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Incidence of Age-Related Macular Degeneration in a Multi-Ethnic United States Population

The Multi-Ethnic Study of Atherosclerosis

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Purpose: To describe the incidence of age-related macular degeneration (AMD) and associated risk factors in 4 racial/ethnic groups (white, black, Hispanic, and Chinese) residing in the United States.

Design: Prospective cohort study.

Participants: A total of 3811 participants, aged 46 to 86 years, from the Multi-Ethnic Study of Atherosclerosis (MESA) cohort, with retinal data collected twice, on average, 8 years apart.

Methods: Fundus images, taken using a digital camera through dark-adapted pupils using a standard protocol and the same equipment at both study visits, were graded centrally for early and late AMD on the basis of drusen size, type and area, increased retinal pigment, retinal pigment epithelial depigmentation, neovascular lesions, and geographic atrophy using the modified Wisconsin Age-Related Maculopathy Grading System. Demographic, clinical, and laboratory measures were included in multivariable regression models to determine their impact on the variation in AMD incidence among racial/ethnic groups.

Main Outcome Measures: Incident early and late AMD.

Results: The overall 8-year age- and sex-standardized incidence of early and late AMD were 4.1% and 2.3%, respectively, with incidence of early and late AMD highest in whites (5.3% and 4.1%, respectively), intermediate in Chinese (4.5% and 2.2%, respectively) and Hispanics (3.3% and 0.8%, respectively), and lowest in blacks (1.6% and 0.4%, respectively). By adjusting for age and sex, blacks had a 70% lower risk of developing early AMD than whites, and this decreased only slightly to a 67% lower risk after multivariable adjustment. By adjusting for age, sex, and race/ethnicity, hyperopia was associated with early AMD (odds ratio [OR], 1.51; 95% confidence interval [CI], 1.04−2.20), as was astigmatism (OR, 1.47; 95% CI, 1.00−2.16), but not myopia ($P = 0.29$). Age, race/ethnicity, current smoking, hyperopia, and AMD-susceptibility genotypes *Complement Factor H (CFH)* RS1061170 and *Age Related Maculopathy Susceptibility 2 (ARMS2)* RS3793917 were independently associated with incident early AMD in multivariable models for the combined sample. However, the only statistically significant factor consistently associated with incident early AMD across the 4 racial/ethnic groups was increasing age. Risk factors for late AMD were not assessed because of its low incidence, particularly across racial/ethnic groups.

Conclusions: Variation in the incidence of early AMD exists among racial/ethnic groups in the United States and is not explained by the clinical, genetic, and environmental factors included in this study. *Ophthalmology 2016;■:1−12 © 2016 Published by Elsevier on behalf of the American Academy of Ophthalmology.*

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Age-related macular degeneration (AMD) is an important cause of vision loss in older adults.[1] Previous population-based epidemiologic studies, mostly involving a single race or ethnicity, have provided estimates of the prevalence and incidence of AMD in whites, blacks, and other racial/ethnic groups,[2−13] with significant variability reported and confirmed in a meta-analysis.[1] Few studies have directly compared the prevalence or incidence of AMD among racial/ethnic groups. An earlier analysis[2] from the Multi-Ethnic Study of Atherosclerosis (MESA) cohort showed that prevalent early AMD was highest in whites (5.4%) and lowest in blacks (2.4%), while controlling for age and sex. The highest prevalence of any AMD occurred in individuals aged 75 to 84 years, varying from 7.4% in blacks to 15.8% in whites and Chinese Americans. Similar variation in the prevalence of AMD for whites, blacks, and Mexican Americans was reported in a National

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Health and Nutrition Examination Survey study.[3] Yet, most intra-study racial/ethnic comparisons of AMD have been based on cross-sectional prevalence data,[2–7] and few had longitudinal data to report on incident AMD.[11,14–16]

The reasons for racial/ethnic variations are unclear. Differences in the prevalence of AMD among the racial/ethnic groups have been attributed to differences in the frequency and impact of genetic markers (e.g., AMD candidate genes[17,18] such as *Age Related Maculopathy Susceptibility 2* [*ARMS2* RS10490924] and *Complement Factor H* [*CFH* Y402H]) and clinical/environmental factors (e.g., smoking status).[19,20] However, in cross-sectional analyses in the MESA cohort, the distribution of these AMD candidate genes explained only a small proportion of the variability, and age, sex, pupil size, body mass index, smoking history, alcohol use, diabetes, hypertension, and measures of inflammation did not explain the differences in prevalence among the 4 racial/ethnic groups.[2,21] This suggests the need to better understand putative risk factors underlying racial/ethnic differences, which might be more readily discerned in an analysis of AMD incidence.

The MESA cohort is a well-characterized sample of adults from 4 racial/ethnic groups living in the United States,[22] with longitudinal data providing an opportunity to investigate incident AMD and its associated risk factors. The current study examines the incidence of AMD lesions and the associations between relevant risk factors and AMD outcomes overall and within the different racial/ethnic groups in the cohort.

Methods

Subjects and Study Design

The MESA is a prospective cohort study of adults, aged 45 to 84 years sampled from 6 communities in the United States, who were free of clinical cardiovascular disease at enrollment between July 2000 and July 2002. Briefly, the MESA cohort was composed of 6814 men and women who were recruited at 6 field centers in Baltimore, Maryland; Chicago, Illinois; Forsyth County, North Carolina; Los Angeles, California; New York, New York; and St. Paul, Minnesota, using locally available resources, such as lists of residences, dwellings, and telephone exchanges. Supplemental sources were used to ensure adequate samples of minorities and elders during the final recruitment period. The details of the MESA study design and methodology have been described.[22]

Fundus photography was included in the second (2002–2004) and fifth (2010–2012) examinations of the study. Of the 6814 participants examined at baseline, 6176 returned for a second examination when retinal images were first acquired, of whom 5867 (95.0%) had sufficient retinal imaging data to determine baseline AMD status. Among the 5867 with AMD status at baseline, 3811 individuals participated in the fifth study visit (first follow-up retinal examination) approximately 8 years later, were not aphakic, and had gradable retinal photographs at both baseline and follow-up visits to determine incident AMD status.

The Tenets of the Declaration of Helsinki were adhered to, and all necessary institutional review board approvals were granted. Written informed consent was obtained from all participants.

Fundus Photography and Image Grading

A standardized study protocol was followed at baseline and follow-up examinations. Fundus photography has been described in detail.[23] In brief, participants were seated in a darkened room where a 45-degree, 6.3-megapixel digital nonmydriatic camera (Canon, Lake Success, NY) was used to capture 2 photographic fields of each eye, the first centered on the optic disc and the second centered on the fovea. Images were sent to the University of Wisconsin-Madison Ocular Epidemiology Reading Center. The images were evaluated twice (preliminary and detailed) using EyeQ Lite software (an image-processing database for storage, retrieval, and manipulation of digital images)[23] by trained graders who followed a modification of the Wisconsin Age-Related Maculopathy Grading scheme[24,25] and were masked to the health status of the participant.

Participants were evaluated for early AMD lesions, including soft distinct drusen (defined by size between 63 and 300 μm in diameter with sharp margins and a round nodular appearance with a uniform density from center to periphery), soft indistinct drusen (defined by same size as soft distinct drusen but having indistinct margins and a softer, less solid appearance), increased retinal pigment (deposition of granules or clumps of gray or black pigment in or beneath the retina), and retinal pigment epithelium depigmentation (faint grayish-yellow or pinkish-yellow areas of varying density and configuration without sharply defined borders), and advanced features of maculopathy, including pure geographic atrophy and signs of exudative macular degeneration (e.g., subretinal hemorrhage, subretinal fibrous scar, retinal pigment epithelial detachment, or serous detachment of the sensory retina or laser or photodynamic treatment for neovascular AMD). 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 ≥125 μm in diameter with a large drusen area >500 μm in diameter or large ≥125 μm indistinct soft drusen in the absence of signs of late AMD. Late AMD was defined by the presence of geographic atrophy or exudative macular degeneration or both.

Covariates

Detailed questionnaires and clinical examinations were administered to all participants. Demographic and lifestyle characteristics in this analysis included age at baseline retinal examination, sex, race/ethnicity (white, black, Hispanic, Chinese), birth place (United States or foreign-born), education (less than high school, completed high school/graduate record examination equivalent, completed some college, college graduate), marital status (single, married, divorced, widowed), occupation (employed, unemployed, not seeking employment), annual family income (<$20 000, $20 000–39 999, $40 000–74 999, $75 000+), cigarette smoking status (never, past, current smoker), pack-years of cigarette smoking, exposure to secondhand smoke (hours per week), alcohol use (current use and drinks per week), and physical activity measured in metabolic equivalent minutes per week.

Individual health risk factors, including seated systolic and diastolic blood pressure (millimeters of mercury), hip and waist circumference (centimeters), hypertension, body mass index, body surface area, weight at age 20 years, weight at age 40 years, diabetes, microalbuminuria, periodontitis or gum disease, refractive error status, self-reported health conditions, and medication use (e.g., aspirin use, antihypertensives, lipid-lowering agents) were assessed. Body mass index was calculated as measured weight (kilograms) divided by height (meters) squared. Hypertension (yes or no) was defined as systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg or self-reported hypertension with use of antihypertensive medication. Diabetes status (yes/no) was defined as fasting glucose ≥7.0 mmol/l (≥126 mg/dl) or use of insulin or oral hypoglycemic medicine. Microalbuminuria was defined as a urine albumin-to-creatinine ratio ≥30 mg/g. Refractive error status was determined on the basis of the spherical equivalent in the eye with the