Intraocular Pressure and Its Associations in a Russian Population: The Ural Eye and Medical Study

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• PURPOSE: To assess the normal distribution of intraocular pressure (IOP) and its associations with ocular, medical, and socioeconomic factors in a Russian population.
• DESIGN: Population-based cross-sectional study.
• METHODS: The Ural Eye and Medical Study conducted in a rural and urban area in Ufa/Bashkortostan included 5899 (80.5%) participants out of 7328 eligible individuals aged 40+ years. IOP was measured by noncontact tonometry.
• RESULTS: After exclusion of individuals after glaucoma surgery or with antiglaucomatous therapy, mean IOP was 13.6 ± 3.8 mm Hg (median: 13 mm Hg; range: 3-49 mm Hg; 95% confidence interval [CI]: 8-23 mm Hg). The IOP range within the mean ± 2 standard deviations was 6.0-21.2 mm Hg. In multivariable analysis higher IOP was associated (regression coefficient r: 0.40) with the systemic parameters of female sex (nonstandardized regression coefficient B: 0.44; 95% CI: 0.22, 0.66; standardized regression coefficient beta: 0.06; $P < .001$), urban region of habitation (B: -0.27; 95% CI: 0.51, 0.03; beta: 0.03; $P = .03$), Russian ethnicity (B: 0.47; 95% CI: 0.20, 0.74; beta: 0.05; $P = .001$), higher body mass index (B: 0.06; 95% CI: 0.04, 0.08; beta: 0.08; $P < .001$), lower physical activity score (B: -0.02; 95% CI: -0.03, -0.002; beta: -0.03; $P = .02$), higher prevalence of diabetes mellitus (B: 0.42; 95% CI: 0.08, 0.76; beta: 0.03; $P = .02$), higher systolic blood pressure (B: 0.01; 95% CI: 0.01, 0.02; beta: 0.08; $P < .001$), fewer days with intake of fruits (B: -0.07; 95% CI: -0.12, -0.01; beta: 0.03; $P = .01$), lower blood concentration of bilirubin (B: -0.01; 95% CI: -0.02, -0.003; beta: -0.04; $P = .008$) and urea (B: -0.11; 95% CI: -0.17, -0.04; beta: -0.04; $P = .003$), worse best-corrected visual acuity (B: 0.64; 95% CI: 0.38, 0.90; beta: 0.13; $P < .001$), thicker central corneal thickness (B: 0.036; 95% CI: 0.033, 0.039; beta: 0.32; $P < .001$), higher anterior corneal refractive power (B: 0.11; 95% CI: 0.04, 0.18; beta: 0.05; $P = .003$), lower anterior chamber depth (B: -0.57; 95% CI: -0.83, -0.30; beta: -0.07; $P < .001$) (or lower prevalence of cataract surgery [B: -0.78; 95% CI: -1.44, -0.13; beta: -0.03; $P = .02$]), longer axial length (B: 0.30; 95% CI: 0.18, 0.42; beta: 0.07; $P < .001$), and higher prevalence of pseudoexfoliation (B: 1.08; 95% CI: 0.52, 1.63; beta: 1.01; $P < .001$). Measured IOP decreased by 0.36 mm Hg (95% CI: 0.33, 0.39) for each increase in central corneal thickness by 10 μm.
• CONCLUSIONS: IOP was associated with a multitude of systemic and ocular parameters, the associations of which may be considered in defining the normal range of IOP. (Am J Ophthalmol 2019;204:130–139. © 2019 Elsevier Inc. All rights reserved.)

INTRAOCULAR PRESSURE (IOP) IS ESSENTIAL FOR THE function of the eye and it is in multiple manners, directly or indirectly, involved in the physiology and pathophysiology of the eye. Previous hospital-based investigations and population-based studies have assessed the distribution of IOP and its associations with ocular and general parameters in several populations of Western European, American, East Asian, and Southeast Asian countries and regions.[1–14] For Russia, however, as the world's largest and one of the most populous countries, the normal distribution of IOP and its correlations with other ocular and systemic parameters have not been examined yet. In addition, most of the previous population-based studies were performed in urban or semi-urban populations but not in markedly rural regions, and most of the previous studies examined mostly ophthalmologic parameters. We therefore conducted the present study in which we measured IOP in a rural and urban population living in the Ural region of Russia and which included, besides a variety of ocular parameters, also medical, socioeconomic, and lifestyle parameters.

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METHODS

THE POPULATION-BASED URAL EYE AND MEDICAL STUDY was performed in the urban region of Kirovskii of the city of Ufa and in villages of the rural region of the Karmaskalinsky District withinin a distance of 65 km from Ufa.[15,16] The study was approved by the Ethics Committee of the Academic Council of the Ufa Eye Research Institute. Informed written consent was obtained from all participants. Ufa, with a population of 1.1 million inhabitants, is the capital of the republic of Bashkortostan in Russia. The population of Ufa and the population of the entire republic of Bashkortostan, with a population of 4.07 million, is ethnically composed of Russians, Tatars, Bashkirs, Ukrainians, and other ethnicities. Ufa is located in the west of the southern Ural Mountains at a distance of 1300 km east of Moscow. Inclusion criteria for the participation in the Ural Eye and Medical Study were living in the study region and an age of 40+ years. There were no exclusion criteria.

The study participants underwent a series of examinations, which started with a standardized interview conducted by trained social workers. It consisted of more than 250 questions about socioeconomic parameters, such as the level of education, family income and properties, family structure, living conditions; about diet, smoking or other types of tobacco consumption, physical activity, alcohol consumption, and depression and suicidal ideas; and about known major diseases like arterial hypertension, diabetes mellitus, and cardiovascular diseases. A physical activity score was calculated based on information obtained from questions such as "Does your work or leisure time involve physically vigorous activity (like heavy lifting or digging), physically moderate-intensity activity (like brisk walking or carrying light loads), or does your work involve mostly sitting or standing with less than 10 minutes of walking at a time; and how much time do you spend with such activities?" "Do you walk or use a bicycle (pedal cycle) for at least 10 minutes continuously to get to and from places?" and "Over the past 7 days, how much time did you spend sitting or reclining on a typical day?" A socioeconomic score was based on the possession of items such as a car and second car, refrigerator, television set, laptop, and smartphone; self-reported monthly income; and education level. The list of examinations included the assessment of the arterial blood pressure at both upper arms and both ankles, pulse, body height, body weight, circumference of the hip and waist, and handgrip strength. Blood samples taken under fasting conditions were biochemically analyzed. All participants underwent a pulmonary function test with spirometric measurement of the forced expiratory volume in 1 second and the forced vital capacity. Diabetes mellitus was defined by a glucose concentration of ≥7.0 mmol/L or by a self-reported history of a physician-made diagnosis of diabetes mellitus or a history of drug treatment for diabetes (insulin or oral hypoglycemic agents). Applying the new guidelines of the American College of Cardiology and the American Heart Association for the detection, prevention, management, and treatment of high blood pressure, we differentiated between normal blood pressure (systolic blood pressure [SBP]/diastolic blood pressure [DBP] less than 120/80 mm Hg), elevated blood pressure (SBP between 120 and 129 mm Hg and DBP less than 80 mm Hg), stage 1 of arterial hypertension (SBP between 130 and 139 mm Hg or DBP between 80 and 89 mm Hg), stage 2 of arterial hypertension (SBP at least 140 mm Hg and ≤180 mm Hg or DBP at least 90 mm Hg and ≤120 mm Hg), and a hypertensive crisis (SBP >180 mm Hg and/or DBP >120 mm Hg).[17] In this new definition, the category of arterial prehypertension has been dropped and patients with previous arterial prehypertension have now been described as having either elevated blood pressure or stage I of arterial hypertension. Depression was assessed with the help of the Center for Epidemiologic Studies Depression Scale scoresheet, and anxiety with the help of the State-Trait Anxiety Inventory. Hearing loss was examined in a standardized interview with questions on self-reported hearing difficulties. The study design has been described in detail previously and followed the Guidelines for Accurate and Transparent Health Estimates Reporting: the GATHER statement guidelines.[15,16,18]

The ophthalmologic part of the examinations included automatic and subjective refractometry and assessment of presenting visual acuity; uncorrected visual acuity and best-corrected visual acuity; perimetry (screening test program with 82 test points and an extension of 50 degrees in all directions; PTS 1000 Perimeter; Optopol Technology Co, Zawercie, Poland); assessment of heterophorias; tear film examination (tear film break-up time test and Schirmer test); keratometry using a Scheimpflug camera (Pentacam HR, Typ70900; OCULUS, Optikgeräte GmbH Co, Wetzlar, Germany) for measurement of corneal curvature radius, corneal thickness, corneal volume, keratoconus indices, anterior chamber volume, anterior chamber angle width, and pupil diameter; and slit-lamp biomicroscopy of the anterior ocular segment as performed by a fellowship-trained ophthalmologist. The IOP was measured by noncontact tonometry (Tonometer Kowa KT-800; Kowa Company Ltd, Hamamatsu City, Japan). The tonometry was repeated if the measurements were higher than 21 mm Hg. After inducing medical mydriasis (tropicamide 0.8% and phenylephrine 5% given twice in a 10-minute interval), a second slit-lamp examination was performed to assess the presence of pseudoexfoliation of the lens. Special attention was paid to the anterior surface of the lens and the pupillary margin to search for signs of pseudoexfoliation syndrome. Pseudoexfoliation syndrome was graded into 7 stages, ranging from "no pseudoexfoliation" (stage 0), to faint pseudoexfoliation (small dark islands in the intermediary annular region corresponding to the moving pupillary margin) (stage 1), confluent dark islands in the annular region (stage 2), visible edges of pseudoexfoliative material clearly detectable in at least 1 location on the lens surface (stage 3), complete circular edge of pseudoexfoliative material on the lens surface (central island or in the lens periphery) (stage 4), pseudoexfoliative dandruff on the pupil margin (stage 5), and pseudoexfoliative material on the corneal endothelium and/or in the anterior chamber angle, and/or lens subluxation (stage 6). This grading system was partially similar to the description of pseudoexfoliation by Prince and associates.[19] Digital photographs of the cornea and lens were taken for the assessment of lens opacities (Topcon slit lamp and camera; Topcon Corp, Tokyo, Japan). We differentiated nuclear lens opacities into 6 grades using the classifying scheme for cataract of the Age-Related Eye Disease Study.[20] We combined standard photograph 6 and 7 into 1 grade (ie, "grade 6"). Grade "1" was no nuclear opacity in the lens, and grade "6" was very dense nuclear lens opacity. Cortical lens opacities and posterior subcapsular opacities were graded using photographs taken by retro-illumination (Topcon slit lamp and camera; Topcon Corp). The percentage area of opacity was measured using a grid. The optic disc and macula were examined on digital monoscopic 60-degree photographs (VISUCAM 500; Carl Zeiss Meditec AG, Jena, Germany) and by spectral-domain optical coherence tomography (OCT) (RS-3000; NIDEK Co, Ltd, Aichi, Japan). Using the OCT scans, we measured the peripapillary retinal nerve fiber layer thickness, the width and shape of the neuroretinal rim and the depth of the optic cup, and the thickness of the retina as a whole and stratified into various retinal layers in the foveola and in the perifoveal region. The degree of fundus tessellation was examined on the fundus photographs centered on the macula and centered on the optic nerve head.[21] Fundus tessellation was differentiated between grade "0" (no tessellation) and grade "3" (marked tessellation).

Inclusion criteria for the present study were the availability of IOP measurements and no history of previous glaucoma surgery and no history of antiglaucomatous therapy. The statistical analysis was performed using the software program SPPS (Statistical Package for Social Science, version 25.0; IBM-SPSS Inc, Chicago, Illinois, USA). We calculated the mean IOP values expressed as mean ± standard deviation, and we looked for associations between the IOP and other ocular and systemic parameters, firstly in univariate analysis, then in a multivariable linear regression analysis. In the latter, the IOP was the dependent variable and independent variables were all those parameters that were significantly associated with IOP in the univariate analysis. We calculated and presented the standardized correlation coefficient beta to make a comparison between the various parameters with respect to their influence on the association with IOP possible, and we calculated and presented the nonstandardized correlation coefficient B and its 95% confidence intervals (CI) as a surrogate for odds ratios to show by which amount the IOP changed if the independent parameter changed by 1 measurement unit. All *P* values were 2-sided and were considered statistically significant when smaller than .05.

RESULTS

OUT OF A POPULATION OF 7328 ELIGIBLE INDIVIDUALS residing in the study regions and fulfilling the inclusion criterion of an age of 40+ years, 5899 (80.5%) individuals participated in the Ural Eye and Medical Study. The composition of the study population with respect to sex and age corresponded to the sex and age distribution in the Russian population according to the most recent census carried out in 2010.[22] It showed 2 constrictions for the birth groups from 1940 to 1946 and for the birth groups from 1962 to 1970, directly and indirectly caused by the consequences of World War II.

Out of the 5899 individuals, 5519 (93.6%) individuals had measurements of the IOP and fulfilled the other inclusion criteria of no history of prior glaucoma surgery and no history of antiglaucomatous therapy. The group of individuals included into the present study as compared with the group of subjects excluded from the present investigation were significantly younger (58.5 ± 10.6 years [range: 40-94 years] vs 65.5 ± 10.5 years; $P < .001$), had a higher level of education (6.0 ± 1.7 vs 5.6 ± 1.7 years; $P = .006$), and had a higher percentage of men (2440 (44.2%) men/3079 (55.8%) women vs 140 (36.8%) men/240 (63.2%) women; $P = .007$). Mean body height was 165.0 ± 8.8 cm (median: 164 cm; range: 112-196 cm), mean body weight was 75.9 ± 14.6 kg (median: 75 kg; range: 31-170 kg), and mean body mass index was 27.9 ± 5.0 kg/m^2 (median: 27.3 kg/m^2; range: 13.96-60.96 kg/m^2).

Mean IOP in the right eyes was 13.4 ± 3.7 mm Hg and in the left eyes 13.8 ± 4.0 mm Hg. For further statistical analysis, we randomly chose 1 eye per study participant to be included. The mean IOP in the randomly chosen eyes was 13.6 ± 3.8 mm Hg (median: 13 mm Hg; range: 3-49 mm Hg) (Figure 1). The 95% CI ranged from 8 mm Hg to 23 mm Hg. The distribution of the IOP measurements showed a right-sided skew with a skewness of 1.39 (standard error: 0.03) and a kurtosis of 5.35 (standard error: 0.07). The range of IOP measurements within the mean ± 2 standard deviations was 6.0 mm Hg to 21.2 mm Hg.

In univariate analysis, higher IOP was significantly associated with the systemic parameters of female sex (Figure 2); urban region of habitation; Russian ethnicity; lower body height; higher body weight and body mass index; longer waist and hip circumference and higher waist-to-hip circumference ratio; higher socioeconomic score; lower physical activity score; higher prevalence of history of arterial

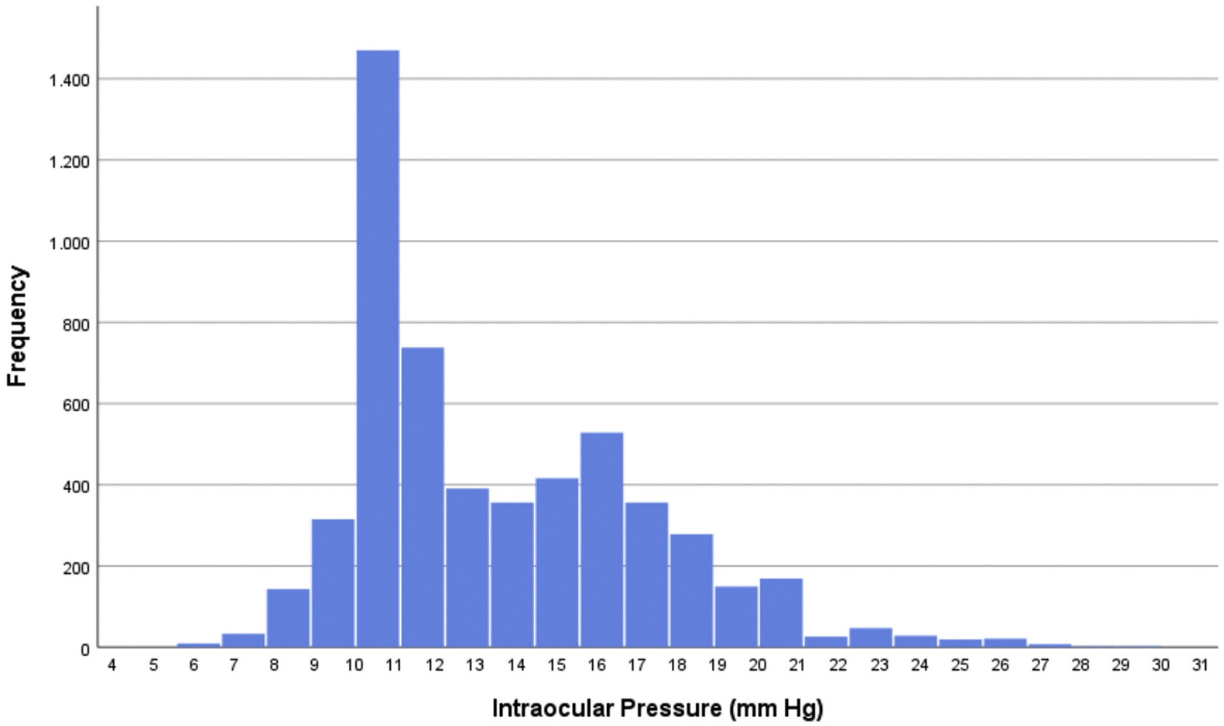

FIGURE 1. Histogram showing the distribution of intraocular pressure measurements in the Ural Eye and Medical Study.

hypertension, cardiovascular disorders including stroke, and diabetes mellitus; higher blood concentrations of alanine aminotransferase, aspartate aminotransferase, triglycerides, glucose, and rheumatoid factor; lower blood concentrations of total bilirubin, creatinine, and urea; higher systolic, diastolic, and mean blood pressure; lower frequency of vegetable and fruit intake; and lower hearing loss score (Table 1). Higher IOP was associated with the ocular parameters of worse best-corrected visual acuity, more myopic refractive error, longer axial length (Figure 3), thicker central corneal thickness (Figure 4) and higher corneal volume, lower anterior chamber depth, smaller anterior chamber volume and narrower anterior chamber angle, higher degree of nuclear cataract, and higher prevalence of pseudoexfoliation and of previous cataract surgery (Table 2). IOP was not significantly associated with age ($P = .20$), level of education ($P = .13$), reported monthly income ($P = .09$), history of angina pectoris ($P = .52$), asthma ($P = .24$), arthritis ($P = .11$), cancer ($P = .85$), previous bone fracture ($P = .96$), low back pain ($P = .23$), thoracic spine back pain ($P = .63$), neck pain ($P = 1.00$), headache ($P = .99$), heart attack ($P = .54$), dementia ($P = .27$), diarrhea ($P = .39$), iron-deficiency anemia ($P = .68$), low blood pressure with hospital admittance ($P = .73$), osteoarthritis ($P = .76$), skin disease ($P = .61$), any thyroid disease ($P = .27$), tumbling or falling ($P = .07$) and unconsciousness ($P = .27$), blood concentration of high-density lipoproteins ($P = .15$), low-density lipoproteins ($P = .97$), cholesterol ($P = .35$), residual nitrogen ($P = .53$), total protein

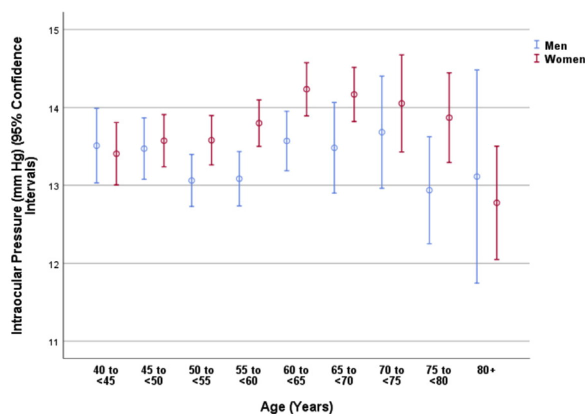

FIGURE 2. Graph showing the distribution of intraocular pressure, stratified by age and sex, in the Ural Eye and Medical Study.

($P = .32$) and hemoglobin ($P = .77$), international normalized ratio ($P = .10$), prevalence of chronic obstructive pulmonary disease ($P = .41$), current smoking ($P = .71$), smoking pack-years ($P = .20$), any alcohol consumption ($P = .40$), depression score ($P = .08$), state-trait anxiety inventory score ($P = .15$), and manual dynamometry ($P = .48$).

In the multivariable regression analysis, we first dropped, owing to collinearity (variance inflation factor >3), the parameters of body weight, waist and hip circumference, mean

TABLE 1. Associations (Univariate Analysis) Between Intraocular Pressure Measurements and Systemic Parameters in the Ural Eye and Medical Study

Parameter	Interval	Nonstandardized Regression Coefficient B	95% Confidence Interval of B	*P* Value	Standardized Regression Coefficient Beta
Age	5-year intervals	0.00006	0.000, 0.000	.20	0.02
Sex	Men/women	0.49	0.29, 0.70	<.001	0.06
Region of habitation	Urban/rural	−0.85	−1.05, −0.64	<.001	−0.11
Ethnicity	Any other ethnicity/Russian	1.22	0.97, 1.48	<.001	0.13
Body height	10 cm	−0.02	−0.03, −0.01	.002	−0.04
Body weight	Kg	0.03	0.02, 0.03	<.001	0.09
Body mass index	kg/m^2	0.10	0.08, 0.12	<.001	0.13
Waist circumference	Cm	0.03	0.02, 0.04	<.001	0.10
Hip circumference	Cm	0.03	0.02, 0.04	<.001	0.10
Waist-to-hip circumference ratio	Ratio	1.23	0.13, 2.33	.03	0.03
Socioeconomic score	Score	0.07	0.1, 0.12	.02	0.03
Physical activity score	Score	−0.03	−0.04, −0.02	<.001	−0.06
History of arterial hypertension	Yes/no	0.69	0.48, 0.89	<.001	0.09
History of cardiovascular disorders including stroke	Yes/no	0.34	0.10, 0.58	.005	0.04
History of diabetes mellitus	Yes/no	1.19	0.82, 1.57	<.001	0.09
Blood concentration of:					
Alanine aminotransferase	IU/L	0.01	0.001, 0.02	.02	0.03
Aspartate aminotransferase	IU/L	0.01	0.001, 0.02	.04	0.03
Bilirubin, total	μmol/L	−0.01	−0.02, −0.003	.01	−0.03
Triglycerides	mmol/L	0.37	0.23, 0.51	<.001	0.07
Rheumatoid factor	IU/mL	0.12	0.01, 0.23	.04	0.03
Glucose	mmol/L	0.18	0.12, 0.25	<.001	0.08
Prevalence of diabetes mellitus	Yes/no	1.02	0.70, 1.34	<.001	0.08
Creatinine	μmol/L	−0.01	−0.01, −0.003	.001	−0.04
Urea	mmol/L	−0.09	−0.16, −0.02	.008	−0.04
Blood pressure, systolic (SBP)	mm Hg	0.02	0.02, 0.03	<.001	0.13
Blood pressure, diastolic (DBP)	mm Hg	0.04	0.03, 0.05	<.001	0.10
Blood pressure, mean	mm Hg	0.04	0.03, 0.05	<.001	0.12
In a week how many days do you eat fruits?	Number of days	−0.05	−0.10, 0.00	.048	−0.03
In a week how many days do you eat vegetables?	Number of days	−0.10	−0.17, −0.02	.009	−0.04
Hearing loss	Hearing loss score	−0.01	−0.02, 0.00	.047	−0.03

blood pressure, history of diabetes, and blood concentrations of alanine aminotransferase. Owing to lack of significance, we then dropped step-by-step the parameters of history of cardiovascular disease and arterial hypertension; blood concentrations of rheumatoid factor; diastolic blood pressure; hearing loss score; refractive error; nuclear cataract; blood concentration of triglycerides, creatinine, and glucose; body height; anterior chamber volume; previous cataract surgery; number of days with intake of vegetables; blood concentration of aspartate aminotransferase; anterior chamber angle; and the socioeconomic score. If anterior corneal refractive power and age were added to the list of independent parameters, both were significantly associated with IOP (Figure 5). If refractive error was replaced by axial length, the latter was significantly associated with IOP. In the final model, higher IOP was associated (correlation coefficient $r = 0.40$) with the systemic parameters of female sex, urban region of habitation, Russian ethnicity, higher body mass index, less physically vigorous activity during work, higher prevalence of diabetes mellitus, lower blood concentration of bilirubin and urea, higher systolic blood pressure, fewer days with intake of fruits, worse best-corrected visual acuity, thicker central corneal thickness, shallower anterior chamber depth, longer axial length, higher anterior corneal refractive power, and higher prevalence of pseudoexfoliation (Table 3). If the parameter of anterior chamber depth was replaced by the parameter of status after cataract surgery, a lower IOP was associated with the status after cataract surgery (nonstandardized regression coefficient B: -0.78; 95% CI: -1.44, -0.13; standardized regression coefficient beta: -0.03; $P = .02$).

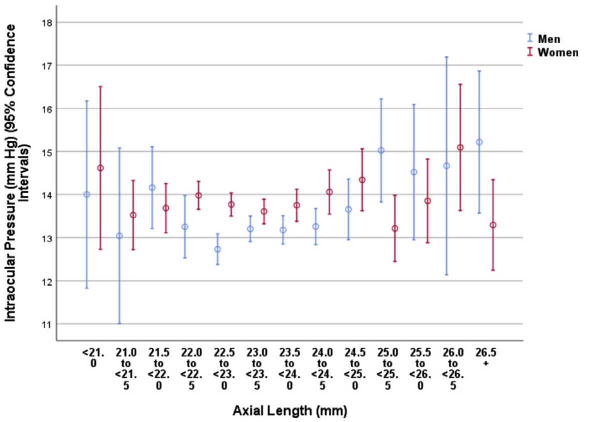

FIGURE 3. Graph showing the distribution of intraocular pressure, stratified by axial length and sex, in the Ural Eye and Medical Study.

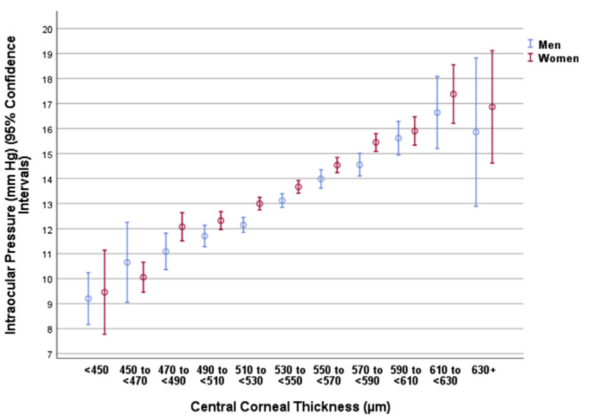

FIGURE 4. Graph showing the distribution of intraocular pressure, stratified by central corneal thickness and sex, in the Ural Eye and Medical Study.

If both eyes of the study participants or only the right eyes or only the left eyes were included into the statistical analysis, similar results were obtained.

DISCUSSION

IN OUR STUDY POPULATION FROM RUSSIA, THE IOP MEAsurements with a mean 13.6 ± 3.8 mm Hg were associated with a multitude of parameters including sex, region of habitation and ethnicity, systolic blood pressure, body mass index, diabetes mellitus and physical activity, central corneal thickness and anterior corneal curvature, axial length, and status after cataract surgery. The 95% CI ranged from 8 mm Hg to 23 mm Hg.

The mean IOP determined in our investigation (13.6 ± 3.8 mm Hg) was slightly lower than the values reported from other population-based studies, and it was comparable to the measurements reported from Central India (13.6 ± 3.4 mm Hg) and from South India (14.3 ± 3.3 mm Hg).[1,8,23,24] A major reason for discrepancies in the mean IOP values between investigations may be ethnicity-associated differences in central corneal thickness and differences between the various study populations in other parameters, such as body mass index, systolic blood pressure, age, and corneal curvature, which have an influence on the IOP and its measurements. In our study population, the mean central corneal thickness was 542 ± 34 μm, while it was 514 ± 33 μm in the rural Central Indian study population and 556 ± 33 μm in the population of the Beijing Eye Study, to mention only a few examples.[25,26] The IOP readings were the lowest and the central corneal thickness measurements were the thinnest in the Japanese Tajimi study, with a central corneal thickness of 521 μm.[27]

The relationship between higher IOP measurements readings and central corneal thickness are in agreement with multiple previous studies and are based on practical considerations by Goldmann.[26,28–35] In our study population, the IOP readings decreased by 0.36 mm Hg (95% CI: 0.33, 0.39) for each increase in central corneal thickness by 10 μm (Table 2). A value of approximately 0.4 mm Hg IOP correction for 10 μm difference in central corneal thickness was also found in a direct clinical study in which the anterior chamber was cannulated and the IOP was directly determined.[34]

As also found in other investigations such as the Central India Eye and Medical Study and the Beijing Eye Study, higher IOP readings were correlated with a steeper cornea or a higher anterior corneal refractive error.[13,36] The finding of a steeper cornea being correlated with higher IOP readings as observed in our study was in disagreement with observations made in the Reykjavik Eye Study, in which the IOP readings were not significantly correlated with the anterior corneal curvature radius.[32] The reason for the discrepancy may have been that the Reykjavik Eye Study did not perform a multivariable analysis of the relationship between IOP readings and a multitude of other parameters. In addition, the association between the IOP readings and the corneal refractive power (ie, corneal curvature) in our study population hold true for the range of steep corneas only, while beyond a corneal refractive power of 41.0 diopters, the relationship mostly vanished (Figure 5). The association between higher IOP readings and steeper corneas may be due to geometric reasons: a steep cornea as compared to a flat cornea needs a larger force to be flattened to an area of a defined size. The associations of the IOP readings with thinner central corneal thickness and with flatter corneal shape may be taken into account when IOP is measured in eyes that underwent a corneal refractive surgical procedure for myopia.

Higher IOP readings were associated with longer axial length or a higher myopic refractive error

TABLE 2. Associations (Univariate Analysis) Between Intraocular Pressure Measurements and Ocular Parameters in the Ural Eye and Medical Study

Parameter	Interval	Nonstandardized Regression Coefficient B	95% Confidence Interval of B	*P* Value	Standardized Regression Coefficient Beta
Best-corrected visual acuity	logMAR	0.75	0.52, 0.99	<.001	0.09
Refractive error (spherical equivalent)	Diopters	−0.06	−0.10, −0.01	.01	−0.04
Axial length	mm	0.11	0.02, 0.20	.02	0.03
Corneal refractive power	Diopters	−0.001	−0.07, 0.06	.97	−0.001
Central corneal thickness	μm	0.04	0.03, 0.04	<.001	0.37
Corneal volume	mm^3	0.22	0.20, 0.25	<.001	0.23
Anterior chamber depth	mm	−0.35	−0.57, −0.14	.001	−0.04
Anterior chamber volume	μL	−0.005	−0.008, −0.002	.003	−0.04
Anterior chamber angle	Degree	−0.03	−0.05, −0.02	<.001	−0.05
Lens thickness	mm	0.12	−0.13, 0.37	.35	0.01
Nuclear cataract	Grade	0.24	0.13, 0.34	<.001	0.06
Cortical cataract	Percentage	−0.01	−0.02, 0.003	.15	−0.02
Subcapsular cataract	Percentage	0.03	−0.03, 0.08	.33	0.01
Fundus tessellation, macula region	Grade	0.07	−0.05, 0.19	.24	0.02
Fundus tessellation, peripapillary region	Grade	0.02	−0.08, 0.13	.65	0.01
Pseudoexfoliation	Presence	0.97	0.58, 1.35	<.001	0.07
History of prior cataract surgery	Yes/no	−0.84	−1.40, −0.29	<.001	−0.04

(Tables 2 and 3, Figure 3). Although the relationship between higher IOP and longer axial length reached statistical significance, the standardized regression coefficient beta (= 0.09) was relatively low and the graph showed a significant scattering (Table 3, Figure 3). The tendency of higher IOP readings with longer axial length has also been reported from other studies, such as the Liwan Eye Study and the UK Biobank Study, while the Los Angeles Latino Eye Study did not confirm such a relationship.[35,37,38] In the Central India Eye and Medical Study, the IOP was related with myopic refractive error but not with axial length.[13] Interestingly, experimental studies on the development of axial myopia in guinea pigs have also suggested an association between higher IOP and longer axial elongation.[39]

The IOP measurements in our study were associated with a shallower anterior chamber and a narrower anterior chamber angle (Tables 2 and 3). It concurred with the results of previous population-based studies, such as the Singaporean Tanjong Pagar Study.[10] As a corollary and as also shown in previous hospital-based studies, prior cataract surgery (ie, a deeper anterior chamber) was associated with a lower IOP in the multivariable model in our study (Table 3).

In our study population, higher IOP was associated with higher systolic blood pressure and higher body mass index. These results confirmed previous investigations such as the Beaver Dam Study, Blue Mountains Study, Tanjong Pagar Study, Los Angeles Latino Eye Study, Singapore Malay Eye Study, and the UK biobank study.[1,37,38,40–43] Corresponding to the association with higher blood pressure, IOP was also correlated with a higher body mass index in our study population in the multivariable analysis.

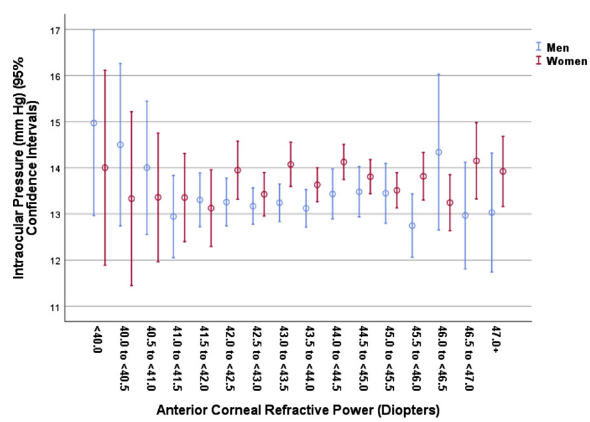

FIGURE 5. Graph showing the distribution of intraocular pressure, stratified by anterior corneal refractive power and sex, in the Ural Eye and Medical Study.

In our study population, IOP showed a nonlinear, overall statistically nonsignificant relationship with age (Figure 2). It increased from an age of 40 years to an age of 70 years and decreased thereafter. Previous investigations often found a positive association between higher IOP and older age, while Japanese studies and the Beijing Eye Study reported on a negative relationship between IOP and age.[1,3,7,9,12,36,44] Reasons for the differences between studies and various ethnicities in the relationship of IOP to age may be differences in the other factors influencing the IOP. To cite an example, blood pressure increases in elderly whites and may decrease in elderly Japanese, with blood pressure influencing the IOP.

TABLE 3. Associations (Multivariate Analysis) Between Intraocular Pressure Measurements and Systemic and Ocular Parameters in the Ural Eye and Medical Study

Parameter	Nonstandardized Regression Coefficient B	95% Confidence Interval of B	Standardized Regression Coefficient Beta	Variance Inflation Factor	*P*-Value
Sex (men/women)	0.44	0.22, 0.66	0.06	1.15	<0.001
Urban/rural region of habitation	−0.27	−0.51, −0.03	−0.03	1.24	0.03
Ethnicity (non-Russian vs Russian)	0.47	0.20, 0.74	0.05	1.19	0.001
Body mass index (kg/m^2)	0.06	0.04, 0.08	0.08	1.16	<0.001
Physical activity score	−0.02	−0.03, −0.002	−0.03	1.08	0.02
Prevalence of diabetes mellitus	0.42	0.08, 0.76	0.03	1.06	0.02
Systolic blood pressure (mm Hg)	0.01	0.01, 0.02	0.08	1.14	<0.001
Number of days per week with intake of fruits	−0.07	−0.12, −0.01	−0.03	1.03	0.01
Blood concentration of bilirubin	−0.01	−0.02, −0.003	−0.04	1.02	0.008
Blood concentration of urea	−0.11	−0.17, −0.04	−0.04	1.02	0.003
Visual acuity (logMAR)	0.64	0.38, 0.90	0.13	1.38	<0.001
Central corneal thickness (μm)	0.036	0.033, 0.039	0.32	1.05	<0.001
Anterior corneal refractive error (diopters)	0.11	0.04, 0.18	0.05	1.38	0.003
Anterior chamber depth (mm)	−0.57	−0.83, −0.30	−0.07	1.32	<0.001
Cataract surgery (instead of anterior chamber depth)	−0.78	−1.44, −0.13	−0.03	1.03	0.02
Axial length (mm)	0.30	0.18, 0.42	0.09	1.69	<0.001
Pseudoexfoliation	1.08	0.52, 1.63	0.05	1.01	<0.001

The relationship between IOP and age and inter-ethnic differences in that relationship, as well as inter-ethnic differences in the spectrum of other parameters influencing the IOP, may also have an impact on the definition of the normal range of IOP with respect to IOP as a risk factor for the development of glaucoma.[36] Depending on the ethnicity and the spectrum of ocular and systemic factors influencing the IOP and its readings, the relationship between an IOP being too high in relationship to the pressure susceptibility of the optic nerve head may be reassessed.[36,45] To cite an example, in elderly Japanese, who usually have a relatively low body mass index, the "normal" IOP may be lower than in elderly North Americans, who usually have a relatively high body mass index. Using the same definition and range of a "normal" IOP, the prevalence of so-called normal-pressure glaucoma is interestingly markedly higher in Japan than in North America. Future studies may therefore explore whether the statistical relationship between IOP readings and the presence of a glaucomatous optic neuropathy can be improved if IOP measurements are adjusted for their physiological associations with a multitude of parameters.

Besides with blood pressure and body mass index, higher IOP was associated with the systemic parameters of female sex, urban region of habitation, Russian ethnicity, higher prevalence of diabetes mellitus, and lower physical activity score (Table 3). All these factors may have to be taken into account when the normal range of IOP in specific societies is defined.

The presence of pseudoexfoliation was another factor associated with IOP. It was in contrast to the results obtained in the Central India and Medical Study and the Beijing Eye Study, and it was in agreement with many clinical studies.[19,46,47] Future studies focusing on pseudoexfoliation may further explore the relationship between pseudoexfoliation, IOP, and the prevalence of glaucomatous optic neuropathy and potential inter-ethnic differences.

Potential limitations of our study should be mentioned. First, IOP was examined by pneumotonometry. Previous investigations have revealed that IOP readings obtained by noncontact tonometry can differ from those measured by Goldmann applanation tonometry. Some previous population-based studies also used pneumotonometry while others applied applanation tonometry. Second, the participation rate in our study was 80.5% and the age and sex distribution in our study population was comparable to the results of the Russian census 2010. It may thus be unlikely that a major bias in the inclusion of study participants might have occurred. Third, the coefficients for the associations between IOP and other parameters were relatively small, indicating that only a fraction of the variability of IOP could be explained by that association. Strengths of the study were that it is the first population-based study from Russia, as the world's largest and one of the most populous countries; that the study sample size was relatively large; and that besides ocular parameters a multitude of systemic parameters were examined so that associations between IOP and these nonocular parameters could be examined.

In conclusion, IOP was associated with a multitude of parameters including sex, region of habitation and ethnicity, systolic blood pressure, body mass index, diabetes mellitus and physical activity, central corneal thickness and curvature, axial length, and cataract surgery. These associations may be taken into account when the normal range of IOP is defined.

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REFERENCES

1. Klein BE, Klein R, Linton KL. Intraocular pressure in an American community. The Beaver Dam Study. *Invest Ophthalmol Vis Sci* 1992;33(7):2224–2228.
2. Dielemans I, Vingerling JR, Algra D, Hofman A, Grobbee DE, de Jong PT. Primary open-angle glaucoma, intraocular pressure, and systemic blood pressure in the general elderly population. The Rotterdam Study. *Ophthalmology* 1995;102(1):54–60.
3. Leske MC, Connell AM, Wu SY, Hyman L, Schachat AP. Distribution of intraocular pressure. The Barbados Eye Study. *Arch Ophthalmol* 1997;115(8):1051–1057.
4. Wu SY, Leske MC. Associations with intraocular pressure in the Barbados Eye Study. *Arch Ophthalmol* 1997;115(12):1572–1576.
5. Bonomi L, Marchini G, Marraffa M, et al. Prevalence of glaucoma and intraocular pressure distribution in a defined population. The Egna-Neumarkt-Study. *Ophthalmology* 1998;105(2):209–215.
6. Nomura H, Shimokata H, Ando F, Miyake Y, Kuzuya F. Age-related changes in intraocular pressure in a large Japanese population. *Ophthalmology* 1999;106(10):2016–2022.
7. Weih LM, Mukesh BN, McCarty CA, Taylor HR. Association between demographic, familial, medical and ocular factors with intraocular pressure. *Arch Ophthalmol* 2001;119(6):875–880.
8. Rochtchina E, Mitchell P, Wang JJ. Relationship between age and intraocular pressure: the Blue Mountains Eye Study. *Clin Experiment Ophthalmol* 2002;30(3):173–517.
9. Nomura H, Ando F, Niino N, Shimokata H, Miyake Y. The relationship between age and intraocular pressure in a Japanese population: the influence of central corneal thickness. *Curr Eye Res* 2002;24(2):81–85.
10. Foster PJ, Machin D, Wong TY, et al. Determinants of intraocular pressure and its association with glaucomatous optic neuropathy in Chinese Singaporeans: the Tanjong Pagar Study. *Invest Ophthalmol Vis Sci* 2003;44(9):3885–3891.
11. Hennis A, Wu S, Nemesure B, Leske MC, Barbados Eye Studies Group. Hypertension, diabetes and longitudinal changes in intraocular pressure. *Ophthalmology* 2003;110(5):908–914.
12. Fukuoka S, Aihara M, Iwase A, Araie M. Intraocular pressure in an opthalmoscopically normal Japanese population. *Acta Ophthalmol* 2008;86(4):434–439.
13. Jonas JB, Nangia V, Matin A, Sinha A, Kulkarni M, Bhojwani K. Intraocular pressure and associated factors. The Central India Eye and Medical Study. *J Glaucoma* 2011;20(7):405–409.
14. Xu L, Li J, Zheng Y, et al. Intraocular pressure in Northern China in an urban and rural population. The Beijing Eye Study. *Am J Ophthalmol* 2005;140(5):913–915.
15. Bikbov M, Fayzrakhmanov RR, Kazakbaeva G, Jonas JB. Ural Eye and Medical Study: description of study design and methodology. *Ophthalmic Epidemiol* 2018;25(3):187–198.
16. Bikbov MM, Fayzrakhmanov RR, Kazakbaeva GM, et al. Frequency and associated factors of bone fractures in Russians: The Ural Eye and Medical Study. *Sci Rep* 2018;8(1):7483.
17. Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Hypertension* 2018;71(6):1269–1324.
18. 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.
19. Prince AM, Streeten BW, Ritch R, Dark A, Sperling M. Preclinical diagnosis of pseudoexfoliative syndrome. *Arch Ophthalmol* 1987;105(8):1076–1082.
20. Age-Related Eye Disease Study Research Group. The Age-Related Eye Disease Study (AREDS) system for classifying cataracts from photographs: AREDS report no. 4. *Am J Ophthalmol* 2001;131(2):167–175.
21. Yan YN, Wang YX, Xu L, Xu J, Wei WB, Jonas JB. Fundus tessellation: prevalence and associated factors. The Beijing Eye Study 2011. *Ophthalmology* 2015;122(9):1873–1880.
22. Demographics of Russia. Available at: https://en.wikipedia.org/wiki/Demographics_of_Russia. Accessed June 6, 2019.
23. Vijaya L, George R, Paul PG, et al. Prevalence of open-angle glaucoma in a rural south Indian population. *Invest Ophthalmol Vis Sci* 2005;46(12):4461–4467.

24. Nangia V, Bhojwani K, Matin A, Sinha A, Jonas JB. Intraocular pressure and arterial blood pressure. The Central India Eye and Medical Study. *Arch Ophthalmol* 2009;127(3):339–340.
25. Nangia V, Jonas JB, Sinha A, Matin A, Kulkarni M. Central corneal thickness and its association with ocular and general parameters in Indians: The Central India Eye and Medical Study. *Ophthalmology* 2010;117(4):705–710.
26. Zhang H, Xu L, Chen C, Jonas JB. Central corneal thickness in adult Chinese. Association with ocular and general parameters. The Beijing Eye Study. *Graef Arch Clin Exp Ophthalmol* 2008;246(4):587–592.
27. Tomidokoro A, Araie M, Iwase A, Tajimi Study Group. Corneal thickness and relating factors in a population-based study in Japan: the Tajimi study. *Am J Ophthalmol* 2007;144(1):152–154.
28. Goldmann H, Schmidt T. Über Applanationstonometrie. *Ophthalmologica* 1957;134(4):221–242.
29. Hansen FK, Ehlers N. Elevated tonometer readings caused by a thick cornea. *Acta Ophthalmol* 1971;49(5):775–778.
30. Gordon MO, Beiser JA, Brandt JD, et al. The Ocular Hypertension Treatment Study: baseline factors that predict the onset of primary open-angle glaucoma. *Arch Ophthalmol* 2002;120(6):714–720.
31. Foster P, Baasanhu J, Alsbirk PH, et al. Central corneal thickness and intraocular pressure in a Mongolian population. *Ophthalmology* 1998;105(6):969–973.
32. Eysteinsson T, Jonasson F, Sasaki H, et al. Central corneal thickness, radius of the corneal curvature and intraocular pressure in normal subjects using non-contact techniques: Reykjavik Eye Study. *Acta Ophthalmol* 2002;80(1):11–15.
33. Wolfs RC, Klaver CC, Vingerling JR, Grobbee DE, Hofman A. Distribution of central corneal thickness and its association with intraocular pressure: The Rotterdam Study. *Am J Ophthalmol* 1997;123(6):767–772.
34. Kohlhaas M, Boehm AG, Spoerl E, Pürsten A, Grein HJ, Pillunat LE. Effect of central corneal thickness, corneal curvature, and axial length on applanation tonometry. *Arch Ophthalmol* 2006;124(4):471–476.
35. Wang D, Huang W, Li Y, et al. Intraocular pressure, central corneal thickness, and glaucoma in Chinese adults: the Liwan eye study. *Am J Ophthalmol* 2011;152(3):454–462.e1.
36. Wang YX, Xu L, Wei WB, Jonas JB. Intraocular pressure and its normal range adjusted for ocular and systemic parameters. The Beijing Eye Study 2011. *PLoS One* 2018;13(5):e0196926.
37. Chan MP, Grossi CM, Khawaja AP, et al. Associations with intraocular pressure in a large cohort: results from the UK Biobank. *Ophthalmology* 2016;123(4):771–782.
38. Memarzadeh F, Ying-Lai M, Azen SP, Varma R. Los Angeles Latino Eye Study Group. Associations with intraocular pressure in Latinos: the Los Angeles Latino Eye Study. *Am J Ophthalmol* 2008;146(1):69–76.
39. El-Nimri NW, Wildsoet CF. Effects of topical latanoprost on intraocular pressure and myopia progression in young guinea pigs. *Invest Ophthalmol Vis Sci* 2018;59(6):2644–2651.
40. McLeod SD, West SK, Quigley HA, Fozard JL. A longitudinal study of the relationship between intraocular and blood pressures. *Invest Ophthalmol Vis Sci* 1990;31(11):2361–2366.
41. Mitchell P, Lee AJ, Wang JJ, Rochtchina E. Intraocular pressure over the clinical range of blood pressure: Blue Mountains Eye Study findings. *Am J Ophthalmol* 2005;140(1):131–132.
42. Wong TT, Wong TY, Foster PJ, et al. The relationship of intraocular pressure with age, systolic blood pressure, and central corneal thickness in an Asian population. *Invest Ophthalmol Vis Sci* 2009;50(9):4097–4102.
43. Wang YX, Xu L, Zhang XH, You QS, Zhao L, Jonas JB. Five-year change in intraocular pressure associated with changes in arterial blood pressure and body mass index. The Beijing Eye Study. *PLoS One* 2013;8(10):e77180.
44. Shiose Y. The aging effect on intraocular pressure in an apparently normal population. *Arch Ophthalmol* 1984;102(6):883–887.
45. Jonas JB, Aung T, Bourne RR, Bron AM, Ritch R, Panda-Jonas S. Glaucoma. *Lancet* 2017;390(10108):2183–2193.
46. You QS, Xu L, Wang YX, et al. Pseudoexfoliation: normative data and associations. The Beijing Eye Study 2011. *Ophthalmology* 2013;120(8):1551–1558.
47. Jonas JB, Nangia V, Matin A, et al. Pseudoexfoliation: normative data and associations. The Central India Eye and Medical Study. *PLoS One* 2013;8(10):e76770.