Omega-3 long-chain polyunsaturated fatty acid intake is inversely associated with 12-year progression to advanced AMD

John Paul SanGiovanni, ScD[a,*], **Elvira Agrón, MA**[a], **Traci E. Clemons, PhD**[b], and **Emily Y. Chew, MD**[a]

[a] National Eye Institute, Bethesda MD

[b] EMMES Corp., Rockville, MD

To the Editor: Age-related macular degeneration (AMD) is a leading cause of vision loss. Age-related Eye Disease Study (AREDS) participants reporting highest intake of ω-3 long-chain polyunsaturated fatty acids (LCPUFAs) were approximately half as likely as their peers reporting lowest intake of these nutrients to have neovascular (NV) AMD[1] at baseline or to progress across a six year period from bilateral drusen to central geographic atrophy (CGA). [2] AREDS provides data that represent, to our knowledge, the largest longitudinal sample collected and classified with standardized methods as part of a natural history study on AMD. We now report that our baseline and six-year findings persisted in 12-year AMD incidence models. These results are consistent with existing data.[3,7]

Methods

AREDS was a NIH sponsored and administered multi-center study designed to assess the clinical course, prognosis, and risk factors of AMD (http://www.nei.nih.gov/amd/). We examined the relationship of dietary ω-3 LCPUFAs with progression to advanced AMD in 1837 AREDS participants who had a moderate risk for developing sight-threatening AMD (1211 Category 3a and 626 Category 4a participants). Participants in Category 3a had bilateral visual acuity of 20/32-or-better and bilateral large (>125 μm) drusen, extensive intermediate drusen, and/or GA that did not involve the center of the macula in at least one eye. Category 4a participants had visual acuity of 20/32-or-better and no advanced AMD (GA involving the center of the macula or features of NV AMD) in the study eye; the fellow eye had definite lesions of advanced AMD. Category 3b and 4b participants had acuity worse than 20/32. In AREDS Report 1 we describe outcome ascertainment for CGA and NV AMD from centralized grading of annual stereoscopic fundus color photographs; participants progressing to CGA and/ or NV AMD in their study eye(s) were classified with incident advanced AMD. Nutrient density values at baseline defined the LCPUFA variables.[1] We computed odds ratios in repeated measures logistic regression models incorporating generalized estimating equation methodology. This method permitted determination of advanced AMD at each visit for each

participant. All models included terms for baseline age (< 65 vs. 65—69 and ≥ 70), sex, smoking status at diagnosis (never, past, current), total energy intake (modeled as a continuous variable), AREDS treatment (placebo vs. zinc, antioxidants, and zinc + antioxidants), and baseline AMD status (AREDS Category 3a vs. 4a). We estimated dietary intake with a validated semi-quantitative food frequency questionnaire developed for AREDS.[1,2]

Results

Participants reporting highest baseline consumption of ω-3 LCPUFAs were approximately 30% less likely than their peers reporting lowest ω-3 LCPUFA consumption to develop advanced AMD by the end of the 12-year follow-up period (TABLE). Results for CGA and NV AMD were similar; respective multivariate odds ratios (OR) are 0.65 (95%CI 0.45—0.92, $P \leq 0.02$) and 0.68 (95%CI 0.49—0.94, $P \leq 0.02$).

Comment

ω-3 LCPUFAs and their metabolites have the capacity to act on processes implicated in AMD pathogenesis.[3] Although inferences are constrained by the observational nature of our research designs (frequent consumption of ω-3 LCPUFA-rich foods may be a proxy for exposure to unmeasured environmentally- or behaviorally-based protective factors), biologically credible explanations for ω-3 LCPUFA-AMD relationships now exist in studies applying *in vivo*[4,5] and *in vitro*[6] model systems. The findings from these basic studies strengthen conclusions from extant observational studies (reviewed in references [3] & [7]) regarding the association of ω-3 LCPUFA intake with AMD. Since the concentration of retinal ω-3 LCPUFAs is modifiable by and dependent on dietary composition, these nutrients may represent an easily implemented approach to modifying risk of AMD progression; we are now conducting a 5-year, 4000-person clinical trial to examine this issue of public health significance (www.areds2.org).

Acknowledgments

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Table

Odds ratios for progression to advanced AMD.

| ω-3 LCPUFA | Intake Quintile | | | Odds Ratio (95% CI) |
	A	vs.	B	Progression to Advanced AMD
EPA	Bottom 20%		Top 20%	0.69 (0.53,0.90)[a]
DHA	Bottom 20%		Top 20%	0.67 (0.51,0.88)[a]
EPA+DHA	Bottom 20%		Top 20%	0.65 (0.50,0.85)[a]

<u>Note</u>: n=1837. DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid. Advanced AMD = central geographic atrophy and/or choroidal neovascularization. Respective medians of reported EPA, DHA, EPA+DHA intake values for participants in the lower 20% of AREDS sample are 5 mg/d, 15 mg/d and 15 mg/d. Respective medians for people ranked in the 5th quintile (top 20%) are 70 mg/d, 90 mg/d and 160 mg/d. CI = confidence interval.

[a]$P \leq 0.01$.