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Ocular diseases and 10-year mortality: The Beijing Eye Study 2001/2011

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ABSTRACT.

Purpose: **To examine the relationship between major ocular diseases and mortality.**

Methods: **The population-based longitudinal study Beijing Eye Study was performed in 2001 and repeated in 2011. The participants underwent a detailed ophthalmic examination at baseline in 2001.**

Results: **Of 4439 subjects examined in 2001, 2695 (60.7%) subjects returned for the follow-up examination in 2011, while 379 (8.5%) subjects were dead and 1365 (30.8%) subjects were alive, however, did not agree to be re-examined. In multivariate regression analysis, mortality was significantly associated with the systemic parameters of older age ($p < 0.001$; Odds ratio (OR): 1.07; 95% confidence interval (CI): 1.05, 1.09), male gender ($p < 0.001$; OR: 0.56; 95% CI: 0.40, 0.78), lower level of education ($p < 0.001$; OR: 0.66; 95% CI: 0.59, 0.74) and smoking ($p < 0.001$; OR: 1.84; 95% CI: 1.36, 2.49) and with the ocular parameters of presence of diabetic retinopathy ($p = 0.002$; OR: 2.26; 95% CI: 1.34, 3.81), non-glaucomatous optic nerve damage ($p = 0.001$; OR: 4.90; 95% CI: 1.90, 12.7) and higher degree of nuclear cataract ($p = 0.002$; OR: 1.29; 95% CI: 1.10, 1.52). In that model, mortality was not significantly (all $p > 0.05$) associated with refractive error, cortical or subcapsular posterior cataract, intraocular pressure, best corrected visual acuity, visual field defects, prevalence of age-related macular degeneration, retinal vein occlusions, open-angle glaucoma and angle-closure glaucoma.**

Conclusions: **After adjustment for age, gender, level of education and smoking, mortality was significantly higher in subjects with diabetic retinopathy, non-glaucomatous optic nerve damage and nuclear cataract. Other major ophthalmic parameters and disorders such as hyperopia, myopia, high myopia, pterygium, age-related macular degeneration, retinal vein occlusion, glaucoma and cortical or nuclear cataract were not significantly associated with mortality in the multivariate analysis.**

Key words: Beijing Eye Study – cataract – diabetic retinopathy – glaucoma – mortality – retinal vein occlusion

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Introduction

In contrast to disorders of vitally important organs such as heart or brain, diseases of small organs like ears and eyes are not directly related to sudden death. This does not imply, however, that ocular diseases are not associated with an increased mortality in the long term. Knowledge about a potential association between eye diseases and increased mortality is essential to forecast life-threatening conditions and to try to avoid the development of these. Previous studies have suggested that patients with glaucoma, subcapsular cataract, retinal vein occlusions and low vision in general may have an increased mortality (Borger et al. 2003; Cheung et al. 2007; Clemons et al. 2004; Cugati et al. 2007a,b; Foong et al. 2008; Freeman et al. 2005; Hirai et al. 2007; Juutilainen et al. 2007; Klein et al. 1995; Knudtson et al. 2006; Lee et al. 2002, 2006; McCarty et al. 2001; Mitchell et al. 2005; Ramrattan et al. 2001; Thiagarajan et al. 2005; Wang et al. 2001, 2008; Wong et al. 2003, 2007; Wu et al. 2008; Xu et al. 2007, 2009). Most of these studies were focused, however, on one ocular disease only; other potentially confounding factors such as socio-economic parameters were mostly not taken into account, and the follow-up period was relatively short. We therefore conducted a population-based study with a 10-year follow-up on subjects comprehensively examined for ocular disorders at baseline to assess which ocular diseases may lead to an increased mortality.

Methods

The Beijing Eye Study is a population-based study in Northern China. It was carried out in four communities in the urban district of Haidian in the north of Central Beijing and in three communities in the village area of Yufa

of the Daxing District south of Beijing. The study has been described in detail recently (Jonas et al. 2009; Xu et al. 2006; Xu et al. 2008). The Medical Ethics Committee of the Beijing Tongren Hospital approved the study protocol, and all participants gave informed consent according to the Declaration of Helsinki. At the time of the first survey in the year 2001, the seven communities had a total population of 5324 individuals aged 40 years or older. In total, 4439 individuals (2505 women) participated in the eye examination corresponding to an overall response rate of 83.4%. The study was divided into a rural part (1973 subjects; 1143 women) and an urban part (2466 subjects; 1362 women). The mean age was 56.2 ± 10.6 years (median: 56 years; range: 40–101 years). In the year 2011, the study was repeated by reinviting all participants from the survey from 2001 to be re-examined. Information about being alive or dead of subjects, who participated in the baseline survey in 2001 but did not participate in the follow-up examination in 2011, was obtained by house visits, by phone, by asking neighbours and by contacting the local municipal authorities.

All examinations were carried out in the communities, either in schoolhouses or in community houses. At the baseline examination in 2001, trained research technicians asked the study participants questions from a standard questionnaire providing information on demographic variables such as age, gender, known diagnosis and current treatment of arterial hypertension, arterial hypotension, diabetes mellitus, thyroid disorders, cerebral haemorrhages, coronary heart diseases and hyperlipidemia. The socio-economic status was assessed with questions for the level of education, occupation and family income. The level of education was categorized into the stages of 'illiteracy', 'half illiteracy with knowledge of some Chinese words', 'primary school education', 'middle school education' and 'college or higher education'. Individuals were classified as self-reported non-smokers or self-reported current smokers. Uncorrected visual acuity was measured (Snellen charts) in a distance of 5 m. Automatic refractometry (Auto Refractometer AR-610, Nidek Co., Ltd, Tokyo, Japan) was performed if uncorrected visual acuity was lower than 1.0. Visual field examinations were performed by frequency-doubling perimetry using the screening program C-20-1 (Zeiss-Humphrey, Dublin, California, USA). Intraocular pressure was measured using a non-contact pneumotonometer (CT-60 computerized tonometer, Topcon Ltd., Japan). A slit-lamp examination was carried out by an ophthalmologist, and the anterior chamber depth was assessed using van Herick's method (Van Herick et al. 1969). The pupil was dilated using tropicamide once or twice, until the pupil diameter was at least 6 mm. Digital photographs of the cornea and retro-illuminated photographs of the lens were taken using the Neitz CT-R camera (Neitz Instruments Co., Tokyo, Japan). Colour photographs (on film) of the macula and optic disc were taken using a fundus camera (Type CR6-45NM, Canon Inc. USA). Using the findings obtained during the clinical examination and the results of the assessment of the photographs, we checked for trachoma, pterygium, nuclear, cortical and posterior subcapsular cataract, glaucoma, non-glaucomatous optic nerve damage, age-related macular degeneration, diabetic retinopathy, retinal vein occlusions and any other haemorrhagic retinopathy (Xu et al. 2009). On the optic disc photographs, we additionally measured size of the optic disc, neuroretinal rim, optic cup and beta zone of parapapillary atrophy and the diameter of the retinal arteries and veins in the four vessel branches. For the evaluation of the retinal microvascular abnormalities, focal narrowing of arterioles, generalized narrowing of arterioles, sheathing of arterioles and arteriovenous crossing abnormalities (arteriovenous nicking) were assessed. The retinal vascular abnormalities including focal narrowing of arterioles and arteriovenous crossing abnormalities (arteriovenous nicking) were assessed using the protocol of the Atherosclerosis Risk in Communities Study.

Statistical analysis was performed using a commercially available statistical software package (SPSS for Windows, version 20.0, IBM-SPSS Inc. Chicago, IL, USA). Only one eye per subject was taken for statistical analysis to avoid a statistical bias. The eye with the more severe degree of the disease was chosen for the statistical analysis. Continuous data were presented as mean ± standard deviation. Logistic regression models were used to investigate the associations of mortality with systemic parameters such as age and level of education, and ocular parameters such as retinal microvascular abnormalities. All parameters used in the statistical analysis were assessed at the baseline examination in 2001. In a first step of the statistical analysis, we assessed associations between mortality and systemic or ocular parameters after adjusting for age, as mortality was highly significantly associated with higher age. In a second step, we carried out a multivariate analysis with mortality as dependent parameter and all parameters as independent parameters, for which the p-value of their association with mortality was ≤0.10 after adjusting for age. We then dropped those variables from the list of independent parameters which were no longer significantly associated with mortality in the multivariate analysis, starting with the variables with the highest p-values. Odds ratios (OR) were presented, and their 95% confidence intervals (CI) were described. All p-values were two-sided and considered statistically significant when less than 0.05.

Results

Of the 4439 subjects examined in the 2001, 2695 (60.7%) subjects returned for the follow-up examination, while 379 (8.5%) subjects were dead and 1365 (30.8%) subjects were alive, however, did not agree to be re-examined. The prevalence and means of the basic parameters as measured in 2001 are presented in Table 1.

Mortality was highly significantly associated with higher age ($p < 0.001$; OR: 1.11; 95% CI: 1.10, 1.13). As first step of the statistical analysis, we therefore adjusted mortality for age and searched for associations with additional parameters. It revealed that mortality adjusted for age was significantly correlated with the systemic parameters of male gender ($p < 0.001$), lower family income ($p < 0.001$), lower level of education ($p < 0.001$), rural versus urban region ($p < 0.001$) and current or former smoking ($p < 0.001$) and with the ocular parameters of low best corrected

Table 1. Associations between the 10-year mortality and ocular and systemic parameters in the Beijing Eye Study 2001/2011 after adjustment for age

Parameter	Prevalence/means	p-value	Regression coefficient	Odds ratio	95% confidence interval
Gender (male = 1; female = 2)	1928/2511	<0.001	−0.29	0.75	0.60, 0.94
Family income (Yuan)	1116 ± 3165	<0.001	−0.01	0.999	0.999, 0.999
Level of education (per one of 5 levels of education)	3.9 ± 1.1	<0.001	−0.38	0.69	0.63, 0.74
Region of habitation (rural/urban)	1973/2466	<0.001	−1.55	0.21	0.17, 0.27
Current or former smoking	29.0 ± 0.7%	<0.001	0.93	2.53	1.98, .25
Present smoking quantity (0/<10 cigarettes/10-20/20+)	0.43 ± 0.89	<0.001	0.21	1.24	1.10, 1.38
Former smoking quantity (0/<10 cigarettes/10-20/20+)	0.56 ± 0.98	<0.001	0.30	1.35	1.22, 1.49
Best corrected visual acuity (LogMAR)	0.08 ± 0.29	<0.001	0.57	1.76	1.35, 2.29
Visual field defects score	1.0 ± 4.8	<0.001	0.03	1.04	1.02, 1.05
Amount of nuclear cataract	12.9 ± 0.5%	<0.001	0.76	2.13	1.59, 2.87
Degree of subcapsular posterior cataract	3.3 ± 0.3%	0.03	0.58	1.79	1.07, 2.98
Optic disc area (mm^2)	2.61 ± 0.50	0.002	−0.42	0.66	0.50, 0.85
Neuroretinal rim area (mm^2)	1.97 ± 0.39	<0.001	−0.68	0.51	0.37, 0.68
Generalized retinal arteriolar narrowing	0.15 ± 0.48	0.008	0.37	1.45	1.10, 1.90
Diameter of temporal inferior retinal vein (mm)	0.154 ± 0.022	0.045	−7.44	0.001	0.00, 0.86
Prevalence of pterygia	1.6 ± 0.2%	<0.001	1.17	3.22	1.93, 5.37
Prevalence of open-angle glaucoma	2.2% ± 0.2%	0.003	0.58	1.79	1.23, 2.60
Prevalence of angle-closure glaucoma	0.9% ± 0.1	0.06	0.70	2.00	0.96, 4.19
Prevalence of non-glaucomatous optic nerve damage	1.1% ± 0.2%	<0.001	1.59	4.92	2.57, 9.43
Prevalence of diabetic retinopathy	3.7 ± 0.3%	0.006	0.50	1.65	1.15, 2.37
Refractive error (dioptres)	−0.39 ± 2.26	0.78			
Intraocular pressure (mm Hg)	16.1 ± 3.5	0.47			
Degree of cortical cataract	7.7 ± 0.4%	0.72			
Diameter of temporal inferior retinal artery	0.117 ± 0.17	0.41			
Diameter of temporal superior retinal artery	0.111 ± 0.016	0.59			
Diameter of nasal superior retinal artery	0.097 ± 0.015	0.14			
Diameter of nasal inferior retinal artery	0.094 ± 0.014	0.32			
Diameter of temporal superior retinal vein	0.147 ± 0.035	0.11			
Diameter of nasal superior retinal vein	0.114 ± 0.018	0.24			
Diameter of nasal inferior retinal vein	0.112 ± 0.018	0.53			
Arteriolar sheathing temporal inferior arcade	0.10 ± 0.49	0.80			
Arteriolar sheathing temporal superior arcade (degree)	0.04 ± 0.33	0.38			
Arteriolar sheathing nasal superior arcade (degree)	0.02 ± 0.25	0.84			
Arteriolar sheathing nasal inferior arcade (degree)	0.02 ± 0.25	0.86			
Arterio-venous nicking in the temporal inferior arcade (degree)	0.03 ± 0.24	0.65			
Arterio-venous nicking in the temporal superior arcade (degree)	0.10 ± 0.47	0.57			
Arterio-venous nicking in the nasal superior arcade (degree)	0.03 ± 0.22	0.91			
Arterio-venous nicking in the nasal inferior arcade (degree)	0.02 ± 0.18	0.99			
Parapapillary alpha zone area (mm^2)	0.51 ± 0.60	0.59			
Parapapillary beta zone area (mm^2)	0.39 ± 1.26	0.53			
Prevalence of retinal vein occlusions	1.4 ± 0.2%	0.78			
Prevalence of myopia (≤−1 Dioptre)	17.5 ± 0.6%	0.95			
Prevalence of myopia (≤−6 Dioptre)	2.8 ± 0.3%	0.74			
Prevalence of myopia (≤−8 Dioptre)	1.6 ± 0.2%	0.45			
Prevalence of early age-related macular degeneration	5.3 ± 0.3%	0.83			
Prevalence of late age-related macular degeneration	0.3 ± 0.1%	0.89			

visual acuity ($p < 0.001$), higher visual field defect score ($p < 0.001$), higher degree of nuclear cataract ($p < 0.001$) and subcapsular posterior cataract ($p = 0.03$), smaller neuroretinal rim ($p < 0.001$), smaller optic disc ($p = 0.002$), generalized retinal arteriolar narrowing ($p = 0.008$), smaller diameter of the temporal inferior retinal vein ($p = 0.045$), higher prevalence of pterygia ($p < 0.001$), open-angle glaucoma ($p = 0.03$), non-glaucomatous optic nerve damage ($p < 0.001$) and diabetic retinopathy ($p = 0.006$) (Table 1).

After adjustment for age as measured at baseline, mortality was not significantly associated with refractive error ($p = 0.78$), intraocular pressure ($p = 0.47$), higher amount of cortical cataract ($p = 0.72$), diameters of the temporal inferior retinal artery ($p = 0.41$), temporal superior retinal artery ($p = 0.22$), nasal superior retinal artery ($p = 0.14$), nasal inferior retinal artery ($p = 0.32$), temporal superior retinal vein ($p = 0.11$), nasal superior retinal vein ($p = 0.24$) and nasal inferior retinal vein ($p = 0.53$), degree of arterio-venous nicking in the temporal inferior arcade ($p = 0.65$), temporal superior arcade ($p = 0.57$), nasal superior arcade ($p = 0.91$) and nasal inferior arcade ($p = 0.99$), arteriolar sheathing in the temporal inferior arcade ($p = 0.80$), temporal superior arcade ($p = 0.38$), nasal superior arcade ($p = 0.84$) and nasal inferior arcade ($p = 0.86$), alpha zone of parapapillary atrophy ($p = 0.59$), beta zone of parapapillary atrophy ($p = 0.53$), prevalence of angle-closure glaucoma ($p = 0.06$), retinal vein occlusions ($p = 0.78$), myopia (defined as a myopic refractive error of ≤−1 dioptres)

($p = 0.95$), myopia of ≤ -6 dioptres ($p = 0.74$) and myopia of ≤ -8 dioptres ($p = 0.45$) and early ($p = 0.83$) or late ($p = 0.89$) age-related macular degeneration (Table 1).

As second step of the statistical analysis, we carried out a multivariate analysis as described above. Step by step, we dropped from the list of independent variables the parameters of generalized vessel narrowing, perimetric score, best corrected visual acuity, prevalence of pterygium, temporal inferior vein diameter, subcapsular posterior cataract, disc area, neuroretinal rim area, prevalence of open-angle glaucoma and prevalence of angle-closure glaucoma. We finally arrived at a model in which mortality was significantly associated with older age ($p < 0.001$), male gender ($p < 0.001$), lower level of education ($p < 0.001$), former or ever smoking ($p < 0.001$), presence of diabetic retinopathy ($p = 0.002$), presence of non-glaucomatous optic nerve damage ($p = 0.001$) and higher degree of nuclear cataract ($p = 0.002$).

Discussion

In our 10-year population-based follow-up study, mortality was significantly associated with the presence of diabetic retinopathy, presence of non-glaucomatous optic nerve damage and more pronounced nuclear cataract after adjusting for the systemic parameters of older age, male gender, lower level of education and smoking. In this multivariate model, mortality was not significantly (all $p > 0.05$) associated with other major ophthalmic parameters and disorders such as hyperopia, myopia, high myopia, pterygium, age-related macular degeneration, retinal vein occlusion, glaucoma and cortical or subcapsular posterior cataract.

With respect to the systemic factors of age, male gender, smoking and lower socio-economic status as measured by the level of education, the findings of our study confirm previous investigations in which these systemic parameters were significantly associated with mortality. With respect to diabetic retinopathy, our study confirms previous population-based studies such as the Blue Mountains Eye Study and the Beaver Dam Study on other ethnic groups in which diabetic retinopathy was correlated with an increased risk of mortality (Cugati et al. 2007a).

A factor added to the list of ocular factors associated with mortality was the presence of non-glaucomatous optic nerve damage. In the multivariate analysis, subjects with non-glaucomatous optic nerve damage had a higher mortality than those with a healthy appearance of the optic nerve head on the optic disc photographs. Reason for the association may be the various causes for non-glaucomatous optic nerve atrophy such as retinal microinfarcts in the retinal nerve fibre layer, temporary retinal arterial occlusions and neurological disorders. It may indicate that clinically the ophthalmoscopic visibility of the retinal nerve fibre layer, the thickness of the retinal nerve fibre layer as measured by optical coherence tomography and the pallor of the neuroretinal in the optic nerve head may be taken as hints for the general condition of the subject.

The results of our 10-year follow-up study mostly agree with the findings obtained in the previous 5-year follow-up study of the Beijing Eye Study 2001/2006 with respect to the association between an increased mortality and the presence of diabetic retinopathy and of non-glaucomatous optic nerve damage. In previous hospital-based studies and investigations with a shorter follow-up, it has remained unclear so far whether the presence of open-angle glaucoma is a risk factor for mortality. In our study population, after adjusting for age, the presence open-angle glaucoma was significantly ($p = 0.003$) associated with higher mortality, while the prevalence of angle-closure glaucoma showed a tendency ($p = 0.06$) of an association. If, however, an additional adjustment for the systemic risk factors of male gender, lower educational level and smoking was carried out, neither the presence of open-angle glaucoma nor of angle-closure glaucoma were factors associated with higher mortality (Table 2). One may argue that glaucoma-related defects in the visual field may increase the risk of accidents as has also been shown in the Rotterdam study (Ramrattan et al. 2001). Interestingly, increased mortality was significantly associated with a decreased best corrected visual acuity ($p < 0.001$) and increased visual field defects ($p < 0.001$) after adjusting for age in our study (Table 1).

In contrast to the 5-year follow-up of the Beijing Eye Study and in contrast to other studies (Cugati et al. 2007a; Xu et al. 2009), retinal vein occlusions were not significantly associated with increased mortality in the multivariate analysis in our study population. The reason for the difference in this finding between the studies has remained elusive. The 10-year mortality rate of 8.5% in our present study agrees well with the mortality of 3.2% of the same population within a 5-year follow-up period (Xu et al. 2009).

There are limitations of the present study. First, as in any population-based study, non-participation can be of major concern. In the Beijing Eye Study, at the time of the survey in the year 2001, 4439 individuals of 5324 invited individuals participated in the study, resulting in a participation rate of 83.4%. Of these 4439 subjects, 2695 subjects or 60.7% of the participants of 2001 returned for the re-examination in the year 2011, while 379 (8.5%) subjects were dead, and 1365 (30.8%) subjects were alive, however, did not agree to be re-examined. The decreased rate of participation may, however, not have influenced the conclusions of our study as one knew whether the non-participating subjects were dead or alive. Second, blood pressure measurements, blood sample examinations for lipids and glycosylated haemoglobin and measurements of body height, weight and body mass index were not performed at baseline in 2001, so that the multivariate analysis did not include arterial hypertension and dyslipidemia as risk factors for an increased mortality. Third, the elderly population from China has a markedly different history and had profoundly different living conditions in previous years than elderly populations in Western countries, so that it is unclear how far the results of our study can be transferred to other population and societies. Fourth, there was no reliable information on the cause of death for all people who had died, so that associations between the cause of death and pre-existing ocular or systemic diseases or ocular parameters could not be assessed.

In conclusion, after adjustment for age, gender, level of education and smoking, mortality was significantly higher in subjects with diabetic retinopathy, non-glaucomatous optic nerve damage and nuclear cataract. Other major ophthalmic parameters and disorders such as hyperopia, myopia, high

Table 2. Results of a binary logistic regression analysis (multivariate-adjusted model including all variables in the table) between mortality and systemic and ocular parameters in the Beijing Eye Study 2001/2011

Parameter	p-value	Regression coefficient	Odds ratio	95% Confidence interval of odds ratio
Age (years)	<0.001	0.07	1.07	1.05, 1.09
Gender (male = 1; female = 2)	<0.001	−0.58	0.56	0.40, 0.78
Level of education (per one of 5 levels of education)	<0.001	−0.42	0.66	0.59, 0.74
Ever smoking	<0.001	0.61	1.84	1.36, 2.49
Presence of diabetic retinopathy	0.002	0.81	2.26	1.34, 3.81
Presence of non-glaucomatous optic nerve damage	0.001	1.59	4.90	1.90, 12.7
Degree of nuclear cataract	0.002	0.26	1.29	1.10, 1.52

myopia, pterygium, age-related macular degeneration, retinal vein occlusion, glaucoma and cortical or nuclear cataract were not significantly associated with mortality. These findings may have clinical importance as patients in whom one of the associated ocular conditions is detected may undergo an intensified general body examination to detect reasons for it to prevent early death. The findings may pathogenetically be interesting as the associations, and the lack of associations, between the ocular disorders and mortality may give some hints for their pathogenesis.

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