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Progression of Age-Related Macular Degeneration:

Association With Dietary Fat, Transunsaturated Fat, Nuts, and Fish Intake

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Abstract

Background: Individuals with early or intermediate stages of age-related macular degeneration (AMD) make up a large, growing segment of the elderly population. Evidence is sparse regarding modifiable factors that may decrease the risk of progression to the advanced forms of AMD.

Objective: To advise patients with a high risk for advanced forms of AMD about preventive measures through our evaluation of the relationship between dietary fat intake and the progression of early or intermediate AMD to the advanced stages of the disease associated with visual loss.

Design: A prospective cohort study with an average follow-up time of 4.6 years.

Setting: A hospital-based clinical retinal practice specializing in macular degeneration.

Patients: The 261 participants were aged 60 years and older and had some sign of nonexudative AMD and visual acuity of 20/200 or better in at least 1 eye.

Main Outcome Measure: Progression to advanced AMD, which was defined as having geographic atrophy or neovascular disease.

Results: Higher total fat intake increased the risk of progression to the advanced forms of AMD, with a relative risk (RR) of 2.90 (95% confidence interval, 1.15–7.32) for the highest fat-intake quartile relative to the lowest fat-intake quartile, after controlling for other factors (*P* trend=.01). Animal fat intake was associated with a 2-fold increased risk of progression (RR, 2.29 for the highest quartile compared with the lowest quartile; 95% confidence interval, 0.91–5.72),although the trend for increasing risk with higher animal fat intake was not significant (*P*=.09). Higher vegetable fat intake had a stronger relationship with increased risk of AMD progression with an RR of 3.82 (95% confidence interval, 1.58–9.28) for the highest quartile compared with the lowest quartile (*P* trend=.003). Saturated, monounsaturated, polyunsaturated, and transunsaturated fats increased the likelihood of progression (RR, 2.09 and *P* trend=.08; RR, 2.21 and *P* trend=.04; RR, 2.28 and *P* trend=.04; RR, 2.39 and *P* trend = .008, respectively). Higher fish intake was associated with a lower risk of AMD progression among subjects with lower linoleic acid intake. Processed

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baked goods, which are higher in some of these fats, increased the rate of AMD progression approximately 2-fold, and nuts were protective.

Conclusions: Among individuals with the early or intermediate stages of AMD, total and specific types of fat intake, as well as some fat-containing food groups, modified the risk of progression to advanced AMD. Fish intake and nuts reduced risk. Since advanced AMD is associated with visual loss and reduced quality of life, these preventive measures deserve additional research and greater emphasis.

AGE-RELATED MACULAR degeneration (AMD) is the leading cause of irreversible visual impairment and blindness in the United States and other developed countries throughout the world.[1] Among individuals aged 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.[2] The prevalence and burden of this disease continues to rise as the size of our elderly population expands.[3] The etiology is still an enigma and only a few risk factors have been consistently shown to be related to the onset of this disease, including cigarette smoking and increasing age.[2,4–6] Therapeutic options for the advanced stages of AMD with visual loss remain limited. Therefore, a major challenge is to find the causes and mechanisms of this disease to develop preventive measures and better therapies.

Individuals with the early or intermediate stages of AMD represent a large, growing segment of our elderly population. It is estimated that more than 8 million people have the intermediate stage of AMD, and of these, about 1.3 million people will develop advanced AMD with visual loss and reduced quality of life during the next 5 years.[1] A major finding that has altered management of this condition is the reported beneficial effect of a vitamin/mineral supplement,[7] which supports our previous findings about the beneficial effects of dietary antioxidants on AMD.[8] In a randomized trial, the Age-Related Eye Disease Study,[7] individuals with the intermediate form of AMD who were given vitamins C and E, beta carotene, and zinc had a 25% reduction in risk of progressing to the advanced stages of AMD at 5 years compared with a placebo group. Diets rich in lutein and zeaxanthin may also reduce risk.[8] In addition, we recently reported that among individuals with a high risk of developing advanced AMD, overall and abdominal obesity increases the risk of AMD progression and more vigorous physical activity tends to decrease risk.[9] However, despite these advances, evidence is sparse regarding other modifiable factors that could reduce the rate of conversion from early or intermediate disease to the advanced stages that cause irreversible visual loss.

We previously hypothesized that AMD and cardiovascular disease share some common risk factors.[10] For example, it is plausible that dietary fat, which is associated with atherosclerosis,[11–12] could affect ocular blood vessels or could be involved in oxidative processes that contribute to the development of the advanced stage of AMD characterized by atrophy or choroidal neovascularization. In fact, a few studies have demonstrated an association between dietary fat intake and the onset or diagnosis of AMD,[13–16] but others do not,[17] and the type of fat associated with AMD differs across studies. However, to our knowledge, no studies have evaluated the association between dietary fat intake and

progression of AMD among individuals already diagnosed with the early or intermediate stages of the disease.

To determine the effect of dietary fat intake on a large population at risk for visual loss, we evaluated the association between total fat intake, specific types of fat and specific fat-containing foods, and rates of progression in our ongoing prospective longitudinal study of AMD.

METHODS

STUDY POPULATION

The Progression of Age-Related Macular Degeneration Study is a longitudinal study designed to measure multiple risk factors for the onset and progression of AMD. The study population includes patients with AMD who were seen by 1 of us (J.M.S.) for examination at the Massachusetts Eye and Ear Infirmary, Boston. Subjects were aged 60 years and older, were primarily white (99.9%), and had at least 1 eye with a best corrected visual acuity of 20/200 or better and nonexudative AMD. Other inclusion criteria included willingness to participate in a long-term study that involved annual dilated eye examinations and fundus photography. Patients were excluded if they were unable to speak English or had decreased hearing or cognitive function such that they would not be able to understand a health status and dietary interview.

Of the 397 persons who were eligible for enrollment between July 1989 and May 1998, 366 (92%) were enrolled. The Human Subjects Committee at the Massachusetts Eye and Ear Infirmary approved the study, and all subjects signed a consent form to participate. Of the 366 participants enrolled, 36 were not considered for analyses because of inability to complete the initial study examination (n=5), lack of follow-up data (n=17), or lack of 1 or more primary independent variables (n=14). To conduct the analyses, we excluded men and women who reported, at baseline, ever having a diagnosis of cancer (n=61) (except nonmelanoma skin cancer), which could influence the dietary and other variables assessed in these analyses. Finally, to maintain the quality of data for these analyses, we excluded 8 dietary questionnaires owing to inadequate or missing answers (n=6) and extreme values (n=2). Participants whose responses were not included in the analyses (n=8) did not differ significantly by age, sex, or education from those who were included. A total of 261 individuals were included in the analyses, and the mean age was 72.8 years.

FOLLOW-UP STATUS

If a patient was unable to return to our clinical center, we identified a local ophthalmologist who was willing to examine the patient and complete standardized forms and photographs using the protocols we designed for the study. Approximately 4% of patients received off-site examinations.

The average follow-up time was 4.6 years. Six percent of the participants were followed up for less than 1 year, 26% were followed up for 1 to 2.9 years, 24% were followed up for 3 to 4.9 years, 22% were followed up for 5 to 6.9 years, and 22% were followed up for 7 or more years. The total number of person-years of follow-up was 1198. Individuals

whose AMD progressed in at least 1 eye were censored at the date of progression and did not contribute additional years of follow-up beyond this date. Additionally, 47 participants were censored during follow-up because of death. Nineteen individuals (7%) were lost to follow-up because of unwillingness to return for additional follow-up examinations. These individuals did not differ significantly from the remaining participants (n=242) with regard to age (mean age, 72.2 years among those lost to follow-up vs 73.4 years among those not lost) or education (95% with at least a high school degree among those lost to follow-up vs 87% among those not lost) (*P*=.31); however, more women were lost to follow-up (10%) compared with men (3%) (*P*=.03).

DIETARY DATA

Food frequency questionnaires (FFQs) were the source of dietary data. The FFQ, a modification of an extensively validated questionnaire,[18] 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.[19] Reproducibility correlation coefficients for fats, ranging from 0.59 to 0.73, were similar to results from other established diet questionnaires.[19]

The FFQs were mailed to the participants before their study visit. 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+ per day.” The FFQ also included questions about the use of multivitamins and supplements.

We reviewed, coded, and entered the data from all questionnaires 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.[20]

Analyses for this prospective study focused primarily on measures of dietary fat intake, including total fat, as well as specific types of fat and fat-containing foods, as in our previous case-control study.[15] Information about other baseline dietary factors were also obtained from the FFQ, including log energy (calories), energy-adjusted log beta carotene intake, and alcohol intake (grams per day). We adjusted specific types of fat for intake of vitamins C and E, zinc, and total beta carotene intake with and without supplements. None of the participants reported at baseline the simultaneous use of high doses of vitamin C (≥400 mg), vitamin E (≥300 IU), beta carotene (≥15 mg), or zinc (≥75 mg) as used in the Age-Related Eye Disease Study or a supplement similar to the one used in the Age-Related Eye Disease Study.

INTERVIEWS

All subjects were interviewed by a trained interviewer using a standardized risk factor questionnaire. The interview was conducted in person and preceded the ophthalmologic examination. The interviewer was unaware of the subjects' ocular status. 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. Subjects were also asked to report any prior diagnosis of chronic medical conditions, including systemic hypertension, use of antihypertensive medications, angina, myocardial infarction, congestive heart failure, stroke, type 1 and type 2 diabetes mellitus, use of insulin or oral hypoglycemic agents, and malignancies other than nonmelanoma skin cancer. A list of all currently used medications was completed. 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 ever took 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 cardiovascular disease.

MEASUREMENTS

Height, weight, and blood pressure were measured using standard protocols and equipment. Body mass index during the initial examination was calculated as weight in kilograms divided by the height in meters squared. Waist and hip measurements were recorded by participants at home using an established protocol, including instructions and a standard tape measure.[21]

OCULAR EXAMINATION AND CLASSIFICATION OF AMD

At each examination, a refraction was performed and best-corrected visual acuity was determined using the Early Treatment Diabetic Retinopathy protocol.[22] The intraocular pressure was measured and the iris color was noted at the slitlamp examination and classified according to standard photographs.[23] After dilation of the pupils, the examining ophthalmologist (J.M.S.) noted the presence or absence of cataract and clinically graded the cataract according to the Lens Opacities Classification System II (LOCS II)[24] using standard photographs. Signs of maculopathy were noted and graded using a 90-diopter lens at the slitlamp. A peripheral retinal examination was performed using an indirect ophthalmoscope. Results of the eye examination were recorded on standardized forms that we developed for this study.

Stereoscopic color fundus photographs of the macula were obtained. We used a 5-grade classification scale of AMD, which we modified from the Age-Related Eye Disease Study grading system.[25] Macular characteristics were graded within a 3000-μm radius centered on the foveal center. Eyes with extensive small drusen (≥15 small drusen; ˂63 μm), nonextensive intermediate drusen (˂20 drusen; ≥63 μm but ˂125 μm), or pigment abnormalities associated with AMD were assigned a grade of 2. Eyes with extensive intermediate or large (≥125-μm) drusen were assigned a grade of 3. Eyes with geographic

atrophy received a grade of 4. If there was evidence of retinal pigment epithelial detachment or choroidal neovascular membrane, a grade of 5 was assigned. Eyes received a grade of 1 if none of these signs was present. Advanced AMD is defined as grades 4 and 5.

To evaluate intergrader reliability, fundus photographs of participants with at least 3 years of follow-up (n=222) were sent to the Wisconsin Fundus Photographic Reading Center, Madison, for detailed age-related maculopathic grading. The reading center uses a 4-point grading system to measure AMD; so we created an algorithm to convert their 4-point grade scale into our 5-grade scale for comparison. Reading center grade 3 was converted to grade 4 if geographic atrophy was present; otherwise it remained grade 3. Reading center grade 4 was converted to grade 5 if any of the following signs were present: subsensory retinal hemorrhage, subretinal pigment epithelial hemorrhage, nondrusenoid pigment epithelial detachment, or subretinal fibrosis. Additionally, if there was indication of treatment for exudative macular degeneration, then the reading center grade 4 was converted to grade 5. Otherwise, reading center grade 4 remained the same. Reading center grades 1 and 2 did not require conversion because they were similar to our grades 1 and 2.

The level of agreement between one of us (J.M.S.) and the reading center grades was determined using the κ statistic. These comparisons included the grade of the worst eye. The κ statistic for interrater reliability was 0.77 and the weighted κ score was 0.84.[26] Cases in which there was inconsistency of 2 or more AMD grades were reevaluated and adjudicated by one of us (J.M.S.).

STATISTICAL ANALYSES

Progression to advanced AMD was defined either as eye progressing from a grade of less than 4 to grades 4 or 5 or progressing from grade 4 to grade 5 at any follow-up visit. Although both grades 4 and 5 are classified as advanced disease, eyes with geographic atrophy (grade 4) can progress to neovascular disease (grade 5). Sunness et al[27] reported 4-year conversion rates of 11% for individuals with bilateral atrophy, 34% for those with unilateral atrophy and choroidal neovascular membrane in the fellow eye, and 19% rate of progression overall. They also noted that the development of choroidal neovascular membrane had a negative effect on the degree of visual acuity loss. Therefore, we also included progression from atrophy to choroidal neovascular membrane (grade 4 to 5) as an outcome.

Regression was not considered in the analyses. Each subject was considered to have progressed only once during the follow-up period, counting the first eye that progressed. The rationale for this definition of progression was that AMD is a progressive disease and regression at this advanced stage is uncommon. Specifically, in our data, among 107 people who progressed from baseline, only 2 individuals regressed at a subsequent visit; both of these subjects then subsequently progressed to advanced AMD.

First, age-adjusted analyses were performed relating progression of disease to total fat intake, adjusting for age-sex groups coded as dummy variables (men aged 60 to 69 years, men aged 70 to 79 years, men aged 80 years and older, women aged 60 to 69 years, women aged 70 to 79 years, and women aged 80 years and older) and energy intake by

including log total energy intake (calories) as an additional covariate. Our principal method of analysis was the Cox proportional hazards model. We first computed an adjusted relative risk (RR) of progression for sex-specific quartiles 2 to 4 of total fat vs sex-specific quartile 1 after controlling for age-sex group, energy (log), and protein intake (quartiles). The full multivariate model also included the number of years of education (<12 or ≥12), smoking status (current, past, or never), body mass index (<25, 25 to 29, or ≥30 kg/m^2), systolic blood pressure (analyzed continuously in 10–mm Hg increments), cardiovascular disease, log energy (continuous), protein intake (quartile), energy-adjusted log beta carotene intake (continuous), self-reported alcohol intake (grams per day as a continuous variable), physical activity (number of times per week of vigorous physical activity as a continuous variable), and initial AMD grade (1–5, categorical). Tests for trend were also conducted corresponding to the adjusted and multivariate RRs by substituting a single trend variable of total fat coded as 1 to 4 and interpreted as a continuous variable. Because protein and alcohol intake were also included in the previous model, as well as total energy intake, the total fat variables can be interpreted as substitution effects of fat for carbohydrate intake, holding total energy constant. Ninety-five percent confidence intervals (CIs) were computed for the multivariate RRs, and 2-sided *P* values were computed for all models.

A similar approach was used to separate total fat into saturated fat, monounsaturated fat, polyunsaturated fat, and transunsaturated fat. Similar models were also run substituting animal fat and vegetable fat for total fat intake. Furthermore, an additional multivariate model was run simultaneously, adjusting for animal and vegetable fat in the same model. The RRs from the latter models can be interpreted as approximate substitution effects of animal fat and vegetable fat for carbohydrates, holding total energy constant. Furthermore, the analyses concerning total fat and specific types of fat were repeated, adjusting for the individual nutrients reported to be beneficial in the Age-Related Eye Disease Study: total intake of zinc and vitamins C and E from food and supplements. Finally, similar additional models were run relating the number of servings of fish consumed per week (< 1 serving per week, 1 serving per week, or ≥2 servings per week) to progression of AMD within low (quartiles 1 and 2) and high (quartiles 3 and 4) levels of linoleic acid as in our previous case-control analyses relating fat intake to the diagnosis of AMD.[15]

Analyses also included the association between the risk for AMD and the intake of specific food groups that contribute to fat intake. The food groups analyzed were high-fat dairy, meat, processed baked goods, and nuts. The specific foods in the groups were whole milk, ice cream, hard cheese, and butter for the high-fat dairy food group; hamburger, hot dogs, processed meat, bacon, beef as a sandwich, and beef as a main dish for the meat food group; commercial pie, cake, cookies, and potato chips for the processed baked goods food group; and any type of nut for the nut food group. All of the analyses were performed using SAS software, version 6.12 (SAS Institute Inc, Cary, NC).

Additional models were run, including the initial best eye grade and the initial worst eye grade. Results were unchanged after the additional adjustment and are not presented in the tables. Finally, a test of proportionality in the Cox proportional hazards models was performed by including cross-product terms of follow-up time, total fat intake in quartiles,

and similar terms in the models for specific types of fat. No significant deviations from proportionality were found.

RESULTS

Two hundred sixty-one participants were included in the analyses. All participants were aged 60 years or older at baseline without a history of cancer (excluding nonmelanoma skin cancer). There were 101 patients with AMD who progressed to advanced AMD.

Table 1 presents the characteristics of the study population according to intake of specific types of fat and fish. Physical activity was inversely related to intake of total, animal, saturated, monounsaturated, and transunsaturated fats and positively related to fish intake. Current smoking was positively related to animal fat intake and inversely related to intake of vegetable fat and fish, while past smoking was inversely associated with animal fat and saturated fat intake. Alcohol intake was lower in the highest quartile of vegetable fat and polyunsaturated fat intake. Energy intake was higher for the higher intake of most types of fat, with a smaller positive association seen for fish intake. Beta carotene intake was inversely related to intake of total, saturated, monounsaturated, and transunsaturated fats and positively related to fish intake. Zinc intake was somewhat higher at baseline for the highest intake of fish and was slightly lower for the highest intake of vegetable fat. Vitamin C intake was lowest in the highest quartiles of intake of total, vegetable, saturated, monounsaturated, and polyunsaturated fats. Vitamin E was lowest in the highest quartile of total fat, and higher with more intake of fish.

Table 2 summarizes the RRs for progression to advanced AMD according to the main categories of fat intake. There was an increasing risk of progression with increasing levels of total fat intake when adjusting for age-sex group and energy and protein intake, with an RR of 1.96 for the third quartile and an RR of 2.74 for the fourth quartile, compared with the lowest quartile of fat intake. This trend was statistically significant (P=.007). After controlling for several other factors, the effect was similar with a multivariate RR of 2.70 for the highest quartile (95% CI, 1.10–6.62) (P trend=.01). Given that energy and protein intake were held constant in these multivariate analyses, these results could be interpreted as an isocaloric substitution of fat for carbohydrates being related to increased risk of AMD progression. Further adjustments for intake of zinc, vitamin C, and vitamin E slightly strengthened the association between AMD and total fat, with an RR of 2.90 for the highest quartile of total fat compared with the lowest (P trend=.01). In a separate analysis of total fat, substituting lutein and zeatanthin for total beta carotene, the results were not materially different. Animal fat and vegetable fat contributions to total fat intake were analyzed separately. For both, there was an increased rate of progression associated with the highest intake, and results were somewhat stronger and statistically significant for vegetable fat. After adjustment for total zinc, vitamin C, and vitamin E, results for animal fat remained nonsignificant, whereas results for vegetable fat were strengthened (RR, 3.17 for quartile 4 vs quartile 1; P trend=.006). Similar results were found for animal and vegetable fat after controlling for the other types of fat, suggesting that vegetable fat was more consistently associated with AMD progression than animal fat. These results suggest

that a direct substitution of vegetable fat for carbohydrate, keeping animal fat and total energy intake constant, is related to rate of progression.

Table 3 presents the RRs for progression to advanced AMD according to saturated and unsaturated fats. For saturated fat, there was a trend for an increase in risk for higher intake, with a multivariate RR of 2.03 (95% CI,0.84–4.89) for the highest intake compared with the lowest intake, which was statistically significant (*P* trend=.07). These results were similar after adjustment for zinc and vitamins C and E. For monounsaturated fat intake, the results were similar with an RR of 2.18 (95% CI, 0.90–5.26) for the highest intake compared with the lowest intake, which was significant (*P* trend=.04), with similar results after including the other nutrients (*P* trend=.04). There was a nonsignificant, positive association between polyunsaturated fat intake and progression of AMD, which became stronger and significant (RR, 2.28; *P*=.04) after consideration of the other nutrients. Transunsaturated fats were significantly associated with the progression of AMD in all models. For the fully adjusted model, the RR was 2.39 (95% CI, 1.10–5.17) (*P* trend=.008), comparing the highest intake with the lowest intake.

As seen in Table 4, there was no significant effect of fish intake on the rate of progression of AMD in both the age-adjusted and multivariate models. However, when subjects were stratified by linoleic acid, the major source of ω−6 fatty acids, fish intake decreased the risk of AMD progression when linoleic acid intake was below the median, with a multivariate RR of 0.36 (95% CI, 0.14–0.95) (*P* trend =.045). Conversely, no significant effect of fish intake was found for linoleic acid intake above the median (*P*=.58).

In Table 5, specific food groups contributing to dietary fat intake were evaluated according to combined servings per day of each food in the groups. High-fat dairy foods (RRs = 1.91) and meat (RRs = 2.09) tended to increase risk, although the overall trend was not statistically significant. Processed baked goods increased risk for progression of AMD (RR = 2.42 for highest intake vs lowest intake), and the trend for increasing risk with increasing intake was statistically significant (*P* trend = .005). In contrast, the nut food group was associated with a lower rate of progression of AMD, with a multivariate RR of 0.60 (95% CI, 0.32–1.02) for 1 or more servings per week, compared with no intake, with a statistically significant trend (*P*=.05) (Table 6).

COMMENT

In this prospective longitudinal study, we found that higher levels of dietary fat intake were associated with the progression of AMD to the advanced stages associated with visual loss. Specifically, higher intake of vegetable fat, and to a lesser extent animal fat, increased rates of progression. Saturated, monounsaturated, polyunsaturated, and transunsaturated fats were also related to progression. Food groups with higher levels of these fats, particularly processed baked goods, were also associated with a higher rate of progression of AMD, except for nuts, which were protective. Thus, dietary intake of fat, including specific types of fat as well as fat-containing foods, is a potentially important behavior that can modify the outcome for patients who already have the early or intermediate forms of AMD.

To our knowledge, these results represent the first assessment of the effect of dietary fats on the rate of AMD progression. Findings are generally consistent with the results of our previous case-control study in which we compared the dietary habits of individuals with advanced, exudative disease with control subjects.[15] In that study, specific types of fat, including vegetable, monounsaturated, and polyunsaturated, were associated with a higher risk for AMD diagnosis. Both studies suggest a protective effect of fish intake among individuals with lower linoleic acid intake. Long-chain ω−3 fatty acids, especially docosahexanoic acid found primarily in fish, have been associated with an inverse risk for cardiovascular disease in some studies.[28] There is biological plausibility of a relationship between the intake of ω−3 fatty acids and the progression of AMD because there are high levels of ω−3 fatty acids, especially docosahexanoic acid, in the retina. Our finding of a possible protective relationship between higher intake of fish with low linoleic acid intake and progression of AMD warrants further research.

Although no studies in the literature are directly comparable to these prospective data on the progression of AMD among subjects with less advanced forms of the disease, there are similarities and differences in other reports that evaluated prevalence or onset of disease. Cross-sectional data from the Beaver Dam Study[13] and the Blue Mountains Eye Study[14] both reported significantly increased prevalence of age-related maculopathy with greater dietary fat intake, although these results were not consistent for specific types of fat. The Beaver Dam Study reported odds ratios of 1.8 for the highest saturated fat intake compared with the lowest saturated fat intake and prevalence of early age-related maculopathy.[13] The Blue Mountains Eye Study reported odds ratios of 1.48 for monounsaturated fat for early age-related maculopathy.[14] However, more recent results from the Third National Health and Nutrition Examination Survey[17] suggested no relationship between any type of fat intake and prevalence of early or late age-related maculopathy, although the number of advanced cases was small (n=51).

Epidemiological findings continue to point to a possible cardiovascular risk profile among some persons with AMD, suggesting that the 2 conditions may be interrelated.[10] Our results regarding the effect of dietary fat and specific food groups, such as processed baked goods, on AMD progression support and expand upon this growing literature relating cardiovascular risk factors to AMD. One mechanism could involve atherosclerosis of the blood vessels supplying the choroid and retina. Dietary fat might also increase oxidative damage in the macula, an area that is susceptible to oxidation owing to high oxygen tension and light exposure.

We have previously demonstrated an association between progression of AMD and obesity, another risk factor for cardiovascular disease, so it is important to consider this exposure as well.[9] In this article, we demonstrate that after controlling for body mass index, dietary fat intake is independently related to an increased rate of progression to advanced AMD. Additionally, obesity, independent of fat intake, remained significantly related to the progression of AMD (data not shown). Furthermore, increased fat intake and obesity are known to be associated with inflammation, and inflammatory factors are known to be associated with cardiovascular disease and may possibly be associated with AMD.[10] Other mechanisms, such as genetic and dietary interactions, might also play a role.

The potential beneficial effect of the nut food group on risk of AMD progression complements other literature reporting a protective role for nuts and cardiovascular disease[29–31] and type 2 diabetes mellitus.[32] The Physicians' Health Study reported nearly a 50% reduction in risk for sudden cardiac death (RR, 0.53) (95% CI, 0.30–0.92) and a 30% lowered risk for total coronary heart disease death among men who consumed nuts 2 or more times per week.[30] Additionally, the Nurses' Health Study found a 35% lower risk of coronary heart disease and a 27% decrease in risk for type 2 diabetes mellitus among women who consumed nuts 5 or more times per week vs none.[29,32] One of the bioactive compounds in nuts, resveratrol, has antioxidant, antithrombotic, and anti-inflammatory properties.[33] In addition, nuts may lower total cholesterol levels and protect against coronary heart disease and atherosclerosis because they are dietary sources of vitamin E, copper, magnesium, and dietary fiber.[34] This lends further support to the potential relationship between risk factors for cardiovascular disease and AMD.

Our results also show that consumption of transunsaturated fatty acids increases the risk of AMD and its progression. Metabolic studies have shown that trans fats have adverse effects on blood lipid levels by increasing low-density lipoprotein cholesterol while decreasing high-density lipoprotein levels,[35] and this effect can be twice that of saturated fatty acids. Trans fats are also known to be associated with an increased risk of coronary heart disease.[36] Because of the weight of the evidence about these harmful effects, the Food and Drug Administration has recently proposed the inclusion of the content of transfatty acids on food labels.

Unique features of this study include the evaluation of the progression of AMD, as opposed to its onset or diagnosis. Further strengths of the study include the prospective assessment of progression rates; standardized data collection instruments, including interviews and direct measurements of height, weight, and blood pressure; assessment of AMD end points by standardized ophthalmologic examination and fundus photography, and low rate of loss to follow-up. Furthermore, the prospective design of this study has the advantage of minimizing bias attributable to the influence of disease on reporting of these risk factors, since they were reported prior to the progression of AMD. One cannot rule out the possibility that some reporting of risk factors could have been related to the initial level of AMD at baseline. Any random misclassification would tend to bias our associations toward an RR of 1.0 (no association). The results regarding fat were not weakened after adjustment for carotenoids, vitamins C and E, and zinc. It is possible that the adverse effect of dietary fat found in our study may represent the deleterious effect of other aspects of high-fat diets rather than fat. Although some unmeasured and therefore uncontrolled factors might still be confounding the relationships seen, they would have to be highly associated with dietary fat intake and a strong risk factor for AMD progression to explain these results.

Identification of modifiable risk factors for AMD may improve our ability to identify and treat the approximately 8 million persons in the United States with signs of AMD who are at high risk of progressing to the more severe forms of the disease. More than 200000 people develop advanced AMD with visual loss every year, and these numbers are expanding as the percentage of elderly people in the population continues to grow.[37] Modification of the rate of AMD progression associated with specific types of dietary fat intake, which we describe

in this report, provides yet another reason for health professionals to intensify their public health message about healthy behaviors and lifestyles. A substantial number of people may benefit from raising awareness about the importance of a healthy, fat conscious diet as a means of maintaining good eye health, as well as cardiovascular health, in later years. These and other preventive measures to reduce the growing burden of visual loss among the elderly population warrant further investigation and greater emphasis.

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Table 1.

Characteristics of Study Population According to Intake of Specific Types of Fat

	Quartile															
	Total Fat				Animal Fat				Vegetable Fat				Saturated Fat			
	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
Sample size	64	66	66	65	64	66	66	65	64	66	66	65	64	66	66	65
Age, y	72	72	72	73	72	72	73	72	71	72	73	73	72	72	73	73
Male, %	39	39	39	38	39	39	39	38	39	39	39	38	39	39	39	38
Education, %	88	88	83	91	89	86	85	89	86	85	89	89	89	85	83	92
Initial worst eye																
Grade 2	16	15	17	6	17	15	14	8	11	21	14	8	16	15	17	6
Grade 3	39	35	41	37	36	41	27	48	41	38	33	40	38	36	36	42
Grade 4	17	20	6	17	11	15	21	12	20	15	12	12	14	17	15	14
Grade 5	28	30	36	40	36	29	38	32	28	26	41	40	33	32	32	38
Physical activity, mean	2.1	1.8	1.5	1.3	2.0	2.0	1.4	1.2	1.8	1.8	1.3	1.6	2.1	1.7	1.6	1.2
Current smoker, %	6	12	11	6	3	12	9	11	14	6	12	3	6	11	9	9
Past smoker, %	59	62	55	52	63	55	65	46	52	67	52	58	61	59	59	49
Systolic blood pressure, mm Hg, mean	140	137	138	140	139	137	139	141	139	139	136	142	139	137	139	140
Cardiovascular disease	27	27	12	17	27	27	15	14	20	21	18	23	31	26	12	14
Body mass index, kg/m^2	27	28	27	28	26	28	28	28	26	28	29	27	26	28	28	28
Alcohol, g/d	8	9	7	7	7	6	10	7	12	7	8	4	8	7	8	7
Energy/d, geometric mean	1028	1248	1528	1887	1054	1331	1440	1832	1136	1252	1477	1764	1023	1268	1536	1856
Beta carotene intake, µg/d *	4088	3175	3401	2972	3474	3620	3374	3072	3404	3899	3167	3110	3581	4010	3024	3004
Zinc, mg/d *	17	16	15	15	14	16	15	17	16	18	16	13	17	15	16	15
Vitamin C, mg/d *	274	227	218	166	264	258	166	199	238	232	213	191	276	227	216	167
Vitamin E, mg/d *	29	28	20	20	27	30	19	21	18	33	20	27	30	25	20	22

	Quartile														
	Monounsaturated Fat				Polyunsaturated Fat				Transunsaturated Fat				Fish Intake		
	1	2	3	4	1	2	3	4	1	2	3	4	<1/wk	1/wk	≥2/wk
Sample size	64	66	66	65	64	66	66	65	65	66	65	65	93	86	82

	Quartile														
	Monounsaturated Fat				Polyunsaturated Fat				Transunsaturated Fat				Fish Intake		
	1	2	3	4	1	2	3	4	1	2	3	4	<1/wk	1/wk	≥2/wk
Age, y	72	72	72	73	72	71	73	73	72	71	71	74	71	73	73
Male, %	39	39	39	38	39	39	39	38	38	39	40	38	37	38	43
Education, %	88	88	85	89	81	89	91	88	88	85	89	88	85	85	93
Initial worst eye															
Grade 2	16	15	15	8	11	23	12	8	15	21	11	6	12	11	18
Grade 3	41	30	45	35	38	33	41	40	43	33	42	34	33	7	44
Grade 4	13	24	8	15	28	8	15	9	8	20	12	20	20	19	5
Grade 5	31	30	32	42	23	36	32	43	34	26	35	40	34	34	33
Physical activity, mean	2.2	1.7	1.5	1.3	1.9	1.5	1.8	1.4	2.2	1.7	1.3	1.3	1.2	1.6	2.2
Current smoker, %	6	12	11	6	14	8	8	6	9	6	9	11	15	6	5
Past smoker, %	58	64	52	55	58	70	48	52	52	61	62	54	55	57	60
Systolic blood pressure, mm Hg, mean	140	138	138	139	139	137	139	141	137	140	140	138	137	143	137
Cardiovascular disease	25	27	15	15	14	24	21	23	25	24	11	23	17	19	27
Body mass index, kg/m^2	27	28	28	28	26	28	28	28	27	28	28	28	27	28	28
Alcohol, g/d	8	8	8	6	11	6	7	6	7	11	8	5	8	7	7
Energy/d, geometric mean	1043	1221	1555	1869	1082	1256	1521	1791	1083	1352	1518	1673	1305	1389	1489
Beta carotene intake, μg/d *	4084	3187	3508	2875	3453	3713	3113	3272	4001	3218	3565	2845	3002	3173	4130
Zinc, mg/d *	16	15	16	15	17	16	14	15	14	19	19	12	15	13	20
Vitamin C, mg/d *	271	221	230	163	232	244	203	195	235	263	233	156	263	199	259
Vitamin E, mg/d *	24	30	23	19	19	36	20	24	23	30	27	17	21	22	30

* Values are expressed as geometric mean after sex-specific energy adjustment. Education refers to percentage with at least a high school education. Physical activity refers to the mean number of times per week of vigorous activity.

Table 2.

Relative Risks for Progression to Advanced Age-Related Macular Degeneration by Quartiles of Fat Intake

Type of Fat	Quartile 1	2	3	4	*P* Value (Trend)
Total fat					
Sample size	64	66	66	65	…
Progression rate, %	23	29	45	51	…
Median intake, g	24.4	36.0	49.7	70.1	…
Adjusted RR*	1.0	1.26	1.96	2.74	.007
Multivariate RR 1 (95% CI)†	1.0	1.11 (0.56–2.18)	2.00 (0.96–4.16)	2.70 (1.10–6.62)	.01
Multivariate RR 2 (95% CI)‡	1.0	1.27 (0.63–2.53)	2.29 (1.08–4.88)	2.90 (1.15–7.32)	.01
Animal fat					
Sample size	64	66	66	65	…
Progression rate, %	28	31	41	47	…
Median intake, g	15.4	23.0	31.0	53.8	…
Adjusted RR*	1.0	0.92	1.42	2.19	.02
Multivariate RR 1 (95% CI)†	1.0	0.73 (0.38–1.39)	1.18 (0.59–2.36)	1.96 (0.85–4.53)	.08
Multivariate RR 2 (95% CI)‡	1.0	0.69 (0.35–1.32)	1.14 (0.55–2.32)	1.59 (0.66–3.82)	.19
Multivariate RR 3 (95% CI)§	1.0	0.81 (0.41–1.57)	1.14 (0.55–2.37)	2.29 (0.91–5.72)	.09
Vegetable fat					
Sample size	64	66	66	65	…
Progression rate, %	25	38	40	44	…
Median intake, g	6.3	10.2	16.7	28.8	…
Adjusted RR*	1.0	1.52	2.03	2.14	.03
Multivariate RR 1 (95% CI)†	1.0	1.55 (0.84–2.88)	1.90 (0.97–3.72)	2.43 (1.10–5.37)	.03
Multivariate RR 2 (95% CI)‡	1.0	1.56 (0.83–2.96)	2.09 (1.06–4.11)	3.17 (1.37–7.32)	.006
Multivariate RR 3 (95% CI)§	1.0	1.64 (0.86–3.13)	2.27 (1.12–4.59)	3.82 (1.58–9.28)	.003

Abbreviations: CI, confidence interval; RR, relative risk.

[*] Adjusted for age-sex group (men aged 60–69 years, men aged 70–79 years, men aged ≥80 years, women aged 60–69 years, women aged 70–79 years, and women aged ≥80 years), log energy (continuous), and protein intake (quartile).

[†] Adjusted for age-sex group (men aged 60–69 years, men aged 70–79 years, men aged ≥80 years, women aged 60–69 years, women aged 70–79 years, and women aged ≥80 years), education (≥high school vs <high school), smoking (current, past, or never), body mass index (<25, 25–29.9, and ≥30), systolic blood pressure, cardiovascular disease, log energy (continuous), protein intake (quartile), energy-adjusted log beta carotene intake (continuous), alcohol intake (continuous), physical activity (continuous, mean number of times per week of vigorous activity), and initial age-related macular degeneration grade (categorical).

[‡] Adjusted for variables in multivariate RR 1 plus total intake of energy-adjusted log zinc, vitamin C, and vitamin E.

[§] Adjusted for variables in multivariate RR 2 plus other types of fat (ie, vegetable fat in the animal fat model and animal fat in the vegetable fat model).

Table 3.

Relative Risks for Progression to Advanced Age-Related Macular Degeneration by Energy-Adjusted Quartiles of Various Types of Saturated and Unsaturated Fat*

Type of Fat	Quartile 1	2	3	4	*P* Value (Trend)
Saturated fat					
Sample size	64	66	66	65	…
Progression rate, %	27	35	37	47	…
Median intake, g	8.9	13.1	18.3	27.5	…
Adjusted RR	1.0	1.24	1.39	2.17	.06
Multivariate RR 1 (95% CI)†	1.0	0.93 (0.48–1.81)	1.37 (0.64–2.90)	2.03 (0.84–4.89)	.07
Multivariate RR 2 (95% CI)‡	1.0	0.97 (0.49–1.93)	1.46 (0.66–3.20)	2.09 (0.83–5.28)	.08
Monounsaturated fat					
Sample size	64	66	66	65	…
Progression rate, %	22	32	48	47	…
Median intake, g	9.2	13.7	19.6	27.4	…
Adjusted RR	1.0	1.48	2.16	2.27	.02
Multivariate RR 1 (95% CI)†	1.0	1.18 (0.61–2.28)	2.00 (0.97–4.12)	2.18 (0.90–5.26)	.04
Multivariate RR 2 (95% CI)‡	1.0	1.27 (0.65–2.45)	2.13 (1.03–4.43)	2.21 (0.90–5.47)	.04
Polyunsaturated fat					
Sample size	64	66	66	65	…
Progression rate, %	30	31	38	48	…
Median intake, g	3.6	5.3	7.0	10.4	…
Adjusted RR	1.0	1.24	1.40	1.82	.09
Multivariate RR 1 (95% CI)†	1.0	1.33 (0.71–2.49)	1.44 (0.74–2.79)	1.64 (0.80–3.39)	.19
Multivariate RR 2 (95% CI)‡	1.0	1.57 (0.82–3.02)	1.90 (0.94–3.84)	2.28 (1.04–4.99)	.04
Transunsaturated fat					
Sample size	65	66	65	65	…
Progression rate, %	28	36	52	37	…
Median intake, g	0.64	1.24	2.14	3.73	…

Type of Fat	Quartile				*P* Value (Trend)
	1	2	3	4	
Adjusted RR	1.0	1.80	3.66	2.65	<.001
Multivariate RR 1 (95% CI)[†]	1.0	1.86 (0.93–3.74)	3.71 (1.90–7.23)	2.44 (1.12–5.30)	.007
Multivariate RR 2 (95% CI)[‡]	1.0	1.67 (0.83–3.36)	3.22 (1.63–6.36)	2.39(1.10–5.17)	.008

Abbreviations: CI, confidence interval; RR, relative risk.

[*]Adjusted for age-sex group (men aged 60–69 years, men aged 70–79 years, men aged ≥80 years, women aged 60–69 years, women aged 70–79 years, and women aged ≥80 years), log energy (continuous), and protein intake (quartile).

[†]Adjusted for age-sex group (men aged 60–69 years, men aged 70–79 years, men aged ≥80 years, women aged 60–69 years, women aged 70–79 years, women aged ≥80 years), education (≥high school vs <high school), smoking (current, past, or never), body mass index (<25, 25–29.9, and ≥30), systolic blood pressure, cardiovascular disease, log energy (continuous), protein intake (quartile), energy-adjusted log beta carotene intake (continuous), alcohol intake (continuous), physical activity (continuous, mean number of times per week of vigorous activity), and initial age-related macular degeneration grade (categorical).

[‡]Adjusted for variables in multivariate RR 1 plus total intake of energy-adjusted log zinc, vitamin C, and vitamin E

Table 4.

Relative Risks for Progression to Advanced 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			
	<1	1	≥2	*P* Value (Trend)
By Frequency Alone				
Median intake	0.07	0.14	0.43	…
Adjusted RR*	1.0	1.24	0.87	.42
Multivariate RR 1 (95% CI)†	1.0	1.31 (0.79–2.18)	0.95 (0.53–1.71)	.58
Multivariate RR 2 (95% CI)‡	1.0	1.30 (0.78–2.16)	0.88 (0.49–1.60)	.42
By Frequency Within Strata of Linoleic Acid Intake				
Linoleic acid intake, quartiles 1 and 2 (≤4.9 g) (n = 129)				
Median intake (servings per day)	0.07	0.14	0.43	…
Adjusted RR*	1.0	0.68	0.79	.83
Multivariate RR 1 (95% CI)†	1.0	0.68 (0.26–1.78)	0.42 (0.16–1.08)	.07
Multivariate RR 2 (95% CI)‡	1.0	0.62 (0.23–1.70)	0.36 (0.14–0.95)	.045
Linoleic acid intake, quartiles 3 and 4 (>4.9 g) (n = 132)				
Median intake (servings per day)	0.07	0.14	0.43	…
Adjusted RR*	1.0	2.09	1.21	.76
Multivariate RR 1 (95% CI)†	1.0	3.05 (1.43–6.47)	1.78 (0.75–4.20)	.73
Multivariate RR 2 (95% CI)‡	1.0	2.77 (1.26–6.08)	2.0 (0.82–4.91)	.58

Abbreviations: Ci, confidence interval; RR, relative risk.

*Adjusted for age-sex group (men aged 60–69 years, men aged 70–79 years, men aged ≥80 years, women aged 60–69 years, women aged 70–79 years, and women aged ≥80 years), log energy (continuous), and protein intake (quartile).

†Adjusted for age-sex group (men aged 60–69 years, men aged 70–79 years, men aged ≥80 years, women aged 60–69 years, women aged 70–79 years, women aged ≥80 years), education (≥high school vs <high school), smoking (current, past, or never), body mass index (<25, 25–29.9, and ≥30), systolic blood pressure, cardiovascular disease, log energy (continuous), protein intake (quartile), energy-adjusted log beta carotene intake (continuous), alcohol intake (continuous), physical activity (continuous, mean number of times per week of vigorous activity), and initial age-related macular degeneration grade (categorical).

‡Adjusted for variables in multivariate RR 1 plus total intake of energy-adjusted log zinc, vitamin C, and vitamin E.

Table 5.

Relative Risks for Progression to Advanced Age-Related Macular Degeneration According to Intake of Select Food Groups*

Type of Food Group	Quartile 1	2	3	4	*P* Value (Trend)
High-fat dairy					
Sample size	70	59	63	67	…
Median intake	0.08	0.36	0.67	2.23	…
Adjusted RR†	1.0	1.67	2.09	1.86	.02
Multivariate RR 1 (95% CI)‡	1.0	1.92 (1.02–3.60)	1.82 (0.99–3.35)	1.98 (1.05–3.73)	.06
Multivariate RR 2 (95% CI)§	1.0	2.08 (1.09–3.97)	1.80 (0.96–3.38)	1.91 (0.98–3.73)	.10
Meat					
Sample size	62	71	64	64	…
Median intake	0.12	0.38	0.56	1.16	…
Adjusted RR†	1.0	2.07	1.92	2.93	.007
Multivariate RR 1 (95% CI)‡	1.0	1.85 (0.98–3.48)	1.71 (0.86–3.37)	2.43 (1.18–5.02)	.04
Multivariate RR 2 (95% CI)§	1.0	1.75 (0.91–3.34)	1.62 (0.81–3.24)	2.09 (0.98–4.47)	.11
Processed baked goods					
Sample size	65	64	69	63	…
Median intake	0.08	0.37	0.80	2.5	…
Adjusted RR†	1.0	1.25	1.71	1.59	.10
Multivariate RR 1 (95% CI)‡	1.0	1.28 (0.69–2.38)	2.17(1.13–4.16)	2.17 (1.08–4.38)	.01
Multivariate RR 2 (95% CI)§	1.0	1.21 (0.69–2.26)	2.02 (1.06–3.85)	2.42 (1.21–4.84)	.005

Abbreviations: CI, confidence interval; RR, relative risk.

*High-fat dairy refers to number of servings per day of whole milk, ice cream, hard cheese, and butter. Meat refers to number of servings per day of hamburger, hot dogs, processed meat, bacon, beef as a sandwich, and beef as a main dish. Processed baked goods refers to servings per day of commercial pie, cake, cookies, and potato chips.

†Adjusted for age-sex group (men aged 60–69 years, men aged 70–79 years, men aged ≥80 years, women aged 60–69 years, women aged 70–79 years, women aged ≥80 years), log energy (continuous), and protein intake (quartile).

‡Adjusted for age-sex group (men aged 60–69 years, men aged 70–79 years, men aged ≥80 years, women aged 60–69 years, women aged 70–79 years, women aged ≥80 years), education (≥high school vs <high school), smoking (current, past, or never), body mass index (<25, 25–29.9, and ≥30), systolic blood pressure, cardiovascular disease, log energy (continuous), protein intake (quartile), energy-adjusted

log beta carotene intake (continuous), alcohol intake (continuous), physical activity (continuous, mean number of times per week of vigorous activity), and initial age-related macular degeneration grade (categorical).

§Adjusted for variables in multivariate RR 1 plus total intake of energy-adjusted log zinc, vitamin C, and vitamin E.

Table 6.

Relative Risks for Progression to Advanced Age-Related Macular Degeneration According to Intake of Nuts

	No. of Servings of Nuts per Week			
	Never	**<1**	**≥1**	***P* Value (Trend)**
Nuts [*]				
Sample size	136	66	59	…
Median intake	0	0.08	0.14	…
Adjusted RR [†]	1.0	0.74	0.46	.008
Multivariate RR 1 (95% CI) [‡]	1.0	0.66 (0.39–1.10)	0.54 (0.29–1.01)	.02
Multivariate RR 2 (95% CI) [§]	1.0	0.69 (0.40–1.17)	0.60 (0.32–1.02)	.05

Abbreviations: CI, confidence interval; RR, relative risk.

[*] Nuts refers to servings per day of any type of nut.

[†] Adjusted for age-sex group (men aged 60–69 years, men aged 70–79 years, men aged ≥80 years, women aged 60–69 years, women aged 70–79 years, and women aged ≥80 years), log energy (continuous), and protein intake (quartile).

[‡] Adjusted for age-sex group (men aged 60–69 years, men aged 70–79 years, men aged ≥80 years, women aged 60–69 years, women aged 70–79 years, women aged ≥80 years), education (≥high school vs <high school), smoking (current, past, or never), body mass index (<25, 25–29.9, and ≥30), systolic blood pressure, cardiovascular disease, log energy (continuous), protein intake (quartile), energy-adjusted log beta carotene intake (continuous), alcohol intake (continuous), physical activity (continuous, mean number of times per week of vigorous activity), and initial age-related macular degeneration grade (categorical).

[§] Adjusted for variables in multivariate RR 1 plus total intake of energy-adjusted log zinc, vitamin C, and vitamin E.