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Erythrocyte omega-3 fatty acids are inversely associated with incident dementia: Secondary analyses of longitudinal data from the Women's Health Initiative Memory Study (WHIMS)

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ABSTRACT

Objective: To assess whether red blood cell (RBC) docosahexaenoic acid and eicosapentaenoic acid (DHA + EPA) levels have a protective association with the risk of dementia in older women.

Methods: RBC DHA + EPA levels were assessed at baseline, and cognitive status was evaluated annually in a cohort of 6706 women aged ≥65 years who participated in the Women's Health Initiative Memory Study (WHIMS). Cox regression was used to quantify the association between RBC DHA + EPA and the risk of probable dementia, independent of major dementia risk factors.

Results: During a median follow-up period of 9.8 years, 587 incident cases of probable dementia were identified. After adjusting for demographic, clinical, and behavioral risk factors, a one standard deviation increase in DHA + EPA levels was associated with a significantly lower risk of dementia (HR = 0.92, 95% CI: 0.84, 1.00; $p < 0.05$). This effect estimate did not meaningfully change after further adjustment for baseline cognitive function and *APOE* genotype. For women with high DHA + EPA exposure (1 SD above mean) compared to low exposure (1 SD below mean), the adjusted 15-year absolute risk difference for dementia was 2.1% (95% CI: 0.2%, 4.0%). In secondary analyses, we also observed a protective association with longitudinal change in Modified Mini-Mental State (3MS) Exam scores, but no significant association with incident MCI, PD/MCI, or baseline 3MS scores.

Discussion: Higher levels of DHA + EPA may help protect against the development of dementia. Results from prospective randomized controlled trials of DHA + EPA supplementation are needed to help clarify whether this association is causal.

1. Introduction

With the aging of the U.S. population, developing interventions to prevent and treat Alzheimer's disease and dementia (AD/D) has become an increasingly important public health priority. Due to their longer life expectancy, the disease burden of AD/D is especially high for women. For a woman aged 65 years, the subsequent lifetime risk of dementia is 20% [1].

No truly effective pharmacological or non-pharmacological strategy exists for the prevention and/or treatment of AD/D [2,3]. Interest in a potential role of long-chain, marine omega-3 fatty acids (FAs) including eicosapentaenoic and docosahexaenoic acids (EPA and DHA, respectively) has grown based on a variety of observations. These include the structural presence of DHA in neural tissues [4], the anti-inflammatory properties of these FAs [5], and the ability of the DHA metabolite resolvin-D1 to increase phagocytosis of amyloid-β by monocytes [6]. In addition, epidemiologic studies have shown that diets richer in fish are associated with reduced risk for dementia [7,8] and less

Abbreviations: 3MS, Modified Mini-Mental State; CEE, Conjugated equine estrogens; CEE + P, (CEE) + Progestin; CI, Confidence interval; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; FA, fatty acid; HT, hormone therapy; HR, hazard ratio; MCI, mild cognitive impairment; PD, Probably dementia; RBC, red blood cell; SD, standard deviation; WHIMS, Women's Health Initiative Memory Study; WHIMS-ECHO, (WHIMS) Epidemiology of Cognitive Health Outcomes

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neuropathology [9].

In the present study, we evaluated the association between DHA + EPA exposure and incident dementia in the Women's Health Initiative (WHI) Memory Study (WHIMS), a large and well-characterized cohort of older U.S. women. Secondary analyses explored relationships with other cognitive outcomes, including incident mild cognitive impairment (MCI) and longitudinal changes in Modified Mini-Mental State (3MS) scores. We hypothesized that higher levels of RBC DHA + EPA would have protective associations with these outcomes.

2. Methods

2.1. Study population

This study was a secondary analysis of longitudinal data collected for the WHIMS study cohort. WHIMS was an ancillary study of cognitive outcomes in 7479 older women who participated in the WHI randomized trials of hormone therapy (HT). In the trials, women with a prior hysterectomy were randomized to receive 0.625 mg conjugated equine estrogens (CEE) or placebo daily, and women with an intact uterus received a combination of 0.625 mg CEE and 2.5 mg progestin (CEE + P) or placebo daily [10,11]. All participants gave informed consent, and institutional review boards approved the study protocols. At the time of enrollment in WHIMS, participants were 65–80 years of age and free of dementia. The CEE + P and CEE-only trials were terminated in 2002 and 2004, respectively, when it was determined that the risk-benefit ratio was unfavorable for participants assigned to active treatment [12,13]. Observational follow-up continued after the end of the trial interventions.

For the present study, we excluded women who were missing biomarker data on omega-3 FA exposure, had no longitudinal data available on cognitive status following enrollment, or who had missing covariate values (Fig. 1). Median length of follow-up was approximately 10 years (maximum = 20.8) in WHIMS and its subsequent extension study (WHIMS-ECHO).

2.2. Outcomes

WHIMS participants' cognitive status was evaluated at annual follow-up assessments. Participants were classified as having probable dementia (PD), mild cognitive impairment (MCI), or no cognitive impairment based on criteria from the *DSM-IV* [14]. During the WHIMS study period (1995–2007), participants were screened in person for dementia with the 100-point Modified Mini-Mental State (3MS) exam on an annual basis. Those who screened positive underwent additional cognitive testing and clinical evaluation [15]. All potential cases were centrally adjudicated based on neuropsychiatric test results, questionnaire data, and relevant contextual information on recent health events (e.g., stroke). Details on outcome ascertainment and case adjudication have been described previously [10,11,16]. After the original in-person follow-up phase of WHIMS finished, extended follow-up (2008–2016) was conducted under the WHIMS-ECHO (Epidemiology of Cognitive Health Outcomes) protocol where cognitive evaluation was conducted by telephone interview. Participants were screened for dementia with the Modified Telephone Interview for Cognitive Status (TICS-M) [17]. The Dementia Questionnaire [18], a validated instrument that assesses cognitive, behavioral, and functional status, was administered to participants who screened positive. In addition, Dementia Questionnaire proxy interviews were used if a woman's cognitive status could not be assessed directly. As occurred during WHIMS, potential cases were centrally adjudicated based on *DSM-IV* criteria using on all available information, which included scores from the TICS-M and Dementia Questionnaire, and information on recent health events.

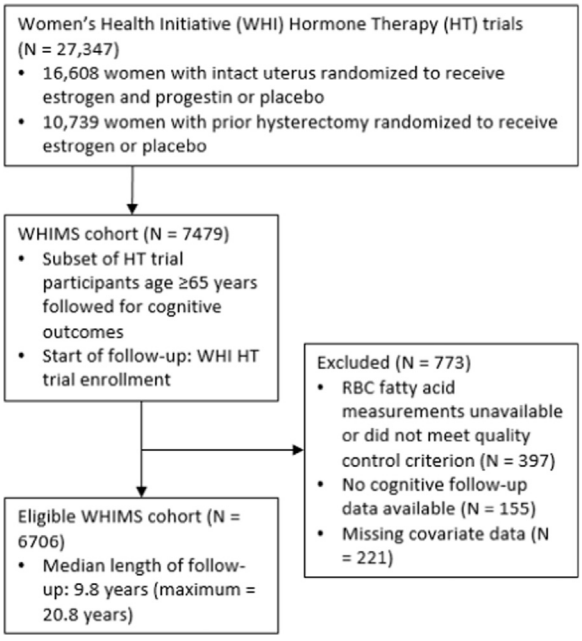

Fig. 1. Flow diagram showing identification of eligible Women's Health Initiative Memory Study (WHIMS) participants.

In the present study, the primary endpoint was incident PD ascertained over the WHIMS and WHIMS-ECHO study periods. Secondary endpoints included a composite endpoint of PD or MCI, MCI alone, longitudinal changes in 3MS scores, and 3MS scores at baseline. Participants were censored at their last cognitive assessment.

2.3. Exposure assessment

Participants' baseline omega-3 FA status was assessed using a validated RBC biomarker [19,20]. RBC FA composition was analyzed using gas chromatography with flame ionization detection. The individual RBC FAs were quantified and expressed as a percent of total identified FAs. The primary exposure of interest was the combination of RBC DHA and EPA content. RBC DHA + EPA, referred to as "the omega-3 index", has been shown to be associated with reduced risks of dementia and cardiovascular disease, and with larger cerebral and hippocampal tissue volumes in prior research [19,21–23]. The intra-assay coefficient of variation for RBC DHA + EPA was < 5.0%. There were 7299 participants with analyzed RBC samples. During aliquoting, the RBC samples were stored improperly at −20C for a period of approximately two weeks, causing oxidative degradation of the polyunsaturated FAs before measurement. The original FA levels were estimated with multiple (i.e., 10) imputations using independent data on FA degradation rates and the length of time the samples were exposed to −20C, as described previously by Pottala et al. [24] After correction and the exclusion of samples not meeting quality-control criteria described by Pottala et al., 7082 participants were eligible for analysis. Among these women, correlations between the corrected RBC biomarkers and participants' intakes of DHA and EPA, as estimated from food frequency questionnaires, were similar to those reported in a sample of participants in the Nurses' Health Study [25,26]. Descriptive statistics on the RBC FA profiles for the study cohort are provided in Appendix Table A1. Parameter estimates were then pooled using Rubin's technique to account for the uncertainty in the corrected DHA + EPA measurements [27].

2.4. Covariates

Covariates reflecting participant HT trial assignment, demographics, health conditions, and health behaviors were selected *a priori* based on their importance as predictors of cognitive and cardiovascular health. (See Tables 1 and 2.) As with DHA + EPA status, all covariates