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Association Between Dietary Fat Intake and Age-Related Macular Degeneration in the Carotenoids in Age-Related Eye Disease Study (CAREDS)

An Ancillary Study of the Women's Health Initiative

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Objective: To evaluate the relationships between the amount and type of dietary fat and intermediate age-related macular degeneration (AMD).

Design: Women aged 50 to 79 years with high and low lutein intake from 3 sites of the Women's Health Initiative Observational Study were recruited into the Carotenoids in Age-Related Eye Disease Study. Fat intake from 1994 through 1998 was estimated using food frequency questionnaires, and AMD was assessed photographically from 2001 through 2004.

Results: Intakes of ω-6 and ω-3 polyunsaturated fatty acids, which were highly correlated (r=0.8), were associated with approximately 2-fold higher prevalence of intermediate AMD in high vs low quintiles. However, monounsaturated fatty acid intake was associated with lower prevalence. Age interactions were often observed. In women younger than 75 years (n=1325), total fat and saturated fatty acid intakes were associated with increased prevalence of AMD (multivariate adjusted odds ratios [95% confidence interval] for intermediate AMD, 1.7 [1.0-2.7] for quintile 5 vs quintile 1 for total fat [P=.10 for trend] and 1.6 [0.7-3.6] for saturated fatty acids [P=.23 for trend]). The associations were reversed in older women.

Conclusions: These results support a growing body of evidence suggesting that diets high in several types of fat may contribute to the risk of intermediate AMD and that diets high in monounsaturated fatty acids may be protective.

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AGE-RELATED MACULAR DEgeneration (AMD) is the third leading cause of blindness worldwide[1] and the leading cause of legal blindness in the United States, where 8% of people older than 65 years have intermediate AMD and 12% of people older than 80 years have advanced AMD.[2] With increasing longevity, and with the projected doubling of the population 65 years or older by 2020, advanced AMD is expected to increase in prevalence by 50%.[3] For this reason, it is important to identify modifiable aspects of lifestyle that can lower the impact of this condition.

Although genetics appears to explain a large proportion of the variability in risk,[4,5] epidemiological studies consistently suggest the influence of smoking[6] (or associated lifestyles) and cardiovascular disease or its risk factors.[7,8] Dietary factors that lower oxidative stress and/or inflammation also are sometimes related to AMD.[4,9,10] Results of the Age-Related Eye Disease Study (AREDS) demonstrated that the use of high-dose antioxidant and zinc supplements reduced progression of intermediate to late AMD,[11] although not necessarily in people with certain known genetic risk factors.[12] There is a need to better understand modifiable dietary risk factors, particularly for earlier stages of AMD.

Previous epidemiological studies generally indicate a higher prevalence or progression of AMD among people with diets high in total fat,[13-18] although associations are not always statistically significant. However, the associations with individual types of fats have been less consistent, with the exception of long-chain ω-3 polyunsaturated fatty acid (PUFA) or fish intake, which was generally related to decreased risk of AMD.[14-16,18-23] Previous studies[13-16,18,20,22] that examined the associations of saturated fatty

acid (SFA), PUFA, and monounsaturated fatty acid (MUFA) intakes with AMD observed an increased risk (not always statistically significant) for the highest vs lowest levels of intake of these fats. Although all previous studies addressed advanced AMD, few studies[13,16,17,20] addressed earlier stages that were detectable photographically, and in only 1 of these studies[20] was diet assessed before photographic ascertainment of AMD.

We investigated the amount and specific type of dietary fat intake in relation to the prevalence of photographically determined intermediate AMD in the Carotenoids in Age-Related Eye Disease Study (CAREDS), in which estimates of diet were available 4 to 7 years before AMD ascertainment and lifetime histories of suspected and known AMD risk factors were available.

METHODS

THE CAREDS POPULATION

As an ancillary study of the Women's Health Initiative Observational Study (WHI-OS),[24] CAREDS recruited women at 3 of 40 nationwide study sites: the University of Wisconsin, Madison; The University of Iowa, Iowa City; and the Kaiser Permanente Center for Health Research in collaboration with Oregon Health and Science University, Portland. The sample has been described previously.[25] Briefly, women from WHI-OS at the 3 study sites were invited to participate in CAREDS if their dietary intake of lutein plus zeaxanthin was above the 78th percentile or below the 28th percentile, as recorded on the WHI-OS baseline (1994-1998) food frequency questionnaire (N=3143 women), to study the impact of these dietary carotenoids on AMD.[25] Of the 3143 women, 93 died or were lost to follow-up between selection in 2000 and enrollment in CAREDS from 2001 through 2004. In addition, 1045 women declined participation and 2005 women were enrolled in CAREDS. Of the 2005 enrolled, 1894 participated in study visits, and gradable fundus photographs were available for 1853 participants; an additional 4 participants who had a physician-confirmed diagnosis of AMD were added to the analyses data set. Of these 1857 women, 70 were excluded from the analysis data set because of missing covariate data. Thus, there were 1787 women in the final analysis data set.

CAREDS participants are comparable to women in the larger WHI-OS cohort in the distribution of age, education, income, employment, and most potential risk factors (blood pressure, body mass index, high cholesterol levels, diabetes mellitus, history of cancer, smoking, alcohol intake, and physical activity). However, the fat intake (as a percentage of energy) was significantly lower in CAREDS participants (with a median intake of 31% vs 37% for the overall WHI-OS cohort).

Differences between those included and excluded in the analyses were evaluated to assess potential biases that may have arisen from nonparticipation of the excluded individuals. Briefly, the 1787 women included in the final data set had rates of self-reported AMD at the WHI 3-year follow-up in 1997 through 2000 that were similar to those of the 1356 women excluded from our analysis data set (4% vs 5%). Women included in the final analysis data set were younger (median age, 63 vs 65 years; $P<.001$), had more than a high school education (77% vs 69%; $P<.001$), and had a lower median intake of total fat (31% vs 32% of energy; $P<.001$) and a higher median intake of zinc (10 vs 8 mg/d) than the women excluded.

DATA COLLECTION

Diet and Other Covariate Data

The 122-item semiquantitative WHI food frequency questionnaire[26] was administered at entry into the WHI study (1994-1998). Participants were queried on the types of fats added to foods and food preparation techniques. The correlation coefficient between fat intake (percentage of energy) estimated using this questionnaire and using 8 days of records/recalls was 0.62.[26]

The CAREDS participants completed additional mailed food frequency questionnaires in 2001 through 2004 on their diets in the recent (2001-2004) and long-term (1986-1988) past to use in exploratory analyses of stable diets over time. Responses to all food frequency questionnaires were used by the Fred Hutchinson Cancer Research Center, Seattle, Washington, to compute nutrient estimates using their nutrient database, which was designed using the Minnesota Nutrient Data System, version 2.6 (Nutrition Coordinating Center Food and Nutrient Database, Minneapolis, Minnesota). Data regarding other risk and protective factors for AMD[25] were collected at WHI baseline visits (smoking, physical activity, height, weight, use of hormone therapy, alcohol, and history of chronic diseases) or collected at CAREDS study visits (history of sunlight exposure, updated histories of diabetes mellitus and supplement use, iris color, and family history of AMD).

Ascertainment of AMD and Definitions of AMD End Points

Stereoscopic fundus photographs were obtained during the CAREDS baseline study visits in 2001 through 2004 and graded for AMD at the University of Wisconsin Fundus Reading Center using slight modifications of the protocols established in the Age-Related Eye Disease Study (AREDS)[27] as previously described.[25] Overall intermediate AMD was the primary end point and was defined (similar to the definition used in AREDS) as the presence of extensive drusen (AREDS stage 3) but also included the presence of pigmentary abnormalities with at least 63 μm of drusen. There were too few cases of advanced AMD (those with exudative/neovascular macular degeneration and/or geographic atrophy) (n=34) to describe associations with fat intake reliably. The nondiseased referent group included women without intermediate or advanced AMD.

STATISTICAL ANALYSES

Fat intake evaluated at the WHI baseline visit (1994-1998), which was about 4 to 7 years before AMD ascertainment, was used in all statistical analyses. Intakes of total dietary fat, ω-6 PUFA, SFA, and MUFA (expressed as a percentage of energy) and intake of long-chain, short-chain, and total ω-3 PUFAs (expressed as a nutrient density in milligrams per 1000 kilocalories) were divided into quintiles. Odds ratios (ORs) and 95% confidence intervals (CIs) for AMD, adjusted only for age, were first computed for overall intermediate AMD, large drusen, and pigmentary abnormalities using logistic regression, by quintile of dietary fat intake (amount and type). Quintile 1 constituted the reference group. *P* values for trend were calculated using quintile medians of fat intake. We tested medical, lifestyle, ocular, and dietary factors as potential confounders by entering these additional variables singly into the regression models. If the addition of the variable singly in the model changed the OR for intermediate AMD by 10% or more, the variable was added to the final regression model. (The use of a criterion of inclusion of changing the OR by ≥5% did not alter the observations [data not shown].) The variables tested as

potential confounders included age (in years); cigarette smoking history (in 3 categories of pack-years smoked: 0, >0 to <7, and ≥7 pack-years); alcohol consumption (in grams per day); body mass index (calculated as weight in kilograms divided by height in meters squared); hormone therapy (never, past, or current); current physical activity (in metabolic equivalents per day); use of high-dose antioxidant supplements for less than 5 years vs 5 or more years; self-reported presence or absence of hypertension, cardiovascular disease, and diabetes mellitus; family history of AMD (having ≥1 first-degree relative diagnosed as having AMD when >55 years); and iris color (blue vs other). We also tested the impact of adjusting for intake of the following dietary attributes: lutein plus zeaxanthin (in micrograms per day); vitamin C (in milligrams per day); vitamin A (in micrograms per day); vitamin E (in milligrams per day); vitamin D (in micrograms per day); energy (in kilocalories per day); protein (as a percentage of total energy); carbohydrates (as a percentage of total energy); beta carotene (in micrograms per day); and zinc (in milligrams per day).

In a combined model, we further tested associations by including the following statistically significant risk factors for any type of AMD in this sample: pack-years smoked (0, >0 to <7, and ≥7 pack-years), history of diabetes mellitus (yes or no), family history of AMD (yes or no, having ≥1 immediate family member with suspected AMD), blue iris color (yes or no), history of cardiovascular disease (yes or no), and postmenopausal hormone therapy use (never, past, or current). However, additional adjustment for these risk factors combined did not change the ORs. Final models were adjusted for the lutein intake group variable to control for the unique participant selection strategy because the CAREDS sample was selected only from the WHI-OS parent population of participants with high and low intakes of lutein.

We tested for potential interactions (considered significant for the purpose of these analyses at $\alpha \leq .10$) to explore whether the associations between total and specific types of fat intake and intermediate AMD differed by age and by variables that might reflect susceptibility to AMD, that is, personal history of cardiovascular disease and family history of AMD. Furthermore, in exploratory analyses, we restricted analyses to a subgroup of women who had stable fat intakes from the 1986-1988 to the 1994-1998 examinations to ascertain whether the associations were consistent with the analyses performed for the diets assessed at the WHI baseline. Women were classified as having stable fat diets if their quintile ranking for total or specific type of fat intake at the WHI baseline differed by no more than 1 quintile from their ranking for total or specific fat intake at 6 to 7 years previously.

In addition, to further interpret associations of dietary fats with AMD, we computed ORs for intermediate AMD by intakes of food sources of fats—that is, foods that were top contributors to the total dietary fat or a specific type of dietary fat—in this sample. We also evaluated the relationship between AMD and the intakes of fish and nuts, foods that have been suggested to confer protection in other samples. For these analyses, the number of monthly servings of each food group was divided into tertiles. All analyses were conducted using SAS statistical software, version 9.1 (SAS Institute, Inc; Cary, North Carolina).

RESULTS

We evaluated the distribution of risk factors for AMD and other participant characteristics by quintiles of total fat and specific type of dietary fat intakes. These data are summarized in **Table 1** for quintiles 1 and 5 of intakes of total fat and ω-6 and ω-3 PUFAs. (Data are not presented separately for SFA and MUFA because the characteristics were very similar to those for total fat intake.) The associations presented in Table 1 are also similar when analyzed separately for women younger than 75 years (data not shown). Higher intakes of these and total fats were associated with higher body mass index, rates of hypertension and diabetes mellitus, and intakes of energy and vitamin E, but lower intakes of lutein plus zeaxanthin, vitamins C and D, and zinc.

We next evaluated the interrelationships of total and specific types of fats. Total fat intake was positively and significantly correlated with intakes of SFA (r=0.90), MUFA (r=0.97), ω-6 PUFA (r=0.75), and ω-3 PUFA (r=0.70). Similarly, intakes of all of the specific types of fats were positively and significantly correlated with each other (data not shown). Briefly, ω-6 PUFA intake was most correlated with ω-3 PUFA intake (r=0.8) and least with SFA intake (r=0.4); MUFA intake was most correlated with SFA intake (r=0.8) and least with ω-3 PUFA intake (r=0.6).

OVERALL INTERMEDIATE AMD

Total Dietary Fat

Age-adjusted ORs for intermediate AMD did not differ among women across the different levels of total fat intake in the overall population (**Table 2**). The ORs for the specific end points of extensive drusen and pigmentary abnormalities were generally consistent with those observed for overall intermediate AMD (data not shown). Because we noted significant age interactions (P=.02), the associations were evaluated separately in women younger than 75 years and those 75 years or older. In women younger than 75 years, those in the highest quintile of total dietary fat intake had 70% higher odds for overall intermediate AMD compared with those in the lowest quintile, although the linear trend was only marginally significant across all quintiles (P=.10). In contrast, women 75 years or older in the highest quintile for total dietary fat intake had about 50% lower odds for overall intermediate AMD compared with those in the lowest quintile (P=.02 for trend).

Types of Dietary Fats

Saturated Fatty Acids. In the overall sample that included women of all ages, the age-adjusted OR (95% CI) for overall intermediate AMD among women in high vs low quintiles was 1.7 (1.0-2.7). A significant interaction (P=.01) between SFA and age (as a continuous variable) was observed. Higher SFA intake was associated with a higher prevalence of overall intermediate AMD in women younger than 75 years (Table 2) but not in women 75 years or older (multivariate OR [95%CI] in quintile 5 vs quintile 1, 0.9 [0.3-2.6]).

Monounsaturated Fatty Acids. In women of all ages, the age-adjusted OR for overall intermediate AMD did not differ among women across quintiles of MUFA intake (OR [95% CI] in quintile 5 vs quintile 1, 1.0 [0.7-1.5]; P=.87 for trend). However, after adjusting for the ω-6 PUFA, SFA, and lutein intake groups, MUFA intake was associated with a significantly decreased risk of overall in-

Table 1. Characteristics of 1787 CAREDS Participants in Quintile 5 vs Quintile 1 of Intakes of Total and Specific Types of Fat at WHI Baseline, 1994-1998[a]

Characteristic	Total Fat			ω-6 PUFAs			ω-3 PUFAs		
	Quintile 1	Quintile 5	*P* Value	Quintile1	Quintile 5	*P* Value	Quintile 1	Quintile 5	*P* Value
Demographics									
White, %	97	98	.46	96	97	.24	97	96	.06
Education completed, %									
High school	15	34	<.001	16	31	<.001	19	25	.31
College	48	51		48	46		48	48	
Graduate school	37	15		36	23		33	27	
Age, mean (SE), y[b,c]	70 (0.37)	69 (0.36)	.40	70 (0.36)	69 (0.36)	.70	70 (0.36)	69 (0.36)	.70
Intake from foods, mean (SE)[b]									
Energy, kcal/d	1552 (34)	1682 (33)	.009	1549 (33)	1628 (33)	.02	1591 (33)	1623 (33)	.04
Total fat, % kcal	20 (0.14)	44 (0.14)	<.001	23 (0.31)	41 (0.31)	<.001	24 (0.35)	39 (0.35)	<.001
PUFA, % kcal	4 (0.08)	9 (0.08)	<.001	4 (0.05)	10 (0.05)	<.001	4 (0.08)	9 (0.08)	<.001
SFA, % kcal	7 (0.10)	15 (0.09)	<.001	9 (0.17)	13 (0.17)	<.001	8 (0.16)	13 (0.16)	<.001
MUFA, % kcal	7 (0.07)	16 (0.07)	<.001	8 (0.13)	15 (0.13)	<.001	9 (0.15)	14 (0.15)	<.001
Lutein + zeaxanthin, μg/d	3032 (85)	1526 (84)	<.001	2566 (88)	1886 (87)	<.001	2174 (88)	2329 (88)	.50
Vitamin C, mg/d	152 (3.3)	74 (3.2)	<.001	140 (3.4)	89 (3.4)	<.001	128 (3.5)	101 (3.5)	<.001
Vitamin E, mg/d	8 (0.23)	9 (0.23)	<.001	7 (0.23)	9 (0.23)	<.001	7 (0.23)	9.5 (0.23)	<.001
Vitamin D, μg/d	6 (0.20)	5 (0.20)	.004	6 (0.19)	5 (0.19)	.04	7 (0.20)	5 (0.20)	<.001
Zinc, mg/d	11 (0.28)	10 (0.28)	.001	11.5 (0.27)	10 (0.27)	<.001	11 (0.27)	10 (0.27)	.04
Lifestyle									
Pack-years ≥7, % of smokers[c]	20	21	.50	19	22	.90	21	24	.30
Physical activity, mean (SE), MET/wk[b]	21 (0.77)	9 (0.76)	<.001	19 (0.78)	11 (0.77)	<.001	17 (0.79)	12 (0.79)	<.001
High-dose antioxidant users, %[c,d]	12	6	<.001	9	8	<.001	11	7	<.001
Medical history									
BMI, mean (SE)[b]	26 (0.31)	29 (0.30)	<.001	27 (0.31)	29 (0.30)	<.001	27 (0.31)	29 (0.31)	<.001
Cardiovascular disease, %	22	25	.90	22	24	.50	24	25	.90
Hypertension, %	21	34	.005	24	33	.05	24	34	.006
Diabetes mellitus, %	1	6	.009	2	6	.004	2	6	.03
Family history of AMD, %[c]	16	17	.80	13	16	.21	15	19	.10
Ocular outcomes, %[c]									
Intermediate AMD	18	19	.70	17	21	.60	16	25	.01
Large drusen	16	17	.30	13	18	.40	12	21	.01
Pigmentary abnormalities	9	11	.70	9	12	.50	10	15	.07

Abbreviations: AMD, age-related macular degeneration; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CAREDS, Carotenoids in Age-Related Eye Disease Study; MET, metabolic equivalents; MUFA, monounsaturated fatty acid; PUFA, polyunsaturated fatty acid; SFA, saturated fatty acid; WHI, Women's Health Initiative.

[a] Data are age adjusted, directly standardized for the age groups 69 years or younger, 70 to 74 years, and 75 years or older, except for age. *P* values were calculated using regression coefficients from the analyses of covariance for continuous variables and using the Cochran-Mantel-Haenszel statistic for general association for categorical variables.

[b] Indicates continuous variable; data are given as least squares mean (SE).

[c] Assessed in CAREDS questionnaires or study visits.

[d] Indicates daily intake of at least 2 of the following 3 antioxidants from supplements containing at least 120 mg of vitamin C, at least 60 IU (40 mg) of vitamin E, or at least 10 000 μg of beta carotene at the CAREDS baseline examination for 10 or more years.

termediate AMD among women in quintiles 3 through 5 compared with quintile 1 (*P*=.12 for trend) (quintile 2 OR, 0.9 [95%, CI 0.5-1.4]; quintile 3, 0.5 [0.3-0.97]; quintile 4, 0.5 [0.2-0.9]; and quintile 5, 0.5 [0.2-1.0]). Associations, again, differed by age (*P*=.02 for interaction). Although the inverse occurred in both women younger than 75 (Table 2) and women 75 years or older, associations in the older group were stronger (multivariate OR [95% CI] for AMD in quintile 5 vs quintile 1, 0.2 [0.1-0.8]; *P*=.02 for trend).

ω-6 Polyunsaturated Fatty Acids. In women of all ages, ω-6 PUFA intake was directly associated with intermediate AMD (OR [95% CI] in high vs low quintiles, 2.0 [1.1-3.5]) after adjustment for age and MUFA, SFA, and lutein intake groups. As with other fats, we stratified analyses by age because of the presence of age interactions (*P*=.10). However, the association remained direct in both younger (Table 2) and older age groups (multivariate OR [95% CI], 2.7 [1.1-6.9]; *P*=.04 for trend). When we restricted the analyses to women with stable ω-6 PUFA intake, the ORs were even further from unity (Table 2).

ω-3 Polyunsaturated Fatty Acids. The intake of ω-3 and ω-6 PUFAs were highly correlated in this sample (*r*=0.82; *P*<001). In women of all ages, the OR (95% CI) for intermediate AMD (quintile 5 vs quintile 1) was 1.8 (1.2-2.6; *P*=.003 for trend) after adjusting for age and other fatty acids. The associations with shorter-chain (α-linolenic acid and stearidonic acid) and long-chain (docosahexaenoic, docosapentaenoic, and eicosapentaenoic acids) ω-3 PUFAs analyzed separately were similar in direction in the overall sample (data not shown) and in women younger than 75 years, in whom ORs (95% CIs)

Table 2. Odds for Overall Intermediate AMD by Quintiles of Intakes of Total and Specific Types of Dietary Fat in 1781 CAREDS Participants, 2001-2004

	Quintile					*P* Value	
	1	2	3	4	5	For Trend[a]	For Interaction[b]
Total Fat							
All ages							
Median intake, % of energy	21	26	31	36	43		.02
No. with outcome/at risk	65/339	72/355	61/360	62/346	67/353		
Age-adjusted OR (95% CI)	1 [Reference]	1.1 (0.7-1.6)	0.8 (0.6-1.2)	0.9 (0.6-1.3)	1.0 (0.7-1.5)	.89	
Multivariate OR (95% CI)[c]	1 [Reference]	1.1 (0.7-1.6)	0.8 (0.6-1.3)	0.9 (0.6-1.3)	1.0 (0.7-1.5)	.79	
Restricted to women with stable fat intake[d]	1 [Reference]	1.3 (0.8-2.0)	0.8 (0.5-1.3)	0.9 (0.6-1.5)	1.0 (0.6-1.7)	.72	
Age <75 y							
Median intake, % of energy	21	26	31	36	43		
No. with outcome/at risk	29/262	38/262	39/264	36/263	48/262		
Age-adjusted OR (95% CI)	1 [Reference]	1.4 (0.8-2.3)	1.4 (0.8-2.3)	1.2 (0.8-2.2)	1.8 (1.1-3.0)	.05	
Multivariate OR (95% CI)[c]	1 [Reference]	1.3 (0.8-2.2)	1.4 (0.8-2.3)	1.2 (0.7-2.0)	1.7 (1.02-2.7)	.10	
Restricted to women with stable fat intake[d]	1 [Reference]	1.6 (0.8-3.2)	1.2 (0.6-2.5)	1.5 (0.7-2.9)	1.8 (0.9-3.7)	.19	
Age ≥75 y							
Median intake, % of energy	20	26	30	35	42		
No. with outcome/at risk	34/86	33/88	24/88	24/89	22/89		
Age-adjusted OR (95% CI)	1 [Reference]	0.9 (0.5-1.7)	0.6 (0.3-1.1)	0.6 (0.3-1.1)	0.5 (0.3-1.0)	.008	
Multivariate OR (95% CI)[c]	1 [Reference]	0.9 (0.5-1.7)	0.6 (0.3-1.1)	0.6 (0.3-1.1)	0.5 (0.3-1.0)	.02	
SFA[e]							
Median intake, % of energy	7	9	10	12	15		.01
No. with outcome/at risk	30/263	36/261	35/265	45/262	45/262		
Age-adjusted OR (95% CI)	1 [Reference]	1.2 (0.7-2.2)	1.2 (0.6-2.3)	1.6 (0.8-3.3)	1.6 (0.7-3.7)	.02	
Multivariate OR (95% CI)[f]	1 [Reference]	1.2 (0.7-2.2)	1.2 (0.6-2.3)	1.6 (0.8-3.3)	1.6 (0.7-3.6)	.23	
Restricted to women with stable SFA intake[d]	1 [Reference]	1.4 (0.7-3.1)	1.8 (0.7-4.1)	2.4 (1.0-6.1)	2.4 (0.9-6.7)	.12	
MUFA[e]							
Median intake, % of energy	8	10	11	13	16		.02
No. with outcome/at risk	29/245	35/261	38/266	38/269	50/272		
Age-adjusted OR (95% CI)	1 [Reference]	1.2 (0.7-2.0)	1.2 (0.7-2.1)	1.2 (0.7-2.0)	1.7 (1.0-2.8)	.04	
Multivariate OR (95% CI)[f]	1 [Reference]	0.9 (0.5-1.7)	0.8 (0.4-1.7)	0.6 (0.3-1.5)	0.8 (0.3-2.1)	.67	
Restricted to women with stable MUFA intake[d]	1 [Reference]	0.8 (0.4-1.7)	0.5 (0.2-1.3)	0.4 (0.1-1.1)	0.5 (0.2-1.7)	.29	
ω-6 PUFA[e]							
Median intake, % of energy	3	4	5	6	8		.10
No. with outcome/at risk	28/261	39/264	35/250	38/255	50/283		
Age-adjusted OR (95% CI)	1 [Reference]	1.5 (0.8-2.6)	1.4 (0.8-2.6)	1.5 (0.8-2.8)	1.7 (0.8-3.3)	.04	
Multivariate OR (95% CI)[f]	1 [Reference]	1.5 (0.8-2.6)	1.5 (0.7-2.7)	1.5 (0.8-2.9)	1.7 (0.8-3.4)	.07	
Restricted to women with stable ω-6 PUFA intake[d]	1 [Reference]	1.5 (0.7-3.1)	2.3 (1.1-5.0)	2.1 (0.9-4.8)	2.1 (0.9-5.2)	.17	
ω-3 PUFA[e]							
Median intake, mg/1000 kcal	500	634	748	880	1,106		.10
No. with outcome/at risk	26/232	35/227	30/226	36/229	63/209		
Age-adjusted OR (95% CI)[g]	1 [Reference]	1.5 (0.9-2.6)	1.2 (0.7-2.1)	1.6 (0.9-2.7)	2.7 (1.6-4.4)	<.001	
Multivariate OR (95% CI)	1 [Reference]	1.5 (0.9-2.6)	1.2 (0.7-2.1)	1.6 (0.9-2.7)	2.6 (1.6-4.4)	<.001	
Restricted to women with stable ω-3 PUFA intake[d]	1 [Reference]	1.8 (0.9-3.6)	1.2 (0.6-2.5)	1.8 (0.9-3.6)	3.4 (1.8-6.6)	<.001	

Abbreviations: AMD, age-related macular degeneration; CAREDS, Carotenoids in Age-Related Eye Disease Study; CI, confidence interval; MUFA, monounsaturated fatty acid; OR, odds ratio; PUFA, polyunsaturated fatty acid; SFA, saturated fatty acid.

[a] Calculated using quintile medians of the fats.

[b] Indicates interaction for age and total and specific fats, calculated with age as a continuous variable in the model.

[c] Included age and lutein intake groups (high vs low).

[d] Women were considered to have stable fat intakes for total and specific fats if their quintile ranking for total or specific type of fat intake at the Women's Health Initiative baseline examination (1994-1998) differed from their ranking for total fat intake at the 1986-1988 examination by no more than 1 quintile (n = 1325).

[e] Restricted to women younger than 75 years.

[f] Models contained MUFA, PUFA, SFA, age, and lutein intake group (low vs high).

[g] Adjusted for age and energy.

in quintile 5 vs quintile 1 were 2.7 (1.7-4.5; $P<.001$ for trend) and 1.3 (0.8-2.0) for short- and long-chain ω-3 PUFAs, respectively.

Previous investigations have observed a protective influence of ω-3 PUFA or fish to be stronger among people with lower intake of ω-6 PUFA,[14,18,21] possibly because ω-6 PUFA replaces ω-3 PUFA in membranes and competes with ω-3 PUFA for cyclooxygenases to form proinflammatory eicosanoids.[28] Therefore, we computed associations of long-chain ω-3 PUFA intake with AMD separately, stratifying by intake level of ω-6 PUFA (above and below the median intake of 6% as a percentage of total energy). The ORs (95% CIs) for AMD (adjusted for age and energy) in the highest vs lowest quintile for long-

chain ω-3 PUFA intake were 1.0 (0.5-2.1) vs 2.7 (1.7-4.5) for women below vs above the median for ω-6 PUFA intake ($P=.38$ for interaction).

Finally, we conducted exploratory analyses of potential interactions between lutein and fat intake to evaluate the effect on associations of dietary fat intake with AMD created by limiting our sample to women whose intakes of lutein plus zeaxanthin were below the 28th percentile and above the 78th percentile; that is, less than 1.1 and more than 2.0 mg/d. There was a wider range of fat intake among women in the low compared with the high lutein intake group (25th, 50th, and 75th percentiles of 28%, 34%, and 40% compared with 24%, 28%, and 33% of energy, respectively). This persisted across all types of fat (data not shown). There were no significant interactions of fat intake with lutein intake except for ω-3 PUFA. In this case, ω-3 PUFA intake was associated with a higher risk of AMD only when lutein intake was low (multivariate adjusted ORs [95% CIs] among women with lutein intakes of <1.1 and >2.0 mg, 2.7 [1.6-4.6] and 1.1 [0.6-1.9], respectively; $P=.08$ for interaction). This may reflect the wider range of fat intake among women with lower lutein intake.

FOOD SOURCES OF FATS

To interpret associations of fat intake with AMD, we explored associations of AMD with specific food sources of fat. In **Table 3**, we list associations in the youngest group at risk for AMD (women <75 years) because these associations are least likely to reflect biases due to selective mortality or diet change. Most of the fat intake in the CAREDS sample was provided by dairy foods (26%), added fats (24%), and meats (16%). Intake of added animal or vegetable fats or high-fat versions of dairy foods or meats was consistently associated with a higher prevalence of AMD, although the associations with the intake of no one food group was statistically significant. Although the intake of low-fat dairy foods supplied 39% of total dairy fat, intake in the highest vs lowest tertile was related to half the risk for AMD.

The ω-3 PUFAs come from a wide variety of foods. These PUFAs include short-chain PUFAs, of which linolenic acid predominates, and long-chain ω-3 PUFAs, mostly from docosahexaenoic and eicosapentaenoic acids. In this sample, the largest proportion of ω-3 PUFAs of any type came from dairy products (16% from milk, cheese, yogurt, and butter); mayonnaise (13%); other salad dressings (13%); vegetable cooking oils (11%); fish (11%); meat (10%); eggs (1%); cereals (1%); fruits and vegetables (9%); salty snacks (4%); breads, rice, and pasta (3%); desserts (3%); and margarine (2%). These sources reflect the frequency of eating these foods and the ω-3 PUFA concentrations in them. Rich sources of ω-3 PUFAs include nuts and dark fish. No associations of AMD with food sources of ω-3 PUFAs, nuts, and dark fish were observed, but the consumption frequency of these foods was low. Moreover, the predominant intake of dark fish, a primary source of long-chain ω-3 PUFAs, was in the form of tuna salad, and most fat (approximately 70%-90%) in tuna salad comes from added vegetable fat (mayonnaise), which was directly (although nonsignificantly) associated with AMD.

COMMENT

TOTAL DIETARY FAT

In this sample, total fat intake was not associated with overall intermediate AMD; however, associations varied with age. Direct associations of total fat intake with AMD in the younger women (three-fourths of our sample) were consistent with the large body of evidence that suggests that AMD risk is directly associated with the level of total fat intake. High levels of fat intake have been significantly associated with higher prevalence, incidence, or progression in several studies.[14,15,29] In several additional studies, associations with total fat intake have been direct, even if not statistically significant.[13,14,16-18,29] Data from the present study extend the body of evidence to suggest that this association could reflect early stages in the development of AMD. It is common knowledge that high-fat diets are often micronutrient poor, and this trend can be observed in Table 1. Consequently, high-fat diets might be a marker for diets that are poor in many micronutrients that could protect against AMD. Although associations in this study persisted, after adjusting for the level of lutein in the diet (Table 2) and other individual micronutrients (data not shown), some level of residual confounding is likely to persist owing to imperfect measurement of diet and the fact that diet over a short time is queried relative to the decades of adult life, over which diet could influence the health of the retina.

The inverse associations between AMD and total fat intake in the older segment of the population could be the result of selective mortality bias. Similar reversals of associations in older compared with younger persons were observed with the intake of lutein plus zeaxanthin in the same sample[25] and a separate sample.[30] Moreover, the older women who enrolled in this study were more likely to have healthier diets and lifestyles than women in their birth cohorts who did not survive. In addition, evidence exists that having AMD is associated with increased risk of mortality.[31-34] Thus, potentially adverse relationships between diets high in fat and AMD could be masked in older segments of the sample. These biases are likely to contribute to the inconsistency in nutrition and other modifiable risk factors for AMD observed across epidemiological studies.

TYPES OF DIETARY FAT

The intake of ω-6 PUFAs, primarily provided by added vegetable fats (salad dressing, mayonnaise, and margarine), was associated with an increased prevalence in intermediate AMD in the CAREDS sample. Similar associations with overall ω-6 PUFA intake or that of the major ω-6 PUFA (linoleic acid) have been observed in 5 previous investigations in American samples,[13-15,18,21] although in some the association was most direct in women[13,15] (possibly reflecting that this is a more important contributor to fat intake in women than in men). In another American sample[35] and in Australian[16,20] and French[29] cohorts, the ORs for AMD among persons with high compared with low intake of ω-6 PUFAs or linoleic acid were close to unity. Nevertheless, more studies than not suggest direct associations of vegetable fat intake with AMD.

Table 3. Multivariate Adjusted Odds for Intermediate AMD by Tertiles of Food Sources of Dietary Fat Among CAREDS Participants Younger than 75 Years[a]

	% of Total Fat	Tertile 1	Tertile 2	Tertile 3
Dairy foods	26			
High-fat,[b] 61% of dairy fat				
Median servings/mo		9.0	18	36
OR (95% CI)		1 [Reference]	1.3 (0.9-1.9)	1.1 (0.8-1.7)
Low-fat,[c] 39% of dairy fat				
Median servings/mo		11.0	36	87
OR (95% CI)		1 [Reference]	1.2 (0.8-1.6)	0.5 (0.3-0.8)
Added vegetable fats,[d] 79% of added fats	24			
Median servings/mo		10.0	26	54
OR (95% CI)		1 [Reference]	1.2 (0.8-1.7)	1.4 (0.9-2.0)
Animal fats[e]	4			
Median servings/mo		1.0	4.0	21
OR (95% CI)		1 [Reference]	0.9 (0.6-1.3)	1.2 (0.9-1.8)
Meats	16			
High-fat,[f] 20% of total meat fat				
Median servings/mo		0.0	1.0	4.5
OR (95% CI)		1 [Reference]	1.0 (0.7-1.5)	1.2 (0.9-1.8)
Low-fat,[g] 80% of total meat fat				
Median servings/mo		9.0	18	34
OR (95% CI)		1 [Reference]	0.8 (0.6-1.2)	1.0 (0.7-1.4)
Candy/high-fat desserts[h]	8			
Median servings/mo		3.0	12	32
OR (95% CI)		1 [Reference]	1.1 (0.8-1.6)	0.9 (0.6-1.4)
Peanuts and nuts	5			
Median servings/mo		0.5	2.3	11.0
OR (95% CI)		1 [Reference]	0.9 (0.6-1.3)	1.1 (0.7-1.5)
Salty snacks[i]	2			
Median servings/mo		1.0	6	20
OR (95% CI)		1 [Reference]	1.0 (0.7-1.4)	1.1 (0.7-1.6)
Fish	1			
Total				
Median servings/mo		2.0	5.2	11.5
OR (95% CI)		1 [Reference]	1.0 (0.7-1.5)	1.0 (0.7-1.6)
Fried or white fish				
Median servings/mo		0.0	2.3	5.3
OR (95% CI)		1 [Reference]	0.9 (0.6-1.3)	0.9 (0.6-1.3)
Dark fish, 20% of fat from fish				
Median servings/mo		1.0	2.5	6.7
OR (95% CI)		1 [Reference]	1.1 (0.8-1.7)	1.3 (0.8-1.9)

Abbreviations: AMD, age-related macular degeneration; CAREDS, Carotenoids in Age-Related Eye Disease Study; CI, confidence interval; OR, odds ratio.
[a] N = 1313 after excluding women with late AMD. Adjusted for age and lutein intake groups (high vs low).
[b] Includes cheese and cheese dishes, butter, ice cream and custards, cream, and dishes made with cream and whole milk.
[c] Includes skim or 2% fat milk, low-fat cheeses, yogurt, and low-fat dairy products and desserts.
[d] Includes margarine, mayonnaise, salad dressing, and vegetable oils.
[e] Includes butter, gravy, and lard.
[f] Includes hot dogs, sausages, luncheon meat, fried chicken, organ meats, gravy, and lard.
[g] Includes beef, pork, lamb, poultry, and mixed dishes containing them. This represents 80% of fat from meats.
[h] Includes chocolate candy, donuts, pastries, cookies, and pies.
[i] Includes popcorn (popped in oil) and potato and snack chips.

These direct associations of ω-6 PUFA intake with AMD could reflect the fact that this is a common source of fat in this sample and that fat simply replaces calories spent on eating more nutrient-dense foods. It could also reflect a specific deleterious influence of these fats. Omega-6 PUFAs promote inflammation,[36] which is thought to contribute to retinal damage that may promote AMD.[37] (Although PUFAs lower levels of atherogenic blood lipids,[38] ω-6 PUFAs may be atherogenic because they promote inflammatory processes.[36] Some studies have found atherosclerosis to be associated with AMD.[8,39])

The overall effect of fatty acids on the inflammatory process seems to depend on the level of other fatty acids from which proinflammatory and anti-inflammatory cytokines and eicosanoids are synthesized. The ω-6 and ω-3 PUFAs have been found to have antagonist effects on inflammation, which may be explained by competition for shared enzymes.[28] However, the effects of ω-6 PUFAs on inflammation and atherosclerosis are complex and also appear to depend on levels of other fatty acids. Levels of other fatty acids, such as ω-9 fatty acids, may also influence the overall inflammatory effect of ω-6 PUFAs.[36] It has been suggested that the low ratio of ω-6 to the sum of ω-3 plus ω-9 fatty acids (the most abundant of which is oleic acid, an MUFA) in Mediterranean diets may explain the low prevalence of cardiovascular disease and

chronic inflammatory diseases in populations that follow these dietary patterns.[36]

Another potential explanation for the direct association of ω-6 PUFAs with AMD in this and some other samples could be that solid vegetable fats—in America—are also a source of *trans*-fatty acids, which may be atherogenic. *Trans*-fatty acid intake in 3 American samples was associated with a high risk of AMD.[14,15,18] However, in the present study, the intake of *trans*-fatty acids was not associated with AMD (data not shown).

An adverse effect of ω-6 PUFA could reflect the possibility that PUFAs enhance oxidative damage of the retina.[40-42] The unsaturated fats, because of double bonds, are more susceptible to attack by reactive oxygen species. It is well known that photoreceptors concentrate ω-6 PUFAs,[43] accrued partially from the diet.[44] Evidence suggests that peroxidized lipids that increase in the retinal membrane with age could promote AMD progression.[42,45]

We also observed direct (adverse) associations between AMD and the intake of dietary long-chain (from marine oils) and shorter-chain ω-3 PUFAs. This is in contrast to protective associations between overall ω-3 PUFA intake reported in 1 study[21] and long-chain ω-3 PUFA or fish intake and AMD reported in numerous previous studies.[14,16,18-21,23,35] We did not find inverse associations between AMD and higher intake of ω-3 PUFAs in general or of fish specifically. In fact, associations with the intake of ω-3 PUFAs were direct both for linolenic acid, the main source of dietary ω-3 PUFAs, and for long-chain ω-3 PUFAs, which include docosahexaenoic and eicosapentaenoic acids, which are mainly provided by fish from cold waters. This may be because ω-3 PUFA consumption was highly correlated with the ω-6 PUFA consumption in this sample and to consuming both fat types concurrently. For example, a major source of ω-3 PUFA was tuna salad, which supplies not only long-chain ω-3 PUFAs but also high levels of ω-6 PUFAs in the form of mayonnaise.

Results of 2 previous studies also suggest direct relations between ω-3 PUFAs and AMD.[15,46] However, in 1 study, although the intake of linolenic acid, the major short-chain ω-3 PUFA, was associated with a higher risk of AMD, the intake of long-chain ω-3 PUFAs was associated with lower risk. Fish intake was directly related to the progression of AMD in another study,[46] but the authors state that this is likely due to recent diet change in study participants, given that diet was assessed after baseline AMD was assessed.

A protective influence of ω-3 PUFAs may depend on the intake of ω-6 PUFAs. In 3 past studies in which ω-6 PUFAs were associated with higher risk, a protective association with long-chain ω-3 PUFA was observed only in conjunction with low levels of ω-6 PUFAs.[14,18,21] In the present study, direct associations with ω-3 PUFA intake were stronger in women whose intake of ω-6 PUFAs was above—rather than below—6% of energy, but the interaction was not statistically significant.

Overall, despite the results of the present study, the larger body of epidemiological evidence suggests that the intake of long-chain ω-3 PUFAs and/or fish is related to a lower risk of AMD. This evidence may reflect a benefit of long-chain ω-3 PUFAs, which appear to have an anti-inflammatory effect,[22] or a benefit of other nutrients provided by fish, such as selenium and/or vitamin D. The impact of long-chain ω-3 PUFA supplements on the progression of AMD is currently being tested in a large multicenter clinical trial.[47]

The direction of association of AMD with the intake of other specific types of fats was similar to that of PUFAs (direct) except for MUFAs, raising the possibility that these fats, or other food components they are associated with, may not increase the risk of AMD or may protect against it. Associations of MUFA with AMD across other studies are quite inconsistent. This could reflect, in part, different strategies for the adjustment of these associations for other aspects of diet in general or fat in particular. The MUFAs in this and other samples contribute the most or the second most to total fat intake and could reflect associations with the level of fat intake. In this sample and in a previously reported study,[15] the direction of associations between MUFAs and AMD changed only after adjusting for the intake of other fats that were significant sources of energy (PUFAs and SFA), better reflecting the relative contributions of fat types rather than the level of fat in diets. Direct (albeit not always significant) associations were observed in 3 previous studies in which the intake of other energy-yielding fats was not adjusted for.[13,14,16,29,35] In only 1 previous study was an association of MUFA intake with AMD direct, even after adjusting for the intake of other fats.[18]

In the present study, lower prevalence of AMD among women in quintiles 3 to 5 for MUFA intake, compared with quintile 1, could reflect the fact that these foods provide other nutrients that could protect against AMD. For example, dairy and meat products, which are important contributors of MUFA in American diets,[48] are also important sources of zinc.[49] In the present study, although high-fat versions of these foods were associated with a high prevalence of AMD, the lower-fat versions reduced the risk (low-fat dairy) or were not associated with risk (medium- or low-fat meat) (Table 3). However, zinc intake was not related to AMD in the present study, and it did not influence associations with MUFAs (data not shown). The intake of foods that provide MUFAs in Mediterranean diets (nuts and olive oil) was too low in this population to adequately evaluate the associations with the intake of these foods.

The MUFAs may protect against AMD via their antiatherogenic role. It has been hypothesized that atherosclerosis and its risk factors are related to the development of AMD.[8,39,50-53] Previous epidemiological studies and intervention trials of diets high in MUFAs suggest a protective effect toward atherosclerosis and coronary heart disease.[54] Because olive oils[55] and nuts[56] that are rich in MUFAs are also rich in vitamin E and other plant antioxidants, high MUFA intake may be a marker of other aspects of diet that may be associated with lower risk of AMD in some samples.

In addition to those already discussed, additional limitations of the present study must be considered. First, although we tested the influence of adjusting for a large number of potential risk or protective factors (ie, smoking, history of diabetes mellitus and cardiovascular disease, family history of AMD, iris color, and postmenopausal hormone therapy use), we did not have information about the genetic risk for AMD. Adjustment for self-reports of family history of AMD did not influence or modify the associations we observed.

Second, the sample selection strategy in the present study differed from that in previously published studies; only women who had lutein intake of less than 1.1 or more

than 2.0 mg/d were included. Women with lutein intake ranging from 1.1 to 2.0 mg were excluded to maximize the power to study relationships of lutein with age-related eye diseases. The impact of excluding women in the middle ranges cannot be known with certainty, but is not likely to have explained the associations observed because they were generally consistent in groups with low and higher lutein intake.

Third, there may be limitations in the generalizability of these results to the larger US population of women or to men. Unlike the overall US population in the Third National Health and Nutrition Examination Survey, conducted during a period similar to that of WHI recruitment, women in the CAREDS sample are primarily white (98%). Women in the CAREDS sample are also more educated, have higher incomes, and are generally healthier than American women overall, except for being more likely to be overweight (37% vs 26%) or obese (26% vs 19%). Fewer CAREDS participants currently smoke (4% vs 19%), but a larger proportion smoked in the past (39% vs 31%). Overall, 43% of the CAREDS participants and 50% of US women older than 40 years ever smoked.

We were unable to ascertain whether AMD antedated recruitment into the WHI study. However, retinal photographs were taken 4 to 7 years after dietary assessments were performed in the WHI baseline study visits. It is unlikely that knowledge of having large drusen would influence diet patterns because it was assessed photographically at a stage not often associated with awareness of the condition; most of the women with intermediate AMD in this sample (72%) reported not having been told by a physician that they had it. However, changes in diet just before entry into the WHI, which are associated with the presence of other chronic diseases that may increase risk for AMD (ie, cardiovascular diseases, diabetes mellitus, or hypertension), could bias findings. Next, the unavoidable imprecision of the food frequency questionnaire may have attenuated our study findings toward the null. Furthermore, given the number of comparisons made in analyzing the amount and type of fat in relation with AMD, some borderline significant results may be by chance, in the absence of a real association.

CONCLUSIONS

Associations of the intake of total and specific types of fat with AMD are complex in this sample and across different study populations. However, some generalities can be made. Our study adds to the growing body of evidence that diets that are high in fat may influence the development of AMD and extends the adverse associations reported in past studies to provide more evidence of an influence of fat intake on earlier stages of AMD. Inconsistencies in the relationships of specific fats with AMD across study samples and age strata may also reflect different patterns of fat intake, other dietary characteristics for which fat intake is a marker, selective mortality bias, and different strategies used to adjust for other aspects of diet across studies. In this particular sample, adverse associations were particularly attributed to diets high in ω-6 PUFAs, which may have masked potential protective influences of consuming diets high in ω-3 PUFAs.

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Ophthalmic Images

Rapid Optic Nerve Infiltration by Diffuse Large B-Cell Lymphoma

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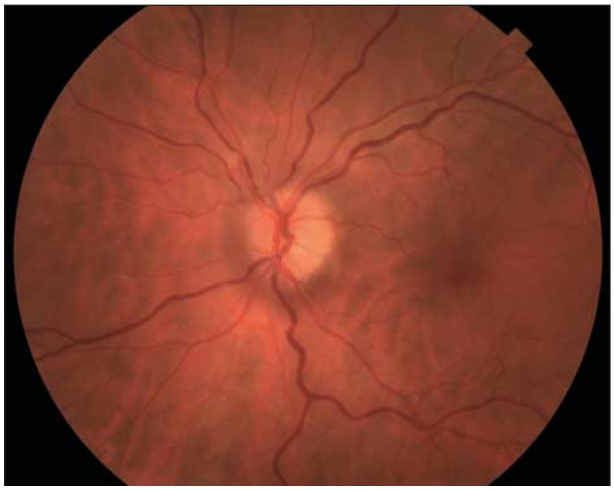

Figure 1. A 51-year-old woman with diffuse large B-cell lymphoma presented with 2 days of fluctuating vision in her left eye; mild disc edema was seen. Four days later, her visual acuity worsened to hand movements. Photograph by Beth Selkirk, COA.

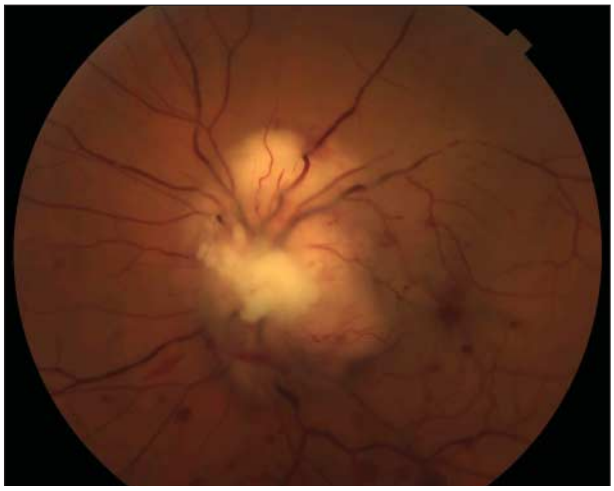

Figure 2. An elevated mass on the surface of the left optic nerve head was seen protruding into the patient's vitreous. Also visible were diffuse retinal vein engorgement, scattered retinal hemorrhages, and box-carring of the retinal arterioles. A diagnosis of direct lymphomatous infiltration of the optic nerve producing simultaneous central retinal venous and arterial occlusions was made. Photograph by Beth Selkirk, COA.