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The Relationship of Dietary Carotenoid and Vitamin A, E, and C Intake With Age-Related Macular Degeneration in a Case-Control Study

AREDS Report No. 22

*Age-Related Eye Disease Study Research Group**

Objective: To evaluate the relationship of dietary carotenoids, vitamin A, alpha-tocopherol, and vitamin C with prevalent age-related macular degeneration (AMD) in the Age-Related Eye Disease Study (AREDS).

Methods: Demographic, lifestyle, and medical characteristics were ascertained on 4519 AREDS participants aged 60 to 80 years at enrollment. Stereoscopic color fundus photographs were used to categorize participants into 4 AMD severity groups and a control group (participants with <15 small drusen). Nutrient intake was estimated from a self-administered semiquantitative food frequency questionnaire at enrollment. Intake values were energy adjusted and classified by quintiles. The relationship between diet and AMD status was assessed using logistic regression analyses.

Results: Dietary lutein/zeaxanthin intake was inversely associated with neovascular AMD (odds ratio [OR], 0.65; 95% confidence interval [CI], 0.45-0.93), geographic atrophy (OR, 0.45; 95% CI, 0.24-0.86), and large or extensive intermediate drusen (OR, 0.73; 95% CI, 0.56-0.96), comparing the highest vs lowest quintiles of intake, after adjustment for total energy intake and nonnutrient-based covariates. Other nutrients were not independently related to AMD.

Conclusion: Higher dietary intake of lutein/zeaxanthin was independently associated with decreased likelihood of having neovascular AMD, geographic atrophy, and large or extensive intermediate drusen.

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AGE-RELATED MACULAR DEgeneration (AMD) is a leading cause of irreversible vision loss and blindness in elderly people of European ancestry.[1,2] Analyses by The Eye Diseases Prevalence Research Group suggest that approximately 1.22 million US residents have neovascular (NV) AMD, 970 000 are living with geographic atrophy (GA) in at least 1 eye, and 3.6 million have bilateral large drusen.[2] Estimates for the presence of NV AMD or GA in at least 1 eye for Western European and Australian residents are 3.35 million and 130 000, respectively. In the next 20 years, these values are expected to increase by 50%.[2]

Age-related metabolic and structural changes in the neural and vascular retina may alter the risk of AMD pathogenesis and progression.[3-6] The risk of AMD may be further modified in the context of chronic environmental exposures.[3,4] A number of diet-based compounds concentrated in the retina may have the capacity to modulate exogenous and endogenous defense and repair systems that operate in response to oxidative stress and inflammation.[7,8] These nutrients include lutein and zeaxanthin (macular xanthophylls), provitamin A carotenoids (beta- and alpha-carotene and beta-cryptoxanthin), vitamin A, retinol, alpha-tocopherol (a form of vitamin E), and vitamin C. Biologic plausibility of nutrient-AMD relationships is discussed in a number of recent reviews.[7,9,10]

We have examined nutrient-based interventions for AMD in the Age-Related Eye Disease Study (AREDS).[11] AREDS includes a completed randomized clinical trial designed to evaluate the effect of high doses of zinc and/or a formulation of vitamins with antioxidant properties (vitamin C, alpha-tocopherol, and beta-carotene) on the rate of progression to advanced AMD and visual acuity change.[12] To our knowledge, AREDS also contains the largest well-phenotyped cohort of people with sight-threatening AMD who have provided dietary intake data. This report describes the relationships between AMD and dietary carotenoids, retinol, alpha-tocopherol, and vitamin C.

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Group Information: A complete list of the members of the AREDS Research Group appears in *Arch Ophthalmol*. 2004;122(5):716-726.

METHODS

STUDY POPULATION

Details of the AREDS design and methods appear in earlier publications.[11-13] In summary, 11 retinal specialty clinics enrolled 4757 participants from 1992 through 1998. Participants were 55 to 80 years of age at enrollment and had best-corrected visual acuity of 20/32 or better in at least 1 eye. Ocular media were sufficiently clear to obtain adequate-quality stereoscopic fundus photographs of the macula in all study eyes. At least 1 eye of each participant was free from advanced AMD (defined as NV AMD or foveal GA) and any eye disease that could complicate assessment of AMD or lens opacity progression (eg, optic atrophy, acute uveitis), and that eye could not have had previous ocular surgery (except cataract surgery). Potential participants were excluded for illness or disorders that would make long-term follow-up or compliance with the study protocol unlikely or difficult. Persons aged 55 through 59 years were recruited only if they had intermediate AMD (AREDS recruitment category 3) or unilateral advanced AMD (AREDS recruitment category 4 [see Table 1 in "The Age-Related Eye Disease Study (AREDS): Design Implications. AREDS Report No. 1"[11] for details]). The present analysis of 4519 persons excludes all 110 persons in this age group because there were no age-matched controls for these cases. This analysis also excludes the 128 persons with bilateral aphakia for whom refractive error data were not available.

STUDY GROUP DEFINITIONS

Persons were recruited for AREDS in 4 AMD categories determined by the size and extent of drusen in each eye, the presence of manifestations of advanced AMD, and visual acuity.[11] Based on reading center grading of stereoscopic photographs taken at enrollment, participants for this analysis were then divided into 5 groups according to the size and extent of drusen, the presence of pigmentary abnormalities, and the presence of manifestations of advanced AMD.[13]

The 5 groups analyzed in this report, numbered serially and based on increasing severity of drusen or type of AMD, were defined as follows. The eyes of subjects in the group of study participants with little or no evidence of the lesions associated with AMD, group 1 (n=1115), were free of drusen or had nonextensive small (<63 µm) drusen. Group 1 represented our referent controls. Subjects in group 2 (n=1060) had at least 1 eye with 1 or more intermediate (63 µm-124 µm) drusen, extensive (cumulative area ≥ 1/12 diameter of AREDS standard disc area) small drusen, or pigment abnormalities (hyperpigmentation or hypopigmentation) associated with AMD. Subjects in group 3 (n=1568) had at least 1 eye with 1 or more large (≥125 µm) drusen or extensive intermediate drusen (soft, indistinct drusen present in a cumulative area equivalent to that occupied by 20 drusen each having a diameter of 100 µm or 65 distinct drusen each having a diameter of 100 µm). Subjects in group 4 (n=118) had at least 1 eye with definite GA anywhere within 3000 mm of the fovea. Subjects in group 5 (n=658) had evidence suggesting choroidal neovascularization or retinal pigment epithelial cell detachment in 1 eye (nondrusenoid retinal pigment epithelial detachment, serous sensory or hemorrhagic retinal detachment, subretinal hemorrhage, subretinal pigment epithelial hemorrhage, subretinal fibrosis) or scars of photocoagulation for AMD. The term *neovascular* was used as a summary term for AMD group 5 because almost all persons in this group had direct evidence of choroidal neovascularization based on a history of laser treatment for AMD or on the assessment of fundus photographs.

RECRUITMENT

Sources of participants included medical records of patients being seen at AREDS clinics; referring physicians; patient lists from hospitals and health maintenance organizations; screenings at malls, fairs, senior centers, and other gathering places; public advertisements (radio, television, newspapers, flyers); and friends and family of participants and of clinical center staff. The estimated percentage of participants by recruitment source for AMD groups 1 and 2 differed from groups 3, 4, and 5 mainly for medical records (17% vs 63%), public advertisements (53% vs 24%), and friends and family of participants (13% vs 7%).[13]

PROCEDURES

Before study initiation, the protocol was approved by a data and safety monitoring committee and by the institutional review board for each clinical center. Informed consent was obtained from all participants prior to enrollment. Detailed questionnaires were administered to obtain demographic information, history of smoking and sunlight exposure, medical history, history of specific prescription drug and nonprescription medication use, and history of vitamin and mineral use. General physical and ophthalmic examinations included measurement of height, weight, blood pressure, manifest refraction, best-corrected visual acuity, intraocular pressure, slitlamp biomicroscopy, and ophthalmoscopy. Stereoscopic fundus photographs of the macula were taken in each clinical center and graded at a photograph reading center, where the various lesions associated with AMD were assessed through standardized procedures.[14]

At enrollment, subjects completed a self-administered, 90-item, semiquantitative food frequency questionnaire (AREDS FFQ). The food list contained items rich in a variety of nutrients that have putative associations with AMD, such as lipids, lutein, zeaxanthin, provitamin A carotenoids, and vitamins and minerals with antioxidant properties. Subjects were asked to indicate how often, on average, they had consumed each food or beverage item during the past year. Average frequency of consumption was recorded across 9 levels that ranged from "never or less than once per month" to "2 or more per day." For each item, average serving size was also recorded as "small," "medium," or "large," with respect to standard examples.

The AREDS FFQ was based on the validated 1987 National Cancer Institute Health Habits and History Questionnaire version 2.1. The instrument was modified for use in AREDS with data obtained from 2-day food records sampled from 78 study-eligible persons selected from all 11 AREDS clinics. The instrument was then validated using a telephone-administered 24-hour dietary recall at 3- and 6-month postenrollment in 197 randomly selected participants.[15] Correlations of 24-hour recall data with the AREDS FFQ were corrected for attenuation with the method of Rosner and Willett.[16] Values for correlation coefficients were 0.1 for vitamin E, 0.6 for vitamin C, 0.9 for vitamin A, 0.7 for alpha-carotene, 0.8 for beta-carotene, 0.7 for beta-cryptoxanthin, 0.6 for lutein/zeaxanthin, and 0.7 for lycopene.

Dietary intake data were processed with DIETSys software (version 3.0; National Cancer Institute, Information Management Services, Inc, Bethesda, Maryland, and Block Dietary Data Systems, Berkeley, California) at the University of Minnesota Nutrition Coordinating Center (NCC), School of Public Health, University of Minnesota. The DIETSys system produced daily nutrient intake estimates for each subject by first multiplying the average age- and sex-adjusted portion size (derived from National Health and Nutrition Examination Survey II data) by the subject's reported serving size. This value was then adjusted for nutrient composition and quantified with the NCC

Table 1. Characteristics of the AREDS Population[a]

Variable	Subjects Within Group, %				
	1	2	3	4	5
	No AMD (n=1115)	Extensive Small or Nonextensive Intermediate Drusen (n=1060)	Extensive Intermediate or Large Drusen (n=1568)	Geographic Atrophy (n=118)	Neovascular AMD (n=657)
Age, ≥71 y	25	30	44	50	53
Race, nonwhite	7	6	4	0	2
Female	55	59	54	50	55
College degree	42	38	32	27	23
BMI ≥31	20	17	21	25	24
Ever smoked, ≥6 mo	51	51	57	64	66

Abbreviations: AMD, age-related macular degeneration; AREDS, Age-Related Eye Disease Study; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared).

[a] An expanded version of this Table is presented in AREDS Report 3.[13]

Food Composition Database (version 31, November 2000). Cumulative estimates for each nutrient were then computed by summation of nutrient values across all foods and items. The NCC staff were masked to AMD status of study participants.

STATISTICAL MODELING AND ANALYSES

We designed our analytic framework to address the questions of whether dietary nutrient–AMD relationships exist after considering the influence of nonnutritional factors, and, if so, whether these relationships are likely to be explained by other nonnutritional factors and/or other nutrients.

Our 4 AMD case groups (groups 2-5) were defined by the various levels of AMD at enrollment. Each of these AMD groups was compared with the AMD-free control group (group 1). Details of statistical modeling and analysis of nonnutritional risk factors appear in AREDS Report 3.[13] Briefly, demographic factors, medical history, treatment history, and ocular factors associated with AREDS AMD categories were identified through polychotomous logistic regression analyses. Factors significant at $P<.15$ in any group were retained for multivariable modeling. Final models were the starting point for the multivariable analyses described in this report.

Nutrient intake values were adjusted for total energy intake (TEI) by computing nutrient densities (nutrient intake/TEI) and then modeling categories of this variable (in this case, quintiles) with TEI. When nutrient density scores are entered into models with a term for TEI, the nutrient density coefficient represents the relation of nutrient composition with AMD status, independent of energy intake; the TEI coefficient represents the effect of caloric intake. Habitual dietary intakes of the study nutrients across the year prior to enrollment were the primary independent variables in these analyses. In this report, we include findings for carotenoids, vitamin A, alpha-tocopherol, and vitamin C intake. The term *vitamin A* represents dietary retinol (preformed vitamin A) and the potential contribution of provitamin A carotenoids (precursors to retinol) to retinol biosynthesis.

Vitamin and mineral supplement intake represented a source of nutrient consumption. To address the potential for negative bias introduced by disease-based modifications (increases) in supplement use among subjects with advanced AMD, we constructed a variable representing duration and frequency of supplement intake at the time of AREDS enrollment. This variable (supplement-years) was the average number of tablets taken per day × intake duration in years. Supplement-year variables were developed for vitamin A, beta-carotene, vitamin E, vitamin C, zinc, selenium, calcium, iron, and multivitamins. These factors were evaluated separately from food-based nutrients.

We calculated odds ratios (ORs) and 95% confidence intervals (CIs) using multiple logistic regression to examine the relationship of AREDS AMD case groups (relative to group 1) with levels of dietary nutrient intake. To determine existence of relationships between single dietary nutrients and AMD, we ran models with each nutrient and all AREDS AMD group–specific factors from AREDS Report 3 (each AMD group had a unique set). Dietary nutrients identified as independent predictors of AMD in these single-nutrient analyses were retained for multivariable models containing other AMD-associated nutrients if the OR for highest vs lowest quintile of intake was significant at $P\leq.05$. To detect relationships between a given nutrient and nonnutritional risk factors for AMD, we used logit analysis for ordered categories, with quintile of a given nutrient as the dependent variable and predictive factors identified in AREDS Report 3 as independent variables. All models contained terms for age at baseline (60-65, 66-70, and 71-80 years), sex, and TEI.

After identifying single nutrient–AMD relationships and nonnutritional covariates, we constructed multinutrient models. In this process, we considered the influence of collinearity in the nutrient data and factors with the potential to act as effect modifiers. To detect collinearity, we used multiple linear regression, with log-transformed nutrient density scores of each AMD-associated dietary nutrient as the dependent variable; all other dietary nutrients were entered as independent variables and tested with a stepwise-model selection procedure. In these models, we computed partial correlation coefficients of each nutrient relative to the others persisting in each final model. Factors contributing to more than 10% of the variance in nutrients associated with at least 1 AMD group were evaluated as potential collinear terms and not entered simultaneously with the factor-sharing variance. In the final modeling step, energy-adjusted quintiles of primary study nutrients, other noncollinear dietary nutrients associated with AMD (ω-3 long-chain polyunsaturated fatty acids and arachidonic acid), and nonnutritional risk factors from AREDS Report 3 were simultaneously added to logistic models of AREDS AMD groups.

RESULTS

Table 1 displays select demographic, lifestyle, medical, and ocular characteristics of the sample. Additional

Table 2. Age-, Sex-, and Calorie-Adjusted ORs for Extensive Small Drusen or Nonextensive Intermediate Drusen and Nutrient Intake[a]

			Outcome, OR						
	Exposure		AMD Group 2: Extensive Small or Nonextensive Intermediate Drusen	Nutrient					
Factor	A	B		Beta-carotene	Beta-cryptoxanthin	Lutein/zeaxanthin	Lycopene	Vitamin C	Alpha-tocopherol
Age	71-80 y	60-65 y	1.51	1.28[b]	0.86[b]	0.88	0.95	1.03	1.09
Sex	F	M	1.22	1.19[b]	1.29[b]	1.33[b]	1.01	1.41[b]	0.97
Angina	Present	Absent	0.80	0.91	1.19	1.05	0.90	1.10	1.05
Arthritis	Present	Absent	1.30	0.95	0.90	1.00	0.86[b]	0.91	0.87[b]
HClz use	Yes	No	1.35	0.99	1.09	1.12	0.87	1.31[b]	1.39[b]

Abbreviations: AMD, age-related macular degeneration; HClz, hydrochlorothiazide; OR, odds ratio.
[a]Variables listed in the "Factor" column are those used in final multivariable models for AREDS Report 3.[13] All ORs are adjusted for age and sex. The ORs for nutrients are also adjusted for total caloric intake. Standard logistic regression was used to compute ORs for AMD outcome. Logistic regression for ordered categories was used to compute ORs for nutrient quintile outcome (lowest-intake quintile represented the reference category). An OR greater than 1 implies that persons with exposure A show an increased likelihood of having AMD or being in a higher–nutrient intake quintile as compared with subjects with exposure B. Subjects with no AMD (n=1115) and subjects with extensive small drusen or nonextensive intermediate drusen (n=1060) were included in the analyses.
[b]$P \leq .15$.

Table 3. Age-, Sex-, and Calorie-Adjusted ORs for Extensive Intermediate Drusen or Large Drusen and Nutrient Intake[a]

			Outcome, OR						
	Exposure		AMD Group 3: Extensive Intermediate or Large Drusen	Nutrient					
Factor	A	B		Beta-carotene	Beta-cryptoxanthin	Lutein/zeaxanthin	Lycopene	Vitamin C	Alpha-tocopherol
Age	71-80 y	60-65 y	3.30	1.32[b]	0.83[b]	0.79[b]	0.79[b]	0.94	0.99
Education	College	≤HS	0.63	1.69[b]	1.41[b]	1.87[b]	1.16[b]	1.70[b]	1.15[b]
Hyperopia	Hyperopic	Myopic	1.35	1.04	0.92	1.17[b]	1.02	0.88	0.95
Sex	F	M	1.00	1.30[b]	1.34[b]	1.40[b]	1.12[b]	1.43[b]	0.95
Race	White	Other	1.75	0.39[b]	0.90	0.28[b]	1.86[b]	0.80	1.43[b]
Ever smoked, ≥6 mo	Yes	No	1.31	0.75[b]	0.70[b]	0.82[b]	0.95	0.71[b]	0.87[b]
Hypertension	Present	Absent	1.24	1.03	1.12[b]	0.99	0.88[b]	1.11[b]	0.96
Arthritis	Present	Absent	1.33	0.90[b]	0.96	0.88	0.81[b]	0.95	0.94
HClz use	Yes	No	1.58	1.03	1.10	1.09	0.80[b]	1.05	1.09
Diuretic use	Yes	No	1.08	1.23[b]	1.09	1.12	0.81[b]	1.05	1.13
Lens opacity	Present	Absent	1.22	0.96	0.86[b]	1.02	0.88[b]	0.89[b]	0.99

Abbreviations: AMD, age-related macular degeneration; HClz, hydrochlorothiazide; HS, high school; OR, odds ratio.
[a]See Table 2. Subjects with no AMD (n=1115) and subjects with extensive intermediate drusen or large drusen (n=1568) were included in the analyses.
[b]$P \leq .15$.

details on the distribution of these and other factors exist in a previous report.[13] Of 4519 participants in this report, 38% were older than 70 years, 95% identified themselves as white, 56% were female, 35% had a college degree, 55% smoked for at least 6 months, and 40% had hypertension. **Tables 2**, **3**, **4**, and **5** contain sex-, age-, and TEI-adjusted ORs for the 4 AMD groups, which can be used to identify nonnutritional factors associated both with AMD and the nutrients representing the primary independent variables. All variables in the "Factor" column are from final models presented in AREDS Report 3.[13] The ORs greater than 1 for AMD outcomes indicate an increased likelihood of having AMD among participants with exposure A; ORs less than 1 indicate a decreased likelihood with exposure A. In the nutrient outcome columns, an OR greater than 1 that is also followed by a superscript *b* indicates that people with exposure A have an increased likelihood ($P \leq .15$) of being in a higher-intake quintile of the nutrient represented in that column; an OR less than 1 that is also followed by a superscript *b* suggests a decreased likelihood. For example, Table 2 indicates that people aged 71 to 80 years at enrollment were more likely than people aged 60 to 65 years at enrollment to have extensive small drusen or nonextensive intermediate drusen. People in this category were also more likely than their younger peers to be in a higher quintile of beta-carotene intake and a lower quintile of beta-cryptoxanthin intake.

Table 6 contains ORs for age-, sex-, and calorie-adjusted and multivariable analyses of single nutrients for each AREDS AMD category. Values represent the comparisons of the persons above the highest-intake quintile vs persons below the lowest-intake quintile. Age-, sex-, and calorie-adjusted analyses yielded relationships in the direction of benefit for vitamin A and extensive intermediate drusen or large drusen, GA, and NV AMD. Lutein/zeaxanthin intake showed the same pattern. There was a reduced likelihood of GA and NV AMD among people

Table 4. Age-, Sex-, and Calorie-Adjusted ORs for Geographic Atrophy and Nutrient Intake[a]

			Outcome, OR						
	Exposure		AMD Group 4: Geographic Atrophy	Nutrient					
Factor	A	B		Beta-carotene	Beta-cryptoxanthin	Lutein/zeaxanthin	Lycopene	Vitamin C	Alpha-tocopherol
Age	71-80 y	60-65 y	3.33	1.28[b]	0.81[b]	0.81[b]	0.88	0.93	0.95
Education	College	≤HS	0.34	1.38[b]	1.57[b]	1.49[b]	1.11	1.78[b]	1.30[b]
Sex	F	M	0.85	1.22[b]	1.31[b]	1.38[b]	0.93	1.47[b]	0.97
Ever smoked, ≥6 mo	Yes	No	1.77	0.79[b]	0.68[b]	0.77[b]	0.98	0.67[b]	0.91
Antacid use	Yes	No	2.75	0.97	0.86	1.11	1.12	0.80	1.70[b]
Thyroid hormone use	Yes	No	2.16	0.94	0.98	0.91	1.05	0.96	0.88[b]

Abbreviations: AMD, age-related macular degeneration; HS, high school; OR, odds ratio.
[a] See Table 2. Subjects with no AMD (n=1115) and subjects with geographic atrophy (n=118) were included in the analyses.
[b] $P \leq .15$.

Table 5. Age-, Sex-, and Calorie-Adjusted ORs for Neovascular AMD and Nutrient Intake[a]

			Outcome, OR						
	Exposure		AMD Group 5: Neovascular AMD	Nutrient					
Factor	A	B		Beta-carotene	Beta-cryptoxanthin	Lutein/zeaxanthin	Lycopene	Vitamin C	Alpha-tocopherol
Age	71-80 y	60-65 y	5.12	1.28[b]	0.85[b]	0.79[b]	0.91	0.97	0.94
BMI	≥31	≤23.6	1.68	0.87	0.81[b]	0.78[b]	1.06	0.80[b]	0.85
Education	College	≤HS	0.35	1.46[b]	1.56[b]	1.56[b]	1.09	1.83[b]	1.31
Refractive error	Hyperopic	Myopic	2.41	1.20	0.98	1.34[b]	1.02	0.91	0.98
Sex	F	M	1.04	1.22[b]	1.32[b]	1.41[b]	1.14[b]	1.44[b]	0.97
Race	White	Other	3.93	0.38[b]	0.97	0.28[b]	2.24[b]	0.83	1.18
Ever smoked, ≥6 mo	Yes	No	1.98	0.79[b]	0.71[b]	0.77[b]	1.02	0.63[b]	0.82[b]
Hypertension	Present	Absent	1.52	0.99	1.16[b]	0.96	0.90	1.16[b]	0.93
Lens opacity	Yes	No	1.31	1.00	0.92	1.06	0.86[b]	0.88[b]	1.08

Abbreviations: AMD, age-related macular degeneration; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); HS, high school; OR, odds ratio.
[a] See Table 2. Subjects with no AMD (n=1115) and subjects with neovascular AMD (n=657) were included in the analyses.
[b] $P \leq .15$.

reporting highest beta-cryptoxanthin intake and a reduced likelihood of NV AMD among those reporting highest beta-carotene, vitamin C, and vitamin E intake. Those relationships persisting after addition of covariates identified in AREDS Report 3 are (1) lutein with extensive intermediate drusen or large drusen, GA, and NV AMD; (2) vitamin A with NV AMD; and (3) beta-carotene with NV AMD. The relationship of supplement years with AMD was negligible for all vitamins/minerals and was not considered in subsequent models (data not shown).

Table 7 displays ORs for NV AMD and GA by quintiles of nutrient intake; models contain terms for nutritional factors independently associated both with NV AMD and GA and factors from AREDS Report 3. Lutein/zeaxanthin intake persisted as an independent factor for NV AMD and GA after adjustment for caloric intake, age, sex, and nutritional and nonnutritional covariates. Beta-carotene persisted for NV AMD; however, this relationship was not observed in comparison of highest to lowest quintiles. AREDS subjects reporting higher intakes of lutein/zeaxanthin were also less likely to have large or extensive intermediate drusen than subjects in the lowest quintile of intake. In analyses restricted to participants taking neither a multivitamin-multimineral supplement nor an individual vitamin supplement, the direction of associations was unchanged. Magnitudes of association (ORs) were unchanged or increased, except for beta-carotene (decreased).

COMMENT

This report adds diet-based nutrient variables to the risk factor analyses for AMD previously published in AREDS Report 3.[13] Study participants reporting the highest dietary intake of lutein/zeaxanthin were statistically less likely to have advanced AMD (both NV and GA) or large or extensive intermediate drusen than those reporting lowest dietary intake. Table 7 contains energy-adjusted median lutein/zeaxanthin intake values by quintile. The absolute (unadjusted for TEI) median for daily lutein/zeaxanthin intake was 686 µg for quintile 1, 1056 µg for quintile 2, 1426 µg for quintile 3, 1942 µg for quintile 4, and 3544 µg for quintile 5. Two published studies found similar results for the association of dietary lutein/zeaxanthin with neovascular AMD,[17,18] while 1 did not.[19]

Table 6. Sex-, Age-, and Calorie-Adjusted and Multivariable Single-Nutrient ORs for AMD by Highest vs Lowest Energy-Adjusted Intake Quintiles of Dietary Vitamins A, C, and E and Carotenoids[a]

Nutrient	Model	Quintile 5 vs Quintile 1, OR (95% CI)			
		Group 2: Extensive Small or Nonextensive Intermediate Drusen (n=1060)	Group 3: Extensive Intermediate or Large Drusen (n=1568)	Group 4: Geographic Atrophy (n=118)	Group 5: Neovascular AMD (n=658)
Vitamin A					
Vitamin A	Age + Sex	1.0 (0.8-1.3)	0.8 (0.6-1.0)[b]	0.6 (0.3-1.0)[b]	0.6 (0.4-0.8)[b]
	AREDS 3	1.0 (0.8-1.3)	0.9 (0.7-1.1)	0.7 (0.4-1.3)	0.7 (0.5-1.0)[b]
Retinol	Age + Sex	0.9 (0.7-1.2)	1.1 (0.9-1.4)	0.8 (0.5-1.5)	0.9 (0.7-1.3)
	AREDS 3	0.9 (0.7-1.2)	1.1 (0.9-1.4)	0.9 (0.5-1.6)	0.9 (0.7-1.3)
Provitamin A carotenoids					
Beta-carotene	Age + Sex	1.1 (0.8-1.5)	0.8 (0.6-1.1)	0.5 (0.3-1.0)	0.6 (0.4-0.8)[b]
	AREDS 3	1.1 (0.8-1.5)	1.0 (0.7-1.2)	0.7 (0.4-1.4)	0.7 (0.5-1.0)[b]
Alpha-carotene	Age + Sex	1.2 (0.9-1.5)	1.0 (0.8-1.3)	0.9 (0.5-1.6)	0.9 (0.7-1.3)
	AREDS 3	1.2 (0.9-1.6)	1.1 (0.8-1.4)	1.2 (0.6-2.2)	1.0 (0.7-1.4)
Beta-cryptoxanthin	Age + Sex	1.0 (0.8-1.3)	0.9 (0.7-1.1)	0.5 (0.3-0.9)[b]	0.7 (0.5-0.9)[b]
	AREDS 3	1.0 (0.8-1.3)	0.9 (0.7-1.2)	0.6 (0.3-1.2)	0.8 (0.5-1.1)
Non–provitamin A carotenoids					
Lutein/zeaxanthin	Age + Sex	0.9 (0.7-1.2)	0.6 (0.5-0.8)[b]	0.4 (0.2-0.7)[b]	0.5 (0.3-0.6)[b]
	AREDS 3	0.9 (0.7-1.2)	0.7 (0.6-1.0)[b]	0.5 (0.2-0.9)[b]	0.6 (0.4-0.8)[b]
Lycopene	Age + Sex	1.2 (0.9-1.6)	0.8 (0.7-1.1)	0.7 (0.4-1.3)	0.9 (0.6-1.2)
	AREDS 3	1.2 (0.9-1.6)	0.9 (0.7-1.2)	0.7 (0.4-1.4)	0.9 (0.6-1.2)
Vitamin C					
	Age + Sex	1.1 (0.8-1.4)	0.9 (0.7-1.2)	0.7 (0.4-1.3)	0.6 (0.4-0.8)[b]
	AREDS 3	1.1 (0.8-1.4)	1.0 (0.8-1.4)	0.8 (0.4-1.6)	0.8 (0.5-1.1)
Alpha-tocopherol					
	Age + Sex	0.9 (0.7-1.2)	0.8 (0.6-1.0)[b]	1.1 (0.7-1.7)	0.7 (0.5-0.9)[b]
	AREDS 3	0.9 (0.7-1.2)	0.8 (0.6-1.1)	1.2 (0.6-2.1)	0.8 (0.5-1.1)

Abbreviations: AMD, age-related macular degeneration; AREDS, Age-Related Eye Disease Study; CI, confidence interval; AREDS 3, model from AREDS Report 3; OR, odds ratio.

[a] Odds ratios comparing each category of AMD with controls for highest vs lowest calorie-adjusted quintile of nutrient intake. All models include terms for total energy intake (represented as a continuous variable), age (60-65, 66-70, and 71-80 y), and sex. Estimates for AREDS 3 models are also controlled for factors identified in AREDS Report 3.[13] For group 2, risk factors include angina (present/absent), arthritis (present/absent), and current use of hydrochlorothiazide (yes/no). For group 3, these factors include education (≤12 y, some college, or college degree), refractive error (hyperopia, mixed, or myopia), race (white/nonwhite), smoking history (ever ≥6 mo/<6 mo or never), existing hypertension (systolic pressure ≥160 mm Hg or diastolic pressure ≥90 mm Hg or current antihypertensive medication (yes/no), arthritis, hydrochlorothiazide use, current use of diuretics (yes/no), and lens opacity (present/absent). For group 4, these factors include education, smoking history, current use of antacids (yes/no), and current use of thyroid hormones (yes/no). For group 5, these factors include body mass index (calculated as weight in kilograms divided by height in meters squared) (≤23.6, 23.7-30.9, or ≥31.0), education, refractive error, race, smoking history, existing hypertension, and lens opacity.

[b] $P \leq .05$.

Previous studies did not report results for GA separately. Population-based studies have not yielded consistent results suggesting relationships of dietary lutein/zeaxanthin with late AMD[20]/age-related maculopathy (ARM)[21], early ARM,[21,22] soft drusen,[20] large drusen,[23] pigmentary abnormalities,[20,23] or intermediate AMD.[24] The single published study examining serum lutein/zeaxanthin–NV AMD relationships showed a significant inverse (beneficial) association.[25] Reports on serum lutein/zeaxanthin and late AMD,[20] soft drusen,[20] pigmentary abnormalities,[20] or any ARM[26,27] do not present significant or consistent findings.

There is biologic plausibility to our findings because lutein and zeaxanthin are the major diet-based macular carotenoids.[28] These compounds may affect processes modulating light or oxidant exposure.[29] Lutein and zeaxanthin have the capacity to filter short-wavelength light associated both with photochemical damage and the generation of reactive oxygen species that attack cellular lipids, proteins, and nuclear material[7]; these carotenoids also have the capacity to reduce the potency of nascent reactive oxygen species.

No clear associations with other nutrients were seen. Our equivocal findings of a possible benefit with higher vitamin E intake (Table 6) do not show a significant trend (Table 7) and, when combined with the results from other studies, suggest no clear effect of vitamin E intake from diet on the development of AMD. Specifically, the Dietary Ancillary Study of the Eye Disease Case-Control Study (EDCCS)[17] and the Vitamin E, Cataract, and Age-related Maculopathy Trial (VECAT)[30] found a trend in the direction of harm, and the Beaver Dam Eye Study[21] found mild trends in the direction of benefit. Similarly, there were no consistent findings for vitamin C[17,21] or carotenoids.[17,21,31] Final NV AMD models for all nutrients contained terms for ω-3 and ω-6 long-chain polyunsaturated fatty acid intake because these factors were associated with this outcome. Lipid-AMD relationships are the subject of a separate AREDS report.[32]

It is possible that uncontrolled confounding is contributing to the association between lutein/zeaxanthin intake with AMD. The sampling scheme for our clinic-based case-control design, with more controls recruited

Table 7. Multivariable Multinutrient ORs (95% CIs) for Neovascular AMD and Geographic Atrophy by Energy-Adjusted Intake of Dietary Vitamin A, Carotenoids, Vitamin C, and Alpha-Tocopherol[a]

Nutrient Quintile	Median/ 1000 Kcal	No. of Controls	No. of Neovascular Cases	Neovascular AMD, OR (95% CI)	*P* Trend	No. of GA Cases	GA, OR (95% CI)	*P* Trend
Vitamin A, IU					.78			.54
1	2567	195	157	1 [Reference]		28	1 [Reference]	
2	3486	242	133	0.83 (0.59-1.17)		24	1.03 (0.55-1.92)	
3	4335	223	121	0.86 (0.59-1.23)		21	1.18 (0.60-2.32)	
4	5429	234	126	0.93 (0.64-1.37)		27	1.56 (0.80-3.06)	
5	7634	221	120	0.97 (0.64-1.47)		18	1.18 (0.54-2.59)	
Retinol, µg					.42			.50
1	194	233	134	1 [Reference]		27	1 [Reference]	
2	292	230	143	0.99 (0.71-1.38)		24	0.82 (0.44-1.51)	
3	367	207	124	0.95 (0.67-1.34)		25	0.86 (0.46-1.60)	
4	458	222	131	0.96 (0.68-1.35)		19	0.70 (0.36-1.32)	
5	642	223	125	0.88 (0.62-1.24)		23	0.84 (0.46-1.56)	
Beta-carotene, µg					.19			.43
1	729	203	160	1 [Reference]		29	1 [Reference]	
2	1156	218	139	0.87 (0.62-1.22)		22	0.92 (0.49-1.72)	
3	1574	231	109	0.66 (0.47-0.93)[b]		24	0.92 (0.50-1.69)	
4	2120	244	132	0.75 (0.54-1.06)		24	0.95 (0.51-1.75)	
5	3303	219	117	0.77 (0.54-1.10)		19	0.74 (0.38-1.41)	
Lutein/zeaxanthin, µg					.08			.03
1	521	178	174	1 [Reference]		34	1 [Reference]	
2	763	219	138	0.74 (0.53-1.04)		25	0.61 (0.34-1.11)	
3	1000	237	112	0.54 (0.38-0.76)[b]		24	0.59 (0.33-1.07)	
4	1333	233	116	0.68 (0.48-0.97)[b]		17	0.50 (0.26-0.95)[b]	
5	2095	248	117	0.65 (0.45-0.93)[b]		18	0.45 (0.24-0.86)[b]	
Vitamin C, mg					.15			.95
1	31	202	166	1 [Reference]		28	1 [Reference]	
2	51	220	131	0.83 (0.59-1.16)		23	0.83 (0.44-1.54)	
3	70	218	109	0.76 (0.54-1.08)		32	1.41 (0.78-2.56)	
4	90	254	134	0.86 (0.61-1.22)		15	0.67 (0.33-1.36)	
5	129	221	117	0.98 (0.67-1.43)		20	1.14 (0.56-2.33)	
Alpha-tocopherol, alpha-tocopherol equivalent					.39			.84
1	4.3	199	145	1 [Reference]		24	1 [Reference]	
2	5.3	225	131	0.88 (0.62-1.24)		23	0.93 (0.48-1.79)	
3	6.0	236	143	0.89 (0.64-1.25)		22	0.85 (0.45-1.63)	
4	7.0	224	127	0.83 (0.58-1.17)		19	0.76 (0.39-1.48)	
5	9.8	231	111	0.80 (0.56-1.14)		30	1.26 (0.69-2.31)	

Abbreviations: AMD, age-related macular degeneration; CI, confidence interval; GA, geographic atrophy; OR, odds ratio.

[a] See Table 6. All models included terms listed in the footnote for Table 6 and quintiles of total ω-3 long-chain polyunsaturated fatty acids, arachidonic acid, and lutein/zeaxanthin (with the exception of the beta-carotene model; this model did not contain a separate term for quintiles of lutein intake).

[b] $P \leq .05$.

from volunteers in response to public advertising and more cases from the clinic base, may have increased the possibility of confounding. In addition, there may have been biased reporting of intake that could have affected our results. The accuracy of dietary recall may have varied between participants with eye disease and those in the comparison group, or some participants with severe eye disease may have altered their diets in the period immediately prior to enrollment to conform to "healthy diet" recommendations. Ancillary analyses in this AREDS cohort suggest these situations may not have occurred (data not shown); however, such bias cannot be ruled out. On the other hand, the EDCCS Dietary Ancillary Study, which found similar results,[17] recruited only newly diagnosed cases of NV AMD, which would have decreased the likelihood of such differential reporting of dietary behaviors. Furthermore, nutrient-AMD relationships were not frequently reported when those data were collected (1985-1990).

Although there are inherent limitations in the nature of this case-control sampling design, a number of factors increased the strength of our inference. The AREDS sample contains the largest number of participants with NV AMD, GA, and dietary intake data within the set of observational studies examining the relationship of diet with eye disease. All data were collected with a standardized protocol by centrally trained staff.

CONCLUSIONS

This report provides further evidence that people reporting higher intake of lutein/zeaxanthin from foods have a reduced likelihood of having NV AMD. We also report

novel findings on GA and large or extensive intermediate drusen. If these cross-sectional results can be confirmed in prospective samples and experimental studies, lutein and zeaxanthin may be considered as useful agents in food or supplement-based interventions designed to reduce the risk of AMD.

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