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Omega-3 Fatty Acid Biomarkers and Subsequent Depressive Symptoms

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Abstract

Objective—We sought to determine the relationship between the omega-3 fatty acid content of red blood cell membranes (RBC), in particular docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), and baseline and new-onset depressive symptoms in postmenopausal women. We secondarily sought to characterize the association between dietary omega-3 fatty acid intake and depressive symptomatology.

Methods—Study participants included 7,086 members of the Women's Health Initiative Memory Study (aged 63–81) who had an assessment of RBC omega-3 fatty acid concentrations at the baseline screening visit. Depressive symptoms at baseline and follow-up were characterized using the Burnam 8-item scale for depressive disorders (CES-D/DIS short form), and secondarily additionally inferred by antidepressant medication use.

Results—In multivariable-adjusted models, our primary exposure, RBC DHA+EPA, was not related to depressive symptoms by any measure at baseline or follow-up, nor were RBC total omega-3, DHA, or EPA (all $p>0.2$). In contrast, dietary intake of omega-3 was positively

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associated with depressive symptoms at baseline (adjusted OR 1.082, 95% C.I. 1.004–1.166; p=0.04 for dietary DHA+EPA and Burnam Score ≥ 0.06), although this generally did not persist at follow-up.

Conclusion—No relationship between RBC omega-3 levels and subsequent depressive symptoms was evident, and associations between dietary omega-3 and depressive symptoms were variable. Biomarkers of omega-3 status do not appear to be related to risk of new depression in post-menopausal women.

Keywords

Omega-3 Fatty Acids; Biological Markers; Diet; Eicosapentaenoic Acid; Depression; Epidemiologic Studies

Introduction

There is evidence to suggest that women tend towards higher biological concentration of DHA compared to men, due to the effects of estrogen (Burdge and Wootton, 2002, Salisbury *et al.*, 2011). This information, along with evidence of higher brain concentration of DHA compared to other body tissues, suggests relevance for DHA content in the CNS in post-menopausal depression. In some – but not all – observational studies, low levels of omega-3 fatty acids have been shown to be associated with depressive symptomatology (Lin *et al.*, 2010). A 31-year follow-up study of the Northern Finland 1966 Birth Cohort showed an increased risk of depression among female subjects with low fish intake (Timonen *et al.*, 2004); however, several other large longitudinal studies found no such associations - a prospective analysis of older women (50–77 years of age at baseline) from the Nurses' Health Study found no association between omega-3 dietary intake and incident depression (Lucas *et al.*, 2011), nor did a 13-year follow-up of individuals from the SU.VI.MAX study (Kesse-Guyot *et al.*, 2012). Omega-3 fatty acid supplementation has, however, been shown to be effective in the treatment of depression in several small clinical trials (Freeman *et al.*, 2011, Rondanelli *et al.*, 2011, Sinn *et al.*, 2012, Sublette *et al.*, 2011, Tajalizadekhoob *et al.*, 2011). Further, a recent meta-analysis determined EPA-rich oils appear to be more effective in treating depression than DHA-rich oils (Sublette *et al.*, 2011).

Given the inconsistency of the literature and the heterogeneous nature of depression, additional research is warranted to better understand the role of omega-3 fatty acids in specific populations with depression. To further examine this issue, we evaluated the relationship between omega-3 fatty acid levels and depression in postmenopausal women participating in the Women's Health Initiative Memory Study (WHIMS). Using longitudinal data from the WHIMS cohort (aged 63 to 81 years at baseline), we assessed the relationship between baseline levels of red blood cell (RBC) membrane DHA+EPA - a validated biomarker of tissue omega-3 status (Harris *et al.*, 2004), and subsequent onset of depressive symptoms. We predicted that the risk of developing symptoms of depression in post-menopause decreases as erythrocyte membrane concentration of DHA+EPA increases. We additionally sought to determine whether a similar association exists between depression and omega-3 dietary intake as assessed by food frequency questionnaire.

Methods

Sample

Subjects were 7,086 participants of the Women's Health Initiative Memory Study, a WHI ancillary study, for whom baseline erythrocyte fatty acid concentration values were available. Baseline screening for the Women's Health Initiative began in 1993 and occurred over the course of six months, consisting of three visits in total. Blood samples used for fatty acid analyses were collected at the first WHI screening visit, on average 2.7 months prior to randomization to hormone therapy (estrogen-only or estrogen plus progestin) or placebo.

Assessment of Depressive Symptoms

Depressive symptoms were assessed via the Burnam 8-item scale for depressive disorders- a combined Center for Epidemiologic Studies/Diagnostic Interview Schedule short form (CES-D/DIS short form). Baseline depressive symptoms were assessed at the second screening visit and follow-up assessment occurred at study closeout, a mean (sd) of 90 (7) months after the baseline assessment. We selected *a priori* for primary analysis a score of 0.06 as the established cut-point for presence of depressive symptoms, in accordance to a prior study by Bertone-Johnson et al. (Bertone-Johnson *et al.*, 2011). The CES-D/DIS short form was selected over the Geriatric Depression Scale (GDS), which was measured in only a small subset of participants and not concurrently. A previous study determined the Burnam Scale to provide an accurate assessment of presence of depressive symptoms (sensitivity 74%, specificity 87%), when evaluated against the Structured Clinical Interview for DSM-IV (Tuunainen *et al.*, 2001).

For the assessment of new depression at follow-up, prevalent cases at baseline were excluded from analysis. New depression at follow-up was used in lieu of incident depression, as it cannot be determined based on the available data whether these are true incident cases or if the participant has experienced a previous depression episode outside of the data collection time points.

In a secondary analysis, we expanded our primary outcome definition to include participants with the primary Burnam threshold (0.06) or new antidepressant use, which was not considered in our primary definition of depressive symptomatology due to the potential for antidepressant medications to be prescribed off-label for the treatment of vasomotor symptoms following menopause. As a sensitivity analysis, we expanded our primary outcome definition to include participants with a Burnam score of 0.009 or higher (Burnam *et al.*, 1988). Case counts for all analyses are available in Table 1.

Fatty Acid Measurement

For both RBC membrane and dietary intake levels, our *a priori* primary exposure indicator was DHA + EPA. Secondary analyses were conducted with total omega-3 [combined alpha-linolenic (ALA), docosapentaenoic acid, DHA and EPA], DHA-only, and EPA-only. Subjects included in the analysis had a mean (sd) RBC concentration of 5.26 (1.52) % for DHA+EPA, 4.56 (1.27) % for DHA-only, 0.71 (0.35) % for EPA-only, and 7.96 (1.69) % for total omega-3.

Omega-3 fatty acid content in the central nervous system may be relevant in the development of depression in post-menopausal women - fatty acid concentrations in the red blood cell membrane, while not capturing CNS concentrations, are likely to correspond (Connor *et al.*, 1990) and can be obtained by routine blood draw, a procedure far less invasive than brain tissue biopsy; as such, we selected RBC omega-3 fatty acid levels as our primary measurement. Blood samples were collected by the respective WHI field centers at the first screening visit and stored at −80 °C by Fisher BioServices in Rockville, MD, the central repository for WHI blood samples. It was determined that the blood samples available for analyses had undergone some fatty acid oxidation as a result of short-term exposure to temperatures of −20 °C during sample aliquoting (Pottala *et al.*, 2012a). Multiple imputation was used to correct for sample degradation to provide a more accurate depiction of RBC fatty acid composition.

Dietary fatty acid intake was assessed via the Women's Health Initiative Food Frequency Questionnaire. This diet assessment tool was originally created for use in the low-fat dietary modification arm of the WHI clinical trial, and as such was designed to provide an accurate measure of dietary fat intake (Patterson *et al.*, 1999). Data on omega-3 fatty acid supplement use was not available. Subjects included in the analysis had a mean (sd) dietary intake of 0.11 (0.11) grams/day for DHA+EPA, 0.07 (0.07) grams/day for DHA-only, 0.04 (0.04) grams/day for EPA-only, and 1.38 (0.81) grams/day for total omega-3.

Statistical Analysis

All statistical analyses were performed using SAS 9.3 (SAS Institute Inc., Cary, NC). In order to account for the effects of degradation due to storage at −20 degrees, each RBC fatty acid value was replaced with ten imputed probable values, derived using methods described in greater detail elsewhere (Pottala *et al.*, 2012a). For the purpose of baseline reporting, fatty acid values represent the mean imputed value from the screening visit blood sample. The multiple imputations were used in logistic regression analyses described below. Even after imputation, 3.1% of the WHIMS study sample had blood samples that remained technically unacceptable, defined as having a highly unsaturated to saturated fatty acid ratio of 0.52 or below, and were excluded from the analysis (Pottala *et al.*, 2012a).

Participants were contrasted on a variety of sociodemographic and clinical variables by case status, using chi-square tests for categorical variables and the Wilcoxon rank-sum test for continuous variables. The covariates considered for inclusion are those that are associated with depression or omega-3 status based on WHIMS data or the available literature. Logistic regression was used to assess the relationships between fatty acid measures and new depression at follow-up. Regression analysis was conducted first with only age and WHI hormone treatment assignment as covariates (crude model), and repeated with more extensive adjustment. In addition to age and WHI hormone treatment assignment, the multivariable-adjusted model also included: U.S. region, marital status, race, education, income, obesity, high blood pressure, high cholesterol, smoking status, bilateral oophorectomy, arthritis, cardiovascular disease, diabetes, prescription narcotic use, physical activity, and alcohol consumption. Analysis of new depression at follow-up also adjusted for baseline Burnam score and number of days between screening and follow-up. A reduced

model included: U.S. region, marital status, race, education, and income, in addition to age and WHI hormone treatment assignment; however, the results of these analyses did not appreciably differ from the fully adjusted models, and for clarity of presentation are not reported.

To assess for potential non-linear effects, our primary new-onset depression models were reevaluated using tertile categories for each erythrocyte membrane and dietary DHA+EPA, DHA, EPA, and total omega-3, with the lowest tertile as the reference category. Additionally, we modeled each RBC membrane omega-3 fatty acid measurement for a linear + quadratic effect; however the results of such were not contributory, and thus are not shown.

Secondarily, we examined the association between depressive symptoms, both present at baseline and new at follow-up, and fatty acid intake as assessed by food frequency questionnaire, to render comparison between methods of measurement of omega-3 status. Dietary data was not used for primary analyses on the assumption that biological concentrations were more reliable and relevant.

Results

Prevalent Depression at Baseline

Descriptive statistics for the study cohort by depression status can be seen in greater detail in Table 2. Participants reporting depression at baseline were more likely to have lower educational and income status, live in the south and northeast, be divorced or widowed, have participated in the estrogen-alone hormone trial, smoke, drink less alcohol, engage in less physical activity, and have lower RBC total omega-3 levels and higher dietary total omega-3 intake, relative to participants below the Burnam score cut-point for depressive symptoms.

At baseline, in models adjusted only for age and WHI hormone treatment assignment, RBC DHA+EPA, as well as total omega-3 and DHA were associated with depressive symptoms as measured by Burnam Score ≥ 0.06 or antidepressant use (Table 3). However, after adjusting for demographic and health behavior characteristics, no significant association was found between any RBC omega-3 fatty acid metric (DHA+EPA, total omega-3, DHA-only, or EPA-only) and depression by any measure (Burnam Score ≥ 0.06, Burnam Score ≥ 0.06 or antidepressant use, Burnam Score ≥ 0.009).

In adjusted models, dietary intakes of total omega-3, DHA, and DHA+EPA were associated with a higher prevalence of depressive symptoms at baseline using any of the 3 definitions for depression. Dietary intake of EPA was marginally associated with a higher prevalence of depressive symptoms at baseline when depressive symptoms were defined as Burnam Score ≥ 0.06 (p=0.072) and as Burnam Score ≥ 0.06 or antidepressant use (p=0.068) (Table 3). In the sensitivity analysis using depression defined as a Burnam Score Score ≥ 0.009, the adjusted OR estimates did not substantively differ although dietary intake of EPA became significantly associated with depression in adjusted models (aOR 1.232, 95% C.I. 1.048–1.448, p=0.011).

New Depression at Follow-up

After exclusion of prevalent cases at baseline, no associations were found for any of the RBC omega-3 fatty acid levels and the development of depressive symptoms by any of the three definitions during the follow-up period (Table 4), nor were associations between most measures of dietary omega-3 fatty acid intake and new depression identified, with the exception of an association between greater dietary intake of total omega-3 and an increasing risk of depressive symptoms as defined by the secondary measure of Burnam score ≥0.06 or starting an antidepressant. In the sensitivity analysis, the results using a Burnam score threshold of ≥0.009 did not substantively differ from the a priori threshold of ≥0.06.

Omega-3 Tertile Analysis

No associations were found between RBC or dietary omega-3 fatty acid measures and baseline depressive symptoms (data not shown), nor was an association found for any measure of RBC omega-3 and new-onset depression over the follow-up period (Table 5). Subjects in the third tertile of dietary DHA+EPA intake (0.12g – 2.03g) were at a 0.707 (95% C.I. 0.503– 0.993, p= 0.04) odds of developing depressive symptoms during the follow-up period, relative to subjects in the first tertile (0g – 0.05g). RBC DHA+EPA percent concentration in the third tertile relative to the first tertile (OR 0.690, C.I. 0.460–1.036) was similarly suggestive of an inverse association with new depression at follow-up; however the results did not cross the threshold of significance.

Discussion

Our primary analysis failed to demonstrate an association between RBC DHA+ EPA and new depressive symptoms, assessed after an average of 7.5 years of follow-up; nor was evidence of a relationship between RBC total omega-3, DHA, or EPA found for baseline or new depressive symptoms. Dietary intakes of DHA+EPA, DHA, and total omega-3at baseline were associated with a modestly increased risk of depressive symptoms by any measure, with similar trends for EPA. This positive relationship between dietary omega-3 intake and a greater prevalence of depressive symptoms at baseline is likely attributable to reverse causality, considering no similar trend is seen in follow-up analysis. In a secondary categorical analysis of new depression at follow-up, the highest tertile of dietary, but not RBC, DHA+EPA was associated with a lower risk of depression, suggesting that dietary consumption is only one factor in determining body omega-3 concentration and that there may be other biological variables influencing the use and conversion of dietary omega-3 to tissue omega-3.

Our findings may help begin to explain inconsistencies in the existing literature on omega-3 fatty acids and depression, particularly among post-menopausal women. While RBC omega-3 levels were not associated with depressive symptoms, the reduced odds of new depression at follow-up in those with dietary DHA+EPA in the highest tertile of intake relative to the lowest tertile would be consistent with that of previous studies in a variety of populations (Ali *et al.*, 2009, Amin *et al.*, 2008, Baghai *et al.*, 2011, Freeman *et al.*, 2011, Park *et al.*, 2012, Pottala *et al.*, 2012b). The Freeman et al. trial supplemented with EPA and

DHA at 2 g/day, which although somewhat higher, corresponds to the third tertile of dietary DHA+EPA intake noted in our study (0.12g – 2.03g). The complex relationship seen between dietary measures and our depression measures may also explain some of the variability in the literature. Although a growing body of literature suggests a strong correlation between dietary measures and biological concentrations of omega-3 fatty acids (Block *et al.*, 2008, Harris *et al.*, 2012, Harris *et al.*, 2007, Sala-Vila *et al.*, 2011, Salisbury *et al.*, 2011, Sands *et al.*, 2005), this relationship may be confounded by a variety of factors. Among our study participants, dietary DHA+EPA was only moderately correlated with RBC DHA+EPA (r = 0.44); however this value only takes into consideration the linear association between RBC and dietary DHA+EPA – the true relationship between dietary and body levels of omega-3 fatty acids may be much more complex.

Our biological measures experienced some degradation due to inconsistency in storage, which represents a limitation that we attempted to mitigate through multiple imputation. For the analysis of dietary omega-3 fatty acids, supplement use was not captured, which may obscure its true association with depressive symptoms, as well as the correlation between RBC and dietary omega-3 fatty acid levels.

Measurement of depressive symptoms, obtained via the 8-item Burnam scale for depressive symptoms, was assessed at only two time points and we were thus unable to assess onset of depressive symptoms as a time-to-event variable in survival analysis. Further, the Burnam scale is not sufficient for identification of treated depression or for the diagnosis of Major Depressive Disorder, which is ideally made by a structured clinical interview; however, the tool has relatively high sensitivity and specificity to detect Major Depression and can identify the presence of clinically significant depressive symptoms.

Our study is the largest prospective study of its kind to date (Conklin *et al*., 2010, Hakkarainen *et al*., 2004, Hoffmire *et al*., 2012, Huan *et al*., 2004, Lucas *et al*., 2011, Sanchez-Villegas *et al*., 2007, Sublette *et al*., 2006, Suominen-Taipale *et al*., 2010, Tanskanen *et al*., 2001, Tiemeier *et al*., 2003, Timonen *et al*., 2004). Many previous studies assessed dietary indicators of omega-3 fatty acids, although percent concentration within the RBC membrane more accurately reflects body omega-3 levels - few studies integrate both and fewer still utilize a longitudinal design. The baseline prevalence of depressive symptoms among study participants was 7.65% (n=542), which corresponds well to what might be expected from data in representative populations (Kessler *et al*., 2003). Further, among our study sample, crude mean RBC membrane concentration of DHA+EPA was 5.3%, also approximating that expected (Harris *et al*., 2012). We attempted to address confounding through use of multivariable models, controlling for a variety of clinical and sociodemographic variables; however, exposure is not randomized in this observational study and potential for residual confounding persists. To control for type 1 error, we opted for a single *a priori* primary model for analysis - secondary analyses did not control for multiple comparisons and should be considered exploratory. The presence of biological assessments of omega-3 concentrations in a large, well-characterized sample represents a notable strength of this study. Another major strength of the Women's Health Initiative is its prospective design, which allowed us to identify incident cases and reasonably account for temporality.

Overall, our findings do not support a linear association between depressive symptoms and omega-3 fatty acid levels in the RBC membrane. Additionally, conflicting relationships between dietary omega-3 and depressive symptoms were found, although tertile analysis does suggest that higher intake of DHA+EPA may be associated with a lower risk of depression. Future studies are needed to further evaluate for any potential protective effects of omega-3 fatty acids on depression in this and other populations.

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Table 1

Case counts by Depression Measure

	Prevalent Depression		New Depression at Follow-up	
Depression Measure	**n (yes/no)**	**%**	**n (yes/no)**	**%**
Burnam Score 0.06	542/6544	7.65	319/6225	4.87
Burnam Score 0.06 or Antidepressant	967/6119	13.65	800/5319	13.07
Burnam Score 0.009	1350/5736	19.05	603/5133	10.51

Table 2

Demographic and Selected Risk Factors by Baseline Depression

		Depression (as indicated by Burnam score >0.06)				
Characteristics	***Missing***	***n***	**Yes**	**No**	**Total**	**p-value**
	0	**7086**	**542 (7.7%)**	**6544 (92.3%)**	**100%**	
Age	0	7086	70	70	70	0.252
Ethnicity	15					0.059
American Indian		26	3 (0.6%)	23 (0.3%)	0.4%	
Asian		120	8 (1.5%)	112 (1.7%)	1.7%	
African-American		497	53 (9.8%)	444 (6.8%)	7.0%	
Hispanic		166	18 (3.3%)	148 (2.3%)	2.4%	
White		6164	450 (83.5%)	5714 (87.5%)	87.2%	
Other		98	7 (1.3%)	91 (1.4%)	1.4%	
School past high school?	20					<**0.001**
Yes		4958	338 (62.8%)	4620 (70.8%)	70.2%	
No		2108	200 (37.2%)	1908 (29.2%)	29.8%	
Income	429					<**0.001**
<$50,000		5190	429 (85.8%)	4761 (77.3%)	78.0%	
$50,000+		1467	71 (14.2%)	1396 (22.7%)	22.0%	
U.S. region	0					**0.014**
Northeast		1928	171 (31.5%)	1757 (26.8%)	27.2%	
South		1507	124 (22.9%)	1383 (21.1%)	21.3%	
Midwest		1682	103 (19.0%)	1579 (24.1%)	23.7%	
West		1969	144 (26.6%)	1825 (27.9%)	27.8%	
Marital status	16					<**0.001**
Never married		234	13 (2.4%)	221 (3.4%)	3.3%	
Divorced		889	81 (14.9%)	808 (12.4%)	12.6%	
Widowed		2195	220 (40.6%)	1975 (30.4%)	31.1%	
Married		3689	225 (41.5%)	3464 (52.9%)	52.2%	
S.O, not married		63	3 (0.5%)	60 (0.9%)	0.89%	
Obese						0.057
Yes	41	2368	201 (37.4%)	2167 (33.3%)	33.6%	
No		4677	336 (62.6%)	4341 (66.7%)	66.4%	
High blood pressure						0.780
Yes	0	2392	180 (33.2%)	2212 (33.8%)	33.8%	
No		4694	362 (66.8%)	4332 (66.2%)	66.2%	
High Cholesterol						
Yes	90	1274	104 (19.4%)	1170 (18.1%)	18.2%	0.449
No		5722	431 (81.9%)	5291 (80.6%)	81.8%	
Hormone treatment	0					**0.003**
E-alone intervention		1387	124 (22.8%)	1263 (19.3%)	19.6%	
E-alone control		1399	129 (23.8%)	1270 (19.4%)	19.7%	

Characteristics	Depression (as indicated by Burnam score >0.06)					
	Missing	*n*	Yes	No	Total	p-value
	0	**7086**	**542 (7.7%)**	**6544 (92.3%)**	**100%**	
E+P-intervention		2118	146 (26.9%)	1972 (30.1%)	29.9%	
E+P-control		2182	143 (26.4%)	2039 (31.2%)	30.8%	
Smoking status	105					<**0.001**
Non-smoker		3709	266 (50.1%)	3443 (53.4%)	53.1%	
Former smoker		2781	200 (37.7%)	2581 (40.0%)	39.8%	
Current smoker		491	65 (12.2%)	426 (6.6%)	7.1%	
Alcohol (servings/wk)	16	7070	1.77	2.43	2.38	**0.002**
Physical Activity (MET hr/wk)	16	7070	9.53	11.52	11.37	<**0.001**
RBC total n-3 (%)	0	7086	7.80	7.98	7.96	**0.002**
total n-3 dietary intake (g)	8	7078	1.48	1.37	1.38	**0.015**

Table 3

Baseline Depression by RBC and Dietary Omega-3

		RBC (per 1% increase)				Dietary Intake (per 100mg increase)			
	Depression Measure[1]	**Crude OR (95% CI)[2]**	**p-value**	**Adjusted OR (95% CI)[3]**	**p-value**	**Crude OR (95% CI)[2]**	**p-value**	**Adjusted OR (95% CI)[3]**	**p-value**
Total Omega3									
	Burnam Score 0.06	0.952 (0.904, 1.003)	0.0662	0.985 (0.922, 1.052)	0.6565	**1.018 (1.006, 1.025)**	**0.0021**	**1.017 (1.006, 1.028)**	**0.0027**
	Burnam Score 0.06 or Antidepressant	**0.938 (0.900, 0.977)**	**0.0023**	0.978 (0.926, 1.033)	0.4189	**1.008 (1.000, 1.016)**	**0.0532**	**1.010 (1.001, 1.019)**	**0.0310**
DHA									
	Burnam Score 0.06	0.950 (0.888, 1.016)	0.1367	0.975 (0.894, 1.063)	0.5591	1.059 (0.953, 1.176)	0.2861	**1.128 (1.011, 1.257)**	**0.0306**
	Burnam Score 0.06 or Antidepressant	**0.930 (0.879, 0.983)**	**0.0102**	0.970 (0.901, 1.043)	0.4040	1.022 (0.938, 1.113)	0.6221	**1.103 (1.005, 1.211)**	**0.0398**
EPA									
	Burnam Score 0.06	0.845 (0.624, 1.145)	0.2743	1.011 (0.713, 1.435)	0.9486	1.095 (0.889, 1.349)	0.3931	1.226 (0.982, 1.531)	0.0723
	Burnam Score 0.06 or Antidepressant	0.805 (0.627, 1.035)	0.0892	0.998 (0.761, 1.308)	0.9891	1.027 (0.867, 1.217)	0.7547	1.192 (0.987, 1.439)	0.0682
DHA+EPA									
	Burnam Score 0.06	0.954 (0.899, 1.012)	0.1180	0.982 (0.910, 1.059)	0.6338	1.037 (0.966, 1.114)	0.3120	**1.082 (1.004, 1.166)**	**0.0378**
	Burnam Score 0.06 or Antidepressant	**0.936 (0.893, 0.982)**	**0.0069**	0.977 (0.918, 1.040)	0.4607	1.013 (0.956, 1.073)	0.6607	**1.068 (1.002, 1.138)**	**0.0440**

[1] depression (yes/no) n = 542/6544 (Burnam Score >0.06), 967/6119 (Antidepressant or Burnam Score >0.06)

[2] crude model adjusted for age and WHI hormone treatment assignment

[3] multivariable-adjusted model adjusted for U.S. region, marital status, race, education, income, obesity, high blood pressure, high cholesterol, smoking status, bilateral oophorectomy, arthritis, cardiovascular disease, diabetes, prescription narcotic use, physical activity, and alcohol consumption

Table 4

New Depression at Follow-up by RBC and Dietary Omega-3 Intake

		RBC (per 1% increase)				Dietary Intake (per 100mg increase)			
	Depression Measure[1]	**Crude OR (95% CI)[2]**	**p-value**	**Adjusted OR (95% CI)[3]**	**p-value**	**Crude OR (95% CI)[2]**	**p-value**	**Adjusted OR (95% CI)[3]**	**p-value**
Total omega3									
	Burnam Score 0.06	0.976 (0.910, 1.052)	0.5273	0.958 (0.872, 1.052)	0.3661	1.004 (0.989, 1.018)	0.6199	1.005 (0.988, 1.021)	0.5852
	Burnam Score 0.06 or Antidepressant	0.960 (0.920, 1.008)	0.1005	1.007 (0.950, 1.072)	0.8282	1.009 (1.000, 1.018)	0.0543	**1.015 (1.003, 1.026)**	**0.0118**
DHA									
	Burnam Score 0.06	0.965 (0.880, 1.065)	0.4788	0.930 (0.828, 1.045)	0.2212	0.935 (0.791, 1.105)	0.4306	0.947 (0.786, 1.142)	0.5716
	Burnam Score 0.06 or Antidepressant	0.950 (0.890, 1.008)	0.0854	0.993 (0.920, 1.076)	0.8555	0.943 (0.847, 1.051)	0.2888	1.027 (0.905, 1.165)	0.6823
EPA									
	Burnam Score 0.06	0.982 (0.690, 1.388)	0.9156	1.013 (0.676, 1.519)	0.9503	0.864 (0.625, 1.196)	0.3783	0.869 (0.598, 1.263)	0.4613
	Burnam Score 0.06 or Antidepressant	0.830 (0.660, 1.053)	0.1252	1.053 (0.770, 1.436)	0.7408	0.908 (0.737, 1.119)	0.3645	1.078 (0.837, 1.387)	0.5616
DHA+EPA									
	Burnam Score 0.06	0.973 (0.900, 1.057)	0.5162	0.947 (0.856, 1.048)	0.2918	0.953 (0.852, 1.067)	0.4043	0.960 (0.845, 1.090)	0.5260
	Burnam Score 0.06 or Antidepressant	0.950 (0.900, 1.003)	0.0630	0.998 (0.930, 1.070)	0.9446	0.963 (0.896, 1.035)	0.3046	1.021 (0.937, 1.112)	0.6349

[1] depression (yes/no) n = 319/6225 (Burnam Score >0.06), 800/5319 (Antidepressant or Burnam Score >0.06)

[2] crude model adjusted for age, WHI hormone treatment assignment, and baseline Burnam Score

[3] multivariable-adjusted model adjusted for U.S. region, marital status, race, education, income, obesity, high blood pressure, high cholesterol, smoking status, bilateral oophorectomy, arthritis, cardiovascular disease, diabetes, prescription narcotic use, physical activity, alcohol consumption, days to follow-up

Table 5

New Depression at Follow-up by RBC Membrane and Dietary Omega-3 Tertiles

	RBC %				Dietary Intake (g/d)			
	Tertile range	**Depression[1] (yes/no)**	**Crude OR (95% CI)**	**Adjusted OR (95% CI)**	**Tertile range**	**Depression[1] (yes/no)**	**Crude OR (95% CI)**	**Adjusted OR (95% CI)**
Total omega3	3.9077–7.1081	119/2012	--ref--	--ref--	0.0890–0.9508	91/2086	--ref--	--ref--
	7.1081–8.3968	111/2118	0.884 (0.560, 1.393)	0.835 (0.478, 1.461)	0.9508–1.5178	115/2127	1.181 (0.885, 1.576)	1.239 (0.891, 1.722)
	8.3968–19.8454	89/2095	0.814 (0.560, 1.181)	0.734 (0.481, 1.120)	1.5178–8.0049	112/2005	1.183 (0.883, 1.584)	1.235 (0.882, 1.729)
p-value			0.2733	0.1528			0.4408	0.3683
DHA	1.7514–3.9037	118/2012	--ref--	--ref--	0.0000–0.0345	113/2018	--ref--	--ref--
	3.9037–4.9424	109/2116	0.883 (0.600, 1.292)	0.804 (0.488, 1.325)	0.0345–0.0781	104/2123	0.858 (0.649, 1.134)	0.824 (0.601, 1.129)
	4.9424–11.6267	92/2097	0.787 (0.530, 1.179)	0.667 (0.432, 1.029)	0.0781–1.3119	101/2077	0.759 (0.570, 1.012)	0.718 (0.512, 1.006)
p-value			0.2481	0.0661			0.1681	0.1495
EPA	0.0428–0.5386	110/2026	--ref--	--ref--	0.0000–0.0172	111/2024	--ref--	--ref--
	0.5386–0.7359	109/2120	0.994 (0.640, 1.554)	0.920 (0.543, 1.557)	0.0172–0.0411	107/2113	0.892 (0.675, 1.179)	0.826 (0.602, 1.134)
	0.7359–5.8678	100/2079	0.944 (0.660, 1.351)	0.909 (0.596, 1.396)	0.0411–0.7924	100/2081	0.786 (0.590, 1.048)	0.740 (0.530, 1.032)
p-value			0.7539	0.6484			0.2594	0.1937
DHA+EPA	2.0446–4.4680	118/2009	--ref--	--ref--	0.0000–0.0527	111/2020	--ref--	--ref--
	4.4680–5.6498	107/2122	0.863 (0.590, 1.256)	0.803 (0.535, 1.205)	0.0527–0.1193	110/2116	0.917 (0.695, 1.210)	0.861 (0.629, 1.178)
	5.6498–15.6179	94/2093	0.798 (0.560, 1.130)	0.690 (0.460, 1.036)	0.1193–2.0328	97/2082	0.753 (0.563, 1.007)	**0.707 (0.503, 0.993)**
p-value			0.2188	0.0715			0.1511	0.1354

[1] Burnam Score > 0.06