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Do sex hormones or hormone therapy modify the relation of n-3 fatty acids with incident depressive symptoms in postmenopausal women? The MESA Study

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ABSTRACT

Introduction: Considering that estradiol (E2) and n-3 polyunsaturated fatty acids (PUFAs) have roles in neurogenesis and in neurotransmission, we examined whether the association of PUFAs with incident depressive symptoms in postmenopausal women is modified by hormone therapy (HT) use or estrogen status.

Methods: Women (N = 1616) free of depressive symptoms at baseline (2000–2002) in the Multi-Ethnic Study of Atherosclerosis were classified by HT usage and quartiles of dietary eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), and the sum EPA + DHA. Women with serum E2 ≤0.073 nmol/L (sample median), were classified low on E2. Poisson regression was used to model incident depressive symptoms at examination 3 (2004-05), defined by the Center for Epidemiological Studies Depression Scale ≥16 or taking an antidepressant, first as a function of HT use and n-3 PUFA quartiles, and second, as a function of low E2 status and n-3 PUFA quartiles.

Results: Among HT non- users, positive, graded relationships (p-trends ≤ 0.003) were found between PUFAs and incident depressive symptoms. Compared to the lowest quartile, the adjusted risk ratios (RRs) for the highest were 2.10, 2.39, and 2.04 for EPA, DHA, and EPA + DHA, respectively. For HT users, no associations were seen. When analyses were run for E2 status, the RRs over quartiles of the PUFAs were positive and graded for low E2 women, but were null for High E2 women.

Conclusions: Higher intakes of DHA and EPA were associated with higher risk of depressive symptoms in nonusers of HT, contrary to hypothesis.

1. Introduction

Eicosapentaenoic acid (EPA) and docosahexanoic acid (DHA) are key n-3 polyunsaturated fatty acids (PUFAs) studied over the past two decades for a relation with depressive disorders or symptoms in a literature that, while quite sizable, has not produced clear and unequivocal findings. The earlier literature supporting a protective association of n-3 PUFAs with depression includes ecologic (Hibbeln, 1998, 2002) and clinical studies (Peet et al., 1998; Edwards et al., 1998; Maes et al., 1999). Some studies through the 2000 s that did not support this association include cross-sectional (Suzuki et al., 2004), prospective (Lucas et al., 2011; Persons et al., 2014), and randomized clinical trials (Marangell et al., 2003; Hakkarainen et al., 2004; Silvers et al., 2005). Although a review and meta-analysis of 31 observational studies concluded that dietary n-3 PUFA intake was associated with lower risk of depression (Grosso et al., 2016), a recent Cochrane review (Appleton et al., 2015) of 26 randomized clinical trials concluded that there was insufficient high quality evidence to determine the effects of n-3 PUFAs as a treatment for major depressive disorder. On the other hand, apart

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from randomized clinical trials, several cross-sectional (Timonen et al., 2004; Colangelo et al., 2009; Beydoun et al., 2013) and incidence (Sanchez-Villegas et al., 2007; Smith et al., 2014) studies with no fewer than 1300 participants have found inverse associations of n-3 PUFAs or fish, the primary source of n-3 PUFAs, with depressive symptoms or disorders in women but not in men. This gender-specific relation has been attributed to estrogenic effects on n-3 PUFAs (Giltay et al., 2004a,b). Studies indicate that estrogen stimulates and testosterone inhibits the conversion of essential fatty acids into their longer chain metabolites, such as the case with α-linolenic acid conversion into DHA (Decsi and Kennedy, 2011).

Apart from its effects on DHA synthesis, estrogens – namely estradiol – may also have a role in depression in women through its effects on neurotrophic function and the serotonergic system in several brain areas, such as the raphe nucleus, the hippocampus, the amygdala, the anterior cingulate cortex, and the prefrontal cortex (Borrow and Cameron, 2014). Some animal studies have shown that estradiol affects neurogenesis in the dentate gyrus of the hippocampus (Galea et al., 2013) and improves hippocampal synaptic plasticity (Bredemann and McMahon, 2014), processes implicated in the pathophysiology of depression (Christoffel et al., 2011). Given that DHA biosynthesis depends on estrogens (Giltay et al., 2004a,b) and considering that estradiol (E2) and n-3 PUFAs have roles in neurogenesis (Crupi et al., 2013) and in neurotransmission, a potential interplay between sex hormones and n-3 PUFAs with respect to depression might be conjectured. The Multi-Ethnic Study of Atherosclerosis (MESA) provides an opportunity to examine whether sex hormones, in particular E2–endogenous or exogenous – modifies the association of n-3 PUFAs with incident depressive symptoms. We hypothesize that in postmenopausal women, there will be a significant interaction between hormone therapy (HT) use and n-3 PUFA intake such that, in women taking HT, an inverse association between n-3 PUFA intake and incident depressive symptoms will be observed, but in women not taking HT, there will be no association. Additionally, for women with serum E2 levels below the median in the cohort, an inverse association of incident depressive symptoms with n-3 PUFA will be observed and there will be no association for women with E2 above the median.

2. Methods

2.1. Study population

Initiated in 2000 to investigate the prevalence and progression of subclinical cardiovascular disease, 6814 non-Hispanic white, African American, Chinese American, and Hispanic men and women without known cardiovascular disease, aged 45–84 years, were recruited from six US communities: Baltimore City and County, MD; Chicago. IL; Forsyth County, NC; New York, NY; Los Angeles County, CA; and St. Paul, MN. Details on the design, recruitment, and cohort examination procedures (Bild et al., 2002) and methods for blood collection (Golden et al., 2007) were published elsewhere. All participants gave informed consent, and the MESA protocol was approved by the Institutional Review Board at each participating site.

2.2. Blood collection and assessment of endogenous sex hormones

Blood specimens from fasting participants were collected in the clinic between 7:30 am and 10:30 am, processed within 30 min of phlebotomy, and stored at −70 °C using a standardized protocol and shipped to two central laboratories. Using stored blood collected from the baseline MESA exam, serum sex hormone and binding protein concentrations were measured at the University of Massachusetts Medical Center in Worcester, MA. E2 was measured using an ultra-sensitive radioimmunoassay kit from Diagnostic System Laboratories (Webster, TX). Total testosterone (T) and dehydroepiandrosterone (DHEA) were measured directly using RIA kits, and sex hormone binding globulin (SHBG) was measured by chemiluminescent enzyme immunometric assay using Immulite kits obtained from Diagnostic Products Corporation (Los Angeles, CA). Bioavailable T was calculated using total T and SHBG concentrations according to the method of Södergard et al. (1982). Assay variability was monitored by including ∼10% blind, quality control samples in each batch. The intra- and inter-assay technical errors were 8.13 and 9.31%, respectively, for total T; 5.22 and 6.39%, respectively, for SHBG; 8.75 and 5.86%, respectively, for E2; and 7.45 and 8.49% for DHEA. Because clinically meaningful cutpoints for sex hormones have not been established, we classified women as having high or low hormone status on a given hormone if her serum hormone level was above/below the median for the cohort. In this cohort the median and standard deviation (SD) for the hormones were: 0.073 (0.171) nmol/L for E2, 0.90 (1.01) nmol/L for total T, 0.21 (0.30) nmol/L for bioavailable T, 10.17 (6.34) nmol/L for DHEA, and 60.10 (55.60) nmol/L for SHBG.

2.3. Menopausal status

Women were classified as postmenopausal if (a) they responded 'yes' to the question, 'Have you gone through menopause (change of life)?', or (b) had a prior hysterectomy and bilateral oophorectomy. Years of post-menopause were computed as baseline age minus self-reported age at menopause, unless the woman had a hysterectomy and a bilateral oophorectomy, in which case years post-menopause was taken to be years from age at hysterectomy.

2.4. Diet assessment

At the baseline examination a self-administered 120-item food frequency questionnaire (FFQ) assessed the usual dietary intake over the past year. The FFQ was modified from the validated Insulin Resistance Atherosclerosis study in which comparable validity was observed for non-Hispanic white, African American, and Hispanic individuals (Mayer-Davis et al., 1999). The MESA dietary assessment was modified to include foods typically eaten by Chinese groups. The criterion validity of the MESA FFQ was established by quantifying the concordance of the FFQ known relationships between macronutrients and plasma lipid concentrations (Nettleton et al., 2009). De Oliveira Otto et al. (2013) showed in MESA that higher circulating EPA and DHA and higher dietary EPA and DHA were inversely associated with markers of inflammation and with lower cardiovascular disease incidence. A section on vitamins, minerals, and other nutritional supplements – which was not self-administered – was completed at the time of the medication inventory supplement form. Participants were instructed to bring in bottles of any vitamin or other nutritional supplements they took, along with all prescription and over-the-counter medications. Nutrients including n-3 PUFAs were derived from the Minnesota Nutrition Data System NDS software (version 4.02/30; Nutrition Coordinating Center, University of Minnesota, Minneapolis, MN). EPA and DHA were expressed as the percentage of total energy intake.

2.5. Outcome variable assessment

Depressive symptoms were measured at the baseline (2000–2002) and the third examinations (2004-05) using the 20-item CES-D scale (Radloff, 1977), which has a maximum score of 60. The CES-D, which was self-administered in English, Spanish, Cantonese, and Mandarin, asks participants to indicate how often