Cigarette Smoking, Fish Consumption, Omega-3 Fatty Acid Intake, and Associations With Age-Related Macular Degeneration

The US Twin Study of Age-Related Macular Degeneration

Johanna M. Seddon, MD, ScM; Sarah George, MPH; Bernard Rosner, PhD

Objective: To evaluate modifiable risk and protective factors for age-related macular degeneration (AMD) among elderly twins.

Methods: The US Twin Study of Age-Related Macular Degeneration comprises elderly male twins from the National Academy of Sciences–National Research Council World War II Veteran Twin Registry. To determine genetic and environmental risk factors for AMD, twins were surveyed for a prior diagnosis of AMD and underwent an eye examination, fundus photography, and food frequency and risk factor questionnaires. This environmental component of the study includes 681 twins: 222 twins with AMD (intermediate or late stages) and 459 twins with no maculopathy or early signs. Risk for AMD according to cigarette smoking and dietary fat intake was estimated using logistic regression analyses.

Results: Current smokers had a 1.9-fold increased risk (95% confidence interval, 0.99-3.68, $P=.06$) of AMD while past smokers had about a 1.7-fold increased risk (95% confidence interval, 1.2-2.6, $P=.009$). Increased intake of fish reduced risk of AMD, particularly for 2 or more servings per week (P trend$=.04$). Dietary omega-3 fatty intake was inversely associated with AMD (odds ratio, 0.55; 95% confidence interval, 0.32-0.95) comparing the highest vs lowest quartile. Reduction in risk of AMD with higher intake of omega-3 fatty acids was seen primarily among subjects with low levels (below median) of linoleic acid intake, an omega-6 fatty acid (P trend$<.001$). The attributable risk percentage was 32% for smoking and the preventive fraction was 22% for higher omega-3 intake.

Conclusions: This study of twins provides further evidence that cigarette smoking increases risk while fish consumption and omega-3 fatty acid intake reduce risk of AMD.

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Age-related macula degeneration (AMD) is the leading cause of severe visual impairment and blindness among the expanding elderly population in the United States.[1] It is estimated that there are 16.5 million people who are 75 years and older living in the United States,[2] and 29% of these individuals have various signs of age-related maculopathy while 6% to 8% have the advanced form of AMD.[3] Since the elderly population has a longer life expectancy, the prevalence and burden related to this disease will increase in the years to come. With limited treatment options currently available for this public health concern, an effective approach for reducing the impact of this disease is prevention.

We previously hypothesized that AMD and cardiovascular disease (CVD) share similar modifiable factors such as cigarette smoking, nutritional factors, obesity, and lipid levels and common antecedents such as inflammatory and oxidative processes that play a role in altering the normal function of blood vessels in the choroid.[4,5] Smoking, an established risk factor, has been linked to increasing oxidative stress, platelet aggregation, and fibrinogen levels as well as to reduction in high-density lipoprotein levels and antioxidants in the blood.[6-8] Blood flow to the choroid may also be compromised.

It has also been reported that fish intake may serve as a protective factor in lowering the risk of AMD.[9-13] For example, the long-chain polyunsaturated omega-3 fatty acids, particularly docosahexaenoic acid, that are mainly found in fish have been shown to have beneficial effects in reduc-

Author Affiliations: Massachusetts Eye and Ear Infirmary (Dr Seddon and Ms George) and Channing Laboratory, Harvard Medical School (Dr Rosner), Boston.

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ing the risk of progression of AMD when linoleic acid levels were low.[9,10] This finding suggests the importance of maintaining a healthy ratio between 2 essential fatty acids (omega-3 and omega-6 fatty acids) in the diet.[14]

We explored these associations in a unique cohort of elderly twins from a population-based national registry for which we previously reported the proportion of AMD due to genetic and environmental influences.[15,16] Advantages of this design include the similar age and socioeconomic status of participants as well as a control for shared environmental factors in early life. Subjects classified as cases and controls are derived from the same source population, which reduces selection bias in an epidemiologic study. To the best of our knowledge, this is the first study to evaluate behavioral and nutritional factors for AMD among a large cohort of elderly male twins.

METHODS

STUDY POPULATION

The study population was derived from the National Academy of Sciences–National Research Council World War II Veteran Twin Registry as described previously.[16] This registry is the largest population-based twin registry in the United States and includes information for 15 924 white male twin pairs born between 1917 and 1927 who served in the US armed forces.[17] This cohort of elderly twins provides a unique opportunity to study genetic and environmental risk factors for age-related diseases, including AMD.

In total, 12 126 twins living at the start of this study were surveyed for diagnosis of AMD and participants included all pairs in which one or both twins reported a diagnosis of AMD, a subset of twin pairs in which neither twin reported AMD, and enrolled twins for whom the co-twin was subsequently unable to participate. For the previous assessment of heritability of AMD, a total of 840 twins were analyzed, including 340 pairs (n=680) in which one or both twins reported AMD, 51 pairs (n=102) in which neither twin reported AMD, and 58 singletons.[16] For this case-control study of risk factors, the analysis included 666 of those 840 individual twins plus an additional 15 singleton twins whose co-twin was deceased at the beginning of the study with data available on all covariates: 358 were monozygotic and 323 were dizygotic twins. Two hundred twenty-two twins were classified as affected (AMD grades 3, 4, and 5) and 459 were unaffected (AMD grades 1 and 2).[18] When comparing the group of 681 participants with the 174 individual twins who were not included, there were no significant differences in AMD grades and age.

STUDY EXAMINATIONS

The twin's current ophthalmologist or an ophthalmologist in the geographic area of the twin was recruited to perform the study examination. We designed detailed protocols and standardized clinical data forms, and these were sent to ophthalmologists to complete. The ophthalmologists were not informed about twin zygosity or disease status of co-twins. Refraction and best-corrected visual acuity were assessed.[19] Intraocular pressure was measured and iris color was classified according to standard photographs.[20] Cataract status was assessed by comparison with standard photographs.[21] Signs of AMD were recorded using slitlamp biomicroscopy with the aid of sample photographs we provided that depicted signs of maculopathy. Retinal photography was performed according to standard protocol, which required stereo pair 30° fundus photographs centered on the disc and fovea and temporal to the fovea of each eye. We provided film that was returned to us and developed by the same processing laboratory throughout the study. Study examination data and photographs were evaluated by J.M.S. and were assigned an AMD grade. The Massachusetts Eye and Ear Infirmary's institutional review board approved all study protocols, and appropriate consents were obtained from all participants.

DIETARY DATA

Food frequency questionnaires were the source of dietary data. The food frequency questionnaire, a modification of an extensively validated questionnaire,[22] contained a list of food items that were selected as the major sources of a variety of nutrients. This questionnaire, which we modified and adapted to facilitate its use among elderly subjects with eye disease, was found to be reliable in an age-related eye disease study population.[23]

The food frequency questionnaires were mailed to the participants to complete. We assisted by telephone those twins 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+ per day." The questionnaire also included questions about the use of multivitamins and supplements. Assessment of long-chain polyunsaturated omega-3 fatty acids included docosahexaenoic acid and eicosapentaenoic acid.

Data from all questionnaires were reviewed, coded, and entered into the computer without knowledge of the ocular status of the participant. We used a computer program developed at the Channing Laboratory in Boston to generate the intake scores for various micronutrients. The scores were calculated by multiplying the reported frequency 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.[24]

RISK FACTOR QUESTIONNAIRES

All subjects were interviewed over the telephone by a trained interviewer using a standardized risk factor questionnaire. The interviewer was unaware of the subject's ocular status or twin zygosity. The risk factor questionnaire included information about demographic characteristics, cigarette smoking, alcohol intake, and physical activity. Smokers were defined as having smoked at least 1 cigarette per day for at least 6 months. Current physical activity was assessed as the self-reported number of times per week of vigorous activity sufficient enough to work up a sweat. Cardiovascular disease was determined based on the participants' responses to whether a physician had ever told them that they had a myocardial infarction, angina, congestive heart failure, heart surgery, or stroke and whether they had ever taken medications for these conditions. If a participant responded yes to any of the conditions, either in the past or currently, they were considered to have CVD. Subjects were also asked to report any prior diagnosis of systemic hypertension, use of antihypertensive medications, diabetes mellitus, use of insulin or oral hypoglycemic agents, and malignancies.

MEASUREMENTS

Height, weight, and blood pressure were measured. Body mass index during the initial examination was calculated as weight in kilograms divided by the square of height in meters.

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CLASSIFICATION OF AMD AND SIGNS OF MACULOPATHY

Classification of specific macular characteristics was based on the grading of color fundus photographs of the macula using a grid with a 3000 µm radius centered on the foveal center according to an established protocol.[25] The grader was masked to zygosity status and clinical diagnosis. All study examination and photographic data were evaluated and assigned an AMD grade by J.M.S. (who was masked to zygosity status) using the 5-grade, mutually exclusive clinical age-related maculopathy staging system (CARMS)[18] as previously described.[9,10,15,16] The CARMS is our modification of the Age-Related Eye Disease Study grading system.[26] Eyes with extensive small drusen (≥15 small drusen, <63 µm in size), nonextensive intermediate drusen (<20 drusen, ≥63 µm but <125 µm), or retinal pigment epithelial abnormalities associated with AMD were assigned grade 2 (early disease). Eyes with extensive intermediate or large (≥125 µm) drusen with or without retinal pigment epithelial abnormalities and drusenoid retinal pigment epithelial detachments were assigned grade 3 (intermediate disease). Eyes with geographic atrophy, central or noncentral, were assigned grade 4, and eyes with serous retinal pigment epithelial detachment or with choroidal neovascular membrane were assigned grade 5. Unlike in the Age-Related Eye Disease Study system, level of visual acuity was not considered in this classification system, geographic atrophy included noncentral as well as central atrophy, and neovascular disease was classified separately. Eyes were assigned a grade 1 if none of these signs were present.

ZYGOSITY STATUS

In most cases (90%), zygosity status was determined by using questionnaire data from the National Academy of Sciences–National Research Council World War II Veteran Twin Registry; these data have 95% agreement with blood typing.[17,27] Among the 10% of the sample with unknown zygosity, DNA specimens were evaluated and zygosity was established by polymerase chain reaction and microsatellite typing using multiplex analyses of 8 microsatellite loci from 8 different chromosomes with polymorphic information content of 0.8 or greater.

STATISTICAL ANALYSES

Energy adjusted scores for omega-3 fatty acid and linoleic acid were categorized into quartiles of intake based on the distribution of nutrient scores among all subjects. Because of the possible interrelationships between intake of omega-3 and omega-6 fatty acids,[9,10] we also performed stratified analyses of omega-3 fatty acids within strata of subjects with low intake of linoleic acid, an omega-6 fatty acid (below the median or less than or equal to 11.79 g) and high intake of linoleic acid (above the median or greater than or equal to 11.8 g).

Odds ratios (ORs) and 95% percent confidence intervals (CIs) were calculated. Analyses were based on generalized estimating equations using PROC GENMOD of the software SAS (SAS Institute Inc, Cary, NC) to control for correlation between outcome status of twins within a twinship.[28] We calculated adjusted ORs to control for age (60-69, 70-79, and 80+ years), total energy intake (log calories, continuous), and protein intake (quartiles). We also computed ORs from a multivariate model (OR1), which in addition included the number of years of education (<12 or ≥12), smoking status (current, past, or never), body mass index (<25, 25-29, or ≥30), systolic blood pressure (analyzed continuously), CVD, log energy (continuous), protein intake (quartile), energy-adjusted log beta-carotene intake (continuous), self-reported alcohol intake (grams per day as a continuous variable), and physical activity (number of times per week of vigorous physical activity as a continuous variable). Furthermore, these analyses were repeated to generate odds ratios (OR2) with additional adjustment for quartiles of energy adjusted, log total intake of zinc, and intake of vitamins C and E from food and supplements because these were the supplements evaluated in the Age-Related Eye Disease Study.[29] Finally, subsets of discordant twins as well as monozygotic and dizygotic twins were analyzed separately to assess the direction of the relationships between the above variables and AMD.

RESULTS

A total of 681 individual twins were included in the analyses. Cases were twins classified as grades 3, 4, or 5 (n=222) and controls were grades 1 or 2 (n=459). The mean±SD ages of the twins in these 2 groups were 75.9±0.22 years and 74.5±0.15 years, respectively.

Table 1 displays the relationships between baseline characteristics and fish intake levels, omega-3 fatty acid intake levels, and cigarette smoking, unadjusted for other variables. Physical activity was positively related to fish intake but was inversely associated with cigarette smoking. Systolic blood pressure had a weak inverse association with fish intake and omega-3 intake. Body mass index was positively related to fish intake and omega-3 intake. Energy intake and alcohol were positively related to all 3 variables. Beta-carotene intake was positively related to fish intake and omega-3 intake but showed an inverse association with cigarette smoking. Vitamin C and protein intake were positively related to fish intake and omega-3 intake. Vitamin E intake was positively related to omega-3 intake and inversely associated with cigarette smoking. Individuals who never used multivitamins were somewhat more likely to be cigarette smokers while current multivitamin use showed a slight inverse association with cigarette smoking.

The ORs for AMD according to fish intake and cigarette smoking are presented in **Table 2** and **Table 3**. There was a significant trend for reduced risk of AMD with increasing intake of fish. Intake of 2 or more servings per week compared with less than one serving per week in the 2 multivariate models (multivariate OR1, 0.63; 95% CI, 0.41-0.97; and OR2, 0.64; 95% CI, 0.41-1.00) was associated with a protective effect (*P* trend, .03 and .04, respectively). Smoking was positively related to AMD with a 1.9-fold greater risk for current smokers in comparison with patients who were never smokers after controlling for covariates (OR2, 1.9; 95% CI, 0.99-3.68). Past smoking and a history of ever smoking also increased risk (OR2, 1.72; *P*=.009, and OR2, 1.74; *P*=.007, respectively). In a separate analysis of the relationship between AMD and time since quitting smoking (not shown), there was a reduction in risk of AMD 30 years after quitting (OR, 0.74), but this was not statistically significant.

The relationships between AMD and omega-3 fatty acid intake and linoleic acid intake as well as omega-3 fatty acid quartiles within strata of linoleic acid intake are shown in **Table 4**. There was a statistically significant beneficial effect of omega-3 fatty acid intake (multivariate OR1, fourth quartile vs first, 0.56; 95% CI, 0.33-

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Table 1. Characteristics of Study Population According to Fish Intake, Omega-3 Intake, and Cigarette Smoking

	Fish Intake			Omega-3 Intake				Cigarette Smoking		
	Servings of Fish per Week, No.			Quartiles						
Characteristic	<1 (n = 205)	1 (n = 219)	≥2 (n = 257)	1 (n = 166)	2 (n = 181)	3 (n = 163)	4 (n = 171)	Never (n = 178)	Past (n = 437)	Current (n = 66)
Age, %										
<70 y	4	7	6	4	8	5	6	1	6	14
70-79 y	88	84	85	88	82	87	87	88	85	85
≥80 y	8	9	9	8	10	9	8	11	9	2
Education, %*	84	87	89	85	86	88	88	94	84	86
Physical activity, mean†	1.0	1.2	1.7	1.0	1.2	1.2	2.0	2.0	1.2	0.6
Systolic BP, mean, mm Hg	141	138	138	141	138	135	140	139	139	134
Cardiovascular disease, %	36	30	34	34	30	37	32	30	37	18
Body mass index, %‡										
<25	41	36	35	42	33	40	35	46	32	53
25-29	46	52	49	46	54	45	50	44	52	38
≥30	13	12	16	11	13	15	15	10	16	9
Alcohol, g/d	7	8	10	7	9	8	10	6	9	16
Energy/d, geometric mean	1647	1829	2023	1562	1783	1929	2137	1834	1808	2096
Beta-carotene intake, μg/d§	3147	3371	4016	2914	3368	3641	4326	4174	3406	2823
Zinc, mg/d§	17	16	18	16	18	18	17	16	18	17
Vitamin C, mg/d§	197	211	228	184	204	212	257	184	251	204
Vitamin E, IU/d§	42	35	44	34	37	36	58	55	37	30
Protein intake, mg/d	67	76	90	60	75	83	95	80	76	85
Multivitamin, %‖										
Never	40	45	44	42	45	45	41	40	44	47
Past	13	17	13	13	14	18	12	14	15	11
Current	47	38	43	45	41	37	46	46	41	42

Abbreviation: BP, blood pressure.
*Education refers to percentage with at least high school education.
†Physical activity refers to mean number of times per week of vigorous activity.
‡Body mass index is calculated as weight in kilograms divided by the square of height in meters.
§Geometric mean after sex-specific calorie-adjustment; other values are means or percents.
‖Missing 3 subjects due to incomplete dietary assessments.

Table 2. Odds Ratios for AMD According to Fish Intake

	<1 Serving/wk	1 Serving/wk	≥2 Servings/wk	*P* Trend
Cases/controls, No.	74/131	75/144	73/184	
Median intake (servings per day)	0.080	0.18	0.36	
Adjusted OR*	1.0	0.97	0.68	.07
Multivariate OR1 (95% CI)†	1.0	0.94 (0.64-1.38)	0.63 (0.41-0.97)	.03
Multivariate OR2 (95% CI)‡	1.0	1.0 (0.67-1.48)	0.64 (0.41-1.00)	.04

Abbreviations: AMD, age-related macular degeneration; CI, confidence interval; OR, odds ratio.
*Adjusted for age (60-69, 70-79, and 80+ years), log calories (continuous), and protein intake (quartiles).
†Adjusted for education (≥high school vs <high school); smoking (current/past/never in the multivariate fish models); age (60-69, 70-79, and 80+ years); body mass index, calculated as weight in kilograms divided by the square of height in meters (<25, 25-29.9, and 30+); systolic blood pressure; cardiovascular disease; log calories (continuous); protein intake (quartile); log calorie-adjusted beta-carotene intake (continuous); alcohol intake (continuous); and physical activity (continuous, times per week vigorous).
‡Adjusted for variables in model 1 plus total intake of zinc, vitamin C, and vitamin E (log scale for all 3).

0.94; and OR2, 0.55; 95% CI, 0.32-0.95) while linoleic acid intake showed a nonsignificant effect in the opposite, adverse direction in adjusted and multivariate models (ORs, 1.56 and 1.46, respectively). When subjects were stratified by linoleic acid intake, higher omega-3 fatty acid intake decreased the risk of AMD among subjects with low levels (below median) of linoleic acid intake (multivariate OR1, fourth quartile vs first, 0.30; 95% CI, 0.12-0.74; and OR2, 0.23; 95% CI, 0.09-0.57). The trend for decreasing risk of AMD with higher intake of omega-3 fatty acid was statistically significant ($P = .002$ and $P < .001$, respectively). Conversely, among subjects with high levels of linoleic acid intake (above median), no association was seen between intake of omega-3 fatty acid and AMD.

Analyses of 77 discordant twin pairs in which one twin had AMD and the other did not (n = 154 individual twins) showed similar relationships between AMD and ever

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Table 3. Odds Ratios for AMD According to Cigarette Smoking

	Never	Past	*P* Value (Past vs Never)	Current	*P* Value (Current vs Never)	Ever	*P* Value (Ever vs Never)
Cases/controls, No.	45/133	150/287		27/39		177/326	
Adjusted OR*	1.0	1.66	.01	1.91	.04	1.69	.008
Multivariate OR1 (95% CI)†	1.0	1.66 (1.13-2.44)	.01	1.86 (0.97-3.58)	.06	1.68 (1.15-2.47)	.008
Multivariate OR2 (95% CI)‡	1.0	1.72 (1.14-2.60)	.009	1.91 (0.99-3.68)	.06	1.74 (1.16-2.60)	.007

Abbreviations: AMD, age-related macular degeneration; CI, confidence interval; OR, odds ratio.
*Adjusted for age (60-69, 70-79, and 80 years), log calories (continuous), and protein intake (quartiles).
†Adjusted for education (≥high school vs <high school); smoking (current/past/never in the multivariate fish models); age (60-69, 70-79, and 80+ years); body mass index, calculated as weight in kilograms divided by the square of height in meters (<25, 25-29.9, and 30+); systolic blood pressure; cardiovascular disease; log calories (continuous); protein intake (quartile); log calorie-adjusted beta-carotene intake (continuous); alcohol intake (continuous); and physical activity (continuous, times per week vigorous).
‡Adjusted for variables in model 1 plus total intake of zinc, vitamin C, and vitamin E (log scale for all 3).

Table 4. Odds Ratios for AMD by Quartile of Omega-3 Intake, Linoleic Acid Intake, and Omega-3 Intake Within Strata of Linoleic Acid Intake

	Quartile of Omega-3 Intake				
Fatty Acid Intake	1	2	3	4	*P* Trend
Omega-3 intake					
Cases/controls, No.	64/102	61/120	49/114	48/123	
Median intake, g	0.06	0.12	0.20	0.35	
Adjusted OR*	1.0	0.82	0.62	0.60	.02
Multivariate OR1 (95% CI)†	1.0	0.79 (0.52-1.21)	0.60 (0.36-0.97)	0.56 (0.33-0.94)	.01
Multivariate OR2 (95% CI)‡	1.0	0.80 (0.53-1.21)	0.60 (0.36-0.99)	0.55 (0.32-0.95)	.02
Linoleic acid intake					
Cases/controls, No.	43/127	60/110	65/107	54/115	
Median intake, g	7.12	10.45	13.34	18.46	
Adjusted OR*	1.0	1.72	1.81	1.37	.42
Multivariate OR1 (95% CI)†	1.0	1.89 (1.15-3.11)	2.07 (1.17-3.63)	1.56 (0.79-3.08)	.26
Multivariate OR2 (95% CI)‡	1.0	1.85 (1.12-3.08)	1.99 (1.12-3.54)	1.46 (0.72-2.96)	.32
Linoleic acid intake, quartiles 1 and 2 (≤11.79 g)					
Cases/controls, No.	41/66	35/65	17/54	10/52	
Median intake of omega-3, g	0.06	0.12	0.20	0.35	
Adjusted OR*	1.0	0.79	0.90	0.92	.001
Multivariate OR1 (95% CI)†	1.0	0.97 (0.54-1.76)	0.48 (0.22-1.04)	0.30 (0.12-0.74)	.002
Multivariate OR2 (95% CI)‡	1.0	0.94 (0.52-1.72)	0.39 (0.18-0.88)	0.23 (0.09-0.57)	<.001
Linoleic acid intake, quartiles 3 and 4 (≥11.80 g)					
Cases/controls, No.	23/36	26/55	32/60	38/71	
Median intake of omega-3, g	0.06	0.12	0.20	0.36	
Adjusted OR*	1.0	0.79	0.90	0.92	.98
Multivariate OR1 (95% CI)†	1.0	0.74 (0.37-1.47)	0.82 (0.40-1.69)	0.85 (0.41-1.77)	.93
Multivariate OR2 (95% CI)‡	1.0	0.73 (0.35-1.55)	0.84 (0.37-1.89)	1.07 (0.46-2.50)	.66

Abbreviations: AMD, age-related macular degeneration; CI, confidence interval; OR, odds ratio.
*Adjusted for log calories (continuous) and protein intake (quartile).
†Adjusted for education (≥high school vs <high school); smoking (current/past/never); age (60-69, 70-79, and 80+ years); body mass index, calculated as weight in kilograms divided by the square of height in meters (<25, 25-29.9, and 30+); systolic blood pressure; cardiovascular disease; log calories (continuous); protein intake (quartile); log calorie-adjusted beta-carotene intake (continuous); alcohol intake (continuous); and physical activity (continuous, times per week vigorous).
‡Adjusted for variables in model 1 plus total intake of zinc, vitamin C, and vitamin E (log scale for all 3).

smoking (multivariate OR1, 5.28; $P=.06$) and omega-3 fatty acid intake (multivariate OR1, 0.34; $P=.06$). Analyses of the monozygotic twins (n=358) and dizygotic twins (n=323) separately revealed similar directions for the effects of smoking and omega-3 intake with somewhat different magnitude of the effects. For monozygotic twins, the ORs for smoking were 3.2 ($P=.01$) for current and 1.7 ($P=.07$) for past, and the OR for omega-3 intake (fourth quartile vs first) was 0.58 ($P=.18$). For dizygotic twins, the ORs for smoking were 1.3 for current ($P=.60$) and 1.6 for past ($P=.19$) while the OR for omega-3 intake (fourth quartile vs first) was 0.44 ($P=.06$, P for trend=.01).

To evaluate the potential impact of these modifiable behavioral factors on risk of AMD, after controlling for the effect of the other risk factors, we also calculated the

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attributable risk [(OR−1)/OR) × proportion exposed among cases] = [(1.68 for ever smoking −1)/1.68) × 0.797] and found that 32% of the cases in this cohort could be attributed to cigarette smoking, which is similar to our previous estimate of 29% in another study population.[6] Furthermore, if everyone consumed a diet with omega-3 fatty acid levels in the range of the highest quartile in this study (median intake of 0.35 g/d), then the estimated preventive fraction is 22% (summing the values in the preceding equation for the first 3 quartiles relative to the highest quartile).

COMMENT

In this population-based registry of male twins, results indicate that current and past cigarette smoking increases risk for AMD. Current smokers had almost a 2-fold increased risk of AMD and past smokers had a 1.7-fold increase in risk in comparison with those who never smoked. More frequent fish intake and higher levels of omega-3 fatty acid intake reduced risk of AMD, even after adjustment for other risk factors. The protective effect of long-chain polyunsaturated omega-3 fatty acid intake was seen only when linoleic acid intake (an omega-6 fatty acid) was below the median, similar to our previous studies in 2 different cohorts.[9,10]

These findings support other evidence in the literature regarding the need to maintain a healthy ratio between omega-6 and omega-3 fatty acids. The ideal omega-6/omega-3 ratio is 3:1 to 4:1.[14] However, the average American's diet has an omega-6/omega-3 ratio that ranges from 10:1 to 50:1.[14] This imbalance is attributed to a diet rich in processed foods containing or cooked in vegetable oils, which we have previously shown to increase the risk of AMD.[9,10] Our results suggest that when our diet is rich in these omega-6 fatty acids (as measured here by linoleic acid), the protective effect of omega-3 fatty acids is dampened. The importance of a diet rich in omega-3 fatty acids has also been observed in studies of CVD and stroke.[30-32] Furthermore, regular intake of omega-3 fatty acids along with a healthy lifestyle has been shown to have a protective effect in reducing the risk of chronic inflammatory diseases, most notably, heart disease, as well as Crohn disease, asthma, rheumatoid arthritis, Alzheimer disease, and mental illnesses such as depression.[30,32-34]

Docosahexaenoic acid, an omega-3 fatty acid, plays an essential role in the formation of the human brain, retina, and nervous central system. Both docosahexaenoic acid and eicosapentaenoic acid, another long-chain polyunsaturated omega-3 fatty acid also found primarily in fish, have been shown to reduce inflammatory and autoimmune diseases. There is increasing evidence of an inflammatory component for AMD.[35-40] The unique properties of docosahexaenoic acid and eicosapentaenoic acid therefore suggest a plausible mechanism regarding how omega-3 fatty acids could be helpful in promoting healthy eye tissue, regulating inflammatory and immune responses in the retina, improving endothelial cell function,[32] and thereby reducing risk of AMD.

It may be reasonable for physicians to make dietary recommendations for eye health, including intake of fish along with fruits and vegetables. We hypothesize that this will be especially important for patients who have high levels of inflammatory biomarkers such as C-reactive protein or genotypes associated with increased risk of AMD.[35-41] Changing an individual's diet by increasing omega-3 fatty acid intake may reduce systemic and local inflammatory responses and repair damaged cells in the body and therefore reduce levels of C-reactive protein.[42] A good source of omega-3 fatty acids is the diet, and there is an increasing trend for the addition of this nutrient to many common foods in the American diet. Further studies are needed, including randomized trials to determine if dietary changes related to increasing intake of omega-3 fatty acids or supplements will reduce onset or progression of AMD.

Despite the current surgeon general's warnings on the dangers of cigarette smoking, 46 million Americans continue to smoke each year and 28.5% of these current smokers are individuals between the ages of 18 and 24 years old, leaving future generations at risk for diseases such as CVD and AMD.[43] Smoking not only increases oxidative stress but also increases inflammatory responses, and both of these mechanisms are associated with AMD. Age-related macular degeneration is a common eye disease in older persons, smoking is a common avoidable behavior, and dietary habits are modifiable; therefore, a proportion of visual impairment and blindness due to AMD could be prevented with attention to healthy lifestyles.

Unique features of this design that strengthen the results from this study include the narrow age range of the cohort (10 years) and standardized data-collection instruments, including assessment of AMD end points by clinical examination and fundus photography. The AMD status and risk factor data were determined independently of knowledge of zygosity or co-twin diagnosis. This unique case-control twin design also has the advantage of better control for age and shared environment at younger ages. Because the study is limited to male twins from a specific birth cohort, the study results may not be generalizable to women or to other birth cohorts. Because this is a case-control design, we cannot exclude the possible effect of unmeasured lifestyle or dietary differences. However, such factors would need to be associated with dietary omega-3 intake and smoking as well as AMD to materially alter these results.

The burden of chronic diseases is expected to increase with projections that older adults will more than double in number to 70 million by the year 2030 in the United States.[44] The current pattern of the high-fat, high-calorie American diet has been attributed to the increase in obesity, diabetes, and CVD in younger generations. Obesity is known to be related to AMD.[45]

In summary, this study provides evidence for an adverse effect from smoking as well as an inverse association between long-chain polyunsaturated omega-3 fatty acid dietary intake and AMD. About a third of the risk of AMD in this twin study cohort could be attributable to cigarette smoking, and about a fifth of the cases were estimated as preventable with higher fish and omega-3 fatty acid dietary intake. These and other modifiable behaviors and preventive measures deserve increased attention and evaluation to reduce the increasing burden of AMD.

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Correspondence: Johanna M. Seddon, MD, ScM, Epidemiology Unit, Massachusetts Eye and Ear Infirmary, 243 Charles St, Boston, MA (johanna_seddon@meei.harvard.edu).
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