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Dietary Intakes of Eicosapentaenoic Acid and Docosahexaenoic Acid and Risk of Age-Related Macular Degeneration

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Purpose: To evaluate the associations between intakes of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) and the intermediate and advanced stages of age-related macular degeneration (AMD).

Design: Prospective cohort study.

Participants: We followed 75 889 women from the Nurses' Health Study and 38 961 men from the Health Professionals Follow-Up Study who were at least 50 years old, from 1984 to 2012 and 1986 to 2010, respectively. Cohort participants are mostly white (≥95%).

Methods: We assessed dietary intake by a validated food frequency questionnaire (FFQ) at baseline and every 4 years. We calculated cumulative average intakes of EPA and DHA from FFQs and also computed predicted erythrocyte and plasma scores directly from food intake using regression models. Cox proportional hazards models were used to compute the associations with AMD outcomes.

Main Outcome Measures: We confirmed 1589 incident intermediate and 1356 advanced AMD cases (primarily neovascular AMD) with a visual acuity of 20/30 or worse, owing primarily to AMD, by medical record review.

Results: For intermediate AMD, the pooled hazard ratio (HR) between the 2 cohorts for DHA comparing the extreme quintiles of intake was 0.78 (95% confidence interval [CI], 0.66−0.92; *P* trend, 0.008) and for EPA + DHA was 0.83 (95% CI, 0.71−0.98; *P* trend, 0.03). The pooled HR for fatty fish, comparing ≥5 servings per week to almost never, was 0.61 (95% CI, 0.46−0.81; *P* trend, <0.001). For advanced AMD, the pooled HR for DHA was 1.01 (95% CI, 0.84−1.21; *P* trend, 0.75) and for fatty fish was 0.80 (95% CI, 0.59−1.08; *P* trend, 0.11). Secondary analyses using predicted erythrocyte and plasma scores of EPA and DHA yielded slightly stronger inverse associations for intermediate AMD and similar results for advanced AMD.

Conclusions: Higher intakes of EPA and DHA may prevent or delay the occurrence of visually significant intermediate AMD. However, the totality of current evidence for EPA and DHA and advanced AMD is discordant, though there was no association with advanced AMD in the present study. *Ophthalmology 2017;124:634-643 © 2017 by the American Academy of Ophthalmology*

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Age-related macular degeneration (AMD) is a chronic, degenerative disease of the macula, which can result in loss of the ability to read, write, and drive.[1] Although the advanced stages of AMD are often debilitating, some forms of advanced AMD can now be successfully managed with intravitreal injection of anti−vascular endothelial growth factor (VEGF) agents, allowing patients to maintain or even restore vision for variable periods of time.[2,3] However, although usually less visually debilitating, early/intermediate AMD affects a much larger number of people worldwide and increases risk of development of advanced AMD. According to the 2005−2008 US National Health and Nutrition Examination Survey, the estimated prevalence in persons aged 40 years and older was 5.7% for early/intermediate AMD versus 0.8% for advanced AMD.[4] Globally, among people of European ancestry, the prevalence was 11.2% for early/intermediate AMD versus 0.5% for advanced AMD.[5] Although decreasing exposure to some risk factors (e.g., smoking and high blood pressure) in recent years might eventually help mitigate the incidence of early/intermediate AMD,[4] the number of early/intermediate AMD cases is expected to double in the next few decades owing to rapidly aging populations and lack of other effective means of primary prevention.[5−7] Therefore, identification of other means of primary prevention, especially for vision-threatening early/intermediate AMD cases, would carry marked public health significance.

Docosahexaenoic acid (DHA), a long-chain omega-3 (n3) fatty acid, is a major lipid component of retinal photoreceptor outer segment membranes that has anti-inflammation and antiangiogenesis properties that could protect against AMD.[8] The retinal concentration of DHA is dependent upon and modifiable by diet. Eicosapentaenoic acid (EPA), although not concentrated in the retina, is a precursor to DHA, and its metabolites could similarly affect the pathogenic processes of AMD.[8] Our earlier

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study[9] and investigations by others[10–12] suggested that long-chain n3 fatty acids (DHA, EPA, and other 20-carbon and 22-carbon n3 fatty acids) may reduce the risk of early/intermediate AMD. With respect to advanced AMD, intake of DHA was inversely associated with advanced AMD in several prospective cohort studies,[10,13–15] but this finding was not corroborated by the Age-Related Eye Disease Study 2 (AREDS2) trial, in which supplementation with DHA and EPA for 5 years did not slow the progression to advanced AMD among patients with intermediate AMD.[16]

In light of the mixed findings from the literature, we aimed to evaluate the relation of intakes of EPA and DHA to different forms of AMD in large prospective cohorts over 28 years of follow-up.

Methods

Study Population

The 2 large ongoing US prospective cohorts, the Nurses' Health Study (NHS) and the Health Professionals Follow-up Study (HPFS), have been described in detail before.[17,18] Briefly, the NHS includes 121 701 US female registered nurses aged 30 to 55 years in 1976. The HPFS includes 51 529 US male health professionals aged 40 to 75 years in 1986. Both cohorts are predominantly white (96.8% in the NHS and 95.7% in the HPFS). The long-term follow-up rates are >95%. Questionnaires were mailed to all participants biennially to acquire updated lifestyle factors and disease outcomes. Food frequency questionnaires (FFQs) were mailed every 4 years to assess diet in the preceding year. Submission of a completed self-administered questionnaire was deemed to imply informed consent. The study protocol was approved by the institutional review boards at the Brigham and Women's Hospital and Harvard T.H. Chan School of Public Health.

At study baseline (1984 in the NHS and 1986 in the HPFS), we excluded participants who did not return the initial FFQ, left more than 70 food items blank, reported implausible dietary intake (<600 or >3500 kcal/day for the NHS and <800 or >4200 kcal/day for the HPFS), had prevalent AMD, or had serious chronic diseases including cancer (except nonmelanoma skin cancer), diabetes, and cardiovascular disease. To minimize detection bias, we also excluded participants who never reported an eye examination over the entire follow-up and excluded from analysis the person-time during any 2-year interval in which a participant did not report an eye examination. Results did not materially change in sensitivity analyses including time intervals lacking an eye examination. Participants were included in the analysis when ≥50 years old, and were censored at age 90 to alleviate concerns of low reporting validity (NHS, n = 15; HPFS, n = 528). By the end of follow-up, a total of 75 889 women and 38 961 men contributed to the analysis. Those excluded participants tended to be slightly older and less physically active, and smoked more, than those included (Table S1, available at www.aaojournal.org).

Ascertainment of Age-Related Macular Degeneration

Our case definition has been previously described[19] and also validated by comparison with retinal images and medical records.[20] Briefly, when a participant reported a diagnosis of AMD on a biennial questionnaire, we requested informed consent and then contacted the participant's eye doctor to confirm the diagnosis by reviewing medical records. We defined intermediate AMD as having at least 1 of the following signs: intermediate drusen (≥63 and <125 μm), pigment abnormalities, large drusen (≥125 μm), or any noncentral geographic atrophy (GA). Cases with only small, hard drusen (<63 μm diameter) were excluded. We defined neovascular AMD as having any of the following: retinal pigment epithelium detachment, subretinal neovascular membrane, disciform scar, or history of treatment with laser, photodynamic, or anti-VEGF therapies for AMD. Central GA was defined as having a GA lesion involving the center of the macula. Advanced AMD included neovascular AMD and central GA. Additionally, all case definitions, except those recent neovascular AMD cases that had anti-VEGF therapies, included a visual acuity of 20/30 or worse owing primarily to AMD. This magnitude of vision loss not only is of clinical significance, but also is severe enough to warrant medical attention so as to minimize potential detection bias arising from differential health consciousness. The person was used as the unit of analysis, and the worse eye was used for classification.

Dietary Assessment

We began follow-up in 1984 for the NHS and 1986 for the HPFS, when the first comprehensive FFQ with an expanded section on fish was administered, and assessed dietary intake every 4 years thereafter. Food frequency questionnaire items on fish or seafood consumption include (1) canned tuna (3–4 oz); (2) dark-meat fish (3–5 oz); (3) other fish (mainly white fish, 3–5 oz); and (4) shrimp, lobster, or scallops as main dish (3–5 oz). On the FFQs, commonly used units or portion sizes (e.g., 1 orange or 1/2 cup broccoli) are specified for the approximately 130 items. Participants were asked to report how often, on average over the past year, they had consumed each food item (responses ranging from "≤1 time per month" to "≥6 times per day"). Fish oil supplements including marine and cod liver oils were assessed from 1990 in the NHS and 1988 in the HPFS. We calculated nutrient intakes by multiplying the consumption frequency of each food by the nutrient content of the specified food portion, summing across all foods. The nutrient composition data were primarily based on the US Department of Agriculture Nutrient Database, supplemented with information from manufacturers and published reports. Nutrient values were energy-adjusted using the residual method.[21]

The validity and reproducibility of FFQs in measuring polyunsaturated fatty acids and fish intake have been assessed in a random sample of 118 HPFS participants who completed 2 consecutive FFQs (1986 and 1987), completed 2 1-week dietary records ~7 months apart, and provided subcutaneous fat samples.[22] The correlation was 0.61 for fish between 2 FFQs.[23] The correlation between energy-adjusted EPA from FFQs and percentage of EPA in the adipose tissue was 0.47.[22] Earlier validation studies in the NHS cohort had similar findings.[24,25]

Measurement of Erythrocyte and Plasma Eicosapentaenoic Acid and Docosahexaenoic Acid

Measurement error in FFQs and imprecision in the nutrient composition database may introduce error into the calculated intakes of EPA and DHA. Because erythrocyte and plasma EPA and DHA reflect long-term dietary intake,[26] we used an empirical prediction model to predict the erythrocyte and plasma levels of EPA and DHA directly from food intake based on previous blood measurements among participants of nested case-control studies of cardiovascular disease in the NHS and HPFS. We included all the cases and controls because all were free of disease at the time of blood collection. The details on blood collection and measurements have been described previously.[26] Briefly, we collected whole-blood samples from 32 826 women between