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Age-Related Macular Degeneration and Mortality in the Age-Related Eye Disease Study (AREDS)

The Effect of Sex and Time

Charlotte E. Joslin, OD, PhD,[1,2] *Thasarat S. Vajaranant, MD,*[1] *Lawrence J. Ulanski II, MD*[1]

Purpose: Age-related macular degeneration (AMD) shares similar risk factors and pathogeneses with cardiovascular diseases (CVDs). Epidemiologic studies over the past 2 decades analyzing the association between AMD and all-cause and CVD-specific mortality have failed to yield conclusive results. The purpose of this analysis is to investigate the sex-specific association between AMD and all-cause and CVD-specific mortality, and to assess whether duration of follow-up alters the strength of association.

Design: The database of Genotypes and Phenotypes (dbGaP) data set for the Age-Related Eye Disease Study, a randomized clinical trial of high-dose antioxidants in AMD prevention, with participants enrolled from 1992 to 1998 and followed through 2005, was used in the analysis.

Participants: There were 4757 Age-Related Eye Disease Study participants aged 55 through 80 years (mean, 69.4 years; 44.1% male) recruited from 11 retinal specialty clinics. Participants had standard Age-Related Eye Disease Study AMD categories (category 1, n = 1117; category 2, n = 1062; category 3, n = 1621; category 4, n = 957).

Methods: The sex-specific adjusted hazard ratio (HR_{adj}) between baseline AMD and all-cause and CVD-specific mortality was determined at multiple time points (e.g., 5, 7, 10, and all years), adjusting for age, race, diabetes, hypertension, angina, cancer, smoking, obesity, clinical trial antioxidant treatment category, and education.

Main Outcome Measures: Sex-specific all-cause and CVD-specific mortality.

Results: Mean follow-up was 9.6 years (range, 0.5–12.5 years), with 1087 deaths (category 1, n = 197 [17.6%]; category 2, n = 200 [18.8%]; category 3, n = 356 [22.0%]; category 4, n = 326 [34.1%]). Sex-stratified models demonstrated sex differences; in women, a significant association between AMD category 4 and all-cause mortality existed compared with category 1 at each period (HR_{adj}, 1.5-2.3; all $P \leq 0.005$); similar category 4 findings were present with CVD-specific mortality, strengthening with shorter periods (HR_{adj}, 1.9-4.6; all $P \leq 0.01$). Among men, a significant association between all AMD stages and all-cause (HR_{adj}, 1.5-2.3; all $P \leq 0.05$) and CVD-specific mortality (HR_{adj}, 1.6-4.0; all $P \leq 0.05$) existed for nearly all periods.

Conclusions: Substantial late AMD cases and deaths exceed those in previous population-based studies to better test mortality-related hypotheses. Age-related macular degeneration was significantly associated with all-cause and CVD-specific mortality. Relationships weakened over a longer duration of follow-up, and sex seems to modify the association. Future analyses are warranted to interrogate the possible clinical usefulness of these relationships. *Ophthalmology Retina 2017;1:49-58 © 2016 by the American Academy of Ophthalmology*

Age-related macular degeneration (AMD) has risk factors and a pathogenesis similar to those of cardiovascular diseases (CVDs).[1–10] Despite substantial decreases in age-adjusted CVD mortality rates over the past 2 decades, CVD remains the leading cause of death in the United States.[1,11] Epidemiologic studies over the past 2 decades[12–32] analyzing the association between AMD and all-cause and CVD-specific mortality have failed to yield conclusive results, with some,[12–21] but not all,[22–32] identifying a significant association. Included with these is the Age-Related Eye Disease Study (AREDS),[33] which identified a significant association in sex-combined results between mortality and advanced AMD in analyses assessing the intervention of high-dose antioxidants and zinc.[12,18] Three recent papers reported a significant relationship, including (1) an increased risk of all-cause and CVD-related mortality among participants with late AMD (Reykjavik Study)[19]; (2) CVD mortality in late AMD (women <80 years), and all-cause and non-CVD, noncancer mortality in early AMD, as well as all-cause and CVD mortality in any AMD (women ≥80 years of age; Study of Osteoporotic Fractures)[20]; and (3) all-cause mortality in men and

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stroke-related mortality in women (Blue Mountains Eye Study).[21] In contrast, the Singapore Malay Eye Study, also published in 2015, found no association between AMD and mortality.[32]

Potential explanations for the mixed findings include differences in analyzed follow-up times that minimize death outcomes and study power, or alter competing risks over time (e.g., cancer). Alternatively, most analyses report sex-combined[12,14,15,17–19,22–32] as opposed to sex-specific results,[13,16,20,21] which may mask sex differences.[34] Sex differences are well described in the incidence and prevalence of CVD morbidity and mortality,[35–39] and age-related CVD mortality differs by age between men and women, with risk steeply increasing in older women.[1,11,38] Further, risk factors vary by sex: sex differences in hormones differentially influence vascular function,[40] sex-specific polymorphisms are associated with coronary artery disease,[41] and sociocultural factors vary by gender.[39] Finally, sex differences exist in the association between AMD and coronary heart disease,[42,43] a more common event than death (which increases the statistical power to detect an association), suggesting that sex differences could result with other CVD-related outcomes (e.g., CVD mortality) if assessed in a cohort appropriately powered for inferential testing.

As such, evidence suggests mixed historical study findings between AMD and mortality may be due in part to methodologic challenges with existing cohorts. Given the significant overlap in risk factors and pathogenesis between AMD and CVD, a more definitive, sex-specific understanding and explanation for the inconclusive historical results between AMD and mortality is warranted, particularly if AMD may serve as a marker for physiologic aging[19] or mortality that could be modified through risk reduction strategies, including tighter control of systemic disease by primary care physicians. The purpose of this analysis is to identify in the AREDS cohort, which is unique in that it includes ample late AMD cases (category 4, n = 957) and deaths (n = 1087), whether a sex-specific association exists between AMD and all-cause and CVD-specific mortality, and to assess whether duration of follow-up alters the strength of association.

Methods

Overview, Study Population, and Data Set

The University of Illinois at Chicago Institutional Review Board reviewed the protocol and determined that analyses were exempt. Authorization for access to individual-level data files was obtained via the database of Genotypes and Phenotypes (dbGaP) authorized access portal (dbGaP accession number #14756-1).[44,45] The dbGaP data set for AREDS,[45] a longitudinal randomized clinical trial of high-dose antioxidants in the prevention of AMD and cataracts,[33] was used in the analysis. The AREDS study design and population have been described extensively. The analyses include 4757 participants aged 55 to 80 years recruited and enrolled from 11 retinal specialty clinics from 1992 to 1998.[12,33,45,46] Participants were followed in the clinical trial for a median of 6.5 years, and through December 2005 (an additional 5 years) to collect natural history data.[12,18,46] Standard AREDS AMD categories (1, 2, 3, and 4)[33,47] were used to assess the sex-specific association between AMD status at baseline and the hazard of mortality from (1) all causes and (2) CVD. Analyses were performed at 4 time points after randomization to compare the effects of varying durations of follow-up.

Ascertainment of AMD

Stereoscopic fundus photographs taken at baseline and graded at a central reading center using standardized grading procedures were used to determine AMD status, as described previously.[18,33,47] Briefly, AREDS used the following AMD classifications for participants: category 1 was free of AMD, with <5 small drusen (<63 μm); category 2 had early AMD with multiple small drusen or nonextensive intermediate drusen (63–124 μm), and/or pigment abnormalities; category 3 had no advanced AMD but had ≥1 large drusen (125 μm), extensive intermediate drusen, or geographic atrophy not involving the center of macula; and category 4 had advanced AMD, central geographic atrophy, or neovascular AMD in 1 eye.

Ascertainment of Mortality

Deaths were documented by the study's Death Report and were supplemented after AREDS concluded with a National Death Index (NDI) search to identify subsequent deaths and cause of death.[48] Cause of death on the Death Report was determined by a certified *International Classification of Diseases 9th Revision* coder and reviewed by the study's Morbidity and Mortality Committee, with discrepancies adjudicated by the medical monitor.[12] The NDI is a centralized death registry maintained by the National Center for Health Statistics that includes all deaths and causes of death occurring in the United States, Puerto Rico, and the Virgin Islands since 1979.[49,50] The NDI procedures to ascertain vital status use a probabilistic linkages of the case file with NDI death files on common individual identifying data elements (e.g., social security number, first name, middle initial, last name, sex, state of birth, birth month, and birth year),[49] and their accuracy and sensitivity have been demonstrated in adult populations.[50–52] The NDI is used commonly to study mortality, including assessment of CVD-specific and all-cause mortality, in various cohorts, including eye.[16,53–63] To obtain more complete mortality data in this analysis, AREDS deaths documented by the Death Report during the study[12,18] were supplemented after study closure with deaths ascertained through the NDI linkage.[14,16] The final cause of death variable was assigned to match the Death Report determined during AREDS in the instance of a conflict.

Ascertainment of Covariates

Demographic information and medical history were obtained at baseline and included data on age, race, sex, education, smoking, use of medications, and self-reported history of diabetes, angina, and cancer, as previously described.[33] Body mass index was calculated by dividing body mass (kilograms) by the square of the height (in meters) measured at baseline. Hypertension was defined as a systolic measurement of ≥140 mm Hg, a diastolic measurement ≥90 mm Hg, or antihypertensive medication use at baseline.

Statistical Modeling and Analysis

Sex-specific demographic and baseline characteristics were compared in univariate analysis using SAS (version 9.4, Cary, NC). The proportionality of the hazard function over time between men and women was assessed with Kaplan-Meier survival curves. All analyses were conducted for 2 survival outcomes: (1) any death