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ARTICLE

Mortality and ocular parameters and diseases

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BACKGROUND: To assess associations between mortality and major ocular parameters and diseases.
METHODS: The population-based Ural Eye and Medical Study (UEMS) and Ural Very Old Study (UVOS) included 5899 individuals (age: 40+ years) and 1526 individuals (age: 85+ years), respectively. Cause-specific mortality was determined using the government regional information and analytical system.
RESULTS: In the UEMS, 689 (11.7%) participants had died during the follow-up of 7.0 ± 0.4 years (median: 6.9 years). Higher death occurrence was associated (multivariable analysis) with lower best corrected visual acuity (OR: 1.86; 95%CI:1.10, 2.68) and higher prevalence of diabetic retinopathy (OR: 2.97; 95%CI: 1.68, 5.26), with adjusting for older age (OR: 1.08), male sex (OR: 4.18), higher waist-hip ratio (OR: 5.53), current smoking (OR: 2.25), history of cancer (OR: 1.93) and dementia (OR: 2.54), higher serum concentration of glucose (OR: 1.13) and lower serum concentration of high-density lipoproteins (OR: 0.89) and haemoglobin (OR: 0.99), higher leucocyte count (OR: 1.07), higher prevalence of chronic obstructive pulmonary disease (OR: 1.67), higher stage of arterial hypertension (OR: 1.15), and higher depression score (OR: 1.04). Death occurrence was not significantly associated with prevalence of age-related macular degeneration ($P = 0.90$), macular reticular pseudodrusen ($P = 0.90$), open-angle glaucoma ($P = 0.11$), angle-closure glaucoma ($P = 0.98$), nuclear cataract ($P = 0.07$), cortical cataract ($P = 0.46$), axial length ($P = 0.44$) and intraocular pressure ($P = 0.87$). In the UVOS, 791 (51.9%) participants had died during the follow-up of 4.8 ± 1.0 years (median: 5.2 years). None of the ophthalmological parameters was significantly associated with death occurrence.
CONCLUSIONS: Diabetic retinopathy was the only major ophthalmic disease or parameter, in addition to vision impairment, which was associated with an increased death risk.

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INTRODUCTION

Ocular diseases such as diabetic retinopathy, age-related macular degeneration (AMD), cataract and glaucoma markedly increase in their prevalence and degree with older age. They are directly or indirectly related with systemic parameters and diseases such as arterial blood pressure and diabetes mellitus, to name only a few, and lead to vision impairment with consequences for lifestyle including a decrease in physical activity. All these factors are associated with, or influence, mortality. Although it is of clinical interest whether ophthalmological diseases are directly or indirectly associated with remaining life expectancy, the direct association of major ocular parameters and diseases with mortality has remained inconclusive so far [1–12]. Reason has been that previous studies examining the relationship between ocular diseases and mortality were either limited in their sample size or did not fully take into account the panoply of systemic and ocular diseases and parameters and their interdependencies with respect to their influence on mortality so that confounding factors might have played a role [1–12]. Here, we re-addressed the question of associations between the prevalence and stage of ocular diseases and parameters with mortality, taking into account, and adjusting for, the prevalence and stage of a whole series of systemic diseases like arterial hypertension, diabetes mellitus, chronic kidney disease, chronic obstructive pulmonary disease, cardiovascular and cerebrovascular disease including cardiac arrhythmias, hepatopathies, depression, suicidal ideas, and anxiety as well as considering general risk factors such as smoking and alcohol consumption. We included all major ophthalmological disorders and ocular parameters into the statistical analysis to assess collinearity between these ocular factors in their relationship with mortality. We assessed the associations in two study cohorts, recruited in a population-based manner in the same geographic region and examined by a similar series of examinations, while both cohorts differed in the minimal age as inclusion criterion.

METHODS

The Ural Eye and Medical Study (UEMS) and the Ural Very Old Study (UVOS) are population-based studies conducted in the Russian republic of

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Bashkortostan which is located in the southeastern region of the Volga Federal District in Russia [13, 14]. The studies were approved by the Ethics Committee of the Academic Council of the Ufa Eye Research Institute (Dates of the ethics committee approvals: 25.8.2015 (protocol # 2) and 10.8 2017 (protocol # 3), respectively) and informed written consent was obtained from all participants. Study regions were the urban region of the Kirovskii district in Ufa as the capital of Bashkortostan and a rural region in the Karmaskalinsky District in a distance of 65 km from Ufa. Bashkortostan is the most populous republic of Russia with a multiethnic population consisting of Russians, Bashkirs, Tatars, Chuvash, Mari, and other minorities.

The UEMS was conducted in the period from 2015 to 2017. Inclusion criteria were living in the study regions and a minimal age of 40 years. Out of 7328 subjects eligible, the study included 5899 (80.5%) participants (2580 (43.7%) men; 3319 (56.3%) women). The UVOS was performed in the period from 2017 to 2020 with the inclusion criteria of living in the study regions and a minimal age of 85 years. It included 1526 (81%) participants (390 (25.6%) men) out of 1882 eligible inhabitants. The study populations of the UEMS and UVOS did not differ markedly in the distribution of sex and age from the population of whole Russia, as examined in the national census conducted in 2021 [15, 16]. Due to the location of the study regions in Bashkortostan which forms the southeastern part of the Volga Federal District, both study populations as compared to the total population of Russia had a higher proportion of Tatars and Bashkirs and a smaller fraction of individuals with Russian ancestry.

As described in detail previously, the participants of both studies underwent a standardised interview conducted by trained social workers [13, 14]. This interview was conducted in the home of the participants of the UVOS and in the hospital for the participants of the UEMS. The questionnaire included more than 300 questions on the socioeconomic background, diet, smoking, alcohol consumption, physical activity, quality of life and quality of vision, chronic obstructive pulmonary disease, asthma, kidney disease and orthopaedic disorders, history of any type of injuries, inter-personal violence, medical history, cognitive function and hearing loss (Table 1). The questions had been validated in previous investigations such as the Folstein test, Zung's self-rated depression scale, and the National Eye Institute Visual Functioning Questionnaire-25 (VFQ-25) [17–19]. The physical examinations included measurement of the anthropomorphic parameters, arterial blood pressure, dynamometric assessment of the hand grip strength, biochemical analysis of blood samples taken under fasting conditions, spirometry, and electrocardiography (Table 1). We applied the Guidelines for Accurate and Transparent Health Estimates Reporting (GATHER statement guidelines) [20]. Using the government regional information and analytical system as death registry and the International Classification of Diseases 11th Revision codes, we assessed in September 2023 whether the study participants had died and what the coded causes of death were. The ophthalmological examinations consisted of a series of assessment including measurement of best corrected visual acuity, non-contact tonometry, sonographic measurement of axial length, and imaging of the anterior and posterior ocular segment including spectral-domain optical coherence tomography of the optic nerve head and macula.

We defined arterial hypertension according to the criteria published by the American Heart Association, and criteria for the diagnosis of diabetes mellitus were a fasting glucose concentration of ≥7.0 mmol/L or a self-reported history of physician diagnosis of diabetes mellitus or a history of drug treatment for diabetes (insulin or oral hypoglycaemic agents) [21]. Anaemia was present with a haemoglobin concentration of <140 g/L for men and <130 g/L for women. The estimated glomerular filtration rate (eGFR) was calculated using the chronic kidney disease (CKD) Epidemiology Collaboration (CKD-EPI) equation. Chronic obstructive pulmonary disease (COPD) was spirometrically defined by the ratio of the forced expiratory volume in one second divided by forced vital capacity, in association of having symptoms of COPD like chronic coughing. We diagnosed depression in dependence of the score of the standardised questions on depression and suicidal ideas. We assessed dysakusis by a series of standardised questions, which were derived from the 'Hearing Handicap Inventory for the Elderly Screening Version' [22]. The degree of nuclear cataract was graded in 6 grades according to the lens photographs using the classifying scheme for cataract of the Age-Related Eye Disease Study [23]. We graded pseudoexfoliation into six stages [24]. Using the macula and optic nerve head photographs, the amount of fundus tessellation was differentiated between grade '0' for 'no tessellation' and grade '3' for 'marked tessellation'. We applied the criteria published by the ISGEO (International Society of Geographical and Epidemiological Ophthalmology) for the definition of glaucoma [25]. A non-glaucomatous optic nerve damage was defined as a decreased age-related visibility of the retinal nerve fibre layer, an increased pallor of the neuroretinal rim, a decreased diameter of the retinal arteries, and a normal shape of the neuroretinal rim according to the ISNT-rule. A non-glaucomatous optic nerve damage was considered only if an ocular condition, such as a retinal vein occlusion was not detected as possible cause of the optic nerve atrophy. We applied the criteria recommended by the Beckman Initiative for Macular Research Classification Committee to define age-related macular degeneration [26]. Myopic maculopathy was graded according to the International Photographic Classification and Grading System for Myopic Maculopathy [27]. According to the Early Treatment of Diabetic Retinopathy Study (ETDRS) criteria, the minimum criterion for diagnosis of diabetic retinopathy was the presence of at least one microaneurysm [28].

For the statistical analysis we used a commercially available statistical software package (SPSS for Windows, version 27.0, SPSS, Chicago, IL). Univariate binary regression analyses of the relationship between death occurrence as dependent variable and the systemic and ocular parameters as independent variables were followed by multivariable analyses. The latter included as independent variables all those systemic parameters which were associated ($P < 0.10$) with death occurrence in the univariate analyses. Out of the list of independent variables, we dropped in a step-by-step manner those variables which either showed a collinearity with the occurrence of death or which had lost their statistical significance. In a second step of the analysis, we added to the multivariable model the ocular parameters which were associated ($P < 0.10$) with the occurrence of death in the univariate analysis and had been dropped from the model in the previous step of the analysis. We additionally examined the risk of all-cause mortality and cause-specific mortality with Cox proportional hazards models adjusted for the parameters which were significantly associated with the occurrence of death in the multivariable analysis. Time to death was calculated from the examination date to date of death or September 15, 2023, whichever came first. We described linear parameters by their means and standard deviations and categorical parameters by their mean and 95% confidence intervals (CIs). We determined the odds ratios (ORs) and hazard ratios (HRs) and their 95% CIs. All *P*-values were two-sided and considered statistically significant when the values were less than 0.05.

RESULTS

The UEMS cohort consisted of 5899 participants (3319 (56.3%) women) with a mean age of 59.5 ± 10.7 years (median: 58.7 years, range: 40.0–93.7 years). It included 1185 (20.1%) Russians, 1061 (18.0%) Bashkirs, 2439 (41.3%) Tatars, 587 (10.0%) Chuvash, 21 (0.4%) Mari, and 606 (10.3%) individuals without self-reported ancestry. In the follow-up of 7.0 ± 0.4 years (median: 6.9 years; range: 6.2–7.9 years) between the dates of examination and of assessment of mortality on 15.9.2023, 689 (11.7%) participants (385 (55.9%) men; 304 (44.1% women)) had died. Causes of death were chronic kidney disease ($n = 8$; 1.2%), chronic respiratory failure ($n = 3$; 0.4%), cerebrovascular disease ($n = 34$; 4.9%), cardiovascular disease ($n = 127$; 18.4%), acute respiratory failure and pulmonary oedema ($n = 102$; 14.8%), cancer-related causes (87; 12.6%), trauma (18; 2.6%), and other unspecific causes such as cerebral oedema ($n = 147$; 21.3%) and senility ($n = 9$; 1.3%) and others (154; 22.4%). The participants who had died had at baseline a mean age of 69.0 ± 11.1 years (median: 69.0 years; range: 40.9–92.8 years), and at death an age of 73.3 ± 11.4 years (median: 74.0 years; range: 41.8–98.2 years). The mean duration of follow-up for the participants who died (i.e. the interval between examination and death) was 4.2 ± 1.9 years (4.46 years; range: 0.02–7.76 years).

In univariate analysis, occurrence of death correlated with a multitude of systemic and ocular parameters (Tables 1 and 2). In the multivariable analysis, a higher death occurrence was associated with lower best corrected visual acuity (OR: 1.86) and higher prevalence of diabetic retinopathy (OR: 2.97), with adjusting for older age (OR: 1.08), male sex (OR: 4.18), higher waist-hip ratio (OR: 5.53), current smoking (OR: 2.25), history of

Table 1. Associations (univariate analysis) of mortality with systemic parameters in the Ural Eye and Medical Study and in the Ural Very Old Study.

	Ural Eye and Medical Study			Ural Very Old Study		
	Odds ratio	**95% confidence interval**	***P*-value**	**Odds ratio**	**95% confidence interval**	***P*-value**
Age (years)	1.10	1.09, 1.11	<0.001	1.10	1.06, 1.14	<0.001
Sex (men/women)	0.58	0.49, 0.68	<0.001	0.54	0.43, 069	<0.001
Region of habitation (rural/urban)	1,68	1.43, 1.97	<0.001	1.80	1.39, 2.34	<0.001
Ancestry (non-Russian/Russian)	1.33	1.09, 1.61	0.005	1.04	0.84, 1.28	0.74
Body height (cm)	1.00	0.00, 1.01	0.37	1.00	0.99, 1.02	0.77
Body weight (kg)	1.00	0.99, 1.00	0.39	1.01	0.995, 1.02	0.32
Body mass index (kg/m^2)	1.00	0.98, 1.01	0.77	1.01	0.98, 1.04	0.52
Waist circumference (cm)	1.02	1.01, 1.02	<0.001	1.01	0.999, 1.02	0.07
Hip circumference (cm)	1.00	0.99, 1.01	0.95	1.00	0.99, 1.01	0.61
Waist/hip circumference ratio	32.6	14.8, 72.1	<0.001	4.37	1.08, 17.7	0.04
Waist/height ratio	19.6	7.63, 50.2	<0.001	2.74	0.61, 12.3	0.19
Level of education (1-8)	0.76	0.72, 0.80	<0.001	1.07	1.01, 1.12	0.01
Smoking, currently (no/yes)	1.44	1.16, 1.79	0.001	1.29	0.39, 4.25	0.67
Alcohol consumption, any (no/yes)	1.25	1.02, 1.54	0.03	0.95	0.69, 1.31	0.76
Diet						
Number of daily meals	0.86	0.77, 0.95	0.004	1.03	0.91, 1.16	0.67
In a week, on how many days do you eat fruits?	0.91	0.87, 0.94	<0.001	1.05	0.997, 1.11	0.06
Amount of fruits per serving	0.998	0.998, 0.999	<0.001	1.00	1.00, 1.00	0.94
In a week, on how many days do you eat vegetables?	0.89	0.85, 0.94	<0.001	1.03	0.96, 1.10	0.46
Amount of vegetables per serving	0.998	0.998, 0.999	<0.001	1.00	1.00, 1.00	0.41
Type of oil for cooking used: vegetable cooking oil —animal fat (butter)	0.43	0.20, 0.93	0.03	1.15	0.89, 1.48	0.28
Food containing whole grains (no/yes)	1.54	1.27, 1.87	<0.001	0.61	0.39, 0.95	0.03
Self-reported salt consumption per day (g)	1.03	0.998, 1.07	0.07	1.00	0.95, 1.06	0.88
Degree of processing meat (weak—medium—strong)	0.84	0.72, 0.98	0.03	0.86	0.72, 1.03	0.10
Number of cups of coffee taken daily	–	–	–	0.94	0.77, 1.14	0.52
Number of cups of tea taken daily	–	–	–	0.96	0.87, 1.04	0.34
Preference of green or black tea	–	–	–	1.19	0.66, 2.14	0.57
Physical activity						
Length of working day (h)	0.998	0.998, 0.999	<0.001	–	–	–
Do you mostly sit and walk less than 10 min (no/yes)	0.47	0.40, 0.55	<0.001	–	–	–
Work with moderate to vigorous physical activity (no/yes)	0.50	0.42, 0.59	<0.001	–	–	–
How many days per week with vigorous physical work	1.18	1.07, 1.29	<0.001	–	–	–
How much time spent with vigorous physical work per day	0.998	0.998, 0.998	<0.001	–	–	–
Work with moderate physical activity (no/yes)	0.48	0.41, 0.56	<0.001	–	–	–
How many days per week with moderate physical activity at work	0.90	0.88, 0.93	<0.001	–	–	–
How much time spent with moderate physical activity at work per day	0.998	0.997, 0.998	<0.001	–	–	–
How many days per week do walk or use or bicycle for at least 10 min	0.57	0.46, 0.71	<0.001	1.08	0.91, 1.29	0.39
Do you spent leisure time mostly with sitting without physical activity	0.68	0.58, 0.80	<0.001	1.04	0.83, 1.29	0.75
In your leisure time, do you do any physically vigorous activities like running, strenuous sports or weight lifting for at least 10 min at a time?	0.67	0.55, 0.81	<0.001	1.02	0.68, 1.53	0.91

Table 1. continued

	Ural Eye and Medical Study			Ural Very Old Study		
	Odds ratio	**95% confidence interval**	***P*-value**	**Odds ratio**	**95% confidence interval**	***P*-value**
In your leisure time, do you do any moderate intensity activities like brisk walking, cycling or swimming for at least 10 min at a time?	0.61	0.52, 0.73	<0.001	0.78	0.63, 0.95	0.02
Over the past 7 days, how much time did you spend sitting or reclining on a typical day? (h)	1.01	1.01, 1.02	<0.001	1.00	1.00, 1.00	0.06
History of systemic diseases						
Self-reported history of angina pectoris	0.67	0.49, 0.92	0.01	0.90	0.58, 1.40	0.65
Self-reported history of asthma	1.90	1.28, 2.83	0.001	1.23	0.60, 2.55	0.57
Self-reported history of prevalence of chronic obstructive pulmonary disease	1.37	1.00, 1.88	0.05	1.44	0.83, 2.51	0.20
Self-reported history of arterial hypertension	1,71	1.46, 2.00	<0.001	0.80	0.63, 1.02	0.07
Self-reported history of arthritis	1.34	1.13, 1.58	<0.001	0.92	0.75, 1.13	0.43
History of previous bone fractures	1.26	1.06, 1.51	0.01	0.93	0.75, 1.14	0.47
Self-reported history of low back pain	0.83	0.70, 0.99	0.03	1.03	0.84, 1.27	0.75
Self-reported history of thoracic spine pain	0.88	0.71, 1.08	0.21	1.14	0.92, 1.42	0.23
Self-reported history of neck pain	0.67	0.55, 0.82	<0.001	1.24	0.96, 1.60	1.24
Self-reported history of headache	0.83	0.70, 0.99	0.03	0.96	0.79, 1.18	0.71
Self-reported history of cancer	2.48	1.74, 3.54	<0.001	1.33	0.91, 1.94	0.14
Self-reported history of cardiovascular disorders including stroke	1.76	1.48, 2.11	<0.001	0.85	0.69, 1.05	0.13
Self-reported history of dementia	5.61	2.89, 10.9	<0.001	1.55	1.05, 2.29	0.03
Self-reported history of diabetes mellitus	2.82	2.26, 3.52	<0.001	1.55	1.10, 2.18	0.01
Self-reported history of diarrhoea	0.64	0.15, 2.72	0.55	0.81	0.29, 2.25	0.69
Self-reported history of iron-deficiency anaemia	0.52	0.33, 0.84	0.007	1.01	0.63, 1.62	0.97
Self-reported history of low blood pressure and hospital admittance	1.24	0.83, 1.83	0.29	0.71	0.31, 1.63	0.42
Self-reported history of osteoarthritis	1.16	0.92, 1.46	0.21	1.19	0.92, 1.55	0.19
Self-reported history of skin disease	1.33	0.94, 1.87	0.11	1.14	0.75, 1.75	0.54
Self-reported history of thyroid disease	0.65	0.48, 0.88	0.005	0.83	0.54, 1.26	0.37
Self-reported history of falls	1.20	0.98, 1.46	0.07	0.93	0.68, 1.26	0.62
Self-reported history of unconsciousness	1.44	1.11, 1.86	0.006	1.03	0.74, 1.44	0.85
Age of the last menstrual bleeding (years)	1.01	0.99, 1.04	0.40	1.00	0.96, 1.03	0.79
Age of last regular menstrual bleeding (years)	1.01	0.99, 1.04	0.34	1.00	0.97, 1.03	0.85
Alanine aminotransferase (IU/L)	1.00	0.997, 1.01	0.31	1.00	0.99, 1.02	0.71
Aspartate aminotransferase (IU/L)	1.00	0.99, 1.01	0.43	0.99	0.98, 0.998	0.02
Aspartate aminotransferase/alanine aminotransferase ratio	0.87	0.68, 1.10	0.24	1.01	0.94, 1.10	0.74
Bilirubin, total (μmol/L)	0.99	0.99, 1.00	0.13	1.00	0.99, 1.02	0.71
High-density lipoproteins (mmol/L)	0.86	0.78, 0.95	0.004	0.94	0.81, 1.08	0.37
Low-density lipoproteins (mmol/L)	0.92	0.85, 0.99	0.03	0.86	0.77, 0.96	0.01
Cholesterol (mmol/L)	0.98	0.93, 1.03	0.33	0.85	0.77, 0.93	<0.001
Triglycerides (mmol/L)	1.06	0.96, 1.18	0.27	0.73	0.61, 0.86	<0.001
Rheumatoid factor (IU/mL)	1.16	1.09, 1.23	<0.001	0.99	0.93, 1.06	0.79
Erythrocyte sedimentation rate (mm/h)	1.002	1.009, 1.02	0.007	1.01	0.999, 1.02	0.09
Glucose (mmol/L)	1.21	1.17, 1.26	<0.001	1.08	1.01, 1.17	0.03
Creatinine (μmol/L)	1.004	1.001, 1.01	0.003	1.01	1.003, 1.01	0.002
Urea (mmol/L)	1.20	1.15, 1.26	<0.001	1.06	1.001, 1.11	0.045
Residual nitrogen (g/L)	9.96	2.57, 36.7	<0.001	5.04	0.90, 28.3	0.07
Total protein (g/L)	0.98	0.97, 0.99	<0.001	1.00	0.98, 1.02	0.94
International normalised ratio (INR)	0.54	0.30, 0.98	0.04	2.81	1.11, 7.12	0.03
Prothrombin time (%)	1.001	0.998, 1.01	0.14	0.99	0.98, 1.002	0.09

Table 1. continued

	Ural Eye and Medical Study			Ural Very Old Study		
	Odds ratio	**95% confidence interval**	***P*-value**	**Odds ratio**	**95% confidence interval**	***P*-value**
Haemoglobin	0.995	0.988, 1.000	0.05	1.00	0.99, 1.001	0.13
Erythrocytes (10^6 cells/μL)	0.81	0.65, 0.99	0.04	0.84	0.67, 1.05	0.13
Leucocytes (10^9 cells/L)	1.13	1.07, 1.18	<0.001	0.99	0.92, 1.06	0.99
Rod-core granulocyte (% of leucocytes)	1.04	0.98, 1.10	0.19	1.06	0.98, 1.14	0.14
Segment nuclear granulocyte (% of leucocytes)	1.01	0.999, 1.02	0.07	0.99	0.98, 1.01	0.26
Eosinophil granulocytes (% of leucocytes)	1.05	0.98, 1.12	0.20	1.07	0.94, 1.21	0.31
Lymphocytes (% of leucocytes)	0.98	0.97, 0.99	<0.001	1.00	0.99, 1.02	0.73
Monocytes (% of leucocytes)	1.02	0.99, 1.06	0.24	1.03	0.98, 1.08	0.22
Prevalence of chronic obstructive pulmonary disease	1.59	1.19, 2.13	0.002	–	–	–
Prevalence of diabetes mellitus	2.72	2.23, 3.32	<0.001	1.57	1.15, 2.14	0.005
Anaemia (serum haemoglobin concentration <140 g/L in men, <130 g/L in women)	1.49	1.25, 1.77	<0.001	1.20	0.95, 1.51	0.13
Blood pressure, systolic (SBP) (mmHg)	1.02	1.02, 1.02	<0.001	0.994	0.990, 0.99	0.01
Blood pressure, diastolic (DBP) (mmHg)	1.02	1.01, 1.02	<0.001	1.00	0.99, 1.01	0.58
Blood pressure, mean (mmHg)	1.03	1.02, 1.03	<0.001	1.00	0.99, 1.003	0.29
Arterial hypertension (no/yes)	2.48	1.85, 3.33	<0.001	0.86	0.62, 1.21	0.40
Arterial hypertension, stages	1.51	1.38, 1.66	<0.001	0.89	0.79, 1.00	0.04
Ankle-brachial index, right	0.34	0.17, 0.68	0.002	1.74	0.27, 11.4	0.56
Ankle-brachial, left	0.37	0.19, 0.75	0.006	1.93	0.30, 12.4	0.49
Metabolic syndrome (no/yes)	1.54	1.30, 1.82	<0.001	0.89	0.70, 1.13	0.33
Cognitive score (Mini Mental Test)	–	–	–	0.99	0.97, 1.00	0.05
Hearing loss score	1.03	1.02, 1.03	<0.001	1.012	1.005, 1.02	<0.001
Depression Score	1.05	1.03, 1.07	<0.001	1.01	0.999, 1.02	0.09
State-Trait Anxiety Inventory	1.04	1.02, 1.07	<0.001	1.01	1.003, 1.02	0.01
Manual dynamometry, right hand	0.97	0.96, 0.97	<0.001	0.99	0.98, 1.01	0.48
Manual dynamometry, left hand	0.96	0.95, 0.97	<0.001	0.99	0.97, 1.004	0.15

cancer (OR: 1.93) and dementia (OR: 2.54), higher serum concentration of glucose (OR: 1.13) and lower concentration of high-density lipoproteins (OR: 0.89) and haemoglobin (OR: 0.99), higher leucocyte count (OR: 1.07), higher prevalence of chronic obstructive pulmonary disease (OR: 1.67), higher stage of arterial hypertension (OR: 1.15), and higher depression score (OR: 1.04) (Table 3). Using the model and adding the prevalence or stage of ocular parameters to the list of independent variables, such as the prevalence of AMD (any AMD: $P = 0.90$; early AMD: $P = 0.90$; intermediate AMD: $P = 0.15$, late AMD: $P = 0.32$), reticular pseudodrusen ($P = 0.90$), open-angle glaucoma prevalence ($P = 0.11$) and stage ($P = 0.10$), angle-closure glaucoma prevalence ($P = 0.98$) and stage ($P = 0.65$), nuclear cataract prevalence ($P = 0.07$) and degree ($P = 0.14$), cortical cataract prevalence ($P = 0.46$) and degree ($P = 0.64$), axial length ($P = 0.44$) and intraocular pressure ($P = 0.87$), these parameters were not significantly associated with the occurrence of death.

Analysing all-cause mortality in the Cox proportional hazards models, with adjustment for older age, male sex, moderate to intensive physical activities during work, current smoking, hand grip force, history of cancer and dementia, serum concentration of glucose, high-density lipoprotein and haemoglobin, arterial hypertension stage, best corrected visual acuity and prevalence of diabetic retinopathy, all-cause mortality was not significantly associated with the prevalence of AMD (any AMD:$P = 0.44$ ($P = 0.34$ after dropping the parameter of best corrected visual acuity from the model), early AMD:$P = 0.46$ ($P = 0.46$), intermediate AMD:$P = 0.11$ ($P = 0.90$), late AMD:$P = 0.37$ ($P = 0.21$), prevalence ($P = 0.53$) and stage ($P = 0.68$) of glaucoma, prevalence ($P = 0.15$) and degree ($P = 0.17$) of nuclear cataract, prevalence ($P = 0.67$) and degree ($P = 0.86$) of cortical cataract, intraocular pressure ($P = 0.49$), and axial length ($P = 0.80$). Similar results were obtained for the risk of cardiovascular/cerebrovascular diseases as death cause. With adjusting for age, sex, physical activity (moderate to intensive physical activities during work), current smoking, hand grip force, history of dementia, serum concentration of glucose, arterial hypertension stage, best corrected visual acuity and prevalence of diabetic retinopathy, the risk of cardiovascular/cerebrovascular diseases as cause of death was not associated (Cox proportional hazard analysis) with the prevalence of AMD (any:$P = 0.74$; early AMD:$P = 0.76$; intermediate AMD:$P = 0.71$; late AMD:$P = 0.55$), prevalence ($P = 0.65$) and stage ($P = 0.63$) of glaucoma, prevalence ($P = 0.15$) and degree ($P = 0.19$) of nuclear cataract, prevalence ($P = 0.49$) and degree ($P = 0.88$) of cortical cataract, intraocular pressure ($P = 0.29$) and axial length ($P = 0.52$).

The UVOS cohort consisted of 1526 participants (1136 (74.5%) women) with a mean age of 88.8 ± 2.9 years (median: 88.1 years, range: 85.0–103.1 years). It included 559 (36.7%) Russians, 171 (11.2%) Bashkirs, 668 (43.8%) Tatars, 49 (3.2%) Chuvash, 8 (0.5%) Mari, and 70 (4.6%) individuals without self-reported ancestry. In the follow-up of 4.8 ± 1.0 years (median: 5.2 years; range: 2.8–5.8 years) between the dates of examination and of assessment of mortality on 15.9.2023, 791 (51.9%) participants (245 (31.0%) men;

Table 2. Associations (univariate analysis) of mortality with ocular parameters in the Ural Eye and Medical Study and in the Ural Very Old Study.

Parameter	Interval	Odds ratio (OR)	95% confidence interval of OR	*P*-value	Odds ratio (OR)	95% confidence interval of OR	*P*-value
	Ural Eye and Medical Study				Ural Very Old Study		
Refractive error, spherical equivalent	Dioptres	1.04	0.99, 1.08	0.07	0.98	0.94, 1.02	0.36
Refractive error, cylindrical value	Dioptres	0.67	0.62, 0.72	<0.001	1.01	0.91, 1.11	0.92
Axial length	mm	0.94	0.87, 1.01	0.10	1.10	0.96, 1.25	0.18
Corneal refractive power	Dioptres	1.10	1.04, 1.16	<0.001	0.91	0.83, 0.99	0.04
Central corneal thickness	µm	0.999	0.996, 1.001	0.26	0.999	0.996, 1.003	0.63
Corneal volume	mm^3	0.96	0.94, 0.98	<0.001	1.000	0.997, 1.003	0.89
Anterior chamber depth	mm	1.27	1.09, 1.45	0.002	1.03	0.87, 1.21	0.74
Anterior chamber volume	µL	0.998	0.997, 1.000	0.07	1.00	0.997, 1.003	0.89
Anterior chamber angle	Degree	1.01	0.99, 1.02	0.41	1.00	0.98, 1.01	0.56
Lens thickness	mm	1.84	1.47, 2.29	<0.001	1.02	0.76, 1.38	0.87
Intraocular Pressure	mmHg	1.84	1.47, 2.29	<0.001	0.99	0.97, 1.02	0.58
Nuclear cataract degree	Grade	1.39	1.30, 1.47	<0.001	1.13	0.99, 1.28	0.07
Nuclear cataract, presence	No/Yes	2.69	2.22, 3.24	<0.001	1.38	0.84, 2.26	0.20
Cortical cataract, degree	Percentage	1.02	1.01, 1.03	<0.001	1.09	0.97, 1.22	0.16
Cortical cataract, presence	No/Yes	2.35	1.89, 2.92	<0.001	2.60	0.79, 8.54	0.12
Any cortical or nuclear cataract	No/Yes	1.65	1.40, 1.93	<0.001	1.69	0.75, 3.81	0.21
Status after cataract surgery	No/Yes	4.73	3.60, 6.23	<0.001	1.07	0.85, 1.35	0.58
Fundus tessellation, macula region	Grade	1.51	1.38, 1.66	<0.001	1.03	1.00, 1.07	0.05
Fundus tessellation, peripapillary region	Grade	1.43	1.31, 1.56	<0.001	1.03	0.996, 1.06	0.09
Retinal thickness (total), fovea	µm	0.998	0.996, 0.999	<0.001	1.001	0.999, 1.003	0.38
Retinal thickness (total), 300 µm temporal to the fovea	µm	1.000	0.998, 1.002	0.98	1.02	1.003, 1.03	0.02
Retinal thickness (total), 300 µm nasal to the fovea	µm	1.000	0.998, 1.003	0.75	1.007	0.999, 1.02	0.08
Retinal nerve fibre layer thickness	µm	0.982	0.977, 0.986	<0.001	0.999	0.994, 1.005	0.82
Pseudoexfoliation of the lens, presence	No/Yes	1.54	1.12, 2.12	0.008	0.95	0.86, 1.05	0.34
Pseudoexfoliation of the lens, degree	0–5	1.16	1.05, 1.27	0.003	1.11	0.96, 1.30	0.16
Glaucoma	No/Yes	3.31	2.42, 4.54	<0.001	1.59	1.06, 2.38	0.02
Glaucoma stage	0–5	1.69	1.49, 1.92	<0.001	1.14	1.02, 1.27	0.02
Open-angle glaucoma	No/Yes	3.67	2.54, 5.29	<0.001	1.57	1.04, 2.39	0.03
Open-angle glaucoma, stages	0–5	1.74	1.51, 2.02	<0.001	1.14	1.02, 1.28	0.02
Angle-closure glaucoma	No/Yes	2.30	1.24, 4.28	0.008	1.96	0.66, 5.80	0.22
Angle-closure glaucoma, stages	0–5	1.45	1.13, 1.87	0.004	1.29	0.94, 1.78	0.12
Age-related macular degeneration (AMD), any	No/Yes	2.20	1.55, 3.11	<0.001	1.28	0.99, 1.67	0.06
AMD, early stage, prevalence	(No/Yes)	1.95	1.44, 2.64	<0.001	1.07	0.73, 1.56	0.74
AMD, intermediate stage, prevalence	(No/Yes)	2.80	1.90, 4.14	<0.001	1.46	1.05, 2.02	0.02
AMD, late stage, prevalence	(No/Yes)	6.09	2.89, 12.8	<0.001	0.95	0.66, 1.39	0.81
Reticular pseudodrusen prevalence	(No/Yes)	2.12	1.60, 3.06	<0.001	1.20	0.88, 1.63	0.25
Diabetic retinopathy	No/Yes	5.10	3.25, 8.00	<0.001	–	–	1.00
Diabetic retinopathy, ETDRS grading	Scale	1.06	1.05, 1.08	<0.001	–	–	1.00
Myopic maculopathy, prevalence (stage 2+)	No/Yes	1.30	0.64, 2.65	0.47	1.84	0.73, 4.59	0.19
Myopic maculopathy, stage	0–4	1.04	0.82, 1.31	0.78	1.16	0.90, 1.49	0.26

Table 3. Associations (multivariable analysis) between occurrence of death and systemic and ocular parameters in the Ural Eye and Medical Study.

	Ural Eye and Medical Study		
	Odds ratio	**95% confidence interval**	***P*-value**
Age (years)	1.08	1.06, 1.09	<0.001
Sex (women/men)	3.99	2.86, 5.56	<0.001
Waist-hip circumference ratio	5.28	1.67, 16.7	0.005
Smoking current (no/yes)	2.32	1.67, 3.23	<0.001
Dynamometric hand grip force, right hand (dekaNewton)	0.97	0.95, 0.98	<0.001
Physical activity (Does your work involve physically vigorous activity (like heavy lifting or digging) or physically moderate intensity activity (like brisk walking or carrying light loads during work for at least 10 min at a time?)	0.72	0.58, 0.90	0.004
History of cancer (no/yes)	2.15	1.30, 3.57	0.003
History of dementia (no/yes)	2.58	1.12, 5.95	0.03
Serum concentration of glucose (mmol/L)	1.12	1.06, 1.18	<0.001
Serum concentration of haemoglobin (g/dL)	0.99	0.98, 0.995	0.002
Serum concentration of high-density lipoproteins (mmol/L)	0.87	0.77, 0.99	0.04
Leucocytes cell count (cells/μL)	1.08	1.01, 1.16	0.02
Chronic obstructive pulmonary disease (no/yes)	1.62	1.13, 2.31	0.008
Arterial hypertension (stages)	1.15	1.02, 1.30	0.02
Depression score (0–20)	1.04	1.01, 1.07	0.01
Visual acuity, best corrected (logMAR), binocular	1.86	1.10, 2.68	0.02
Diabetic retinopathy, prevalence (no/yes)	2.97	1.68, 5.26	<0.001
If added separately to the model:			
Age-related macular degeneration, any	0.97	0.61, 1.54	0.90
Age-related macular degeneration, early stage	0.98	0.66, 1.45	0.90
Age-related macular degeneration, intermediate stage	1.44	0.87, 2.39	0.15
Age-related macular degeneration, late stage	1.61	0.63, 4.11	0.32
Reticular pseudodrusen	0.97	0.61, 1.54	0.90
Open-angle glaucoma, prevalence	1.53	0.92, 2.54	0.11
Open-angle glaucoma, stage	1.19	0.97, 1.46	0.10
Angle-closure glaucoma, prevalence	0.99	0.39, 2.48	0.98
Angle-closure glaucoma, stage	0.89	0.53, 1.48	0.65
Nuclear cataract, prevalence	1.27	0.99, 1.63	0.07
Nuclear cataract, stage	1.06	0.98, 1.15	0.14
Cortical cataract, prevalence	1.11	0.84, 1.47	0.46
Cortical cataract, stage	1.00	0.99, 1.01	0.64
Axial length (mm)	0.96	0.87, 1.06	0.44
Intraocular pressure (mmHg)	1.00	0.98, 1.03	0.87

546 (69.0% women)) had died. Causes of death were chronic kidney disease ($n = 16$; 2.0%), chronic respiratory failure ($n = 25$; 3.2%), cerebrovascular disease ($n = 46$; 5.8%), cardiovascular disease ($n = 164$; 20.7%), acute respiratory failure and pulmonary oedema ($n = 64$; 8.1%), cancer-related causes (24; 3.0%), trauma (14; 1.8%), and other unspecific causes such as cerebral oedema ($n = 247$; 31.2%) and senility ($n = 81$; 10.2%) and others (110; 13.9%). The participants who had died had at baseline a mean age of 89.1 ± 2.9 years (median: 88.6 years; range: 85.0–100.6 years), and at death an age of 91.7 ± 3.1 years (median: 91.5 years; range: 85.0–104.4 years). The mean duration of follow-up for the participants who died was 2.6 ± 1.3 years (4.46 years; range: 0.01–5.7 years).

In univariate analysis, higher risk of death was associated with parameters like older age, male sex, region of habitation, and prevalence of diabetes (Table 1). In the multivariable analysis, higher risk of death remained to be significantly associated with older age, male sex, urban region of habitation, lower physical activity, higher serum concentration of glucose and creatinine, higher prevalence of diabetes, and lower cognitive score (Table 4). Using this model and adding the prevalence or stage of ocular parameters to the list of independent variables, such as the prevalence of AMD (any AMD: $P = 0.90$; early AMD: $P = 0.90$; intermediate AMD: $P = 0.15$, late AMD: $P = 0.32$), reticular pseudodrusen ($P = 0.90$), open-angle glaucoma prevalence ($P = 0.11$) and stage ($P = 0.10$), angle-closure glaucoma prevalence ($P = 0.98$) and stage ($P = 0.65$), nuclear cataract prevalence ($P = 0.07$) and degree ($P = 0.14$), cortical cataract prevalence ($P = 0.46$) and degree ($P = 0.64$), axial length ($P = 0.21$) and intraocular pressure ($P = 0.87$), these parameters were not significantly associated with the occurrence of death (Table 4).

Similar results were obtained in Cox proportional hazards models analysing all-cause mortality. With adjustment for older age, male sex, region of habitation, physical activity, serum concentration of glucose and cognitive function score, the prevalence of AMD (any AMD: $P = 0.95$; early AMD: $P = 0.72$; intermediate AMD: $P = 0.82$; late AMD: $P = 0.44$), prevalence ($P = 0.54$) and stage ($P = 0.38$) of

Table 4. Associations (multivariable analysis) between occurrence of death and systemic and ocular parameters in the Ural Very Old Study.

	Ural Very Old Study		
	Odds ratio	**95% confidence interval**	***P*-value**
Age (years)	1.16	1.10, 1.22	<0.001
Sex (women/men)	2.01	1.50, 2.77	<0.001
Region of habitation (rural/urban)	3.20	2.25, 4.55	<0.001
Physical activity (In your leisure time, do you do any moderate intensity activities like brisk walking, cycling or swimming for at least 10 min at a time?)	0.70	0.53, 0.93	0.01
Serum concentration of triglycerides (mmol/L)	0.75	0.62, 0.91	0.003
Serum concentration of glucose (mmol/L)	1.12	1.01, 1.24	0.03
Serum concentration of creatinine (mmol/L)	1.007	1.001, 1.014	0.03
Diabetes mellitus, prevalence (no/yes)	1.70	1.07, 2.71	0.02
Mini Mental Test score	0.94	0.92, 0.97	<0.001
Parameters, added separately to the model:			
Visual acuity, best corrected (logMAR), binocular	1.06	0.86, 1.31	0.58
Diabetic retinopathy, prevalence (no/yes)	–	–	1.00
Age-related macular degeneration, any	1.15	0.85, 1.55	0.38
Age-related macular degeneration, early stage	1.01	0.66, 1.65	0.97
Age-related macular degeneration, intermediate stage			
Age-related macular degeneration, late stage	0.79	0.50, 1.23	0.30
Reticular pseudodrusen	1.08	0.74, 1.56	0.69
Open-angle glaucoma, prevalence	1.41	0.89, 2.23	0.14
Open-angle glaucoma, stage	1.09	0.96, 1.23	0.19
Angle-closure glaucoma, prevalence			
Angle-closure glaucoma, stage			
Nuclear cataract, prevalence	1.63	0.90, 2.95	0.11
Nuclear cataract, stage	1.14	0.97, 1.34	0.11
Cortical cataract, prevalence	2.22	0.54, 9.19	0.27
Cortical cataract, stage	0.99	0.85, 1.14	0.85
Axial length (mm)	1.10	0.95, 1.28	0.21
Intraocular pressure (mmHg)	1.02	0.99, 1.05	0.21

glaucoma, prevalence ($P = 0.47$) and degree ($P = 0.63$) of nuclear cataract, prevalence ($P = 0.63$) and degree ($P = 0.27$) of cortical cataract, best corrected visual acuity ($P = 0.06$; HR: 1.11; 95%CI: 0.998, 1.22), intraocular pressure ($P = 0.06$; HR: 1.01; 95%CI: 1.000, 1.03), and axial length ($P = 0.53$). The risk of cardiovascular/cerebrovascular diseases as death cause was not associated with the prevalence of AMD (any: $P = 0.18$; early AMD: $P = 0.42$; intermediate AMD: $P = 0.10$; late AMD: $P = 0.46$), prevalence ($P = 0.30$) and stage ($P = 0.18$) of glaucoma, prevalence ($P = 0.85$) and degree ($P = 0.38$) of nuclear cataract, prevalence ($P = 0.35$) and degree ($P = 0.77$) of cortical cataract, intraocular pressure ($P = 0.37$) and axial length ($P = 0.21$). The model was adjusted for older age, male sex, region of habitation, physical activity, serum concentration of glucose and cognitive function score,

DISCUSSION

In the UEMS, higher death occurrence was associated with lower best corrected visual acuity (OR: 1.86) and higher prevalence of diabetic retinopathy (OR: 2.97), with adjusting for a multitude of systemic parameters. Other ocular parameters were not significantly associated with death occurrence. In the UVOS, none of the tested ocular parameters was correlated with mortality in multivariable analysis.

The findings made in both of our study cohorts agree with, and partially are contradictory to, observations made in previous investigations. In the Age-Related Eye Disease Study (AREDS), advanced AMD was associated with an increased mortality (relative risk: 1.41), with advanced AMD being related to cardiovascular deaths [1]. In addition, higher mortality was associated with lower visual acuity, nuclear cataract and status after cataract surgery [1]. In a similar manner in the AREDS-2 project, higher prevalence of late AMD, bilateral cataract surgery, and visual acuity of <20/40 correlated with increased mortality [10]. In the Indian Andhra Pradesh Eye Disease Study, any type of cataract and status after cataract surgery and visual impairment were related to an increased mortality [6]. As in our study, a population-based screening of more than 30,000 elderly citizens of Malmö/Sweden revealed that in that cohort mortality was not associated with glaucoma [2]. In the Singapore Malay Eye Study, as in our study, visual impairment and diabetic retinopathy correlated with higher all-cause mortality and cardiovascular mortality, and cataract, glaucoma and AMD were not related with mortality [7]. In contrast to findings of our study, late AMD in the Melbourne Collaborative Cohort Study was associated with an increased rate of all-cause mortality, and choroidal neovascularization and geographic atrophy were related with death from cardiovascular disease and tobacco-related cancer, respectively [8]. Reticular pseudodrusen or the earlier AMD stages, as in our study cohorts, were not correlated with mortality [8]. As in our study, diabetic retinopathy was a risk factor for death in the Wisconsin Epidemiologic Study of Diabetic Retinopathy conducted by Klein and colleagues and in a meta-analysis [12, 29]. With respect to the relationship between glaucoma and mortality, the Blue Mountains Eye Study reported on an increased

cardiovascular mortality in persons with previously diagnosed glaucoma [3]. In the population-based National Health and Nutrition Examination Survey as a representative health survey in the United States, glaucoma was not related with an increased mortality in multivariable analysis [30]. While these previous studies and our investigation differ in the associations of AMD, glaucoma and cataract with mortality, they agree that vision impairment and diabetic retinopathy, if examined, were related to an increased mortality. The reasons for the discrepancies between the studies may be differences in the type of recruitment of study participants (population-based based versus hospital-based or referral centre-based), differences in the ethnic background and age of the study populations, differences in the number of ocular parameters and diseases assessed in the same study, and differences in the number of non-ophthalmological parameters and general medical disease examined and included into the multivariable analysis. While all previous studies examined mostly only one or few ocular parameters and diseases and only few general diseases and mortality-related risk factors, the present investigation included all major ocular diseases and ocular major risk for ocular diseases such as intraocular pressure and axial length, in addition to a panoply of major systemic, mortality-related disorders such as arterial hypertension, diabetes mellitus, hyperlipidaemia, chronic obstructive pulmonary disease, depression and anxiety, obesity, socioeconomic parameters including level of education, smoking and alcohol consumption, diet, physical activity, and others. It may have markedly reduced the risk of a bias due to confounding factors which may not have been taken fully into account in previous, smaller-scaled studies. In addition, the present investigation included two cohorts, one of them with a high minimum age of 85 years and correspondingly, a high mortality during the follow-up. In this present investigation, diabetic retinopathy in the UEMS cohort was the only ocular disorder which was related to an increased mortality, showing the importance of fundus examination to stage the damage caused by diabetes. The lack of an association between diabetic retinopathy and mortality in the UVOS population may likely have been due to the low prevalence of diabetic retinopathy in that study cohort, with 2 out of 1526 participants affected.

Interestingly, vision impairment was an additional risk factor for death, independent of other ocular parameters. It may suggest that vision impairment-related changes in lifestyle may play a role in a shortened life expectancy. It may also show the importance to provide best correcting glasses for the elderly population, for distant and for near vision. The finding that all other ocular disease examined in the study were not related with remaining life expectancy suggests that their aetiology is mostly independent of major systemic parameters, including cardiovascular and cerebrovascular disorders.

Limitations of our study should be mentioned. First, our two study cohorts differed from the general population of Russia in the ethnic background. In the multivariable analysis, however, ancestry was not correlated with mortality, so that this limitation might not have markedly affected the conclusions of the study. Second, the increased mortality during the COVID-19 pandemic will have influenced the death numbers, while it remained unexplored whether the pandemic-related increase in the mortality affected the mortality of the specific eye diseases.

In conclusion, diabetic retinopathy was the only major ophthalmic disease, in addition to vision impairment, which was associated with an increased death risk.

SUMMARY

What was known before

- The results of previous studies were not conclusive on associations between the prevalence and severity of major ocular diseases with mortality.

What this study adds

- Diabetic retinopathy and vision impairment were the only ocular parameter and disease which were associated with an increased mortality in middle-aged individuals.

DATA AVAILABILITY

The microdata will be available from the corresponding author upon reasonable request.

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AUTHOR CONTRIBUTIONS

Study design: MMB, GMK, SPJ, JBJ; conducting the research: MMB, GMK, EMR, SPJ, AMT, AAF, JBJ; interpreting the results: MMB, GMK, EMR, SPJ, AMT, AAF, JBJ; funding: MMB; statistical analysis: SPJ, JBJ; writing the first manuscript draft: SPJ, JBJ; revision and final approval of the manuscript: MMB, GMK, EMR, SPJ, AMT, AAF, JBJ.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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