odds models that adjusted for year 10 SES and lifestyle covariates. The patterns of associations for these analyses were similar to those seen in Table 2. However, the results for the entire cohort and for women were slightly stronger. Of note, the association of fish intake with chronic depressive symptoms was statistically significant for women. Because SES and lifestyle characteristics might change over a ten year period, this analysis was rerun adjusting for year 20 SES and lifestyle characteristics in place of those recorded at year 10. For the entire cohort none of the odds ratios attenuated and in women, only the odds ratio for quartile 5 of fish intake attenuated and all other odds ratios maintained or slightly increased in magnitude (data not shown).

For the linear regression analyses of the CES-D scores with a constant added to the scores of treated participants, the beta coefficients for the dietary exposures increased slightly in magnitude as the constant that was added increased. However, since the results of these analyses were consistent with the censored normal regression analyses, the results of the censored normal regression models are presented (Table 4). None of the tests of interaction between sex and dietary exposure were statistically significant for the year 10 CES-D score.

For the entire cohort, the beta coefficients of the transformed omega-3 exposures were all negative and significant, but after stratifying by sex they were only marginally significant in women. For the year 20 CES-D scores, all interactions of sex with dietary exposure were statistically significant and all of the associations were inverse and significant in women.

Two additional subsidiary analyses were conducted. First, because participants taking antidepressant medication may represent a subgroup with greater severity of depressive symptoms or clinical depression, an analysis was done excluding these participants. Results of this analysis were similar to the primary analysis (data not shown). Second, some participants did not return for the year 15 or the year 20 exams, which could result in an underestimate of their number of visits with depressive symptoms. Therefore, we reanalyzed the data treating a participant's missed visit as a visit with depressive symptoms. Results for women were similar, though slightly attenuated. There were still no associations for men (data not shown).

## DISCUSSION

In this observational study, we found that fish and omega-3 fatty acid intakes are inversely associated with risk of chronic depressive symptoms in women, but not in men. These relations were independent of other major lifestyle variables.

Our results are consistent with four other epidemiologic studies that have examined the association of fish intake or dietary omega-3 PUFAs with depressive disorders [13,14,20] or mental disorders [44]. Three of these studies were conducted in large homogenous Finnish populations [13,14,20] with one restricted to men [20], while the fourth was conducted in a well-educated Spanish cohort [44]. Two studies conducted in men and women [13,44] found overall associations between fish consumption or omega-3 PUFA intake and decreased risk of depressive symptoms or mental disorders. However, when those analyses were stratified by sex, the associations were found among women, but not men. Similarly, a study in a 1966 birth cohort found that in women, but not in men, that rare consumers of fish had 2.5-fold higher odds of having depression compared to regular consumers of fish [14]. The fourth study [20], in men only, did not find any associations of fish consumption or dietary intake of omega-3 PUFAs with depressed mood, major depressive episodes, or suicide. Finally, a fifth epidemiologic study conducted in a Japanese cohort did not find associations for EPA or DHA with depressive symptoms in men or women [45].

In addition, several small randomized, double blind trials [15–17] found that adjunctive treatment with omega-3 PUFAs improved depression. Su et al. compared 14 patients receiving 440 mg EPA and 220 mg DHA to 14 patients receiving placebo. Nemets et al. compared 10 patients receiving 2 g/d of ethyl ester of EPA to 10 receiving placebo. Peet et al. compared 18 patients receiving placebo to three treatment groups, receiving dosages of 1, 2, and 4 g/d, respectively, of ethyl-eicosapentaenoate. Both Su et al. and Nemets et al. found the omega-3 groups superior to placebo. Peet et al. reported efficacy for the 1 g/d dosage group only.

However, a single-arm, open-label trial [25] and two randomized trials [19,21] of omega-3 fatty acids for depression have failed to find an effect. The single-arm study of 2,960 mg of EPA and DHA as prophylaxis for postpartum depression in high risk women was terminated due to the high relapse rate after enrollment of 7 women, with 4 experiencing relapse [25]. In this study treatment was initiated between weeks 34–36 of pregnancy. The authors commented that a longer trial of omega-3 PUFAs initiated earlier in pregnancy might have produced more promising results. This is notable because for 5 of the 7 women enrolled, their previous episodes of postpartum depression had onsets within 7 days postpartum. In a double-blind, placebo controlled study with 18 patients randomized to 2 g/day of DHA, and 17 to placebo, Marangell et al. reported depression improvement rates of 27.8% and 23.5% in the DHA and placebo

groups, respectively [19]. The difference in response rates was not statistically significant, but the authors commented that the study did not have enough power to detect a difference between groups in the depression rating scale. Thus, it is difficult to interpret the negative findings of two of these studies [19,25]. Furthermore, heterogeneity in the meta-analyses that have been conducted permits only equivocal conclusions regarding trials [22–24].

It should be noted that in most of these intervention studies [15–17,19,25], both those with positive findings and those with null findings, the majority of participants were women. Taken together with the findings of the present study and with four other epidemiological studies [13,14,20,44], this suggests that dietary omega-3 PUFAs may be effective in women in reducing the risk of having depressive symptoms.

In contrast, the available evidence suggests that omega-3-PUFAs are not associated with depression in men. One possible explanation for the gender difference is that the endogenous omega-3 fatty acid is higher in women. One study found that when fed identical diets, the plasma DHA concentrations in women are higher than they are in men [46].

Several biological mechanisms have been proposed that might account for an association between omega-3 PUFA intake and depression [23,24]. One is derived from animal studies. Delion and colleagues observed increased serotonin 5-$HT_2$ receptor density and lower dopamine $D_2$ receptor density in the frontal cortex of rats fed an ALA deficient diet compared with control rats [47,48]. Some [49,50], but not all research [51], indicates that 5-$HT_2$ receptor density is greater with depression. In another study, when rats were fed a diet in fish oil, high in DHA and EPA, dopamine levels were found higher in the frontal cortex and higher binding to dopamine $D_2$ receptors occurred when compared to control rats [52]. More recently it has been shown [53] that rats fed a diet supplemented with omega-3 PUFAs for 30 days were found to have reduced immobility during a forced swim test, an indication of anti-depressant-like action.

Another mechanism that has been described involves inflammatory pathways [23,24], which have been implicated in the pathophysiology of depression [54]. Arachidonic acid (AA), an omega-6 PUFA, can be metabolized to proinflammatory eicosanoids, whereas ALA, an omega-3 PUFA, can be converted to EPA, which is further converted to anti-inflammatory eicosanoids. In the process of their conversions, AA and ALA share the same series of enzymes, thus invoking a competition for their metabolism. In this competition, an excess of one acid causes a decrease in the conversion of the other [55]. In short, increased consumption of EPA and DHA leads to reduced synthesis of inflammatory eicosanoids. Details of the processes, which are greatly oversimplified here, are given elsewhere [55].

Appleton and colleagues have suggested that associations between depressed mood and omega-3 PUFA intake from fish might be attributed to confounding by lifestyle [56,57]. However, we adjusted for important lifestyle variables including BMI, cigarette smoking, alcohol intake, physical activity, education, unemployment, income, and marital status. These variables were indeed important in our analyses (data not shown). However, despite their statistical significance in the multivariable models, the omega-3 PUFA associations for women, although somewhat attenuated, remained significant.

A potential limitation of the present study is that we used dietary data collected at Year 7 as a surrogate for data that would have been collected at Year 10. It might be expected that stronger associations would be found had the dietary data been collected at the same year. However, we observed strong associations with the CES-D scores collected at year 20 as well. Regardless, given the cross-sectional design, no conclusions regarding the temporality of associations could be drawn.

Our reliance on the CES-D to classify depressive symptoms as opposed to using a clinical structured interview for depressive disorders is a limitation. However, the CES-D has demonstrated high sensitivity for detecting clinically diagnosed depression [58]. For a cutpoint of 16, reported sensitivities ranged from 73% to 99% in various patient groups [58]. Using self-reported antidepressant usage as an aid in defining depressive symptoms is another potential source of misclassification if a participant was taking an antidepressant for long term maintenance therapy rather than for current symptoms.

Finally, participants excluded from the study tended to have a few less favorable characteristics at Year 0 (i.e. smoking, alcohol consumption, and education) than those included. This suggests that those excluded might have a greater risk for depressive symptoms.

Strengths of this study include our large sample size which permitted testing of interactions between sex and omega-3 PUFAs. Thus, we were able to examine whether these data support the previous observations of a gender difference in associations [13,14]. The use of multiple assessments of depressive symptoms also allowed us to examine associations with chronicity.

## CONCLUSION

High dietary intake of fish and omega-3 fatty acids appear to be related to lower risk of chronic depressive symptoms in women, but not in men, in this cohort.

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**Table 1**

Characteristics of 3317 CARDIA participants by sex.

| **Characteristics**[b] | **Men** | | **Women** | | **p-value**[a] |
|---|---|---|---|---|---|
| N | 1481 | | 1836 | | |
| Age (years) | 35.1 | (3.6) | 35.2 | (3.7) | 0.66 |
| CES-D score | 9.7 | (7.2) | 11.1 | (8.6) | <0.001 |
| CES-D ≥ 16, N (%) | 248 | (17) | 442 | (24) | <0.001 |
| Anti-depressant medication, N (%) | 24 | (2) | 75 | (4) | <0.001 |
| Total caloric intake (kJ) | 13,727 | (5442) | 9776 | (3878) | <0.001 |
| EPA (gm) | 0.07 | (0.10) | 0.05 | (0.07) | <0.001 |
| DHA (gm) | 0.12 | (0.13) | 0.09 | (0.10) | <0.001 |
| Total fish intake (servings/day), median (quartile range) | 0.7 | (1.2) | 0.5 | (0.9) | <0.001 |
| Linoleic acid (gm) | 23.5 | (12.2) | 16.7 | (9.9) | <0.001 |
| Folic acid (mcg) | 588 | (458) | 542 | (507) | 0.007 |
| Body mass index (kg/m$^2$) | 27.1 | (5.1) | 27.7 | (7.4) | 0.01 |
| Cigarettes (no./day) | 3.6 | (8.0) | 2.6 | (6.1) | <0.001 |
| Alcohol (ml/day) | 15.7 | (27.0) | 6.3 | (12.8) | <0.001 |
| Total physical activity | 415 | (294) | 261 | (227) | <0.001 |
| Education: | | | | | |
| < High school, N (%) | 95 | (6) | 84 | (5) | |
| High School, N (%) | 326 | (22) | 379 | (21) | |
| Some college, N (%) | 390 | (26) | 544 | (30) | |
| College graduate, N (%) | 670 | (45) | 829 | (45) | 0.03 |
| Marital status: | | | | | |
| Unmarried, N (%) | 413 | (28) | 419 | (23) | |
| Married or marriage-like relationship, N (%) | 886 | (60) | 1048 | (57) | |
| Separated or divorced, N (%) | 176 | (12) | 352 | (19) | |
| Widow or other, N (%)[c] | 6 | (0) | 17 | (1) | <0.001 |
| Unemployed, N (%) | 117 | (8) | 220 | (12) | <0.001 |
| Income: | | | | | |
| ≤11,999, N (%) | 110 | (7) | 196 | (11) | |

| Characteristics[b] | Men | | Women | | p-value[a] |
|---|---|---|---|---|---|
| 12,000–24,999, N (%) | 224 | (15) | 302 | (16) | |
| 25,000–49,999, N (%) | 516 | (35) | 639 | (35) | |
| 50,000+, N (%) | 631 | (43) | 699 | (38) | 0.002 |

[a] Sex groups are compared using analysis of variance or Chi-square tests.

[b] Numbers presented are mean (SD) or N (%) unless otherwise indicated.

[c] Widow or other category pooled with separated or divorced in statistical analysis.

## Table 2

Multivariate adjusted odds ratios (OR) of having depressive symptoms qt Year 10 according to categories of fish intake and omega-3 fatty acids intake (% energy) for all CARDIA participants and stratified by sex.

| | | Entire cohort | | Men | | Women | |
|---|---|---|---|---|---|---|---|
| **No. of subjects (cases)** | | **3317** | **(744)** | **1481** | **(259)** | **1836** | **(485)** |
| | | **OR[a]** | **(95% CI)** | **OR** | **(95% CI)** | **OR** | **(95% CI)** |
| Quintiles of fish intake | sexXfish p-value=0.69 | | | | | | |
| Q1 | | 1.00 | | 1.00 | | 1.00 | |
| Q2 | | 1.09 | (0.83–1.43) | 1.11 | (0.71–1.75) | 1.09 | (0.78–1.52) |
| Q3 | | 0.99 | (0.75–1.31) | 0.94 | (0.59–1.50) | 1.02 | (0.72–1.44) |
| Q4 | | 0.98 | (0.74–1.29) | 1.03 | (0.65–1.62) | 0.93 | (0.66–1.33) |
| Q5 | | 0.97 | (0.73–1.28) | 1.16 | (0.73–1.83) | 0.87 | (0.61–1.24) |
| P for trend | | 0.59 | | 0.56 | | 0.25 | |
| Quintiles of EPA | sexXEPA p-value=0.33 | | | | | | |
| Q1 | | 1.00 | | 1.00 | | 1.00 | |
| Q2 | | 0.89 | (0.68–1.16) | 0.76 | (0.48–1.19) | 0.97 | (0.69–1.36) |
| Q3 | | 0.96 | (0.74–1.25) | 0.83 | (0.53–1.29) | 1.04 | (0.74–1.45) |
| Q4 | | 0.77 | (0.59–1.01) | 0.85 | (0.55–1.31) | 0.72 | (0.51–1.03) |
| Q5 | | 0.83 | (0.63–1.09) | 0.91 | (0.59–1.41) | 0.78 | (0.55–1.11) |
| P for trend | | 0.16 | | 0.92 | | 0.07 | |
| Quintiles of DHA | sexXDHA p-value=0.21 | | | | | | |
| Q1 | | 1.00 | | 1.00 | | 1.00 | |
| Q2 | | 0.96 | (0.73–1.25) | 0.84 | (0.53–1.31) | 1.05 | (0.75–1.47) |
| Q3 | | 0.87 | (0.66–1.14) | 0.81 | (0.52–1.28) | 0.91 | (0.65–1.28) |
| Q4 | | 0.89 | (0.68–1.17) | 1.10 | (0.71–1.70) | 0.79 | (0.56–1.12) |
| Q5 | | 0.79 | (0.60–1.05) | 0.91 | (0.58–1.42) | 0.72 | (0.51–1.04) |
| P for trend | | 0.10 | | 0.91 | | 0.02 | |
| Quintiles of sum of EPA | sexX(EPA+DHA) p-value=0.06 | | | | | | |

| | Entire cohort | | Men | | Women | |
|---|---|---|---|---|---|---|
| **No. of subjects (cases)** | **3317** | **(744)** | **1481** | **(259)** | **1836** | **(485)** |
| | **OR[a]** | **(95% CI)** | **OR** | **(95% CI)** | **OR** | **(95% CI)** |
| and DHA intake | | | | | | |
| Q1 | 1.00 | | 1.00 | | 1.00 | |
| Q2 | 1.09 | (0.83–1.41) | 0.76 | (0.48–1.20) | 1.33 | (0.96–1.86) |
| Q3 | 0.94 | (0.72–1.24) | 0.97 | (0.63–1.51) | 0.92 | (0.65–1.31) |
| Q4 | 0.83 | (0.63–1.10) | 0.91 | (0.58–1.42) | 0.80 | (0.56–1.14) |
| Q5 | 0.80 | (0.61–1.06) | 0.89 | (0.57–1.38) | 0.75 | (0.53–1.08) |
| P for trend | 0.03 | | 0.87 | | 0.008 | |

[a]Odds ratio adjusted for age, race, gender, educational level(<high school, high school, some college, or ≥college graduate), body mass index (continuous), cigarettes/d (continuous), alcohol intake (ml/d) (continuous), total physical activity (continuous), marital status (3 categories: unmarried, married or in a marriage-like relationship, or widowed, separated, divorced, or other), employment status (unemployed, employed), income (≤11,999, 12,000–24,999, 25,000–49,999, or 50,000 and higher), and intakes of linoleic acid (continuous) and folic acid (continuous). Fish intake is further adjusted for energy intake (continuous).

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## Table 3

Multivariate adjusted odds ratios (OR) for number of visits with depressive symptoms according to categories of fish intake and omega-3 fatty acids intake (% energy) for all CARDIA participants and stratified by sex.

| | | Entire cohort | | Men | | Women | |
|---|---|---|---|---|---|---|---|
| No. of visits with depressive symptoms: | | N | | N | | N | |
| 3 | | 206 | | 65 | | 141 | |
| 2 | | 328 | | 117 | | 211 | |
| 1 | | 701 | | 265 | | 436 | |
| 0 | | 2082 | | 1034 | | 1048 | |
| Quintiles of fish intake | sexXfish p-value=0.19 | OR[a] | (95% CI) | OR | (95% CI) | OR | (95% CI) |
| Q1 | | 1.00 | | 1.00 | | 1.00 | |
| Q2 | | 0.90 | (0.72–1.12) | 0.76 | (0.53–1.10) | 1.00 | (0.76–1.32) |
| Q3 | | 0.89 | (0.71–1.11) | 0.80 | (0.56–1.15) | 0.94 | (0.70–1.25) |
| Q4 | | 0.81 | (0.65–1.01) | 0.88 | (0.62–1.26) | 0.75 | (0.56–1.01) |
| Q5 | | 0.80 | (0.64–1.01) | 0.89 | (0.62–1.28) | 0.75 | (0.55–1.01) |
| P for trend | | 0.07 | | 0.96 | | 0.02 | |
| Quintiles of EPA | sexXEPA p-value=0.06 | | | | | | |
| Q1 | | 1.00 | | 1.00 | | 1.00 | |
| Q2 | | 0.83 | (0.66–1.03) | 0.85 | (0.60–1.21) | 0.80 | (0.60–1.07) |
| Q3 | | 0.95 | (0.76–1.18) | 0.75 | (0.52–1.08) | 1.07 | (0.81–1.41) |
| Q4 | | 0.80 | (0.64–1.00) | 0.84 | (0.59–1.20) | 0.76 | (0.57–1.02) |
| Q5 | | 0.75 | (0.60–0.94) | 0.88 | (0.62–1.25) | 0.66 | (0.50–0.89) |
| P for trend | | 0.02 | | 0.80 | | 0.005 | |
| Quintiles of DHA | sexXDHA p-value=0.13 | | | | | | |
| Q1 | | 1.00 | | 1.00 | | 1.00 | |

| | | Entire cohort | | Men | | Women | |
|---|---|---|---|---|---|---|---|
| Q2 | | 0.86 | (0.69–1.08) | 0.77 | (0.54–1.10) | 0.92 | (0.69–1.22) |
| Q3 | | 0.89 | (0.72–1.12) | 0.88 | (0.61–1.25) | 0.90 | (0.68–1.20) |
| Q4 | | 0.83 | (0.67–1.04) | 0.95 | (0.67–1.36) | 0.76 | (0.57–1.02) |
| Q5 | | 0.76 | (0.60–0.95) | 0.92 | (0.64–1.32) | 0.66 | (0.49–0.89) |
| P for trend | | 0.03 | | 0.85 | | 0.002 | |
| Quintiles of sum of EPA and DHA intake | sexX(EPA+DHA) p-value=0.05 | | | | | | |
| Q1 | | 1.00 | | 1.00 | | 1.00 | |
| Q2 | | 0.97 | (0.78–1.20) | 0.76 | (0.53–1.10) | 1.12 | (0.84–1.48) |
| Q3 | | 0.99 | (0.80–1.24) | 1.01 | (0.71–1.43) | 0.98 | (0.74–1.30) |
| Q4 | | 0.81 | (0.65–1.02) | 0.89 | (0.62–1.27) | 0.76 | (0.57–1.02) |
| Q5 | | 0.78 | (0.62–0.99) | 0.91 | (0.64–1.30) | 0.71 | (0.52–0.95) |
| P for trend | | 0.01 | | 0.93 | | 0.001 | |

[a]Odds ratio adjusted for age, race, gender, educational level(<high school, high school, some college, or ≥college graduate), body mass index (continuous), cigarettes/d (continuous), alcohol intake (ml/d) (continuous), total physical activity (continuous), marital status (3 categories: unmarried, married or in a marriage-like relationship, or widowed, separated, divorced, or other), employment status (unemployed, employed), income (≤11,999, 12,000–24,999, 25,000–49,999, or 50,000 and higher), and intakes of linoleic acid (continuous) and folic acid (continuous). Fish intake is further adjusted for energy intake (continuous).

**Table 4**

Multivariable associations of Y10 and Y20 CES-D scores with Y7 fourth root transformed fish intake and omega-3 fatty acids for all CARDIA participants and stratified by sex.

| | Sex X dietary exposure | Entire cohort | | Men | | Women | |
|---|---|---|---|---|---|---|---|
| **Outcome=continuous CES-D score at Y10** | **P-value** | **Beta[a] for dietary exposure** | **P-value** | **Beta for dietary exposure** | **P-value** | **Beta for dietary exposure** | **P-value** |
| Fish | 0.63 | −0.40 | 0.29 | −0.31 | 0.53 | −0.53 | 0.34 |
| EPA | 0.40 | −1.85 | 0.04 | −1.09 | 0.37 | −2.36 | 0.07 |
| DHA | 0.97 | −3.12 | 0.03 | −2.87 | 0.13 | −3.26 | 0.11 |
| EPA+DHA | 0.81 | −2.58 | 0.03 | −2.20 | 0.16 | −2.79 | 0.10 |
| Outcome=continuous | | | | | | | |
| CES-D score at Y20 | | | | | | | |
| Fish | 0.02 | −0.70 | 0.10 | 0.21 | 0.70 | −1.59 | 0.01 |
| EPA | 0.04 | −2.21 | 0.03 | −0.14 | 0.92 | −3.62 | 0.01 |
| DHA | 0.03 | −2.41 | 0.13 | 1.25 | 0.55 | −5.20 | 0.03 |
| EPA+DHA | 0.03 | −2.27 | 0.09 | 0.75 | 0.67 | −4.54 | 0.02 |

[a]Adjusted for age, race, gender, educational level, body mass index, cigarettes/d, alcohol intake (ml/d), total physical activity, marital status, employment status, income, and intakes of linoleic acid, and folic acid. Fish intake is further adjusted for energy intake. SES and lifestyle covariates are from Y10 for the Y10 CES-D scores and from Y20 for Y20 CES-D scores.