

# Visual Impairment, Age-Related Macular Degeneration, Cataract, and Long-term Mortality

## *The Blue Mountains Eye Study*

Sudha Cugati, MS; Robert G. Cumming, MPH, PhD; Wayne Smith, MPH, PhD; George Burlutsky, MStat; Paul Mitchell, MD, PhD; Jie Jin Wang, MMed, PhD

**Objective:** To assess the association of visual impairment, age-related macular degeneration (ARMD), and cataract with long-term mortality.

**Methods:** At baseline, 3654 persons 49 years and older were examined in the Blue Mountains Eye Study (1992-1994). Standardized photographic grading was used to assess ARMD and cataract. Mortality and causes of death occurring between baseline and December 31, 2003, were obtained via data linkage with the Australian National Death Index. Age-standardized mortality rates were calculated. Hazard ratios (HRs) and 95% confidence intervals (CIs) were assessed using Cox models.

**Result:** Age-standardized mortality was higher in persons with vs without visual impairment (54.0% vs 34.0%), ARMD (45.8% vs 33.7%), and cataract (39.2% vs 29.5%).

After adjusting for factors that predict mortality, neither visual impairment (HR, 1.3; 95% CI, 0.98-1.7) nor ARMD (HR, 1.0; 95% CI, 0.8-1.3) was significantly associated with all-cause mortality in all ages. Among persons younger than 75 years, however, ARMD predicted higher all-cause mortality (HR, 1.6; 95% CI, 1.0-2.4). Any cataract (HR, 1.3; 95% CI, 1.0-1.5) and cortical (HR, 1.2; 95% CI, 0.97-1.4), nuclear (HR, 1.2; 95% CI, 0.98-1.5), and posterior subcapsular (HR, 1.3; 95% CI, 1.0-1.7) cataract were also associated with higher all-cause mortality.

**Conclusion:** Cataract predicted increased mortality in persons 49 years and older, and ARMD predicted mortality in persons aged 49 to 74 years.

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**Author Affiliations:** Centre for Vision Research, Department of Ophthalmology, Westmead Millennium Institute (Dr Cugati and Mr Burlutsky and Drs Mitchell and Wang) and Department of Public Health and Community Medicine (Dr Cumming), University of Sydney, Sydney, Australia; and Centre for Clinical Epidemiology and Biostatistics, University of Newcastle, Newcastle, Australia (Dr Smith).

SEVERAL STUDIES<sup>1-8</sup> HAVE CONSISTENTLY shown an association between visual impairment and increased mortality in older persons. The mechanisms for higher mortality associated with visual impairment remain unclear. It could be attributed to age-related ocular conditions, such as age-related macular degeneration (ARMD) or cataract, which can be markers of biological aging. Alternatively, visual impairment and its related ocular conditions could share a similar pathogenesis with other conditions associated with increased mortality.<sup>9-12</sup> To date, studies reporting mortality associations with ARMD<sup>1-7,13-15</sup> and cataract<sup>2,6,10,14-21</sup> have been inconsistent.

Earlier population-based studies<sup>1-4,6,14</sup> investigating relatively short-term (4- to 6-year) mortality associated with ARMD reported either no association<sup>1-4</sup> or a positive association<sup>6</sup> with higher mortality. Participants in the Age-Related Eye Disease Study<sup>6</sup> with advanced ARMD had increased mortality compared with partici-

pants with few drusen (multivariate-adjusted relative risk, 1.4; 95% confidence interval [CI], 1.1-1.9). In Rotterdam Study analyses,<sup>14</sup> although an association between late ARMD and higher mortality rates was observed after adjusting for age and sex, it was not significant after adjusting for other confounding variables.

Findings from long-term follow-up studies have been inconsistent. Whereas no association was observed between ARMD and 13-year mortality in the Beaver Dam Eye Study<sup>5</sup> (relative risk, 0.97; 95% CI, 0.87-1.07), a positive association with 14-year mortality was observed in the Copenhagen City Eye Study<sup>15</sup> (relative risk, 1.3; 95% CI, 1.1-1.5). Wang et al<sup>1</sup> reported a significant association of mortality with visual impairment and cataract during a 7-year period but found no significant association between ARMD and mortality.

In the present study, we aimed to assess the longer-term (11-year) mortality risk associated with visual impairment and its 2 principal causes—ARMD and cata-

tract—in the same older Australian cohort, the Blue Mountains Eye Study.

## METHODS

The Blue Mountains Eye Study is a population-based cohort study of vision and common eye diseases in a suburban Australian population 49 years and older at baseline. The study was approved by the Human Research Ethics Committee of the University of Sydney and was conducted adhering to the tenets of the Helsinki Declaration. Signed informed consent was obtained from all the participants at each examination. Survey methods and procedures have been described previously.<sup>22,23</sup>

Briefly, at baseline (1992-1994) 3654 of 4433 eligible residents (82.4%) 49 years and older living in the Blue Mountains area, west of Sydney, were examined. Visual acuity (VA) was assessed using a logarithm of the minimum angle of resolution chart.<sup>23</sup> Initially VA was assessed with patients wearing their current eyeglasses. If initial VA was less than 54 letters read correctly (20/20 Snellen equivalent), refraction was performed. Best-corrected VA was VA after subjective refraction. Visual impairment included best-corrected VA less than 20/40 Snellen equivalent (<39 letters read correctly) in the better eye.

At baseline, 30° stereoscopic retinal photographs (FF3; Zeiss, Oberkochen, Germany) of macula and other retinal fields<sup>22</sup> of both eyes were taken and graded for ARMD lesions.<sup>22</sup> These grades closely followed the Wisconsin age-related maculopathy grading system.<sup>24</sup> Early ARMD lesions include indistinct soft or reticular drusen and coexisting distinct soft drusen and retinal pigmentary abnormalities. Late ARMD lesions include geographic atrophy at least 175 μm in diameter at the macula (regardless of foveal involvement) and neovascular ARMD, as described by the International ARM Epidemiologic Study classification.<sup>25</sup> A retinal specialist (P.M.) confirmed all baseline late ARMD cases.

Baseline cataract was documented from slitlamp (Topcon Optical, Tokyo, Japan) and retroillumination (Neitz Instruments, Tokyo) lens photographs. The presence of cataract was assessed in each eye.<sup>26</sup> Severity of nuclear cataract was defined on a 5-level scale by comparison with 4 standard slitlamp photographs; nuclear cataract included level 4 or 5. Cortical cataract included cortical opacity involving 5% or more of the lens area.<sup>26</sup> The presence of posterior subcapsular cataract was recorded and graded into 3 severity levels: none, mild (<5% of the lens area), and significant (≥5% of the lens area). Baseline aphakia/pseudophakia was defined by a history of cataract surgery, confirmed by slitlamp examination and lens photographic grading.

At baseline, systolic and diastolic blood pressure were recorded. We adapted the 2003 World Health Organization/International Society of Hypertension guidelines to define hypertension.<sup>27</sup> Participants were classified as having hypertension stage I if systolic blood pressure was 140 to 159 mm Hg or if diastolic blood pressure was 90 to 99 mm Hg and as having severe hypertension (stage II or greater) if they were previously diagnosed as having hypertension and were using antihypertensive medications, if systolic blood pressure was 160 mm Hg or greater, or if diastolic blood pressure was 100 mm Hg or greater at examination. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Current smokers included those who had stopped smoking within the past year. Diabetes mellitus was defined as a history of physician-diagnosed diabetes mellitus and use of diabetic medications or diet control or a fasting blood glucose level of 126 mg/dL or greater (to convert to millimoles per liter, multiply by 0.0555). History of angina, myocardial infarction, and stroke was taken in all participants at baseline.

Deaths occurring between baseline examination and December 31, 2003, were confirmed by matching the demographic information of the 3654 participants with the Australian National Death Index data using probabilistic record linkage.<sup>28,29</sup> Causes of death were provided by the National Death Index, which records cause of death documented on death certificates using *International Classification of Diseases, Ninth Revision*<sup>30</sup> and *International Statistical Classification of Diseases, 10th Revision* codes.<sup>31</sup> Each person can have a maximum of 4 causes of death listed in the registry. Vascular mortality was defined to include cardiovascular and stroke-related causes. The Australian National Death Index data have estimated sensitivity of 93.7% and specificity of 100% for all deaths and 92.5% and 89.6%, respectively, for cardiovascular deaths.<sup>28,29</sup>

Statistical software (SAS version 9.1; SAS Institute Inc, Cary, North Carolina) was used for analyses. Age-standardized mortality rates were obtained after direct age standardization of participants with visual impairment, ARMD, and cataract to the entire study population. Cox regression models assessed associations between visual impairment, ARMD, and cataract and mortality risk during 11 years after adjusting for age, sex, BMI, hypertension (stage II), diabetes mellitus, current smoking, and history of stroke, angina, or myocardial infarction (model 1). In the multivariate models, BMI was categorized as underweight (BMI <20) or obesity (BMI ≥30), with BMI values of 20 to 29 as the reference group, respectively. In supplementary analyses, we also adjusted for visual impairment in models for ARMD and cataract (model 2) and for cataract in the ARMD model (model 3) and tested for the significance of socioeconomic variables (educational level and home ownership), biological variables (such as cholesterol, high-density lipoprotein cholesterol, triglyceride, and fibrinogen levels), alcohol intake, and walking disability in all models. The significant variables (educational level, triglyceride level, fibrinogen level, and walking disability) were included in the final model (model 4) in these analyses. We tested for interactions on selected study variables with mortality. Interaction terms between age and all-cause or vascular mortality were statistically significant. Because age was found to violate the proportional hazards assumption ( $P < .001$ ) in the Cox models that included all participants (mortality rates were significantly different between younger and older subgroups), we adjusted for age by stratification in the models for all ages using 10-year intervals for each stratum in younger participants and 5-year intervals in older individuals. We also repeated the analyses in 2 stratified age groups: younger than 75 years and 75 years and older. The proportional assumption was met for the models of these 2 separate age groups. No significant interactions were found between sex and mortality, sex and ARMD, and sex and visual impairment. Hazard ratios (HRs) and 95% CIs are given.

## RESULTS

Cumulative follow-up of the study cohort was 11 years (median, 10.7 years; minimum, <1 year; and maximum, 12.0 years). Data on mortality or cause of death were missing for 21 participants (0.6%). The remaining 3633 participants were considered to be at risk. During an average 11-year period, 1051 participants (28.9%) died of any cause and 483 (13.3%) died of vascular causes. **Table 1** gives the baseline characteristics of participants associated with mortality. Participants who died were older and were more likely to be male, current smokers, and underweight and to have diabetes mellitus, hypertension, and a history of angina, acute myocardial infarction, and stroke.

## ASSOCIATION BETWEEN VISUAL IMPAIRMENT AND MORTALITY

Visual impairment was detected in 132 participants (3.6%), including 24 participants who were younger than 75 years and 108 participants who were 75 years and older at baseline.

### All-Cause Mortality

Cumulative 11-year mortality was higher in participants with vs without visual impairment (75.0% vs 26.9%), with age-standardized mortality of 54.0% and 34.0% in participants with and without visual impairment, respectively. An association between visual impairment and reduced survival was observed in the age- and sex-adjusted model (HR, 1.4; 95% CI, 1.1-1.7), but this association became weaker after adjusting for other factors significantly associated with poor survival (HR, 1.3; 95% CI, 0.98-1.7). However, among persons younger than 75 years, visual impairment predicted higher all-cause mortality (HR, 2.9; 95% CI, 1.6-5.5) (**Table 2** and **Figure 1**). This association remained in persons younger than 75 years but became attenuated after further adjustment for triglyceride level, fibrinogen level, educational level, and walking disability (model 4) (HR, 1.97; 95% CI, 0.8-4.8). Note that model 4 gave reduced statistical power because not all participants underwent blood testing.

### Vascular Mortality

A similar association between visual impairment and vascular mortality was observed in persons younger than 75 years after age and sex adjustment, but the association became nonsignificant after adjusting for other factors (HR, 1.1; 95% CI, 0.2-8.4) (Table 2).

## ASSOCIATION BETWEEN ARMD AND MORTALITY

After excluding participants with ungradable or missing retinal photographs, 3553 participants had data available to assess the mortality risk associated with ARMD. Of these, ARMD was detected in 6.9% of participants at baseline (n=244), including 4.8% with early ARMD (n=172) and 2.0% with late ARMD (n=72). Of the participants with late ARMD, 12 were younger than 75 years at baseline.

### All-Cause Mortality

Cumulative 11-year mortality was higher in participants with vs without ARMD (55.8% vs 25.9%), with age-standardized mortality of 45.8% and 33.7% in persons with and without ARMD, respectively. There was no significant difference in all-cause mortality risk between persons with vs without any ARMD (HR, 1.0; 95% CI, 0.8-1.3). In participants younger than 75 years, however, any ARMD predicted higher all-cause mortality (HR, 1.7; 95% CI, 1.2-2.4) (**Table 3** and **Figure 2**). After further adjusting for visual impairment (model 2) and any cata-

**Table 1. Baseline Characteristics Associated With Mortality in the Multivariate-Adjusted Cox Regression Model<sup>a</sup>**

Status at Baseline	Participants	
	Died (n = 1051)	Survived (n = 2582)
Age, mean ± SD, y	73.7 ± 9.36	63.1 ± 8.11
Sex		
F	516 (49.1)	1546 (59.9)
M	535 (50.9)	1036 (40.1)
Body mass index <sup>b</sup>		
<20 (underweight)	90 (9.2)	108 (4.3)
20-25	397 (40.6)	957 (37.6)
25-30 (overweight)	341 (34.9)	1021 (40.2)
>30 (obese)	150 (15.3)	457 (18.0)
Diabetes mellitus	113/1051 (10.8)	169/2582 (6.6)
Hypertension	563/1034 (54.4)	1073/2572 (41.7)
Current smoker	165/982 (16.8)	330/2507 (13.2)
History of angina	204/1039 (19.6)	245/2574 (9.5)
History of acute myocardial infarction	154/1039 (14.8)	179/2574 (7.0)
History of stroke	114/1042 (10.9)	77/2571 (3.0)

<sup>a</sup>Data are given as number (percentage) except where noted otherwise.  $P < .001$  for all characteristics.

<sup>b</sup>Calculated as weight in kilograms divided by height in meters squared. Data were missing for some patients.

ract (model 3) at baseline, this association remained significant (HR, 1.8; 95% CI, 1.2-2.6) (Table 3). The association in persons younger than 75 years remained similar after further adjustment for triglyceride level, fibrinogen level, educational level, and walking disability in model 4 (HR, 1.6; 95% CI, 1.0-2.4). In participants younger than 75 years, early ARMD (HR, 1.5; 95% CI, 1.0-2.2) and late ARMD (HR, 2.5; 95% CI, 1.2-5.0) significantly predicted higher all-cause mortality.

### Vascular Mortality

Cumulative 11-year vascular mortality was higher in participants with vs without any ARMD (26.5% vs 11.9%), although ARMD was not associated with higher adjusted vascular mortality risk for all ages (Table 3). In participants younger than 75 years, any ARMD (model 1) predicted increased vascular mortality risk (HR, 2.1; 95% CI, 1.2-3.8) (Table 3). This association remained after further adjustment for visual impairment (model 2) and cataract (model 3) (Table 3). However, the association became attenuated in persons younger than 75 years after also adjusting for triglyceride level, fibrinogen level, educational level, and walking disability (model 4) (HR, 1.4; 95% CI, 0.6-3.1). In analyses using 3 categories for ARMD (none, early, and late), in participants younger than 75 years, late ARMD predicted higher vascular mortality (HR, 3.8; 95% CI, 1.4-10.4), although early ARMD did not (HR, 1.4; 95% CI, 0.7-2.7).

## ASSOCIATION BETWEEN AGE-RELATED CATARACT AND MORTALITY

Of 3654 participants at baseline, slitlamp photographs were either missing or ungradable for 895 participants

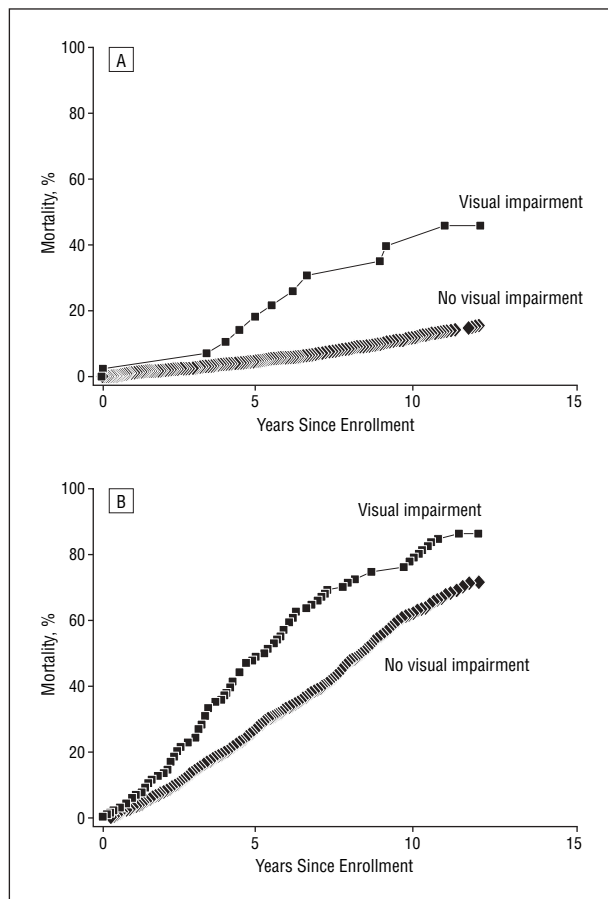
**Table 2. 11-Year Mortality in Participants With and Without Baseline Visual Impairment**

Baseline Visual Impairment	Participants at Risk, No.	Affected, %	HR (95% CI)		
			Age and Sex Adjusted	Model 1 <sup>a</sup>	Model 4 <sup>b</sup>
<b>All-cause mortality</b>					
All ages					
Absent	3489	26.9	1 [Reference]	1 [Reference]	1 [Reference]
Present	132	75.0	1.36 (1.09-1.70)	1.27 (0.98-1.66)	1.18 (0.86-1.61)
Aged <75 y					
Absent	2826	17.6	1 [Reference]	1 [Reference]	1 [Reference]
Present	24	45.8	2.92 (1.61-5.33)	2.93 (1.55-5.53)	1.97 (0.80-4.84)
Aged ≥75 y					
Absent	663	67.0	1 [Reference]	1 [Reference]	1 [Reference]
Present	108	81.5	1.30 (1.02-1.66)	1.11 (0.83-1.48)	1.09 (0.78-1.53)
<b>Vascular mortality</b>					
All ages					
Absent	3217	2.6	1 [Reference]	1 [Reference]	1 [Reference]
Present	404	11.9	1.31 (0.94-1.85)	1.10 (0.74-1.64)	0.93 (0.58-1.48)
Aged <75 y					
Absent	2826	5.2	1 [Reference]	1 [Reference]	1 [Reference]
Present	24	16.7	3.40 (1.25-9.23)	2.30 (0.72-7.38)	1.11 (0.15-8.37)
Aged ≥75 y					
Absent	663	31.5	1 [Reference]	1 [Reference]	1 [Reference]
Present	108	40.7	1.37 (0.97-1.94)	1.02 (0.67-1.54)	0.95 (0.59-1.55)

Abbreviations: CI, confidence interval; HR, hazard ratio.

<sup>a</sup>Adjusted for age, sex, body mass index (<20 vs ≥30 [calculated as weight in kilograms divided by height in meters squared]), presence of hypertension and diabetes mellitus, current smoking, and baseline history of angina, acute myocardial infarction, or stroke.

<sup>b</sup>Adjusted for factors in model 1 and triglyceride level, fibrinogen level, educational level, and walking disability.



**Figure 1.** Age- and sex-adjusted all-cause mortality by age group and visual impairment status. Survival curves are shown for individuals younger than 75 years (A) and those 75 years and older (B) at baseline.

(24.5%), largely due to a random camera malfunction that affected nuclear cataract images. Any cataract was seen in 1204 participants (33.0%).

### All-Cause Mortality

Cumulative 11-year mortality was higher in participants with vs without any cataract (43.3% vs 17.4%), cortical cataract (44.2% vs 21.5%), nuclear cataract (50.3% vs 21.3%), and posterior subcapsular cataract (47.0% vs 25.6%) and after cataract surgery (61.4% vs 26.9%). Age-standardized all-cause mortality was 39.2% and 29.5% for persons with and without any cataract, respectively. Any cataract plus cortical, nuclear, and posterior subcapsular cataract considered separately were predictors of mortality after adjusting for factors significantly associated with mortality (model 1) (**Table 4**). The association between nuclear cataract and mortality became weaker after further adjusting for visual impairment (model 2) (Table 4). The association between cataract and all-cause and vascular mortality remained similar after also adjusting for triglyceride level, fibrinogen level, educational level, and walking disability (model 4) (Table 4).

### Vascular Mortality

Any cataract and cortical, nuclear, and posterior subcapsular cataracts considered separately were significantly associated with vascular mortality in the multivariate logistic regression models after adjusting for factors significantly associated with mortality (model 1) and visual impairment (model 2) (Table 4).

**Table 3. 11-Year Mortality in Participants With and Without Baseline Age-Related Macular Degeneration (ARMD)**

Baseline ARMD	Participant, at Risk, No.	Affected, %	HR (95% CI)				
			Age and Sex Adjusted	Model 1 <sup>a</sup>	Model 2 <sup>b</sup>	Model 3 <sup>c</sup>	Model 4 <sup>d</sup>
All-cause mortality							
All ages							
Absent	3290	25.9	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
Present	242	55.8	1.09 (0.91-1.32)	1.03 (0.84-1.26)	1.0 (0.81-1.23)	1.14 (0.90-1.44)	1.11 (0.85-1.45)
<75 y							
Absent	2699	16.6	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
Present	100	38.0	170 (1.21-2.40)	1.66 (1.17-2.35)	1.61 (1.14-2.29)	1.78 (1.23-2.59)	1.59 (1.04-2.43)
≥75 y							
Absent	591	68.4	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
Present	142	68.3	0.93 (0.74-1.16)	0.84 (0.66-1.07)	0.81 (0.63-1.05)	0.90 (0.68-1.21)	0.90 (0.65-1.26)
Vascular mortality							
All ages							
Absent	3290	11.9	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
Present	242	26.5	2.09 (1.21-3.60)	0.93 (0.68-1.28)	0.92 (0.66-1.27)	0.96 (0.66-1.40)	0.75 (0.48-1.19)
<75 y							
Absent	2699	6.2	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
Present	100	16.0	1.75 (1.04-2.95)	2.10 (1.17-3.77)	2.08 (1.15-3.74)	2.03 (1.07-3.84)	1.41 (0.64-3.09)
≥75 y							
Absent	591	37.9	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
Present	142	33.8	0.82 (0.60-1.13)	0.75 (0.52-1.09)	0.74 (0.51-1.07)	0.75 (0.48-1.17)	0.62 (0.36-1.06)

Abbreviations: CI, confidence interval; HR, hazard ratio.

<sup>a</sup>Adjusted for age, sex, body mass index (<20 vs ≥30 [calculated as weight in kilograms divided by height in meters squared]), presence of hypertension and diabetes mellitus, current smoking, and baseline history of angina, acute myocardial infarction, or stroke.

<sup>b</sup>Adjusted for all factors in model 1 plus visual impairment.

<sup>c</sup>Adjusted for all factors in model 2 plus cataract.

<sup>d</sup>Adjusted for all factors in model 3 and triglyceride level, fibrinogen level, educational level, and walking disability.

## CAUSES OF DEATH

The primary (first-listed) causes of death were compared between participants with and without visual impairment, any ARMD, and any cataract. Vascular deaths were the more frequent cause in participants with visual impairment or cataract compared with those without visual impairment or cataract ( $P = .004$  and  $P < .001$ , respectively). Cancer-related deaths were significantly less frequent in participants with visual impairment or cataract ( $P < .001$ ). No significant difference in respiratory or other causes of death between persons with and without visual impairment or cataract was observed. In participants with and without ARMD, proportions of each major cause of death were similar between the 2 groups.

## COMMENT

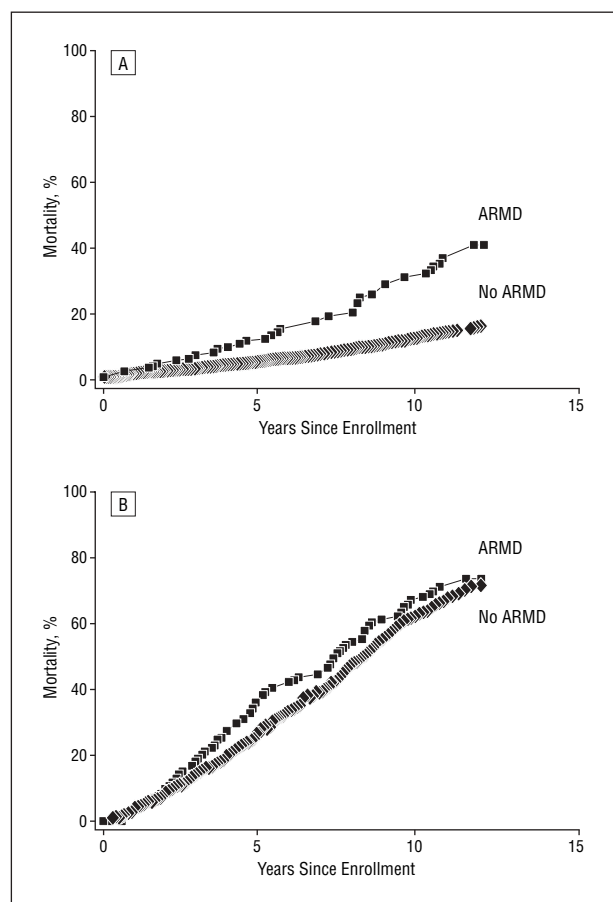
In this population-based study of older Australians, among individuals younger than 75 years we found that visual impairment significantly predicted higher all-cause mortality and that signs of ARMD significantly predicted higher all-cause and vascular mortality. However, the association of visual impairment and all-cause mortality among persons younger than 75 years became nonsignificant after adjusting for other potential economic and biological confounders, although reduced power could have contributed here. The ARMD-mortality associations in persons younger than 75 years remained significant after further adjustment for visual impairment, cataract, and other potential economic and biological

confounders. We found that any cataract and cortical, nuclear, and posterior subcapsular cataracts considered separately were significant predictors of all-cause mortality in the overall population. Any cataract significantly predicted vascular mortality in all persons 49 years and older even after accounting for visual impairment and other potential economic and biological confounders.

The association of visual impairment and mortality has been consistently reported from different populations.<sup>1-8</sup> Nevertheless, it remains unclear whether the observed association is due to residual confounding factors not completely adjusted for or whether there is a true, direct or indirect, link between visual impairment and mortality.

The implications of these findings also remain uncertain: whether such an association indicates that visual impairment, age-related eye disease, or both are markers of aging and frailty or whether these ocular conditions accelerate aging, thus leading to relatively earlier death in older persons. The present findings suggest that the association between visual impairment and all-cause mortality is mainly observed in persons younger than 75 years at baseline in the initial analysis considering the known potential risk factors associated with mortality. However, after also adjusting for other potential economic and biological confounders, this association became attenuated but remained in the same direction. This is an important finding given that a major proportion of visual impairment is due to treatable causes. In the older group, it could be likely that other age-related conditions dominate the effect on mortality.

Apart from residual confounding there are several possible hypothetical explanations for an apparent relationship between visual impairment and earlier mortality. Vi-



**Figure 2.** Age- and sex-adjusted all-cause mortality by age group and age-related macular degeneration (ARMD) status. Survival curves are shown for individuals younger than 75 years (A) and those 75 years and older (B) at baseline.

sual impairment is related to functional disability,<sup>32,33</sup> loss of independence, need for community support,<sup>34</sup> and reduced social interaction and depression.<sup>35-37</sup> Depression has been reported to predict cardiovascular mortality.<sup>38-41</sup> Accidents,<sup>42</sup> falls,<sup>43</sup> and fractures<sup>44</sup> could also be associated with visual impairment, which may be responsible in part for poor survival among persons with visual impairment. The present data on causes of death, however, do not support a likely role for falls and fractures in mortality. The reason for a low frequency of cancer-related mortality in persons with visual impairment is unclear. It is possible that this represents a chance finding or has resulted from confounding factors that we did not control for in this analysis.

In this study, findings of an association between ARMD and earlier mortality confirm previous findings from 2 studies: the Age-Related Eye Disease Study<sup>6</sup> and the Copenhagen City Eye Study.<sup>15</sup> In particular, we found that ARMD was a significant predictor of vascular mortality in persons younger than 75 years, and the association became attenuated after further adjustment for potential cardiovascular risk factors (triglyceride and fibrinogen levels) and socioeconomic factors. This finding seems to support the hypothesis that ARMD may share common antecedents with cardiovascular disease,<sup>45-47</sup> including chronic inflammation.<sup>48,49</sup> Systemic inflammation has been identified as a significant risk factor for the development of ARMD<sup>48</sup> and has also been associated with all-cause and cardiovascular mortality in the elderly.<sup>50-52</sup> The observed ARMD-mortality association in individuals younger than 75 years remained after also accounting for visual impairment and cataract in the models, suggesting that it was independent of the effects of decreased vision.

Most previous studies<sup>2,5,6,10,16-20</sup> have indicated an association between nuclear cataract (or cataract surgery) and mortality. Data from the Blue Mountains Eye Study 5-year follow-up<sup>1</sup> also indicated separate mortality asso-

**Table 4. 11-Year Risk of Mortality in Participants With Baseline Cataract**

Baseline Cataract	Participants at Risk, No.	Affected, No. (%)	HR (95% CI)			
			Age and Sex Adjusted	Model 1 <sup>a</sup>	Model 2 <sup>b</sup>	Model 4 <sup>c</sup>
<b>All-cause mortality</b>						
Any cataract	1198	519 (43.3)	1.27 (1.08-1.51)	1.32 (1.11-1.57)	1.31 (1.10-1.56)	1.26 (1.04-1.53)
Cortical cataract	810	358 (44.2)	1.24 (1.08-1.43)	1.28 (1.10-1.48)	1.27 (1.10-1.48)	1.15 (0.97-1.35)
Nuclear cataract	461	232 (50.3)	1.21 (1.02-1.45)	1.21 (1.00-1.46)	1.20 (0.99-1.45)	1.21 (0.98-1.49)
Posterior subcapsular cataract	213	100 (47.0)	1.40 (1.13-1.73)	1.46 (1.17-1.82)	1.43 (1.14-1.79)	1.34 (1.04-1.71)
Aphakia/pseudophakia	215	132 (61.4)	1.17 (0.96-1.41)	1.12 (0.90-1.39)	1.12 (0.90-1.38)	0.99 (0.78-1.30)
<b>Vascular mortality</b>						
Any cataract	1198	231 (19.3)	1.61 (1.21-2.15)	1.67 (1.24-2.25)	1.66 (1.23-2.24)	1.57 (1.13-2.19)
Cortical cataract	810	162 (20.0)	1.40 (1.12-1.74)	1.47 (1.16-1.86)	1.47 (1.16-1.86)	1.22 (0.94-1.59)
Nuclear cataract	461	108 (23.4)	1.37 (1.13-1.67)	1.40 (1.04-1.89)	1.40 (1.04-1.88)	1.48 (1.06-2.07)
Posterior subcapsular cataract	231	45 (19.5)	1.53 (1.11-2.09)	1.54 (1.09-2.17)	1.53 (1.08-2.17)	1.46 (1.00-2.12)
Aphakia/pseudophakia	215	58 (27.0)	1.08 (0.81-1.44)	1.16 (0.84-1.61)	1.14 (0.82-1.58)	1.01 (0.69-1.47)

Abbreviations: CI, confidence interval; HR, hazard ratio.

<sup>a</sup>Adjusted for age, sex, body mass index (<20 vs ≥30 [calculated as weight in kilograms divided by height in meters squared]), presence of hypertension and diabetes mellitus, current smoking, and baseline history of angina, stroke, or acute myocardial infarction.

<sup>b</sup>Adjusted for all factors in model 1 plus visual impairment.

<sup>c</sup>Adjusted for all factors in model 2 and triglyceride level, fibrinogen level, educational level, and walking disability.

ciations with nuclear, posterior subcapsular, and cortical cataract. In the present 11-year follow-up data, we found that any cataract and nuclear, posterior subcapsular, and cortical cataracts separately predicted all-cause and vascular mortality even after accounting for visual impairment. Reasons for the association with cataract, particularly for vascular mortality, are unclear, although the present findings are similar to the Beaver Dam Eye Study<sup>53</sup> finding of an association between nuclear cataract and stroke-related mortality and to the Framingham Study<sup>53</sup> findings of increased risk of cardiovascular events in diabetic individuals with cataract. In the large prospective Nurses Health Study,<sup>54</sup> a positive association between cataract surgery and coronary heart disease was observed (HR, 1.37; 95% CI, 1.13-1.66). It has been suggested that oxidative damage to lipoproteins, which may be involved in the etiology of cataract<sup>55</sup> and also an atherosclerosis risk factor,<sup>56</sup> could indirectly be responsible for the pathogenesis of coronary heart disease and vascular mortality.<sup>54</sup>

The lack of association between past cataract surgery and mortality in the present study is consistent with some previous studies.<sup>1,5,6</sup> This could be partly explained by the likely healthier lifestyle and health awareness among persons undergoing cataract surgery<sup>5</sup> and could provide evidence to support benefits from interventions to correct visual impairment in older persons.

The strengths of this study include its population-based sample with high participation, long-term follow-up, well-documented cataract and ARMD using photographic grading, and ascertainment of mortality and its causes using validated Australian National Death Index data. Limitations include the likelihood that some important confounding factors may not have been controlled for and that we cannot completely exclude the possibility of chance findings. The relatively small number of individuals younger than 75 years who had late ARMD in this cohort (n=12) represents an important limitation of this study. The possibility of chance findings will need to be excluded by future studies.

In summary, in this Australian population-based cohort we found that ARMD independently predicted all-cause and vascular mortality in persons aged 49 to 75 years and that cataract predicted mortality in persons 49 years and older. The visual impairment, ARMD, cataract, and mortality associations seemed to be independent of each other. Further studies are needed to confirm these findings, to clarify whether visual impairment in older persons accelerates aging and frailty, and to elucidate possible mechanisms for the association between ARMD and mortality and between cataract and vascular mortality. If a direct or indirect causal effect from visual impairment on earlier death is confirmed, regular assessment of vision in older persons may lead to early detection, facilitating treatments that could reduce the impact of visual impairment.

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**Correspondence:** Jie Jin Wang, MMed, PhD, Centre for Vision Research, Department of Ophthalmology, Westmead Millennium Institute, University of Sydney, West-

mead Hospital, Hawkesbury Road, Westmead, New South Wales, Australia 2145 (jiejn\_wang@wmi.usyd.edu.au).

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#### From the Archives of the Archives

Two new pedigrees are presented which lend support to evidence that retinoblastoma is a hereditary form of neoplasia. The first case was that of a girl aged 6 months. The diagnosis was bilateral retinoblastoma. There was minimal intraocular calcification in both eyes. Enucleation of the right eye was advised for pathologic study. The parents refused consent. In a twin sister, seen at the age of 11 months, a bilateral gray reflex had been observed at the age of 6 months. The diagnosis was bilateral retinoblastoma.

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