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Age-related macular degeneration and risk of total and cause-specific mortality over 15 years

Bamini Gopinath*, Gerald Liew, George Burlutsky, Paul Mitchell

Centre for Vision Research, Department of Ophthalmology, Westmead Millennium Institute, The University of Sydney, Sydney, Australia

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ABSTRACT

Objective: We aimed to investigate the independent association between AMD and risk of ischemic heart disease (IHD), stroke, and cardiovascular (CVD) mortality, and all-cause mortality over 15 years.
Methods: 3654 participants aged 49+ years at baseline were followed over 15 years. AMD was assessed from retinal photographs. Deaths and cause of death were confirmed by data linkage with the Australian National Death Index. Hazard ratios (HRs) and 95% confidence intervals (CIs) were assessed using Cox models.
Results: 71.4% (n = 162) and 34.6% (n = 1037) of participants with any AMD and no AMD, respectively, died over 15 years. After multivariable-adjustment, no significant associations were observed between AMD and total- and cause-specific mortality in the overall cohort. However, among men, late AMD at baseline was associated with an increased risk of all-cause mortality (n = 22; 95.7%), 15 years later: multivariable-adjusted HR, 1.80 (95% CI 1.04–3.11). Women with late AMD had 2-fold increased risk of stroke mortality (n = 15; 28.9%), HR 2.10 (95% CI 1.08–4.06). Early-stage AMD was not associated with mortality risk.
Conclusion: Late AMD independently predicted all-cause mortality in men and stroke mortality in women, over 15 years. Although underlying mechanisms are unclear, these findings indicate that late AMD is a marker of biological aging.

1. Introduction

Age-related macular degeneration (AMD) is a progressive, chronic disease of the central retina, and is a leading cause of blindness and low vision among older adults [1]. AMD has both early and late stages. Early AMD is usually not associated with loss of vision. Vision loss in late AMD is caused either by neovascular disease, with growth of new blood vessels that leak and scar underneath the central retina, or by geographic atrophy in which an area of the retina in the macula atrophies. Neovascular or wet AMD is responsible for most AMD-related severe visual loss [2–9]. The most important risk factor for any stage of AMD is old age. Pooled data from seven population-based studies showed that the prevalence of geographic atrophy in the United States was 0.3% in 60–64 year olds, 0.5% in 65–69 year olds, 0.9% in 70–74 year olds, 1.8% in 75–79 year olds, and 6.9% in those 80 or older [5]. The respective rates for neovascular disease were 0.4%, 0.6%, 1.2%, 2.2%, and 8.2%. Therefore, as life expectancy improves with advances in medicine and public health, the number of patients affected by AMD is also likely to increase [5,10].

Several studies have attempted to establish whether persons with AMD are at increased risk of death, particularly resulting from vascular causes, but results have been equivocal [11–15]. This inconsistency in findings is speculated to be due to AMD being associated with other systemic conditions that are risk factors for mortality, so that controlling for these risk factors nullified the association between AMD and mortality in some [15,16] but not all studies [11–14]. Differences in study design, age-sex population distribution, and follow-up duration could also explain these differences [11]. It was suggested in one study that longer follow-up (i.e., at least 15 years) would be needed to establish the relationship between AMD and mortality risk [11,13]. To best of our knowledge, only the recent Study of Osteoporotic Fractures [11] has looked at the relationship between AMD and mortality risk over 15 years. This study showed that women aged 80+ years with any AMD had increased risk of death from any cause or cardiovascular disease (CVD). However, the results of this study are not applicable to all older adults, given that this study did not examine AMD and 15-year mortality risk in men.

Therefore, in this report we aimed to enhance current understanding of whether AMD is a useful prognostic indicator in

* Corresponding author at: Centre for Vision Research, University of Sydney, Westmead Millennium Institute, Westmead, NSW 2145, Australia. Fax: +61 2 86273099.
E-mail address: bamini.gopinath@sydney.edu.au (B. Gopinath).

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identifying older adults at risk of poorer survival. Specifically, we assessed the association between AMD (any, early or late) and all-cause and cause-specific mortality (CVD; ischemic heart disease, IHD; and stroke mortality) 15 years later, independent of the effects of various potential confounders (e.g., age, sex, smoking, body mass index, diabetes, hypertension, cancer, angina, myocardial infarction, walking disability and self-rated health).

2. Methods

2.1. Study population

The Blue Mountains Eye Study (BMES) is a population-based cohort study of common eye diseases and other health outcomes in a suburban Australian population located west of Sydney. Study methods and procedures have been described elsewhere [17]. Baseline examinations of 3654 residents aged >49 years were conducted during 1992–4 (BMES-1; 82.4% participation rate). Surviving baseline participants were invited to attend examinations after 5- (1997–9, BMES-2), 10- (2002–4, BMES-3), and 15 years (2007–9, BMES-4) at which 2334 (75.1% of survivors), 1952 participants (75.6% of survivors) and 1149 (55.4% of survivors) were re-examined, respectively. For the current report we have analyzed data from BMES-1 through to BMES-3. The University of Sydney and the Western Sydney Area Human Ethics Committees approved the study, and written, informed consent was obtained from all participants at each examination.

2.2. Assessment of AMD

For the current analyses, the primary study factor was the presence/absence of early and late AMD at baseline i.e., BMES-1. We took two 30° stereoscopic color retinal photographs of the macula of both eyes, which were graded for presence of early and late AMD using the Wisconsin AMD Grading System [7,18]. Inter- and intra-grader reliability showed good agreement for grading of specific AMD lesions with quadratic weighted kappa values ranging from 0.64 to 0.93 and 0.54–0.94 respectively [2]. The detailed methodology of AMD ascertainment in this population has been previously reported [7,18]. Early AMD was defined as the absence of late AMD and presence of either: (1) large (>125-μm diameter) indistinct soft or reticular drusen or (2) both large distinct soft drusen and retinal pigmentary abnormalities (hyperpigmentation or hypopigmentation) in either eye [18]. Similarly, late AMD was defined as the presence of neovascular AMD or geographic atrophy in either eye [18]. Any AMD was defined as having early or late AMD. A retinal specialist (P.M.) adjudicated all uncertain retinal pathology and confirmed all late AMD cases. Patients and their physicians were informed by mail if they were diagnosed with AMD through these photographs.

Table 1
Baseline characteristics of Blue Mountains Eye Study participants stratified by gender ($n = 3654$).

Variable	Women ($n = 2072$)	Men ($n = 1582$)	*P*-value
Age, years	66.4 (9.9)	65.9 (9.5)	0.16
Tertiary education	1016 (52.4)	970 (65.5)	<0.0001
Smoking status			<0.0001
Never smoked	1215 (61.3)	485 (32.3)	
Former smoker	488 (24.6)	772 (51.3)	
Current smoker	278 (14.0)	247 (16.4)	
Alcohol consumption			
<1 Drink/week	1254 (63.1)	638 (42.2)	<0.0001
1–4 Drinks/week	292 (14.7)	313 (20.7)	
>4 Drinks/week	440 (22.2)	562 (37.1)	
Body mass index kg/m^2	26.1 (5.0)	26.2 (3.8)	0.72
Walking disability	170 (8.2)	96 (6.1)	0.01
Low self-rated health	78 (3.8)	62 (4.0)	0.99
Hypertension	986 (48.0)	659 (41.9)	0.0003
Diabetes	132 (6.9)	149 (10.3)	0.001
Cancer	200 (9.7)	110 (7.0)	0.004
Angina	231 (11.2)	223 (14.2)	0.01
Myocardial infarction	134 (6.5)	204 (13.0)	<0.0001
Stroke	52 (2.5)	23 (1.5)	0.03

All data are presented as mean (SD) or *n* (%).

2.3. Assessment of mortality

Mortality data since baseline (15 years) were obtained via data linkage with the Australian National Death Index (NDI). Information provided by family members during follow-up was also included if the participant was reported to have died on or before December 2007. The International Classification of Diseases, 9th and 10th Revision [19] cause of death codes were obtained. Validity of NDI data has been reported to have high sensitivity and specificity for cardiovascular mortality (92.5% and 89.6%, respectively) [20]. The census cut-off point for mortality was end of December 2007 (i.e., a 15-year period from the baseline examination).

2.4. Assessment of covariates

At face-to-face interviews with trained interviewers, a comprehensive medical history that included information about demographic factors, socio-economic characteristics and lifestyle factors like smoking was obtained from all participants. For the current analyses, we used covariate information that was obtained at baseline (BMES-1) only. History of smoking was defined as never, past, or current smoking. Current smokers included those who had stopped smoking within the past year. Alcohol intake was assessed by questions about the frequency of consuming alcoholic drinks (days per week), and consumption was split into 3 groups (<1 drink/week; 1–4 drinks/week; >4 drinks/week). A history of angina, myocardial infarction, diabetes mellitus, hypertension, stroke, or cancer at baseline was determined by responses to questions starting with "Has a doctor advised you that you have . . . ?" Fasting blood samples were processed on the same day for serum lipids, plasma glucose concentrations, white blood cell count, and fibrinogen at the Westmead Hospital Clinical Pathology laboratory, in western Sydney, Australia. Diabetes was defined either from history or by fasting blood glucose ≥7.0 mmol/L. Body mass index (BMI) was calculated from measured weights and heights (kg/m^2). Disability in walking at baseline was assessed as present if the participant was observed by a trained examiner to have walking difficulties or used walking aids or a wheelchair. Self-rated health was assessed by asking, "For somebody your age, would you say your health is excellent, very good, good, fair, or poor?" Low self-rated health was defined as fair/poor.

2.5. Statistical analysis

SAS (SAS Institute, Cary NC) version 9.2 was used for analyses. The association between presence of AMD and total and cause-specific mortality was examined with Cox regression models to estimate hazard ratios (HR) and 95% confidence intervals (CI). Because risk of AMD and mortality are strongly associated with increasing age, age was used as the time scale in the Cox proportional hazards regression, allowing the models to compare risk for people of comparable age (instead of length of follow-up) [12]. Covariates adjusted for in mortality analyses were those previously shown to be associated with total and cause-specific mortality in the BMES: age, sex, educational status (tertiary qualified or not), current smoking, alcohol consumption, BMI, walking disability, doctor-diagnosed history of cancer, angina, acute myocardial