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RETINAL DISORDERS

Prevalence of age-related macular degeneration and retinal pseudodrusen in an elderly population. The ural very old study

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Abstract

Purpose To assess the prevalence of age-related macular degeneration (AMD) and reticular pseudodrusen (RPD) in very old individuals.

Methods The population-based Ural Very Old Study consisted of 1526 (81.1%) out of 1882 eligible individuals aged 85 + years. All individuals living in the study regions and having an age of 85 + years were eligible for the study. The presence of AMD and RPDs was assessed on color fundus photographs, red-free fundus images, and optical coherence tomographic images.

Results The study included 932 (61.1% of 1526) individuals (age:88.6 ± 2.7 years) with available fundus images. Prevalence of any, early, intermediate and late AMD was 439/932 (47.1%; 95%CI:44.0,50.0), 126/932 (13.5%; 95% CI:11.0,16.0), 185/932 (19.8%; 95% CI:17.3,22.3) and 128/932 (13.7%; 95% CI:11.7,15.7), respectively. Neovascular AMD was present in 63 eyes (6.8%;95%CI:5.3,8.3) and geographic atrophy in 65 eyes (7.0%;95%CI:5.0,9.0). Higher prevalence of any AMD and late AMD was significantly correlated with urban region of habitation (OR:3.34; 95% CI:2.37,4.71; $P < 0.001$), and with older age (OR:1.12; 95% CI:1.04,1.19; $P = 0.001$), female sex (OR:1.63; 95%CI:1.02,2.60; $P = 0.04$), and urban region of habitation (OR:2.89; 95% CI:1.59,5.26; $P < 0.001$), respectively. RPDs (assessed in 889 (58.3%) study participants) were present in 220/889 participants (24.7%; 95%CI:21.7,27.7). Higher RPD prevalence was associated (multivariable analysis) with higher serum concentration of the rheumatoid factor (OR:1.15; 95% CI:1.04,1.28; $P = 0.008$), shorter axial length (OR :0.84;95%CI:0.71,0.00;$P = 0.04$), and higher degree of nuclear cataract (OR:1.06; 95% CI:1.01,1.12; $P = 0.02$). AMD was the main cause for vision impairment in 230 (24.7%) participants, for moderate-to-severe vision impairment in 75 (8.0%; 95% CI: 6.4, 10.0) individuals, and for blindness in 15 (1.6%; 95%CI: 0.8, 2.5) persons respectively.

Conclusions In this ethnically mixed, very old population, AMD prevalence (any AMD:47.1%;late AMD:13.7%) was statistically independent of most systemic and ocular parameters. Higher RPD prevalence correlated with shorter axial length.

Key messages

What is known

- The prevalence of age-related macular degeneration (AMD) has been explored in many studies and societies. Information is missing about its prevalence and associations in very old individuals. The same holds true for reticular pseudodrusen of the macula.

What is new

- In an ethnically mixed, very old population in Bashkortostan / Russia, the prevalence of AMD (any AMD: 47.1%; late AMD:13.7%) was statistically independent of most systemic and ocular parameters.
- Higher prevalence of reticular pseudodrusen correlated with shorter axial length.

Songhomitra Panda-Jonas and Jost B. Jonas equally contributed to the study and share the last authorship.

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Keywords Age-related macular degeneration · Reticular pseudodrusen · Subretinal drusenoid deposits · Population-based study · Ural Very Old Study

Introduction

Age-related macular degeneration (AMD) belongs to the most common causes of irreversible vision impairment and blindness worldwide, with prevalence rates higher for individuals of European descent as compared to Asians and Africans [1, 2]. A recent systematic review and meta-analysis revealed that in the year 2020 about 6.2 million individuals were moderately to severely visually impaired and 1.8 million persons were blind due to AMD [2]. Despite the relatively high number of previous studies addressing the AMD prevalence, only few investigations have been performed so far on study populations with an age of 80 + or 85 + years [3–8]. In addition, information about the prevalence of AMD in Russia and Central Asia has been scarce so far, and many previous studies examined the prevalence of AMD without markedly focusing on associations between the AMD prevalence and other ocular and systemic parameters.

Besides of drusen of the retinal pigment epithelium (RPE) and pigmentary RPE changes, subretinal drusenoid deposits or reticular pseudodrusen (RPD) are part of the spectrum of age-related changes in the macular region [9–14]. Clinical studies showed that RPDs indicate an increased risk for late AMD, including the development of retinal angiomatous proliferations, outer retinal atrophy, and geographic atrophy [9–14]. Upon ophthalmoscopy and on color fundus images, RPDs appear as a reticular pattern of small yellow-white lesions with a diameter of 125 µm to 250 µm and are often visible first in the superior outer macula region before extending circumferentially. In contrast to conventional drusen of the RPE, RPDs do not fluoresce on fluorescein or indocyanine green angiography and they are ophthalmoscopically better visible in red-free light, on near-infrared reflectance images using a confocal scanning laser ophthalmoscopy, and on spectral-domain optical coherence tomographic (OCT) images than on conventional color fundus images [3, 9, 10, 15]. Based on clinical investigations using OCT and confocal scanning laser ophthalmoscopy, and according to histological investigations, RPDs are the ophthalmoscopical equivalent of subretinal deposits. These are positioned on top of the RPE, in contrast to conventional RPE drusen which are found under the RPE layer [11, 12]. Only few population-based studies have examined the prevalence of RPDs so far and analyzed their associations with other ocular and systemic parameters, and none of these investigations were focused on a very elderly population [4–8]. In addition, some of the previous studies did not apply OCT imaging for the detection of RPDs.

In view of the importance of AMD and RPDs and considering the gap of information on their prevalence in the very elderly population group in general and in particular in Russia and Central Asia, and considering the importance of knowing the associations of RPDs with other ocular and systemic parameters, we performed the present study on a very elderly, multi-ethnic population group in Southern Russia to explore the prevalence and associations of AMD and RPDs in a population aged 85 + years and recruited in a population-based manner.

Methods

The Ural Very Old Study (UVOS) is a population-based survey conducted in the Republic of Bashkortostan / Russia in the Kirovskii district of the capital Ufa and in a rural region in the Karmaskalinsky district in a distance of 65 km from Ufa [16]. Inclusion criteria were living in the study regions and an age of 85 + years. The Ethics Committee of the Academic Council of the Ufa Eye Research Institute approved the study and informed written consent was obtained from all participants. Bashkortostan has a population of about 4 million people and is geographically located in the Volga district in the west of the southern Ural Mountains about 1300 km east of Moscow. Its capital Ufa is an economic, scientific and cultural center and has a population of 1.1 million inhabitants including Russians, Bashkirs, Tatars, and other ethnicities.

Study population

The study included 1526 (81%) out of 1882 eligible inhabitants (390 (25.6%) men; 1136 (74,4%) women). The urban group (1238 (81.3%) out of 1523 persons) and the rural group (288 (80.2%) out of 359 persons) did not vary significantly in the participation rate. The sex distribution (74.4% and 77%) was comparable between the study population and the Russian population with an age of 85 + years as examined in the recent census carried out in Russia in 2021 [17]. The same held true for the comparison in the age distribution, in particular in view of the high age of 85 years as inclusion criterion. The population of Russia with an age of 85 + years and the UVOS study population both show a marked preponderance of females.

Examinations

The study team visited the participants in their homes and medical doctors and trained nurses undertook a standardized interview with more than 300 questions on the socioeconomic background, including the self-reported ethnicity, level of education, former occupation, family income and family estate (ownership of a house and second house, telephone, smartphone, laptop, television, bicycle and car), and size and structure of the family; diet (number of meals per day, frequency and amount of intake of vegetables, fruits, whole grain and meat, consumption of tea and coffee, use of animal fat or cooking oil); smoking (since when or stopped, cigarettes or other types of tobacco products, symptoms of smoking cessation); house heating by wood stove; alcohol consumption (since when or stopped, alcohol consumption-related wrongdoing); physical activity (frequency and intensity of daily work, leisure time activities, sitting or reclining); quality of life and quality of vision; symptoms of chronic obstructive pulmonary disease, asthma, kidney disease and orthopedic disorders; history of any type of injuries and inter-personal violence; and health assessment questions. The questionnaire additionally included questions on the medical history including known diagnosis and therapy of major disorders such as diabetes mellitus, arterial hypertension, cardiovascular diseases, headache, neck pain, thoracic spine and low back pain, depression, suicidal ideas, anxiety, questions on previous neurologic attacks including stroke, epilepsy, polyneuropathy and unconsciousness, and questions on cognitive function and hearing loss. 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) [16].

As also already described in detail previously, the physical examinations included measurement of anthropomorphic parameters, arterial blood pressure and pulse rate, and dynamometric assessment of the handgrip strength (dynamometer—dk 140, ZAO Nizhnetagilskiy Medical Instrument Plant, Nizhniy Tagil, Russia). Using blood samples taken under fasting conditions, we measured the serum concentrations of various substances and molecules including transaminases, bilirubin, blood lipids, C-reactive protein, rheumatoid factor, glucose, creatinine, urea, nitrogen, hemoglobin, and blood count. Arterial hypertension was defined as recommended by the American College of Cardiology/American Heart Association in 2017. 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 hypoglycemic agents) were the criteria of the definition of diabetes. Applying the Center for Epidemiologic Studies Depression Scale (CES-D) Scoresheet, we assessed prevalence and degree of depression. We applied the Guidelines for Accurate and Transparent Health Estimates Reporting (GATHER statement guidelines) [18].

The ophthalmological examinations consisted of the automated refractometry, measurement of best corrected visual acuity, static perimetry (PTS 1000 Perimeter, Optopol Technology Co., Zawercie, Poland; screening test program: 50° in all directions; 82 test points), anterior segment imaging using the Scheimpflug camera (Pentacam HR, Typ70900, OCULUS, Optikgeräte GmbH Co., Wetzlar, Germany), slit lamp biomicroscopy of the anterior and posterior ocular segment, non-contact tonometry (Tonometer Kowa KT-800, Kowa Company Ltd., Hamamatsu City, Japan), examination for the presence of pseudoexfoliation of the lens after medical mydriasis, photography of the cornea and lens (Topcon slit lamp and camera, Topcon Corp. Tokyo, Japan), photography of the optic disc and macula (VISUCAM 500, Carl Zeiss Meditec AG, Jena, Germany), spectral-domain optical coherence tomography (RS-3000, NIDEK co., Ltd., Aichi Japan) of the optic nerve head and macula, and measurement of the axial length by sonography (Ultra-compact A/B/P ultrasound system, Compact touch; Quantel Medical, Cournon d'Auvergne, France).

While the interview was conducted in the homes for all study participants, the other examinations were scheduled to be undertaken in the hospital. A part of individuals, who were interviewed but could not go the hospital for the other assessments, were examined in their homes by portable devices.

Using the fundus photographs and the OCT images, we defined AMD as suggested by the Beckman Initiative for Macular Research Classification Committee [19]. AMD was graded into an early stage (RPE drusen diameter ≥ 63 and < 125 µm, without pigmentary abnormalities), intermediate stage (RPE drusen diameter > 125 µm, or pigmentary abnormalities associated with drusen with a diameter of ≥ 63 and < 125 µm), and a late stage AMD (neovascular AMD or geographic atrophy). The macular region within two-disc diameters of the fovea was examined for the AMD staging. For the diagnosis of RPDs, we additionally used the OCT images and the near infrared reflectance images. RPDs were defined as small yellow-white lesions with a diameter of about 125–250 µm on the fundus photographs, corresponding to subretinal material, located on top of the RPE as detectable on the OCT images. In contrast to the definition of AMD, the RPDs could be located outside of the region within two-disc diameters of the fovea. The minimal number of lesions for them to be counted as RPDs was 3. For the purpose of the study, eyes with RPDs and without typical drusen of the retinal pigment epithelium were categorized as not having AMD. Eyes presenting with RPDs and with typical drusenwere classified as having AMD. These eyes having AMD and simultaneously RPDs were included in the

analyses of both groups. All fundus images and OCT images were examined and graded by an experienced ophthalmologist (JBJ) in addition to a team of trained ophthalmologists. When the presence of AMD and RPD was assessed, both the fundus photographs and the OCT images were simultaneously available and were examined in a parallel manner. In the case of a unilateral occurrence of RPDs, the individual was considered to have RPDs. As recommended by the World Health Organization, we defined moderate to severe vision impairment as BCVA worse than 6/18 but equal to or better than 3/60 in the better eye or both eyes, and blindness as BCVA worse than 3/60 in the better eye or both eyes [2].

Statistical analysis

A commercially available statistical software package (SPSS for Windows, version 27.0, SPSS, Chicago, IL) was used for the statistical analysis. We calculated the mean values (presented as mean ± 95% confidence interval (CI)) of the main outcome parameters, i.e. prevalence of AMD and RPDs, and performed univariate binary analyses of the associations between the AMD prevalence or the RPD prevalence and other ocular and systemic parameters. It was followed by a multivariable binary regression analysis, with the AMD prevalence or RPD prevalence as the dependent parameter and as independent parameters all those variables that were associated ($P < 0.10$) with the AMD prevalence of the RPD prevalence in the univariate analyses. In a step-by-step manner, we dropped those variables out of the list of independent parameters that either showed a collinearity or which were no longer significantly associated with the outcome parameter. We determined the odds ratio (OR) and its 95% CIs. Comparisons in prevalence of parameters between groups were conducted using the Chi-square test, and comparisons in quantitative variables between groups were performed applying the Mann–Whitney test. All *P*-values were two-sided and considered statistically significant when the values were less than 0.05. We included only one randomly chosen eye per study participant into the statistical analysis.

Results

Study population

Out of 1882 eligible inhabitants aged 85 + years and living in the study regions, 1526 (81.1%) individuals participated in the study, were visited in their homes and underwent the interview (Fig. 1). Out of these 1526 individuals, 105 (6.9%) individuals had died after the interview before they could be taken to the hospital for the hospital-based examinations as part of the study; 246 (16.1%) individuals did not attend the hospital-based examinations and did not undergo any clinical examinations by portable examination devices in their homes, 423 (27.7%) individuals did not attend the hospital-based examinations but were clinically examined by portable devices in their homes; and 751 (49.2%) individuals were examined in the hospital. Out of the 1174 (76.9%) individuals who had undergone examinations in the hospital or at their homes, 932 individuals (61.1% out of the

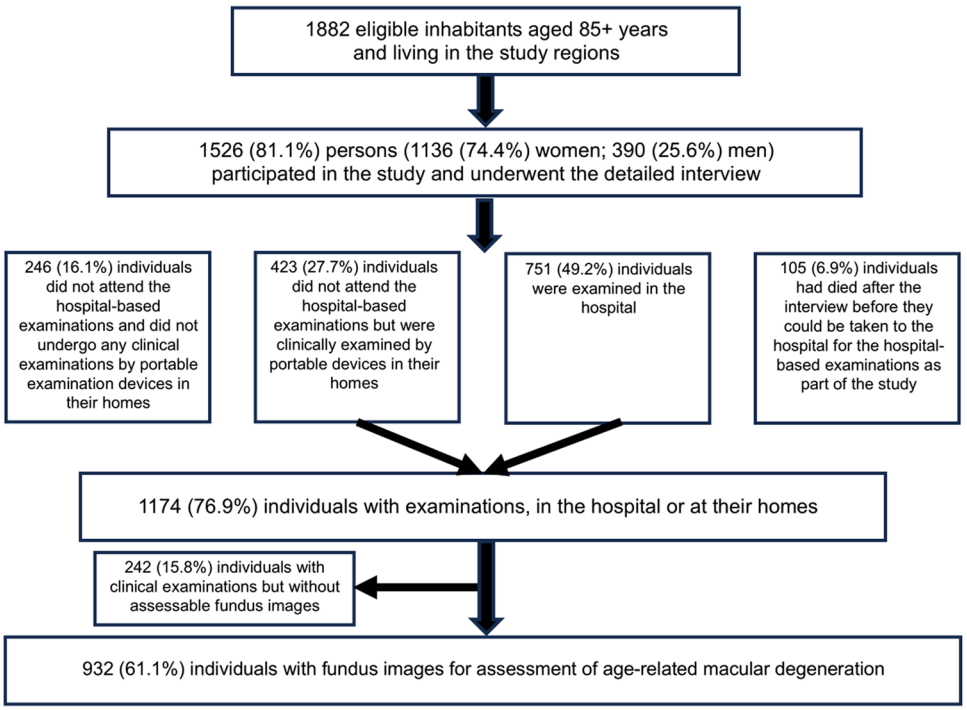

Fig. 1 Flowchart showing the composition of the population of the Ural Very Old Study

study participants or 49.5% out of the eligible population) (248 (26.6%) men; 684 (73.4%) women) had fundus images assessable for the examination for the presence and degree of AMD (Fig. 1). Reasons for an insufficient quality of the fundus images were mainly opacities of the optic media, such as dense cataracts or corneal scars, insufficient cooperation of the study participants for taking the fundus photographs, or other reasons. The study population was composed of 338 (36.3%) individuals of Russian ethnicity, 400 (42.9%) Volga Tatars, 111 (11.9%) Bashkirs, 32 (3.4%) Chuvash, 5 (0.5%) Mari, and 46 (5.0%) others. Volga Tatars and Bashkirs are Kipchak-Bulgar Turkic ethnic groups indigenous to Russia. Chuvash are a Turkic ethnic group, a branch of the Ogurs, native to an area stretching from the Idel-Ural (Volga-Ural) region to Siberia. Mari are a Finno-Ugric people in Eastern Europe, who have traditionally lived along the Volga and Kama rivers in Russia. The mean age was 88.6 ± 2.7 years (median: 88.0 years; range: 85 – 98.3 years), and the mean axial length was 23.1 ± 1.1 mm (median: 23.0; range: 19.37 – 28.63 mm). The individuals with macula images as compared to those without macula images were significantly younger (88.6 ± 2.7 years versus 89.1 ± 3.1 years; $P = 0.002$), while both groups did not differ significantly in sex (248 (26.6%) men; 684 (73.4%) women versus 142 (23.9%) men; 452 (76.1%) women; $P = 0.24$), and axial length (23.1 ± 1.1 mm versus 23.1 ± 1.2 mm; $P = 0.61$).

AMD and related factors (univariate analysis, multivariate analysis)

The prevalence of any, early, intermediate, and late AMD was 439/932 (47.1%; 95%CI: 44.0, 50.0), 126/932 (13.5%; 95%CI: 11.0, 16.0), 185/932 (19.8%; 95%CI: 17.3, 22.3), and 128/932 (13.7%; 95%CI: 11.7, 15.7), respectively. Within the group of individuals with late AMD (n = 128), 63 eyes (49.2% in the late AMD group or 128/932 (6.8%; 95%CI: 5.3, 8.3) in the total study population) had neovascular AMD, and 65 eyes (50.8% in the late AMD group or 65/932 (7.0%; 95%CI: 5.0, 9.0) in the total study population) showed a geographic atrophy, with the prevalence of GA being slightly ($P = 0.02$) higher.

In univariate analysis, higher AMD prevalence (any type) was associated ($P<0.05$) with the systemic parameters of urban region of habitation, lower body height, higher body mass index, waist circumference, and hip circumference, higher socioeconomic score and higher level of education, more physical activities, higher number of days with fruit intake and vegetable consumption, smaller number of cups of tea taken, higher prevalence of a history of thyroid gland disease, higher serum concentration of high-density lipoproteins and cholesterol, lower serum concentration of aspartate aminotransferase, low-density lipoproteins, and C-reactive protein, lower erythrocyte sedimentation rate, lower count of eosinophilic granulocytes, lower systolic and diastolic blood pressure, higher right ankle-brachial index, higher cognitive score, and stronger hand grip force (Table 1). A higher AMD prevalence (any type) was associated ($P<0.10$) with the ocular parameters of deeper anterior chamber depth and wider anterior chamber angle, lower intraocular pressure (IOP), lower degree and higher prevalence of nuclear cataract, higher degree and prevalence of cortical cataract, and higher prevalence of status after cataract surgery (Table 2).

The multivariable analysis included as independent parameters all variables with a P-value of <0.10 in their univariate analysis with the AMD prevalence. After dropping out of the list of independent parameters those which either showed a collinearity or which were no longer significantly associated with the AMD prevalence, a higher AMD prevalence remained to be significantly associated with urban region of habitation (OR: 3.34; 95%CI: 2.37, 4.71; $P<0.001$). After adding the ocular parameters, which were significantly associated with the AMD prevalence in the univariate model, we dropped the parameters of cortical cataract prevalence ($P=0.82$) and degree ($P=0.69$), pseudophakia ($P=0.97$), nuclear cataract prevalence ($P=0.50$) and degree ($P=0.35$), anterior chamber depth ($P=0.62$), IOP ($P=0.40$), and anterior chamber angle ($P=0.05$), so that finally a higher AMD prevalence remained to be correlated with urban region of habitation. If we added the parameters of age ($P=0.99$), sex ($P=0.74$), current smoking ($P=0.51$), serum concentration of rheumatoid factor ($P=0.12$) or axial length ($P=0.41$) separately to the model, none of these parameters was significantly associated with the AMD prevalence.

The prevalence of late AMD (geographic atrophy and neovascular AMD combined) was correlated (multivariable analysis) with older age (OR: 1.12; 95%CI: 1.04, 1.19; $P=0.001$), female sex (OR: 1.63; 95%CI: 1.02, 2.60; $P=0.04$), and urban region of habitation (OR: 2.89; 95%CI: 1.59, 5.26; $P<0.001$), while other parameters when added separately to the model, were not significantly associated with the prevalence of late AMD (waist circumference, $P=0.45$; level of education, $P=0.51$; number of days with fruit consumption, $P=0.63$; current smoking: $P=0.99$; serum concentration of aspartate aminotransferase, $P=0.12$; high-density lipoproteins, $P=0.18$, rheumatoid factor, $P=0.22$; cognitive score, $P=0.12$; axial length, $P=0.39$; intraocular pressure, $P=0.35$; nuclear cataract prevalence, $P=0.10$).

RPD and related factors (univariate analysis, multivariate analysis)

Reticular pseudodrusen were assessed in 889 study participants (242 (27.2%) men, 647 (72.8%) women) with a mean age of 88.5 ± 2.6 years (median: 87.9 years; range: 85 to 98.3 years) and a mean axial length of 23.1 ± 1.1 mm (median:

Table 1 Associations (univariate analysis) between the prevalence of any age-related macular degeneration and systemic parameters in the Ural Very Old Study. AMD was defined as suggested by the Beckman Initiative for Macular Research Classification Committee

Any Age-related Macular Degeneration					Reticular Pseudodrusen		
Parameter	Interval	Odds Ratio (OR)	95% Confidence Interval of OR	*P*-Value	Odds Ratio (OR)	95% Confidence Interval of OR	*P*-Value
Age	1-year intervals	1.00	0.96, 1.05	0.88	1.02	0.97, 1.08	0.46
Gender	Men / Women	1.00	0.74, 1.33	0.68	1.09	0.77, 1.55	0.61
Region of habitation	Rural / Urban	3.34	2.37, 4.71	*< 0.001*	4.77	2.79, 8.15	*< 0.001*
Ethnicity	Any other ethnicity / Russian	1.05	0.80, 1.38	0.71	1.20	0.88, 1.64	0.26
Body height	1 cm	0.99	0.97, 1.00	*0.046*	0.97	0.96, 0.99	*0.002*
Body weight	kg	1.01	0.99, 1.02	0.31	1.00	0.98, 1.01	0.44
Body mass index	kg/m^2	1.04	1.01, 1.07	*0.03*	1.02	0.99, 1–06	0.25
Waist circumference	cm	1.02	1.01, 1.04	*< 0.001*	1.01	0.997, 1.03	0.12
Hip circumference	cm	1.02	1.01, 1.04	*< 0.001*	1.01	0.997, 1.03	0.13
Waist/hip circumference ratio	Ratio	4.57	0.94, 22.2	0.06	1.34	0.21, 8.43	0.75
Socioeconomic Score	Score	1.14	1.08, 1.21	*< 0.001*	1.07	1.003, 1.15	*0.04*
Level of education	Illiteracy / Passing 5th Grade / 8th Grade / 10th Grade / 11th Grade / Graduates / Specialized Secondary Education / Post Graduates	1.16	1.09, 1.23	*< 0.001*	1.10	1.02, 1.18	*0.02*
Do you spent leisure time mostly with sitting without physical activity	No/Yes	1.00	1.00, 1.00	0.24	0.91	0.65, 1.27	0.56
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?	No/Yes	1.81	1.11, 2.98	*0.02*	2.22	1.32, 3.71	*0.002*
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?	No/Yes	1.18	0.90, 1.54	0.23	1.12	0.82, 1.54	0.49
In a typical week, on how many days do you do physically moderate to intensive activities as part of your leisure time?	Number of days	1.08	0.99, 1.18	0.09	1.09	0.68, 1.73	0.73
Smoking currently	No/Yes	0.56	0.14, 1.25	0.41	1.53	0.38, 6.16	0.55
Alcohol consumption, any	No/Yes	1.17	0.79, 1.72	0.43	0.90	0.57, 1.43	0.65
Number of daily meals	Number of days	0.99	0.84, 1.16	0.86	1.10	0.92, 1.32	0.32
In a week how many days do you eat fruits?	Number of days	1.13	1.06, 1.21	*< 0.001*	1.17	1.09, 1.27	*< 0.001*
In a week how many days do you eat vegetables?	Number of days	1.09	1.01, 1.18	*0.04*	1.08	0.98, 1.19	0.14
Type of cooking oil	Vegetarian / Butter	1.21	0.86, 1.69	0.28	0.82	0.55, 1.24	0.35
Food containing whole grain	No/Yes	1.06	0.62, 1.82	0.82	1.00	0.53, 1.86	0.99
Self-reported salt consumption per day	g	1.00	0.94, 1.07	0.99	1.08	0.99, 1.16	0.08

Table 1 (continued)

Any Age-related Macular Degeneration					Reticular Pseudodrusen		
Parameter	Interval	Odds Ratio (OR)	95% Confidence Interval of OR	*P*-Value	Odds Ratio (OR)	95% Confidence Interval of OR	*P*-Value
Degree of processing meat (weak – medium – strong)	weak – medium – strong	0.98	0.79, 1.22	0.87	0.76	0.59, 0.98	*0.04*
Number of cups of coffee taken daily	Number	1.07	0.83, 1.38	0.59	0.93	0.69, 1.26	0.63
Number of cups of tea taken daily	Number	0.88	0.78, 0.99	*0.03*	0.93	0.81, 1.07	0.32
Preference of green or black tea	Green / Equal / Black	0.64	0.30, 1.34	0.23	0.54	0.24, 1.22	0.14
History of cardiovascular disorders including stroke	Yes/No	0.90	0.691.18	0.45	0.85	0.62, 1.16	0.31
History of angina pectoris	No/Yes	0.89	0.53, 1.50	0.65	0.63	0.31, 1.27	0.20
History of asthma	No/Yes	094	0.35, 2.55	0.90	0.46	0.13, 1.64	0.23
History of arthritis	No/Yes	0.89	0.68, 1.16	0.40	0.92	0.67, 1.26	0.61
History of previous bone fractures	No/Yes	1.04	0.79, 1.35	0.80	1.15	0.84, 1.57	0.39
History of low back pain	No/Yes	0.92	0.71, 1.20	0.55	1.00	0.73, 1.37	0.99
History of thoracic spine pain	No/Yes	1.04	0.79, 1.37	0.81	1.03	0.75, 1.43	0.84
History of neck pain	No/Yes	0.97	0.70, 1.34	0.83	1.03	0.70, 1.51	0.89
History of headache	No/Yes	0.82	0.63, 1.06	0.12	0.85	0.63, 1.16	0.30
History of cancer	No/Yes	1.27	0.80, 2.03	0.31	0.94	0.54, 1.63	0.82
History of dementia	No/Yes	0.73	0.41, 1.28	0.27	0.79	0.39, 1.62	0.52
History of diarrhea	No/Yes	2.27	0.56, 9.13	0.25	1.53	0.38, 6.16	0.55
History of iron-deficiency anemia	No/Yes	1.26	0.66, 2.42	0.48	1.25	0.61, 2.57	0.54
History of low blood pressure and hospital admittance	No/Yes	0.34	0.11, 1.05	0.06	0.18	0.02, 1.40	0.10
History of osteoarthritis	No/Yes	0.83	0.59, 1.17	0.29	0.66	0.43, 1.02	0.06
History of skin disease	No/Yes	1.18	0.69, 1.99	0.55	0.56	0.27, 1.17	0.13
History of thyroid disease	No/Yes	1.99	1.19, 3.32	*0.009*	1.49	0.86, 2.60	0.16
History of falls	No/Yes	0.80	0.62, 1.04	0.09	1.00	0.78, 1.27	0.98
History of unconsciousness	No/Yes	0.87	0.56, 1.35	0.53	0.59	0.33, 1.07	0.08
Age of the last menstrual bleeding	Years	1.02	0.98, 1.06	0.27	1.03	0.98, 1.08	0.24
Age of last regular menstrual bleeding	Years	1.02	0.98, 1.06	0.32	1.04	0.99, 1.08	0.15
History of diabetes mellitus	Yes / No	1.30	0.83, 2.04	0.26	0.72	0.40, 1.29	0.26
Serum concentration of:							
Alanine aminotransferase	IU/L	1.02	1.00, 1.03	0.05	1.01	0.99, 1.03	0.23
Aspartate aminotransferase	IU/L	0.98	0.96, 0.99	*<0.001*	0.97	0.96, 0.99	*<0.001*
Aspartate aminotransferase-to- Alanine aminotransferase ratio	Ratio	0.84	0.75, 0.93	*0.001*	0.80	0.69, 0.94	*0.005*

Table 1 (continued)

Any Age-related Macular Degeneration					Reticular Pseudodrusen		
Parameter	Interval	Odds Ratio (OR)	95% Confidence Interval of OR	*P*-Value	Odds Ratio (OR)	95% Confidence Interval of OR	*P*-Value
Bilirubin, total	µmol/L	0.99	0.98, 1.01	0.24	1.00	0.98, 1.02	0.87
High-density lipoproteins	mmol/L	1.50	1.27, 1.78	*< 0.001*	1.72	1.42, 2.10	*< 0.001*
Low-density lipoproteins	mmol/L	0.88	0.78, 0.995	*0.04*	0.86	0.74, 1.001	0.05
Cholesterol	mmol/L	1.11	1.001, 1.023	*0.047*	1.15	1.02, 1.30	*0.02*
Triglycerides	mmol/L	0.84	0.70, 1.01	0.06	0.94	0.76, 1.17	0.58
Rheumatoid factor	IU/mL	1.07	0.99, 1.16	0.09	1.10	1.01, 1.20	*0.02*
Erythrocyte sedimentation rate	Mm/min	0.99	0.98, 1.00	*0.045*	0.98	0.97, 0.997	*0.02*
C-reactive protein	mg/L	0.94	0.88, 0.997	*0.04*	0.96	0.89, 1.04	0.34
Glucose	mmol/L	0.95	0.88, 1.03	0.22	0.88	0.78, 0.99	*0.03*
Urea	mmol/L	1.03	0.97, 1.09	0.34	1.02	0.95, 1.10	0.52
Creatinine (µmol/L)	µmol/L	1.00	0.99, 1.01	0.99	1.002	0.996, 1.01	0.49
Hemoglobin	g/L	1.002	0.995, 1.01	0.51	1..04	0.996, 1.01	0.32
Erythrocyte count	10^6 cells / µL	1.15	0.89, 1.48	0.28	1.15	0.85, 1.56	0.37
Leukocyte count	10^9 cells / L	1.07	0.98, 1.16	0.16	1.00	0.90, 1.11	0.95
Rod-core granulocytes	% of leukocytes	0.97	0.89, 1.05	0.40	0.97	0.88, 1.07	0.50
Segment nuclear granulocyte	% of leukocytes	1.00	0.99, 1.02	0.79	0.99	0.97, 1.01	0.30
Eosinophil granulocytes	% of leukocytes	0.85	0.74, 0.98	*0.02*	0.88	0.74, 1.03	0.12
Lymphocytes	% of leukocytes	1.00	0.98, 1.02	0.79	1.01	0.99, 1.03	0.34
Monocytes	% of leukocytes	0.99	0.94, 1.05	0.83	1.00	0.94, 1.06	0.88
Prevalence of diabetes mellitus	Yes/No	1.01	0.69, 1.48	0.98	0.77	0.47, 1.25	0.29
Estimated glomerular filtration rate	mL/min/1.73m^2	0.99	0.98, 1.01	0.48	1.00	0.99, 1.02	0.77
Anemia (serum hemoglobin concentration < 140 g/L in men, < 130 g/L in women)	No/Yes	0.83	0.64, 1.08	0.17	0.77	0.56, 1.05	0.10
Blood pressure, systolic (SBP)	mm Hg	0.994	0.989, 0.999	*0.02*	0.998	0.992, 1.004	0.61
Blood pressure, diastolic (DBP)	mm Hg	0.994	0.985, 1.004	0.20	0.994	0.982, 1.01	0.28
Blood pressure, mean	mm Hg	0.992	0.984, 1.00	0.055	1.00	0.99, 1.01	0.36
Arterial hypertension	No/Yes	1.00	0.68, 1.47	0.99	1.11	0.70, 1.75	0.67
Arterial hypertension, stage	0–4	0.88	0.77, 0.99	*0.04*	0.95	0.82, 1.10	0.51
Ankle-brachial index, right		16.2	1.81, 145.6	*0.01*	4.11	0.33, 52.0	0.27
Ankle-brachial index, left		4.91	0.59, 41.2	0.14	3.41	0.28, 41.8	0.34
Metabolic syndrome	No/Yes	1.07	0.82, 1.40	0.60	0.86	0.63, 1.17	0.33
Cognitive score (Mini Mental Test)		1.03	1.01, 1.06	*0.006*	1.06	1.03, 1.10	*< 0.001*

Table 1 (continued)

Any Age-related Macular Degeneration					Reticular Pseudodrusen		
Parameter	Interval	Odds Ratio (OR)	95% Confidence Interval of OR	*P*-Value	Odds Ratio (OR)	95% Confidence Interval of OR	*P*-Value
Prevalence of chronic obstructive pulmonary disease	No/Yes	0.82	0.48, 1.41	0.48	0.87	0.48, 1.59	0.66
Hearing loss	Hearing loss score (0–44)	1.00	0.99, 1.01	0.68	1.01	0.995, 1.02	0.37
Depression Score	Depression score unit (range: -4 to + 15)	1.00	0.99, 1.01	1.00	1.00	0.98, 102	0.91
State-Trait Anxiety Inventory	State-Trait Anxiety Inventory Score (range: -7 to 13)	1.00	0.99, 1.02	0.70	1.01	0.996, 1.03	0.13
Manual dynamometry, right hand	dekaNewton	1.01	1.001, 1.04	*0.04*	1.03	1.01, 1.05	*0.005*
Manual dynamometry, left hand	dekaNewton	1.02	0.999, 1.04	0.07	1.03	1.01, 1.05	*0.007*

23.0 mm; range: 19.37 – 28.63 mm). The group of individuals with RPD assessment did not differ from the group of participants with AMD assessment in age, gender and axial length (all $P > 0.05$). The reason, why RPDs could not be examined in all participants in whom the prevalence and stage of AMD were examined, were insufficient quality of the fundus images.

The RPD prevalence was 220/889 or 24.7% (95%CI: 21.7, 27.7). The RPD prevalence increased from the group of participants without AMD (3.1%; 95%CI: 1.6, 4.6) to the group of early AMD (50.0%; 95%CI: 41.0, 59.0), intermediate AMD (55.2%; 95%CI: 47.7, 62.7), and late AMD (46.7%; 95%CI: 31.7, 61.7).

In univariate analysis, a higher RPD prevalence correlated ($P < 0.10$) with the systemic parameters of urban region of habitation, smaller body height, higher socioeconomic score and higher level of education, more vigorous physical activity in the leisure time, higher number of days with fruit consumption, higher degree of meat processing, lower serum concentration of aspartate aminotransferase, glucose, higher serum concentration of high-density lipoproteins, cholesterol and rheumatoid factor, lower aspartate aminotransferase-to-alanine aminotransferase ratio, lower erythrocyte sedimentation rate, higher cognitive function score, and higher hand grip force (Table 1). The RPD prevalence was associated with the ocular parameters of lower intraocular pressure, higher prevalence of nuclear cataract, higher degree and prevalence of cortical cataract, higher prevalence of previous cataract surgery, and higher stage of glaucomatous optic nerve damage.

In the multivariable analysis, we dropped due to collinearity the parameter of socioeconomic score, and due to missing statistical significance, we dropped the parameters of serum concentration of cholesterol ($P = 0.83$), high-density lipoproteins ($P = 0.62$), aspartate amino transferase ($P = 0.86$), erythrocyte sedimentation rate ($P = 0.95$), vigorous physical activity in the leisure time ($P = 0.77$), salt consumption per day ($P = 0.81$), hand grip force ($P = 0.65$), serum concentration of low-density lipoproteins ($P = 0.47$), level of education ($P = 0.34$), degree of meat processing ($P = 0.09$), history of osteoarthritis ($P = 0.18$), serum glucose concentration ($P = 0.13$), alanine to aspartate aminotransferase ratio ($P = 0.27$), and anemia prevalence ($P = 0.07$). After adding the ocular parameters, which were significantly associated with the AMD prevalence in the univariate model, to the multivariable analysis, we dropped the parameters of cortical cataract prevalence ($P = 0.98$) and degree ($P = 0.82$), glaucoma prevalence ($P = 0.88$), IOP ($P = 0.66$), body height ($P = 0.17$), region of habitation ($P = 0.34$), number of days with fruit intake ($P = 0.11$), history of unconsciousness ($P = 0.17$), cognitive function score ($P = 0.06$), and pseudophakia ($P = 0.11$). In the final model, a higher RPD prevalence was associated with a higher serum concentration

Table 2 Associations (univariate analysis) between the prevalence of any age-related macular degeneration and ocular parameters in the Ural Very Old Study. AMD was defined as suggested by the Beckman Initiative for Macular Research Classification Committee

Any Age-related Macular Degeneration					Reticular Pseudodrusen		
Parameter	Interval	Odds Ratio (OR)	95% Confidence Interval of OR	*P*-Value	Odds Ratio (OR)	95% Confidence Interval of OR	*P*-Value
Refractive error, spherical equivalent	Diopters	0.99	0.94, 1.04	0.63	1.01	0.96, 1.07	0.64
Refractive error, cylindrical value	Diopters	0.99	0.90, 1.10	0.89	0.98	0.87, 1.10	0.70
Axial length	mm	0.94	0.82, 1.09	0.43	0.87	0.74, 1.02	0.08
Corneal refractive power	Diopters	1.07	0.97, 1.18	0.21	1.03	0.93, 1.15	0.55
Central corneal thickness	µm	1.00	0.997, 1.005	0.55	1.00	0.996, 1.01	0.89
Corneal volume	mm^3	1.01	0.99, 1.03	0.64	1.00	0.98, 1.02	0.78
Anterior chamber depth	mm	1.20	1.01, 1.44	*0.04*	1.13	0.94, 1.37	0.19
Anterior chamber volume	µL	1.003	0.999, 1.01	0.12	1.003	0.999, 1.02	0.12
Anterior chamber angle	Degree	1.02	1.00, 1.03	*0.047*	1.01	0.996, 1.03	0.13
Lens thickness	mm	0.94	0.82, 1.09	0.43	1.11	0.74, 1.66	0.61
Intraocular Pressure	mmHg	0.94	0.91, 0.97	*< 0.001*	0.95	0.91, 0.98	*0.005*
Nuclear cataract degree	Grade	0.75	0.63, 0.89	*0.001*	0.86	0.69, 1.06	0.15
Nuclear cataract, presence	Yes/No	1.07	1.03, 1.11	*< 0.001*	1.09	1.04, 1.14	*< 0.001*
Cortical cataract, degree	Percentage	1.27	1.11, 1.46	*< 0.001*	1.30	1.10, 1.54	*0.002*
Cortical cataract, presence	Yes/No	1.08	1.04, 1.12	*< 0.001*	1.08	1.04, 1.13	*< 0.001*
Status after cataract surgery	Yes / No	1.59	1.22, 2.06	*< 0.001*	1.52	1.12, 2.06	*0.008*
Fundus tessellation, macula region	Grade	1.00	0.96, 1.04	0.95	1.01	0.97, 1.06	0.59
Fundus tessellation, peripapillary region	Grade	1.00	0.96, 1.04	0.98	1.01	0.96, 1.06	0.76
Retinal nerve fiber layer thickness	µm	1.001	0.996, 1.01	0.67	1.00	0.99, 1.002	0.18
Pseudoexfoliation of the lens, degree	0–6	1.02	0.91, 1.14	0.76	1.09	0.96, 1.24	0.18
Pseudoexfoliation of the lens, presence	Yes/No	0.87	0.53, 1.42	0.58	0.95	0.53, 1.70	0.87
Glaucoma	Yes/No	0.84	0.64, 1.09	0.18	0.85	0.61, 1.17	0.31
Glaucoma stage	0–5	0.97	0.87, 1.08	0.52	1.13	1.01, 1.127	0.04
Diabetic retinopathy	Yes/No	0.000	0.000	1.00	0.000	0.000	1.00
Diabetic retinopathy, ETDRS grading	Scale	0.000	0.000	1.00			

Table 3 Associations (multivariable binary regression analysis) between the prevalence of age-related macular degeneration (AMD) or the prevalence of reticular pseudodrusen and systemic and ocular parameters in the Ural Eye and Medical Study

Parameter	Interval	Odds Ratio (OR)	95% Confidence Interval of OR	*P*-Value
Any AMD				
Region of habitation	rural / urban	3.34	2.37, 4.71	< 0.001
Late AMD (geographic atrophy and neovascular AMD combined)				
Age	years	1.12	1.04, 1.19	< 0.001
Sex	male / female	1.63	1.02, 2.60	0.04
Region of habitation	rural / urban	2.89	1.59, 5.26	< 0.001
Reticular Pseudodrusen				
Serum concentration of rheumatoid factor	IU/mL	1.15	1.04, 1.28	0.008
Axial length	mm	0.84	0.71, 0.99	0.037
Nuclear cataract presence	No / yes	1.06	1.01, 1.12	0.02

of the rheumatoid factor (OR: 1.15; 95% CI: 1.04, 1.28; $P = 0.008$), shorter axial length (OR: 0.84; 95% CI: 0.71, 0.99; $P = 0.037$), and higher degree of nuclear cataract (OR: 1.06; 95% CI: 1.01, 1.12; $P = 0.02$) (Table 3).

AMD was the main cause for vision impairment in 230 (24.7%) participants. It was the cause for moderate to severe vision impairment in 75 (8.0%; 95%CI: 6.4, 10.0) individuals, and for blindness in 15 (1.6%; 95%CI: 0.8, 2.5) persons.

Discussion

In our population-based study population, the prevalence of any, early, intermediate and late AMD was 47.1%, 13.5%, 19.8% and 13.7%, respectively. Within the group of individuals with late AMD, neovascular AMD as compared to geographic atrophy had a slightly higher prevalence (49.2% versus 50.8%). A higher prevalence of any AMD was significantly correlated with urban region of habitation. A more frequent occurrence of late AMD was associated with urban region of habitation, older age and female sex. In these models, other systemic parameters and ocular parameters were not significantly associated with the AMD prevalence. Prevalence of RPDs (24.7%) correlated with higher serum concentration of the rheumatoid factor, shorter axial length, and higher degree of nuclear cataract.

The prevalence of any AMD and of any stage of AMD in our elderly study population with an age of 85 + years markedly exceeded those reported in previous investigations on younger study populations. In a worldwide meta-analysis, the pooled prevalence of early, late, and any AMD for the population aged 45–85 years was 8.01% (95% credible intervals (CrI): 3.98, 15.49), 0.37% (CrI: 0.18, 0.77), and 8.69% (CrI: 4.26, 17.40), respectively, with no significant sex-related difference [1]. In that meta-analysis, persons of European descent as compared to Asians and Africans had a higher prevalence of early AMD and any AMD (early AMD: 11.2% versus 6.8% (Asians); any AMD: 12.3% versus 7.4% (Asians)), with no significant difference between Asians and Africans [1]. The AMD prevalence in our very elderly population was also markedly higher than the AMD prevalence in the population of the Ural Eye and Medical Study (UEMS) which was conducted in the same region by the same group of examiners, and which showed a prevalence of any AMD, early AMD, intermediate AMD and late AMD of 18.2%, 11.6%, 5.0%, and 1.6%, respectively, for individuals aged > 55 years [20]. For individuals with an age of 40 + years in the UEMS, the figures correspondingly were lower with a prevalence of any AMD, early AMD, intermediate AMD and late AMD of 14.1%, 9.4%, 3.8% and 1.0%, respectively [20]. While the AMD prevalence figures found in our study cannot directly be compared with the those obtained in other studies due to a lack of investigations focusing on such an old group of participants, the findings of the present study show and agree with the marked dependence of the AMD prevalence on age in a non-linear relationship.

Correspondingly, the prevalence of neovascular and geographic atrophy AMD (6.8% and 7.0%, respectively) in our study population was profoundly higher than in the UEMS population (geographic atrophy and neovascular AMD: 0.7% and 0.9% in the persons aged > 55 years; 0.4% and 0.5%, respectively in the individuals aged 40 + years) [20]. In the Alienor Study on a population aged 75 + years, which has been the ophthalmology-related population-based study with the oldest age inclusion criterion so far, the prevalence of late AMD (geographic atrophy and exudative type combined) increased in a curvilinear manner with older age, from 3.5% and 1.8% in men and women aged 73 to 79 years, to 6.8% and 10.4% in men and women aged 80 years or more, respectively [21, 22]. These figures for the very old group are comparable with the results obtained in our investigation.

The prevalence of AMD in our study population correlated only with the region of habitation, while it was not significantly associated in the multivariable analysis with a panoply of other systemic and ocular parameters tested in the study. In previous epidemiological studies on younger populations, a higher AMD prevalence had correlated with shorter axial length [23, 24]. Interestingly, shorter axial length in our study population was associated with a higher prevalence of RPDs, with the reason for that association still unknown.

In contrast to the AMD prevalence in the current study, a higher AMD prevalence in the UEMS was associated with rural region of habitation, lower prevalence of diabetes, shorter axial length, lower prevalence of nuclear cataract, and higher prevalence of cortical cataract. As in the UVOS so in the UEMS, the AMD prevalence was not significantly associated with other systemic or ocular parameters. Also in the Beijing Eye Study as in the UEMS, a higher AMD prevalence was associated with the rural region of habitation [24]. For the current study as for the preceding investigations, it has remained elusive which underlying parameters of living in the countryside or in the urban region were causative for the relationship between higher AMD prevalence and rural region for the younger individuals (in the UEMS) and urban region for the elderly individuals (in the UVOS), respectively. The finding that, as in the preceding studies (such as the UEMS and the Beijing Eye Study), the AMD prevalence was not significantly associated with most of the systemic parameters suggests that presence and severity of AMD were mostly independent of the general health of the patients in terms of cardiovascular and cerebrovascular disorders and internal medical diseases. It corresponds to the results of previous investigations, which showed that

the AMD prevalence was mainly independent of extraocular conditions [25]. The AMD prevalence was not associated with the serum concentration of creatinine as surrogate for a chronic kidney disease. In contrast, Leisy and associates had found a correlation between RPDs as part of AMD and renal dysfunction [26]. A reason for the discrepancy between the studies may be that the subgroup analysis focused on RPDs in the study by Leisy, and the marked difference in age of the study populations.

While in our elderly population, the AMD prevalence was not correlated with the prevalence and degree of arterial hypertension, there are conflicting reports of an association of arterial hypertension and age-related macular degeneration in the literature [27, 28]. Neither was diet as assessed in the questionnaire correlated with the AMD prevalence in our elderly study population (Table 1). In previous studies, AMD prevalence was associated more with Western food than with Oriental food [29]. In the study by Chong and associates, a diet low in trans-unsaturated fat and rich in omega-3 fatty acids and olive oil correlated with a reduced the risk of AMD [30]. Neither was hearing loss associated with the prevalence of AMD in our study, in contrast to a previous study performed by Bozkurt and colleagues [31]. Interestingly and in contrast to some previous studies and in agreement with other investigations, the prevalence of any type of AMD was not significantly correlated with the prevalence of smoking and the number of self-reported smoking package years (Table 1) [20, 24, 32]. It may suggest that the association between AMD and smoking may not be very strong for all study populations, as also found in some previous population-based investigations [20, 25]. In particular, if axial length was included into the multivariable analysis of the relationship between AMD prevalence and smoking in previous studies, the relationship between smoking and AMD prevalence was not statistically significant [20, 24]. Since shorter axial length is associated with a lower level of education, which is associated with a higher prevalence of smoking, one may discuss the possibility that the main risk factor for AMD was shorter axial length (although not significantly associated in the present study population), and that the association between smoking and higher AMD prevalence might have been influenced by that correlation. In our study as in the UEMS, the AMD prevalence was not correlated with the prevalence of pseudoexfoliation of the lens. It is in contrast to the study by Kozobolis and colleagues [33].

The RPD prevalence in our study (24.7%) was markedly higher than the RPD prevalence in the UEMS population with an age of 40 + years (186/4914 or 3.8%), and it was higher than in the French Alienor Study on individuals aged 77 + years with a RPD prevalence of 13.4% [6, 34]. In that study, a higher RPD prevalence was associated with older age and female sex [6]. In the same Alienor study, the annual incidence rate of RPD (2.9% per participant, with an estimated 5-year risk of 13.5%) was associated with subfoveal choroidal thinning and presence of genetic risk factors [8]. In the Montrachet Study using color fundus photography and macular OCT images, the RPD prevalence was 18.1% in persons aged 65 + years [3]. The RPD prevalence increased with older age, female sex, higher plasma lutein/zeaxanthin level, lower frequency of lipid-lowering drug use and thinner subfoveal choroidal thickness [3]. Using fundus autofluorescence images, the Age-Related Eye Disease Study (ARMS) reported on a RPD prevalence of 24% per eye and 29% per participants [35]. The RPD prevalence was 6% in early AMD, 26% in intermediate AMD, 36% in late AMD with geographic atrophy, and 19% in neovascular AMD. As in the Rotterdam Study and in the Alienor Study, a higher RPD prevalence was associated with female sex, and it was correlated with a genetic risk score and ARMS2 risk alleles [35]. In the population of the Rotterdam Study with an age of 65 + years, the RPD prevalence was 4.9%, with the caveat that only color fundus photographs and not OCT images were available for the detection of RPDs [5].

When the results of our study are discussed, the study limitations should be taken into account. First, AMD could be detected only if the clarity of the optic media allowed to take fundus images. Any advanced cataract thus led to the exclusion of that eye or individual from the study, leading to a potential bias. In particular, it might have led to an underdiagnosis of AMD in eyes with advanced cataract. Second, we did not specifically assess the intake of fish that has previously been discussed to be associated with a decreased risk of AMD. The rivers in the study region are frozen for about 4–5 months of the year and the distance to the Black Sea is about 1700 km, so that the fish consumption in the study region may have been lower in winter than in summer. Third, participation rate in the study (932 individuals or 61.1% out of the whole group of study participants or 49.5% out of the eligible population) was relatively low. It may be considered however, that due to the old age many participants had a decreased mobility to come to the hospital or even had died before the hospital examination could be performed. The age and sex distribution in the study population was comparable to the results of the Russian census 2021. It may thus be unlikely that a major bias in the recruitment of the study participants might have occurred. Fourth, we did not perform genotyping so that the genetic pattern could not be correlated with the AMD and RPD prevalence. Fifth, we did not measure subfoveal choroidal thickness, so that we could not test for an association between the prevalence of RPDs and choroidal thickness, in contrast to the Alienor study [8]. Sixth, while all study participants had fundus photographs, taken either at their homes or in the hospital, 496 out of the 932 study participants additionally had OCT images of sufficient quality to assess them for the

prevalence AMD. This weakness of the study is due to the old age of the study participants leading to a relatively high immobility so that they could not be brought to the hospital for an OCT examination. Strengths of the study were that it is one of the first population-based studies worldwide on a group of individuals aged 85 + years, that the study population size was relatively large, that the study examined a relatively high number of ocular and systemic parameters for the analysis of associations, and that the study was performed in Russia / Central Asia, a region for which information on the prevalence of AMD and RPDs and their associations has been scarce so far.

In conclusion, in this typical, ethnically mixed, urban and rural population from Russia with an age of 85 + years, AMD prevalence (any AMD:47.1%; late AMD:13.7%) was statistically independent of most systemic and ocular parameters. Higher rheumatoid factor serum concentration and shorter axial length were factors associated with higher RPD prevalence. AMD was a major cause for vision impairment including blindness.

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Declarations

Ethical approval All procedures performed in this study were in accordance with the ethical standards of the Ethics Committee of the Academic Council of the Ufa Eye Research Institute, which approved the study, and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

Conflict of interest J Jost B. Jonas, Songhomitra Panda-Jonas: Patent application US 2019 0085065 A1„Agents for use in the therapeutic or prophylactic treatment of myopia or hyperopia); Patent application: European patent application 23170806.6 „EGFR Antagonists for the treatment of diseases involving unwanted migration, proliferation, and metaplasia of retinal pigment epithelium (RPE) cells. All other authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

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