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Prevalence of Myopic Maculopathy Among the Very Old: The Ural Very Old Study

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Purpose. To assess the prevalence of myopic macular degeneration (MMD) in very old individuals.

Methods. The population-based Ural Very Old Study (UVOS) included 1526 (81.1%) of 1882 eligible inhabitants aged ≥85 years. Assessable fundus images were available for 930 (60.9%) individuals (mean age, 88.6 ± 2.7 years). MMD was defined by macular patchy atrophies (i.e., MMD stage 3 and 4 as defined by the Pathologic Myopia Study Group).

Results. MMD prevalence was 21 of 930 (2.3%; 95% CI, 1.3–3.3), with 10 individuals (1.1%; 95% CI, 0.4–1.7) having MMD stage 3 and 11 participants (1.2%; 95% CI, 0.5–1.9) MMD stage 4 disease. Within MMD stage 3 and 4, prevalence of binocular moderate to severe vision impairment was 4 of 10 (40%; 95% CI, 31–77) and 7 of 11 (64%; 95% CI, 30–98), respectively, and the prevalence of binocular blindness was 2 of 10 (20%; 95% CI, 0–50) and 3 of 11 (27%; 95% CI, 0–59), respectively. In minor myopia (axial length, 24.0 to <24.5 mm), moderate myopia (axial length, 24.5 to <26.5 mm), and high myopia (axial length, ≥26.5 mm), MMD prevalence in the right eyes was 0 of 46 eyes (0%), 3 of 40 eyes (8%; 95% CI, 0–16), and 7 of 9 (78%; 95% CI, 44–100), respectively; MMD prevalence in the left eyes was 1 in 48 eyes (2%; 95% CI, 0–6), 4 of 36 eyes (11%; 95% CI, 0–22), and 3 of 4 eyes (75%; 95% CI, 0–100), respectively. In multivariable analysis, a higher MMD prevalence (odds ratio, 8.89; 95% CI, 3.43–23.0; $P < 0.001$) and higher MMD stage (beta, 0.45; B, 19; 95% CI, 0.16–0.22; $P < 0.001$) were correlated with longer axial length but not with any other ocular or systemic parameter.

Conclusions. MMD prevalence (stages 3 and 4) in very old individuals increased 8.89-fold for each mm axial length increase, with a prevalence of ≥75% in highly myopic eyes. In old age, highly myopic individuals have a high risk of eventually developing MMD with marked vision impairment.

Keywords: myopic macular degeneration, myopia, macular degeneration, ural very old study, epidemiology

Myopic macular degeneration (MMD) has become one of the most common causes for irreversible vision impairment and blindness in the adult population worldwide, and in particular in East and Southeast Asia.[1,2] Previous population-based and hospital-based, cross-sectional and longitudinal studies have shown that long ocular axial length, further axial elongation, older age, female sex, and smaller parapapillary gamma zone were risk factors for the prevalence, incidence and progression of MMD.[3–5] In the last three decades, the prevalence of myopia has markedly increased in the young generation, again in particular in East and Southeast Asia, as well as globally.[6–9] Considering that older age is one of the risk factors for the development of MMD, it has been discussed that, as this young myopic generation gets older, the role of MMD as cause of vision impairment and blindness may increase even further.[9] To estimate the lifetime risk of developing MMD for a young or middle-aged myopic individual, it is helpful to know the MMD prevalence in the oldest group of myopic persons in a general population; such information has, however, not been available yet. We, therefore, conducted a study that included a group of very old individuals recruited in a population-based manner in which we assessed the prevalence of and associations of MMD, the results of which could be compared with the findings obtained in another population-based study previously conducted with a

similar study design and in the same geographic region on a younger population.

Methods

The population-based study (Ural Very Old Study [UVOS]) was carried out in the Russian Republic of Bashkortostan with a total population of approximately 4 million people. It 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 areas were the urban region of the Kirovskii district in the capital Ufa and the rural region in the Karmaskalinsky district in a distance of 65 km from Ufa.[11] Living in the study regions and an age of ≥85 years were the eligibility criteria to be included into the study. The Ethics Committee of the Academic Council of the Ufa Eye Research Institute approved the study (date: 10.8.2017; protocol number 3) and informed written consent was obtained from all participants.

As already described in detail previously, 1526 of 1882 eligible inhabitants (81%; 390 [25.6%] men; 1136 [74.4%] women) participated in the study.[10,11] The participation rate did not vary significantly ($P = 0.65$) between the urban group (1238 of 1523 persons [81.3%]) and the rural group (288 of 359 persons [80.2%]). With respect to the distribution of age and sex, the study population did not differ markedly from the whole population of Russia with an age of ≥85 years as examined in the recent census carried out in Russia in 2021.[12] Both populations with an age of ≥85 years showed a marked preponderance of females. The inhabitants of retirement homes (i.e., three small private retirement homes in the urban study region) were equally eligible.

The study team visited the participants in their homes and medical doctors and trained nurses undertook a standardized interview with >300 questions on their socioeconomic background, including 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 interpersonal 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 ideation, and anxiety, and questions regarding previous neurological attacks including stroke, epilepsy, polyneuropathy and unconsciousness, as well as 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.

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 Scoresheet, we assessed the prevalence and degree of depression. We applied the Guidelines for Accurate and Transparent Health Estimates Reporting (GATHER statement guidelines).[13]

The ophthalmological examinations consisted of the automated refractometry (Auto-2Ref/Keratometer HRK-7000A Huvitz Co, Ltd., Gyeonggi-do, Korea), measurement of best-corrected visual acuity (BCVA), 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 Scheimflug camera (Pentacam HR, Typ70900, OCULUS, Optikgeräte GmbH Co., Wetzlar, Germany), slit lamp biomicroscopy of the anterior and posterior ocular segment, noncontact 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 OCT (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).

The interview was carried out in the homes for all study participants, and the other examinations were scheduled to be performed in the hospital. A subgroup of individuals who were interviewed but could not go to the hospital for the other assessments were examined in their homes using portable devices. These devices included a portable autorefractometer (HandyRef, Nidek Co, Hiroishi-cho, Japan), a portable slit lamp (PLS One, Keeler Co., Windsor, Windsor and Maidenhead, UK), a portable noncontact tonometry (PT 100 Portable Non-Contact Tonometer, Reichert Co, Depew/Buffalo, NY, USA), and a portable fundus camera (Smartscope, Optomed Co., Oulu, Finland).

All images of the anterior and posterior ocular segments, including those of the macula and optic nerve, were preassessed by the researchers in Russia, and all images were re-assessed by J.B.J. and S.P.J. Based on the fundus photographs and OCT images of the macula, we applied the recommendations made by the Pathologic Myopia (META-PM) Study Group for the definition of MMD.[14] As inclusion criterion, the quality of the fundus images had to allow the clear detection of macular abnormalities, including macular drusen and reticular pseudodrusen. For the assessment of MMD in our study, we took only MMD stage 3

("patchy atrophies") and MMD stage 4 ("macular atrophy") into account, because the differentiation of MMD stage 1 and MMD stage 2 required a relatively high quality of the fundus images. Owing to the age of the study participants and concurrent cataract or other opacities of the ocular optic media, such an image quality could not be achieved for all images taken. MMD stage 3 and stage 4 were relatively easily detectable by the presence of patchy atrophies, the hallmarks of these MMD stages. In addition, marked vision impairment has usually been associated with MMD stage 3 and MMD stage 4, whereas MMD stage 1 (fundus tessellation) has not been considered to be pathologic, and MMD stage 2 ("diffuse chorioretinal atrophy") neither has a pathognomonic morphological sign nor is associated with a profound vision loss.[14] Based on axial length, we divided myopia into minor myopia with an axial length ranging between 24.0 mm and <24.5 mm, moderate myopia with an axial length ranging from 24.5 mm to <26.5 mm, and high myopia with an axial length of ≥26.5 mm. In a parallel manner, and based on refractive error (with pseudophakic or aphakic eyes excluded), minor myopia was defined by a refractive error ranging between 0 diopter (D) D and −0.5 D, moderate myopia with a refractive error of >−0.5 D and >−8 D, and high myopia with a refractive error of ≤−8 D.

As recommended by the World Health Organization, we defined moderate-to-severe vision impairment as a BCVA of <6/18 but ≥3/60 in the better eye or both eyes, and blindness as a BCVA of <3/60 in the better eye or both eyes.[15]

A commercially available statistical software package (SPSS for Windows, version 27.0, SPSS, Chicago, IL, USA) was applied for the statistical analysis. We calculated the mean values (presented as mean and 95% confidence interval [CI]) of the main outcome parameter, that is, the prevalence of MMD, and performed univariate binary analyses of the associations between the MMD prevalence and other ocular and systemic parameters. It was followed by a multivariable binary regression analysis, with the MMD prevalence as the dependent parameter and as independent parameters all those variables that were associated ($P < 0.10$) with the MMD 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 assessed the statistical significance of differences in prevalences of parameters between groups using the χ^2 test. We determined the odds ratio (OR) and its 95% CIs. All P values were two-sided and considered statistically significant when the values were <0.05.

Results

Of 1882 eligible inhabitants aged ≥85 years and living in the study regions, 1526 individuals (81.1%) participated in the study, were visited in their homes, and participated in the interview (Fig. 1). Of these 1526 individuals, 105 (6.9%) had died after the interview but before they could be taken to the

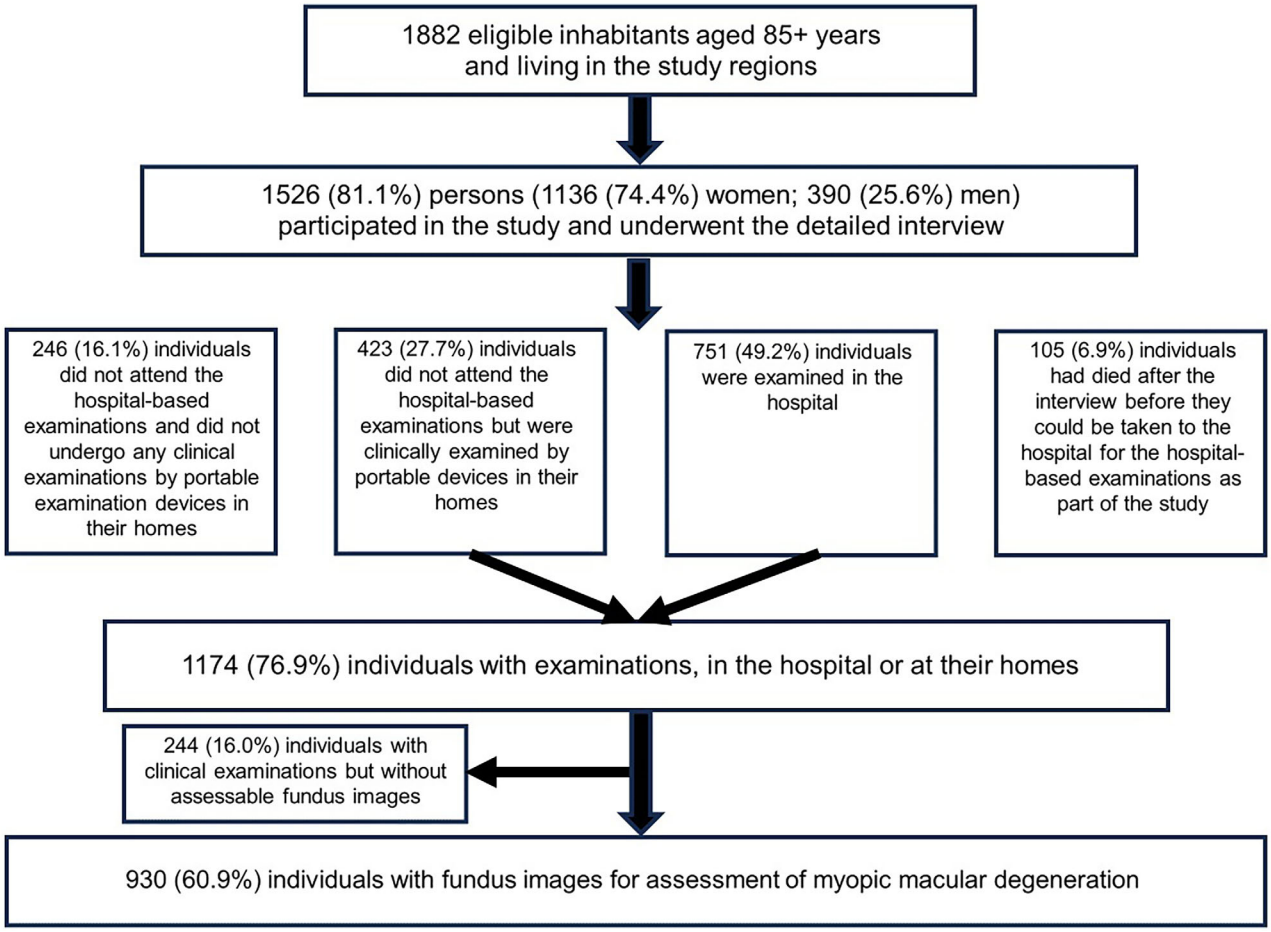

Figure 1. Flowchart showing the composition of the population of the UVOS.

hospital for the hospital-based examinations as part of the study; 246 individuals (16.1%) did not attend the hospital-based examinations and did not undergo any clinical examinations by portable examination devices in their homes, 423 individuals (27.7%) did not attend the hospital-based examinations but were clinically examined by portable devices in their homes, and 751 individuals (49.2%) were examined in the hospital. Of the remaining 1174 individuals (76.9%) who had undergone examinations in the hospital or at their homes, 930 (60.9% of the study participants or 49.4% of the eligible population; 246 men [26.5%] and 684 women [73.5]) had fundus images assessable for the examination for the presence and degree of MMD (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 individuals of Russian ethnicity (36.3%) , 397 Tatars (42.7%), 112 Bashkirs (12.0%), 32 Chuvash (3.4%), 5 Mari (0.5%), and 46 others (5.0%). The mean age was 88.6 ± 2.7 years (median, 88.0 years; range, 85.0–98.3 years). The individuals with assessable macula images as compared with those without assessable macula images were significantly younger (88.6 ± 2.7 years vs. 89.1 ± 3.1 years; $P = 0.002$), although both groups did not differ significantly by sex (246 men [26.5%] and 684 women [73.45%] vs. 144 men [24.2%] and 452 women [75.8%]; $P = 0.34$), and axial length (23.1 ± 1.1 mm vs. 23.1 ± 1.2 mm; $P = 0.43$). Within the group of individuals with assessable fundus images, refractive error measured in 756 individuals was −0.28 ± 2.89 D (median, −0.13 D; range, −27.37 D to +13.25 D) in the right eyes and −0.20 ± 2.83 D

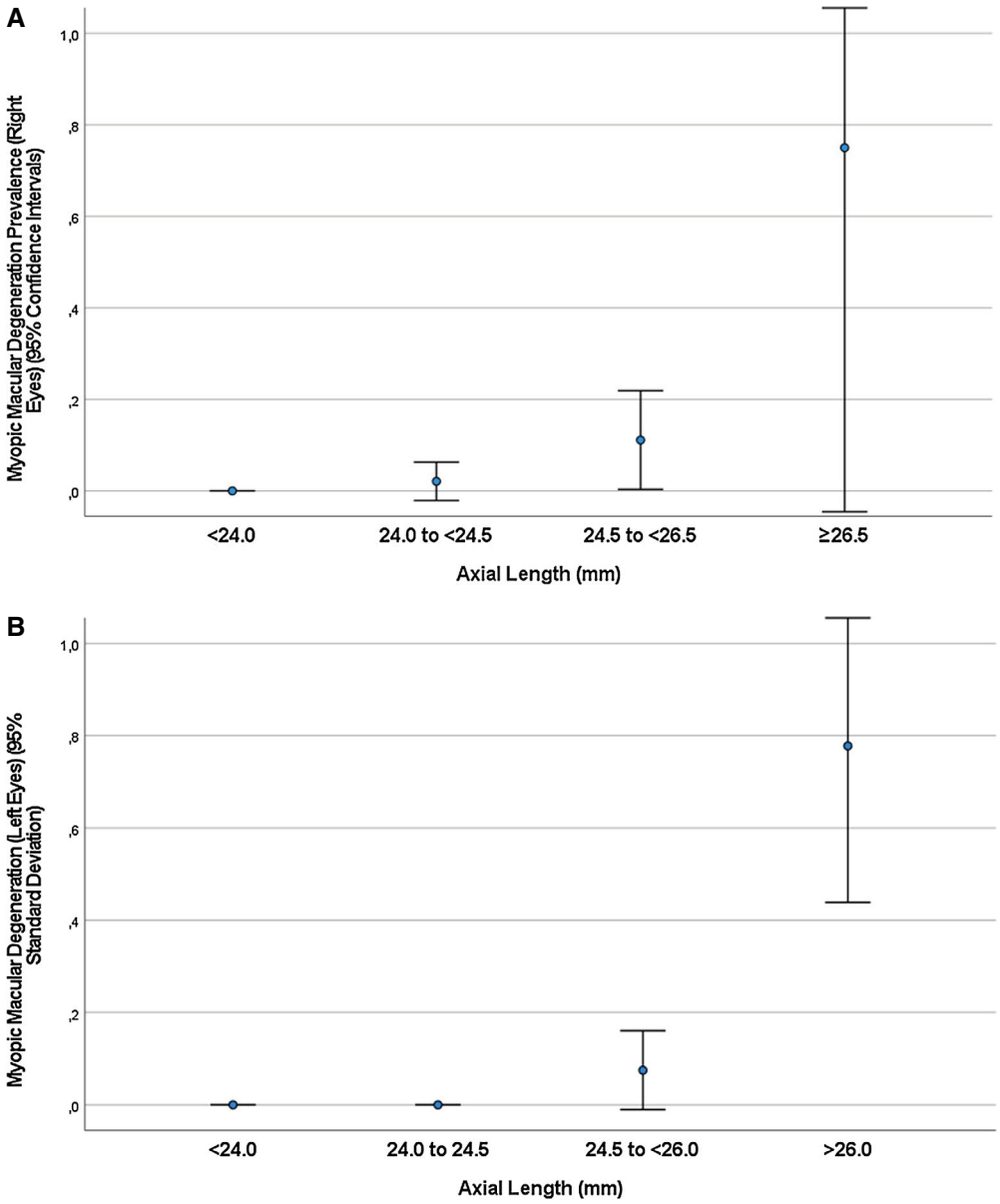

Figure 2. (**A**) Graph showing the distribution of the prevalence of MMD (stage 3 and stage 4 combined) (right eyes) in dependence of axial length groups in the UVOS. (**B**) Graph showing the distribution of the prevalence of MMD (stage 3 and stage 4 combined) (left eyes) in dependence of axial length groups in the UVOS.

Table 1. Associations (Binary Univariate Analysis) Between the Prevalence of Myopic Maculopathy (Stage 3 and Stage 4 Combined) and Systemic and Ocular Parameters in the Ural Eye and Medical Study

Parameter	Interval	OR	95% CI of OR	*P* Value
Age	1-year intervals	0.98	0.82, 1.17	0.83
Gender	Men/women	1.96	0.57, 6.80	0.29
Region of habitation	Urban/rural	1.03	0.34, 3.14	0.96
Ethnicity	Non-Russian ethnicity/Russian	0.88	0.33, 2.36	0.79
Body height	1 cm	1.05	0.99, 1.11	0.13
Body weight	kg	1.01	0.96, 1.05	0.81
Body mass index	kg/m^2	0.96	0.85, 1.08	0.49
Waist circumference	cm	0.99	0.95, 1.03	0.57
Hip circumference	cm	0.99	0.95, 1.04	0.80
Waist/hip circumference ratio	Ratio	0.21	0.001, 58.0	0.58
Level of education	Illiteracy/passing 5th grade/8th grade/10th grade/11th grade/graduates/specialized secondary education/post graduates	0.97	0.78, 1.22	0.81
Smoking, currently	No/yes	0.00	—	1.00
Alcohol consumption, any	No/yes	0.36	0.39, 0.05	2.92
In a week how many days do you eat fruits?	Number of days	0.97	0.77, 1.22	0.78
In a week how many days do you eat vegetables?	Number of days	0.99	0.73, 1.33	0.92
History of cardiovascular disorders including stroke	No/yes	0.84	0.33, 2.16	0.72
History of angina pectoris	No/yes	0.00	0.00	1.00
History of asthma	No/yes	0.00	0.00	1.00
History of arthritis	No/yes	1.21	0.48, 3.04	0.69
History of previous bone fractures	No/yes	0.47	0.15, 1.42	0.18
History of low back pain	No/yes	0.77	0.31, 1.94	0.58
History of thoracic spine pain	No/yes	1.03	0.39, 2.74	0.95
History of neck pain	No/yes	1.14	0.37, 3.48	0.82
History of headache	No/yes	1.69	0.66, 4.33	0.28
History of cancer	No/yes	1.29	0.29, 5.71	0.74
History of dementia	No/yes	0.98	0.13, 7.52	0.99
History of diarrhea	No/yes	0.00	0.00	1.00
History of iron-deficiency anemia	No/yes	0.00	0.00	1.00
History of low blood pressure and hospital admittance	No/yes	0.00	0.00	1.00
History of osteoarthritis	No/yes	1.20	0.39, 3.66	0.75
History of skin disease	No/yes	0.82	0.11, 6.25	0.85
History of thyroid disease	No/yes	0.00	0.00	1.00
History of falls	No/yes	0.88	0.35, 2.18	0.78
History of unconsciousness	No/yes	1.12	0.26, 4.96	0.88
Age of the last menstrual bleeding	Years	0.95	0.83, 1.09	0.45
Age of last regular menstrual bleeding	Years	0.95	0.83, 1.09	0.45
Serum concentration of:				
Alanine aminotransferase	IU/L	1.01	0.96, 1.06	0.77
Aspartate aminotransferase	IU/L	1.02	0.98, 1.06	0.42
Aspartate aminotransferase-to- alanine aminotransferase ratio	Ratio	1.10	0.84, 1.42	0.49
Bilirubin, total	µmol/L	1.00	0.94, 1.05	0.88
High-density lipoproteins	mmol/L	0.86	0.47, 1.58	0.63
Low-density lipoproteins	mmol/L	0.91	0.59, 1.42	0.68
Cholesterol	mmol/L	0.96	0.68, 1.37	0.83
Triglycerides	mmol/L	1.16	0.69, 1.96	0.58
Rheumatoid factor	IU/mL	1.02	0,79, 1.34	0.86
Erythrocyte sedimentation rate	mm/min	1.01	0.97, 1.04	0.69
Glucose	mmol/L	1.07	0.89, 1.29	0.49
Urea	mmol/L	0.96	0.77, 1.20	0.71
Creatinine	µmol/L	0.98	0.96, 1.01	0.16
Protein total	g/L	1.05	0.99, 1.11	0.13
International normalized ratio INR	—	5.39	0.20, 148	0.32
Blood coagulation time	Minutes	0.92	0.28, 3.00	0.89
Hemoglobin	g/L	1.00	0.98, 1.02	0.95
Erythrocyte count	10^6 cells/µL	0.97	0.41, 2.30	0.95
Leukocyte count	10^9 cells/L	0.98	0.72, 1.33	0.89
Prevalence of diabetes mellitus	No/yes	1.91	0.62, 5.86	0.26
Estimated glomerular filtration rate	30 $mL/min/1.73m^2$	0.94	0.48, 1.85	0.86

Table 1. Continued

Parameter	Interval	OR	95% CI of OR	*P* Value
Anemia, prevalence (serum hemoglobin concentration <140 g/L in men, <130 g/L in women)	No/yes	0.91	0.37, 2.26	0.83
Blood pressure, systolic	mm Hg	1.00	0.98, 1.02	0.94
Blood pressure, diastolic	mm Hg	1.03	0.999, 1.06	0.06
Blood pressure, mean	mm Hg	1.02	0.99, 1.04	0.29
Arterial hypertension	No/yes	0.80	0.23, 2.80	0.73
Arterial hypertension, stage	0–4	0.92	1.02, 1.60	0.92
Prevalence of chronic obstructive pulmonary disease	No/yes	0.00	0.00	1.00
Hearing loss	Hearing loss score (0–44)	0.98	0.95, 1.02	0.29
Depression Score	Depression score unit (range, −4 to +15)	1.0198	0.96, 1.07	0.62
State-Trait Anxiety Inventory	State-Trait Anxiety Inventory Score (range, −7 to 13)	0.99	0.94, 1.04	0.74
Manual dynamometry, right hand	dekaNewton	0.96	0.90, 1.03	0.23
Manual dynamometry, right hand	dekaNewton	0.96	0.90, 1.03	0.29

Table 2. Associations (Binary Univariate Analysis) Between the Prevalence of Myopic Maculopathy (Stage 3 and Stage 4 Combined) and Ocular Parameters in the Ural Eye and Medical Study

Parameter	Interval	OR	95% CI of OR	*P* Value
Refractive error, spherical equivalent	D	0.79	0.68–0.92	0.003
Refractive error, cylindrical value	D	0.62	0.39–0.97	0.04
Axial length	mm	8.89	3.43–23.0	<0.001
Corneal refractive power	D	0.89	0.61–1.28	0.52
Central corneal thickness	µm	1.00	0.98–1.01	0.58
Corneal volume	mm^3	0.99	0.92–1.06	0.74
Anterior chamber depth	mm	1.90	0.99–3.64	0.053
Anterior chamber volume	µL	1.02	1.002–1.03	0.03
Anterior chamber angle	Degree	1.04	0.99–1.09	0.11
Lens thickness	mm	0.25	0.02–3.61	0.31
Nuclear cataract degree	Grade	1.38	0.54–3.53	0.51
Nuclear cataract, presence	No/yes	1.14	0.995–1.31	0.06
Cortical cataract, degree	Percentage	0.93	0.47–1.84	0.84
Cortical cataract, presence	No/yes	1.10	0.96–1.26	0.18
Subcapsular cataract, degree	Percentage	1.97	0.87–4.47	0.10
Fundus tessellation, macula region	Grade	0.69	0.46–1.03	0.07
Fundus tessellation, peripapillary region	Grade	0.67	0.44–1.02	0.06
Intraocular pressure,	mmHg	1.03	0.95–1.12	0.43
Retinal thickness (total), fovea	µm	1.001	0.995–1.008	0.76
Retinal thickness (total), 300 µm temporal to the fovea	µm	1.00	0.97–1.03	0.92
Retinal thickness (total), 300 µm nasal to the fovea	µm	1.00	0.98–1.02	0.88
Retinal nerve fiber layer thickness	µm	0.93	0.88–0.97	0.002
Glaucoma	No/yes	3.26	0.84–12.7	0.09
Glaucoma stage	0–5	1.46	1.13–1.90	0.004
Open-angle glaucoma	No/yes	3.26	0.84–12.7	0.09
Angle-closure glaucoma	No/yes	0.00	0.00	1.00
Diabetic retinopathy	No/yes	0.00	0.00	1.00

(median, −0.13 D; range, −13.75 D to 14.63 D) in the left eyes. Cataract surgery had been performed in 396 right eyes (42.6%) and in 407 of 930 left eyes (43.8%). In eyes without previous cataract surgery, the mean refractive error was −0.36 ± 3.32 D in right eyes (n = 398) and −0.16 ± 2.98 D in the left eyes (n = 378). Axial length determined in 608 participants was 23.1 ± 1.1 mm (median, 23.00 mm; range, 19.37–28.63 mm) in the right eyes and 23.1 ± 1.1 mm (median, 23.00 mm; range, 19.50–28.36 mm) in the left eyes.

The prevalence of MMD in the total study population was 21 of 930 (2.3%; 95% CI, 1.3–3.3), with 10 individuals (1.1% of the total study population; 95% CI, 0.4–1.7) affected by MMD stage 3, and 11 participants (1.2%; 95% CI, 0.5–1.9) affected by MMD stage 4. The BCVA worsened significantly with advancing stage of MMD, with a BCVA of 0.52 ± 0.46 logMAR in the group of participants without MMD to 1.68 ± 3.30 logMAR in the group of individuals with MMD stage 3, and to 1.76 ± 2.79 logMAR in the group of participants with MMD stage 4. Within MMD stage 3 and MMD stage 4, the prevalence of binocular moderate-to-severe vision impairment was 4 of 10 (40%; 95% CI, 31–77) and 7 of 11 (64%; 95% CI, 30–98), respectively, and the prevalence of binocular blindness was 2 of 10 (20%; 95% CI, 0–50) and 3 of 11 (27%; 95% CI, 0–59), respectively.

In the minor myopia group (as defined by axial length), the MMD prevalence in the right eyes and left eyes was 0 of 46 eyes (or 0%) and 1 eye of 48 eyes (2%; 95% CI, 0–6), respectively. In the moderately myopic group, MMD prevalence was 3 of 40 eyes (8%; 95% CI, 0–16) and 4 of 36 eyes (11%; 95% CI, 0–22), respectively; and in the highly myopic group, it was 7 or 9 or 78% (95% CI, 44–100) and 3 of 4 eyes (75%; 95% CI, 0–100), respectively (Fig. 2).

In univariate analysis, a higher MMD prevalence was associated ($P < 0.10$) with none of the systemic parameters examined (Table 1). It correlated with the ocular parameters of a more myopic refractive error (spherical equivalent), smaller cylindrical refractive error, longer axial length, deeper anterior chamber depth and larger anterior chamber volume, higher prevalence of nuclear cataract, lower degree of fundus tessellation, thinner peripapillary retinal nerve fiber layer thickness, and higher prevalence and stage of open-angle glaucoma (Table 2). In the multivariable analysis, only the association between higher MMD prevalence and longer axial length remained to be statistically significant (OR, 8.89; 95% CI, 3.43–23.0; $P < 0.001$). In that model, the associations between the MMD prevalence and the parameters of refractive error ($P = 0.37$), cylindrical refractive error ($P = 0.68$), anterior chamber depth ($P = 0.27$), anterior chamber volume ($P = 0.27$), degree of peripapillary fundus tessellation ($P = 0.056$) and macular fundus tessellation ($P = 0.056$), prevalence of nuclear cataract ($P = 0.99$) glaucoma ($P = 0.52$), glaucoma stage ($P = 0.45$), and peripapillary retinal nerve fiber layer thickness ($P = 0.27$), were no longer statistically significant. In a similar manner, a higher MMD stage correlated only with longer axial length (standardized regression coefficient beta, 0.45; nonstandardized regression B, 19; 95% CI, 0.16–0.22; $P < 0.001$), but not with any other parameter when adjusted for axial length.

Discussion

In this multiethnic very old study population, MMD prevalence (2.3%) was associated with binocular moderate-to-severe vision impairment in 4 of 10 individuals with MMD stage 3 and 7 of 11 individuals with MMD stage 4, and with binocular blindness in 2 of 10 individuals with MMD stage 3 and 3 of 11 participants with MMD stage 4. MMD prevalence steeply increased from minor myopia (0/46 right eyes, 1/48 left eyes) to moderate myopia (3/40 right eyes, 4/36 left eyes), and to high myopia (7/9 right eyes; 3/4 left eyes). Despite the high number of systemic and ocular parameters included in the statistical analysis, a higher MMD prevalence and degree were eventually associated only with longer axial length.

The prevalence of MMD (defined as MMD stage 3 [prevalence, 1.1%] and MMD stage 4 [prevalence, 1.2%]) of 2.3% (95% CI, 1.3–3.3) in our study was significantly ($P < 0.001$) higher than the corresponding prevalence of both stages in the Ufa Eye and Medical Study (UEMS), which used the same study design as the present study, except for a minimal age of 40 years as inclusion criterion, and which was conducted in same geographic region as the present study. In the UEMS, 14 individuals (0.2%; 95% CI, 0.1%–0.4%) of 5794 study participants (mean age, 58.9 ± 10.7 years) had MMD stage 3, and 13 individuals (0.2%; 95% CI, 0.1%–0.4%) had MMD stage 4.[16] In a similar manner, the MMD prevalence was, as compared with the present study cohort, lower as well in other, younger study populations, such as in the Australian Blue Mountains Eye Study with a minimal age of 49 years as an inclusion criterion and in which the prevalence of all MM stages together was 1.2%.[3] Also in studies from East Asia on populations younger than the present study population, the MMD prevalence based on MMD stage 3 and MMD stage 4 was lower in the present study. In the Beijing Eye Study 2011 with a mean age of 64.6 ± 9.8 years, the prevalence of MMD stage 3 was 12 of 6712 eyes (0.2%) and the prevalence of MMD stage 4 was 8 of 6712 (0.1%).[3] In the Central India Eye and Medical Study, conducted in a very rural region in Central India on individuals aged ≥30 years, the prevalence of MMD stage 3 was 14 of 8955 eyes (0.2%) and the prevalence of MMD stage 4 was 8 of 8955 eyes (0.1%).[17] The comparison between the various study populations agrees with the association between a higher MMD prevalence and older age, as also found in each of the studies separately.

Because the participants in the UVOS during their long lifetime have not lived in metropolitan regions and have led a life more typical for rural regions than for highly urbanized areas, one may infer that the relatively high prevalence of MMD in the UVOS population as compared with the populations of the other investigations was markedly due to the older age and that it was not associated with a profoundly urban lifestyle. The latter is a strong risk factor for the marked increase in the prevalence of myopia in the young generations. Correspondingly, the MMD prevalence in the UVOS population was not significantly associated with the level of education (Table 1). It agrees with the Central India Eye Study, the Beijing Eye Study, and the UEMS on younger populations.[3,16,17] It may suggest that the highly prevalent myopia in the young generation with a strong dependence on education-related parameters may not be completely the same disease as the pathologic high myopia in adult patients with MMD.

The MMD prevalence in our study population increased in the linear regression analysis by a factor of 8.89 (95% CI, 3.43–23.0) for each mm increase in axial length (Table 2) (Fig. 2). Taking into account the curvilinear character of the relationship, an even slight increase in axial length in markedly highly myopic eyes may profoundly further increase the risk of MMD. It is clinically important, since recent studies have shown that adult highly myopic patients can undergo further axial elongation, and correspondingly, that further axial elongation is a major risk factor for the development and progression of MMD.[4,18,19] It may suggest that even a small reduction of an ongoing axial elongation in adult highly myopic eyes may therefore be helpful. The observation on an association between higher MMD prevalence and longer axial length is in agreement with numerous previous investigations.

In previous investigations, a higher MMD prevalence was related to older age. The observation that the MMD prevalence was not related with older age in the UVOS population may be due to the limited range of age of the study population, with a minimum age of 85 years. The relationship between the MMD prevalence and sex has remained unclear so far. In the present study, as in the Blue Mountains Study, Beijing Eye Study and in the UEMS, the MMD prevalence did not correlate with sex, while in longitudinal studies, the MMD progression was more marked in women than in men.[3–5,16,20] The reasons why the various investigations differed in the association between MMD prevalence and sex have remained unclear. Biometric measures of the anterior part of the eye like corneal curvature radius and anterior chamber measurements were not associated with

MMD prevalence in our study cohort. It is in agreement with observations made in the younger UEMS population and in histomorphometric investigations in which the sagittal elongation of the eyes was related to changes in the posterior part of the eye.[16,22]

As in previous studies, including the UEMS, the MMD prevalence was statistically independent of any major systemic diseases assessed in our study.[1,3,4,16–21] In particular, the MMD prevalence was not related to the level of education, as was the case in the very rural population of the Central India Eye and Medical Study.[17] This observation may be interesting for addressing the question of whether the markedly education-related increase in the prevalence of high myopia in the young generations observed during the last 30 years is related to an increased risk for an eventual development of MMD in later life.

The most important finding of our study may the high MMD prevalence in the highly myopic group (Fig. 2). It may suggest that the majority of highly myopic eyes will eventually develop stage 3 or stage 4 of MMD, if the individual gets old enough. Since MMD stage 3 and MMD stage 4 are associated with marked loss in vision, strategies are warranted to stop a continuing axial elongation in highly myopic eyes of adult patients. Such an ongoing axial elongation has been shown to be a major risk factor for the development and progression of MMD.[4]

When the results of our study are discussed, its limitations have to be taken into account. First, MMD 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 MMD in eyes with advanced cataract. In a similar manner, we defined MMD as stage 3 or higher of the classification of MMD given by the Pathologic Myopia (META-PM) Study group.[14] The reason not to include stage 2 as selection criterion of pathological myopia in our study was that the differentiation of stage 2 ("diffuse chorioretinal atrophy") and stage 1 ("increased fundus tessellation"), based on ophthalmoscopy and OCT, can be difficult in eyes with partially opaque media. Including only stage 3 with a patchy atrophy as clear morphologic hallmark and stage 4 into the definition of MMD in our study, thus, led to an underestimation of the MMD prevalence and may only serve to strengthen the conclusion that the prevalence of pathologic MMD in very old, highly myopic individuals can be as high as 75%, or even higher. Second, participation rate in the study (930 individuals or 60.9% of the whole group of study participants or 49.4% of the eligible population) was relatively low. It may be considered, however, that owing to old age, many participants had decreased mobility and were unable to travel 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 with the age and sex distribution of the population of Russia as examined in the Russian census of 2021. It may, thus, be unlikely that a major bias in the recruitment of the study participants might have occurred. Third, a survival bias may be discussed. There may be the possibility that highly myopic individuals with MMD and correspondingly low vision had a shorter life expectancy, as also discussed for the population of the Central India Eye and Medical Study.[17] It would have led, however, to an underestimation of the MMD prevalence in the very old population. In view of the high MMD prevalence in the highly myopic subgroup of our study population, this potential bias may thus only serve to strengthen the observation of our study, that highly myopic eyes have a high risk of eventually developing MMD. Fourth, beside the analysis of the relationship of axial length with MMD prevalence, an analysis of the association between myopic refractive error and MMD prevalence would have been interesting. The statistical power of such an analysis would, however, be relatively small, because the prevalence of previous cataract surgery was >40% in the study population and because >90% of the remaining eyes without cataract surgery had a marked degree of nuclear cataract, highly likely associated with lentogenic myopization. It indicated that only a relatively small fraction of the original study population remained for an analysis of the relationship between axial myopia defined by the refractive error, and the prevalence of MMD. Strengths of the study were that it is one of the first population-based studies worldwide on a group of individuals aged ≥85 years in any field of epidemiology, 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, that the study was performed in Russia or Central Asia, a region for which information on the prevalence of AMD and RPDs and their associations has been scarce so far, and that it is the first study on MMD as one of the most common causes for impairment worldwide in a very old study population.

In conclusion, MMD prevalence (stage 3 and 4) (2.3%) in the UVOS was higher than in the younger UEMS study population (0.4%), corresponding to the association between higher MMD prevalence and older age. MMD prevalence was strongly associated with vision impairment and blindness. Its prevalence increased 8.89-fold for each mm increase in axial length, leading to a prevalence of approximately 75% in the highly myopic group of our elderly study population. Highly myopic eyes have a high risk of eventually developing MMD with marked vision impairment.

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References

1. Hsu WM, Cheng CY, Liu JH, Tsai SY, Chou P. Prevalence and causes of visual impairment in an elderly Chinese population in Taiwan: the Shihpai Eye Study. *Ophthalmology*. 2004;111(1):62–69.
2. Xu L, Wang Y, Li Y, et al. Causes of blindness and visual impairment in urban and rural areas in Beijing: the Beijing Eye Study. *Ophthalmology*. 2006;113(7):1134–1141.
3. Vongphanit J, Mitchell P, Wang JJ. Prevalence and progression of myopic retinopathy in an older population. *Ophthalmology*. 2002;109(4):704–711.

4. Fang Y, Yokoi T, Nagaoka N, et al. Progression of myopic maculopathy during 18-year follow-up. *Ophthalmology*. 2018;125(6):863–877.
5. Yan YN, Wang YX, Yang Y, et al. Ten-year progression of myopic maculopathy: the Beijing Eye Study 2001-2011. *Ophthalmology*. 2018;125(8):1253–1263.
6. Sun J, Zhou J, Zhao P, et al. High prevalence of myopia and high myopia in 5060 Chinese university students in Shanghai. *Invest Ophthalmol Vis Sci*. 2012;53(12):7504–7509.
7. Wu JF, Bi HS, Wang SM, et al. Refractive error, visual acuity and causes of vision loss in children in Shandong, China. The Shandong Children Eye Study. *PLoS One*. 2013;8(12):e82763.
8. Holden BA, Fricke TR, Wilson DA, et al. Global prevalence of myopia and high myopia and temporal trends from 2000 through 2050. *Ophthalmology*. 2016;123(5):1036–1042.
9. Morgan IG, Ohno-Matsui K, Saw SM. Myopia. *Lancet*. 2012;379(9827):1739–1748.
10. Bikbov MM, Kazakbaeva GM, Rakhimova EM, et al. Prevalence factors associated with vision impairment and blindness among individuals 85 years and older in Russia. *JAMA Netw Open*. 2021;4(8):e2121138.
11. Bikbov MM, Gilmanshin TR, Kazakbaeva GM, et al. Prevalence of depression, anxiety and suicidal ideas and associated factors, in particular sensory impairments, in a population of Bashkortostan in Russia. *Sci Rep*. 2023;13(1):17256.
12. Wikipedia, https://en.wikipedia.org/wiki/Demographics_of_Russia. Retrieved 19.10.2023.
13. Stevens GA, Alkema L, Black RE, et al. Guidelines for Accurate and Transparent Health Estimates Reporting: the GATHER statement. *Lancet*. 2016;388(10062):e19–23.
14. Ohno-Matsui K, Kawasaki R, Jonas JB, et al. International classification and grading system for myopic maculopathy. *Am J Ophthalmol*. 2015;159(5):877–883.
15. Flaxman SR, Bourne RRA, Resnikoff S, et al. Global causes of blindness and distance vision impairment 1990-2020: a systematic review and meta-analysis. *Lancet Glob Health*. 2017;5(12):e1221–e1234.
16. Bikbov MM, Gilmanshin TR, Kazakbaeva GM, et al. Prevalence of myopic maculopathy among adults in a Russian population. *JAMA Netw Open*. 2020;3(3):e200567.
17. Jonas JB, Nangia V, Gupta R, Bhojwani K, Nangia P, Panda-Jonas S. Prevalence of myopic retinopathy in rural Central India. *Acta Ophthalmol*. 2017;95(5):e399–e404.
18. Du R, Xie S, Igarashi-Yokoi T, et al. Continued increase of axial length and its risk factors in adults with high myopia. *JAMA Ophthalmol*. 2021;139(10):1096–1103.
19. Lee MW, Lee SE, Lim HB, Kim JY. Longitudinal changes in axial length in high myopia: a 4-year prospective study. *Br J Ophthalmol*. 2020;104(5):600–603.
20. Liu HH, Xu L, Wang YX, Wang S, You QS, Jonas JB. Prevalence and progression of myopic retinopathy in Chinese adults: the Beijing Eye Study. *Ophthalmology*. 2010;117(9):1763–1768.
21. Lai TY, Fan DS, Lai WW, Lam DS. Peripheral and posterior pole retinal lesions in association with high myopia: a cross-sectional community-based study in Hong Kong. *Eye*. 2008;22(2):209–213.
22. Jonas JB, Jonas RA, Bikbov MM, Wang YX, Panda-Jonas S. Myopia: histology, clinical features, and potential implications for the etiology of axial elongation. *Prog Retin Eye Res*. 2023:96:101156.

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