Dietary Fat and Risk for Advanced Age-Related Macular Degeneration

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Objective: To evaluate the relationship between intake of total and specific types of fat and risk for advanced age-related macular degeneration (AMD), the leading cause of irreversible blindness in adults.

Design: A multicenter eye disease case-control study.

Setting: Five US clinical ophthalmology centers.

Patients: Case subjects included 349 individuals (age range, 55-80 years) with the advanced, neovascular stage of AMD diagnosed within 1 year of their enrollment into the study who resided near a participating clinical center. Control subjects included 504 individuals without AMD but with other ocular diseases. Controls were from the same geographic areas as cases and were frequency-matched to cases by age and sex.

Main Outcome Measures: Relative risk for AMD according to level of fat intake, controlling for cigarette smoking and other risk factors.

Results: Higher vegetable fat consumption was associated with an elevated risk for AMD. After adjusting for age, sex, education, cigarette smoking, and other risk factors, the odds ratio (OR) was 2.22 (95% confidence interval [CI], 1.32-3.74) for persons in the highest vs those in the lowest quintiles of intake (*P* for trend, .007). The risk for AMD was also significantly elevated for the highest vs lowest quintiles of intake of monounsaturated (OR, 1.71) and polyunsaturated (OR, 1.86) fats (*P*s for trend, .03 and .03, respectively). Higher consumption of linoleic acid was also associated with a higher risk for AMD (*P* for trend, .02). Higher intake of ω-3 fatty acids was associated with a lower risk for AMD among individuals consuming diets low in linoleic acid, an ω-6 fatty acid (*P* for trend, .05; *P* for continuous variable, .03). Similarly, higher frequency of fish intake tended to reduce risk for AMD when the diet was low in linoleic acid (*P* for trend, .05). Conversely, neither ω-3 fatty acids nor fish intake were related to risk for AMD among people with high levels of linoleic acid intake.

Conclusion: Higher intake of specific types of fat—including vegetable, monounsaturated, and polyunsaturated fats and linoleic acid—rather than total fat intake may be associated with a greater risk for advanced AMD. Diets high in ω-3 fatty acids and fish were inversely associated with risk for AMD when intake of linoleic acid was low.

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AGE-RELATED macular degeneration (AMD) is the leading cause of irreversible visual impairment and blindness in the United States and other developed countries.[1,2] Among individuals 75 years and older, more than 25% have some signs of age-related maculopathy and 6% to 8% have the advanced stages of AMD that are associated with visual loss.[3] Underscoring the importance of this problem in our society, the prevalence and burden of this disease continues to rise as the size of our elderly population expands.[4] There is no proven treatment for the early and moderate forms of the disease, and therapeutic options for the advanced stages of AMD are limited. Therefore, a major challenge facing vision researchers at the beginning of this new millennium is to find the causes and mechanisms of this disease to develop preventive measures and better therapies.

Age-related macular degeneration and cardiovascular disease (CVD) share some common risk factors, most notably cigarette smoking.[5,6] Several cardiovascular risk factors may underlie the mechanisms for the development of AMD.[7] Atherosclerosis, the underlying cause of most ischemic events, is associated with intake of specific types of fat.[8,9] Intake of saturated fat and *trans*-fatty acids, the latter derived primarily from processed vegetable oil, increase the risk for coronary heart disease.[8] Dietary fats could affect ocular blood vessels or be involved in oxidative processes that contribute to the development of the advanced stage of macular degeneration characterized by choroidal neovasculariza-

The affiliations of the authors appear in the acknowledgment section at the end of this article.

SUBJECTS AND METHODS

The Eye Disease Case-Control Study[6] sponsored by the National Eye Institute, Bethesda, Md, was designed to identify potential risk factors for a number of retinal disorders, including advanced AMD. The dietary component was an ancillary study initiated and directed by the principal investigator of the clinical center in Boston, Mass (J.M.S.). Institutional review boards at each participating center approved the main and ancillary studies.

CASES AND CONTROLS

The identification of study subjects is described in detail elsewhere.[6] Cases and controls were selected from May 1, 1986, through December 31, 1990, from patients treated at the following 5 large ophthalmology centers: the Manhattan Eye, Ear and Throat Hospital, New York, NY; the Massachusetts Eye and Ear Infirmary, Boston; the Medical College of Wisconsin, Milwaukee; the Illinois Eye and Ear Infirmary, University of Illinois, Chicago; and the Wilmer Eye Institute, Baltimore, Md.

Eligible cases were patients aged 55 to 80 years who had exudative AMD diagnosed within 1 year of their enrollment into the study and who resided in or near the community in which the clinical center was located as defined by ZIP code listings. Cases were identified by reviewing ocular photography lists and screening medical records. In addition, physicians were asked to refer potential cases and controls who met the criteria for the study. Diagnostic criteria for AMD included a visual acuity of less than 20/20 in the affected eye or distortion on the Amsler grid, drusen in either eye, and at least 1 of the following signs of exudative AMD: (1) macular fibrous scar and/or (2) subretinal hemorrhage or fluorescein angiographic signs of choroidal neovascularization with 1 or more of the following clinical signs involving the macula: a neurosensory detachment, lipid deposits, gray subretinal membrane, and/or a retinal pigment epithelium detachment. Patients with ocular diseases other than AMD that are associated with choroidal neovascularization and patients with a history of intraocular surgery were excluded from both groups. All cases of AMD were confirmed by results of an examination conducted by a retina specialist. Of the cases identified as eligible for the study, 82% agreed to participate.

Controls were enrolled concurrently with cases and were selected from a similar pool of outpatients who had undergone a complete dilated ocular examination and did not have the diseases under study. Eligible controls were identified from the same general population and geographic area as the cases and resided in or near the community in which the clinical center was located as defined by ZIP code listing. Potential controls were identified by using the same sources with which the cases were identified. For example, if a general ophthalmology clinic was used to identify cases, then general clinic records were screened for controls. When cases were identified from specialty clinics, controls were selected from the same or from other specialty clinics. The diagnoses among enrolled controls included lid disorders (31%), vitreous disorders (18%), cataract (14%), conjunctivitis (10%), other retinal disorders (8%), corneal problems (7%), and a miscellaneous group of other diagnoses (12%). Controls received these diagnoses within 1 year of their enrollment into the study.

Of the controls identified as eligible for the study, 78% agreed to participate. Reasons for nonparticipation were similarly distributed among cases and controls and included lack of interest, being too busy, or unable to miss work. Cases and controls were frequency-matched by age, sex, and clinic. The balance between cases and controls on these factors was monitored quarterly by the coordinating center.

DATA COLLECTION

Data were derived from a standardized interview and results of a limited physical examination, an ophthalmic examination, and a laboratory analysis of blood specimens. A semiquantitative food-frequency questionnaire (FFQ) was also administered at all 5 centers. The FFQ, a modification of an extensively validated questionnaire,[12] contained a list of food items that were selected as the major sources of a variety of nutrients. This questionnaire, which was adapted for use among elderly subjects with eye disease, was found to be reliable in this study population.[13] Reproducibility correlation coefficients for fats ranging from 0.59 to 0.73 were similar to results from other established diet questionnaires.[12,13]

tion. A preliminary analysis suggested that the type of fat intake may influence risk for advanced AMD.[10] Subsequently, evidence of a relationship between fat intake and earlier stages of maculopathy was reported.[11] To further explore the potential association between dietary intake of fat and risk for the visually disabling form of AMD, we compared case subjects with advanced AMD and control subjects without AMD with respect to their intake of total fat, specific types of fat, and specific foods.

RESULTS

The average age of the 349 cases was 71 years (range, 55-81 years). The average age of the 504 controls was 68 years (range, 55-80 years). Women constituted 58% of cases and 58% of controls.

Table 1 displays the characteristics of the study population and risk factors for AMD according to intake of specific types of fat and overall fish intake. The mean values of carotenoid intake for the first, third, and fifth quintiles of the various types of fats decreased as the fat consumption increased, except for ω-3 fatty acids and fish, for which the trend was in the opposite direction. Regarding sex, the percentage of men increased with increasing consumption of fats, except for ω-3 fatty acids and fish, for which we saw no consistent pattern. The percentage of current smokers increased as the amount of fat consumed increased, with the exception of the ω-3 fatty acids and fish, for which the opposite trend was noted (fewer smokers with higher intake). However, no consistent trend was seen for past smoking or number of pack-years of smoking according to fat intake.

Other characteristics, including age, body mass index, systolic blood pressure, and caloric intake appeared balanced across levels of various types of fat, except for ω-3 fatty acids, for which there was an inverse trend for decreasing caloric intake with increasing intake of this type of fat.

Questionnaires were mailed to the participants before their study visit. Participants completed the FFQ at home or in the clinic; 58% of cases and 49% of controls completed them mainly in the clinic. On the day of the study visit, we assisted people who had questions about the form. Participants were asked to indicate the average frequency of consumption for each food or beverage item during the past year. Each food was specified in a standardized portion size. The questionnaire had 9 possible responses, ranging from "almost never or less than once per month" to "6 or more per day." The FFQ also included questions about the use of multivitamin and other supplements.

We reviewed, coded, and entered the data from all questionnaires into the computer without knowledge of the case or control status of the participant, using data-entry software with a double-entry and verification system as a quality control measure. For this FFQ, we used a computer program that was developed at the Channing Laboratory, Boston, Mass, to generate the intake scores for various micronutrients. The scores were calculated by multiplying the reported frequency of intake of each food by its nutrient content and then summing the nutrient contributions of each food. Nutrient values were primarily derived from US Department of Agriculture sources.[14]

The FFQ was added as an ancillary study shortly after the onset of the main project. Of the 1036 enrolled subjects, 922 (89%) completed the diet questionnaire. To maintain the quality of data for these analyses, we excluded 69 of these questionnaires because of inadequate or missing answers (n=17) and extreme values (n=52). Therefore, we used 853 observations, including 349 (83%) of the 421 cases and 504 (82%) of the 615 controls for these dietary analyses. Participants whose responses were not included in the analyses (n=183) did not differ significantly from those included (n=853) with regard to age (median age, 69 vs 70 years), sex (61% vs 55% female), or education (at least high school degree, 72% vs 76%) ($P>.05$ for all comparisons).

ANALYSES

Advanced AMD is uncommon among nonwhite persons, and only 6 nonwhite subjects were enrolled in this study. Since genetic and cultural factors may be related to the low prevalence of AMD in nonwhite subjects, and since there were insufficient numbers of cases to address this possibility, analyses were restricted to white subjects. We used the dietary fat values adjusted for total energy intake as described elsewhere.[15] Briefly, we computed energy-adjusted intakes as the difference between expected and observed nutrient intake (residuals), using a simple linear regression with the logarithm of the nutrient modeled as the dependent variable and the logarithm of the total energy intake as the independent variable (separately for men and women). The residuals were added to a constant value (the predicted logarithm nutrient for the sex-specific population mean of the logarithm of energy intake) to avoid negative values, and exponentiated to return to the original scale. These adjusted nutrients represent the nutrient composition of diet with the total energy intake held constant.

Energy-adjusted nutrient scores were categorized into quintiles of intake on the basis of the distribution of nutrient scores among all subjects. Analyses also included the association between the risk for AMD and the intake of specific foods contributing to fat intake. Because of the possible interrelationships between intake of ω-6 and ω-3 fatty acids, we also performed stratified analyses of ω-3 fatty acids within strata of subjects with low intake of linoleic acid (≤5.5 g) vs high intake of linoleic acid (≥5.6 g).[16]

We calculated odds ratios (ORs) and 95% confidence intervals (CIs) using multiple logistic regression, and 2-sided P values for the χ^2 test for trend.[17] We calculated adjusted ORs to control initially for age, sex, and clinical center. We also constructed multivariate models to control for factors potentially related to dietary intake and the risk for AMD. Therefore, in addition to age, sex, clinical center, and education (>12, <12, or 12 years of school), these models also included calorie-adjusted carotenoid intake, measured systolic blood pressure, self-reported physical activity level (continuous), alcohol intake, body mass index (calculated as weight in kilograms divided by the square of height in meters) (continuous), smoking status (current, past, or never), amount smoked (pack-years), and calorie intake (continuous variable).

When we adjusted only for age, sex, and clinic, there were significant increases in risk for AMD with increasing intake of total and vegetable fats (**Table 2**). After adjusting for other confounding factors (most notably cigarette smoking), the test for trend for total fat intake became nonsignificant ($P=.10$), whereas the test for trend for vegetable fat intake remained about the same. The OR comparing the highest quintile of vegetable fat intake with the lowest was 2.22 (95% CI, 1.32-3.74) (P for trend, .007). No significant effects were seen for intake of animal fat or cholesterol in multivariate analyses.

In demographically adjusted analyses of various types of saturated and unsaturated fats (**Table 3**), there were significant associations with saturated (P for trend, .04), monounsaturated (P for trend, <.001), and polyunsaturated fats (P for trend, .009) and borderline significant results for *trans*-unsaturated fat (P for trend, .05). After adjusting for other confounding variables in multivariate analyses, the associations of AMD with saturated fat and *trans*-fatty acids became nonsignificant. Conversely, associations with monounsaturated and polyunsaturated fats weakened slightly but remained statistically significant. In particular, the OR for the fifth compared with the first quintile of intake of monounsaturated fat was 1.71 (95% CI, 1.00-2.94) (P for trend, .03). Similarly, for polyunsaturated fat, the OR for the fifth compared with the first quintile was 1.86 (95% CI, 1.11-3.14) (P for trend, .03).

Because major food sources of monounsaturated fat in the United States (beef, dairy fats, and partially hydrogenated vegetable oil) can also have a high saturated, *trans*-unsaturated, or polyunsaturated fat content, we included all 4 types simultaneously in our multivariate analyses (Tables 2 and 3). The directions of the associations between AMD and intake of monounsaturated and polyunsaturated fats remained positive but were no longer statistically significant, possibly because of correlations among these types of fat. The direction

Table 1. Characteristics of Study Population According to Intake of Specific Types of Fat and Fish*

	Quintiles of																	
	Total Fat			Animal Fat			Vegetable Fat			Cholesterol			Saturated Fat			Monounsaturated Fat		
	1	3	5	1	3	5	1	3	5	1	3	5	1	3	5	1	3	5
Age, y	70	69	68	70	68	69	69	69	69	70	69	69	70	69	69	70	69	69
BMI, kg/m^2	26	27	27	26	27	28	27	27	26	26	27	27	26	27	27	26	27	27
SBP, mm Hg	139	140	139	137	138	141	138	140	137	139	138	139	137	139	139	138	139	140
Alcohol, g/d	9	8	6	7	10	7	14	7	6	8	8	9	8	12	6	10	10	6
Calories	1465	1517	1543	1479	1533	1574	1494	1498	1576	1501	1512	1504	1449	1536	1521	1473	1543	1535
Carotenoids, IU	8546	7696	5314	8142	7753	6222	7436	7303	6443	7347	7353	6863	8729	6999	5855	8793	7242	5326
Male, %	25	38	71	31	42	60	39	42	60	29	40	57	27	37	64	27	41	69
Current smoking, %	9	18	22	9	18	19	14	17	18	12	17	21	9	19	19	9	17	22
Past smoking, %	47	41	54	51	47	52	47	44	56	48	47	54	47	47	51	52	42	54
Pack-years of smoking	42	39	50	41	46	47	46	44	43	41	46	48	42	45	46	41	43	51

*Number of participants in each of the 5 quintiles is approximately 170 for each characteristic (only first, third, and fifth quintiles are shown). Values are means unless otherwise indicated. BMI indicates body mass index (calculated as weight in kilograms divided by the square of height in meters); SBP, systolic blood pressure. All nutrients except fish intake were calorie adjusted.

Table 2. Odds Ratios for Advanced, Exudative Age-Related Macular Degeneration by Energy-Adjusted Quintiles of Fat Intake*

	Quintiles					
Type of Fat	1	2	3	4	5	*P* (Trend)
Total fat						
No. of cases/controls	57/114	76/94	72/99	77/93	67/104	. . .
Median intake, g	30.0	39.4	46.2	52.4	63.2	. . .
Adjusted OR†	1.0	1.81	1.84	2.26	1.93	.004
Multivariate OR (95% CI)‡	1.0	1.84 (1.13-2.99)	1.65 (1.01-2.71)	1.94 (1.18-3.21)	1.44 (0.83-2.47)	.10
Animal fat						
No. of cases/controls	77/93	65/105	73/98	63/105	69/103	. . .
Median intake, g	14.4	21.1	26.3	32.7	42.3	. . .
Adjusted OR†	1.0	0.79	1.17	0.93	1.12	.56
Multivariate OR (95% CI)‡	1.0	0.69 (0.43-1.11)	1.00 (0.62-1.61)	0.76 (0.46-1.24)	0.87 (0.53-1.45)	.65
Multivariate OR (95% CI) after additional adjustment for protein and vegetable and *trans*-unsaturated fats	1.0	0.67 (0.41-1.10)	1.04 (0.62-1.74)	0.78 (0.45-1.35)	0.97 (0.53-1.78)	.94
Vegetable fat						
No. of cases/controls	55/115	76/95	62/109	73/97	83/88	. . .
Median intake, g	8.2	13.5	17.2	21.8	30.1	. . .
Adjusted OR†	1.0	1.93	1.28	1.73	2.26	.003
Multivariate OR (95% CI)‡	1.0	1.97 (1.20-3.24)	1.30 (0.79-2.16)	1.81 (1.09-3.00)	2.22 (1.32-3.74)	.007
Multivariate OR (95% CI) after additional adjustment for protein and animal and *trans*-unsaturated fats	1.0	2.12 (1.24-3.62)	1.41 (0.79-2.52)	2.15 (1.15-4.04)	2.84 (1.45-5.57)	.006
Cholesterol						
No. of cases/controls	74/97	63/106	65/107	76/94	71/100	. . .
Median intake, mg/dL§	109.8	162.1	203.4	251.4	366.5	. . .
Adjusted OR†	1.0	0.81	0.85	1.22	1.08	.55
Multivariate OR (95% CI)‡	1.0	0.78 (0.48-1.27)	0.83 (0.52-1.34)	1.13 (0.70-1.84)	0.89 (0.94-1.46)	.90

*OR indicates odds ratio; CI, confidence interval; and ellipses, not applicable.
†Adjusted for age, sex, and clinic.
‡Included terms for age (continuous), sex, clinic (Massachusetts, New York, Illinois, Wisconsin, or Maryland), education (>12, <12, or 12 years, dietary calorie-adjusted carotenoid intake, systolic blood pressure, self-reported physical activity level (continuous), alcohol intake, body mass index (described in the footnote to Table 1), smoking status (current, past, never), amount smoked (pack-years), and calories (continuous).
§To convert to millimoles per liter, divide by 0.0259.

of the associations between AMD and intake of saturated and *trans*-unsaturated fats became negative or inverse but were not statistically significant. A similar analysis was performed by decomposing total fat into animal and vegetable fat components when considered simultaneously (Table 2). Animal fat was not significantly related to AMD, but the positive association between vegetable fat and AMD became somewhat stronger and remained statistically significant ($P=.006$). One interpretation of these results is that substitution of carbohydrate calories with vegetable fat calories is positively associated with risk for AMD.

Polyunsaturated Fat			Trans-Fatty Acids			Linoleic Acid			ω-3 Fatty Acids			Fish Intake, Times per Week		
1	3	5	1	3	5	1	3	5	1	3	5	<1/wk	1/wk	≥2/wk
70	69	68	69	69	69	70	70	68	70	69	70	69	69	69
26	27	27	26	27	27	26	27	27	27	27	27	27	27	27
139	141	138	136	136	139	139	140	137	140	139	137	140	140	137
12	6	7	12	8	6	12	7	7	12	10	7	10	8	7
1484	1537	1564	1458	1564	1513	1484	1548	1534	1749	1504	1253	1517	1500	1538
7432	6860	6392	9278	7368	5519	7835	6546	6293	5507	6690	9086	5580	6984	9220
27	39	60	34	41	56	29	40	61	44	75	46	41	44	42
9	16	17	9	16	20	11	16	17	19	18	9	20	17	11
47	44	58	51	48	53	46	47	60	48	51	50	47	46	52
45	46	49	47	42	47	44	44	48	44	57	39	45	51	38

Table 3. Odds Ratios for Advanced, Exudative Age-Related Macular Degeneration by Energy-Adjusted Quintiles of Intake of Various Types of Saturated and Unsaturated Fat*

	Quintiles					
Type of Fat	1	2	3	4	5	*P* (Trend)
Saturated fat						
No. of cases/controls	66/104	63/108	75/95	76/95	69/102	. . .
Median intake, g	10.6	14.2	16.8	20.3	25.3	. . .
Adjusted OR†	1.0	0.96	1.46	1.71	1.37	.04
Multivariate OR (95% CI)‡	1.0	0.88 (0.54-1.42)	1.20 (0.74-1.94)	1.35 (0.82-2.22)	1.07 (0.64-1.78)	.39
Multivariate OR (95% CI) after additional adjustment for protein and monounsaturated, polyunsaturated, and *trans*-unsaturated fats	1.0	0.54 (0.30-0.97)	0.61 (0.31-1.21)	0.76 (0.35-1.64)	0.60 (0.25-1.41)	.29
Monounsaturated fat						
No. of cases/controls	55/115	69/101	85/87	68/101	72/100	. . .
Median intake, g	10.2	13.8	16.7	19.4	23.9	. . .
Adjusted OR†	1.0	1.62	2.64	1.96	2.27	.001
Multivariate OR (95% CI)‡	1.0	1.64 (1.01-2.68)	2.45 (1.44-4.01)	1.68 (1.01-2.77)	1.71 (1.00-2.94)	.03
Multivariate OR (95% CI) after additional adjustment for protein and saturated, polyunsaturated, and *trans*-unsaturated fats	1.0	2.15 (1.11-4.17)	3.69 (1.67-8.17)	2.28 (0.91-5 .74)	2.39 (0.81-7.04)	.07
Polyunsaturated fat						
No. of cases/controls	56/114	77/93	68/104	74/95	74/98	. . .
Median intake, g	4.2	5.7	7.0	8.4	11.1	. . .
Adjusted OR†	1.0	1.96	1.51	1.92	2.03	.009
Multivariate OR (95% CI)‡	1.0	1.94 (1.18-3.19)	1.44 (0.87-2.37)	1.96 (1.19-3.24)	1.86 (1.11-3.14)	.03
Multivariate OR (95% CI) after additional adjustment for protein and saturated, monounsaturated, and *trans*-unsaturated fats	1.0	1.86 (1.06-3.26)	1.34 (0.72-2.49)	1.85 (0.94-3.62)	1.88 (0.91-3.89)	.23
Trans-unsaturated fat						
No. of cases/controls	64/106	61/109	80/91	71/99	73/99	. . .
Median intake, g	1.3	2.0	2.5	3.1	4.2	. . .
Adjusted OR†	1.0	0.96	1.68	1.29	1.49	.05
Multivariate OR (95% CI)‡	1.0	0.79 (0.48-1.31)	1.52 (0.93-2.47)	1.04 (0.63-1.72)	1.14 (0.68-1.91)	.41
Multivariate OR (95% CI) after additional adjustment for protein and saturated, monounsaturated, and polyunsaturated fats	1.0	0.49 (0.27-0.86)	0.79 (0.43-1.86)	0.50 (0.26-0.97)	0.51 (0.25-1.06)	.17

*Abbreviations are explained in the first footnote to Table 2.
†Adjusted for age, sex, and clinic.
‡Included terms for age, sex, clinic, education, dietary calorie adjusted carotenoid intake, systolic blood pressure, physical activity, alcohol intake, body mass index, smoking status or, amount smoked, and calories. Terms are described in the third footnote to Table 2.

Table 4. Odds Ratios for Advanced, Exudative Age-Related Macular Degeneration by Quintile of Intake of Various Types of Fatty Acids and by Quintiles of Intake of ω-3 Fatty Acids Within Strata of Linoleic Acid Intake*

Fatty Acid	Quintiles 1	2	3	4	5	*P* (Trend)†	*P* (Continuous)‡
By Quintile of Intake							
Linoleic acid							
No. of cases/controls	114/56	97/73	98/74	100/70	95/76	. . .	. . .
Median intake, g	3.5	5.0	6.1	7.5	10.1	. . .	. . .
Adjusted OR§	1.0	1.78	1.73	1.72	2.19	.004	. . .
Multivariate OR (95% CI)‖	1.0	1.74 (1.06-2.85)	1.61 (0.97-2.65)	1.76 (1.06-2.91)	2.00 (1.19-3.37)	.02	. . .
ω-3 Fatty acids EPA and DHA							
No. of cases/controls	76/95	73/97	74/96	63/108	63/108	. . .	. . .
Median intake, g	1.02	1.04	1.05	1.15	1.16	. . .	. . .
Adjusted OR§	1.0	0.93	0.88	0.69	0.59	.01	. . .
Multivariate OR (95% CI)‖	1.0	0.87 (0.53-1.42)	0.86 (0.52-1.43)	0.81 (0.49-1.32)	0.75 (0.44-1.25)	.29	. . .
By Quintile of Intake of ω-3 Fatty Acids							
Linoleic acid intake, quintiles 1 and 2 (≤5.5 g)							
No. of cases/controls	25/38	31/39	24/30	23/52	26/53	. . .	. . .
Median intake, g	0.017	0.036	0.049	0.142	0.152	. . .	. . .
Adjusted OR (95% CI)§	1.0	1.48 (0.70-3.14)	1.22 (0.54-2.75)	0.65 (0.30-1.38)	0.62 (0.29-1.29)	.01	.02
Multivariate OR (95% CI)‖	1.0	1.23 (0.55-2.76)	1.30 (0.53-3.15)	0.73 (0.32-1.65)	0.61 (0.26-1.42)	.05	.03
Linoleic acid intake, quintiles 3, 4, and 5 (≥5.6 g)							
No. of cases/controls	51/57	42/58	50/66	40/56	37/55	. . .	. . .
Median intake, g	0.017	0.036	0.049	0.142	0.152	. . .	. . .
Adjusted OR (95% CI)§	1.0	0.67 (0.36-1.23)	0.72 (0.40-1.30)	0.73 (0.40-1.34)	0.63 (0.34-1.16)	.34	.05
Multivariate OR (95% CI)‖	1.0	0.67 (0.35-1.27)	0.74 (0.39-1.38)	0.88 (0.46-1.67)	0.78 (0.39-1.56)	.97	.20

*EPA indicates eicosapentanoic acid; DHA, docosahexaenoic acid. Other abbreviations are given in the first footnote to Table 2.
†For linoleic acid intake by quintiles of intake of ω-3 fatty acids, based on median value within specific population quintiles of ω-3 fatty acid.
‡For linoleic acid intake by quintiles of intake of ω-3 fatty acids, treating ω-3 fatty acids as a continuous variable.
§Adjusted for age, sex, and clinic.
‖Included terms for age, sex, clinic, education, dietary calorie-adjusted carotenoid intake, systolic blood pressure, physical activity, alcohol intake, body mass index, smoking status, amount smoked (pack-years), and calories. Terms are described in the third footnote to Table 2.

In **Table 4**, we describe the associations between intake of linoleic acid and ω-3 fatty acids and their joint effect on risk of AMD. In demographically adjusted analyses, increasing intake of linoleic acid was significantly associated with higher prevalence of AMD (*P* for trend, .004). This association persisted in multivariate analyses, with an OR for the fifth vs first quintile of 2.00 (95% CI, 1.19-3.37) (*P* for trend, .02). Conversely, intake of ω-3 fatty acids showed an inverse relationship with AMD in demographically adjusted analyses (*P* for trend, .01). This association became nonsignificant after controlling for confounding variables, most notably, cigarette smoking. However, when the study population was stratified by linoleic acid intake (≤5.5 g or ≥5.6 g), the risk for AMD was significantly reduced with higher intake of ω-3 fatty acids among those with low linoleic acid intake (*P* for trend, .05; *P* for continuous variable, .03). Conversely, among individuals with high linoleic acid intake, no significant association was seen for ω-3 fatty acid intake after controlling for other confounding variables.

In **Table 5**, we describe the association between fish intake and AMD and the joint effect of fish and linoleic acid intake. Overall (Table 5), there was a nonsignificant effect of fish intake when adjusting for other variables (*P* for trend, .29). However, among individuals with low linoleic acid intake (Table 5), there was a significant relationship between fish intake and AMD for 2 or more servings per week vs less than 1 serving per week (OR, 0.60; *P* for trend, .05). Notably, there was no relationship between fish intake and AMD among individuals with high linoleic acid intake (≥5.6 g) for 2 or more servings per week vs less than 1 serving per week (OR, 1.08; *P* for trend, .83). Thus, the findings regarding the ω-3 fatty acids and fish intake were similar.

As noted above, it appeared that there were significant associations between AMD and vegetable, monounsaturated, and polyunsaturated fats and between AMD and linoleic acid, whereas no significant associations were observed for saturated fat (Tables 2-4). Therefore, we examined foods with high levels of at least 1 of these nutrients but relatively low levels of saturated fat. We analyzed each specific food, represented in servings per day, and adjusted for the same variables in multivariate analyses as in Tables 2 through 5. Results are shown in **Table 6**. No statistically significant effects were seen for any specific type of food. However, elevated ORs were seen for commercially prepared pie (2.70), cake (1.64), french fries (1.68), and nuts (1.34).

COMMENT

In this large case-control study of advanced, exudative macular degeneration, we found that higher intake of vegetable, monounsaturated, and polyunsaturated fats were

Table 5. Odds Ratios for Advanced, Exudative Age-Related Macular Degeneration by Frequency of Fish Intake and by Frequency of Fish Intake Within Strata of Linoleic Acid Intake*

	No. of Servings of Fish per Week			*P* (Trend)
	<1	1	≥2	
By Frequency Alone				
No. of cases/controls	112/157	130/163	107/184	. . .
Median intake, servings per day	0.07	0.14	0.43	. . .
Adjusted OR (95% CI)†	1.0	1.02 (0.71-1.40)	0.68 (0.47-0.98)	.02
Multivariate OR (95% CI)‡	1.0	1.08 (0.74-1.58)	0.86 (0.58-1.27)	.29
By Frequency Within Strata of Linoleic Acid Intake				
Linoleic acid intake, quintiles 1 and 2 (≤5.5 g)				
No. of cases.controls	42/63	46/58	41/91	. . .
Median intake, servings per day	0.07	0.14	0.43	. . .
Adjusted OR (95% CI)†	1.0	1.06 (0.59-1.90)	0.54 (0.30-0.96)	.02
Multivariate OR (95% CI)‡	1.0	1.10 (0.58-2.07)	0.60 (0.32-1.14)	.05
Linoleic acid intake, quintiles 3, 4, and 5 (≥5.6 g)				
No. of cases/controls	70/104	84/105	88/93	. . .
Median intake, servings per day	0.07	0.14	0.43	. . .
Adjusted OR (95% CI)†	1.0	0.96 (0.61-1.53)	0.82 (0.51-1.34)	.36
Multivariate OR (95% CI)‡	1.0	1.08 (0.67-1.76)	1.08 (0.64-1.83)	.83

*Abbreviations are explained in the first footnote to Table 2.
†Adjusted for age, sex, and clinic.
‡Included terms for age, sex, clinic, education, dietary calorie-adjusted carotenoid intake, systolic blood pressure, physical activity, alcohol intake, body mass index, smoking status, amount smoked (pack-years), and calories. Terms are described in the third footnote to Table 2.

Table 6. Odds Ratios for Advanced, Exudative Age-Related Macular Degeneration According to Foods High in Vegetable Fat, Monounsaturated Fat, Polyunsaturated Fat, or Linoleic Acid, Relative to Saturated Fat*

	Grams per Serving						
Food Item (Serving Size)	**Vegetable Fat**	**Monounsaturated Fat**	**Polyunsaturated Fat**	**Linoleic Acid**	**Saturated Fat**	**OR (95% CI)†**	***P* (Trend)**
Margarine (tsp)	4.0	1.7	1.4	1.3	0.8	1.06 (0.94-1.21)	.34
Chocolate (28 g)	9.2	3.1	0.3	0.3	5.5	1.27 (0.90-1.78)	.17
Pie (slice, commercially prepared)	13.0	5.8	3.5	3.4	3.4	2.70 (0.75-9.42)	.13
Cake (slice)	7.6	3.6	1.9	1.9	2.8	1.64 (0.88-3.04)	.12
Cookies (1)	2.5	1.0	0.8	0.7	0.6	1.05 (0.89-1.23)	.57
Peanut Butter (15 mL)	8.3	3.8	2.4	2.4	1.7	0.94 (0.65-1.36)	.75
Potato Chips (small bag or 28 g)	11.3	2.4	6.0	5.6	2.9	0.89 (0.40-1.98)	.77
French Fries (112 g)	9.4	2.0	4.9	4.7	2.5	1.68 (0.35-8.18)	.52
Nuts (28 g)	14.1	6.4	4.0	4.0	2.6	1.34 (0.90-1.99)	.16

*Abbreviations are given in the first footnote to Table 2.
†Included terms for age, sex, clinic, education, dietary calorie-adjusted carotenoid intake, systolic blood pressure, physical activity, alcohol intake, body mass index, smoking status, amount smoked, and calories. Terms are described in the third footnote to Table 2.

associated with a higher risk for AMD. We also observed an adverse relationship between consumption of linoleic acid and AMD. Some foods with relatively high levels of these types of fat tended to be associated with a higher risk. Furthermore, results indicate an inverse (or protective) relationship between ω-3 fatty acid and fish intake and risk for AMD in the lower quintiles of linoleic acid intake. These results suggest that specific types of fat, rather than total fat intake, are potentially important factors related to risk for AMD.

Our results are noteworthy in light of the CVD hypothesis that AMD and CVD share some common risk factors.[7] *Trans*-unsaturated fat intake has been positively related to CVD.[8,9] Our results suggest only a small positive association between *trans*-unsaturated fats and AMD that is not statistically significant. Long-chain ω-3 fatty acids, especially docosahexanoic acid found primarily in fish, have been associated with an inverse risk for CVD in some studies.[18] Our results suggest a similar trend for AMD, but only among individuals with lower intake of linoleic acid (an ω-6 fatty acid). This latter finding supports other evidence in the literature that there may be a competition between ω-3 and ω-6 fatty acids and that both the level of ω-3 fatty acids and its ratio to the ω-6 fatty acids are important.[16] Polyunsaturated fat is an important protective factor for CVD,[8] but we observed a positive association between AMD and polyunsaturated fat intake in our data. It is possible that high intake of polyunsaturated fat may increase unsaturation of lipids in the macula and hence increase oxidative dam-

age. We found no association between exudative AMD and dietary cholesterol, animal fat, and saturated fat, which are related to CVD.[8,9] Thus, some but not all of our results do not suggest a relationship between AMD and the forms of dietary fat intake that are commonly related to vascular disease.

Previous data on the relationship between fat intake and AMD are limited, and, to our knowledge, there are no studies based on as large a cohort of subjects with exudative disease as we report herein. High intake of saturated fat and cholesterol was associated with an increased risk for early age-related maculopathy in the Beaver Dam Eye Study.[11] These results were based on questions asked about foods consumed 10 years before the interview. Analyses of 46 cases of late age-related maculopathy in the Blue Mountains Study suggested an inverse relationship with fish intake, although most comparisons were not statistically significant and a trend was not apparent.[19]

Our study has several advantages, ie, the large sample size of patients with a uniform diagnosis of the most advanced or exudative form of AMD, examination of all cases and controls according to a standard protocol by ophthalmologists who are retina specialists, use of a reliable and valid dietary questionnaire, and control for a large number of potential confounders for which data were collected. We evaluated the effect of postmenopausal estrogen use, since this exposure may be related to AMD.[6,7] However, this variable was not related to fat intake; therefore, it was not included in the multivariate models. We had limited information for some other factors, including family history of AMD. However, it is unlikely that this and other measured risk factors are strongly related to fat intake, and inclusion of such data would thus not appreciably affect the results. One concern related to case-control studies is that exposure (ie, dietary habits) occurs before disease diagnosis. However, the advantage of our study design is that all cases were newly diagnosed within 1 year of enrollment into the study, which reduces potential bias related to the reporting of dietary habits. Prospective studies would be useful for confirmation and expansion of these findings.

The potential effect of specific types of dietary fat intake on risk for AMD may be related to various mechanisms. Atherosclerosis of the blood vessels supplying the choroid and retina has long been hypothesized to contribute to the risk for AMD.[20] The antithrombotic and hypolipidemic effects of the long-chain n-3 fatty acids (ω-3 fatty acids, as found in fish) on the cardiovascular system[18] could also exert a beneficial effect on the vasculature of the choroid. Furthermore, photoreceptor outer segments have a high docosahexanoic acid content and require a constant supply of these ω-3 fatty acids due to their continuous renewal.[21] Diets rich in docosahexanoic acid (fish) may enhance retinal function and influence the development of degenerative diseases such as AMD.

Our results also suggest an association between AMD and higher intake of vegetable, monounsaturated, and polyunsaturated fats and linoleic acid. Although the mechanism for an association with AMD is not entirely clear, foods with higher levels of these types of fat overall tend to be highly processed, store-bought snack foods. Such foods might contain products that adversely affect blood vessels supplying the choroid or retina. These and other similar foods might also increase oxidative damage in the macula, which is susceptible to oxidation due to high oxygen tension in the presence of light exposure. However, the possibility cannot be excluded that the excess risk may be due to other factors in the foods most strongly associated with risk. Other mechanisms, such as genetic and dietary interaction, might also be operative.

CONCLUSIONS

This study raises the possibility that some individual dietary fats, not necessarily total fat consumption, increase or decrease the risk for advanced macular degeneration. Since the impact of AMD on our growing elderly population is rising, finding means of prevention is of utmost importance. Thus far, only cigarette smoking is a well-established, modifiable risk factor.[5] Additional studies of dietary factors might lead to nutritional means to reduce the risk for development of this important disease among susceptible individuals.

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Crossword Puzzle

Answer: Double Talk

William H. Schutten, MD

This is the answer to the July crossword puzzle (*Arch Ophthalmol*. 2001;119:1081). Answers are immediately available at *www.archophthalmol.com*.