Progression of Age-Related Macular Degeneration

Association With Body Mass Index, Waist Circumference, and Waist-Hip Ratio

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Background: Individuals with early or intermediate stages of age-related macular degeneration (AMD) make up a large and growing segment of our elderly population. To advise these high-risk patients regarding preventive measures, we evaluated anthropomorphic, behavioral, and medical factors associated with progression to the advanced stages of AMD associated with visual loss.

Methods: The design was a prospective cohort study in a hospital-based retinal practice. The 261 participants were 60 years or older, with some sign of nonadvanced AMD and visual acuity of 20/200 or better in at least 1 eye. The average follow-up time was 4.6 years, and the total person-years of follow-up was 1198. Factors associated with rates of progression to advanced AMD were assessed by the Cox proportional hazards model.

Outcome Measures: Progression to geographic atrophy and neovascular disease.

Results: Higher body mass index (calculated as weight in kilograms divided by the square of height in meters) increased the risk for progression to the advanced forms of AMD. Relative risk (RR) was 2.35 (95% confidence interval [CI], 1.27-4.34) for a body mass index of at least 30, and 2.32 (95% CI, 1.32-4.07) for a body mass index of 25 to 29, relative to the lowest category (<25) after controlling for other factors (P = .007 for trend). Higher waist circumference was associated with a 2-fold increased risk for progression (RR for the highest tertile compared with the lowest, 2.04; 95% CI, 1.12-3.72), with a significant trend for increasing risk with a greater waist circumference (P = .02). Higher waist-hip ratio also increased the risk for progression (RR, 1.84; 95% CI, 1.07-3.15) for the highest tertile compared with lowest (P = .02 for trend). More physical activity tended to be associated with a reduced rate of progression (25% reduction for 3 times per week vigorous activity vs none, P = .05 to P = .07). Relative risks for smoking ranged from 1.48 to 1.99, but were not statistically significant.

Conclusions: Results provide new information regarding modifiable factors for individuals with the early or intermediate stages of this disease. Overall and abdominal obesity increased the risk for progression to advanced AMD, and more physical activity tended to decrease risk. These preventive measures deserve additional research and greater emphasis.
Ophthalmologists can inform individuals with non-advanced macular degeneration that their eye disease most likely will not progress substantially on the basis of the literature to date. However, in an important minority of individuals, the more advanced stages of the disease will develop, and as a result they will have irreversible and largely untreatable visual loss and reduced quality of life.

Epidemiological studies during the past decade, including cross-sectional, case-control, and cohort studies, have demonstrated factors associated with the onset or the diagnosis of AMD. On the basis of these data, we advise patients not to smoke. We may also advise patients to adhere to a healthy diet rich in fruits and vegetables, to modify specific types of fat intake, and to control blood pressure and cholesterol intake. Evidence is sparse, however, regarding potentially modifiable factors that could decrease the risk for development of the advanced forms of AMD and visual loss among individuals who already manifest some signs of AMD. This population of individuals with AMD at high risk for visual loss includes about 8 million people in the United States older than 55 years, among whom advanced AMD will develop in greater than 1 million in the next 5 years, as estimated from prevalence and incidence rates. Thus far, the only proven means to reduce the rate of progression to advanced AMD for these individuals is vitamin and mineral supplementation. To determine other modifiable factors that differ between high-risk individuals who progress and those who do not and to better advise patients regarding preventive measures, we conducted a prospective study to evaluate whether measures of obesity, physical activity, cigarette smoking, and cardiovascular diseases are associated with progression of early or intermediate disease to the advanced stages of AMD associated with visual loss.

### METHODS

#### STUDY POPULATION

The Progression of Age-Related Macular Degeneration Study is a longitudinal study designed to measure multiple risk factors for the progression of AMD. The study population includes patients with AMD who were examined by one of us (J.M.S.) at the Massachusetts Eye and Ear Infirmary, Boston.

Subjects were 60 years or older, of any ethnicity (99.9% white), and had at least 1 eye with 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 and/or had decreased hearing or cognitive function that would preclude understanding a health status and dietary interview.

Of the 397 persons who were eligible for enrollment from May 9, 1989, through July 28, 1998, we enrolled 366 (92%). 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, 22 were not considered for analyses because of inability to complete the initial study examination (n=5) or lack of follow-up data (n=17). To conduct the analyses herein, we excluded men and women who reported a diagnosis of cancer (n=61) except nonmelanoma skin cancer, which could influence the variables assessed in these analyses (eg, body mass index [BMI]). Finally, an additional 22 individuals were excluded because they were missing data on 1 or more of the primary independent variables. A total of 261 individuals were included in these analyses, with a mean age of 72.8 years.

#### FOLLOW-UP STATUS

To enhance and maintain adequate follow-up, all individuals were sent postcards to remind them about their study appointments. Newsletters describing the status of enrollment and information about macular degeneration were also mailed periodically to participants. If a patient was unable to return to the Massachusetts Eye and Ear Infirmary, we identified a local ophthalmologist who was willing to see the patient and complete standardized forms and photographs using protocols we designed for the study. We also obtained previous ophthalmic records and photographs if possible. 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%, for 1 to 2.9 years; 24%, for 3 to 4.9 years; 22%, for 5 to 6.9 years; and 22%, for 7 years or longer. The total number of person-years of follow-up was 1198. Individuals who 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. In addition, 47 participants were censored during follow-up owing to 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 mean age (72.2 vs 73.4 years) or duration of education (at least high school degree, 95% vs 87%) (P=.31); however, more women were unavailable (10%) compared with men (3%) (P=.03).

#### INTERVIEWS

At the time of enrollment, 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 on demographic characteristics, cigarette smoking, alcohol consumption, and physical activity. Subjects were also asked to report any previous diagnosis of chronic medical conditions, including systemic hypertension, angina, myocardial infarction, congestive heart failure, stroke, diabetes, and malignancies other than nonmelanoma skin cancer, and use of insulin or oral hypoglycemic agents or antihypertensive medications. A list of all currently used medications was completed. Beginning in 1992, all subjects were asked to complete a baseline and annual semiquantitative food frequency questionnaire.

#### RISK FACTOR ASSESSMENT

Analyses for this study focused primarily on measures of obesity, physical activity, smoking status, and vascular conditions. Height, weight, and blood pressure were measured at each annual clinical examination using the same protocols and equipment. Body mass index was determined by measuring the participant’s weight on a balance beam scale during the initial examination, converting it to kilograms, and dividing by the square of the height in meters. Waist and hip measurements were recorded by participants at home using an established protocol, including instructions and a standard tape measure. Waist and hip measurements were used to assess waist circumference and waist-hip ratio, indices of abdominal obesity.
Current physical activity was assessed as self-reported number of times per week of activity vigorous enough to work up a sweat. Smokers were defined as having smoked at least 1 cigarette a day for at least 6 months. Systemic hypertension was assessed by the measured systolic blood pressure. Cardiovascular disease was determined on the basis of the participants’ responses to questions on whether a physician had ever told them that they had a heart attack, angina, congestive heart failure, heart surgery, and/or stroke, and/or whether they ever took medications for those conditions. If a participant responded yes to any of the conditions in the past or present, they were considered to have cardiovascular disease.

Information about dietary factors, including log calories, total carotenoid intake, and alcohol intake (grams per day) was obtained from the baseline food frequency questionnaire. We also considered adjusting for high-dose vitamin and mineral supplementation in doses similar to those reported in the Age-Related Eye Disease Study, but none of the participants reported simultaneous use of high doses of ascorbic acid (≥400 mg), vitamin E (≥300 IU), beta carotene (≥15 mg), and zinc oxide (≥75 mg).

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. Intraocular pressure was then measured, the iris color was noted at the slitlamp examination, and the findings were classified according to standard photographs. After dilation of the pupils, the examining ophthalmologist (J.M.S.) noted the presence or absence of cataract and graded the cataract clinically using standard photographs according to the Lens Opacities Classification System II. Signs of maculopathy were then 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 were obtained of the macula. A 5-grade classification scale of AMD was used, which is our modification of the Age-Related Eye Disease Study grading system. 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 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 evidence of retinal pigment epithelial detachment and/or choroidal neovascular membrane (CNVM) was found, a grade of 5 was assigned. Eyes received a grade of 1 if none of these signs were present. Advanced AMD was 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 Photograph Reading Center, Madison, location for detailed age-related maculopathy grading. The Reading Center used a 4-point grading system to measure AMD, so we created an algorithm to convert the 4-point grade to our 5-point grade scale for comparison. The Reading Center grade 3 was converted to our grade 4 if geographic atrophy was present; otherwise it remained grade 3. The Reading Center grade 4 was converted to our grade 5 if any of the following signs were present: subtensory retinal hemorrhage, subretinal pigment epithelial hemorrhage, nondrusenoid pigment epithelial detachment, or subretinal fibrosis. In addition, if there was indication of photocoagulation (laser treatment) for macular degeneration, then the Reading Center grade 4 was converted to our grade 5. Otherwise, the Reading Center grade 4 remained the same. The Reading Center grades 1 and 2 did not require conversion, since they were similar to our grades 1 and 2.

The level of agreement between our grades and the Reading Center grades was determined using the κ statistic. These comparisons included the grade of the worst eye. The κ statistic for intergrader reliability was 0.77, and the weighted κ score was 0.84. Cases in which there was inconsistency of 2 or more AMD grades underwent recalculation and adjudication by one of us (J.M.S.).

Statistical Analyses

Progression to advanced AMD was defined as progression of either eye from a grade of less than 4 to grade 4 or 5 or progression from grade 4 to 5 at any follow-up visit. Although grades 4 and 5 are classified as advanced disease, geographic atrophy (grade 4) can progress to neovascular disease (grade 5). Sunness et al reported 4-year conversion rates from atrophy to CNVM of 11% for individuals with bilateral atrophy, 34% for those with unilateral atrophy and CNVM in the fellow eye, and 19% overall. They also noted that the development of CNVM had a negative impact on the degree of visual acuity loss. Therefore, we also included progression from atrophy to CNVM (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 is that AMD is a progressive disease and regression at this advanced stage is uncommon. Specifically, in our data, among 101 people with progression from baseline, only 2 individuals showed regression at a subsequent visit; both of these subjects later showed progression to advanced AMD.

First, we performed age-adjusted analyses relating progression to each obesity measurement at baseline, after controlling for the following age-sex groups coded as dummy variables: men aged 60 to 69 years, men aged 70 to 79 years, men 80 years and older, women aged 60 to 69 years, women aged 70 to 79 years, and women 80 years and older. The Cox proportional hazards model was used to estimate relative risks (RRs) for progression adjusting for additional risk factors. Specifically, we used the SAS Procedure PHREG (SAS Institute Inc, Cary, NC) to relate time to AMD progression to anthropomorphic factors (BMI, waist circumference, and waist-hip ratio at baseline) in separate analyses while controlling for the age-sex group, physical activity (times per week of vigorous activity as a continuous variable), cigarette smoking status (current, past, or never), systolic blood pressure (analyzed continuously in 10-mm Hg increments), baseline AMD grade in the worst eye (categorical), education (at least high school vs less than high school), log calories, calorie-adjusted carotenoid intake, and alcohol intake. We divided BMI into 3 categories (<25, 25-29, and ≥30). Waist circumferences and waist-hip ratios were divided into tertiles separately for men and women. Variables were entered in 3 regression models separately for BMI, waist circumference, and waist-hip ratio at baseline. Each model was performed categorically by comparing each BMI, waist circumference, and waist-hip ratio subgroup with the referent group (typically the lowest category). In addition, we also performed tests for trend by scoring BMI, waist circumference, and waist-hip ratio as ordinal variables, eg, test for trend for BMI was scored as 1 if less than 25; 2 if 25 to 29; and 3 if at least 30. Rates of progression were calculated using the Kaplan-Meier estimator. We used SAS software, version 6.12 (SAS Institute Inc), to perform all analyses.

A total of 261 participants were included in the analyses. All participants were 60 years or older at baseline,
with no reported history of cancer (excluding nonmelanoma skin cancer). There were 101 patients with AMD who progressed to advanced AMD. The overall rates of progression to more advanced AMD and the rates of progression according to the initial AMD grade of the worst eye are presented in the Figure. Overall, at year 1, 2% had undergone conversion to a more advanced AMD; at year 5, 18%; and at year 8, 30%. The probability of progression to advanced AMD at year 5 for individuals with an initial worst eye of grade 2 was 9%, compared with 27% for grade 3, and 31% for grade 4.

Table 1 describes the characteristics of the study population and potential AMD risk factors according to the 3 obesity measures. Body mass index was inversely related to smoking, whereas waist circumference and waist-hip ratio were positively related to past smoking. Individuals in the group with a BMI of at least 30 reported somewhat less physical activity than those in the other BMI groups. Waist circumference was inversely related to physical activity. There was no consistent relationship between waist-hip ratio and physical activity, but the lowest waist-hip ratio had the highest amount of physical activity. Inverse relationships were seen between waist circumference and log carotenoid intake and alcohol intake. The highest BMI group had the lowest carotenoid intake and the lowest alcohol intake. Total caloric intake was unrelated to all obesity measures. Waist circumference, BMI, and waist-hip ratio were all positively related to each other.

Table 2 describes the 3 multivariate models relating obesity measures and other variables to AMD progression. There was an increased risk for AMD progression with higher levels of BMI (model A), with a statistically significant trend after adjusting for other factors ($P = .007$). Relative risks were $2.32$ (95% confidence interval [CI], 1.32-4.07) for a BMI of 25 to 29, and $2.35$ (95% CI 1.27-4.34) for a BMI of at least 30.

Higher waist circumference was associated with an increased risk for progression (model B). The RR for the highest tertile compared with the lowest was $2.04$ (95% CI 1.12-3.72), with a significant trend for increasing risk with increase in waist circumference, after controlling for other variables ($P = .02$).

This study provides new data regarding modifiable factors associated with progression of AMD during an average follow-up of almost 5 years. Among individuals with early or intermediate disease, measures of overall and abdominal obesity increased the rate of progression to the advanced forms of AMD associated with visual loss and reduced quality of life. Increased levels of physical activity tended to decrease the risk.

Unique features of this study include the evaluation of the progression of the disease, as opposed to its onset or diagnosis, and the evaluation of several anthropomorphic variables as risk factors for progression. 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 means of standardized ophthalmologic examination and fundus photography, and low rate of unavailability for follow-up. On the other hand, the relatively small sample size may have limited our ability to detect some statistically significant relationships, eg, an effect of smoking on AMD progression.

Some of the risk factor data were self-reported (cardiovascular disease history) or self-measured (waist and hip measurements). These are accepted and widely used means of obtaining risk factor data. 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, because they were reported before 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). Although some unmeasured and therefore uncontrolled factors might still be confounding this relationship, they would have to be highly associated with the significant prognostic factors reported herein and to be a strong risk factor for AMD progression to explain these results.

Our study population consists of patients with AMD who were treated in a retina specialty practice in an outpatient clinical setting. These patients likely represent the typical patient with AMD. In particular, this study popu-
AMD among individuals outside the normal BMI range. Study suggest an increased risk for onset of early or dry Blue Mountains Eye Study and the Physicians’ based studies with varying results. Results from the tions of patients with AMD. likely to differ in major ways among various popula- ment other studies, eg, intervention studies. Moreover, ing status at baseline and rates of progression. This study range and sex distribution for parameters including smoking status at baseline and rates of progression. This study cohort also offers the opportunity to enhance and comple- ditions or overall adiposity. Waist circumference is receiv- a higher waist-hip ratio describes patterns of abdominal adiposity that may have different metabolic conse- 30, compared with lean individuals in their cross-sectional analysis, and the Beaver Dam Eye Study found a significant relationship between BMI and early AMD for women, but not for men. Also, cross-sectional analyses within the Age-Related Eye Disease Study cohort showed that higher BMI was associated with prevalence of neovascular AMD. In contrast to all of these studies, we evaluated the progression of AMD to the advanced stage among individu- als with early or intermediate disease.

Waist circumference and waist-hip ratio have also been considered informative measures of obesity compared with BMI, because a larger waist circumference or a higher waist-hip ratio describes patterns of abdominal adiposity that may have different metabolic consequences compared with other patterns of fat distribution or overall adiposity. Waist circumference is receiving increased attention as an important risk indicator for overall mortality and coronary heart disease. Waist circumference is a simple and convenient measure for as-
higher waist circumference was associated with an increased risk for obesity-related conditions, including hypertension and type 2 diabetes, within each category of BMI.39 Another study using the same database determined that waist circumference is more closely linked to cardiovascular disease risk factors than is BMI.40 We found no other studies in the literature that evaluated waist circumference and eye diseases.

Waist-hip ratio is also associated with cardiovascular diseases and increased rates of mortality. In the Health Professionals’ Follow-up Study, waist circumference, hip circumference, and waist-hip ratio were strong predictors of cardiovascular and coronary disease among older men compared with BMI.38 This study suggests that abdominal adiposity is a good measure of body fat in the elderly, since fat mass tends to accumulate around the abdomen with age. We found 1 study in the literature that reported the association between waist-hip ratio and prevalence of AMD. In that cross-sectional study, stronger associations were found using waist-hip ratio compared with BMI for the presence of early AMD among women in the Beaver Dam Eye Study,38 although no relationship was found for either measure among men.

In our prospective study, we found a statistically significant trend for an increased risk for progression to advanced AMD with larger waist circumference and a higher waist-hip ratio. Our results suggest that these measures of abdominal adiposity may also be an important determinant of AMD progression.

It has been hypothesized that cardiovascular diseases and AMD share a common risk profile.41 The inverse relationship between coronary heart disease and physical activity has been clearly established in epidemiological research. Recent results of the Health Professionals’ Follow-up Study have shown that physical activity reduces the risk for coronary heart disease up to 42% in men.42 Among women, similar benefits were seen for coronary heart disease43,44 and stroke.45 In addition, physical activity has been shown to improve the lipoprotein profile among overweight men and women, which may reduce the risk for cardiovascular disease.46

Table 2. Relative Risks for Progression of AMD: Age-Adjusted and Multivariate Models Including Measures of Obesity and Other Risk Factors*

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<th>Multivariate RR (95% CI)</th>
<th>P Value</th>
<th>Age-Adjusted RR</th>
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Abbreviations: AMD, age-related macular degeneration; BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters); BP, blood pressure; CI, confidence interval; RR, relative risk.
* Risks are 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 calories (continuous), log carotenoid intake (continuous), initial AMD grade (categorical), and education (at least vs less than high school). Tertiles for waist circumference and waist-hip ratio are described in Table 1.
† Relates to vigorous activity 3 times per week.
is very limited research, however, on the beneficial effects of physical activity on AMD. In the Eye Disease Case-Control Study, vigorous activity was associated with a lower risk for exudative AMD in univariate analyses comparing the above-average groups with the below-average groups (odds ratio [OR], 0.5; 95% CI, 0.4–0.8; P = .002); however, this finding did not remain significant in multivariate regressions. Our results suggest a possible beneficial effect of physical activity on the progression to advanced AMD.

Smoking has been consistently shown to be a risk factor for the onset of AMD. A prospective evaluation of this relationship based on the Nurses’ Health Study showed nearly a 2.5-fold increase in the risk for AMD among current smokers and a 2-fold increase for past smokers compared with those who never smoked. Former smokers did not show a decreased risk for AMD up to 15 years after cessation. About 29% of AMD cases in that study population were attributable to smoking. Similar results were reported for men. Other cross-sectional and case-control studies confirmed the importance of cigarette smoking. The POLA study reported greater than a 3-fold increased risk for late AMD in current and former smokers, and the Blue Mountains Eye Study reported a 4-fold increased risk for late AMD among current smokers.

To the best of our knowledge, our study is unique in that it evaluated a potential adverse effect of cigarette smoking on the progression to advanced AMD, but the power is limited, particularly among current smokers. However, the estimates of effect suggest an increased risk for progression among smokers and underscore the importance of avoiding this behavior.

Systemic hypertension has been reported to be associated with AMD in some studies, but not all. In our study, systolic blood pressure was not associated with AMD progression, after controlling for other factors. We also evaluated diastolic blood pressure and systemic hypertension as determined collectively by direct measurement, reported diagnosis, use of antihypertensive medications, and pulse pressure, and the results were not substantially different. The lack of an association with cardiovascular disease in this prospective study, despite the association between AMD and risk factors for cardiovascular diseases, is similar to reports from other study designs.

In this longitudinal study, the collective series of risk factors for progression of AMD to its visually debilitating stages point to a cardiovascular risk profile. Measures of obesity, including BMI, waist circumference, and waist-hip ratio, are well-known risk factors for vascular diseases and their complications, and increased levels of physical activity are known to decrease risk. The effect of these variables may be associated with more than 1 mechanism. Obesity increases the risk for hypertension and lipid abnormalities, and these factors may contribute to vascular compromise. On the other hand, increased physical activity has widespread beneficial effects on the lipoprotein profile and decreases blood coagulability. Obesity is associated with decreased carotenoid intake in this study and may also be associated with decreased intake of other important nutrients that may protect against AMD. Cigarette smoking also reduces serum levels of antioxidants, which is especially noteworthy given the beneficial effects of vitamin and mineral supplementation on the progression of AMD, as demonstrated by the Age-Related Eye Disease Study. An inflammatory mechanism may also be involved: elevated levels of C-reactive protein have been associated with obesity and this factor is known to be related to cardiovascular disease.

Although additional studies are needed to confirm that modifying the risk factors identified in this study would decrease the rate of progression, these results have potential public health significance. Approximately 1.7 million people have decreased visual acuity due to AMD, and advanced AMD with visual loss develops in 200,000 people every year. These numbers are expanding as the percentage of elderly people in the population continues to grow. Furthermore, obesity is becoming an epidemic among adolescents and adults in the United States and in developing countries. In our study population, 38% of men and 57% of women had abdominal obesity (>102 cm in men and >88 cm in women) and 22% of men and 26% of women had overall obesity (BMI ≥30). Therefore, a substantial number of people may benefit from these results. A decade ago, we had little advice for patients with AMD, and now we have an extensive body of evidence regarding modifiable factors to disseminate. These preventive measures to reduce the growing burden of irreversible and largely untreatable visual loss among the elderly warrant further investigation and greater emphasis.

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