Spring 2020

OMEGA-3 FATTY ACIDS AND DEPRESSIVE SYMPTOMOLOGY AND THE INFLUENCE OF PSYCHOSOCIAL STRESS: THE HISPANIC COMMUNITY HEALTH STUDY/STUDY OF LATINOS

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BY

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THESIS

Submitted to the University of New Hampshire

in Partial Fulfillment of

the Requirement for the Degree of

Master of Science

in Nutritional Sciences

May, 2020

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DEDICATION

To my family, friends, educators and colleagues both past and present, this would not have been possible without you. Each of you have helped me get to where I am today.

ACKNOWLEDGEMENTS

I would like to express my sincere gratitude to all who have supported, guided, and educated me during my time as a graduate student at the University of New Hampshire.

First, I would like to thank my thesis advisor, Dr. Sherman Bigornia, for your guidance and all you have taught me throughout the past 2 years. I am grateful for your dedication to my progression as a researcher and professional, and I am thankful for the opportunity to be a part of your lab. You have made me a better researcher, student, and writer, all of which are undoubtedly valuable for my future endeavors.

I would also like to thank my thesis committee members, Dr. Jesse Stabile Morrell and Dr. Semra Aytur. To Dr. Morrell, thank you for your unwavering guidance and support throughout my time as a graduate student. You are truly an inspiring educator, mentor, and researcher. Dr. Aytur, thank you for all of your support and education regarding all things statistics and SAS. This project would not have been possible without your guidance and education.

To my lab mates, Nikki Karazurna and Dustin Moore, your incredible friendship and support were vital to my time in grad school. Nikki, it goes without saying that you have helped me persevere, and I am forever grateful for your friendship and unconditional support as we navigated all that is grad school together. To my 2020 MS Nutritional Sciences peers, I am grateful for all of your friendship throughout our time together.

To members of the ANFS department staff and faculty: Jen Surina, Celeste Dietterle, and Amy Parker, thank you for your all of your assistance, both professionally and personally. No matter what, there is no question you can't answer. In addition, Dr. Dave Mortensen, the department chair of ANFS, I am very grateful for your support and guidance through my time as a graduate student. Your dedication to the ANFS department staff, faculty, and students is unparalleled.

To all of the Nutrition department faculty, I would like to express my sincere gratitude for always providing support and encouragement. In particular, I would like to thank Kevin Pietro and Dr. Joanne Burke. I am very grateful to have had the opportunity to work with you both over the past 2 years. You are both truly inspiring educators who have taught me immensely regarding education and how to provide a meaningful education to our students.

To my family, friends, and Sean, none of this would have been possible without you. From being a listening ear while I practiced my presentations to helping me through the trials and tribulations of grad school, I am beyond grateful.

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ABSTRACT

OMEGA-3 FATTY ACIDS AND DEPRESSIVE SYMPTOMOLOGY AND THE INFLUENCE OF PSYCHOSOCIAL STRESS: THE HISPANIC COMMUNITY HEALTH STUDY/STUDY OF LATINOS

by

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Objectives: The literature on omega-3 fatty acid (FA) intake and depressive symptoms is inconsistent, potentially due in part to the influence of psychosocial stress. Some evidence supports that omega-3 FA intake may have greater benefit on depressive symptoms among individuals with high oxidative stress. We quantified the associations between dietary and plasma omega-3 FA and 6-y depressive symptoms and measured the modifying effect of psychosocial stress.

Methods: Data are from the Hispanic Community Health Study/Study of Latinos (age 48 y, 63% female). At baseline (2008-11), EPA, DHA and omega-3 very-long-chain FAs (VLCFAs) were estimated using two 24-hr recalls and the NCI method. Plasma omega-3 FAs were measured by mass spectrometry. Depressive symptoms were ascertained at baseline and 6-y follow-up with the 10-item Center for Epidemiological Studies Depression Scale (CES-D). Approximately 9 months from baseline, the 10-item Perceived Stress (PSS) and Chronic Burden of Stress scales

were obtained. Unstratified and psychosocial stress-stratified associations were analyzed using survey linear regression among those with dietary (n=3537) and plasma (n=718) FA data. Model covariates included, but were not limited to, baseline CES-D score, Hispanic/Latino background, study site, antidepressant use, total energy intake, and dietary or plasma omega-6 FA.

Results: Baseline DHA and omega-3 VLCFA intake were inversely associated with 6-y CES-D ($P<0.05$). All examined dietary omega-3 FA exposures were inversely associated with CES-D among individuals in the highest PSS quartile (Q4) ($P<0.05$), but this was attenuated after considering omega-6 FA intake. DHA and omega-3 VLCFA intakes were inversely associated with CES-D among individuals with 2 chronic stressors, but not <1 or >2 stressors. Plasma omega-3 FAs were not associated with CES-D in PSS stratified and unstratified analyses. However, plasma omega-3 FA were associated with lower CES-D score among those with only 2 chronic stressors.

Conclusions: Dietary omega-3 VLCFAs, but not plasma, were inversely associated with 6-y CES-D. Psychosocial stress did not clearly modify these associations. These results provide some evidence that greater omega-3 VLCFA intake may reduce depressive symptoms among Hispanic/Latino adults. However, considering the limitations of self-reported intake, further research is needed using biomarkers of long-term omega-3 consumption and psychosocial stress to confirm our findings.

CHAPTER I: INTRODUCTION

Rationale

Depression is a multi-factorial, debilitating disease that affects approximately 7.1% of American adults (1) and 4.4% of adults globally (2). Depression accounts for almost 400 million lost work days each year in the United States (3), and is the leading cause of disability worldwide (2). The economic cost of medical treatment related to major depressive disorder in the United States reached nearly $28 billion in 2010 (3). Hispanic/Latino Americans are one of the fastest growing ethnic groups in the United States and it is projected that by 2060, the Hispanic/Latino population will increase by 61.5 million people, an increase of approximately 67% (4). It has been reported that Hispanic/Latinos are disproportionately affected by depression (5). Hispanic/Latinos have been shown to have more depressive symptoms than other ethnic groups, with the recent data from the Multiethnic Study of Atherosclerosis indicating that 28.2% and 13% of Hispanic/Latino women and men, respectively, experience moderate-severe depressive symptoms compared to 11.4% - 14.7% and 4.7% -7.6% of women and men, respectively, from other ethnic groups including non-Hispanic Whites, non-Hispanic Blacks, and Chinese (6).

Although depression is multifactorial (7), increasing evidence has linked dietary pattern quality to incidence of depression and depressive symptoms (8,9). High diet quality has been associated with lower risk of depression, as well as poor diet quality associated with greater risk of depression (9). Dietary patterns have also been shown to have an independent effect on severity of depressive symptoms, with poor diet quality resulting in increased depressive symptom

severity (8). It has been proposed that cardiometabolic risk factors, such as oxidative stress (10), may increase depression incidence, as cardiovascular disease (CVD) and depression are frequent comorbidities (11). High oxidative stress and psychological stress are known risk factors for the development of depression and depressive symptoms (12). It has been proposed that psychological stress may increase depression risk because psychological stress has been shown to increase oxidative stress in humans and animal models (12,13).

Omega-3 fatty acids (FAs) have been shown in some studies to be associated with less depressive symptoms (14), however the epidemiological evidence has been inconsistent (15), potentially due in part to the modifying effect of oxidative stress. A handful of studies have found a significant modifying effect of oxidative stress, as indicated by smoking status (16,17) and lipid peroxidation (18). Additionally, it was recently found in a cohort of Puerto Rican adults that omega-3 FA status was not associated with depressive symptoms, except in those with high levels of oxidative stress (5), furthering the argument that the antioxidant effect of omega-3 FAs (19) may be an important factor in their effect on reducing depressive symptoms.

Therefore, to continue to move the literature forward we quantified the association between dietary omega-3 FA and omega-3 FA status with self-reported depressive symptoms in a large cohort of Hispanic/Latino adults living in the U.S. Additionally, we evaluated the modifying effects of psychological stress on these associations, to ascertain those who may experience the most benefit of increasing omega-3 FA consumption on depressive symptoms.

Objectives

Aim 1: *Quantify the 6-year longitudinal associations of baseline omega-3 FA consumption with 6-year depressive symptomatology and measure the modifying effect of psychological stress among adults in HCHS/SOL*. We used omega-3 FA consumption estimated by the National Cancer Institute (NCI) method applied to two 24-hr recalls. Psychological stress was measured using the 10-item Perceived Stress Scale (PSS-10) and Chronic Burden of Stress (CBS) scores obtained within 9 months of the baseline study visit, most of which (73%) were completed within 4 months from baseline. We tested whether PSS-10 and CBS each modify the prospective associations between omega-3 FA consumption and CES-D scores. We hypothesized that higher omega-3 FA intake would be associated with lower 6-y depressive symptomatology, and the associations would be modified by PSS-10 and CBS scores.

Aim 2: *Quantify the 6-year longitudinal associations of baseline circulating omega-3 FA levels with depressive symptomatology and measure the modifying effect of psychological stress among adults in HCHS/SOL*. We used baseline plasma omega-3 FA levels generated from untargeted metabolomics as a biomarker of omega-3 FA consumption. Similar to the Aim 1 approach, we examined the associations of baseline omega-3 FA biological levels with 6-y CES-D scores. Further, effect modification of these associations by PSS-10 and CBS scores was determined. We hypothesized that higher plasma omega-3 FA levels would be associated with lower 6-y depressive symptomatology, and the associations would be modified by PSS-10 and CBS scores.

Public Health Relevance

Depression is a costly, chronic disease. Approximately 7.1% of American adults (1) and 4.4% of adults worldwide (2) are affected by depression. Depression is costly in that it is the leading cause of disability worldwide, and accounts for 400 million lost work days each year in the United States alone (2). Further, the economic cost of treating major depressive disorder in the United States reached nearly $28 billion in 2010 (3). Although depression is multifactorial and has many risk factors and etiologies, evidence has shown an association between dietary pattern quality and incidence of depression (9). A healthy diet pattern high in fruits, vegetables, whole grains, olive oil, fish, soy, poultry, and low-fat dairy is associated with lower risk of depression, while an unhealthy, Western-style, diet pattern high in red and processed meat, refined grains, high fat dairy, butter, potatoes, and sweets and low in fruits and vegetables is associated with greater risk of depression (9). Dietary patterns have also been shown to have an independent effect on severity of depressive symptoms (8). Low diet quality, assessed by the Alternative Healthy Eating Index (AHEI) score, which includes eight diet components: fruit, vegetables, nuts and legumes, ratio of white meat to red meat, trans fat, ratio of polyunsaturated fat (PUFA) to saturated fat, and alcohol, was associated with greater severity of depressive symptoms (8). In addition, higher omega-3 FA intake has been shown in some, but not all, epidemiological studies to be associated with less depressive symptoms (17,20–26).

Dietary Omega-3 FA and Depression

Much attention has been given to omega-3 FAs as they pertain to CVD. This is in part due to their known benefits on inflammation and oxidative stress. Omega-3 FAs exert their anti-inflammatory effects by decreasing activity of pro-inflammatory processes including the

metabolism of omega-6 FAs, leukocyte chemotaxis, adhesion molecule activity, and nuclear factor-κB (NF-κB) activation (27). Omega-3 FAs also serve as precursors for anti-inflammatory molecules, such as resolvins and protectins (28). Omega-3 FAs may reduce oxidative stress by attenuating oxidative processes such as lipid peroxidation (29) and reactive oxygen species (ROS) generation (30). Attention has been drawn to their potential benefits on depression, as inflammation (31), oxidative stress (32) and CVD (33) are implicated in the development of depressive symptomatology. However, there are inconsistencies (16,34–38) within the literature with regards to the associations of omega-3 FA consumption and depressive symptoms.

The association between omega-3 FAs and depression has been studied in cross-sectional (17,25,26), longitudinal (38–40), and case-control (41–43) studies as well as in randomized controlled trials (RCTs) (44–46). Although a recent meta-analysis of cross-sectional and prospective studies concluded a protective association of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) consumption, as well as total omega-3 FA intake on depressive symptomatology there was heterogeneity across the studies examined which impedes our ability to draw firm conclusions. For example, although EPA + DHA consumption demonstrated a protective association in the meta-analysis, only 5 studies were examined and of these 3 were cross-sectional (22,23,47). Further, one study examined post-partum depression (37), whereas others were conducted among pregnant women (47) and adolescents (23). Most of these studies independently did not report a significant protective association (23,35,37) and the study with the strongest reported association was conducted among 70-90 year olds (22). For total omega-3 FA intake, there was an overall significant inverse association between total omega-3 FA intake and depression when results were pooled together. However, only 6 studies were examined, and

among them only 2 independently found a significant association (25,26). Grosso et al. (14) also concluded that there was heterogeneity across the studies, mainly in terms of design, population, and omega-3 FA consumption. While some epidemiological studies support a protective association between omega-3 FA consumption and depressive symptoms, the most recent meta-analysis of RCTs found no effect of omega-3 FAs on depressive symptoms among those without depression, but did find a beneficial effect among participants who presented with depression at baseline (48).

Circulating Omega-3 FA and Depression

Some studies have examined the association of omega-3 FA status and depressive symptomatology or risk of depression (5,49,50). Biomarkers of omega-3 FA provide an objective measure of omega-3 FA consumption as humans lack the enzyme to synthesize *de novo* omega-3 FAs and thus may provide a more reliable measure of omega-3 FA exposure as compared to dietary measures. Similar to dietary omega-3 FA, the current literature on omega-3 FA status as it relates to depression or depressive symptoms is inconsistent. Case control studies have demonstrated that circulating levels of omega-3 FA tend to be lower in cases with depression as compared to non-depressed controls (43,51–54). However, there are inconsistent findings as to which omega-3 FAs most strongly relate to depression, as studies have found differential support for total omega-3 FA (43,51,53,54), EPA (54), DHA (43,51,53,54), EPA + DHA (43), and ALA (49). Some cohort studies have been conducted cross-sectionally or prospectively using biomarkers of omega-3 FA status as it relates to depressive symptoms. Results from cohort studies are inconsistent, with cross-sectional studies finding inverse (55–57), non-linear (56,58), positive (58), and null (17,50,59) associations between omega-3 FA status

and depressive symptoms. A limited number of studies have looked at omega-3 FA status and depressive symptoms longitudinally (5,59). One study conducted among older Puerto Rican adults found that the 2-y prospective association of erythrocyte EPA and DHA with depressive symptoms was modified by oxidative stress level (5). Among those with the highest oxidative stress level (top quartile of urinary 8-hydroxy-2'-deoxyguanosine), greater EPA and DHA concentrations were associated with lower 2-y depressive symptoms adjusted for baseline depressive symptoms. Another study did not observe significant associations with depressive symptoms when examining erythrocyte total omega-3 FA, EPA, DHA, and EPA+DHA at baseline or 7.5 year follow up in a cohort of post-menopausal women (59). Given that there are a limited number of studies examining omega-3 FA status and depressive symptoms prospectively, as well as inconsistent associations in cross-sectional studies, more research is needed to elucidate the relationship using this objective measure of omega-3 FA intake.

Psychological Stress, Oxidative Stress, and Depression

Chronic psychological stress is a well-established risk factor for depression (60). Chronic psychological stress has been associated with increased oxidative stress, and it has been established that oxidative stress is related to increased depressive symptomatology (61,62). Therefore, it has been proposed that oxidative stress may serve as the link between psychological stress and depressive symptomatology (12). The brain is particularly vulnerable to oxidative damage, as it is metabolically active and has fewer antioxidant defenses than other tissues (63). Psychological stress may influence depressive symptomatology by increasing oxidative stress which can impair neuronal signaling, contribute to neurodegeneration, and increase neuroinflammation (63). For example, it has been shown that oxidative stress can lead to the

activation of the enzyme indoleamine dioxygenase (IDO), which catabolizes tryptophan (64). The activation of IDO is thought to play a role in depression, as it lowers circulating tryptophan, and subsequently serotonin, as well as produces neurotoxic TRYCATs (tryptophan catabolites along the IDO pathway) (64).

In an aforementioned prospective cohort study, our lab observed that greater omega-3 FA erythrocyte concentrations were associated with lower depressive symptomatology only among those with high oxidative stress levels (5). These result suggest that the association between omega-3 FA consumption and depression may be modified by oxidative stress level and perhaps by psychological stress. This may in part explain the inconsistent associations between omega-3 FA and depressive symptomatology observed in observational studies, as oxidative and psychological stress have not been widely-considered as potential effect modifiers. In a secondary data analysis of an omega-3 FA supplementation trial, those with high baseline lipid peroxidation, a marker of oxidative stress, experienced a greater reduction in depressive symptoms as compared to those with less oxidative stress at baseline (18). More recently, two observational epidemiological studies which examined the association between omega-3 FA consumption and depressive symptomatology stratified their analyses by smoking status (16,17), which is a well-established pro-oxidant (65). Both studies identified significant effect modification by smoking status, when stratifying the association of omega-3 FA or fish consumption with depressive symptomatology by smoking status (16,17). One study in pregnant women found an inverse relationship between EPA + DHA intake and depressive symptoms that became significant when looking at current smokers (16). While another study found that women who were non-smokers and high fish consumers had higher risk of depression, and men who

were occasional or former smokers and high fish consumers had lower risk of depression (17). Of the few data available, oxidative stress may be a significant modifier of the association between omega-3 FA consumption and depressive symptomatology. Considering the impact of psychological stress on oxidative stress burden, it is possible that psychological stress may modify the associations between omega-3 FA and depressive symptoms. However, based on our search of the literature, no study to date has explicitly examined the impact of psychological stress on this association in humans. One study performed in rats observed that omega-3 FA supplementation reduced depressive symptoms in rats exposed to chronic stress (66). To move the literature forward, this project aimed to address this knowledge gap.

Omega-3 FA Intake, Stress, and Depression in Hispanic/Latino Populations

Some evidence suggests that Hispanic/Latino populations are disproportionately affected by psychological stress (67) and depression (68). Hispanic/Latino populations may experience a disproportionate amount of psychological stress for a multitude of reasons including acculturation, low socioeconomic status, and limited access to resources (69). Recently, the Multiethnic Study of Atherosclerosis showed that more Hispanic/Latinos report moderate to high depressive symptoms as compared to other ethnic groups, at 28.2% and 13% of Hispanic/Latino women and men, respectively, compared to 11.4% - 14.7% and 4.7% -7.6% of women and men, respectively, from other ethnic groups including non-Hispanic whites, non-Hispanic blacks, and Chinese (6). The high burden of depression may in part be due to suboptimal consumption of food sources of omega-3 FAs in concert with high oxidative stress. In the Hispanic Community Health Study, average intake of fish among Hispanic/Latino American adults was approximately 0.7 ounces per day (70), which equates to less than 5 ounces per week. The current 2015-2020

Dietary Guidelines for Americans recommend that Americans consume approximately 8 ounces of fish or seafood per week based on a 2,000 calorie diet for general health (71). This recommendation equates to approximately 250 mg per day of combined DHA and EPA (71). Further, Mexican-Americans have been shown to have lower long chain omega-3 FA intakes as compared to non-Hispanic/Latino Whites and non-Hispanic/Latino Blacks, with mean intakes from food and supplements of 0.17, 0.22, and 0.19 g/day, respectively (72). Given the evidence of low omega-3 FA consumption and high depressive and stress burden, it is critical to better clarify the interrelationship between omega-3 FAs, stress, and depressive mood among individuals of Hispanic/Latino descent. Examining these associations could have significant implications for the treatment and prevention of depression, a debilitating and costly disease.

Current Literature Gaps and Future Directions

Currently, there are gaps within the literature that need to be addressed and more research needs to be completed in order to determine the modifying effect of psychological stress on the association between omega-3 FA and depressive symptoms. Lack of consideration for the potential modifying effect of psychological stress may help to explain the inconsistencies in the current literature, which to our knowledge has not been investigated. Further, there has been limited use of objective measures of omega-3 FA intake, which may strengthen the results. The results from this thesis project provide additional evidence that my help to identify populations that may most benefit from omega-3 consumption for the reduction in depressive symptomatology. While depression is multifactorial and does not have one specific etiology, dietary practices may provide significant benefits in terms of symptom reduction.

CHAPTER II: METHODS

Participants

Participants were from the Hispanic Community Health Study/Study of Latinos (HCHS/SOL), a population-based prospective cohort study. Data were collected in the first wave of HCHS/SOL between 2008 and 2011 from 16,415 self-identified Hispanic/Latino adults aged 18-76 years, recruited from four different field centers (Bronx, NY, Chicago, IL, Miami, FL, and San Diego, CA) (69,73). The 45-74 year age group was oversampled to ascertain chronic disease rates (74). Data were collected in the second wave of HCHS/SOL between 2014 and 2017 (n = 11,623).

Of the 16,415 participants in the first wave of HCHS/SOL, 7,321 (45%) were eligible to participate in the Sociocultural Ancillary Study (SCAS) by consenting to future contact and being willing to participate (69) (**Figure 1**). The SCAS was a cross-sectional ancillary study that investigated the associations of social, cultural, and psychological factors with metabolic syndrome, CVD, and their risk factors within HCHS/SOL (69). Data from 5,313 (32% of baseline cohort) participants were collected in the SCAS (69) within 9 months of their baseline HCHS/SOL visit between February 2010 and June 2011 (69). Detailed methods for HCHS/SOL and SCAS have been described elsewhere (69,74,76). SCAS collected measures of psychosocial stress including the 10-item Perceived Stress Scale (PSS-10) and 8-item Chronic Burden of Stress. In addition, of the HCHS/SOL baseline cohort, approximately 25-33% of participants participated in the SOL Whole Genome Sequencing (WGS) and Metabolomics Ancillary Study.

Data from WGS and Metabolomics Ancillary Study include metabolomic measures of plasma omega-3 FAs.

3,896 participants had complete covariate data and participated in both the second wave of HCHS/SOL and SCAS. Further exclusions were applied to individuals missing outcome or effect modifier data: 10-item Center for Epidemiological Studies-Depression Scale (CES-D) score at baseline (n=33) and 6-y follow up CES-D (n=89), PSS-10 (n=71), and Chronic Burden of Stress (n=203). No additional exclusions were necessary for missing exposure data, as missing dietary data were captured when excluding missing covariate data. A final sample of n=3,537 was available for prospective analyses with dietary omega-3 FAs as the exposure (Figure 1). For metabolomic analyses, additional exclusions were applied for those missing metabolomic measures of circulating omega-3 FA (n=2,556). A final sample of n=718 was available for prospective analyses with metabolomic omega-3 FAs as the exposure (Figure 1).

Primary Exposure: Dietary omega-3 FAs

Participants completed two 24-hour dietary recalls during the first wave of HCHS/SOL (2008-2011). The first 24-hour dietary recall was completed in person during the baseline visit (77). The second 24-hour dietary recall was administered over the telephone within 6 weeks of the baseline visit (74,77). Nutrients were analyzed using the Nutrition Data System for Research (NDS-R) (version 11, University of Minnesota, Minneapolis, MN) (70). Further nutrient analysis was conducted using the National Cancer Institute (NCI) Method, a statistical model to estimate usual intake of episodically consumed foods (78). The NCI method estimates an individual's

usual intake of foods and nutrients accounting for sampling weight and adjusting for covariates including: age, sex, Hispanic/Latino background, HCHS/SOL center, day of the week, first or second recall, and self-report of intake being greater, same, or less than usual, and. Omega-3 FAs were expressed as percent of total FA intake (saturated, monounsaturated, polyunsaturated and *trans* FAs). Omega-3 FAs were analyzed as EPA, DHA, and very-long-chain omega-3 FAs (omega-3 VLCFA). Omega-3 VLCFA is the sum of EPA, docosapentaenoic acid (DPA) and DHA. These were grouped together for analyses as they represent animal-derived omega-3 FAs (e.g., fatty fish) (79). It has been previously supported that fish intake is inversely associated with depression, therefore it is of importance to analyze omega-3 VLCFAs separately (80). Dietary omega-3 FAs were analyzed continuously.

Secondary Exposure: Circulating omega-3 FAs

Participants had a fasting blood draw during their baseline exam (81). Plasma was collected in EDTA anticoagulated tubes and centrifuged at 3000 x g at 15°C for 30 minutes (81). Aliquots were frozen at -80°C at the field centers and sent to the central laboratory at the University of Minnesota for biomarker analysis (81). Plasma metabolites were measured by Metabolon, Inc (Morrisville, NC) using untargeted mass spec-based metabolomics profiling. This method incorporates two separate ultra-high performance liquid chromatography/tandem mass spectrometry injections and one gas chromatography/mass spectrometry injection per sample, and can detect metabolites in the range of low nanograms per milliliter (82). Circulating omega-3 FAs were expressed as percent of total circulating FAs (saturated, monounsaturated, polyunsaturated, and *trans* FAs). Circulating omega-3 FAs were analyzed continuously as EPA, DHA and omega-3 VLCFAs as the sum of EPA, DPA, and DHA.

Primary Outcome: 6-year depressive symptomatology

Self-reported depressive symptoms were assessed using the 10-item Center for Epidemiological Studies Depression Scale (CES-D) during the baseline exam and approximate 6-year follow up. CES-D is an abridged version of the 20-item CES-D scale that assesses depressive symptomatology over the past week using a score ranging from 0-30, with a higher score indicating more depressive symptoms (83). CES-D was offered in the participant's preferred language, and was shown to measure the same construct in the English and Spanish versions in HCHS/SOL participants (84). A cut-point of 10 on the CES-D indicates high depressive symptoms with both sensitivity and specificity (85) to the validated cut-off of ≥16 on the 20-item CES-D (86). CES-D was analyzed continuously.

Psychological Stress: Perceived Stress Scale and Chronic Burden of Stress

Self-reported psychological stress was measured via the 10-item Perceived Stress Scale (PSS-10) (87) and 8-item Chronic Burden of Stress scale (88,89) as part of the SCAS. Questionnaires were administered by a trained interviewer within 9 months of the HCHS/SOL baseline exam (75), most (73%) were completed within 4 months (75).

PSS-10 is a 10-item questionnaire which assesses the individual's reaction to and ability to cope with stressors over the past month (87). PSS-10 responses are on a Likert scale of 0-4 (never to very often). PSS-10 responses are added together, with questions 4, 5, 7, and 8 reverse scored. Possible PSS-10 scores range from 0-40, with a higher score indicating more perceived stress

(77). There is no pre-determined cutoff for PSS-10 (90), therefore we categorized PSS-10 scores into quartiles, as has been done in previously in HCHS/SOL (6).

The Chronic Burden of Stress scale measures chronic stress over the past 6 months in 8 domains (personal health, health problems in family members, substance abuse in family members, financial stress, occupational stress, stress related to housing, relationship stress and caregiving stress) (77). This measure of chronic stress has been used in other multi-ethnic studies (92,93) and other Hispanic/Latino American populations (94). Chronic Burden of Stress counts the number of chronic stressors someone has experienced over the past 6 months or more, ranging from 0-8 (77). A chronic stressor was indicated by the participant identifying a problem as ongoing for 6 months or more, and found to be moderately to severely stressful (89). We categorized number of chronic stressors as 0, 1, 2, or ≥3, as has been done previously in HCHS/SOL (77).

PSS-10 and Chronic Burden of Stress have both been associated with chronic disease burden (75,95). In the current study we utilized both measures, as PSS-10 captures more recent stressors (past 30 days) and Chronic Burden of Stress captures longer-term stressors (past 6 months). Both Chronic Burden of Stress and PSS-10 have been associated with high depressive symptoms (CES-D ≥10) in HCHS/SOL (77). In relation to dietary intake, both PSS-10 and Chronic Burden of Stress were associated with significantly higher energy intake in HCHS/SOL (77), while only PSS-10 was associated with significantly lower AHEI-2010 score (77). HCHS/SOL participants

with obesity reported a greater number of chronic stressors than those who were normal or overweight (77).

Covariates

Demographic covariates

Models were adjusted for a number of covariates that may influence the associations of dietary and circulating omega-3 FAs and depression including total energy (25,96), sex (97,98), age (83,97), smoking status (5,99), physical activity (100,101), education level (102,103), history of CVD (83,104) or diabetes (105,106), marital status (83,107), household income (98,100) and Hispanic/Latino background (83,108). Demographic characteristics were self-reported during the baseline visit including sex, age, smoking status, physical activity, education level, marital status, household income and Hispanic/Latino background. Covariates are defined similarly to previous HCHS/SOL studies. Smoking status was defined as those currently smoking at baseline (yes or no) (5). Physical activity was defined as number of MET-mins per week based on self-reported responses to the Global Physical Activity Questionnaire. Education level was defined as less than high school, high school or equivalent, or greater than high school (83). Marital status was defined as married or living with a partner, single and divorced or widowed (83). Household income was reported dichotomously as ≤$30,000 per year or >$30,000 per year (75). Hispanic/Latino background was self-reported as Dominican, Central American, Cuban, Mexican, Puerto Rican, South American, or more than one heritage/other.

Clinical covariates

Clinical covariates include history of CVD and diabetes (DM). Participants were considered to have CVD if they had electrocardiogram record of possible old MI, or self-reported history of myocardial infarction (MI), coronary artery bypass surgery, percutaneous transluminal coronary angioplasty, and/or stroke (83). Participants were considered to have diabetes if they self-reported history of diabetes, had a fasting blood glucose of ≥126 mg/dL, blood glucose of >200 mg/dL on the oral glucose tolerance test, or had a glycosylated hemoglobin of ≥6.5% (109). Antidepressant use was ascertained by participants bringing all medications taken within the past four weeks to the field center during the baseline assessment (74,83).

Dietary covariates

Dietary covariates were collected using two 24-hour recalls and estimated using the NCI method, as described above. Dietary covariates included total energy (kcals/d), intake of fruit (servings/d), vegetables (servings/d), and added sugar (g/d). Further, omega-6 FA consumption and status were considered, as omega-3 FAs and omega-6 FAs share enzymatic pathways, and compete for desaturation and elongation into the longer chain forms (110). For dietary analyses, total omega-6 FA consumption (arachidonic acid and linoleic acid) were expressed as a percentage total FA intake. For metabolomic analyses, total circulating omega-6 FAs (adrenate, arachidonate, dihomolinoleate, docasdienoate, hexadecadienoate, and linoleate) were expressed as a percentage of total circulating fatty acids.

Statistical analysis

All analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC). The significance level was set at $P<0.05$ for analyses and $P<0.10$ for effect modification testing. Data were assessed for normality and skewness. Skewed data, baseline CES-D and 6-y CES-D, were normalized using a Box-Cox transformation (111). Data are presented as back-transformed means and standard errors to increase interpretability. For descriptive purposes, we examined differences in baseline sample characteristics (covariates described above) by quartile of dietary and circulating omega-3 VLCFA using survey linear regression in models adjusted for age and sex accordingly.

Analyses were conducted using survey linear regression to account for the complex survey design in HCHS/SOL. In dietary analyses, associations between baseline omega-3 FA consumption (EPA, DHA, and omega-3 VLCFA) and 6-y CES-D were analyzed. Two models were examined. Model 1 considered sex, age, smoking status, physical activity, education level, marital status, household income, Hispanic/Latino background, HCHS/SOL study site, antidepressant use, CVD status, diabetes status, baseline CES-D, time between visits, total energy intake and consumption of fruits, vegetables, and added sugar. Model 2 was further adjusted for dietary or circulating omega-6 FA. Analyses were stratified *a priori* by quartiles of PSS-10 and number of chronic stressors (0, 1, 2, ≥3). Similar analyses were conducted using circulating omega-3 FAs as the exposure. In a set of sensitivity analyses we excluded fish oil supplement users. Given that our dietary omega-3 FA exposure did not include intake from supplements, fish oil users would inherently consume additional omega-3 VLCFA that were unaccounted for, it is estimated that fish oil supplements contain an average of 180 mg of EPA

and 120 mg DHA (112). In addition, supplement users are more likely to engage in health-promoting behaviors (113) which could introduce residual confounding.

CHAPTER III: RESULTS

Sample Characteristics

Our final analytical sample (n = 3,537) for prospective analyses using dietary omega-3 FAs as the exposure was primarily female (63%) with a mean age of 47.6 ± 0.2 years (data not shown). Average time between baseline and follow up visits was 5.7 ± 0.01 years. At follow up, 26% of participants reported high depressive symptoms (CES-D ≥10) compared to 31% at baseline.

Those consuming greater amounts of omega-3 VLCFA were older, more physically active, and had higher income (**Table 1**). Further, higher omega-3 VLCFA consumption was seen among females and non-smokers. Additionally, higher omega-3 VLCFA consumption was associated with lower PSS-10 score and use of antidepressants ($p < 0.05$ for all). Those consuming more omega-3 VLCFA reported greater consumption of omega-6 FAs and fruit, as well as lower total energy intake and lower consumption of vegetables and added sugar ($p < 0.001$). There were no significant differences according to omega-3 VLCFA intake among BMI, education level, marital status, DM or CVD status, CES-D score at baseline or 6-y, or number of chronic stressors (Table 1).

Those with greater baseline circulating omega-3 VLCFA were more likely to have a lower BMI and higher education, be older, Dominican, from the Bronx, NY area, and married or living with a partner (**Supplemental Table 1**). Additionally, those with the highest baseline circulating

omega-3 VLCFA were less likely to have DM or smoke and report lower perceived and chronic stress ($p < 0.05$ for all, Supplemental Table 1). In terms of dietary characteristics, those with greater baseline circulating omega-3 VLCFA reported lower total energy and added sugar intake, and higher intakes of fruit and omega-3 VLCFA ($p < 0.05$ for all, Supplemental Table 1).

Associations between dietary omega-3 FAs and 6-y CES-D score

Baseline DHA and omega-3 VLCFA consumption were inversely associated with 6-y CES-D score after adjusting for clinical, demographic, and dietary covariates ($p < 0.05$) (**Figure 2**). These associations remained significant after adjusting for total omega-6 FA consumption ($p < 0.05$, Figure 2). Baseline EPA consumption tended to be inversely associated with 6-y CES-D score ($p < 0.10$, Figure 2), however this association was attenuated after adjusting for total omega-6 FA consumption.

When stratified by quartile of PSS-10 score, baseline EPA, DHA and omega-3 VLCFA consumption were associated with lower 6-y CES-D score among those with the highest level of perceived stress (Q4) after adjusting for demographic, clinical, and dietary covariates ($p < 0.05$) (**Table 2**). The strongest effect size was observed with EPA ($\beta = -1.00 \pm 5.59$, Table 2). Further, EPA consumption was inversely associated with 6-y CES-D score in Q2 of perceived stress ($p < 0.05$, Table 2). After adjusting for total omega-6 consumption, the PSS-10-stratified associations between DHA and omega-3 VLCFA consumption and 6-y CES-D score were attenuated (Table 2). However, the inverse association between EPA consumption and 6-y CES-D remained significant in Q2 of PSS-10 ($p < 0.05$, Table 2). Interestingly, after adjusting for total omega-6

FA consumption, DHA became significantly protective of 6-y CES-D score in Q3 of PSS-10 ($p < 0.05$, Table 2).

When stratified by number of ongoing chronic stressors (≥6 months), after adjusting for demographic, clinical, and dietary covariates we observed significant inverse associations between both DHA and omega-3 VLCFA consumption, but not EPA, with 6-y CES-D score among those reporting 2 chronic stressors ($p < 0.05$) (**Table 3**). Similarly, EPA trended towards an inverse association with 6-y CES-D score among those reporting 2 chronic stressors ($p < 0.10$, Table 3). After adjusting for total omega-6 consumption, the inverse associations between DHA and omega-3 VLCFA consumption with 6-y CES-D remained significant ($p < 0.05$, Table 3) and EPA remained trending towards significance ($p < 0.10$, Table 3). We did not observe any significant associations with any dietary omega-3 FA in any model among those reporting 0, 1, or ≥3 chronic stressors (Table 3).

Associations between circulating omega-3 FAs and 6-y CES-D score

Baseline circulating EPA, DHA, and omega-3 VLCFA were not associated with 6-y CES-D score after adjusting for clinical, demographic, and dietary covariates (**Figure 3**). These associations remained non-significant after adjusting for circulating total omega-6 FA (Figure 3).

When stratified by quartile of PSS-10 score, circulating EPA, DHA, and omega-3 VLCFA were not associated with 6-y CES-D score at any level of perceived stress after adjusting for clinical,

demographic, and dietary covariates (**Table 4**). These associations remained non-significant at all levels of perceived stress after adjusting for circulating total omega-6 FAs (Table 4).

When stratified by number of chronic stressors, circulating EPA, DHA, and omega-3 VLCFA were inversely associated with 6-y CES-D score among those reporting 2 chronic stressors after adjusting for clinical, demographic, and dietary covariates ($p < 0.01$) (**Table 5**). The strongest effect size was observed with DHA ($\beta = -0.99 \pm 0.62$, Table 5). EPA trended towards an inverse association among those reporting ≥3 chronic stressors ($p < 0.10$, Table 5). After adjusting for circulating total omega-6 FAs, the associations of circulating EPA, DHA, and omega-3 VLCFA with 6-y CES-D remained significant among those reporting 2 chronic stressors ($p < 0.01$, Table 5) and EPA remained trending towards an inverse association among those with ≥3 chronic stressors ($p < 0.10$, Table 5). DHA and omega-3 VLCFA were not associated with 6-y CES-D score among those reporting 0, 1, or ≥3 chronic stressors in either model (Table 3). EPA was not associated with 6-y CES-D among those reporting 0 or 1 chronic stressor in either model (Table 3).

Sensitivity Analyses

Sensitivity analyses were conducted excluding fish oil supplement users (n = 272, 8% for dietary analyses; n = 48, 7% for circulating analyses). After excluding those who reported using fish oil supplements, unstratified analyses of dietary omega-3 FAs with 6-y CES-D score remained unchanged, as consumption of DHA and omega-3 VLCFA were inversely associated with 6-y CES-D score in both Model 1 and Model 2 ($p < 0.05$) (**Supplementary Table 2**). When stratified

by quartile of PSS-10 score, EPA became positively associated with 6-y CES-D score among those in Q1 in both models (p <0.05, Supplementary Table 2). Further, EPA remained inversely associated with 6-y CES-D score among those in Q2 in Model 1, however the association was attenuated after adjusting for total omega-6 FA consumption (p >0.05, Supplementary Table 2). Additionally, EPA was no longer inversely associated with 6-y CES-D in Q4 in Model 1. Similar to our primary findings, DHA and omega-3 VLCFA were inversely associated with 6-y CES-D in Q4 in Model 1, but the associations were attenuated after adjusting for omega-6 FA consumption. DHA consumption was now significantly inversely associated with 6-y CES-D in Q3 in Model 1 and Model 2, whereas in our main findings DHA was only inversely associated with 6-y CES-D in Q3 of Model 2 (p <0.05, Supplementary Table 2). When stratified by chronic stress, dietary omega-3 VLCFA were no longer associated with 6-y CES-D among those reporting 2 chronic stressors in Model 1, however the association was significant after adjusting for total omega-6 FA consumption, similar to our primary findings. There were no changes in any other dietary omega-3 FA by level of chronic stress. For circulating omega-3 FAs, there were no changes in our results after excluding fish oil consumers (**Supplementary Table 3**).

CHAPTER IV: DISCUSSION

Among a cohort of Hispanic/Latino adults, we observed inverse associations between DHA and omega-3 VLCFA consumption with 6-y depressive symptoms after adjusting for baseline depressive symptoms and demographic, clinical, and dietary covariates. These results remained significant after accounting for total omega-6 FA consumption. When considering psychosocial stress, EPA, DHA, and omega-3 VLCFA consumption were inversely associated with 6-y depressive symptoms among those with the highest (Q4) perceived stress. However, these associations were attenuated after accounting for omega-6 FA consumption. When considering a longer-term measure of stress (past 6 months), DHA and omega-3 VLCFA consumption were inversely associated with 6-y depressive symptoms among those who reported experiencing 2 chronic stressors. These associations remained significant after accounting for total omega-6 FA intake. We observed null associations between circulating omega-3 FA and 6-y depressive symptoms in this cohort in unstratified analyses or at any level of perceived stress. However, similarly to our dietary analyses, there were protective associations on 6-y depressive symptoms with circulating EPA, DHA, and omega-3 VLCFA among those who reported 2 chronic stressors, regardless of total omega-6 FA status. To the best of our knowledge, this is the first study to examine the associations between omega-3 FA and depressive symptoms according to level of psychological stress.

Unstratified associations between dietary and plasma omega-3 FA with 6-y depressive symptoms

We observed protective associations of DHA and omega-3 VLCFA consumption on 6-y depressive symptoms. Previous literature supports inverse associations between omega-3 FA intake and depressive symptoms (55–57). However, the bulk of the literature pertaining to omega-3 FA consumption and depressive symptoms is cross-sectional, therefore interpretations may be hindered by reverse causality. Our findings help to strengthen this body of literature by using a prospective design. Among previous research that has examined these associations longitudinally, the majority found null associations (25,114–116). However, a recent meta-analysis of observational studies found an overall pooled effect of EPA+DHA consumption with a lower risk of depression (RR 0.78 95% CI: 0.67, 0.92) (14). In a sub-analysis, a stronger relationship between EPA+DHA consumption and depression was found in longitudinal studies versus cross-sectional (14). We found DHA consumption, but not EPA, to be protective of 6-y depressive symptoms. In a sub-analysis in the aforementioned meta-analysis of observational studies examining omega-3 FA consumption and depressive symptoms, a null association was found regarding the association between DHA consumption alone and depressive symptoms (14). However, in a study of Greek adults, DHA in the adipose tissue was inversely associated with depressive symptoms in cross-sectional analyses (117). Although EPA is typically considered to be more beneficial than DHA on reducing depressive symptoms, as has been supported by meta-analyses of RCTs (48,118), doses of EPA in RCTs ranged from 0.63 - 6.2 g/d (48), whereas consumption in our sample ranged from 0.008 – 0.12 g/d EPA, which likely limited our ability to detect an effect.

We did not observe an association between circulating omega-3 FA and 6-y depressive symptoms. Consistent with our findings, some studies show that there is no association between omega-3 FA status and depressive symptoms longitudinally (5,119). However, one study sample had a low rate of high baseline depressive symptoms at 8% (119), and another had a relatively short follow up of 2 years (5), which may have contributed to finding null associations. Conversely, a cross-sectional study among Greek adults found that plasma omega-3 FAs were inversely associated with depressive symptoms (55). However, this sample had considerably higher levels of circulating omega-3 FA compared to our sample. Therefore, low circulating levels in our sample may have limited our ability to detect an association. Further, we used plasma levels of omega-3 FAs to determine omega-3 status, which is indicative of omega-3 FA consumption over a short period (days to weeks) (120). Research using biochemical measures of longer-term intake, such as red blood cells or adipose tissue (120) is warranted. Additionally, our sample size for analyses using circulating omega-3 FA was considerably smaller than our sample for dietary analyses, which may have weakened our power to detect an association.

Associations between dietary omega-3 FA and 6-y depressive symptoms stratified by quartiles of PSS-10

In agreement with our hypothesis, dietary DHA and omega-3 VLCFA were inversely associated with depressive symptoms among those experiencing the highest perceived stress (Q4). There is evidence to support that perceived stress is associated with greater levels of markers for inflammation (121) and oxidative stress (122). Therefore, these findings are supported by previous studies that have found the anti-depressant effects of omega-3 FAs to be enhanced among those with higher levels of oxidative stress (5,18). Similar to our findings, a sub-analysis

of one study among Puerto Rican adults found that erythrocyte DHA, not EPA, was significantly protective of 2-y depressive symptoms among those with the highest oxidative stress (5). It is possible that the different metabolites of EPA and DHA may provide unique physiological benefits. For example, the DHA-derived metabolite, neuroprotectin D1, may protect the brain from oxidative damage (123), as evidenced by neuronal cell culture and animal model studies (124,125).

We observed attenuation of the protective associations of EPA, DHA, and omega-3 VLCFA consumption on 6-y depressive symptoms after adjusting for total omega-6 FA consumption. The aforementioned epidemiological studies examining the modifying effect of oxidative stress on the association between omega-3 FA and depressive symptoms did not account for omega-6 FA status or consumption, which impedes our ability to elucidate if this is a unique finding. Our consideration of omega-6 FAs is novel and will help to expand this field of literature. However, a secondary analysis of an RCT found a greater benefit of omega-3 FA supplementation on depressive symptoms among those with high baseline lipid peroxidation, supporting that the beneficial effects were attributable to omega-3 FAs (18). Given that omega-3 FA and omega-6 FA compete for elongation and desaturation by sharing enzymatic pathways, higher consumption of omega-6 FA reduces the metabolism of omega-3 FA into the longer chain forms (110). The handful of epidemiological studies that adjusted for omega-6 FA consumption when analyzing the associations between omega-3 FA and depressive symptoms have mixed findings (25,35). Although commonly thought to be pro-inflammatory, there is evidence that some eicosanoids produced from arachidonic acid, such as prostaglandin E_2 and lipoxin A_4, may have anti-inflammatory properties (126,127). However, there is evidence to support that patients with

major depressive disorder have greater plasma omega-6 FAs compared to non-depressed controls (129) and that omega-6 FA consumption is positively associated with depressive symptoms (130). More longitudinal studies using objective markers of omega-3 FA and omega-6 FA are needed to clarify the relationship between omega-3 FAs, omega-6 FAs, and depressive symptoms.

Associations between dietary and circulating omega-3 FA stratified by number of chronic stressors

In an unexpected finding, both dietary and circulating omega-3 FAs were inversely associated with 6-y depressive symptoms among those who reported experiencing 2 chronic stressors, but not among those with the highest chronic stress (≥3 chronic stressors) as we had hypothesized. In HCHS/SOL, Chronic Burden of Stress has been shown to be positively associated with chronic diseases such as DM, HTN, and CHD cross-sectionally (75), supporting Chronic Burden of Stress as a potential predictor of pathophysiological effects of stress. Further, a shortened version of the Chronic Burden of Stress was positively associated with interleukin (IL) 6 and C-reactive protein in a multi-ethnic cohort (131), suggesting a positive association between this measure of chronic stress and inflammation. To the best of our knowledge, the effect of psychological stress on the association between omega-3 FA and depressive symptoms has yet been studied in humans. However, in animal models omega-3 FA supplementation appears to reduce depressive symptoms after exposure to chronic stress (132,133).

Interestingly, we observed the strongest associations between omega-3 FA status and consumption with 6-y depressive symptoms among those who reported experiencing 2 chronic

stressors. Those who reported experiencing 2 chronic stressors had the highest prevalence of baseline CVD compared to those experiencing 0, 1, or ≥3 stressors (7.4% vs. 3.4-6.9%), potentially suggesting that they had a higher overall oxidative stress load (134). Additionally, those who were experiencing ≥3 chronic stressors had a considerably higher rate of antidepressant medication use (12.7%) compared to those with 0, 1, or 2 stressors (3.1-5.7%). Higher rates of antidepressant use suggests that these individuals may have more access and utilization of health care services. Therefore, although those with ≥3 chronic stressors are experiencing the greatest number stressors, they may have more resources to cope with stress therefore weakening the negative physiological effects. Additionally, it is possible that those experiencing ≥3 chronic stressors may be more resilient towards stress, and therefore have less of a physiological response, as evidence suggests that after repeated exposure to a stressor there can be a diminished response to future stressors of the same type (136).

Biological Plausibility

Oxidative stress, an imbalance of reactive oxygen species (ROS) production and antioxidant activity, can contribute to onset of depressive symptoms through damage of DNA, lipids, and proteins. Oxidative stress-induced damage of DNA and proteins is implicated in neurodegeneration (63,137), a characteristic of depression (138,139) (**Figure 4**). Lipid peroxidation as a result of oxidative stress can alter cellular membrane structure, potentially affecting neuronal signaling (63). Treatment with antidepressant medications has been shown to reduce oxidative stress (140,141), providing further support for the role of oxidative stress in depression.

Inflammation and oxidative stress are related processes, such that inflammation can induce oxidative stress and vice versa (142) (Figure 4). This cyclical relationship occurs via several physiological mechanisms. For example, when activated, immune cells produce ROS as a cellular defense mechanism (143). Conversely, oxidative stress can induce inflammation via several mechanisms. For example, ROS can activate NF-κB (144), a pro-inflammatory transcription factor. Additionally, 8-isoprostane, a byproduct of lipid peroxidation, has been shown to upregulate the production of IL-8, an inflammatory cytokine (145).

Inflammation is implicated in the development of depression by affecting neurotransmitter synthesis and inducing neuroinflammation (31) (Figure 4). Inflammatory cytokines can induce depressive symptoms by activating the IDO pathway, which diverts metabolism of tryptophan away from serotonin production and towards production of TRYCATs (146). TRYCATs are neurotoxic byproducts of the IDO pathway that may contribute to depressive symptoms (146). In mice, lipopolysaccharide-induced systemic inflammation lead to neuroinflammation and subsequent neurodegeneration (147). In humans undergoing treatment for cancer or hepatitis C with the administration of pro-inflammatory cytokines, IL-2 and interferon-α , over one third of patients are estimated to develop depression (148). The influence of inflammation on depressive symptoms is further corroborated by evidence that antidepressant medications reduce inflammation (149).

Psychological stress can induce both oxidative stress and systemic inflammation (61,150). Oxidative stress is hypothesized to be a physiological link between psychological stress and depression (12). Psychological stress can lead to the activation of NF-κB (12) which promotes both oxidative stress and inflammation by increasing production of ROS and pro-inflammatory cytokines (151,152). Omega-3 FAs are widely recognized for exerting anti-inflammatory effects in the body. These anti-inflammatory effects are a result of a number of physiological mechanisms including activation of anti-inflammatory processes and mitigation of pro-inflammatory processes. Metabolic byproducts synthesized from EPA and DHA via cyclooxygenase and lipoxygenase enzyme activity, including E-series resolvins, derived from EPA, and D-series resolvins and protectins derived from DHA, are potent anti-inflammatory mediators (28). These bioactive molecules are able to both dampen the inflammatory response (128), as well as promote resolution of existing inflammation (28). Further, EPA and the omega-6 FA arachidonic acid (ARA) can both lead to the synthesis of eicosanoids, as they each contain a 20-carbon chain. However, while eicosanoids derived from ARA are potently pro-inflammatory, EPA-derived eicosanoids are estimated to be 10-100 times less inflammatory than those from ARA (128). EPA reduces ARA-mediated inflammation by reducing the rate at which ARA-derived eicosanoids are synthesized and leading to the synthesis of much less potent eicosanoids. In addition, omega-3 FAs can mitigate pro-inflammatory cytokine production (153,154) and reduce the activity of NF-κB (155). Some evidence suggests that omega-3 FAs may mitigate oxidative stress by reducing ROS production (30) and upregulating endogenous antioxidant activity (156). However, given the potent anti-inflammatory properties of omega-3 FAs discussed above, the omega-3 FA-induced reduction in inflammation is likely contributing to mitigation of oxidative stress.

Strengths and Limitations

There are several strengths to our current study. We used a prospective design, which reduces the possibility of reverse causality that would be present in a cross-sectional design. Further, our analytical sample size is larger than previous studies in this field. We also used an objective measure of omega-3 FAs in conjunction with dietary measures, which may help clarify some of the error that is inherently introduced when relying on self-reported dietary data. By using measures of both recent (past 30 days) and chronic (past 6 months) psychological stress, we were able to capture a wide range of stressors.

Although there are many strengths of our study, several limitations exist. Dietary intake was only available at baseline, leading us to assume no variation in intake over the six year follow up. Additionally, diet was measured using two 24-hour recalls, whereas the use of three 24-hour recalls is typically recommended to improve accuracy (157,158). This discrepancy may have contributed to misclassification errors. However, the use of the NCI method increased the accuracy of estimating usual dietary intakes. Further, plasma omega-3 FAs are a biomarker that is relevant to the past several days to weeks (120), and do not reflect as long of a time period as other biomarkers of omega-3 FAs. Although we considered a number of potential confounding variables, residual confounding is still a concern.

Conclusions

We found that DHA and omega-3 VLCFA consumption was associated with lower 6-y depressive symptoms in a cohort of Hispanic/Latino adults living in the US. In addition, we found that dietary DHA and omega-3 VLCFA and plasma EPA, DHA, and omega-3 VLCFA were inversely associated with 6-y depressive symptoms among those who reported experiencing two chronic stressors. These findings provide support that omega-3 FA consumption may reduce depressive symptoms in a Hispanic/Latino cohort. Future studies are needed to analyze these associations using objective measures of omega-3 FA that are representative of longer term intake of omega-3 FAs in longitudinal studies.

Table 1. Sample characteristics by quartile of baseline omega-3 VLCFA consumption[1]

	Dietary Omega-3 VLCFA (Quartile)[2]				
	Q1 n=884	**Q2** n=884	**Q3** n=885	**Q4** n=884	**P-trend**
BMI	29.9 ± 0.26	29.5 ± 0.30	29.5 ± 0.25	30.2 ± 0.35	0.09
Age, years	42.4 ± 0.81	43.0 ± 0.66	42.7 ± 0.78	47.6 ± 0.93	<0.001
Female, %	49.9	53.1	60.2	63.2	<0.001
Hispanic/Latino Background					
Dominican, %	1.9	4.5	10.5	27.5	<0.001
Central American, %	6.7	7.6	8.0	5.9	0.38
Cuban, %	37.41	19.32	9.67	4.32	<0.001
Mexican,%	36.6	43.7	48.7	30.9	0.06
Puerto Rican, %	14.0	18.8	15.2	16.1	0.59
South American, %	1.0	3.5	6.2	11.9	<0.001
Multiple/Other, %	2.5	2.6	1.7	3.5	0.30
HCHS Site					
Bronx, %	13.8	21.0	29.2	56.3	<0.001
Chicago, %	19.9	20.0	13.4	8.4	<0.001
Miami, %	45.0	29.2	19.3	10.7	<0.001
San Diego, %	21.2	29.8	38.1	24.6	0.54
<HS, %	26.4	31.9	29.8	34.1	0.09
HS or equivalent, %	34.2	25.1	26.4	26.2	0.37
>HS, %	39.4	43.0	43.8	39.7	0.39
Income >$30,000, %	26.6	29.8	35.5	31.8	<0.05
Marital Status					
Single, %	33.5	31.1	31.3	28.2	0.78
Married/Living with a Partner, %	50.8	50.6	51.6	50.2	0.93
Separated/Divorced, %	15.7	18.4	17.1	21.6	0.87
Diabetes, %	15.5	18.0	16.4	20.5	0.65
Cardiovascular Disease, %	4.3	5.3	4.6	5.7	0.48
Physical Activity, MET-mins/d	626 ± 58.4	543 ± 47.1	554 ± 34.2	741 ± 50.2	<0.05
Smoking, %	24.8	20.8	15.8	13.1	<0.001
Antidepressant use, %	6.9	5.1	6.3	3.9	<0.05
Energy, Kcals	2116 ± 22	2019 ± 21	1905 ± 17	1748 ± 22	<0.001
Vegetables, servings/d	2.10 ± 0.03	2.04 ± 0.03	2.01 ± 0.03	1.89 ± 0.04	<0.001
Fruit, servings/d	1.00 ± 0.03	1.06 ± 0.03	1.18 ± 0.04	1.28 ± 0.04	<0.001
Added sugar g/d	69.0 ± 1.1	69.4 ± 1.2	64.8 ± 1.2	56.3 ± 1.2	<0.001
Dietary Omega-3 VLCFA, %FA	0.117 ± 0.003	0.168 ± 0.003	0.219 ± 0.003	0.333 ± 0.004	<0.001
Dietary EPA, %FA	0.024 ± 0.001	0.035 ± 0.001	0.047 ± 0.001	0.074 ± 0.002	<0.001
Dietary DHA, %FA	0.070 ± 0.002	0.102 ± 0.002	0.132 ± 0.002	0.195 ± 0.003	<0.001
Dietary Total Omega-6, %FA	19.2 ± 0.14	19.6 ± 0.13	19.7 ± 0.12	20.2 ± 0.13	<0.001

Baseline CES-D	6.0 ± 0.1	5.5 ± 0.1	5.2 ± 0.1	5.4 ± 0.1	0.23
6-y CES-D	5.2 ± 0.1	4.9 ± 0.1	4.7 ± 0.1	4.7 ± 0.1	0.50
PSS-10 score	15.2 ± 0.3	14.7 ± 0.3	14.1 ± 0.3	13.9 ± 0.3	<0.001
Number of Chronic Stressors	1.3 ± 0.1	1.3 ± 0.1	1.2 ± 0.1	1.1 ± 0.1	0.32

[1] Values are age- and sex-adjusted means ± SE or proportions by quartile of omega-3 VLCFA consumption as % total fat using proc surveyreg and proc freq, respectively, in SAS. Q, quartile; HCHS, Hispanic Community Health Study; HS, high school education; MET, metabolic equivalent; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid; CES-D, 10-item Center for Epidemiological Studies Depression Scale; PSS-10, 10-Item Perceived Stress Scale.

[2] VLCFA, very-long-chain fatty acids, omega-3 VLCFA was calculated as the sum of EPA, DHA, and DPA.

Table 2. Associations between baseline omega-3 FA consumption and 6-y CES-D score stratified by quartile of PSS-10 score[1,2]

	PSS-10 Score[3]			
	Q1	**Q2**	**Q3**	**Q4**
	5.83 ± 0.09	**12.02 ± 0.05**	**16.97 ± 0.05**	**23.71 ± 0.12**
	n=806	n=915	n=930	n=886
Model 1				
EPA	17.1 ± 5.68†	**-0.977 ± 5.44***	-0.975 ± 5.91	**-0.998 ± 5.59***
DHA	1.30 ± 1.75	-0.902 ± 1.46†	-0.959 ± 1.79†	**-0.984 ± 1.64***
VLCFA[4]	0.747 ± 0.853	-0.729 ± 0.752†	-0.668 ± 0.862	**-0.851 ± 0.828***
Model 2				
EPA	18.6 ± 5.75†	**-0.985 ± 5.56***	-0.987 ± 6.80	-0.999 ± 5.59
DHA	1.45 ± 1.77	-0.884 ± 1.48	**-0.977 ± 1.93***	-0.914 ± 1.62†
VLCFA[4]	0.822 ± 0.863	-0.709 ± 0.766†	-0.717 ± 0.935	-0.707 ± 0.830

[1] Values are β ± SE estimates using multivariable survey linear regression. CES-D, 10-Item Center for Epidemiological Studies Depression Scale; Q, Quartile; PSS-10, 10-Item Perceived Stress Scale; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid; VLCFA, very long chain omega-3 fatty acids. Omega-3 FA consumption expressed as percent of total fat intake. †P=0.05 to <0.10; *P<0.05; **P<0.01.
[2] Model 1 was adjusted for sex, BMI, age, total energy intake, diabetes status, education level, smoking status, study site, physical activity, cardiovascular disease status, marital status, Hispanic/Latino background, income, antidepressant use, baseline CES-D score, time between visits, and intake of total energy, fruit, vegetables, and added sugar. Model 2 adjusting for Model 1 + total omega-6 FA consumption.
[3] Mean ± SE PSS-10 score by quartile.
[4] VLCFA calculated as the sum of EPA, DHA, and DPA (docosapentaenoic acid).

Table 3. Associations between baseline omega-3 FA consumption and 6-y CES-D score stratified by number of chronic stressors[1,2]

	Number of Chronic Stressors			
	0	**1**	**2**	**3+**
	n=1590	n=747	n=527	n=673
Model 1				
EPA	-0.643 ± 3.84	-0.761 ± 7.62	-0.689 ± 14.5†	-0.959 ± 7.27
DHA	-0.701 ± 1.39	-0.735 ± 2.07	**-1.00 ± 3.03***	-0.614 ± 1.85
VLCFA[3]	-0.434 ± 0.67	-0.316 ± 1.02	**-0.944 ± 1.46***	-0.443 ± 0.916
Model 2				
EPA	-0.713 ± 4.16	0.832 ± 7.26	-0.268 ± 15.6†	-0.797 ± 8.23
DHA	-0.751 ± 1.52	0.035 ± 1.99	**-1.00 ± 3.39***	-0.325 ± 1.99
VLCFA[3]	-0.483 ± 0.73	0.386 ± 0.981	**-0.971 ± 1.60***	-0.238 ± 0.988

[1] Values are β ± SE estimates using multivariable survey linear regression. CES-D, 10-Item Center for Epidemiological Studies Depression Scale; Q, Quartile; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid; VLCFA, very long chain omega-3 fatty acids. Omega-3 FA consumption expressed as percent of total fat intake. †P=0.05 to <0.10; *P<0.05; **P<0.01.

[2] Model 1 was adjusted for sex, BMI, age, total energy intake, diabetes status, education level, smoking status, study site, physical activity, cardiovascular disease status, marital status, Hispanic/Latino background, income, antidepressant use, baseline CES-D score, time between visits, and intake of total energy, fruit, vegetables, and added sugar. Model 2 adjusting for Model 1 + total omega-6 FA consumption.

[3] VLCFA calculated as the sum of EPA, DHA, and DPA (docosapentaenoic acid).

Table 4. Associations between circulating omega-3 FAs and 6-y CES-D score stratified by quartile of PSS-10 score[1,2]

	PSS-10 Score[3]			
	Q1	**Q2**	**Q3**	**Q4**
	6.35 ± 0.2	**13.06 ± 0.1**	**17.48 ± 0.08**	**23.53 ± 0.29**
	n=202	n=189	n=170	n=157
Model 1				
EPA	0.293 ± 0.775	-0.893 ± 2.17	-0.169 ± 0.973	-0.481 ± 1.93
DHA	-0.087 ± 0.403	0.114 ± 0.490	-0.192 ± 0.310	-0.014 ± 0.333
VLCFA[4]	-0.022 ± 0.246	-0.064 ± 0.366	-0.159 ± 0.210	-0.058 ± 0.228
Model 2				
EPA	0.296 ± 0.777	-0.906 ± 2.28	0.113 ± 0.999	-0.402 ± 2.16
DHA	-0.088 ± 0.404	0.121 ± 0.483	-0.128 ± 0.298	0.079 ± 0.336
VLCFA[4]	-0.022 ± 0.247	-0.062 ± 0.364	-0.116 ± 0.208	0.006 ± 0.240

[1] Values are β ± SE estimates using multivariable survey linear regression. CES-D, 10-Item Center for Epidemiological Studies Depression Scale; Q, Quartile; PSS-10, 10-Item Perceived Stress Scale; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid; VLCFA, very long chain fatty acids. Circulating omega-3 FA expressed as percent of total circulating fatty acids.*P<0.05.

[2] Model 1 was adjusted for sex, BMI, age, total energy intake, diabetes status, education level, smoking status, study site, physical activity, cardiovascular disease status, marital status, Hispanic/Latino background, income, antidepressant use, baseline CES-D score, time between visits, and intake of total energy, fruit, vegetables, and added sugar. Model 2 adjusting for Model 1 + total circulating omega-6 FA.

[3] Mean ± SE PSS-10 score by quartile.

[4] VLCFA calculated as the sum of EPA, DHA, and DPA (docosapentaenoic acid).

Table 5. Associations between circulating omega-3 FAs and 6-y CES-D score stratified by number of chronic stressors[1,2]

	Number of Chronic Stressors			
	0	**1**	**2**	**3+**
	n=316	n=168	n=101	n=133
Model 1				
EPA	1.14 ± 1.03	0.314 ± 0.924	**-0.863 ± 3.20****	-0.887 ± 1.42†
DHA	0.223 ± 0.327	0.170 ± 0.292	**-0.994 ± 0.618****	-0.279 ± 0.327
VLCFA[3]	0.234 ± 0.218	0.093 ± 0.207	**-0.937 ± 0.387****	-0.288 ± 0.230
Model 2				
EPA	1.23 ± 1.03	0.444 ± 0.893	**-0.815 ± 3.30****	-0.908 ± 1.48†
DHA	0.228 ± 0.325	0.204 ± 0.285	**-0.993 ± 0.629****	-0.277 ± 0.350
VLCFA[3]	0.233 ± 0.218	0.115 ± 0.200	**-0.936 ± 0.393****	-0.292 ± 0.241

[1] Values are β ± SE estimates using multivariable survey linear regression. CES-D, 10-Item Center for Epidemiological Studies Depression Scale; Q, Quartile; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid; VLCFA, very long chain fatty acids. Circulating omega-3 FA expressed as percent of total circulating fatty acids. †P=0.05 to <0.10, *P<0.05, **P<0.01.

[2] Model 1 was adjusted for sex, BMI, age, total energy intake, diabetes status, education level, smoking status, study site, physical activity, cardiovascular disease status, marital status, Hispanic/Latino background, income, antidepressant use, baseline CES-D score, time between visits, and intake of total energy, fruit, vegetables, and added sugar. Model 2 adjusting for Model 1 + total circulating omega-6 FA.

[3] VLCFA calculated as the sum of EPA, DHA, and DPA (docosapentaenoic acid).

Supplementary Table 1. Sample characteristics by quartile of baseline circulating omega-3 VLCFA[1]

	Circulating Omega-3 VLCFA (Quartile)[2]				
	Q1 n=179	**Q2** n=180	**Q3** n=180	**Q4** n=179	**P-trend**
BMI	32.2 ± 0.78	30.9 ± 0.72	29.5 ± 0.55	30.0 ± 0.94	<0.05
Age, years	38.7 ± 1.4	43.6 ± 1.2	44.0 ± 1.6	49.3 ± 2.3	<0.001
Female, %	51.5	46.9	57.0	48.2	0.07
Hispanic/Latino Background					
Dominican, %	3.0	2.0	9.3	18.4	<0.001
Central American, %	6.7	6.2	6.9	3.1	0.07
Cuban, %	13.8	32.1	20.4	20.0	0.47
Mexican,%	43.3	41.0	41.2	26.3	0.28
Puerto Rican, %	23.7	16.0	14.4	23.3	<0.05
South American, %	4.1	2.4	6.3	9.0	0.06
Multiple/Other, %	5.5	0.31	1.6	0	0.07
HCHS Site					
Bronx, %	23.0	25.0	27.0	46.4	<0.05
Chicago, %	20.6	13.5	9.34	9.67	0.13
Miami, %	27.6	34.8	30.6	23.6	<0.05
San Diego, %	28.8	26.7	33.1	20.4	0.70
<HS, %	28.3	24.7	24.2	22.6	0.53
HS or equivalent, %	33.4	35.1	22.7	20.5	<0.05
>HS, %	38.3	40.3	53.1	57.0	<0.05
Income >$30,000, %	35.5	37.3	36.0	38.6	<0.05
Marital Status					
Single, %	43.0	36.7	32.6	16.8	<0.05
Married/Living with a Partner, %	42.2	48.8	50.3	56.1	<0.05
Separated/Divorced, %	14.9	14.5	17.0	27.1	0.41
Diabetes, %	19.4	20.2	10.6	8.49	<0.001
Cardiovascular Disease, %	4.30	3.72	5.05	5.75	0.59
Physical Activity, MET-mins/d	711 ± 147	697 ± 124	615 ± 94.6	658 ± 108	0.77
Smoking, %	17.8	27.6	19.9	10.0	<0.05
Antidepressant use, %	6.09	5.39	2.32	5.15	0.87
Energy, Kcals/d	1947 ± 48	2015 ± 46	1913 ± 43	1905 ± 70	<0.05
Vegetables, servings/d	1.86 ± 0.06	1.99 ± 0.07	1.99 ± 0.08	2.07 ± 0.07	0.35
Fruit, servings/d	0.94 ± 0.06	0.96 ± 0.05	1.06 ± 0.06	1.18 ± 0.09	<0.05
Added sugar, g/d	70.9 ± 2.8	68.9 ± 2.1	64.0 ± 2.0	60.1 ± 2.0	<0.001
Dietary VLCFA, % FA	0.18 ± 0.006	0.18 ± 0.008	0.21 ± 0.008	0.24 ± 0.009	<0.001
Dietary EPA, % FA	0.037 ± 0.003	0.037 ± 0.004	0.044 ± 0.004	0.051 ± 0.005	<0.001
Dietary DHA, % FA	0.11 ± 0.003	0.11 ± 0.005	0.12 ± 0.005	0.14 ± 0.005	<0.001

Dietary Total Omega-6 FA, % FA	19.56 ± 0.3	19.51 ± 0.3	19.93 ± 0.2	19.67 ± 0.3	1.00
Baseline CES-D score	5.7 ± 0.1	5.5 ± 0.2	5.6 ± 0.1	4.3 ± 0.1	0.05
6-y CES-D score	5.6 ± 0.2	5.5 ± 0.2	3.9 ± 0.2	3.4 ± 0.2	<0.05
PSS-10 score	15.4 ± 0.6	15.0 ± 0.7	13.9 ± 0.5	12.1 ± 0.5	<0.001
Number of Chronic Stressors	1.7 ± 0.2	1.3 ± 0.2	1.1 ± 0.1	1.1 ± 0.2	<0.05
Circulating EPA, % FA	0.07 ± 0.003	0.10 ± 0.01	0.13 ± 0.004	0.23 ± 0.01	<0.001
Circulating DHA, % FA	0.40 ± 0.01	0.57 ± 0.01	0.74 ± 0.01	1.10 ± 0.03	<0.001
Circulating VLCFA, % FA	0.61 ± 0.01	0.85 ± 0.01	1.09 ± 0.01	1.59 ± 0.05	<0.001
Circulating Omega-6 FA, % FA	19.8 ± 0.3	19.5 ± 0.2	19.9 ± 0.2	20.1 ± 0.3	0.31

[1] Values are age- and sex-adjusted means ± SE or proportions by quartile of circulating omega-3 VLCFA as % total circulating fatty acids using proc surveyreg and proc freq, respectively, in SAS. Q, quartile; HCHS, Hispanic Community Health Study; HS, high school education; MET, metabolic equivalent; CES-D, 10-item Center for Epidemiological Studies Depression Scale; PSS-10, 10-Item Perceived Stress Scale; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid; VLCFA, very long chain fatty acids.
[2] VLCFA calculated as the sum of EPA, DHA, and DPA (docosapentaenoic acid).

Supplementary Table 2. Associations between baseline omega-3 FA consumption and 6-y CES-D score excluding fish oil users[1,2]

		PSS-10 Score				Number of Chronic Stressors			
	Unstratified	**Q1**	**Q2**	**Q3**	**Q4**	**0**	**1**	**2**	**3+**
Model 1									
EPA	-0.946 ± 2.28	**26.1 ± 6.06***	**-0.998 ± 5.70***	-0.992 ± 6.68	-1.00 ± 5.31†	-0.621 ± 3.94	-0.926 ± 9.42	-0.753 ± 17.0	-0.889 ± 7.39
DHA	**-0.877 ± 0.879***	2.01 ± 1.99	-0.816 ± 1.49	**-0.979 ± 1.89***	**-0.980 ± 1.58***	-0.715 ± 1.46	-0.889 ± 2.34	**-1.00 ± 3.52***	-0.558 ± 1.90
VLCFA[3]	**-0.614 ± 0.447***	1.11 ± 0.939	-0.640 ± 0.773	-0.720 ± 0.915	**-0.833 ± 0.799***	-0.438 ± 0.699	-0.506 ± 1.15	-0.951 ± 1.64†	-0.375 ± 0.935
Model 2									
EPA	-0.919 ± 2.41	**26.8 ± 6.09***	-0.999 ± 5.81†	-0.999 ± 7.70	-1.00 ± 5.32	-0.733 ± 4.20	-0.186 ± 9.11	-0.433 ± 18.3†	-0.611 ± 8.29
DHA	**-0.863 ± 0.936***	2.09 ± 2.00	-0.792 ± 1.51	**-0.993 ± 2.04***	-0.932 ± 1.56†	-0.784 ± 1.58	-0.513 ± 2.24	**-1.00 ± 3.94***	-0.249 ± 2.02
VLCFA[3]	**-0.592 ± 0.474***	1.15 ± 0.944	-0.620 ± 0.788	-0.786 ± 0.994†	-0.731 ± 0.800†	-0.510 ± 0.746	-0.015 ± 1.11	**-0.974 ± 1.81***	-0.160 ± 0.999

[1] Values are β ± SE estimates using multivariable survey linear regression. CES-D 10, 10-Item Center for Epidemiological Studies Depression Scale; Q, Quartile; PSS-10, 10-Item Perceived Stress Scale; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid; VLCFA, very long chain fatty acids. Omega-3 FA consumption expressed as % of total fat intake. N=272 (8%) of original analytic sample used fish oil supplement. †P=0.05 to <0.10; *P<0.05; **P<0.01.

[2] Model 1 was adjusted for sex, BMI, age, total energy intake, diabetes status, education level, smoking status, study site, physical activity, cardiovascular disease status, marital status, Hispanic/Latino background , income, antidepressant use, baseline CES-D score, time between visits, and intake of total energy, fruit, vegetables, and added sugar. Model 2 adjusting for Model 1 + total omega-6 FA consumption.

[3] VLCFA calculated as the sum of EPA, DHA, and DPA (docosapentaenoic acid).

Supplementary Table 3. Associations between baseline circulating omega-3 FA and 6-y CES-D score excluding fish oil users[1,2]

		PSS-10 Score				Number of Chronic Stressors			
	Unstratified	**Q1**	**Q2**	**Q3**	**Q4**	**0**	**1**	**2**	**3+**
Model 1									
EPA	-0.358 ± 1.107	1.19 ± 1.05	-0.895 ± 2.523	-0.083 ± 1.31	-0.879 ± 2.75	1.35 ± 1.19	0.590 ± 4.24	**-0.031 ± 4.62****	-0.837 ± 1.34
DHA	-0.144 ± 0.282	0.195 ± 0.495	0.079 ± 0.595	0.158 ± 0.342	-0.348 ± 0.379	0.238 ± 0.350	0.421 ± 0.354	**-1.00 ± 0.654****	-0.212 ± 0.309
VLCFA[3]	-0.129 ± 0.211	0.174 ± 0.291	-0.119 ± 0.434	0.044 ± 0.248	-0.314 ± 0.272	0.250 ± 0.230	0.255 ± 0.305	**-0.980 ± 0.427****	-0.246 ± 0.218
Model 2									
EPA	-0.287 ± 1.097	1.16 ± 1.09	-0.890 ± 2.57	0.978 ± 1.30	-0.875 ± 2.81	1.42 ± 1.17	1.04 ± 4.02	**0.521 ± 4.875****	-0.820 ± 1.41
DHA	-0.138 ± 0.281	0.200 ± 0.501	0.063 ± 0.579	0.359 ± 0.330	-0.339 ± 0.374	0.253 ± 0.348	0.474 ± 0.344	**-1.00 ± 0.668****	-0.176 ± 0.327
VLCFA[3]	-0.125 ± 0.210	0.183 ± 0.298	-0.127 ± 0.427	0.208 ± 0.241	-0.309 ± 0.272	0.250 ± 0.229	0.292 ± 0.295	**-0.980 ± 0.429****	-0.225 ± 0.230

[1] Values are β ± SE estimates using multivariable survey linear regression. CES-D 10, 10-Item Center for Epidemiological Studies Depression Scale; Q, Quartile; PSS-10, 10-Item Perceived Stress Scale; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid; VLCFA, very long chain fatty acids. Omega-3 FA expressed as % of total circulating fatty acids. N=48 (7%) of original analytic cohort used a fish oil supplement. †P=0.05 to <0.10; *P<0.05; **P<0.01.

[2] Model 1 was adjusted for sex, BMI, age, total energy intake, diabetes status, education level, smoking status, study site, physical activity, cardiovascular disease status, marital status, Hispanic/Latino background , income, antidepressant use, baseline CES-D score, time between visits, and intake of total energy, fruit, vegetables, and added sugar. Model 2 adjusting for Model 1 + total circulating omega-6 FA.

[3] VLCFA calculated as the sum of EPA, DHA, and docosapentaenoic acid (DPA).

Figure 1. Eligibility criteria for analytic sample

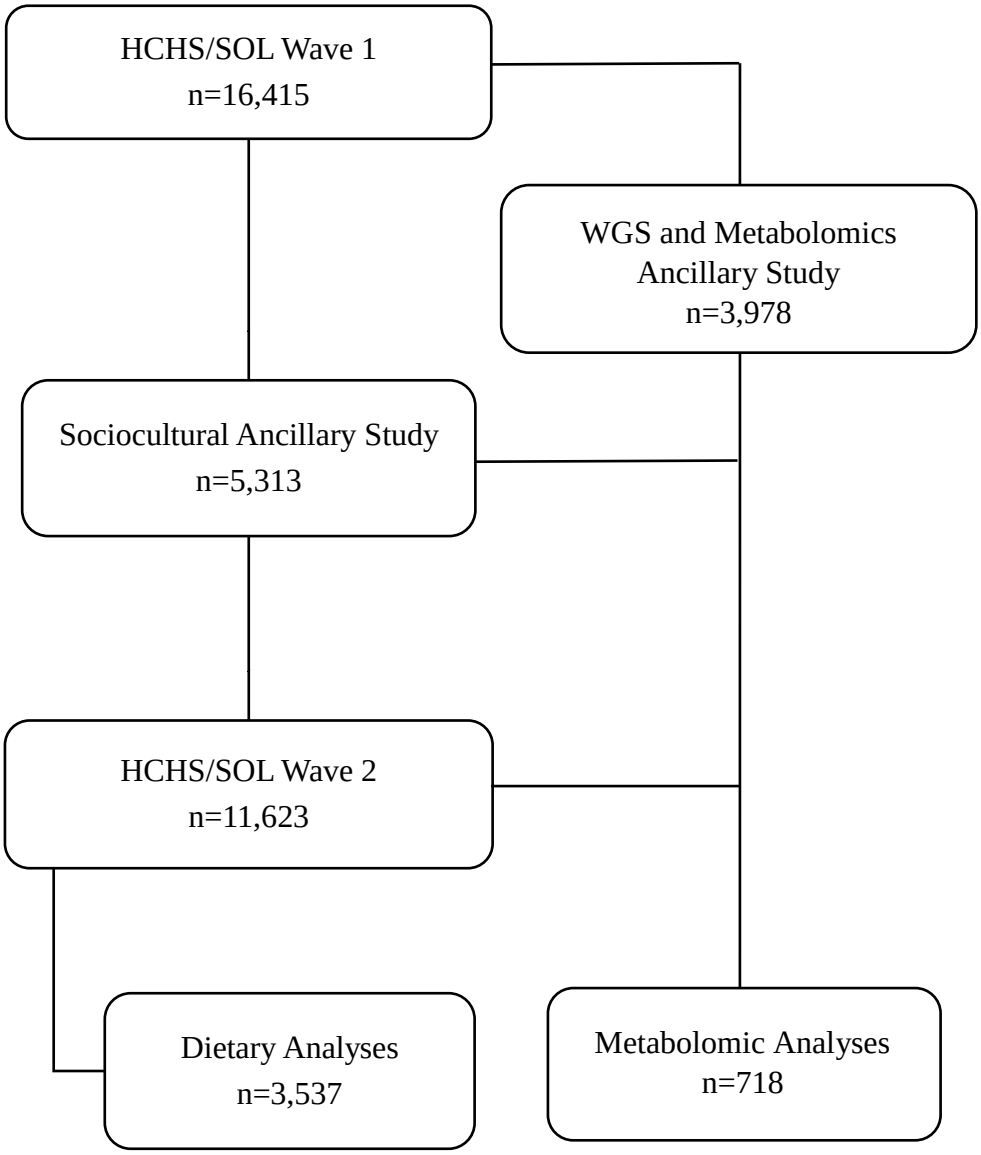
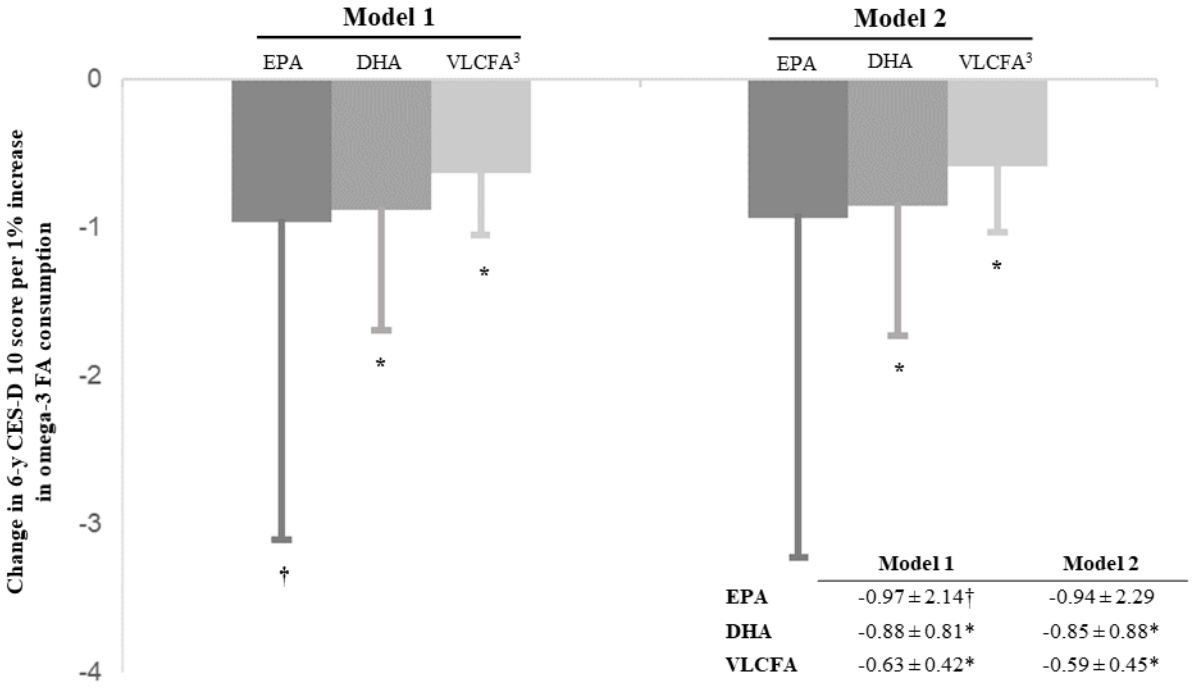


Figure 2. Associations between baseline dietary omega-3 FA consumption and 6-y CES-D score[1,2]

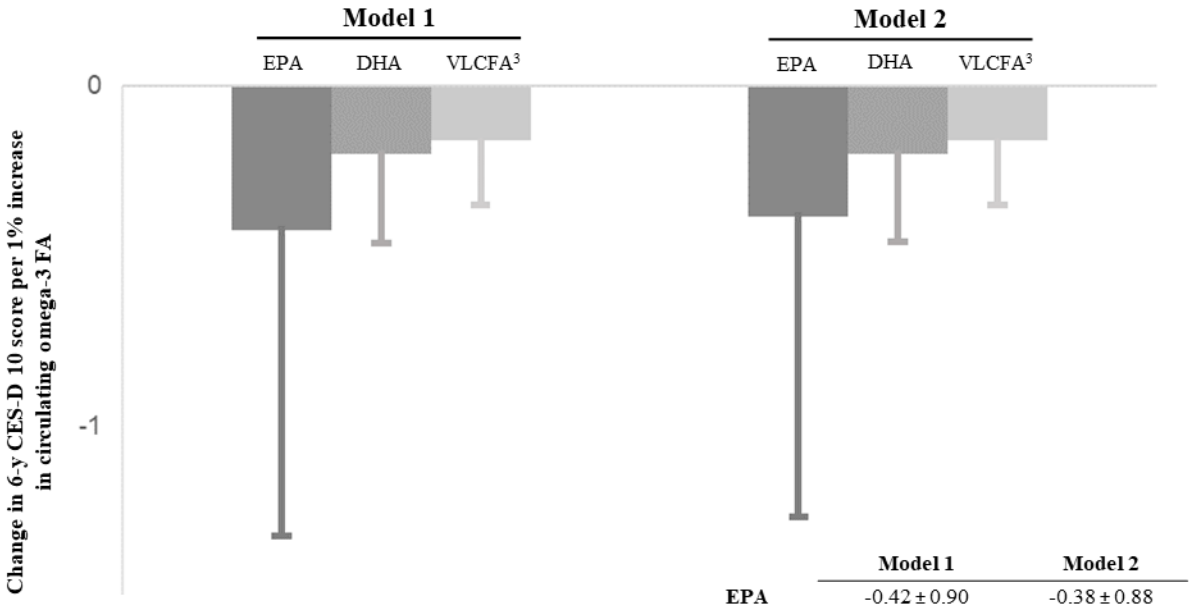


[1] Values are β ± SE estimates using multivariable survey linear regression. CES-D, 10-Item Center for Epidemiological Studies Depression Scale; Q, Quartile; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid, VLCFA, very long chain fatty acids. Omega-3 FA consumption expressed as % total fat intake. †P=0.05 to <0.10, *P<0.05.

[2] Model 1 was adjusted for sex, BMI, age, total energy intake, diabetes status, education level, smoking status, study site, physical activity, cardiovascular disease status, marital status, Hispanic/Latino background, income, antidepressant use, baseline CES-D score, time between visits, and intake of total energy, fruit, vegetables, and added sugar. Model 2 adjusting for Model 1 + total omega-6 FA consumption.

[3] VLCFA calculated as the sum of EPA. DHA, and docosapentaenoic acid (DPA).

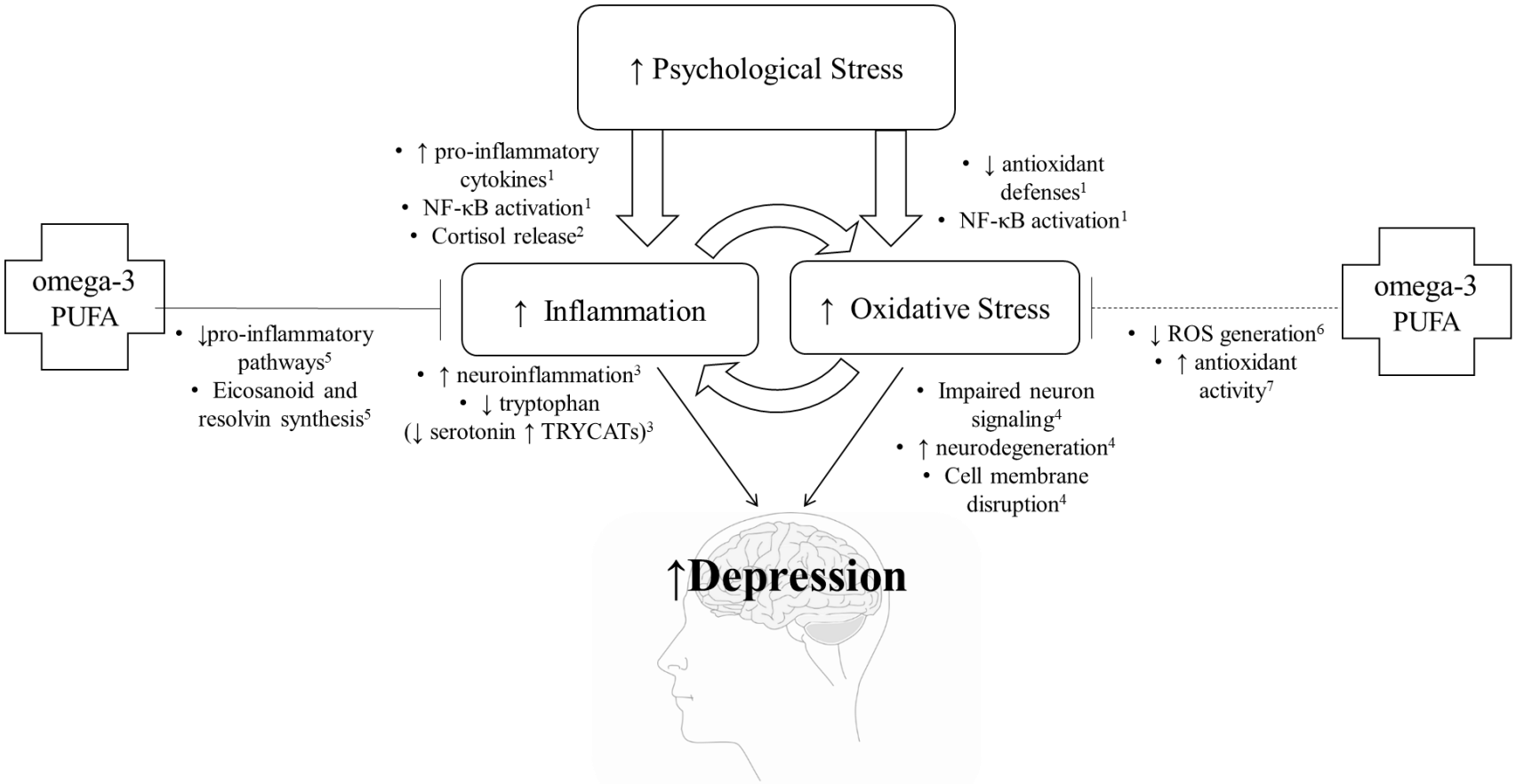
Figure 3. Associations between baseline circulating omega-3 FA and 6-y CES-D score[1,2]



	Model 1	Model 2
EPA	-0.42 ± 0.90	-0.38 ± 0.88
DHA	-0.20 ± 0.26	-0.20 ± 0.26
VLCFA	-0.16 ± 0.19	-0.16 ± 0.19

[1] Values are β ± SE estimates using multivariable survey linear regression. CES-D, 10-Item Center for Epidemiological Studies Depression Scale; VLCFA, very long chain fatty acids. Circulating omega-3 FA expressed as % total circulating fatty acids. *P<0.05.
[2] Model 1 was adjusted for sex, BMI, age, total energy intake, diabetes status, education level, smoking status, study site, physical activity, cardiovascular disease status, marital status, Hispanic/Latino background, income, antidepressant use, baseline CES-D score, time between visits, and intake of total energy, fruit, vegetables, and added sugar. Model 2 adjusting for Model 1 + total circulating omega-6 FA.
[3] VLCFA calculated as the sum of EPA, DHA, and docosapentaenoic acid (DPA).

Figure 4. Biological plausibility of omega-3 FA on depressive symptoms and effect of psychological stress



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