Five-Year Incidence, Progression, and Risk Factors for Age-related Macular Degeneration

The Age, Gene/Environment Susceptibility Study

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Objective: To investigate the incidence and progression of age-related macular degeneration (AMD) and associated risk factors.

Design: Population-based, prospective, cohort study.

Participants: We included 2868 participants from the Age Gene/Environment Susceptibility-Reykjavik Study with retinal data at baseline and 5-year follow-up.

Methods: Digital macular photographs were graded for presence of AMD. Participants completed a questionnaire and extensive clinical battery. Biomarkers were assessed. Risk factors for AMD were analyzed using multivariate regression analysis with odds ratios (ORs) and 95% CIs.

Main Outcome Measures: We assessed AMD, defined as early or late.

Results: Among 2196 participants free of AMD at baseline, 14.9% developed incident AMD. In multivariate models, incident AMD was significantly associated with age (OR per year, 1.14; 95% CI, 1.11–1.17), current smoking (OR, 2.07; 95% CI, 1.38–3.11), former smoking (OR, 1.36; 95% CI, 1.04–1.79), plasma high-density lipoprotein (HDL) cholesterol level (OR, 1.62 per mmol/L; 95% CI, 1.19–2.22), and body mass index (BMI; OR, 1.04 per kg/m²; 95% CI, 1.01–1.07). Among 563 participants with early AMD at baseline, 22.7% progressed to late AMD (11.0% pure geographic atrophy [GA] and 11.7% exudative AMD). On multivariate analyses, age was significantly associated with progression to GA (OR 1.14; 95% CI, 1.07–1.21) and exudative AMD (OR, 1.08; 95% CI, 1.01–1.14). Adjusting for age, female sex was associated with exudative AMD (OR, 2.10; 95% CI, 1.10–3.98) and plasma HDL cholesterol with GA (OR, 2.03 per mmol/L; 95% CI, 1.02–4.05).

Conclusions: By age 85, 57.4% of participants had signs of AMD. Age, smoking, plasma HDL cholesterol, BMI, and female sex are associated with AMD. Elevated HDL cholesterol is associated with GA development.

Methods

Study Population

The AGES trial, as described in detail elsewhere, is a population-based study aimed to investigate genetic and environmental factors contributing to health, disability, and disease in older people born between 1907 and 1935.18,19 Between 2002 and 2006 at its baseline visit (AGES-I), 5764 participated in the AGES study, 5272 had readable AMD photographs of ≥1 eye,18,20 and 4910 had data on AMD and covariates. Survivors were invited to participate in a 5-year follow-up study visit (AGES-II) conducted between November 2007 and September 2011. The AGES-II visit protocol entailed a predetermined battery of tests held in 2 separate sessions on 2 different days. Retinal images were captured at the second...
session. Some of the individuals who agreed to participate in AGES-II attended the first session and thereafter decided either not to return for the second session or agreed to participate only in selected tests offered during the second session. Readable AMD photographs at both visits were available from 2868 participants.

**Interviews and Examinations**

The AGES Study methods, examination protocols, and characteristics of the cohort have been described in detail elsewhere. In brief, during baseline and follow-up assessment at the Icelandic Heart Association Research Center, participants completed a standardized protocol, including a detailed interview and an extensive battery of clinical tests and imaging studies. Blood specimens were drawn and a biomarker profile was assessed. The study offered to participants the option of providing free transport to the clinic. The AGES Study was approved by the Icelandic National Bioethics Committee (VSN: 00-063), which acts as the institutional review board for the Icelandic Heart Association, and by the Institutional Review Board for the US National Institute of Aging, National Institutes of Health.

**Assessment of AMD**

The same standardized study protocol was followed at baseline and at follow-up. Fundus photography, after pharmacologic dilation of the pupils, was performed as described in detail previously. In brief, 2 photographic fields were taken of each eye, the first centered on the optic disc and the second centered on the fovea using a 45°, 6.3-megapixel, digital, nonmydriatic camera (Canon, Lake Success, NY).

Using a modification of the Wisconsin Age-Related Maculopathy Grading scheme, retinal images were evaluated twice by trained graders at the University of Wisconsin Ocular Epidemiology Reading Center, who were masked to the health status of the participant. Images were graded using EyeQ Lite software (an image-processing database for storage, retrieval, and manipulation of digital images). As published previously, early AMD was defined by the presence of any soft drusen and pigmentary abnormalities (increased or decreased retinal pigment) or the presence of large soft drusen \( \geq 125 \text{ mm} \) in diameter with a large drusen area \( >500 \text{ mm} \) in diameter or large \( >125 \text{ mm} \) indistinct soft drusen in the absence of signs of late AMD. Late AMD was defined by the presence of any of the following: geographic atrophy (GA) or exudative AMD including subretinal hemorrhage, subretinal fibrous scar, retinal pigment epithelial detachment, or serous detachment of the sensory retina or signs of treatment for neovascular AMD. Persons suspected of having undergone intravitreal treatment for AMD as determined from retinal image grading or indicating it in the questionnaire had their treatment subsequently confirmed or rejected by cross-validating with the database maintained by the only center administering such treatment in Iceland.

**Characterization of Possible Risk Factors**

All factors reported in the literature as possible mediators of AMD risk for which AGES collected data were considered as covariates. Body mass index (BMI) was calculated as measured weight (in kilograms) divided by height (in meters) squared. Smoking status was categorized as never smoker, former smoker, or current
smoker. Cod liver oil use was based on self-report. Hypertension was defined as self-reported history of hypertension, use of antihypertension drugs, or blood pressure ≥140/90 mmHg. Pulse pressure was measured using arterial tonometry, expressed in units of mmHg, and later categorized by quartiles. Diabetes mellitus was defined as self-reported history of diabetes, use of glucose-lowering medications, or fasting blood glucose of ≥7.0 mmol/L. Blood samples were drawn after overnight fasting, and total cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides, and high-sensitivity C-reactive protein (hsCRP) were measured in the Icelandic Heart Association laboratory using standard methods. Unless otherwise noted, all variables investigated as risk factors were assessed at the baseline visit.

### Statistical Methods

Baseline characteristics of participants who completed both retinal examinations and participants who did not return for the follow-up examination were compared using analysis of covariance and logistic regression with adjustment for age and sex. Multivariate logistic regression was then used to examine the association between the characteristics and incident AMD and progression to late AMD. Covariates in regression models included age (in years), female sex (yes/no), current smoker (yes/no), former smoker (yes/no), use of cod liver oil (yes/no), hypertension (yes/no), diabetes mellitus (yes/no), BMI (kg/m²), total cholesterol (mmol/L), HDL cholesterol (mmol/L), and hsCRP (mg/L). All potential risk factors were included as covariates in the multivariate analyses and retained regardless of their significance in order to facilitate comparisons with results from other studies. Odds ratios (OR) and 95% CI were calculated for each variable; *P* < 0.05 were considered significant. Statistical analyses were conducted using SAS version 9.3 (SAS Institute, Cary, NC).

### Results

At baseline, 4910 AGES participants had gradable AMD photographs and information on covariates. Of these, 2868 (58%) completed a follow-up visit, on average 5 years after the baseline examination, and constitute the sample for this analysis. Their mean age at baseline was 74.7 years and 42.4% were male. Figure 1 provides a flow chart depicting reasons for nonparticipation in the follow-up examination.
Table 3. Association between Incident Age-Related Macular Degeneration and Risk Factors in Multivariate Logistic Regression Analyses among AGES Participants Who Completed Both Retinal Examinations (N = 2868)

<table>
<thead>
<tr>
<th>Baseline Characteristic</th>
<th>Incident AMD (N = 328), OR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, per year</td>
<td>1.14 (1.11, 1.17)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Sex, female vs male</td>
<td>1.31 (0.98, 1.74)</td>
<td>0.07</td>
</tr>
<tr>
<td>Current smoker, yes vs no</td>
<td>2.07 (1.38, 3.11)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Former smoker, yes vs no</td>
<td>1.36 (1.04, 1.79)</td>
<td>0.03</td>
</tr>
<tr>
<td>Cod liver oil use, yes vs no</td>
<td>1.00 (0.78, 1.28)</td>
<td>0.98</td>
</tr>
<tr>
<td>Hypertension, yes vs no</td>
<td>0.88 (0.63, 1.23)</td>
<td>0.46</td>
</tr>
<tr>
<td>Pulse pressure, per mmHg</td>
<td>1.00 (0.99, 1.01)</td>
<td>0.92</td>
</tr>
<tr>
<td>Diabetes, yes vs no</td>
<td>1.05 (0.69, 1.59)</td>
<td>0.64</td>
</tr>
<tr>
<td>BMI, per kg/m^2</td>
<td>1.04 (1.01, 1.07)</td>
<td>0.01</td>
</tr>
<tr>
<td>Total cholesterol, per mmol/L</td>
<td>0.95 (0.85, 1.07)</td>
<td>0.37</td>
</tr>
<tr>
<td>HDL cholesterol, per mmol/L</td>
<td>1.62 (1.19, 2.22)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>C-reactive protein</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate (1–3 mg/L) vs low (&lt;1 mg/L)</td>
<td>1.05 (0.77, 1.43)</td>
<td>0.77</td>
</tr>
<tr>
<td>High (&gt;3 mg/L) vs low (&lt;1 mg/L)</td>
<td>1.11 (0.79, 1.57)</td>
<td>0.55</td>
</tr>
</tbody>
</table>

AGES = Age, Gene/Environment Susceptibility-Reykjavik Study; AMD = age-related macular degeneration; BMI = body mass index; CI = confidence interval; HDL = high-density lipoprotein; OR = odds ratio.

Note: Incidence defined as exhibiting no AMD at baseline examination but presenting with early or late AMD at the follow-up examination.

Characteristics at baseline for participants in AGES-II and those who did not return beyond AGES-I are presented in Table 1. Those who did not return for follow-up were significantly more likely to be older, and, adjusting for age, more likely to be smokers, have diabetes, have elevated levels of hsCRP, and less likely to be regular users of cod liver oil. People with AMD signs at baseline were slightly less likely to participate in the follow-up visit, reflecting perhaps their older mean age at baseline.

Among 2196 individuals without signs of AMD at baseline, 14.9% (328 persons) developed incident AMD by AGES-II, of whom 14.2% (312) developed early AMD and 0.7% (16) late AMD (Table 2, available at www.aaojournal.org). Table 2 shows the distribution of baseline values for possible risk characteristics among incident cases. Among persons aged ≥85 years, 38.6% developed incident AMD over the 5-year follow-up period. An increased incidence of AMD was observed in smokers and persons with higher BMI, HDL cholesterol, and hsCRP compared with persons with lower levels. However, after adjusting for age and sex in a multivariate model, only advancing age, smoking, greater BMI, and higher plasma HDL cholesterol levels were significant independent risk factors associated with the development of incident AMD (Table 3). Females were somewhat but not significantly more likely than males to develop incident AMD (OR, 1.31; 95% CI, 0.98–1.74; P = 0.07; Table 3).

Among the 563 AGES-I participants with early AMD, 128 (22.7%) progressed to late AMD at AGES-II (Table 4, available at www.aaojournal.org). Progression of AMD occurred more often in females compared with males and among persons with higher levels of HDL cholesterol or hsCRP compared with persons with lower levels and among persons who did not use cod liver oil (Table 4, available at www.aaojournal.org). We compared mean differences in plasma HDL cholesterol measurements taken at AGES-I and -II visits to discern if we could identify any significant difference in levels over time for incident cases and,

Table 5. Association between Progression of Age-Related Macular Degeneration (AMD) and Risk Factors in Multivariate Logistic Regression Analyses among Age, Gene/Environment Susceptibility-Reykjavik Study Participants Who Completed Both Retinal Examinations (N = 2868)

<table>
<thead>
<tr>
<th>Baseline Characteristic</th>
<th>Pure Geographic Atrophy (N = 62)</th>
<th>Exudative AMD (N = 66)</th>
<th>Late AMD (N = 128)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI) P Value</td>
<td>OR (95% CI) P Value</td>
<td>OR (95% CI) P Value</td>
</tr>
<tr>
<td>Age, per year</td>
<td>1.14 (1.07, 1.21) P &lt;0.01</td>
<td>1.08 (1.01, 1.14) P &lt;0.01</td>
<td>1.12 (1.06, 1.17) P &lt;0.01</td>
</tr>
<tr>
<td>Sex, female vs male</td>
<td>1.42 (0.75, 2.67) P 0.28</td>
<td>2.10 (1.10, 3.98) P 0.02</td>
<td>1.70 (1.05, 2.75) P 0.03</td>
</tr>
<tr>
<td>Current smoker, yes vs no</td>
<td>1.56 (0.62, 3.90) P 0.35</td>
<td>0.97 (0.39, 2.42) P 0.95</td>
<td>1.27 (0.63, 2.54) P 0.50</td>
</tr>
<tr>
<td>Former smoker, yes vs no</td>
<td>1.34 (0.73, 2.49) P 0.35</td>
<td>0.93 (0.52, 1.65) P 0.80</td>
<td>1.13 (0.72, 1.78) P 0.39</td>
</tr>
<tr>
<td>Cod liver oil use, yes vs no</td>
<td>0.64 (0.37, 1.13) P 0.12</td>
<td>0.88 (0.51, 1.52) P 0.63</td>
<td>0.72 (0.47, 1.09) P 0.12</td>
</tr>
<tr>
<td>Hypertension, yes vs no</td>
<td>0.57 (0.27, 1.20) P 0.14</td>
<td>1.03 (0.48, 2.21) P 0.94</td>
<td>0.73 (0.41, 1.28) P 0.27</td>
</tr>
<tr>
<td>Pulse pressure, per mmHg</td>
<td>0.99 (0.98, 1.01) P 0.50</td>
<td>1.00 (0.99, 1.02) P 0.81</td>
<td>1.00 (0.99, 1.01) P 0.83</td>
</tr>
<tr>
<td>Diabetes, yes vs no</td>
<td>1.30 (0.50, 3.39) P 0.59</td>
<td>1.29 (0.56, 2.98) P 0.55</td>
<td>1.26 (0.64, 2.48) P 0.50</td>
</tr>
<tr>
<td>BMI, per kg/m^2</td>
<td>1.03 (0.96, 1.11) P 0.40</td>
<td>0.96 (0.89, 1.04) P 0.30</td>
<td>1.00 (0.94, 1.06) P 0.93</td>
</tr>
<tr>
<td>Total cholesterol, per mmol/L</td>
<td>0.80 (0.60, 1.07) P 0.13</td>
<td>1.03 (0.80, 1.32) P 0.82</td>
<td>0.91 (0.74, 1.11) P 0.35</td>
</tr>
<tr>
<td>HDL cholesterol, per mmol/L</td>
<td>2.03 (1.02, 4.05) P 0.04</td>
<td>0.67 (0.32, 1.40) P 0.28</td>
<td>1.25 (0.73, 2.14) P 0.43</td>
</tr>
<tr>
<td>C-reactive protein</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate (1–3 mg/L) vs low (&lt;1 mg/L)</td>
<td>1.29 (0.61, 2.72) P 0.51</td>
<td>1.06 (0.52, 2.18) P 0.87</td>
<td>1.19 (0.69, 2.06) P 0.54</td>
</tr>
<tr>
<td>High (&gt;3 mg/L) vs low (&lt;1 mg/L)</td>
<td>1.25 (0.54, 2.89) P 0.60</td>
<td>1.31 (0.60, 2.36) P 0.50</td>
<td>1.32 (0.72, 2.43) P 0.37</td>
</tr>
</tbody>
</table>

BMI = body mass index; CI = confidence interval; HDL = high-density lipoprotein; OR = odds ratio.

Note: Progression defined as exhibiting early AMD at baseline examination but exhibiting late AMD at the follow-up examination.
separately, for people whose AMD progressed. No differences in mean plasma HDL cholesterol level over time were found for either group (data not shown). We examined the possible interaction for HDL cholesterol and hsCRP in separate logistic reaction models for prevalence, incidence, and progression of AMD and, after adjustment for covariates, found no significant association (P = 0.68, P = 0.41, and P = 0.77, respectively). We used the same analysis to test for possible interaction between use of cod liver oil and statins and again found no significant interaction (P = 0.71, P = 0.32, and P = 0.79, respectively).

After multivariate logistic regression, only per-year increase in age (OR, 1.12; 95% CI, 1.06–1.17) and female sex (OR, 1.70; 95% CI, 1.05–2.75) were significant predictors of progression from early to late AMD (Table 5). When considering specific late AMD lesions separately, higher levels of HDL cholesterol were significantly associated with GA (OR, 2.03; 95% CI, 1.02–4.05) and female sex was associated with exudative disease (OR, 1.70; 95% CI, 1.10–3.98).

By age 85 years, 275 of the 479 AGES-II participants (57.4%) had signs of AMD (44.5% had early AMD signs and 16% had signs of late AMD).

**Discussion**

In the aged AGES cohort, we estimated the incidence of AMD to be approximately 3% per year. Over 95% of the incident cases were classified as early lesions. The rate of progression of AMD from early to late was approximately 4.5% per year distributed in roughly equal proportions as GA and exudative disease. More than 55% of adults aged ≥85 years exhibit signs of AMD in ≥1 eye. Risk factors for incident AMD included age, BMI, smoking, and high levels of HDL cholesterol whereas risk factors for AMD progression were mainly age, with females more likely than males to progress to exudative disease and those with higher HDL cholesterol levels more likely than those with lower levels to progress to GA.

The results of our study are generally comparable with incidence and progression rates reported for other populations of European ancestry, particularly the Beaver Dam Eye Study, the Rotterdam Eye Study, and the Blue Mountain Eye Study.\(^{11–13}\) The Beaver Dam Eye Study reported, among persons ages ≥75 years, an incidence of 2% per year and progression of 4% per year.\(^{23}\) Advancing age at baseline was the most significant predictor of AMD status; after adjusting for age, AMD incidence did not differ by sex in the Beaver Dam cohort.\(^{24}\) Compared with men, AGES found women to have a somewhat higher risk of incident AMD, as well as a higher risk of AMD progression to exudative AMD; however, we cannot rule out the possibility that selective survival may explain this finding. Similar to previous studies,\(^ {25–27}\) we find smoking to be a risk factor for incident AMD whereby former smokers seem to be at lower risk than current smokers. Notably, smoking was not associated with AMD progression in the AGES sample. Men, particularly those who smoked at baseline and had other adverse health conditions, may have died, consistent with the suggestion of selective survival, which may explain, in part, the inconsistent findings on sex differences reported in the literature.\(^ {28}\)

There is increasing evidence that HDL cholesterol is involved in inflammation and is associated with AMD.\(^ {29–31}\) Higher levels of plasma HDL cholesterol, but not total cholesterol, low-density lipoprotein cholesterol, or triglycerides were significantly associated with the incidence of AMD in AGES, as well as in the Rotterdam study.\(^ {32}\) In the Beaver Dam study, the association with HDL cholesterol was most striking in persons with pure GA,\(^ {23}\) similar to the present study. The age- and sex-adjusted relative risk of HDL cholesterol was positively associated with the incidence of early AMD in the Blue Mountain Eye Study, but was not significant, possibly owing to reduced power. There was also no association of HDL cholesterol with incident late AMD, although the relative risk of increasing HDL cholesterol seemed to be marginally protective.\(^ {33}\) In recent years, it has become evident that HDL cholesterol concentration as such does not necessarily reflect the protective action of HDL cholesterol. Measurement of circulating HDL particle load may be more important, divided into cholesterol-rich HDL particles and particles containing a small amount of HDL.\(^ {34}\) Furthermore, certain polymorphisms in the hepatic and endothelial lipase genes resulting in low or high HDL cholesterol may not correspond with expected differences in risk.\(^ {30,35}\)

The impact of immune dysfunction and complement dysregulation on AMD pathogenesis is well-established, whereby common and rare variants in multiple members of a proinflammatory alternative pathway of the innate immunity are associated with AMD through overactivation.\(^ {36}\) Genetic variants generally confer similar risk for both late AMD forms.\(^ {37}\) We have reported the AMD genetic profile for this cohort elsewhere, with similar results as in other white populations.\(^ {38}\) A recent article from Iceland reported a rare variant in the C3 to be associated with a high risk of AMD. This variant, associated with inflammation, was found to be significantly more common in GA than in exudative AMD.\(^ {39}\) The association of HDL cholesterol and GA may thus be associated with the anti-inflammatory properties of HDL cholesterol.\(^ {29}\)

Although BMI was significantly associated with incident AMD, it was not associated with progression to late AMD in our multivariate models. Obesity may be a marker for reduced physical activity and increase in inflammation, both of which are associated with AMD in the literature.\(^ {25,40}\) In AGES, high hsCRP was associated with AMD incidence and progression in bivariate analysis; however, after covariate adjustment, hsCRP was no longer associated with either incidence or progression of AMD. This is not consistent with results from a recent, pooled meta-analysis of data from several studies, and a direct role for hsCRP in AMD causation remains a topic of research.\(^ {41}\)

Several factors reported by some other studies as risk indicators, including hypertension, diabetes, total cholesterol, triglycerides, and omega-3 fatty acids/cod liver oil, were investigated in our analysis and were found to be unrelated to AMD status after considering age, sex, and smoking. Icelanders commonly consume cod liver daily, in addition to having a high intake of fish and fish products.\(^ {42}\) Studies from populations where consumption of fish and fish products is much less common have reported omega-3 fatty acids to be protective against the development of
early AMD, although findings from a recent clinical trial did not confirm this supposition. It is possible that below a threshold, omega-3 fatty acids may be beneficial with respect to AMD, but in our cohort where the intake of omega-3 fatty acids is high, there was no association with AMD incidence or progression.

Our study offers several advantages in that it contains a sizeable number of elderly individuals, the participants were drawn from a population sample without regard for AMD status, and the cohort is well-studied for a variety of health conditions common in old age. Fundus photographs were taken by radiographers trained to take retinal images according to a standardized protocol and were graded by an independent reading center using well-established methods. Image quality was good. It is also worth noting some limitations. The AGES trial was designed to study diseases common in old age; therefore, we do not have data in mid-life with which to report incidence for younger ages or to identify risk factors, which may prevent the development or progression of AMD later in life. In addition, although free transport to the clinic was offered to all participants, frailty, morbidity, and mortality did impact continued participation beyond the baseline AGES examination in this aged cohort. Therein, our estimates of incidence and progression are likely to be underestimates and our assessment of risk factors (e.g., smoking, hypertension) may be imprecise.

In conclusion, AMD is very common among those aged ≥85 years. In addition to age, we confirm relationships of smoking, increased BMI, and higher HDL cholesterol levels with increased AMD risk. Smoking has been related to numerous adverse health conditions and because former smokers seem to have a lesser risk, smoking cessation even late in life is a reasonable recommendation to reduce risk of AMD. The relationship of higher plasma HDL cholesterol with risk of early AMD and with progression to GA requires further study. Determining whether different processes or biomarkers, tracked over time, influence the development or progression of the 2 advanced forms of AMD may be important for prognosis, prevention, and future treatment.

References


Footnotes and Financial Disclosures


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Abbreviations and Acronyms:

AGES = Age, Gene/Environment Susceptibility-Reykjavik Study;

AMD = age-related macular degeneration;

BMI = body mass index;

GA = geographic atrophy;

HDL = high-density lipoprotein;

hsCRP = high-sensitivity C-reactive protein;

OR = odds ratio.

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