Age-Related Maculopathy: A Risk Indicator for Poorer Survival in Women

The Copenhagen City Eye Study

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Purpose: To examine patient survival in age-related maculopathy in a 14-year follow-up study.

Design: Population-based 14-year cohort study.

Participants: Nine hundred forty-six residents, aged 60 to 80 years, living in the Østerbro district of Copenhagen, Denmark, participated in the first examination conducted from 1986 to 1988. These participants were followed until death or until May 1, 2002, whichever came first.

Methods: Participants underwent an extensive ophthalmologic examination at Rigshospitalet, the National University Hospital of Copenhagen. Standardized protocols for physical examination, blood samples, and data from the National Central Person Register, the National Death Register, and the National Patient Register were used.

Main Outcome Measures: Mortality and age-related maculopathy.

Results: By May 1, 2002, 60.9% (577 of 946) of the participants of the baseline study cohort had died. The adjusted 14-year cumulative mortality hazard ratio for subjects with early and late age-related maculopathy at baseline was 1.26 (95% confidence interval [CI], 1.06–1.51). We identified a strong correlation between mortality and age-related maculopathy among women (relative risk, 1.59; 95% CI, 1.23–2.07) but not among men.

Conclusions: When adjusting for survival-related factors, age-related maculopathy is a significant risk indicator for poorer survival in women and may be a marker of underlying serious systemic factors or aging processes specific to women. *Ophthalmology 2005;112:305–312 © 2005 by the American Academy of Ophthalmology.*

Age-related maculopathy (ARM) is the predominant cause of visual loss in elderly persons in developed countries, including the countries of northern Europe.[1,2] Previous studies have suggested that visually disabled persons have a decreased survival rate.[3–8] However, little attention has been paid to the relationship between ARM and mortality.[3,4,8–12] Limited population-based data are available to assess whether ARM is associated with survival.[3,8,11,12] In the Beaver Dam Study,[3] data were based on a 4-year cumulative mortality rate of 9.5% (467 of 4926), 2 Australian studies reported on a 5-year cumulative mortality rate of 7.1% (231 of 3271)[12] and of 16.5% (604 of 3654), respectively,[8] whereas the Rotterdam Study[11] reported data based on a 7-year cumulative mortality rate of 21.4% (1359 of 6339). In all 4 studies, the association was not present after adjustment for survival-related factors. However, as previously suggested,[9] mortality may be related to ARM, because ARM may be associated with a major cause of death and thus may be an important marker of underlying comorbidity of serious extraocular diseases or general frailty. The association with mortality could play a role in cost-effectiveness studies of treatment or prevention of these conditions. Because this study is based on a 14-year cumulative mortality rate of 60.99% (577 of 946), it provides an opportunity to examine the relationship between ARM and survival.

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Materials and Methods

The study was approved by the Ethical Committee of Copenhagen, and informed consent was obtained from each participant. The methods used to identify and describe this population have been reported previously.[13]

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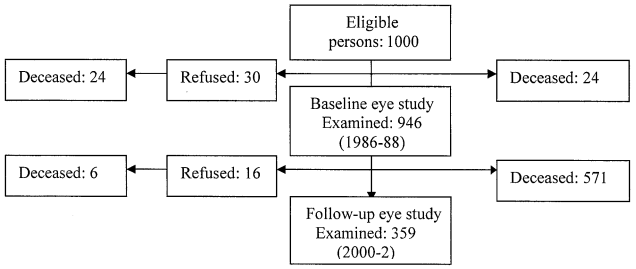

Figure 1. Schematic diagram shows participation in the baseline and follow-up eye examination and the number of deceased persons before May 1, 2002.

Study Population

The Copenhagen City Eye Study is a population-based survey of vision and common eye diseases in an urban population residing in the Copenhagen area. The baseline sample consisted of 1000 randomly selected, age- and gender-stratified subjects (age range, 60–80 years) from the Copenhagen City Heart Study Population. This basis population made up a random sample of 20 000 of 90 000 citizens from the Østerbro district of Copenhagen, with a response rate of 75%, and has been shown to be representative for the general Danish population.[14,15] Of the eligible 976 subjects, 946 (96.9%) participated in the baseline eye examination from 1986 through 1988.[13] Of these participants, 577 (60.9%) persons died during the follow-up period, before May 1, 2002 (Fig 1).

Data on the baseline ARM status were based on available gradable fundus photographs. Photographic documentation of the retinal status at baseline was available for 868 persons. Excluding persons with bilateral confounding lesions, a total of 866 persons of the 946 (91.5%) participants at the first examination provided data for the baseline ARM status (823 both eyes, 43 one eye).

Procedures

The questionnaire used in the study and the details of the ocular examination procedures were reported previously.[13] Briefly, a detailed questionnaire was administered that covered medications and the medical history of systemic disorders. Pertinent portions of the detailed eye examination at both visits consisted of taking color fundus 30° photographs centered on the macula.

Age-related maculopathy was graded according to a modified version of the Wisconsin Age-Related Maculopathy Grading System[16] to assess the presence and severity of lesions associated with ARM. All questionable and late-stage lesions were assessed in a blinded fashion by 1 of the authors (NVN).

Definitions

The definitions of ARM lesions closely followed the definitions developed by Klein et al.[17,18] More detailed descriptions of these lesions are presented elsewhere (unpublished data).[19] *Early* ARM was defined as the presence in the macular area of either soft indistinct drusen (≥63 μm, decreasing in density from the center to the periphery with fuzzy edges) or any distinct drusen plus pigmentary abnormalities (defined as retinal pigment epithelial depigmentation or increased retinal pigmentation). *Late* ARM was defined as the presence of exudative age-related macular degeneration (exudative ARM) or pure geographic atrophy. Exudative ARM included retinal pigment epithelial detachment, serous detachment of the sensory retina, retinal or subretinal hemorrhage, subretinal fibrous scars, or all of these. Pure geographic atrophy was defined by a retinal pigment epithelial atrophic area of 175 μm or more with visible choroidal vessels, sharp edges, circular shape, or all of these.

The ARM status was determined for the participants. When 2 eyes of a participant had lesions of different severity, the grade assigned to the participant was that of the worse eye. Furthermore, when signs of ARM could not be graded in an eye, the participant was assigned a score equivalent to that in the other eye.

Baseline Variables

Data on baseline best-corrected visual acuity and presence of any cataract was obtained from the baseline eye examination, and the methods used have been described previously.[13] Information on baseline cardiovascular risk factors and disease, alcohol intake, and socioeconomic status was obtained from the Copenhagen City Heart Study II and III data files; the procedures used has been described previously.[14,20] Cardiovascular risk factors were assessed by a self-administered questionnaire and by laboratory tests. Hypertension was defined as systolic blood pressure >140 mmHg, diastolic blood pressure >85 mmHg, use of antihypertensive drugs, or all of these. The body mass index (BMI) was calculated as the weight divided by the height squared (kg/m^2), and obesity was defined as a BMI of 27 kg/m^2 or more. Self-reported physical activity during leisure time was classified as sedentary (<2 hours per week), moderate (2–4 hours per week), and high (5 hours or more per week). Cardiovascular disease included data on ischemic heart disease, and stroke was based on a validated self-report by means of the National Patient Register. Alcohol consumption was classified according to weekly intake in 2 categories: 250 g/week or less (~3 drinks per day) and more than 250 g/week, according to the recommendations of the World Health Organization for men. Two self-reported socioeconomic status variables were included: educational level (<8 years of education, 8–10 years of education, and 11 or more years of education) and household income (low, <7000 Danish crone per month; medium, 7000–16,000 crone per month [i.e., US $1129–2580], and high, income > 16,000 crone per month [i.e., > US $2580]).

Mortality

Participants were followed from the first eye examination in 1986 to 1988 to the date of death, or May 1, 2002, whichever came first, using their personal identification number in the National Central Person Register. Data on the vital statistics of persons with photographic retinal documentation were almost complete (99.8%, 866 of 868).

Information on the causes of death was obtained from the Danish National Death Register. This information was available for persons who died before January 1, 2000. The diagnoses are registered after the World Health Organization's International Classification of Diseases, International Classification of Diseases 8 to the end of 1992, and Internation Classification of Diseases 10 from 1993. Data on causes of death were available for the 474 persons with baseline ARM data who died during the follow-up period before January 1, 2000. Of the 54 deceased persons with no available information on cause of death, 40.7% (22 of 54) had early or late ARM at baseline.

Statistical Methods

All tabulations and statistical analyses were performed with SAS[21] and Stata[22] software.

Comparisons of baseline characteristics between surviving participants and deceased persons were done with linear regression analysis and the Cochran-Mantel-Haenszel test of independence to

Table 1. Distribution of Baseline Characteristics among Participants and Deceased Nonparticipants in the Follow-up Study

	Survivors (N = 369)		Deceased (N = 577)		
Characteristics	*Crude %*	*N*	*Crude %*	*N*	P *Value**
Age at baseline (yrs)					
<65	61.5	227	38.7	223	
≥65	38.5	142	61.4	354	<0.001†
Gender					
Female	63.7	235	43.2	249	
Male	36.3	134	56.9	328	<0.001‡
Age-related maculopathy§					
None	81.6	252	63.7	355	
Early	17.2	53	31.4	175	<0.001
Late	1.3	4	4.8	27	
Hypertension					
No	33.1	122	19.6	113	
Yes	66.9	247	80.4	464	<0.001
Cardiovascular disease (ischemic heart disease and stroke)					
No	97.8	361	90.1	520	
Yes	2.2	8	9.9	57	<0.001
Diabetes					
No	98.9	365	94.3	544	
Yes	1.1	4	5.7	33	0.001
Smoking habits					
Never	30.3	111	16.6	96	
Ex-smoker	24.5	90	26.0	150	
Current	45.2	166	57.4	331	<0.001
Alcohol consumption					
≤250 gm/wk	95.9	354	90.1	519	
>250 gm/wk	4.1	15	9.9	57	0.04
Education					
≤7 yrs	46.7	172	55.1	318	
>7 yrs	53.3	196	44.9	259	0.01
Physical activity (hrs/wk)					
<2	11.9	44	21.1	122	
≥2	88.1	325	78.9	455	<0.001
Income (DKK/mo)					
<7.000	33.5	121	50.4	288	
≥7.000	66.5	240	49.6	283	<0.001

	N	Mean (Standard Deviation)	N	Mean (Standard Deviation)	P Value*
Age (yrs)	369	63.6 (5.0)	577	66.8 (5.6)	0.001†‡
Total plasma cholesterol (mmol/l)	364	6.2 (1.1)	573	6.2 (1.2)	0.36
Systolic blood pressure (mmHg)	369	143.9 (21.2)	577	149.9 (21.2)	0.009
Diastolic blood pressure (mmHg)	368	85.2 (12.4)	577	86.3 (11.8)	0.24
BMI (kg/m^2)	368	25.6 (4.0)	576	25.7 (3.9)	0.67

BMI = body mass index; DKK = Danish Crown.
*Comparison of participants with those who died before enrollment in the follow-up study.
†No age adjustment.
‡No gender adjustment.
§Data are based on the eye with the most evaluated according to the modified version of the Wisconsin Age-Related Maculopathy Grading System.

adjust for gender and age (divided into 2 age groups; <65 years and ≥65 years) with continuous (i.e., blood pressure) and categorical (i.e., ARM) characteristics. The continuous normalized data variables are presented as the means and standard deviations. Differences between continuous variables (i.e., mean age differences between participants and nonparticipants) were tested using *t* test analysis of variance. The categorical data were represented by frequency distributions. Fisher exact test was used when comparing groups of causes of death.

To assess the independent contribution of ARM, cataract, and visual loss to death, we used Cox's proportional hazards regression analysis, with age as the underlying time axis and delayed entry accordingly. The use of age as the underlying time scale ensured optimal adjustment for age in the analysis.[23,24] Relative risks were calculated as the proportional hazards ratios. Additional covariates measured at the baseline eye study or at the second or third Copenhagen City Heart Study examination were included as categorical variables to control for potential confounders: age, gender, smoking status, alcohol consumption, BMI, total cholesterol level, hypertension, cardiovascular disease, diabetes mellitus, any cataract, and visual loss (best-corrected visual acuity of ≤20/40 in the better eye). Test for trend and interaction was performed in the Cox model.

Table 2. Number (Percentage) of Deceased Subjects by Age-Related Maculopathy Status at Baseline by Gender

	Age-Related Maculopathy Status				
	No Age-Related Maculopathy	*Early Age-Related Maculopathy*	*Late Age-Related Maculopathy*	*Any (early or late) Age-Related Maculopathy*	*Total*
Gender	*N (n) %*	*N (n) %*	*N (n) %*	*N (n) %*	*N (n) %*
Women	293 (132) 45.1%	121 (88) 72.7%	17 (14) 82.4%	138 (102) 73.9%	431 (234) 54.3%
Men	314 (223) 71.0%	107 (87) 81.3%	14 (13) 92.9%	121 (100) 82.6%	435 (323) 74.3%
Total	607 (355) 58.5%	228 (175) 76.8%	31 (27) 87.1%	259 (202) 78.0%	866 (577) 64.3%

N = number of persons at baseline; (n) = number of deceased persons at follow-up; % = percentage of deceased subjects.

Results

During the follow-up period, a total of 577 persons of the 946 participants of the baseline examination died before May 1, 2002, (Fig 1) resulting in a 14-year cumulative mortality rate of 60.99%.

Comparison between Surviving and Deceased Persons

Comparisons between surviving and deceased participants of the baseline examination at the time of follow-up are presented in Table 1. The 577 deceased persons were more likely to be older and male than the 369 survivors. When controlling for age and gender, the deceased persons by the time of the follow-up study seemed to have had a highly significant poor prognosis at baseline compared with persons who were alive at the time of the follow-up study; that is, they were more likely at baseline to have early, as well as late, ARM lesions, hypertension, higher systolic blood pressure, diabetes, cardiovascular disease, a history of smoking, greater alcohol consumption, fewer years of education completed, and lower income and level of physical activity compared with persons who survived.

Association between Survival and Age-Related Maculopathy

Table 2 shows the ARM status at baseline associated with mortality. Of the 577 persons who died during follow-up, 202 persons had any ARM (early or late ARM) at entry. Of the 31 subjects with late ARM at baseline, 27 (87.1%) died, which was significantly higher than among subjects with no ARM at baseline (58.5%) ($P<0.001$).

Table 3 shows the mortality hazard ratios for subjects with ARM compared with those without ARM at baseline. The hazard ratios adjusted for age and gender for early or any (early or late) ARM, respectively, showed an association with mortality (early ARM, risk ratio [RR], 1.31; 95% confidence interval [CI], 1.09–1.57, any ARM, RR, 1.31; 95% CI, 1.11–1.57). Late ARM was not statistically associated with poorer survival (RR, 1.40; 95% CI, 0.94–2.08). However, a test for trend revealed increasing mortality with increasing severity of ARM (RR, 1.25; 95% CI, 1.08–1.44). After correction for further confounders (best-corrected visual acuity ≤20/40 in the better seeing eye, any cataract, smoking, alcohol consumption, BMI, total cholesterol level, hypertension, ischemic heart disease, stroke, diabetes mellitus), and, additionally, after correction for significant confounders, the strong association remained unchanged (RR, 1.26; 95% CI, 1.06–1.51). When repeating the multivariate tests for men and women separately, ARM was a significant predictor of mortality in women (any ARM [early or late], RR, 1.59; 95% CI, 1.23–2.07) but not in men (any ARM, RR, 1.02; 95% CI, 0.80–1.31). Furthermore, a significant interaction was found between any ARM and gender (RR, 0.67; 95% CI, 0.47–0.95, $P = 0.025$), establishing that ARM has a different impact on mortality between genders in our population.

Table 3. Mortality Hazard Ratios for Age-Related Maculopathy

	No (cases)	**Adjusted Hazard Ratio (95% Confidence Interval)**	**Adjusted Hazard Ratio* (95% Confidence Interval)**	**Adjusted Hazard Ratio† (95% Confidence Interval)**
Early ARM	866 (228)	1.31 (1.09–1.57)‡	1.23 (1.02–1.49)	1.26 (1.05–1.52)
Women	431 (121)	1.70 (1.29–2.23)§	1.60 (1.20–2.13)	1.59 (1.20–2.08)
Men	435 (107)	1.07 (0.83–1.38)§	0.97 (0.74–1.26)	1.02 (0.79–1.31)
Late ARM	866 (31)	1.40 (0.94–2.08)†	1.25 (0.84–1.87)	1.28 (0.86–1.90)
Women	431 (17)	1.78 (1.02–3.11)§	1.71 (0.97–3.01)	1.66 (0.95–2.90)
Men	435 (14)	1.12 (0.64–1.99)§	0.99 (0.55–1.77)	1.03 (0.58–1.82)
Any (early or late) ARM	866 (259)	1.31 (1.11–1.57)†	1.23 (1.03–1.48)	1.26 (1.06–1.51)
Women	431 (138)	1.70 (1.31–2.22)§	1.62 (1.23–2.12)	1.59 (1.23–2.07)
Men	435 (121)	1.08 (0.85–1.37)§	0.97 (0.76–1.24)	1.02 (0.80–1.31)

ARM = age-related maculopathy; No = number of persons.
All hazard ratios were calculated using Cox proportional hazard regression analysis.
*Adjusted for factors that have been correlated to both age-related maculopathy and mortality age, gender, smoking status, alcohol consumption, body mass index, total cholesterol level, hypertension, cardiovascular disease, diabetes mellitus, any cataract, visual loss (≤20/40).
†Adjusted for the significant correlated factors: age, gender, smoking status, hypertension, cardiovascular disease, and diabetes mellitus. Each of these factors was adjusted for in at least one of the analyses.
‡Adjusted for age and gender.
§Adjusted for age.

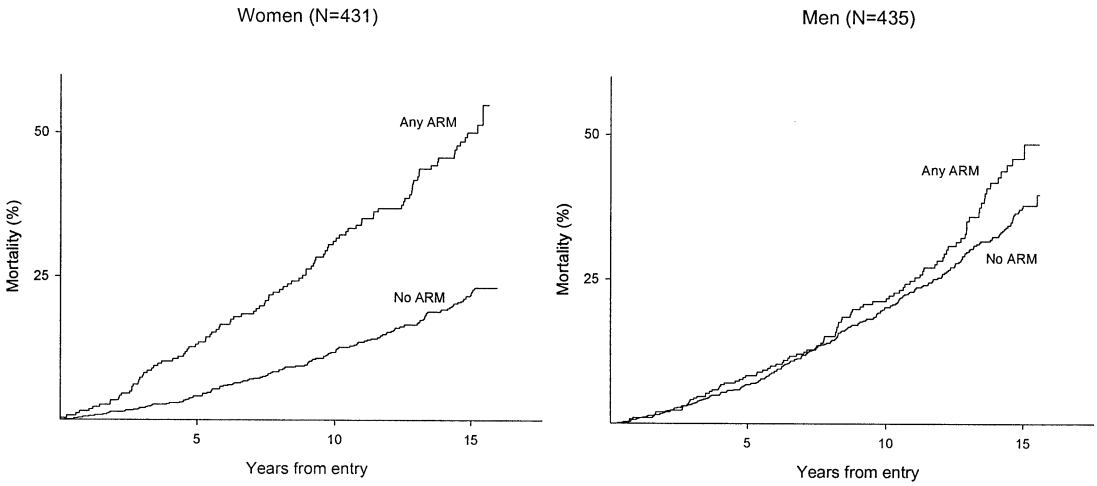

Figure 2. Mortality by gender and age-related maculopathy (ARM) status. Survival curves for 60- to 80 year-old subjects are shown. Any ARM = early or late age-related maculopathy.

Figure 2 shows the mortality curves by gender and ARM status at baseline.

Association between Survival and other Ocular Factors

Of the 577 persons who died during follow-up, 25 had visual loss (best corrected visual acuity of ≤20/40 in the better eye), and 210 had cataract (of any type including incipient cataract) at entry. The presence of visual loss (RR, 1.17; 95% CI, 0.78–1.75) or cataract (RR, 0.98; 95% CI, 0.82–1.17) was not associated with a higher mortality risk when controlling for age and gender. When repeating the tests for men and women separately, neither visual loss (women, RR, 1.13; 95% CI, 0.58–2.21, men, RR, 1.18; 95% CI, 0.68–2.04) nor cataract (women, RR, 1.02; 95% CI, 0.76–1.37, men, RR, 1,02; 95% CI, 0.80–1.32) was a significant predictor of mortality.

Causes of Death

The causes of death were compared between people with and without early and late ARM (Table 4). Death from respiratory conditions that included pulmonary disease caused by cardiac insufficiency were significantly higher in women with early and late ARM than in women without ARM at baseline (32% [28 of 87) vs. 19% [20 of 105), $P = 0.045$). However, women without ARM at baseline were more likely to have died from ischemic heart disease or stroke than women with early and late ARM (50% [52 of 105) vs. 32% [28 of 87), $P = 0.019$).

Discussion

This study offered a unique opportunity to examine the relationship between ARM and survival. This study had the longest follow-up period and thus the highest cumulative mortality rate published. In addition, the study was performed in an elderly population-based cohort in which ARM was assessed carefully with a stringent grading protocol. Moreover, our Danish registration system provided strength to our data collection.

This study demonstrated that any ARM (early or late ARM) was highly significantly associated with decreased survival in women but not in men. Women with any ARM at baseline had a 59% higher mortality risk than women

Table 4. Causes of Death by Baseline Age-Related Maculopathy Status.

	No Age-Related Maculopathy			Any (Early or Late) Age-Related Maculopathy		
Cause of Death	*All N* (%)*	*Men N* (%)*	*Women N* (%)*	*All N* (%)*	*Men N* (%)*	*Women N* (%)*
Ischemic heart disease or stroke	132 (44)	80 (41)	52 (50)	68 (35)	40 (47)	28 (32)
Cancer	105 (35)	79 (40)	26 (25)	48 (25)	21 (25)	27 (31)
Bronchial conditions	67 (22)	47 (24)	20 (19)	46 (24)	18 (21)	28 (32)
Accidents including suicide	12 (4)	3 (2)	9 (9)	6 (3)	3 (4)	3 (3)
Other	45 (15)	29 (15)	16 (15)	28 (14)	13 (15)	15 (17)
Total†	302	197	105	172	85	87

*Each person can have a maximum of 4 causes assigned in the registry. Therefore, the cause categories are not mutually exclusive, and the percentage distribution does not sum up to 100%.
†Total number of diseased persons with known causes of death.

without any ARM. No previous study has reported a gender-specific prognostic difference on survival imposed by ARM. All previous studies of the association between survival and ARM have reported relative risks for men and women combined.[3,8,9,11,12] Nevertheless, our results support the newly published results from the Age-Related Eye Disease Study study[9] and the univariate findings of the Rotterdam Study.[11] However, no previous population-based studies found an association between ARM and survival when correcting for survival-related factors.[3,8,11,12] The reason for the differences among studies is not apparent; however, differences in the length of the follow-up period, the mortality rate, the definitions of confounders, and the number of deceased persons between studies may explain some of the discrepancies.

Accordingly, the fact that the associations were present in the early and any ARM groups and not in the late ARM group may be explained by the higher power in the large early and any ARM groups compared with the small late ARM group. Our finding of a significant trend of increased mortality with increased ARM severity suggests that ARM may reflect the status of systemic processes associated with aging, being a marker of underlying serious somatic factors or diseases, which could be associated with increased physiologic aging and decreased survival in women. The fact that the association was only present among elderly women, of whom only 3 reported on use of postmenopausal exogenous estrogen substitution at baseline, suggests that low estrogen level may be a possible mediator for the underlying mechanisms. This is supported by previous studies reporting on women having a greater probability of ARM developing compared with men[25–27] and suggests that some hormonal factors may play a role in the pathogenesis. In addition, several associations between reproductive factors and a reduced risk of ARM developing have been found,[25,27–29] and estrogen has been suggested to lower the mortality among women.[30–32] The mechanism of these associations is unknown. However, the onset of menopause has been associated with a harmful impact on blood lipids, including lipoprotein (a).[32] These changes place elderly women at a higher risk for cardiovascular diseases[33] and possibly for ARM.[32] This may provide a biologically plausible theory of an association of estrogens, ARM, and mortality and may explain the association between ARM and decreased survival in postmenopausal elderly women.

However, our finding of an association between ARM and poor survival in women, but not in men, could be due to a number of possible reasons. First, residual confounding must be considered. Age-related maculopathy may be associated with underlying aging processes or systemic diseases specific to women, which relate to poor survival in women. Inadequate adjustment for age, cataract, and other confounding factors is likely to be, at least partly, the explanation for the association as previously suggested.[8] This is supported by the fact that the prevalence and incidence of ARM is strongly age-related[18,13,34–38] and that cataract, which frequently coexists with ARM,[39] has been associated with poor survival.[3,8,9,40–42] Although cataract was controlled for in the multivariate analyses, we may not have controlled entirely for its effect, because the lack of intervening examinations prevented us from including cases that had cataract develop after the baseline examination but before death. This may explain the lack of an association between poor survival and cataract in our analyses. However, the lack of an association may also be true or caused by cataract having risk factors that also affect mortality, such as age, as previously suggested.[11] Thus, although age and cataract were included in the Cox proportional hazards analysis, their effects may not have been entirely controlled for. Although many factors were included in the multivariate models, these may only be markers for underlying etiologic factors causing death. This leaves a possibility for unrecognized confounding not totally controlled for. These possible additional confounding factors remain unexplained. However, on the basis of Table 1, the person at risk of death in the presence of early or late ARM has hypertension, high serum cholesterol, cardiovascular disease, and diabetes, with unhealthy lifestyle habits, and low socioeconomic status. Nevertheless, because women without ARM were more likely to die from a cardiovascular disease, which supports a previous lack of association between cardiovascular disease and ARM,[43] these factors may not be cardiovascular. Conversely, because the method used for assigning causes of death is not standardized, it may be prone to misclassification because of lack of autopsy conclusions in most cases. Thus, care must be taken when drawing conclusions regarding causes of death reported in this study. Accordingly, the fact that women with ARM were significantly more likely to have a respiratory cause of death remains unexplained and might be the result of a type 1 error.

Second, possible intervening variables may be of importance linking ARM to poor survival in women. Accidents,[44] falls, and fractures,[45] functional disability caused by visual loss,[46–48] or depression[49,50] have been associated with poor survival and may also be associated with ARM. Our limited data on causes of death did not support accident-related factors to be intervening factors in our population. However, it is likely that older women with visual disability from ARM may be more likely to have depression than older visually impaired men with ARM. Previous findings of an association between visual impairment and poor survival[9,3–8,12,51]suggest that the same intervening pathway could link visual impairment and ARM to poor survival. This postulation is based on the fact that ARM and visual impairment are closely linked, because ARM accounts for the most visual impairment cases having similar impacts on daily living activities. However, we did not observe a relationship between visual loss and mortality, possibly owing to small numbers. Thus, it is possible that the association between ARM and poor survival is partly attributable to visual impairment resulting from ARM.

Third, the association may be spurious, mediated by chance finding only. A future population-based prospective cohort study with a long follow-up period of approximately 15 years will be able to confirm or refute our finding. The recommended sample size for detection of an association between ARM and survival with an α of 0.05 and power of

90%, is approximately 292 persons aged 60 to 80 years at baseline of whom 195 have died at follow-up.[52]

In conclusion, our data indicate that ARM may be a predictor of poorer survival in women. However, ARM is not likely to be a direct risk factor but rather a marker for underlying extraocular risk factors or diseases that also affect mortality. This possible relationship between ARM and mortality clearly warrants further study.

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