

Cause-Specific Visual Impairment and Mortality

Results From a Population-Based Study of Older People in the United Kingdom

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Objective: To assess the association between mortality and cause-specific visual impairment in older people.

Methods: Visual acuity and causes of visual impairment were collected in 13 569 participants 75 years and older participating in a randomized trial of health screening. Participants were followed up for mortality for a median of 6.1 years.

Results: Compared with those with 6/6 (or 20/20 Snellen) or better visual acuity, the age- and sex-adjusted rate ratio for visually impaired people (binocular visual acuity <6/18 or <20/60 Snellen) was 1.60 (95% confidence interval, 1.47-1.74), which was markedly attenuated (rate ratio, 1.17; 95% confidence interval, 1.07-1.27) after adjustment for confounding factors. People whose visual impairment was due to cataract or age-related macular degeneration had ex-

cess risks of all-cause and cardiovascular mortality, which disappeared after adjustment. People with refractive error remained at small risk, despite adjustment, probably owing to residual confounding from factors associated with minimal use of eye services rather than underlying eye disease. There were no associations with cancer mortality.

Conclusion: Associations reported for visual impairment and mortality or for specific causes of visual impairment reflect confounding by comorbidities, risk factors, and other factors related to susceptibility to death rather than an independent biological association of vision problems or specific eye diseases.

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STUDIES¹⁻⁸ HAVE REPORTED AN association between reduced visual acuity and increased mortality. The interpretation of this association remains unclear. If reduced visual acuity is causally related to an increased risk of death, this might reflect the presence of age-related eye diseases, particularly cataract or age-related macular degeneration (AMD), which may be a marker for more generalized biological aging. Studies have reported associations between mortality and cataract^{1,8-21} but not AMD.^{1,8,22} If age-related eye diseases are markers of aging, controlling for confounding factors, particularly chronic disease and indicators of frailty, should reduce or remove the observed association. Previous studies varied in the amount of information available on potential confounding factors, and the results have been conflicting. In the Beaver Dam Eye Study,⁸ visual impairment was associated with reduced survival, but after controlling for a range of systemic factors, the association was attenuated and became nonsignificant, with only severe nuclear sclerotic cataract showing a small association with reduced survival. Investigators for the Rotterdam Study²² and the Melbourne Visual Impairment Project⁴ reported no significant increase in risk with cataract (or with a specific type of cataract

in the latter study) or AMD after adjustment for other risk factors for mortality. Other studies^{1,4,15,19,20} reported that the association with mortality remains after controlling for different comorbid conditions. A further unresolved question relates to sex, with some studies reporting an increased mortality risk associated with cataract in women¹⁰ or with cataract and coronary heart disease in women²¹ but not in men.²³

We examined the mortality and cause-specific mortality risk associated with visual impairment as part of a large population-based trial of health screening of older people in the United Kingdom. In addition to having information about the underlying causes of visual impairment, we had detailed data on a broad range of potential confounding factors. Participants were considerably older than those included in the previously reported studies.

METHODS

MEDICAL RESEARCH COUNCIL TRIAL OF ASSESSMENT AND MANAGEMENT OF OLDER PEOPLE IN THE COMMUNITY

The Medical Research Council (MRC) trial of assessment and management of older people in the community is a cluster randomized trial comparing different methods of population-based

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multidimensional screening in people 75 years and older. Full details of the trial protocol have been published elsewhere.²⁴ A total of 106 general practices (family practices) from the United Kingdom MRC General Practice Research Framework were recruited to the trial. The sampling of practices was stratified by tertiles of the standardized mortality ratio (mortality experience of a local area relative to the national mortality) and the Jarman²⁵ score (a measure of area deprivation) to ensure a representative sample of the mortality experience and deprivation levels of general practices in the United Kingdom. Practices were randomized to 2 groups, universal vs targeted screening. In the universal screening group, all participants were invited to have a detailed health assessment by a study nurse that included visual acuity. All patients 75 years and older who were registered with participating general practices were included in the study unless they resided in a long-stay hospital or psychogeriatric care facility or were terminally ill. People in sheltered or residential housing for older persons were included. For the analyses presented herein, 368 people with severe dementia, defined as a Mini-Mental State Examination²⁶ score less than 12, were excluded because it was considered possible that their visual acuity measurements might be unreliable.

The baseline assessments were performed between 1995 and 1999. The study was approved by the relevant local research ethics committees of the participating practices.

ASSESSMENT OF PARTICIPANTS

People in the 53 general practices randomly allocated to the universal screening arm of the trial were given a visual acuity test as part of a detailed health assessment by the study nurse. Visual acuity was measured at 3 m with Glasgow acuity cards,²⁷ which measure the minimal angle of resolution on a logarithmic scale (logMAR). Binocular visual acuity was measured first, followed by visual acuity in the right and left eyes. All visual acuity measurements were conducted with usual spectacle correction. People with visual acuity of 0.5 (20/60 Snellen visual acuity) or more in either eye (equivalent to <6/18 [20/60 Snellen visual acuity]) were retested with a pinhole occluder. If visual acuity did not improve to less than 0.5 and the cause of visual loss had not previously been investigated, the person was referred to an ophthalmologist. If visual acuity improved to less than 0.5, the patient was advised to see an optometrist. All study nurses and nurse supervisors (responsible for quality control) attended a 2-day training session on the study procedures, which included training by 2 of us (J.R.E. and R.P.L.W.) and practice sessions in the use of the Glasgow acuity cards. In addition, nurse supervisors made visits every 3 months to each general practice during the year the assessment was carried out for quality assurance, including observation of the visual acuity testing.

The detailed assessment also covered a wide range of physical, social, and psychological problems. Potential confounders of any association between visual impairment (and underlying eye problems) and mortality were selected on the basis of previous findings in the literature, hypothesized associations based on known or postulated risk factors for eye diseases (such as smoking for cataract and AMD), markers of frailty and aging (such as low body mass index and functional impairments), and social and socioeconomic indicators that might reflect minimal contact with health services.

CAUSE OF VISUAL IMPAIRMENT

All 53 practices taking part in the universal screening arm of the trial were approached to take part in the study of the cause of visual impairment. Forty-nine general practices agreed to take part. Full details have been published elsewhere.²⁸ In brief, a list was compiled of visually impaired people (defined as having a base-

line binocular visual acuity <6/18 [logMAR (logarithm of minimum angle resolution) score ≥ 0.5]). Among people who achieved a pinhole visual acuity in either eye of 6/18 or better, the principal reason for visual impairment was refractive error, and further information on the cause of visual impairment was only sought for the remaining people who had no pinhole visual acuity or whose pinhole visual acuity did not improve to better than 6/18. The study nurse in each general practice was sent a list of people with visual impairment for their practice. The study nurse abstracted diagnostic information from the general practitioner's notes. This diagnostic information was obtained from correspondence between the hospital ophthalmologist and the general practitioner. The nurse used a form that included the date and source of correspondence, results of any visual acuity test, diagnosis, and treatment. The nurse also recorded the name and location of the last hospital ophthalmologist seen. All correspondence relating to eye disease was abstracted, including the correspondence resulting from the MRC Trial examination. The forms were returned to one of us (J.R.E.), who coded them twice. A maximum of 3 diagnoses was recorded. The main cause of visual impairment was considered the cause of visual loss in the eye that most recently had lost visual acuity. If the main cause of visual loss was unclear, the 2 main diagnoses were each assumed to contribute equally to the visual loss.

To validate the cause of visual loss obtained from coding the diagnostic information obtained from the general practitioner's notes, a 1-page questionnaire was sent to the hospital ophthalmologist who had last seen the patient. This questionnaire was in the form of a checklist by eye that covered AMD (exudative and geographic atrophy), cataract (age related, congenital, and other), glaucoma (primary open angle, primary closed angle, or both), diabetes mellitus (diabetic retinopathy and other), myopic degeneration, and "other." The ophthalmologist was asked to rank, if possible, any conditions noted in order of their contribution to the cause of visual loss. In addition, he or she recorded which eye most recently had lost visual acuity and the visual acuity at the last examination. Agreement between the ophthalmologists and study nurses as to the cause of visual loss was good ($\kappa=0.81$).

MORTALITY OUTCOME

Most participants (13 561/13 569 [99.9%]) were registered for mortality follow-up with the United Kingdom government's Office for National Statistics, which provided factual details and the cause of death (using *International Classification of Diseases, Ninth Revision [ICD-9]* and *Tenth Revision [ICD-10]* codes). Analyses presented in this article are based on deaths recorded up to July 31, 2003. Eighty-five percent of deaths were recorded using ICD-9 codes and 15% by ICD-10 codes. For the major causes of death examined in this article, there were no difficulties encountered in combining ICD-9 and ICD-10 codes.

STATISTICAL ANALYSIS

Analyses were performed using Stata 8 software,²⁹ considering the clustered design of the study (ie, general practice).³⁰ Poisson regression modeling was performed with all-cause, cardiovascular disease, and cancer mortality rates as the outcomes of interest. Initially, all-cause mortality rates by level of visual acuity (irrespective of cause) were modeled, with people having a visual acuity of 6/6 (20/20 Snellen) or better as the baseline reference group. Death rates among people with visual impairment (binocular visual acuity <6/18 not attributable to refractive error) compared with people with visual acuity of 6/6 or better were then modeled separately for the main causes of visual impairment, including refractive error, AMD, and cataract and other less common causes. Because some people with a history of cataract extraction may not have been visually im-

paired, people with any history of cataract irrespective of their visual acuity were compared with people with no history of cataract and visual acuity of 6/6 or better.

Age and sex were included as covariates at all stages. Potential confounding factors were the following: body mass index (lowest fifth), inability (worst fifth) to carry out activities of daily living (washing self, dressing self, cutting toenails, cooking, shopping, doing light housework, walking 50 yards [45.7 m], and going up and down stairs and steps), presence of a major illness at baseline (fractured hip, Parkinson disease, cancer, or depression requiring treatment), history of cardiovascular disease (probable angina on the Rose questionnaire³¹ or reported stroke or heart attack), diabetes mellitus, hypertension (reported or current systolic blood pressure >160 mm Hg or diastolic blood pressure >90 mm Hg), geriatric depression score of 6 or higher,³² daily urinary incontinence, Mini-Mental State Examination score (categorized as 12-17, 18-23, or 24-30), reported number falls in the previous 6 months (categorized as 0, 1, or ≥ 2), hearing problems (failed whispered voice test and not having a hearing aid), socioeconomic indicators (home owner, quintiles of the Carstairs deprivation score³³ derived from postcode linkage to 2001 census variables, and self-reported financial difficulties), self-reported health (excellent/very good, good, or fair/poor), low self-reported physical activity levels, smoking history (never, previous, or current), alcohol intake (never, previous, below the median, or above the median), and social isolation (rare contact with relatives and friends or recent bereavement). Testing for interaction by age and sex was undertaken using the final models obtained.

RESULTS

In the 49 general practices taking part in the study, 19 914 eligible persons were invited to have a health assessment, and 14 375 attended, for a response rate of 72.2%. Among people who responded, 500 had missing data on visual acuity, and an additional 306 persons scored less than 12 on the Mini-Mental State Examination, leaving 13 569 persons included in the analyses.

The mean age of participants was 81.1 years; 38.9% were men. Among 1632 persons (12.0%) who had a baseline binocular visual acuity less than 6/18, visual impairment was attributed to refractive error in 440 (27.0%), AMD in 479 (29.4%), cataract in 328 (20.1%), and other causes in 239 (14.6%). (Some participants had more than 1 diagnosis and were counted more than once.) The latter group comprised 64 persons with glaucoma, 29 with myopic degeneration, 26 with diabetic eye disease, 7 with vascular occlusion, and the rest with rarer conditions. Data were unavailable about the cause of visual loss for 285 persons (17.5%) with visual impairment.

Table 1 gives the distribution of baseline characteristics. Compared with persons with normal visual acuity, visually impaired people were older, were more likely to be female, and had poorer health across several conditions and diseases, including depression and cognitive function (low Mini-Mental State Examination score). Visually impaired people were more likely to report difficulties in performing activities of daily living, rate their health as poor, have low levels of physical activity, and live in areas of higher deprivation, and they were less likely to be home owners. These patterns were similar across the disease and condition groups. In age- and sex-adjusted analyses, there was a strong association be-

tween decreasing visual acuity and increasing mortality (**Table 2**). The rate ratios were substantially attenuated after adjustment for confounders, but a small excess risk remained significant for those with a visual acuity worse than 6/9 compared with those with normal visual acuity ($\geq 6/6$). In analyses by type of eye problem, increased risks of all-cause and cardiovascular mortality were observed for all eye problems, including refractive error and visual impairment in which the underlying problem could not be ascertained (**Table 3** and **Table 4**). Adjustment for potential confounding factors markedly reduced the rate ratios. For example, for all-cause mortality, the excess risk associated with AMD was reduced from 1.40 in an age- and sex-adjusted model to 1.01 (95% confidence interval [CI], 0.81-1.25) in a fully adjusted model. The fully adjusted rate ratio for cataract was 1.04 (95% CI, 0.84-1.28), and for other eye diseases it was 0.90 (95% CI, 0.72-1.12). A small excess risk remained for those whose cause of visual impairment could not be ascertained (rate ratio, 1.33; 95% CI, 1.02-1.75). Similar results were seen for cardiovascular mortality, with high age- and sex-adjusted ratios for different eye diseases much attenuated after adjustment for the full range of potential confounding factors. However, for those with refractive error and whose cause of visual impairment was unknown, an excess risk persisted after adjustment. There were no significant associations between type of eye disease and cancer mortality (**Table 5**). There was little evidence that any of these associations differed by age or sex. None of the interaction terms was statistically significant by adjusted Wald test, including (age [4 groups] or sex) \times (binocular visual acuity [4 groups] or [refractive error or AMD or cataract or other causes]). Approximately 30% of persons reported having had a cataract. Comparing persons who had reported a cataract or currently had a cataract vs persons who had not, the fully adjusted rate ratio was 0.99 (95% CI, 0.90-1.10).

COMMENT

Our study found a strong association between reduced visual acuity and mortality risk, which was markedly attenuated after controlling for a broad range of confounding factors. Previous studies also found an association between visual impairment and mortality. In the Melbourne Visual Impairment Project,⁴ visually impaired persons (visual acuity <6/12 [$<20/40$ Snellen]) had a 2-fold increased risk of death compared with persons not visually impaired (visual acuity $\geq 6/12$), although only a few potential confounding factors was considered. The results of that study also suggested that the highest risk was observed in persons with visual acuity ranging from less than 6/12 to 6/18 or better, with decreasing risk below that cutoff for poorer visual acuity. We found a small increasing mortality risk across the categories of worsening visual acuity. In common with other investigations, we explored whether the risk observed for visual impairment was due to the underlying eye disease or problem. In analyses adjusted for age and sex, we observed strong associations for AMD, cataract, and other ocular diseases with all-cause and cardiovascular mortality, but adjustment for confounders removed these associations. In the Rotterdam Study,²² an

Table 1. Characteristics of Participants by Visual Acuity and Eye Problem*

Characteristic	All Participants (N=13 569)	Normal Visual Acuity (n = 2722)†	Visually Impaired (n = 1632)‡	Refractive Error (n = 440)	Age-Related Macular Degeneration (n = 479)§	Cataract (n = 328)§	Other Causes of Eye Problems (n = 239)§	Cause of Eye Problem Unknown (n = 285)
Age, mean±SD, y	81.1 ± 4.6	79.0 ± 3.4	84.2 ± 5.3	83.0 ± 5.0	85.4 ± 5.1	84.4 ± 5.3	83.2 ± 5.0	85.0 ± 5.8
Male sex	5279 (38.9)	1301 (47.8)	484 (29.7)	140 (31.8)	133 (27.8)	88 (26.8)	82 (34.3)	85 (29.8)
Smoking history								
Never	5588 (41.2)	1055 (38.8)	752 (46.2)	194 (44.2)	214 (44.8)	167 (51.1)	107 (45.0)	138 (48.6)
Previous	6604 (48.7)	1412 (52.0)	682 (41.9)	184 (41.9)	204 (42.7)	131 (40.1)	108 (45.4)	114 (40.1)
Current	1362 (10.0)	249 (9.2)	194 (11.9)	61 (13.9)	60 (12.6)	29 (8.9)	23 (9.7)	32 (11.3)
Alcohol intake								
Never	2383 (17.7)	383 (14.2)	426 (26.3)	108 (24.8)	110 (23.2)	84 (25.7)	71 (29.8)	86 (30.5)
Previous	767 (5.7)	123 (4.6)	108 (6.7)	32 (7.4)	27 (5.7)	19 (5.8)	15 (6.3)	22 (7.8)
Current								
Below the median	7698 (57.2)	1569 (58.3)	842 (52.0)	223 (51.3)	258 (54.4)	192 (58.7)	109 (45.8)	141 (50.0)
Above the median	2613 (19.4)	616 (22.9)	242 (15.0)	72 (16.4)	79 (16.7)	32 (9.8)	43 (18.1)	33 (11.7)
Body mass index in the lowest fifth	2438 (18.0)	447 (16.4)	388 (23.8)	94 (21.4)	117 (24.4)	84 (25.6)	52 (21.8)	73 (25.6)
Diabetes mellitus	884 (6.5)	150 (5.5)	136 (8.3)	28 (6.4)	39 (8.1)	20 (6.1)	37 (15.5)	24 (8.4)
Cardiovascular disease	3031 (22.3)	527 (19.4)	411 (25.2)	97 (22.0)	118 (24.6)	100 (30.5)	70 (29.3)	64 (22.5)
Hypertension	7001 (51.6)	1352 (49.7)	832 (51.0)	215 (48.9)	252 (52.6)	177 (54.0)	135 (56.5)	127 (44.6)
Geriatric depression score ≥6	1036 (7.6)	122 (4.5)	211 (12.9)	41 (9.3)	67 (14.0)	39 (11.9)	30 (12.6)	48 (16.8)
History of falls								
1	1631 (12.0)	260 (9.6)	236 (14.5)	59 (13.4)	64 (13.4)	55 (16.8)	37 (15.5)	42 (14.7)
≥2	1108 (8.2)	133 (4.9)	213 (13.1)	47 (10.7)	62 (12.9)	43 (13.1)	30 (12.6)	50 (17.5)
Self-reported health								
Excellent/very good	6441 (47.7)	1511 (55.9)	612 (37.7)	197 (45.0)	170 (35.8)	123 (37.7)	76 (31.9)	101 (35.8)
Good	4988 (37.0)	936 (34.6)	640 (39.5)	159 (36.3)	197 (41.5)	123 (37.7)	98 (41.2)	112 (39.7)
Fair/poor	2069 (15.3)	257 (9.5)	370 (22.8)	82 (18.7)	108 (22.7)	80 (24.5)	64 (26.9)	69 (24.5)
Low self-reported physical activity level of not very much/not at all	3012 (22.2)	357 (13.1)	598 (36.6)	127 (28.9)	187 (39.0)	117 (35.7)	99 (41.4)	116 (40.7)
Daily urinary incontinence	981 (7.2)	127 (4.7)	166 (10.2)	40 (9.1)	43 (9.0)	38 (11.6)	29 (12.1)	32 (11.2)
Ability to carry out activities of daily living in the worst fifth	2232 (16.4)	186 (6.8)	588 (36.0)	111 (25.2)	196 (40.9)	118 (36.0)	97 (40.6)	119 (41.8)
Mini-Mental State Examination score								
12-17	628 (4.6)	55 (2.0)	216 (13.2)	26 (5.9)	81 (16.9)	33 (10.1)	37 (15.5)	59 (20.7)
18-23	2295 (16.9)	267 (9.8)	528 (32.4)	118 (26.8)	173 (36.1)	86 (26.2)	85 (35.6)	101 (35.4)
24-30	10646 (78.5)	2400 (88.2)	888 (54.4)	296 (67.3)	225 (47.0)	209 (63.7)	117 (49.0)	125 (43.9)
Major illness at baseline	3612 (26.6)	609 (22.4)	412 (25.2)	116 (26.4)	119 (24.8)	78 (23.8)	59 (24.7)	69 (24.2)
Hearing problems	1754 (12.9)	262 (9.6)	308 (18.9)	79 (18.0)	75 (15.7)	71 (21.6)	45 (18.8)	71 (24.9)
Social isolation								
Rare contact with relatives and friends	828 (6.1)	150 (5.5)	91 (5.6)	29 (6.6)	27 (5.6)	17 (5.2)	9 (3.8)	17 (6.0)
Recent bereavement	2253 (16.6)	423 (15.5)	297 (18.2)	90 (20.5)	90 (18.8)	55 (16.8)	40 (16.7)	49 (17.2)
Socioeconomic indicators								
Home owner	8661 (63.9)	1975 (72.6)	887 (54.4)	250 (56.8)	279 (58.2)	177 (54.0)	114 (47.7)	142 (49.8)
Carstairs deprivation score in the most deprived fifth	1319 (9.7)	211 (7.8)	177 (10.8)	48 (10.9)	43 (9.0)	40 (12.2)	27 (11.3)	35 (12.3)
Sheltered or residential housing for older people	1101 (8.1)	146 (5.4)	206 (12.6)	43 (9.8)	61 (12.7)	43 (13.1)	38 (15.9)	39 (13.7)

*Data are given as number (percentage) of participants unless otherwise indicated. Totals under some characteristics do not sum to the total numbers of participants because of missing data, in which case the percentages are derived from the totals under those characteristics.

†Binocular visual acuity of 6/6 (20/20 Snellen equivalent) or better.

‡Binocular visual acuity less than 6/18 (<20/60 Snellen equivalent).

§There were 139 participants with more than 1 diagnosis.

||The median alcohol intake was 4 units weekly.

association between AMD and mortality also disappeared after adjustment for several cardiovascular risk factors, including measures of atherosclerosis and cholesterol.

We found no evidence for an association of cataract with cancer mortality. In 4 studies^{1,8,19,20} among 5 that reported an association of cataract with mortality that persisted after adjustment for confounding, the association was not with cardiovascular mortality but with cancer or other causes of death. Only in the Nurses' Study was cataract associated with fatal and nonfatal coronary heart disease.²¹ The associations with cancer and other causes of death may therefore reflect residual confounding by

other factors related to these causes of death that were not controlled for in the analysis. It could be argued that a lack of specificity with cause of death makes an independent and causal association with cataract less plausible. Conversely, if cataract is regarded as one of a broad spectrum of age-related diseases, including cancer, that are due to common biological processes such as oxidative stress, associations with a range of causes of death might be expected. In our study and in the Blue Mountains Eye Study,¹ an increased mortality was observed for persons with correctable refractive error. We also found an increased risk of cardiovascular mortality for per-

Table 2. Rate Ratios for All-Cause Mortality by Level of Visual Acuity

Binocular Visual Acuity	No. of Participants	No. (%) of Deaths	Rate Ratio (95% Confidence Interval)		
			Adjusted for Age and Sex	Adjusted for Age and Sex for Participants With Full Data on Confounders*	Adjusted for Confounders*
≥6/6 (20/20 Snellen equivalent)	2722	919 (33.8)	1.00	1.00	1.00
<6/6 to ≥6/9 (20/30 Snellen equivalent)	3978	1540 (38.7)	1.10 (1.01-1.19)	1.06 (0.97-1.16)	1.01 (0.93-1.10)
<6/9 to ≥6/18 (20/60 Snellen equivalent)	5237	2568 (49.0)	1.32 (1.22-1.42)	1.24 (1.14-1.35)	1.10 (1.01-1.19)
<6/18	1632	998 (61.2)	1.60 (1.47-1.74)	1.52 (1.39-1.66)	1.17 (1.07-1.27)
Total	13 569	6025 (44.4)	... †	... †	... †

*Participants with missing data on confounders were excluded from this model, which was calculated on 10 364 participants.

†Ellipses indicate not applicable.

Table 3. All-Cause Mortality by Eye Problem in Participants With Visual Impairment Compared With Those With Normal Visual Acuity

Variable	No. (%) of Deaths	Rate Ratio (95% CI) Adjusted for Age and Sex	No. (%) of Participants With Full Data on Confounders	Rate Ratio (95% CI) Adjusted for Age and Sex for Participants With Full Data on Confounders*	Rate Ratio (95% CI) Adjusted for Confounders*
Binocular visual acuity ≥6/6 (n = 2722)	919 (33.8)	1.00	2207 (81.1)	1.00	1.00
Refractive error (n = 440)	258 (58.6)	1.54 (1.36-1.76)	299 (68.0)	1.49 (1.28-1.75)	1.18 (0.99-1.41)
AMD (n = 479) †	294 (61.4)	1.40 (1.20-1.63)	321 (67.0)	1.37 (1.15-1.62)	1.01 (0.81-1.25)
Cataract (n = 328) †	188 (57.3)	1.35 (1.14-1.59)	226 (68.9)	1.35 (1.13-1.61)	1.04 (0.84-1.28)
Other causes of eye problems (n = 239) †	139 (58.2)	1.48 (1.24-1.76)	146 (61.1)	1.32 (1.09-1.60)	0.90 (0.72-1.12)
Cause of eye problem unknown (n = 285)	198 (69.5)	1.92 (1.56-2.38)	164 (57.5)	1.88 (1.47-2.40)	1.33 (1.02-1.75)

Abbreviations: AMD, age-related macular degeneration; CI, confidence interval.

*Participants with missing data on confounders were excluded from this model, which was calculated on 10 364 participants.

†There were 139 participants with more than 1 diagnosis.

Table 4. Cardiovascular Mortality by Eye Problem in Participants With Visual Impairment Compared With Those With Normal Visual Acuity*

Variable	No. (%) of Deaths	Rate Ratio (95% Confidence Interval)		
		Adjusted for Age and Sex	Adjusted for Age and Sex for Participants With Full Data on Confounders †	Adjusted for Confounders †
Binocular visual acuity ≥6/6 (≥20/20 Snellen equivalent) (n = 2722)	412 (15.1)	1.00	1.00	1.00
Refractive error (n = 440)	124 (28.2)	1.76 (1.39-2.23)	1.84 (1.38-2.46)	1.37 (1.03-1.82)
AMD (n = 479) ‡	126 (26.3)	1.46 (1.20-1.78)	1.47 (1.14-1.90)	1.03 (0.72-1.45)
Cataract (n = 328) ‡	81 (24.7)	1.40 (1.06-1.85)	1.44 (1.06-1.96)	0.98 (0.65-1.48)
Other causes of eye problems (n = 239) ‡	61 (25.5)	1.69 (1.28-2.22)	1.47 (1.08-2.01)	0.87 (0.60-1.24)
Cause of eye problem unknown (n = 285)	89 (31.2)	2.25 (1.60-3.18)	2.52 (1.70-3.75)	1.81 (1.17-2.78)

Abbreviation: AMD, age-related macular degeneration.

*Cardiovascular deaths comprised "diseases of the circulatory system," *International Classification of Diseases, Ninth Revision* codes 390 to 459 and *Tenth Revision* codes 100 to 199.

†Participants with missing data on confounders were excluded from this model, which was calculated on 10 364 participants.

‡There were 139 participants with more than 1 diagnosis.

sons with refractive error that persisted after confounder adjustment. It is unlikely that the association of refractive error with mortality reflects biological aging but rather that uncorrected refractive error is indicative of minimal use of optometry services and associated with characteristics prognostic of death. A recent study³⁴ in the United Kingdom reported that 96% of older people

with visually impairing refractive errors had no contact with eye care services. Although we attempted to control for factors expected to be related to minimal health service use (such as social isolation and low socioeconomic status), we had no direct information about contact with optometry services and may have inadequately controlled for this. It is also possible that the associa-

Table 5. Cancer Mortality* by Eye Problem in Participants With Visual Impairment Compared With Those With Normal Visual Acuity

Variable	No. (%) of Deaths	Rate Ratio (95% Confidence Interval)		
		Adjusted for Age and Sex	Adjusted for Age and Sex for Participants With Full Data on Confounders†	Adjusted for Confounders‡
Binocular visual acuity $\geq 6/6$ ($\geq 20/20$ Snellen equivalent) (n = 2722)	247 (9.1)	1.00	1.00	1.00
Refractive error (n = 440)	41 (9.3)	1.42 (0.94-2.14)	1.27 (0.75-2.14)	1.12 (0.67-1.88)
AMD (n = 479)‡	37 (7.7)	1.07 (0.72-1.61)	1.06 (0.64-1.76)	0.83 (0.50-1.40)
Cataract (n = 328)‡	25 (7.6)	0.99 (0.65-1.53)	1.14 (0.71-1.82)	1.01 (0.61-1.66)
Other causes of eye problems (n = 239)‡	21 (8.8)	1.32 (0.80-2.20)	1.42 (0.90-2.23)	1.33 (0.78-2.29)
Cause of eye problem unknown (n = 285)	19 (6.7)	1.16 (0.71-1.90)	0.95 (0.46-1.98)	0.77 (0.35-1.68)

Abbreviation: AMD, age-related macular degeneration.

*Cancer deaths comprised "malignant neoplasms, including neoplasms of lymphatic and hematopoietic tissues," *International Classification of Diseases, Ninth Revision* codes 140 to 239 and *Tenth Revision* codes C00 to C97.

†Participants with missing data on confounders were excluded from this model, which was calculated on 10 364 participants.

‡There were 139 participants with more than 1 diagnosis.

tions between cataract and mortality reported in other studies reflect confounding by factors related to minimal use of health services. Persons with visually impairing unoperated cataracts have been shown to be of lower socioeconomic status and to have reduced contact with eye services in several developed countries,^{34,35} including the United Kingdom, where cataract surgery is free. In our study, we were unable to ascertain the cause of visual impairment in 285 persons. The excess mortality for this group persisted after adjustment for confounders. This group had a higher mortality than other groups, suggesting that the reason for nonascertainment of the cause of visual impairment was linked to poor health. This was confirmed by analyses that found no excess mortality risk for this group after excluding 10.0% of the population with the shortest follow-up (<1.8 years). We found no interaction between sex and mortality, in contrast to a previous United Kingdom study¹⁰ that found a higher mortality in nondiabetic women but not men. Again, we suggest that this may reflect factors associated with minimal health service use because a previous report from that study documented a higher prevalence of untreated visually impairing cataracts in women, with 88% of people with untreated cataracts having no contact with ophthalmic services.³⁴

Our population was 75 years and older (as this was the age criterion for the health screening trial), and in this age group the effects of eye diseases on mortality may be different from those at younger ages. This is unlikely to hold for AMD because most people with this condition are older. For example, in the Rotterdam Study,²² which recruited subjects 55 years and older, the mean age of participants with AMD was 82 years, similar to our study. The mean ages of participants in previous trials have been younger than in our study, although most included people in the same age range as ours. It is likely that the prevalence of comorbid conditions will be lower in studies with proportionately younger people and that the effects of confounding may be less. Studies also varied in the length of follow-up (a median of 6.1 years in our study and 2 years,²⁰ 4 years,¹⁹ 5 years,⁴ 6 years,¹ and 10 years¹⁵ in other studies). The effect

of comorbidity is most likely to be seen in studies with shorter follow-up. Conversely, for studies with longer follow-up, the information on baseline confounders may not reflect changes in these factors during follow-up and so may lead to misclassification of confounders. Most studies with a wider age range would lack power to examine whether the results varied according to age. In the Nurses' Study²¹ of more than 60 000 women (mean age, 53 years), cataract extraction in 2300 women would have had adequate power, but the study did not report the results by age group. Even in that study, with a much younger age group than ours, the effects of confounding were substantial, reducing the risk of mortality from 1.70 in the age-adjusted analyses to 1.37 in the multivariate analyses.

There are several limitations of our study. Other than a visual acuity test, we did not carry out detailed eye examinations of the trial participants; therefore, we have no information on persons with early lens opacities or age-related maculopathy that were not associated with visual impairment (binocular visual acuity <6/18). However, the literature does not suggest that there is an association of mortality with early signs of these conditions. In previous studies, age-related maculopathy, which includes early signs such as drusen and pigmentary irregularities, was not associated with mortality even in analyses adjusted only for age and sex.^{1,4,8,22} However, severe nuclear opacities^{8,20} and mixed lens opacities (an indication of severity)^{15,19} were associated with poorer survival, while the magnitude of association was weaker or nonexistent for earlier lens changes. We were unable to examine whether there were differences in mortality by type of cataract. Most previously reported associations with mortality have been with mixed opacities (always including nuclear opacities) or with nuclear opacities alone. Nuclear opacities are the most common type of opacities in white populations; therefore, it is likely that the type of cataract was nuclear in our predominantly white population. We attempted to minimize errors in measuring visual acuity through training the study nurses, with subsequent quality control. Although an ophthalmologist (R.P.L.W.) was present at the training sessions, we made no formal attempt to examine the inter-

rater agreement. We cannot exclude the possibility that some misclassification of visual acuity may have occurred. The fact that we demonstrated a dose-response effect of mortality by visual acuity group (categorized as $\geq 6/6$, $< 6/6$ to $\geq 6/9$ [$\geq 20/30$ Snellen], $< 6/9$ to $\geq 6/18$, and $< 6/18$) lends credibility to the findings. For the classification of ocular conditions, there was good agreement between the data extracted from the general practitioners' records and those of the hospital ophthalmologists, but again some misclassification may exist as to the main causes of visual impairment. It is implausible that any such misclassification of visual acuity or type of ocular condition would have been biased by outcome, as mortality was independently ascertained from national data. Any possible effect of misclassification would be to dilute the rate ratios toward the null. Bias due to misclassification of visual acuity or specific ocular conditions would not affect the findings that most of the excess risk in mortality associated with visual impairment can be explained by confounding factors. Information on all potential confounders included in the model was available for 76.4% of the cohort, but the age- and sex-adjusted rate ratios for those with full data and those with missing data on all confounders were similar.

A strength of our study was the size of the sample, the information about cause-specific mortality, and the detailed data on health and social status. The latter factor in particular allowed us to control for confounding more fully than many other studies. We conclude that the associations reported for visual impairment with mortality or for specific causes of visual impairment reflect confounding by comorbidities, risk factors, and other variables related to susceptibility to death rather than a true independent biological association with visual problems or specific eye diseases.

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