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/m^2; 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. *Ophthalmology 2014;■:1−7 © 2014 by the American Academy of Ophthalmology.*

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Age-related macular degeneration (AMD) is a leading cause of blindness,[1−5] accounting for ≤75% of incident nonpreventable legal blindness.[6] Many population-based studies have reported on the prevalence of AMD in persons 40−85 years old at baseline[7−9] and several have described the incidence of early AMD based on follow-up visits 4−15 years later.[10−16] From these studies, the most consistent risk factors for the development and progression of AMD have been age and cigarette smoking.

The predominantly Caucasian Icelandic population has among the highest life expectancies in Europe at 79.6 years for men, and 83.0 years for women,[17] making it ideal for selecting an old cohort in which to study the prevalence, incidence, and progression of AMD. The longitudinal Age, Gene/Environment Susceptibility-Reykjavik Study (AGES) with its array of biomarkers, clinical profiles, and genetic risk factors collected prospectively from participants who were ages ≥67 at the baseline study visit, builds on our previous report on the cross-sectional prevalence of AMD[18] by describing the incidence and progression of AMD and their respective risk factors.

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

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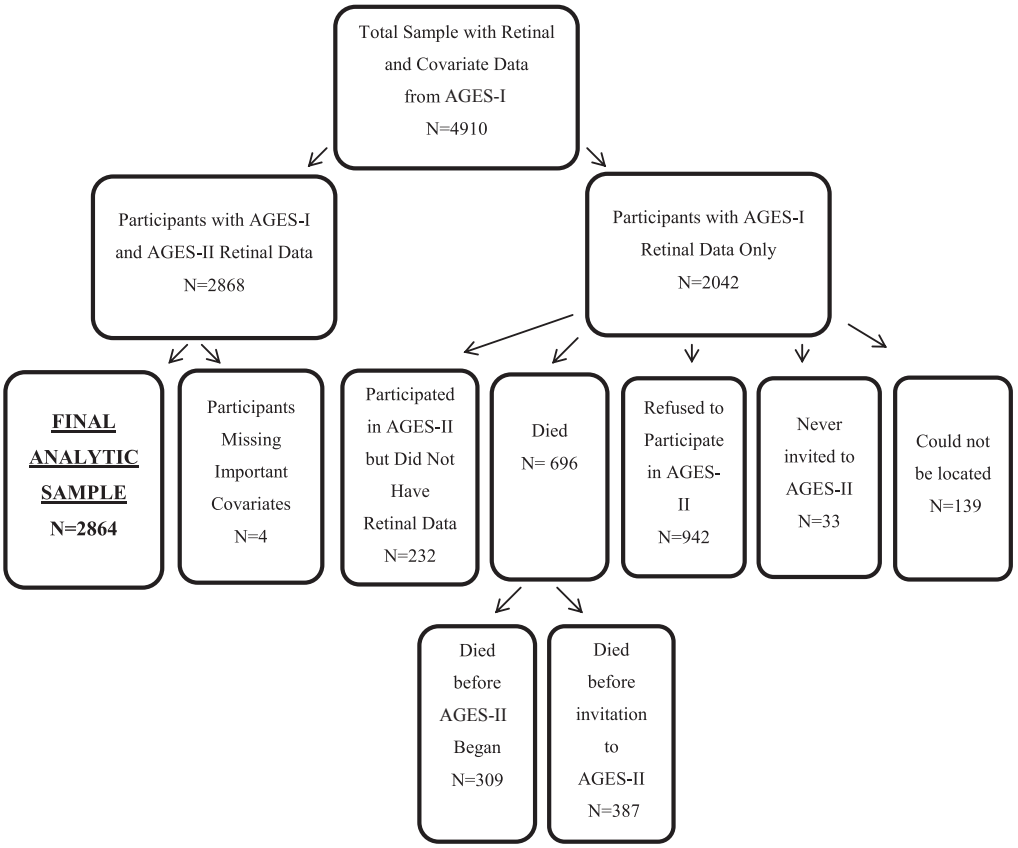

Figure 1. Sample selection, including reasons for nonparticipation in the Age, Gene/Environment Susceptibility-Reykjavik Study (AGES)-II examination.

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.[19,20] 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.[19] Blood specimens were drawn and a biomarker profile was assessed.[18,20,21] 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.[18] 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).[8,22] 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 μm in diameter with a large drusen area $>$500 μm in diameter or large $\geq$125 μm 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.[18] 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