Risk Factors Associated with Age-Related Macular Degeneration

A Case-control Study in the Age-Related Eye Disease Study: Age-Related Eye Disease Study Report Number 3

Objective: To investigate possible risk factors for age-related macular degeneration (AMD) in participants in the Age-Related Eye Disease Study (AREDS).

Design: Case-control study.

Participants: Of the 4757 persons enrolled in AREDS, 4519 persons aged 60 to 80 years were included in this study. The lesions associated with AMD ranged from absent in both eyes to advanced in one eye.

Main Outcome Measures: Stereoscopic color fundus photographs of the macula were used to place participants into one of five groups, based on the frequency and severity of lesions associated with AMD. Participants with fewer than 15 small drusen served as the control group.

Results: Staged model building techniques were used to compare each of the four case groups with the control group. Increased age was a consistent finding of all four of the case groups compared with the control group, and all the following associations were age adjusted. Persons with either intermediate drusen, extensive small drusen, or the pigment abnormalities associated with AMD (group 2) were more likely to be female, more likely to have a history of arthritis, and less likely to have a history of angina. Persons with one or more large drusen or extensive intermediate drusen (group 3) were more likely to use hydrochlorothiazide diuretics and more likely to have arthritis. Hypertension, hyperopia, presence of lens opacities, and white race were also found more frequently in this group as well as in persons with neovascular AMD (group 5). Only persons in group 5 were more likely to have an increased body mass index, whereas persons with geographic atrophy (group 4) as well as those in groups 3 and 5 were more likely to have completed fewer years in school or to be smokers. Those with geographic atrophy were also more likely to use thyroid hormones and antacids.

Conclusions: Our findings for smoking and hypertension, which have been noted in previous studies, suggest that two important public health recommendations, the avoidance of smoking and the prevention of hypertension, may reduce the risk of developing AMD. Other associations, such as those for hyperopia, lens opacities, less education, female gender, increased body mass index, and white race, which have been noted in other studies, are also seen in the AREDS population. The increased use of thyroid hormones and antacids in persons with geographic atrophy and the increased likelihood of arthritis or hydrochlorothiazide use in persons with one or more large drusen or extensive intermediate drusen have not been previously reported and need additional investigation. Ophthalmology 2000;107:2224–2232 © 2000 by the American Academy of Ophthalmology.
unilateral advanced AMD. Data were collected at entry into this longitudinal study on the following possible risk factors for AMD that had been identified in earlier laboratory and clinical studies: smoking, cardiovascular disease, hypertension, sunlight exposure, and dietary intake of various micronutrients. This report is an exploration of the relationship between baseline macular status and prior or concurrent potential nonnutritional risk factors. The role of baseline nutritional intake will be examined in a subsequent report.

Methods

Study Population

Details of the study design and methods presented elsewhere are briefly summarized here. Eleven retinal specialty clinics enrolled 4757 participants from 1992 through 1998. Participants were 55 to 80 years of age at enrollment and had best-corrected visual acuity of 20/32 or better in at least one eye. Media were sufficiently clear to obtain adequate quality stereoscopic fundus photographs of the macula in all study eyes. At least one eye of each participant was free from eye disease that could complicate assessment of AMD or lens opacity progression (except cataract surgery and unilateral photocoagulation for AMD). Finally, potential participants were excluded for illness or disorders that eye could not have had previous ocular surgery (except cataract surgery and unilateral photocoagulation for AMD). In this paper, we considered geographic atrophy anywhere to be probably present if its extent was at least that of AREDS standard.

The study was designed to recruit persons in four AMD categories determined by the size and extent of drusen in each eye, the presence of manifestations of advanced AMD, and visual acuity, as described in Table 1.

To facilitate reaching recruitment goals in each of the four AMD categories, participants were recruited through sources most accessible to and productive for each clinic. Sources of participants included medical records of patients being seen at AREDS clinics; referring physicians; patient lists from hospitals and HMOs; public advertising (radio, TV, newspapers, flyers); and friends and family of participants and of clinical center staff. On average, the estimated percentage of participants by recruitment source for AMD categories 1 and 2 differed from categories 3 and 4 mainly for medical records (17% vs. 63%), public advertisements (53% vs. 24%), and friends and family of participants (13% vs. 7%).

Persons age 55 through 59 years were recruited only if they were in either category 3 or 4. The present analysis of 4519 persons excludes 110 persons in this age group, because there were no age-matched controls for these cases, and 128 persons with bilateral aphakia for whom refractive error was not available. Before study initiation, the protocol was approved by a Data and Safety Monitoring Committee and by the Institutional Review Board for each clinical center, and before their enrollment, informed consent was obtained from all participants.

Procedures

Detailed questionnaires were administered to obtain demographic information, history of smoking and sunlight exposure, medical history, history of specific prescription drug and nonprescription medication use, and history of vitamin and mineral use. General physical and ophthalmic examinations included height, weight, blood pressure, manifest refraction, best-corrected visual acuity, intraocular pressure, slit-lamp biomicroscopy, and ophthalmoscopy. Stereoscopic fundus photographs of the macula and slit lamp and red reflex lens photographs were taken and graded at a central photograph reading center, where the various lesions associated with AMD and the degree of lens opacities by type were assessed through standardized grading procedures (AREDS Manual of Operations) adapted from Klein R et al and Klein BEK et al. Reproducibility of the AMD grading procedure has been reported by Davis et al (Invest Ophthalmol Vis Sci 39:S601, 1998).

Case-control Definitions

Based on reading center grading, participants in the study were divided into five groups according to the size and extent of drusen in each eye, presence of geographic atrophy, and neovascular changes of AMD. The five groups, numbered serially and based on increasing severity of drusen or type of AMD, were defined as follows.

Group 1 (Control). Each eye had no drusen or nonextensive small drusen (AMD category 1; n = 1115).

Group 2 (Intermediate Drusen). At least one eye had one or more intermediate drusen, extensive small drusen, or pigment abnormalities associated with AMD (AMD category 2; n = 1060).

Group 3 (Large Drusen). At least one eye had one or more large drusen or extensive intermediate drusen (most of AMD category 3; n = 1568).

Group 4 (Geographic Atrophy). At least one eye had geographic atrophy (a portion of AMD categories 3 and 4; n = 118). In this paper, we considered geographic atrophy anywhere to be definitely present if its extent was at least that of AREDS standard circle 1-1 (with diameter one eighth that of the average disc).

Group 5 (Neovascular). Evidence suggesting choroidal neovascularization or RPE detachment in one eye (nondrusenoid RPE detachment, serous sensory or hemorrhagic retinal detachment, subretinal hemorrhage, subretinal pigment epithelial hemorrhage, subretinal fibrosis, or evidence of confluent photocoagulation for neovascular AMD; most of category 4; n = 658). The term neovascular was used as a summary term for this group of participants because most persons in this group have direct evidence of choroidal neovascularization based on the assessment of fundus photographs. Despite the fact that some persons in this group probably do not have choroidal neovascularization, such as some of those with RPE detachments, we believe this is a better summary term than exudative AMD. Fluorescein angiograms were not taken as part of the AREDS protocol, so it is impossible to separate those without documented neovascularization from the rest, and we have not tried to subdivide this group.

Risk Factor Definitions

We evaluated risk factors for each macular disease case group by comparing it with the control group. The baseline risk factor variables can be divided into four classes: demographic, medical history, use of medication, and ocular. For analysis, continuous variables were categorized into three groups by the first and last quintiles, except for age in years, which had categories 60–65, 66–70, and 71–80.

Demographic. The demographic variables included age, race, gender, education, history of smoking, body mass index (BMI), weight change since age 20, and sunlight exposure (adult lifetime average annual ocular ultraviolet B exposure, adapted from McCarty et al). Medical History. Medical history variables included hypertension (systolic ≥ 160 mmHg, diastolic ≥ 90 mmHg, or current use of antihypertension medication), angina, diabetes (under treatment...
for diabetes), skin cancer (melanoma, basal or squamous cell), and arthritis.

**Use of Medication.** Use of medication was defined as current use with 5 or more lifetime years of regular use by at least 5% of participants and included diuretics (other than hydrochlorothiazide), aspirin, antacids, hydrochlorothiazide, nonsteroidal anti-inflammatory drugs, thyroid hormones, β-blockers, and estrogen and progesterone use (women).

**Ocular.** Ocular variables included iris color, refractive error, and lens opacity.

Iris color was graded at the Reading Center by comparing photographs of each eye with standards on a scale from 1 (light or blue) to 4 (dark or brown); a person was considered light if both eyes were code 1, dark if both eyes were code 4, and mixed otherwise.

A person was considered myopic if both eyes were myopic by −1.0 diopters (D) spherical equivalent refractive error or more, hyperopic if both eyes had +1.0 D spherical equivalent refractive error or more, or other, which included emmetropes and mixed cases. Persons with bilateral aphakia were excluded because refractive error was not available.

A person had lens opacity or cataract if at least one eye had an opacity of any type (nuclear opacity grade 4 or more, cortical opacity 6% or more of the central 5 mm circle, or posterior subcapsular opacity 1% or more of the central 5 mm circle) or had a history of cataract surgery.

**Statistical Modeling and Analyses**

Risk factors were identified in a three-stage process using polytomous logistic regression (SAS procedure CATMOD). Age and gender were included in all models. In this procedure, each of the four case groups of AMD was compared simultaneously with the referent control group. In stage 1, each risk factor was included separately in a univariate analysis. Variables identified as significant ($P < 0.15$) were retained as risk factors for further analysis. Three-level categoric variables were retained if the high-versus-low (top 20% vs. bottom 20%) comparison was significant.

In stage 2, all variables retained from stage 1 from any of the regressions were entered as a group into a single multivariate polychotomous model. In stage 3, model simplification consistent with chi-square tests of change in deviance was performed. This simplification consisted of identifying nominally nonsignificant ($P > 0.1$) coefficients from stage 2 and replacing them by structural zeros. Variables not significant for any case group were excluded from the model. Model simplification continued until the reduced model yielded a significant ($P \leq 0.05$) worsening of fit according to the likelihood ratio criterion. The significance of hormone use among women was evaluated by including it in the final model restricted to women.

Prevalence odds ratios, which describe the association between presence of disease and the risk factors, were computed for each case group relative to the control group.

**Results**

Table 2 shows the distribution of the following demographic characteristics: age, race, gender and education, as well as the participants’ smoking and hypertension status by AMD group. Age- and gender-adjusted prevalence odds ratios for each risk factor by AMD group from the stage 1 univariate analyses are given in Table 3. Odds ratios significant at $P < 0.15$ are boldface.

The fit of the stage 3 reduced polychotomous multivariate logistic regression model was acceptable, that is, not significantly worsened as assessed by change in deviance, $P = 0.089$. Estimated odds ratios from the stage 3 final model are given in Table 4, with significant associations ($P \leq 0.05$) indicated. When added to the final model, hormone use among women was not significant.

### Significant Associations: Each Case Group versus the Control Group

**Intermediate Drusen.** The presence of one or more intermediate drusen, extensive small drusen, or pigment abnormalities associated with AMD was associated with increasing age (≥ age 70 vs. ≤ age 65; odds ratio [OR] = 1.47), arthritis (OR = 1.26), and...
female gender (OR = 1.20). Persons with angina are at lower risk of these mild macular changes (OR = 0.68).

Large Drusen. The presence of one or more large drusen or extensive intermediate drusen was associated with increasing age (OR = 2.80), white race (OR = 1.88), use of hydrochlorothiazide (OR = 1.51), hyperopia (OR = 1.28), smoking (OR = 1.25), presence of lens opacities (OR = 1.24), arthritis (OR = 1.20), and hypertension (OR = 1.19). Persons with higher education were at lower risk of having one or more large drusen or extensive intermediate drusen (OR = 0.73).

Geographic Atrophy. The presence of geographic atrophy was associated with increasing age (OR = 3.12), use of antacids (OR = 2.13), use of thyroid hormones (OR = 1.99), and smoking (OR = 1.61). Persons with higher education were at lower risk of geographic atrophy (OR = 0.45).

Neovascular. The presence of neovascular AMD was associated with white race (OR = 4.22), increasing age (OR = 4.11), hyperopia (OR = 2.31), smoking (OR = 1.91), hypertension (OR = 1.45), increased BMI (OR = 1.43), and presence of lens opacity (OR = 1.32). Persons with higher education were at lower risk of neovascular AMD (OR = 0.44).

Discussion

We have attempted to identify possible risk factors for the presence of moderate- to large-sized drusen and pigment abnormalities, both of which are prominent features of patients with AMD, and two advanced forms of AMD, geographic atrophy and neovascular AMD. Drusen, in particular soft, indistinct drusen, and pigment abnormalities are considered to be high risk characteristics for the development of geographic atrophy or neovascular AMD and are often viewed as manifestations of “early” AMD. If the presence of intermediate- and large-size drusen and pigment abnormalities do represent early manifestations of AMD, one may expect many similarities in risk factor profiles for the four case groups studied here. Longitudinally collected data from AREDS will eventually provide information on how the presence, size, and extent of drusen and pigment abnormalities relate to the development of late-stage AMD and which risk factors influence the development of such macular changes.

Our finding that smoking, a modifiable exposure, was associated with the three more severe AMD groups is consistent with findings from many earlier observational studies. The mechanism of action by which smoking could affect the retina, RPE, or choroid is not known. However, the finding is consistent with the hypothesis that AMD is the result of cumulative oxidative insults to the outer retina. Smoking is known to lower levels of circulating antioxidants. Stryker et al reported that men who smoked one
A pack of cigarettes per day had only 72% of the plasma \( \beta \)-carotene levels of nonsmokers, even after adjusting for dietary differences between smokers and nonsmokers. This finding is consistent with the observation that smoking was associated with a decrease in luteal pigments in the human retina.\(^{32}\) The decreased availability of compounds with antioxidant capabilities could decrease retinal defenses against oxidative damage. The smoking finding is also consistent with an hypothesis of an underlying vascular basis for AMD,\(^ {14} \) because smoking could damage choroidal vessels or choroidal blood flow by promoting atherosclerotic and hypoxic changes in the choroidal vessels or directly causing vasoconstriction.

The AREDS participants with large drusen or neovascular AMD were statistically significantly more likely to have systemic hypertension, defined as elevated blood pressure levels or current treatment with antihypertensive medications. This finding is consistent with an underlying vascular basis for AMD. Some,\(^ {15–17} \) but not all,\(^ {9,33–35} \) earlier studies of AMD have reported similar associations. As emphasized in one study\(^ {16} \) that found an increasingly strong relationship with longer duration of hypertension, it may be important to take duration of hypertension into account when examining the relationship.

In AREDS, hyperopic refractive error was associated with both more extensive drusen and neovascular AMD. In the Eye Disease Case-Control Study,\(^ {7} \) hyperopia that was similarly defined and adjusted for in multivariate analysis was also associated with an increased risk of neovascular macular degeneration (OR \( = 1.5 \)). This association has been found in some,\(^ {22,36} \) but not all, population-based cohorts.\(^ {37,38} \) The underlying reason for an association of hyperopia with AMD, if it exists, is not known.

In the AREDS population, higher BMI, a measure of obesity, was associated with neovascular AMD. This is consistent with findings from the Oulu study where the investigators speculated that if not a chance finding, it may be the result of excessive caloric intake increasing the risk of ARM because of an increased risk of oxidative damage.\(^ {35} \) Greater BMI was associated with the prevalence of early ARM but not neovascular AMD in the Beaver Dam Study.\(^ {34} \) However, in this study there was no association

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**Table 3. Age- and Gender-adjusted Associations (Odds Ratios) between Prevalence of Age-related Macular Degeneration and Baseline Risk Factors**

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Exposure</th>
<th>A vs. B</th>
<th>Group 2 (Intermediate Drusen, ( n = 1060 ))</th>
<th>Group 3 (Large Drusen, ( n = 1568 ))</th>
<th>Group 4 (Geographic Atrophy, ( n = 118 ))</th>
<th>Group 5 (Neovascular, ( n = 658 ))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>71–80</td>
<td>60–65</td>
<td>1.51</td>
<td>3.30</td>
<td>3.33</td>
<td>5.12</td>
</tr>
<tr>
<td>Race</td>
<td>White</td>
<td>Other</td>
<td>1.11</td>
<td>1.75</td>
<td>—</td>
<td>3.93</td>
</tr>
<tr>
<td>Gender</td>
<td>Female</td>
<td>Male</td>
<td>1.22</td>
<td>1.00</td>
<td>0.85</td>
<td>1.04</td>
</tr>
<tr>
<td>Education</td>
<td>College grad</td>
<td>H.S. or less</td>
<td>0.84</td>
<td>0.63</td>
<td>0.34</td>
<td>0.35</td>
</tr>
<tr>
<td>Ever smoked</td>
<td>Yes</td>
<td>No</td>
<td>1.04</td>
<td>1.31</td>
<td>1.77</td>
<td>1.98</td>
</tr>
<tr>
<td>Body mass index*</td>
<td>Top 20%</td>
<td>Bottom 20%</td>
<td>0.94</td>
<td>1.23</td>
<td>1.38</td>
<td>1.68</td>
</tr>
<tr>
<td>Weight change†</td>
<td>Top 20%</td>
<td>Bottom 20%</td>
<td>0.93</td>
<td>1.03</td>
<td>1.27</td>
<td>1.40</td>
</tr>
<tr>
<td>Sunlight exposure‡</td>
<td>Top 20%</td>
<td>Bottom 20%</td>
<td>1.28</td>
<td>1.32</td>
<td>1.92</td>
<td>1.26</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Present</td>
<td>Absent</td>
<td>1.03</td>
<td>1.24</td>
<td>1.09</td>
<td>1.52</td>
</tr>
<tr>
<td>Angina</td>
<td>Present</td>
<td>Absent</td>
<td>0.80</td>
<td>1.05</td>
<td>1.63</td>
<td>1.30</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Present</td>
<td>Absent</td>
<td>0.93</td>
<td>1.00</td>
<td>0.82</td>
<td>1.04</td>
</tr>
<tr>
<td>Skin cancer</td>
<td>Present</td>
<td>Absent</td>
<td>0.99</td>
<td>1.04</td>
<td>0.89</td>
<td>0.94</td>
</tr>
<tr>
<td>Arthritis</td>
<td>Present</td>
<td>Absent</td>
<td>1.30</td>
<td>1.33</td>
<td>1.66</td>
<td>1.16</td>
</tr>
<tr>
<td>Diuretics use</td>
<td>Present</td>
<td>Absent</td>
<td>0.98</td>
<td>1.12</td>
<td>1.22</td>
<td>1.30</td>
</tr>
<tr>
<td>Aspirin use</td>
<td>Present</td>
<td>Absent</td>
<td>1.25</td>
<td>1.28</td>
<td>0.86</td>
<td>1.15</td>
</tr>
<tr>
<td>Antacids use</td>
<td>Present</td>
<td>Absent</td>
<td>1.06</td>
<td>1.40</td>
<td>2.75</td>
<td>1.41</td>
</tr>
<tr>
<td>Hydrochlorothiazide use</td>
<td>Present</td>
<td>Absent</td>
<td>1.35</td>
<td>1.58</td>
<td>1.87</td>
<td>1.50</td>
</tr>
<tr>
<td>Anti-inflammatory drugs</td>
<td>Present</td>
<td>Absent</td>
<td>1.26</td>
<td>1.28</td>
<td>0.96</td>
<td>1.32</td>
</tr>
<tr>
<td>Thyroid hormones</td>
<td>Present</td>
<td>Absent</td>
<td>1.01</td>
<td>1.02</td>
<td>2.16</td>
<td>1.18</td>
</tr>
<tr>
<td>β-blocker use</td>
<td>Present</td>
<td>Absent</td>
<td>0.93</td>
<td>1.11</td>
<td>1.08</td>
<td>1.12</td>
</tr>
<tr>
<td>Hormone use (women)</td>
<td>Present</td>
<td>Absent</td>
<td>1.18</td>
<td>1.11</td>
<td>0.67</td>
<td>0.70</td>
</tr>
<tr>
<td>Lens opacity</td>
<td>Present</td>
<td>Absent</td>
<td>0.94</td>
<td>1.22</td>
<td>1.39</td>
<td>1.31</td>
</tr>
<tr>
<td>Iris color</td>
<td>Dark</td>
<td>Light</td>
<td>0.78</td>
<td>0.73</td>
<td>0.80</td>
<td>0.77</td>
</tr>
<tr>
<td>Refractive error</td>
<td>Hyperopic</td>
<td>Myopic</td>
<td>1.02</td>
<td>1.35</td>
<td>1.79</td>
<td>2.41</td>
</tr>
</tbody>
</table>

Associations are prevalence odds ratios comparing each age-related macular degeneration disease category with control group, age- and gender-adjusted from stage 1 polychotomous logistic regression.

Odds ratio \( >1 \) implies persons with exposure A show increased risk of disease compared with exposure B. Boldface odds ratios are nominally significant (\( P < 0.15 \)).

\( ^* \)Bottom, \( ±23.6; \) top, \( ±31. \)

\( ^† \)Bottom, \( ±10; \) top, \( ±53 \) pounds since age 20.

\( ^‡ \)Bottom, \( ±0.22; \) top, \( ±1.65 \) adult lifetime annual ocular ultraviolet B exposure (for reference, \( 1.0 \) = ocular exposure from model is equivalent to 1 hour/day outdoors in temperate months in typical United States region, not over water, and not wearing hat, glasses or sunglasses).
AREDS Research Group - Risk Factors for AMD

Table 4. Polychotomous Multivariable Associations (Odds Ratios) between Prevalence of Age-related Macular Degeneration and Baseline Risk Factors

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Group 2 (Intermediate Drusen)</th>
<th>Group 3 (Large Drusen)</th>
<th>Group 4 (Geographic Atrophy)</th>
<th>Group 5 (Neovascular)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variables with 3 levels: top vs. bottom</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>1.47 (1.18–1.84)†</td>
<td>2.80 (2.27–3.47)†</td>
<td>3.12 (1.91–5.07)†</td>
<td>4.11 (3.09–5.45)†</td>
</tr>
<tr>
<td>Body mass index</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Education</td>
<td>—</td>
<td>0.73 (0.62–0.86)†</td>
<td>0.45 (0.28–0.72)†</td>
<td>0.44 (0.35–0.56)†</td>
</tr>
<tr>
<td>Refractive error</td>
<td>—</td>
<td>1.28 (1.04–1.57)*</td>
<td>—</td>
<td>2.31 (1.67–3.20)†</td>
</tr>
<tr>
<td>Binary variables: present vs. absent</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender (female = present)</td>
<td>1.20 (1.01–1.43)*</td>
<td>0.97 (0.82–1.15)</td>
<td>0.74 (0.48–1.12)</td>
<td>1.05 (0.84–1.30)</td>
</tr>
<tr>
<td>Race (white = present)</td>
<td>—</td>
<td>1.88 (1.34–2.64)†</td>
<td>—</td>
<td>4.22 (2.23–7.99)†</td>
</tr>
<tr>
<td>Ever smoked</td>
<td>—</td>
<td>1.25 (1.09–1.44)†</td>
<td>1.61 (1.06–2.42)*</td>
<td>1.91 (1.57–2.33)†</td>
</tr>
<tr>
<td>Hypertension</td>
<td>—</td>
<td>1.19 (1.03–1.38)*</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Angina</td>
<td>0.68 (0.52–0.90)†</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Arthritis</td>
<td>1.26 (1.07–1.47)†</td>
<td>1.20 (1.04–1.39)*</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Hydrochlorothiazide</td>
<td>1.26 (0.93–1.71)</td>
<td>1.51 (1.06–2.14)*</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Diuretics</td>
<td>—</td>
<td>0.81 (0.92–1.67)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Antacids</td>
<td>—</td>
<td>—</td>
<td>2.13 (1.12–4.06)*</td>
<td>—</td>
</tr>
<tr>
<td>Thyroid hormones</td>
<td>—</td>
<td>—</td>
<td>1.99 (1.08–3.65)*</td>
<td>1.32 (1.08–1.60)†</td>
</tr>
<tr>
<td>Lens opacity</td>
<td>—</td>
<td>1.24 (1.07–1.43)†</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

Odds ratios (95% confidence intervals) from stage 3 model, comparing each level of age-related macular degeneration with controls. Coefficients are estimated only for those age-related macular degeneration level-variable combinations with significant coefficients in stage 2; nonsignificant coefficients are modeled by structural zeros (indicated by —).

†P < 0.05.
‡P < 0.01.
§P < 0.001.
*P < 0.0001.

Between either BMI or being overweight at baseline with the 5-year incidence of early ARM or neovascular AMD.36 Most other studies have either not looked for or have not found a cross-sectional association of BMI and AMD.

The AREDS finding of an increased frequency of choroidal neovascularization in white persons compared with nonwhite persons is consistent with findings from other clinical and epidemiologic studies.39–42 Also, the finding in AREDS of a higher frequency of one or more large drusen (≥125 μm) or extensive intermediate drusen in white persons than in nonwhite persons was previously noted in the Baltimore Eye Study where, after adjusting for age, large drusen (≥125 μm) in persons more than 70 years of age were more common in white persons (15.2%) than in nonwhite persons (9.0%).40 Several studies, including AREDS, the Baltimore Eye Study, and the National Health and Nutrition Survey III,39 have found little difference between white persons and nonwhite persons in the frequency of smaller-size drusen. It is unclear why smaller drusen may be equally prevalent in white persons and nonwhite persons, and large drusen, geographic atrophy, and choroidal neovascularization are more common in white persons. There could be an ascertainment bias favoring the identification of smaller drusen in nonwhite persons if smaller drusen are easier to identify against a dark background. This bias may not be present for large drusen because they may be easier to identify regardless of the background pigmentation. It may also be that small drusen are independently associated with age, whereas large drusen and focal hyperpigmentation are the risk factors for the development of geographic atrophy and choroidal neovascularization.43,44 Perhaps increased melanin in RPE cells, acting as a free radical scavenger or simply as a filter for ultraviolet radiation, protects the RPE cells and Bruch’s membrane, reducing the risk of developing large drusen and pigmentary changes and therefore reducing the risk of geographic atrophy, choroidal neovascularization, or both.

Statistically significant associations were found between any lens opacity and the presence of large drusen or the presence of neovascular disease. However, this study represents a limited spectrum of lens opacities because persons with aphakia were excluded from these analyses and persons with moderate media opacities were excluded from the study if the media were not clear enough for AMD assessment. An association between lens opacity and AMD has been inconsistently reported by others. Although a strong cross-sectional association was found between early age-related maculopathy (ARM) and nuclear opacity in the Beaver Dam Eye Study (OR, 1.96; 95% confidence interval, 1.28–3.01), nuclear opacity was not associated with the presence of late ARM at baseline or the 5-year incidence of early or late ARM or progression of ARM in that study.45 In Chesapeake Bay watermen, after controlling for age and other factors, there were significantly higher odds of AMD in the presence of nuclear opacity (OR, 2.50; 95% confidence interval, 1.31–4.80) but not of cortical opacity.46 In the National Health and Nutrition Survey I, there was an increased frequency of AMD in the presence of nuclear opacity.47
cortical opacity.\textsuperscript{47} However, no associations were found between cataract type and ARM in the Blue Mountains Eye Study,\textsuperscript{48} and in the Framingham Eye Study\textsuperscript{49} there was a decreased frequency of age-related macular changes in the presence of nuclear sclerosis and increased frequency in the presence of cortical lens changes.

Education was inversely related to the presence of one or more large drusen or extensive intermediate drusen, geographic atrophy, and choroidal neovascularization in AREDS. This is consistent with the finding in the Eye Disease Case-Control Study where, after adjusting for other risk factors, those who completed 12 years of school or more were 30\% less likely to have neovascular age-related macular degeneration compared with those who completed less than 12 years of school (OR, 0.7; 95\% confidence interval, 0.5–1.1). A similar inverse relationship of education was found in the National Health and Nutrition Examination Survey I. However, no relationship was found in the case-control study of Hyman et al.,\textsuperscript{9} the Framingham Eye Study,\textsuperscript{15} the Beaver Dam Eye Study,\textsuperscript{2} and National Health and Nutrition Examination Survey III,\textsuperscript{39} all studies with few cases of neovascular AMD. The reasons for the differences among studies are not known. It is possible that selection bias in AREDS resulting from the higher participation of more educated persons in the control group and intermediate drusen group contributed to this finding. It is also possible that participation bias and low frequency of advanced disease prevented recognition of this relationship in other studies.

Chance, bias, and unadjusted confounding must be considered when interpreting our findings. We have studied a large number of possible risk factors and conducted multiple tests of significance. Therefore, some of our “significant” findings may be the result of chance alone. This possibility is of particular concern for associations that are seen in only one case group, that are relatively modest in strength, or that have not been reported previously, such as those for arthritis and angina and for antacid, thyroid hormone, or hydrochlorothiazide usage. Chance may be a less likely explanation for the findings on education, refractive error, gender, BMI, and smoking because they had been suggested as possible risk factors by earlier studies, although the possibility of consistent bias across studies cannot be ruled out. In any case, education itself is unlikely to be a direct risk factor, but rather a surrogate for other factors.

Conversely, some of our “nonsignificant” findings may be true associations that were missed because of low power. For example, association with sunlight exposure is in the direction of being a risk factor but is not statistically significant, especially when included in models with other important covariates. The AREDS assessment of sun exposure by use of a questionnaire dependent on participant recall is imprecise, and we can not rule out a true association.

Selection bias is a special concern in clinic-based, case-control studies, and ours is no exception. The control group (group 1) and persons with intermediate size drusen or extensive small drusen (group 2) were substantially more likely to have been volunteers from nonmedical sources. It has been shown that volunteers for prevention studies have more formal education, are more health conscious, and are more often employed in professional and skilled positions,\textsuperscript{50,51} and that smoking is inversely associated with educational achievement.\textsuperscript{52} Indeed, persons with no drusen to intermediate drusen at time of enrollment had greater educational achievement and smoked less than persons with large drusen, geographic atrophy, or choroidal neovascularization. However, the fact that the overall risk factor profile for participants with intermediate drusen, who were drawn from similar sources as the control group, is more like that of the more advanced AMD groups (Table 2) lessens concern about selection bias as an explanation for the AMD findings.

We attempted to minimize the possibility of unadjusted confounding by including in the study nearly all variables that had been previously suggested as possible risk factors and by using multivariate analytic techniques. However, confounding by factors not included in these analyses may exist. For example, it is possible that nutritional factors may modify the association found between AMD and factors such as smoking or education.

In summary, we have noted associations between AMD and multiple risk factors, several of which are modifiable factors. Avoidance of smoking and control of hypertension have benefits beyond potentially reducing the risk of AMD. Perhaps for some patients, prevention of vision impairment can be used as a motivating factor to help them modify these risk factors. Incident cases of geographic atrophy and choroidal neovascularization are developing throughout the AREDS follow-up period. Analyses using these incident cases will provide additional information to investigate which risk factors are associated with the development of AMD.

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APPENDIX: Age-Related Eye Disease Study Research Group

Writing Team
Ravinder Anand, PhD
Susan B. Bressler, MD
Matthew D. Davis, MD
Frederick L. Ferris III, MD
Ronald Klein, MD
Anne S. Lindblad, PhD
Roy C. Milton, PhD
Robert D. Sperduto, MD
and the Age-Related Eye Disease Study Research Group

Affiliations:
1 The Age-Related Eye Disease Study Coordinating Center, The EMMES Corporation, Potomac, Maryland.
2 Wilmer Eye Institute, Johns Hopkins University School of Medicine, Baltimore, Maryland.
3 Fundus Photograph Reading Center, Department of Ophthalmology and Vision Sciences, University of Wisconsin-Madison, Madison, Wisconsin.
4 Division of Biometry and Epidemiology, National Eye Institute, National Institutes of Health, Bethesda, Maryland.
5 The full list of the Age-Related Eye Disease Study Research Group can be found in Control Clin Trials 1999;20:573–600.