Age-Related Eye Disease, Visual Impairment, and Survival

The Beaver Dam Eye Study

Michael D. Knudtson, MS; Barbara E. K. Klein, MD, MPH; Ronald Klein, MD, MPH

Objective: To investigate the relationship of age-related maculopathy, cataract, glaucoma, visual impairment, and diabetic retinopathy to survival during a 14-year period.

Methods: Persons ranging in age from 43 to 84 years in the period from September 15, 1987, to May 4, 1988, participated in the baseline examination of the population-based Beaver Dam Eye Study (n=4926). Standardized protocols, including photography, were used to determine the presence of ocular disease. Survival was followed using standardized protocols.

Results: As of December 31, 2002, 32% of the baseline population had died (median follow-up, 13.2 years). After adjusting for age, sex, and systemic and lifestyle factors, poorer survival was associated with cortical cataract (hazard ratio [HR], 1.21; 95% confidence interval [CI], 1.06-1.37), any cataract (HR, 1.16; 95% CI, 1.03-1.32), diabetic retinopathy (HR per 1-step increase in 4-level severity, 1.36; 95% CI, 1.14-1.63), and visual impairment (HR, 1.24; 95% CI, 1.04-1.48) and marginally associated with increasing severity of nuclear sclerosis (HR, 1.07; 95% CI, 0.99-1.16). Age-related maculopathy and glaucoma were not associated with poorer survival. Associations tended to be slightly stronger in men than women.

Conclusions: Cataract, diabetic retinopathy, and visual impairment were associated with poorer survival and not explained by traditional risk factors for mortality. These ocular conditions may serve as markers for mortality in the general population.

Arch Ophthalmol. 2006;124:243-249

Author Affiliations:
Department of Ophthalmology and Visual Sciences, University of Wisconsin School of Medicine and Public Health, Madison.

MANY STUDIES HAVE investigated associations between ocular disorders and survival.[1-23] In general, persons with ocular disorders have been shown to have an increased mortality risk compared with persons without the disorders. These associations have been shown with cataract,[1,2,4,6,9,13-16,18-21] glaucoma,[7] diabetic retinopathy,[8,10,22,23] and visual impairment[4,9,11,12,17,19] and recently with age-related maculopathy (ARM).[3,4] In many instances, these associations can be explained by controlling for systemic mortality risk factors because ocular disorders are associated with these factors. However, some studies do not show associations with ocular disease and mortality.[2,5,19] Differences in study design, mortality follow-up, and definitions of these ocular conditions may explain some of these inconsistencies. In the present study, we extend a previous study of mortality and eye disease from our group[9] in the large population-based Beaver Dam Eye Study to 14 years of follow-up.

METHODS

SUBJECTS

The Beaver Dam Eye Study population has been described in detail elsewhere.[24] Briefly, a private census of the population of Beaver Dam, Wis, was performed from September 15, 1987, to May 4, 1988. Eligibility requirements for entry into the study included living in the city or township of Beaver Dam and being 43 to 84 years of age at the time of the census. A total of 5924 individuals were eligible to participate, of whom 4926 participated in the baseline examination between March 1, 1988, and September 14, 1990. Differences between participants and nonparticipants have been presented previously.[24] Follow-up examinations were conducted at 5 (n=3722) and 10 (n=2962) years after the baseline examination. Ninety-nine percent of the population was white. All data were collected with institutional review board approval in conformity with all federal and state laws, and the study was in adherence to the tenets of the Declaration of Helsinki.

PROCEDURES AND DEFINITIONS

Participants were examined at the study suite at a local hospital or nursing home. Height and body weight were measured with participants wearing light clothing and no shoes. The pulse rate was

measured. Blood pressure was measured with a random-zero sphygmomanometer according to the Hypertension Detection and Follow-up Program protocol,[25] and the average of the 2 measurements was used for analysis. Hypertension status was defined as a mean systolic blood pressure of 140 mm Hg or more, mean diastolic blood pressure of 90 mm Hg or more, or current use of antihypertensive medications. Nonfasting blood and urine specimens were collected. Measurements obtained included levels of serum cholesterol (total and high-density lipoprotein), glycosylated hemoglobin, random blood glucose, gross proteinuria, hematocrit, serum albumin, and serum creatinine and a white blood cell count.[26] Diabetes was defined as a history of diabetes or hyperglycemia. Hyperglycemia was defined as a glycosylated hemoglobin level of more than 2 SDs above the mean for the appropriate age and sex group or a casual blood glucose level of 200 mg/dL or more (≥1.1 mmol/L).[27]

A standardized questionnaire was administered to collect information on medical history, current medication use, smoking status, alcohol use, and physical activity.[26] A history of cardiovascular disease was defined as a history of angina, myocardial infarction, and/or stroke. Smokers were identified by answering yes to smoking at least 100 cigarettes in their lifetimes. Their status was further categorized as a current smoker if they had not stopped smoking at the baseline examination. Pack-years were defined as the number of packs smoked per day multiplied by the number of years smoked. Heavy drinkers were identified by answering yes to ever having a period in their life when they consumed 4 or more alcoholic beverages on a daily basis. Participants were asked if they engaged in a regular activity long enough to work up a sweat. Persons who on average engaged in such activities less than 3 times a week were considered to have a sedentary lifestyle.

Refraction and measurement of the visual acuity was performed using a modification of the Early Treatment Diabetic Retinopathy Study protocol.[28] Visual impairment was defined as a best corrected visual acuity of 20/40 or worse in the better eye and included eyes that were blind (visual acuity of 20/200 or worse).

The subjects' pupils were pharmacologically dilated, except for those persons with narrow anterior chamber angles. A slitlamp camera (Topcon SL; Topcon America Corp, Paramus, NJ) was used to obtain photographs of the lens of each eye.[29] These photographs were graded for the presence and severity of nuclear sclerosis.[29] Gradings of severity were assigned on a 5-step scale, and the presence of nuclear cataract was defined as level 4 or level 5. Anterior and posterior retroillumination photographs of the lens were obtained (Neitz CRT; Neitz Instruments Co, Ltd, Tokyo, Japan) and graded for the presence and severity of cortical and posterior subcapsular cataracts.[29] A measuring grid was used to divide the retroillumination photographs into a central circular area and 8 sectors of equal size. Cortical cataract was considered to be present if 5% or more of the lens surface was affected. Posterior subcapsular cataract was considered to be present if 5% or more of the surface area of any of the 8 sectors or the central circular area of the grid was involved. Any cataract was defined as the presence of nuclear, cortical, or posterior subcapsular cataract or if the lens had been removed during cataract surgery.

Stereoscopic 30° color fundus photographs centered on the disc (Diabetic Retinopathy Study standard field 1) and macula (Diabetic Retinopathy Study standard field 2) and a nonstereoscopic color fundus photograph temporal to but including the fovea of each eye were obtained.[28] Additional fundus photographs were obtained of any lesions found outside these fields (eg, diabetic retinopathy lesions).

Grading for ARM was performed in a masked fashion with use of the Wisconsin Age-Related Maculopathy Grading System.[30,31] The system assesses the presence and severity of 14 lesions associated with ARM. More details on these lesions appear elsewhere.[30,31] Individual lesions (eg, large drusen and retinal pigment epithelial depigmentation) were each investigated separately and as a 3-level severity scale of ARM. Persons with no or small drusen only and no pigment abnormalities were considered to have no ARM. Persons with signs of geographic atrophy or exudative macular degeneration (ie, retinal pigment epithelial detachment, subretinal hemorrhage, fibrous scar, or treatment) were considered to have late ARM. All other persons were considered to have early ARM.

The procedures to detect and define open-angle glaucoma have been described elsewhere.[32] Briefly, the presence of at least 2 of the 3 following criteria in the same eye was necessary for inclusion as a definite case of glaucoma: a visual field abnormality consistent with the diagnosis of glaucoma; a cup-disc ratio of at least 0.8 or asymmetry of at least 0.2 between the eyes; or an intraocular pressure of 21 mm Hg or greater. A history of using drops or having had surgery for glaucoma with or without any of the previous criteria was defined as a probable glaucoma case. For purposes of this analysis, probable and definite cases were combined.

Diabetic retinopathy was measured on an 18-level scale defined elsewhere.[33] The scale was reduced to a 4-level severity scale of no, mild, moderate, and proliferative retinopathy. Analyses of retinopathy are given only for subjects with diabetes.

Vital status was monitored by reading the obituaries of local newspapers and by making annual telephone contact. Persons not known to have died, but whom we could not reach, had their survival time entered as their last contact date. When a death was identified in the state of Wisconsin, a request was made to the Wisconsin Department of Health and Family Services, Division of Health Care Financing, Bureau of Health Information, Vital Records Section, for death certificate information about these persons. Names of persons known to have died outside of Wisconsin and those with whom we lost contact (no contact since December 31, 2002) but were not known to be dead were submitted to the National Death Index for matching against national death data. We ascertained mortality after the baseline 1988-1990 examination to December 31, 2002. Cause of death was defined as any contributing cause listed in the death certificate according to the codes of the *International Classification of Diseases, Ninth Revision (ICD-9)* for deaths before December 31, 1998, and *International Classification of Diseases, 10th Revision (ICD-10)* for deaths thereafter. Heart disease mortality was defined according to codes 391.0-398.9, 402.0-402.9, 404.0-404.9, and 410.0-429.9 from *ICD-9* and I01.0-I09.9, I11.0-I11.9, I13.0-I13.9, and I20.0-I51.9 from *ICD-10*. Cancer mortality was defined to include deaths according to codes 140.0-208.9 from *ICD-9* and C00.0-C97.9 from *ICD-10*. Stroke mortality was defined to include deaths according to codes 430.0-438.9 from *ICD-9* and I60.0–I69.9 from *ICD-10*.

STATISTICS

For the ocular conditions, when 2 eyes were discrepant in the presence of a lesion, the grade assigned for the person was that of the more severely involved eye. In contrast, we used the better-seeing eye to define visual impairment. We used SAS software, version 9, for all statistical analyses.[34] Simple statistics included computation of means, proportions, and χ^2 and unpaired *t* tests. For univariate analyses, estimates of survival were computed with the product-limit method of Kaplan and Meier. Tests of significance were performed with the log-rank test. Adjustments for age, sex, and other risk factors were made using Cox proportional hazards models. Including a squared or cubic term for age was not significant in the models. Similarly, adjustment for age using 4 age groups in 10-year bands was not as strong a predictor as using age linearly. Therefore, we determined that using age linearly was the most appropriate age adjustment. We tested the proportionality assumption by including an interaction between survival time and the risk factor of interest.[35]

Multivariate adjustment was investigated using several methods. First, a propensity score was determined for each of the ocular disease risk factors. The rationale and methods

Table 1. Characteristics of Population at Baseline by Survival Status: Beaver Dam Eye Study, 1988-1990

Characteristic	Survivors		Died		*P* Value
	No. of Subjects*	Mean (SD)	No. of Subjects*	Mean (SD)	
Age, y	3350	58.1 (9.6)	1576	70.4 (9.7)	<.001
Systolic blood pressure, mm Hg	3350	129.6 (19.0)	1573	137.6 (22.4)	<.001
Diastolic blood pressure, mm Hg	3350	78.5 (10.4)	1573	74.8 (11.7)	<.001
Serum total cholesterol level, mg/dL	3340	234.0 (43.0)	1566	233.0 (46.0)	.34
Serum HDL cholesterol level, mg/dL	3336	53.0 (17.0)	1567	50.0 (18.0)	<.001
Ratio of total-HDL cholesterol level	3335	4.89 (1.88)	1566	5.19 (2.12)	<.001
BMI	3341	28.8 (5.2)	1540	28.7 (5.8)	.83
Alcohol consumption, g/wk	3338	59.5 (127.7)	1564	43.9 (98.6)	<.001
Glycosylated hemoglobin level, %	3337	5.90 (1.31)	1566	6.57 (2.06)	<.001
Pulse rate, beats/min	3350	38.1 (5.6)	1574	38.5 (6.4)	.04
Pack-years smoked	3337	15.2 (23.2)	1557	23.0 (33.1)	<.001

	Survivors, No. (%)*	Died, No. (%)*	*P* Value
Male	3350 (42.0)	1576 (48.0)	<.001
Diabetes present	3336 (5.7)	1563 (16.3)	<.001
Hypertension present	3348 (44.7)	1569 (63.2)	<.001
Cardiovascular disease history present	3314 (8.6)	1541 (29.0)	<.001
Cancer history present	3345 (8.9)	1570 (18.2)	<.001
Emphysema history present	3340 (1.3)	1564 (7.4)	<.001
Gout history present	3343 (6.7)	1562 (11.1)	<.001
Arthritis history present	3335 (34.7)	1558 (46.9)	<.001
Gross proteinuria present	3336 (5.7)	1563 (16.3)	<.001
Sedentary lifestyle present	3350 (74.1)	1574 (82.1)	<.001
Current smoker	3348 (19.5)	1573 (20.1)	.68
Current heavy drinker	3345 (2.6)	1564 (1.9)	.17
Less than high school education	3347 (21.0)	1573 (46.9)	<.001
Current multivitamin use	3350 (25.3)	1576 (24.8)	.73
Current aspirin use	3346 (21.5)	1568 (27.9)	<.001
Current diuretic use	3304 (20.2)	1538 (41.7)	<.001

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters); HDL, high-density lipoprotein.
SI conversion factor: To convert cholesterol to millimoles per liter, multiply by 0.0259.
*Numbers vary because of missing data.

for using a propensity score are described elsewhere.[36-38] In brief, logistic regression was used to determine which characteristics were associated with ocular disease without regard to mortality. The conditional probability of the ocular disease given the observed covariates was output and stratified into quintiles. Cox proportional hazard models investigating ocular disease and mortality were then fit adjusting for the propensity score. Second, a stepwise procedure was used to determine nonocular risk factors for mortality. These models were further reduced to prevent overadjustment. For example, glycosylated hemoglobin level and diabetes status were both significantly associated with mortality. We chose to adjust for diabetes status only. However, reduced models were very similar to the models adjusting for all variables significantly associated with mortality. Some relationships were stronger in men than women, so analyses were run separately by sex. Additional stratified analyses were run for diabetes status and age (using 65 years of age as a cutoff).

RESULTS

By December 31, 2002 (median follow-up, 13.2 years), we confirmed by death certificate that 32% (n=1576) of the baseline cohort had died. Baseline characteristics of the population comparing survivors with those who have died are shown in **Table 1**. Those who died were more likely to be older; have higher systolic and lower diastolic blood pressures, lower high-density lipoprotein cholesterol levels, higher glycosylated hemoglobin levels, and a higher pulse rate; consume less alcohol; and have smoked more pack-years. In addition, those who died were more likely to be male; to have diabetes, hypertension, a history of cardiovascular disease, cancer, emphysema, gout, arthritis, gross proteinuria, a sedentary lifestyle, and less education; and to be currently using diuretics and aspirin.

Univariate analyses for eye disease and mortality showed that persons with cortical cataract, posterior subcapsular cataract, cataract surgery, glaucoma, visual impairment, and more severe levels of nuclear sclerosis, ARM, and diabetic retinopathy had greater mortality than persons without (**Table 2**). After controlling for age and sex, only increasing severity of nuclear sclerosis, cortical cataract, any cataract, diabetic retinopathy, and visual impairment were still significant (**Table 3** and **Figure 1**).

To further evaluate the relationships of ocular disease with mortality, we developed multivariate models using

Table 2. Ocular Conditions by Survival Status

Ocular Condition	No. (%) of Subjects		*P* Value
	Survivors	Died	
Nuclear sclerosis severity			<.001
Level 1	280 (8.6)	25 (1.8)	
Level 2	1571 (48.1)	295 (21.2)	
Level 3	1074 (32.9)	617 (44.3)	
Level 4	311 (9.5)	408 (29.3)	
Level 5	30 (0.9)	48 (3.5)	
Cortical cataract present	3273 (10.2)	1380 (29.2)	<.001
PSC present	3287 (3.7)	1393 (8.3)	<.001
Cataract surgery present	3350 (3.0)	1573 (11.1)	<.001
Any cataract present	3315 (21.0)	1497 (55.9)	<.001
Glaucoma present	3243 (3.0)	1370 (7.4)	<.001
Age-related maculopathy			<.001
None	2733 (83.2)	1026 (70.2)	
Early	527 (16.0)	382 (26.1)	
Late	25 (0.8)	54 (3.7)	
Diabetic retinopathy			.002
None	135 (71.0)	141 (57.3)	
Mild	36 (18.9)	66 (26.8)	
Moderate	19 (10.0)	31 (12.6)	
Proliferative	0	8 (3.3)	
Visual impairment present	3336 (1.9)	1561 (12.2)	<.001

Abbreviation: PSC, posterior subcapsular cataract.
*Numbers vary because of missing data.

2 different methods. First, a propensity score was calculated for each risk factor and then controlled for in Cox proportional hazards models. Second, a fully adjusted multivariate model was developed. A total of 27 characteristics of various medical and lifestyle characteristics (listed in Table 1) were considered, and after an extensive investigation it was determined that the nonocular correlates of death in the population included age, sex, gross proteinuria, history of cancer, body mass index (BMI), BMI^2, ratio of serum levels of total to high-density lipoprotein cholesterol, smoking, pulse rate, diabetes status, history of cardiovascular disease, sedentary lifestyle, education, and systolic blood pressure (data not shown). With the exception of nuclear sclerosis severity and diabetic retinopathy, the results were similar between the propensity and the multivariate models (Table 3). Cortical cataract, any cataract, and visual impairment were all significantly associated with increased mortality after both types of adjustment. Nuclear sclerosis severity remained significantly associated with increased mortality after adjusting for the propensity score but was marginally significant in the fully adjusted model. Diabetic retinopathy severity was marginally significant in association with mortality after adjusting for the propensity score and was significant in the fully adjusted model.

To evaluate these relationships further, we stratified analyses by sex, age (<65 vs ≥65 years), and diabetes status. When restricted to men only, the significant relationships shown in Table 2 remained significant. When restricted to women only, the relationships between cortical cataract (multivariate-adjusted hazard ratio [HR], 1.09; 95% confidence interval [CI], 0.92-1.30), any cataract (multivariate-adjusted HR, 1.12; 95% CI, 0.93-1.34), and visual impairment (multivariate-adjusted HR, 1.17; 95% CI, 0.93-1.46) were attenuated and no longer statistically significant. Restricting the cohort to persons younger than 65 years showed a significant relationship between visual impairment and decreased survival (multivariate HR, 2.18; 95% CI, 1.02-4.67) and a significant relationship of poorer survival with increasing severity of nuclear sclerosis (multivariate HR per 1-step increase in severity, 1.22; 95% CI, 1.03-1.43). Cortical cataract was not associated with mortality in this younger subgroup. Restricting the cohort to persons 65 years or older, the cortical cataract relationship remained; however, the visual impairment relationship was attenuated after multivariate adjustment (HR, 1.19; 95% CI, 0.99-1.43). When persons with diabetes were excluded, all significant relationships shown in Table 3 remained significant. Restricting the analysis to persons with diabetes (n=446), the only significant relationship was for increasing severity of diabetic retinopathy (Table 3).

Of the 1576 deaths, 56% had a mention of heart disease, 28% had a mention of cancer, and 13% had a mention of stroke on their death certificates. Cause-specific mortality was investigated in these 3 groups using the same methods described for all-cause mortality. A separate selection procedure was used for each cause of death to determine multivariate adjustment (results not shown). After multivariate adjustment, persons with ocular conditions generally had an increased specific-cause mortality risk; however, only a few relationships were statistically significant (**Figure 2**). Increasing diabetic retinopathy severity was associated with any mention of heart disease mortality (multivariate-adjusted HR, 1.53; 95% CI, 1.25-1.88), and increasing nuclear sclerosis severity was associated with any mention of stroke mortality (multivariate-adjusted HR, 1.29; 95% CI, 1.03-1.61). There were no significant associations between ocular conditions and cancer mortality.

COMMENT

By using standardized protocols for the examination, photography, and grading of ocular disease, the Beaver Dam Eye Study offers a unique opportunity to investigate ocular disease as a marker for mortality. Although a previous report of mortality in this population[9] included deaths through November 1993 (median follow-up, 4 years), the present analysis included an additional 9 to 10 years of follow-up and 1109 additional deaths. We had found that severity of nuclear sclerosis and visual impairment were associated with poorer survival, but that after controlling for multiple systemic and lifestyle factors, none of the associations were statistically significant. When we used the additional deaths and follow-up and investigated more detailed multivariate adjustments, we found similar associations. These relationships remained significant after adjusting for potential confounders and other risk factors for mortality, although for some analyses the association for nuclear sclerosis was marginally significant. In addition, the presence of cortical cataract and severity of diabetic retinopathy were associated with poorer survival in the current analysis.

Relationships between eye disease and mortality were stronger in men in our study. Women live longer and have a better chance of development of eye and other age-related comorbid conditions, whereas men die earlier in life and are more likely to have fewer comorbid condi-

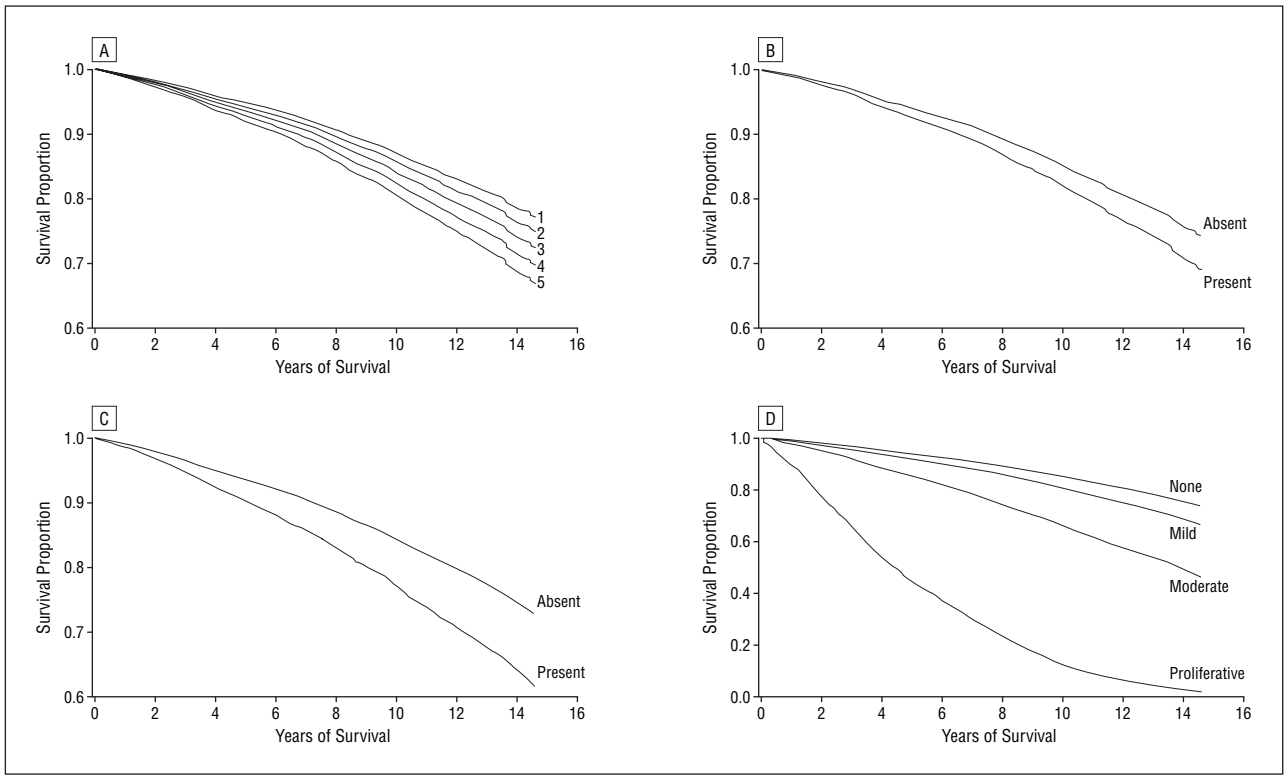

Figure 1. Age- and sex-adjusted survival curves are shown for nuclear sclerosis severity (A), cortical cataract (B), visual impairment (C), and diabetic retinopathy severity (D). For diabetic retinopathy, the population is restricted to 446 persons with diabetes at baseline, and the vertical axis is on a different scale compared with the other ocular conditions.

Table 3. Association of Ocular Variables With Decreased Survival

	Age and Sex Adjusted		Propensity Score Adjusted*		Full Multivariate Adjusted†	
Risk Factor	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Nuclear cataract present	1.11 (0.97-1.26)	.12	1.13 (0.99-1.28)	.07	1.09 (0.96-1.24)	.20
Nuclear sclerosis per 1-step increase in severity‡	1.11 (1.02-1.20)	.01	1.13 (1.05-1.22)	.002	1.07 (0.99-1.16)	.08
Cortical cataract present	1.22 (1.07-1.39)	.002	1.19 (1.05-1.34)	.007	1.21 (1.06-1.37)	.004
PSC present	1.12 (0.92-1.37)	.25	1.03 (0.85-1.25)	.74	1.07 (0.88-1.31)	.48
Cataract surgery present	1.12 (0.95-1.33)	.18	1.16 (0.98-1.36)	.09	0.92 (0.77-1.09)	.34
Any cataract present	1.28 (1.13-1.45)	<.001	1.24 (1.09-1.40)	<.001	1.16 (1.03-1.32)	.02
Glaucoma present	1.09 (0.88-1.34)	.44	1.12 (0.91-1.38)	.27	1.04 (0.84-1.28)	.74
ARM per 1-step increase in severity‡	0.97 (0.88-1.08)	.63	1.03 (0.94-1.14)	.51	0.97 (0.87-1.07)	.54
Diabetic retinopathy per 1-step increase in severity‡§	1.41 (1.18-1.67)	<.001	1.17 (0.99-1.39)	.07	1.36 (1.14-1.63)	<.001
Visual impairment present	1.42 (1.19-1.69)	<.001	1.51 (1.28-1.77)	<.001	1.24 (1.04-1.48)	.02

Abbreviations: ARM, age-related maculopathy; CI, confidence interval; HR, hazard ratio; PSC, posterior subcapsular cataract.

*Indicates a different set of covariates used for each risk factor, including age, sex, education, aspirin use, and smoking for nuclear cataract; age, sex, diabetes status, systolic blood pressure, and education for cortical cataract; age, smoking, diabetes status, and current use of medication for high blood pressure for PSC; age, smoking, diabetes status, diastolic blood pressure, proteinuria, arthritis, and aspirin use for cataract surgery; age, sex, smoking, emphysema, diabetes status, and history of heavy drinking for any cataract; age, sex, systolic blood pressure, and history of gout for glaucoma; age, cholesterol level, and history of heavy drinking for ARM; age, sex, diabetes status, smoking, education, and emphysema for visual impairment; and age, glycosylated hemoglobin level, proteinuria, total cholesterol level, systolic blood pressure, current aspirin use, and body mass index (BMI) for diabetic retinopathy.

†Indicates adjusted for age, sex, proteinuria, history of cancer, BMI, BMI^2, ratio of total to high-density lipoprotein cholesterol level, smoking, pulse rate, diabetes status, cardiovascular disease history, sedentary lifestyle, education, and systolic blood pressure.

‡Described in the "Procedures and Definitions" subsection of the "Methods" section and Table 2.

§Assessed in 446 persons with diabetes.

tions. Therefore, it is possible that other variables are more likely to confound a relationship between ocular disease and mortality in women than in men.

Associations between cataract and mortality have been investigated in many studies.[1,2,4,6,9,13-16,18-21] Nuclear sclerosis or mixed cataract types are more often associated with increased mortality risks than other types of cataract.[6,14,15,18,20,21] There was increased risk of overall mortality and stroke-related mortality with increasing severity of nuclear sclerosis in our study, although the relationship to nuclear cataract, the most severe categorization of sclerosis, was of borderline significance. The association between nuclear cataract and decreased

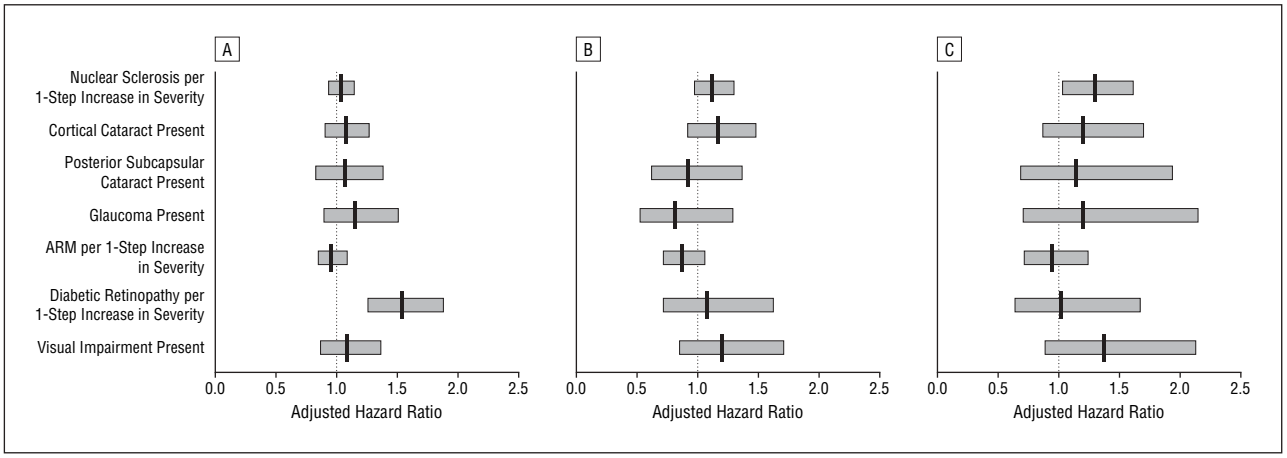

Figure 2. Multivariate-adjusted hazard ratios (and 95% confidence intervals) of ocular disease for specific-cause mortality are plotted for any mention of heart disease (A), any mention of cancer (B), and any mention of stroke (C). Hazard ratios for heart disease mortality were adjusted by age, sex, body mass index (BMI), BMI^2, ratio of total to high-density lipoprotein cholesterol level, smoking history, pulse, diabetes status, sedentary lifestyle, education, and systolic blood pressure. Hazard ratios for cancer mortality were adjusted by age, sex, BMI, BMI^2, cholesterol level, smoking history, pulse, and education. Hazard ratios were adjusted for stroke mortality by age, sex, BMI, BMI^2, proteinuria, systolic blood pressure, and diabetes status. ARM indicates age-related maculopathy. Increasing levels of severity of nuclear sclerosis, ARM, and diabetic retinopathy are described in the "Procedures and Definitions" subsection of the "Methods" section and in Table 2.

survival could be a result of changes in structural proteins that are ubiquitous throughout the body. Such changes have been hypothesized to result from oxidation,[13] the formation of disulfide binding,[18] or other age-related protein changes[39] that cause diminished function. Reasons for an association specifically with stroke death are unclear and may be a result of chance because specific-cause mortality may include some misclassification.

We found a significant association between cortical cataract and increased mortality, independent of other systemic risk factors. Only the Blue Mountains Eye Study[19] has previously reported this finding, but unlike our study, the association was no longer significant after excluding persons with diabetes. Among the personal and environmental risk factors associated with cortical cataract aside from age, diabetes has been the most consistent factor. Glycosylation of lens proteins may in part be responsible.[40] A level of glycemia below the cut point for overt diabetes may be sufficient to cause glycosylation of lens proteins. The level of glycemia in those not diagnosed as having diabetes has been shown to be associated with risk of death, usually caused by cardiovascular factors.[41,42] Also, UV light exposure appears to increase risk of cortical cataract.[43,44] Exposure to UV light can produce oxidative stress in the eye, resulting in cortical cataract; similar sensitivity to other systemic causes of oxidative stress may be a mechanism for increased systemic morbidity.[45,46] Finally, a genetic component to cortical cataract exists.[47] Genetic factors related to cortical cataract may also be linked to decreased longevity.

Other studies have shown an increased risk among persons who have undergone cataract surgery.[1,13,16] We did not find this in our study. It could be that persons who have had cataract surgery are more health conscious and have a healthier lifestyle than those who did not. For example, in our study persons who had undergone cataract surgery were more likely to be taking vitamin supplements (M.D.K., unpublished data, May 2005). Also, persons who have undergone cataract surgery may have better health care and may undergo cataract surgery with less severe lens changes than persons with poorer access to health care services.

Age-related maculopathy was not associated with mortality in the Rotterdam Eye Study[2] or the Blue Mountains Eye Study.[19] However, the Age-Related Eye Disease Study showed an increased mortality risk in persons with advanced-stage macular degeneration.[4] In addition, a recent study from the Copenhagen Eye Study showed an increased mortality risk in women but not men with ARM.[3] Data from our study suggest that there is no relationship between ARM and mortality. The low prevalence of late ARM or differences in cumulated mortality rates may explain some differences. We did not expect to find an association because data from the Beaver Dam Eye Study have shown that ARM is weakly and inconsistently associated with measures of frailty and not associated with cardiovascular disease, stroke, and cancer, the main causes of death.[48,49]

Diabetic retinopathy was significantly associated with mortality. Although our sample size was smaller, these results are consistent with those found in the Wisconsin Epidemiologic Study of Diabetic Retinopathy and other studies.[8,10,22,23] These data are consistent with the speculation that retinopathy severity may be a marker of similar microvascular disease affecting other organ systems in persons with diabetes (eg, heart and kidney).

Frailty has been shown to be a strong predictor of mortality.[50] Recent research has suggested that visual acuity is associated with other frailty markers (eg, handgrip strength and peak expiratory flow) and in itself may be considered another measure of frailty.[51] Therefore, it was not surprising that visual impairment was associated with poorer survival in our study. Decreased visual acuity was associated with mortality in other population-based studies such as the Blue Mountains Eye Study[19] and the Visual Impairment Project[12] and in the case-control arm of the Age-Related Eye Disease Study Clinical trial.[4] The visual system is part of the central nervous system. Retinal ganglion cells decrease in number with increasing age. Therefore, it is not surprising that decreased vision, as a reflection of biological aging independent of the specific age-related eye diseases, is independently associated with mortality.

The Beaver Dam Eye Study has many strengths for investigating relationships between ocular conditions and mortality, including the population-based design, large sample size, long-term follow-up, use of standardized procedures, and a moderately high mortality rate of 32%. However, we cannot exclude the possibility that some of the associations may be false. The conclusions regarding associations or lack of them must be drawn with caution for several reasons. First, uncontrolled confounding is likely to be at least partly the explanation for some of the associations. Eye conditions may only be markers for underlying etiologic factors causing death. Second, some associations may be due to a chance finding, given the relatively large numbers of associations examined. Third, the relatively low frequency of certain variables such as late ARM and outcomes such as stroke mortality limits the ability to detect or reject meaningful relationships because of low power. Fourth, it is possible that no relationships were found between some ocular factors and mortality because of survival bias because subjects who developed ocular factors that also predisposed them to death after the baseline examination were not included. Nevertheless, our data suggest that age-related cortical cataract, nuclear sclerosis severity, diabetic retinopathy, and visual impairment may serve as important markers for mortality in the general population.

Submitted for Publication: June 21, 2005; final revision received July 27, 2005; accepted July 29, 2005.
Correspondence: Michael D. Knudtson, MS, Department of Ophthalmology and Visual Sciences, University of Wisconsin Medical School, Madison, 610 N Walnut St, Fourth Floor WARF, Madison, WI 53726-2336 (knudtson@epi.ophth.wisc.edu).
Financial Disclosure: None.
Funding/Support: This study was supported by grant EY06594 from the National Institutes of Health, Bethesda, Md (Drs R. Klein and B. E. K. Klein).

REFERENCES

1. Benson WH, Farber ME, Caplan RJ. Increased mortality rates after cataract surgery: a statistical analysis. *Ophthalmology*. 1988;95:1288-1292.
2. Borger PH, van Leeuwen R, Hulsman CA, et al. Is there a direct association between age-related eye diseases and mortality? the Rotterdam Study. *Ophthalmology*. 2003;110:1292-1296.
3. Buch H, Vinding T, la Cour M, Jensen GB, Prause JU, Nielsen NV. Age-related maculopathy: a risk indicator for poorer survival in women: the Copenhagen City Eye Study. *Ophthalmology*. 2005;112:305-312.
4. Clemons TE, Kurinij N, Sperduto RD. Associations of mortality with ocular disorders and an intervention of high-dose antioxidants and zinc in the Age-Related Eye Disease Study: AREDS report No. 13. *Arch Ophthalmol*. 2004;122:716-726.
5. Grodum K, Heijl A, Bengtsson B. Glaucoma and mortality. *Graefes Arch Clin Exp Ophthalmol*. 2004;242:397-401.
6. Hennis A, Wu SY, Li X, Nemesure B, Leske MC; Barbados Eye Study Group. Lens opacities and mortality: the Barbados Eye Studies. *Ophthalmology*. 2001;108:498-504.
7. Hiller R, Podgor MJ, Sperduto RD, Wilson PW, Chew EY, D'Agostino RB. High intraocular pressure and survival. *Am J Ophthalmol*. 1999;128:440-445.
8. Klein R, Moss SE, Klein BE, DeMets DL. Relation of ocular and systemic factors to survival in diabetes. *Arch Intern Med*. 1989;149:266-272.
9. Klein R, Klein BE, Moss SE. Age-related eye disease and survival: the Beaver Dam Eye Study. *Arch Ophthalmol*. 1995;113:333-339.
10. Klein R, Klein BE, Moss SE, Cruickshanks KJ. Association of ocular disease and mortality in a diabetic population. *Arch Ophthalmol*. 1999;117:1487-1495.
11. Lee DJ, Gomez-Marin O, Lam BL, Zheng DD. Visual acuity impairment and mortality in US adults. *Arch Ophthalmol*. 2002;120:1544-1550.
12. McCarty CA, Nanjan MB, Taylor HR. Vision impairment predicts 5 year mortality. *Br J Ophthalmol*. 2001;85:322-326.
13. Meddings DR, Hertzman C, Barer ML, et al. Socioeconomic status, mortality, and the development of cataract at a young age. *Soc Sci Med*. 1998;46:1451-1457.
14. Minassian DC, Mehra V, Johnson GJ. Mortality and cataract: findings from a population-based longitudinal study. *Bull World Health Organ*. 1992;70:219-223.
15. Nucci C, Cedrone C, Culasso F, et al. Association between lens opacities and mortality in the Priverno Eye Study. *Graefes Arch Clin Exp Ophthalmol*. 2004;242:289-294.
16. Street DA, Javitt JC. National five-year mortality after inpatient cataract extraction. *Am J Ophthalmol*. 1992;113:263-268.
17. Taylor HR, McCarty CA, Nanjan MB. Vision impairment predicts five-year mortality. *Trans Am Ophthalmol Soc*. 2000;98:91-96.
18. Thompson JR, Sparrow JM, Gibson JM, Rosenthal AR. Cataract and survival in an elderly nondiabetic population. *Arch Ophthalmol*. 1993;111:675-679.
19. Wang JJ, Mitchell P, Simpson JM, Cumming RG, Smith W. Visual impairment, age-related cataract, and mortality. *Arch Ophthalmol*. 2001;119:1186-1190.
20. West SK, Munoz B, Istre J, et al. Mixed lens opacities and subsequent mortality. *Arch Ophthalmol*. 2000;118:393-397.
21. Williams SL, Ferrigno L, Mora P, Rosmini F, Maraini G. Baseline cataract type and 10-year mortality in the Italian-American case-control study of age-related cataract. *Am J Epidemiol*. 2002;156:127-131.
22. Davis MD, Hiller R, Magli YL, et al. Prognosis for life in patients with diabetes: relation to severity of retinopathy. *Trans Am Ophthalmol Soc*. 1979;77:144-170.
23. Sharma NK, Archer DB, Hadden DR, Merrett JD, Maguire CJ. Morbidity and mortality in patients with diabetic retinopathy. *Trans Ophthalmol Soc U K*. 1980;100:83-89.
24. Klein R, Klein BE, Linton KL, De Mets DL. The Beaver Dam Eye Study: visual acuity. *Ophthalmology*. 1991;98:1310-1315.
25. Hypertension Detection and Follow-up Program Cooperative Group. The hypertension detection and follow-up program. *Prev Med*. 1976;5:207-215.
26. Klein R, Klein BE. *The Beaver Dam Eye Study Manual of Operations*. Springfield, Va: US Dept of Commerce; 1991. NTIS accession No. PB91-149823.
27. Klein R, Klein BE, Moss SE. Diabetes, hyperglycemia, and age-related maculopathy: the Beaver Dam Eye Study. *Ophthalmology*. 1992;99:1527-1534.
28. Diabetic Retinopathy Study Research Group. Report No. 7: a modification of the Airlie House classification of diabetic retinopathy. *Invest Ophthalmol Vis Sci*. 1981;21(1, pt 2):1-226.
29. Klein BE, Klein R, Linton KL, Magli YL, Neider MW. Assessment of cataracts from photographs in the Beaver Dam Eye Study. *Ophthalmology*. 1990;97:1428-1433.
30. Klein R, Davis MD, Magli YL, Segal P, Klein BE, Hubbard L. The Wisconsin age-related maculopathy grading system. *Ophthalmology*. 1991;98:1128-1134.
31. Klein R, Klein BE, Linton KL. Prevalence of age-related maculopathy: the Beaver Dam Eye Study. *Ophthalmology*. 1992;99:933-943.
32. Klein BE, Klein R, Sponsel WE, et al. Prevalence of glaucoma: the Beaver Dam Eye Study. *Ophthalmology*. 1992;99:1499-1504.
33. Early Treatment Diabetic Retinopathy Study Research Group. Fundus photographic risk factors for progression of diabetic retinopathy: ETDRS report number 12. *Ophthalmology*. 1991;98:823-833.
34. SAS Institute Inc. *SAT/STAT User's Guide, Version 8*. Cary, NC: SAS Institute Inc; 1999.
35. Allison PD. *Survival Analysis Using the SAS System: A Practical Guide*. Cary, NC: SAS Institute Inc; 1995.
36. Cook EF, Goldman L. Performance of tests of significance based on stratification by a multivariate confounder score or by a propensity score. *J Clin Epidemiol*. 1989;42:317-324.
37. Drake C, Fisher L. Prognostic models and the propensity score. *Int J Epidemiol*. 1995;24:183-187.
38. Joffe MM, Rosenbaum PR. Invited commentary: propensity scores. *Am J Epidemiol*. 1999;150:327-333.
39. Boscia F, Grattagliano I, Vendemiale G, Micelli-Ferrari T, Altomare E. Protein oxidation and lens opacity in humans. *Invest Ophthalmol Vis Sci*. 2000;41:2461-2465.
40. Garlick RL, Mazer JS, Chylack LT Jr, Tung WH, Bunn HF. Nonenzymatic glycation of human lens crystalline. *J Clin Invest*. 1984;74:1742-1749.
41. Balkau B, Bertrais S, Ducimetiere P, Eschwege E. Is there a glycemic threshold for mortality risk? *Diabetes Care*. 1999;22:696-699.
42. Gerstein HC. Is glucose a continuous risk factor for cardiovascular mortality? *Diabetes Care*. 1999;22:659-660.
43. Cruickshanks KJ, Klein BE, Klein R. Ultraviolet light exposure and lens opacities: the Beaver Dam Eye Study. *Am J Public Health*. 1992;82:1658-1662.
44. Taylor HR, West SK, Rosenthal FS, et al. Effect of ultraviolet radiation on cataract formation. *N Engl J Med*. 1988;319:1429-1433.
45. Steinberg D, Parthasarathy S, Carew TE, Khoo JC, Witztum JL. Beyond cholesterol: modifications of low-density lipoprotein that increase its atherogenicity. *N Engl J Med*. 1989;320:915-924.
46. Witztum JL. The oxidation hypothesis of atherosclerosis. *Lancet*. 1994;344:793-795.
47. Iyengar SK, Klein BE, Klein R, et al. Identification of a major locus for age-related cortical cataract on chromosome 6p12-q12 in the Beaver Dam Eye Study. *Proc Natl Acad Sci U S A*. 2004;101:14 485-14 490.
48. Klein R, Klein BE, Knudtson MD. Frailty and age-related macular degeneration: the Beaver Dam Eye Study. *Am J Ophthalmol*. 2005;140:129-131.
49. Klein R, Klein BE, Tomany SC, Cruickshanks KJ. The association of cardiovascular disease with the long-term incidence of age-related maculopathy: the Beaver Dam Eye Study. *Ophthalmology*. 2003;110:1273-1280.
50. Klein BE, Klein R, Knudtson MD, Lee KE. Frailty, morbidity, and survival. *Arch Gerontol Geriatr*. 2005;41:141-149.
51. Klein BE, Klein R, Knudtson MD, Lee KE. Relationship of measures of frailty to visual function: the Beaver Dam Eye Study. *Trans Am Ophthalmol Soc*. 2003;101:191-196.