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## Association between Omega-3 Fatty Acids and Depressive Symptoms among Patients with Established Coronary Artery Disease: Data from the Heart and Soul Study

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Depression is an established risk factor for the development of coronary heart disease (CHD) in healthy patients [1,2] and for adverse cardiovascular outcomes in patients with existing CHD [3,4]. A deeper biological understanding of the causes of depression in patients with cardiovascular disease is critical to improve the prevention and treatment of both conditions [5,6]. Dietary factors resulting in lower levels of  $\omega$ -3 fatty acids not only increase CHD risk [7,8], but may also be involved in the pathophysiology of depression. Lower levels of  $\omega$ -3 fatty acids, particularly docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), have been associated with depression in both healthy adult populations [9,10] and in patients with acute coronary syndrome [11,12]. It is unknown whether low  $\omega$ -3 fatty acid levels are associated with depression in patients with stable CHD.

We measured red blood cell levels of two  $\omega$ -3 fatty acids, EPA and DHA, and assessed depressive symptoms in a cross-sectional study of 987 adults with CHD. The Heart and Soul Study is a prospective cohort study examining psychosocial factors and health outcomes in patients with established CHD. Detailed methods have previously been described [13]. Between 2000 and 2002, a total of 1,024 San Francisco area residents enrolled and completed a baseline study visit. Subjects without frozen blood samples ( $n = 37$ ) were excluded, resulting in a final sample size of 987.  $\omega$ -3 fatty acids were blindly measured in fasting venous blood samples using capillary gas chromatography to measure the fatty acid composition of red blood cell membranes. Red blood cell levels of EPA and DHA are presented as a percentage composition of total fatty acid methyl esters. We assessed current depression using the 9-item Patient Health Questionnaire [14], where a score  $\geq 10$  is consistent with major depression [15,16]. Socioeconomic status (SES) was measured using both education and household income level as previously described [17].

We evaluated the association between  $\omega$ -3 fatty acid levels and depressive symptoms as continuous variables using linear regression. We also examined the association of  $\omega$ -3 fatty

acid tertiles with depression as a dichotomous variable using  $\chi^2$  analysis and logistic regression. Multivariable models were sequentially adjusted for demographic factors and SES. All statistical tests were two-sided, and  $p < 0.05$  was considered statistically significant. Analyses were performed with SAS version 9.1 (SAS Institute, Cary, N.C., USA).

The average age of the study participants was  $67 \pm 11$  years, out of whom 804 study participants (approx. 80%) were men. Participants in the lowest tertile of  $\omega$ -3 fatty acid levels (EPA + DHA) were less likely than participants in the highest tertile to be married, have a college degree or earn a household income over USD 20,000. These same participants were more likely to be Hispanic or black, have a history of hypertension, myocardial infarction or diabetes mellitus, to smoke, or to be physically inactive.

The prevalence of depression ranged from 23% in participants in the lowest tertile of  $\omega$ -3 fatty acids ( $< 3.1\%$  of total blood fatty acids) to 13% in participants in the highest tertile ( $> 14.3\%$  of total blood fatty acids;  $p$  for trend = 0.004). Each unit decrease in EPA + DHA was inversely associated with depressive symptoms as a continuous variable, and these associations persisted after adjustment for age, sex and race (table 1). Similarly, each SD decrease in EPA + DHA was associated with significantly greater odds of depression as a dichotomous variable (Patient Health Questionnaire score  $\geq 10$ ; table 1). However, in both analyses,  $\omega$ -3 fatty acid levels were no longer associated with depression after adjustment for education and household income level. Similar results were obtained for the analyses of EPA and DHA alone.

Prior studies have found an association between  $\omega$ -3 fatty acids and depression in the general population [9]. A recent review of this literature concluded that a causal relationship likely exists between  $\omega$ -3 fatty acids and depression but raised concerns that many studies had inadequate sample size and adjustment for potential confounders like SES [10]. There is a clear association between lower levels of  $\omega$ -3 fatty acids and increased CHD risk [18], but the role of  $\omega$ -3 fatty acids and depression in patients with CHD is not known. Two prior studies of acute coronary syndrome patients found an association between low  $\omega$ -3 fatty acid levels and depression, suggesting that low  $\omega$ -3 fatty acids may contribute to the development of depression in patients with heart disease [11,12].

Our study extends this existing literature by finding a strong association between low  $\omega$ -3 fatty acids and depression in outpatients with stable CHD, a population distinct from sicker, hospitalized patients with acute coronary syndrome. In addition, we examined the role of several important potential confounders and measured erythrocyte membrane levels of fatty acids rather than using less accurate serum measurements or dietary questionnaires. However, the cross-sectional nature of our study precluded us from making any definitive comments on causality. Additionally, our cohort participants were mostly older, urban men and thus are not entirely reflective of the general population.

In an effort to improve current cardiovascular prevention strategies, some have suggested providing  $\omega$ -3 fatty acid supplements to CHD patients with a diagnosis of depression [11]. Because depression increases both cardiovascular risk and cardiovascular disease-related morbidity and mortality [1-4,19-21], a potential reduction in the incidence of depression in patients with CHD by  $\omega$ -3 fatty acid supplementation could lead to less adverse cardiac outcomes. However, given that differences in SES appeared to explain the association between  $\omega$ -3 fatty acids and depression in our study, we are less confident that treatment with  $\omega$ -3 fatty acids can improve depressive symptoms in patients with stable CHD. Since SES is an important risk factor for both poor diet and depression [22], it is possible that  $\omega$ -3 fatty acid levels are not associated with depressive symptoms independent of SES [23]. To better understand the potential efficacy of  $\omega$ -3 fatty acid supplementation for improving depressive symptoms in patients with CHD, future studies should carefully consider the role of SES in this association.

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Table 1

Association of EPA + DHA with depressive symptoms

	Depressive symptoms (continuous PHQ)		Depression (dichotomous PHQ $\geq 10$ )		
	$\beta$ -coefficient $\pm$ SE	p value	OR	95% CI	p value
Unadjusted	-0.22 $\pm$ 0.07	0.002	1.3	1.1-1.5	0.006
Adjusted for age, sex and ethnicity	-0.14 $\pm$ 0.07	0.05	1.1	0.97-1.4	0.11
Adjusted for above plus income and education	-0.06 $\pm$ 0.07	0.42	1.0	0.87-1.2	0.68

Because EPA + DHA levels were not normally distributed, they were log-transformed. The  $\beta$ -coefficient was determined for the association of log EPA + DHA (entered as a continuous predictor variable) with depressive symptoms (log of PHQ score). The odds ratio (OR) was assessed for the association of EPA + DHA (entered as continuous predictor variables, per SD decrease) with depressive symptoms (dichotomous PHQ  $\geq 10$ ). PHQ = Patient Health Questionnaire; CI = confidence interval.