

# Associations between axial length, corneal refractive power and lens thickness in children and adolescents: The Ural Children Eye Study

Mukharram M. Bikbov<sup>1</sup> | Gyulli M. Kazakbaeva<sup>1,2</sup> | Albina A. Fakhretdinova<sup>1</sup> |  
 Azaliia M. Tuliakova<sup>1</sup> | Ellina M. Iakupova<sup>1,2</sup> | Songhomitra Panda-Jonas<sup>3</sup> |  
 Leisan I. Gilemzianova<sup>1</sup> | Liana A. Garipova<sup>1</sup> | Dinar A. Khakimov<sup>1</sup> |  
 Liaisan I. Islamova<sup>1</sup> | Nikolay I. Pokhilko<sup>1</sup> | Jost B. Jonas<sup>3,4,5</sup> 

<sup>1</sup>Ufa Eye Research Institute, Ufa, Russia

<sup>2</sup>Ufa Eye Institute, Ufa, Russia

<sup>3</sup>Privatpraxis Prof Jonas und Dr Panda-Jonas, Heidelberg, Germany

<sup>4</sup>Department of Ophthalmology, Medical Faculty Mannheim, Heidelberg University, Mannheim, Germany

<sup>5</sup>Institute of Molecular and Clinical Ophthalmology Basel, Basel, Switzerland

## Correspondence

Mukharram M. Bikbov, Ufa Eye Research Institute, 90 Pushkin Street, Ufa 450008, Russia.

Email: [bikbov.m@gmail.com](mailto:bikbov.m@gmail.com)

Jost B. Jonas, Department of Ophthalmology, Medical Faculty Mannheim, Theodor-Kutzerufer 1, 68167 Mannheim, Germany.

Email: [jost.jonas@medma.uni-heidelberg.de](mailto:jost.jonas@medma.uni-heidelberg.de)

## Abstract

**Purpose:** To assess relationships between ocular biometric parameters in dependence of age and sex in children and adolescents.

**Methods:** In the Ural Children Eye Study, a school-based cohort study, 4933 children underwent an ophthalmological and general examination.

**Results:** Complete biometric measurements were available for 4406 (89.3%) children. Cycloplegic refractive error (mean:  $-0.87 \pm 1.73$  diopters (D); median:  $-0.38$  D; range:  $-19.75$  D to  $+11.25$  D) increased (multivariable analysis;  $r^2=0.73$ ) with shorter axial length ( $\beta$ :  $-0.99$ ; non-standardized regression coefficient  $B$ :  $-1.64$ ; 95% CI:  $-1.68$ ,  $-1.59$ ) and lower corneal refractive power ( $\beta$ :  $-0.55$ ;  $B$ :  $-0.67$ ; 95% CI:  $-0.70$ ,  $-0.64$ ), in addition to higher cylindrical refractive error ( $\beta$ :  $0.10$ ;  $B$ :  $0.34$ ; 95% CI:  $0.27$ ,  $0.41$ ), thinner lens ( $\beta$ :  $-0.11$ ;  $-0.85$ ; 95% CI:  $-1.02$ ,  $-0.69$ ) and male sex ( $\beta$ :  $0.15$ ;  $B$ :  $0.50$ ; 95% CI:  $0.42$ ,  $0.57$ ). In univariate analysis, decrease in refractive error with older age was more significant ( $\beta$ :  $-0.38$  vs.  $\beta$ :  $-0.25$ ) and steeper ( $B$ :  $-0.22$  (95% CI:  $-0.24$ ,  $-0.20$ ) vs.  $B$ :  $-0.13$  (95% CI:  $-0.15$ ,  $-0.11$ )) in girls than boys, particularly for an age of 11+ years. Axial length increased with older age (steeper for age  $<11$  years) ( $B$ :  $0.22$  (95% CI:  $0.18$ ,  $0.25$ ) vs.  $0.07$  (95% CI:  $0.05$ ,  $0.09$ )). In multivariable analysis, axial length increased with lower refractive error ( $\beta$ :  $-0.77$ ;  $B$ :  $-0.42$ ; 95% CI:  $-0.43$ ,  $-0.40$ ) and lower corneal refractive power ( $\beta$ :  $-0.54$ ;  $B$ :  $-0.39$ ; 95% CI:  $-0.41$ ,  $-0.38$ ), in addition to older age ( $\beta$ :  $0.04$ ;  $B$ :  $0.02$ ; 95% CI:  $0.01$ ,  $0.03$ ), male sex ( $\beta$ :  $0.13$ ;  $B$ :  $0.23$ ; 95% CI:  $0.21$ ,  $0.32$ ), higher cylindrical refractive error ( $\beta$ :  $0.05$ ;  $B$ :  $0.09$ ; 95% CI:  $0.05$ ,  $0.14$ ) and thinner lens ( $\beta$ :  $-0.14$ ;  $B$ :  $-0.62$ ; 95% CI:  $-0.72$ ,  $-0.51$ ). The axial length/corneal curvature (AL/CR) ratio increased until the age of 14 years ( $\beta$ :  $0.34$ ;  $B$ :  $0.017$ ; 95% CI:  $0.016$ ,  $0.019$ ;  $p<0.001$ ), and then became independent of age. The AL/CR ratio increased ( $r^2=0.78$ ) mostly with higher corneal refractive power ( $\beta$ :  $0.25$ ;  $B$ :  $0.02$ ; 95% CI:  $0.02$ ,  $0.02$ ;  $p<0.001$ ), lower refractive error ( $\beta$ :  $-0.75$ ;  $B$ :  $-0.05$ ; 95% CI:  $-0.05$ ,  $-0.05$ ;  $p<0.001$ ), thinner lens thickness ( $\beta$ :  $-0.16$ ;  $B$ :  $-0.09$ ; 95% CI:  $-0.10$ ,  $-0.08$ ;  $p<0.001$ ) and older age ( $\beta$ :  $0.16$ ;  $B$ :  $0.006$ ; 95% CI:  $0.005$ ,  $0.007$ ;  $p<0.001$ ).

**Conclusions:** In this multiethnic group of school children in Russia, the age-related increase in myopic refractive error was more significant and steeper in girls, particularly for the age group of 11+ years. Determinants of higher myopic refractive error were longer axial length, higher corneal refractive power, lower cylindrical refractive error, thicker lens and female sex.

## KEYWORDS

axial length, corneal refractive power, lens thickness, myopia

## 1 | INTRODUCTION

The ocular biometric parameters of axial length, corneal refractive power and lens thickness are major determinants of the optical system of the globe and major factors influencing the refractive error of the eye (Gwiazda et al., 2002; Li et al., 2012; Mutti et al., 2005; Ojaimi et al., 2005; Olsen et al., 2007; Saw et al., 2002; Shih et al., 2009; Twelker et al., 2009; Zadnik et al., 2003). It also holds true for eyes of children and adolescents who physiologically undergo the process of emmetropization (Pärssinen et al., 2014, 2015; Tideman et al., 2018; Yam et al., 2020). The latter describes the change from marked hyperopia at birth to emmetropia in adolescence and adulthood. It includes a primary phase of general eye growth in the first years of life and a following second phase in which mainly an elongation of the optical axis (the so-called axial elongation) leads to a further decrease in hyperopia, so that ideally emmetropia eventually results (Morgan et al., 2012). Achieving emmetropia necessitates an accuracy of about 100–200 µm in regulating axial elongation as part of the process of emmetropization. Previous studies have shown, that during the second phase of emmetropization, it is mainly the axial length which enlarges, while other elements of the optical system of the eye undergo minor changes (Gwiazda et al., 2002; Li et al., 2012; Morgan et al., 2012; Mutti et al., 2005; Ojaimi et al., 2005; Olsen et al., 2007; Saw et al., 2002; Shih et al., 2009; Twelker et al., 2009; Zadnik et al., 2003). These changes are associated with age and sex. Here, we examined the associations between these major components of the ocular optical system in dependence of age and sex in a school-based recruited cohort of children and adolescents.

## 2 | METHODS

The Ural Children Myopia Study included children from four randomly selected schools located in various regions of the Kirovskii district in the city of Ufa. The Ethics Committee of the Academic Council of the Ufa Eye Research Institute approved the study design and confirmed that the study adhered to the Declaration of Helsinki. At least one of the parents gave an informed written consent. The study was performed between January 2019 and April 2022. Ufa is the capital of the republic of Bashkortostan/Russia and is an industrial, economic, scientific and cultural centre. With altogether 1.1 million inhabitants, the citizenship of Ufa is ethnically composed of Russians, Tatars, Bashkirs and other ethnicities. The republic of Bashkortostan, with a population of approximately 4.07 million inhabitants, is situated at the southwestern end of the Ural Mountains. The Kirovskii district as one of seven urban districts of Ufa is located in the southern part of Ufa and includes 165 000 inhabitants. In the Kirovskii district, there are 20 large- and medium-sized industrial enterprises that produce medical products, electrical equipment, communication equipment, clothing and textiles, food and other products. The Kirovskii district includes 18 schools with children of grade 1–11. Out of these 18 schools, we randomly

selected four schools (total number of pupils per school: 598, 1030, 2099, 1936) to be included into the study. Inclusion criterion for the participation in the study was attending one of the four randomly selected schools at the grades of 1–11. Exclusion criteria were the use of topical low-dose atropine eye drops or orthokeratology as procedures to reduce the progression of myopia. At the time of study, low-concentration atropine eye drops, orthokeratology or other measures to prevent further myopia progression had only rarely or not at all been applied in the study region.

All children of the Ural Children Study came to the Ufa Eye Research Institute for the examinations. The children and their parents underwent a standardized interview performed by trained social workers who personally asked the questions and noted the answers. The questionnaire included questions on diet (vegetarian vs. mixed diet, number of daily meals, frequency and amount of intake of vegetables, fruits and meat, type of cooking oil used, intake of food with whole grain, estimated salt consumption, degree of meat processing), daily physical activity (walking, cycling or going by bus to school, time of running or walking per day, time spent with playing sport games (basketball, volleyball, badminton, football)), cognitive function, presence of any specific ocular problems or disorders, hereditary eye diseases in the family, availability and wearing of glasses, sunglasses and medical history including known diagnosis and therapy of major diseases such as arterial hypertension, diabetes mellitus and previous trauma including bone fractures (Bikbov et al., 2019, 2021, 2023). The questions were taken from standardized questionnaires, such as the Mini-Mental Status Examination test for the assessment of cognitive function (Folstein et al., 1975). Additional questions were taken from the 'Convergence Insufficiency Symptom Survey', the 'Computer Vision Syndrome Assessment', the 'Computer Activities and Environment Assessment', the 'Computer Vision Syndrome Assessment' the 'General Health Questionnaire (GHQ) 12' and the 'Generalized Anxiety Disorder Scale-7' (GAD-7) for the assessment of depression and anxiety (Clark & Clark, 2015; Mar Segui et al., 2015).

The non-ophthalmological examinations consisted of measurement of the anthropometric parameters of body height, weight, waist and hip circumference and measurement of the hand grip force by dynamometry. The ophthalmological examinations included testing of uncorrected visual acuity and best-corrected visual acuity by ophthalmologists. We used the modified Early Treatment of Diabetic Retinopathy Study (ETDRS) charts (Light House Low Vision Products) at a distance of 4 m. Best-corrected visual acuity was measured based on the results of automated refractometry (Auto Ref/Kerato/Tono/Pachymeter Tonoref, Nidek), and subsequent subjective refractometry. We additionally performed refractometry under cycloplegic conditions after the children had received tropicamide 0.8% eye drops once (Mydrimax®; Sentiss Co.), and one had waited 30 min. Additional examinations were Schöber's test to assess heterophorias, assessment of corneal hysteresis and corneal resistance using the Ocular Response

Analyzer (ORA, Reichert, Inc.) and the Corvis ST device (Oculus Inc), tonometry, imaging of the anterior ocular segment using a Scheimpflug camera (Pentacam HR, Typ70900, OCULUS, Optikgeräte GmbH Co.), slit lamp-based biomicroscopy carried out by a fellowship-trained ophthalmologist and laser interferometric biometry (AL-Scan, Nidek Co, Ltd) for measurement of axial length. We took digital photographs of the cornea and lens (Topcon slit lamp and camera, Topcon Corp.) and of the optic nerve head and macular (60° images; VISUCAM 500, Carl Zeiss Meditec AG), and we performed a swept-source optical coherence tomography (OCT) (swept-source OCT Triton, Topcon Corporation) with images taken from the macula and optic nerve head.

Low refractive myopia was defined by a refractive error (spherical equivalent) of  $\leq -0.75$  diopter (D) and  $> -6.0$  D, and high refractive myopia by a refractive error of  $\leq -6.00$  D. Low axial myopia was defined by an axial length of 24.0 to  $< 26.0$  mm, and high axial myopia was defined by an axial length of  $> 26.0$  mm.

The statistical analysis was performed using a statistical package analysis program (SPSS for Windows, version 27.0, IBM-SPSS). Inclusion criterion for the present study was the availability of the biometric and refractometric measurements. In a first step, we assessed the mean values of the major outcome parameters, that is, refractive error, axial length, cylindrical refractive error, corneal refractive power and the ratio of axial length divided by corneal curvature radius (AL/CR ratio). Performing a linear regression analysis, we determined relationships between the outcome parameters and other ocular and systemic parameters. We finally performed a multivariable analysis, with the outcome parameter as the dependent variable and all those parameters, which were significantly correlated with the outcome parameter in the univariable analysis, as independent parameters. One eye per individual was included into the statistical analysis. We determined the standardized regression coefficient  $\beta$ , the non-standardized regression coefficient  $B$  and its 95% confidence intervals (CIs). We considered  $p$ -values, all of which were two-sided, as statistically significant if the values were  $< 0.05$ .

### 3 | RESULTS

Out of 4933 children primarily examined in the UCES, the study included 4406 (89.3%) children (2159 (49.0%) boys; 2247 (51.0%) girls) with a mean age of  $11.93 \pm 3.15$  years (median: 11.81 years; range: 6.73–18.82 years) (Table 1). The group of children included into the study were significantly older than the group of excluded children ( $11.9 \pm 3.2$  vs.  $10.8 \pm 2.8$  years;  $p < 0.001$ ), while both groups did not differ significantly in sex ( $p = 0.41$ ).

The mean refractive error was  $-0.87 \pm 1.73$  D in the right eyes (median:  $-0.38$  D; range:  $-19.75$  D to  $+11.25$  D) and  $-0.79 \pm 1.74$  D in the left eyes (median:  $-0.38$  D; range:  $-15.12$  D to  $+10.88$  D), with a significant difference ( $-0.08$  D; 95% CI:  $-0.10$ ,  $-0.06$ ;  $p < 0.001$ ) between both eyes. The mean cylindrical refractive error was  $-0.52 \pm 0.56$  D in the right eyes (median:  $-0.25$  D; range: 0 to  $-6.25$  D) and  $-0.56 \pm 0.59$  D in the left eyes (median:

$-0.50$  D; range: 0.00 D to  $-7.00$  D), with a significant difference (0.04 D; 95% CI: 0.03, 0.05;  $p < 0.001$ ) between both eyes. The mean axial length was  $23.67 \pm 1.03$  mm (median: 23.58 mm; range: 18.50–28.44 mm) in the right eyes and  $23.62 \pm 1.04$  mm (median: 23.54 mm; range: 18.63–28.63 mm) in the left eyes, with a significant difference (0.04 mm; 95% CI: 0.03, 0.05;  $p < 0.001$ ) between both eyes. The mean corneal refractive power was  $43.11 \pm 1.42$  D (median: 43.10; range: 37.60–53.10) in the right eyes and  $43.13 \pm 1.41$  D (median: 43.10; range: 37.20–53.10) in the left eyes, with a significant difference (0.02 D; 95% CI: 0.01, 0.03;  $p < 0.001$ ) between both eyes. The mean AL/CR ratio was  $3.02 \pm 0.12$  (median: 3.01; range: 2.49–3.67) in the right eyes and  $3.02 \pm 0.12$  (median: 3.00; range: 2.52–3.68) in the left eyes, with a significant difference (0.003 D; 95% CI: 0.002, 0.005;  $p < 0.001$ ) between both eyes. Lens thickness was significantly ( $p < 0.001$ ) thinner in the right eyes ( $3.53 \pm 0.23$  mm; median: 3.52 mm; range: 2.17–5.33) than in the left eyes ( $3.56 \pm 0.24$  mm; median: 3.54 mm; range: 1.89–5.51) (difference:  $-0.03$ ; 95% CI:  $-0.04$ ,  $-0.02$ ). The mean value of anisometropia was  $0.42 \pm 0.61$  D (median: 0.42; range: 0.00 to  $+7.50$ ).

In univariate analysis, refractive error decreased with older age (Figure 1), longer axial length (Figure 2) and higher corneal refractive power (Figure 3) (Table 2). The decrease with older age was statistically more significant ( $\beta$ :  $-0.38$  (girls);  $\beta$ :  $-0.25$  (boys)) and steeper ( $B$ :  $-0.22$  (95% CI:  $-0.24$ ,  $-0.20$ ) (girls);  $B$ :  $-0.13$  (95% CI:  $-0.15$ ,  $-0.11$ ) (boys)) in girls than in boys (Figure 1). It particularly holds true for the age period of 11+ years. In multivariable analysis (regression coefficient  $r^2 = 0.73$ ), refractive error increased mostly with shorter axial length and lower corneal refractive power, in addition to higher cylindrical refractive error, thinner lens thickness, older age and male sex (Table 3). It was not correlated with central corneal thickness ( $p = 0.79$ ) or with the ethnic background ( $p = 0.36$ ) in that model.

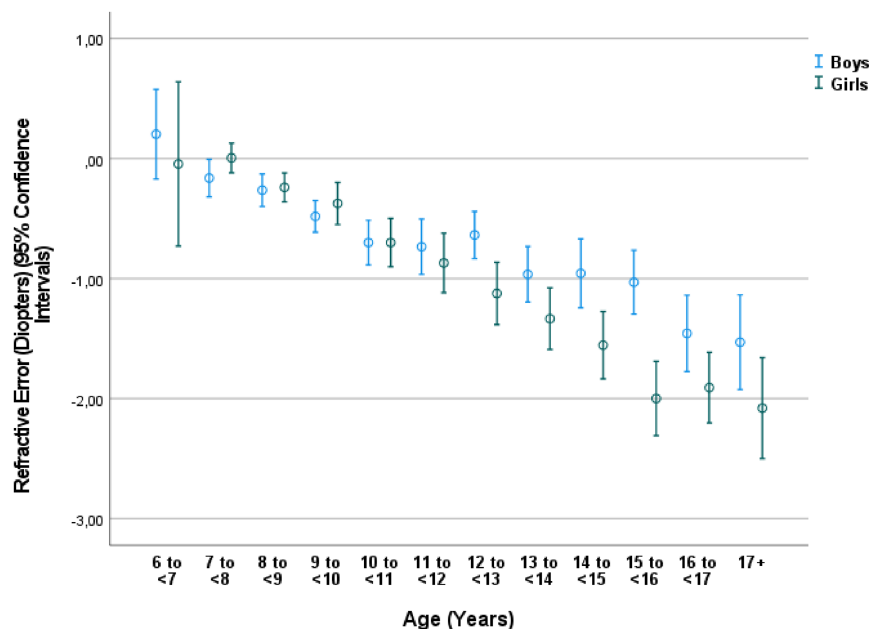
Cylindrical refractive error decreased with older age (Table 2). In multivariable analysis (regression coefficient  $r^2 = 0.05$ ), cylindrical refractive error increased mostly with higher refractive error and decreased with lower corneal refractive power, older age and female sex (Table 3). In that model, it was not correlated with lens thickness ( $p = 0.25$ ) and central corneal thickness ( $p = 0.36$ ). The parameter of axial length was dropped from the multivariable analysis due to collinearity with the parameter of refractive error (variance inflation factor (VIF): 5.26). Cylindrical refractive error was not correlated with the ethnic background ( $p = 0.94$ ) in that model.

Axial length increased in univariate analysis with older age (Table 2) (Figure 4). The increase with older age was statistically steeper for the age group younger than 11 years than for the older age group ( $B$ : 0.22 (95% CI: 0.18, 0.25) vs. 0.07 (95% CI: 0.05, 0.09)) (Figure 4). In multivariable analysis (regression coefficient  $r^2 = 0.82$ ), axial length increased mostly with lower refractive error and lower corneal refractive power, in addition to older age, male sex, higher cylindrical refractive error and thinner lens thickness (Table 3). It was not correlated with central corneal thickness ( $p = 0.12$ ) or ethnic background in that model ( $p = 0.54$ ).

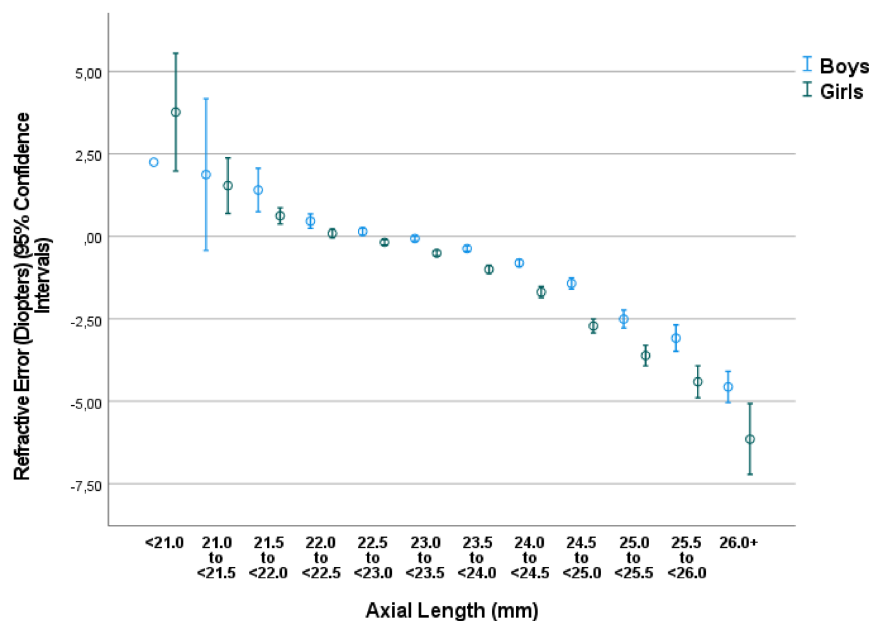
**TABLE 1** Demographic data (mean±standard deviation) and outcome parameters (right eyes) of the Ural Children Eye Study.

| Age (years) | <i>n</i> | Sex (boys/girls) | Refractive error (diop-ters) | Pre-valence of low refractive myopia (≤-0.75 D and >-6.0 D) (n/%) | Pre-valence of high refractive myopia (≤-6.00 D) (n/%) | Pre-valence of low axial myopia (≥24.0 mm and <26.0 mm) (n/%) | Pre-valence of high axial myopia (≥26.0 mm) (n/%) | Cylindrical refractive error (diop-ters) | Aniso-metropia (right eye minus left eye) | Axial length (mm) | Central corneal thick-ness (μm) | Corneal refractive power (diop-ters) | Lens thick-ness (mm) | Axial length/corneal curvature radius |
|-------------|----------|------------------|------------------------------|-------------------------------------------------------------------|--------------------------------------------------------|---------------------------------------------------------------|---------------------------------------------------|------------------------------------------|-------------------------------------------|-------------------|---------------------------------|--------------------------------------|----------------------|---------------------------------------|
| 6 to <7     | 30       | 16/14            | 0.09±0.95                    | 3/10%                                                             | 0/0%                                                   | 2/6.7%                                                        | 0/0%                                              | -0.43±0.31                               | 0.30±0.35                                 | 22.91±0.73        | 549±31                          | 43.19±1.49                           | 3.59±0.16            | 2.93±0.09                             |
| 7 to <8     | 468      | 245/223          | -0.08±1.11                   | 80/17.1%                                                          | 1/0.2%                                                 | 37/7.9%                                                       | 1/0.2%                                            | -0.45±0.44                               | 0.33±0.51                                 | 22.99±0.76        | 556±31                          | 43.22±1.39                           | 3.60±0.19            | 2.94±0.09                             |
| 8 to <9     | 595      | 302/293          | -0.25±1.13                   | 154/26.0%                                                         | 2/0.3%                                                 | 84/14.1%                                                      | 1/0.2%                                            | -0.46±0.51                               | 0.29±0.40                                 | 23.18±0.78        | 557±31                          | 43.19±1.37                           | 3.54±0.22            | 2.96±0.09                             |
| 9 to <10    | 469      | 249/220          | -0.43±1.19                   | 118/25.2%                                                         | 0/0%                                                   | 120/25.6%                                                     | 0/0%                                              | -0.46±0.50                               | 0.31±0.42                                 | 23.40±0.87        | 558±34                          | 43.22±1.41                           | 3.49±0.21            | 2.99±0.09                             |
| 10 to <11   | 350      | 165/185          | -0.70±1.30                   | 142/40.7%                                                         | 1/0.3%                                                 | 121/35.1%                                                     | 5/1.4%                                            | -0.46±0.43                               | 0.44±0.63                                 | 23.62±0.97        | 558±33                          | 43.05±1.42                           | 3.49±0.21            | 3.01±0.10                             |
| 11 to <12   | 370      | 190/180          | -0.81±1.64                   | 155/42.1%                                                         | 2/0.5%                                                 | 145/39.6%                                                     | 4/1.1%                                            | -0.47±0.51                               | 0.39±0.52                                 | 23.78±0.92        | 559±31                          | 43.01±1.40                           | 3.50±0.6             | 3.03±0.11                             |
| 12 to <13   | 398      | 213/185          | -0.86±1.64                   | 169/42.8%                                                         | 3/0.8%                                                 | 164/42.1%                                                     | 8/2.0%                                            | -0.52±0.56                               | 0.43±0.48                                 | 23.85±0.98        | 561±33                          | 43.00±1.46                           | 3.51±0.24            | 3.04±0.11                             |
| 13 to <14   | 415      | 195/220          | -1.16±1.80                   | 194/47.5%                                                         | 7/1.7%                                                 | 180/4.4%                                                      | 10/2.4%                                           | -0.58±0.68                               | 0.56±0.87                                 | 23.91±1.00        | 558±34                          | 42.98±1.46                           | 3.51±0.23            | 3.04±0.12                             |
| 14 to <15   | 327      | 147/180          | -1.29±1.87                   | 166/52.0%                                                         | 8/2.4%                                                 | 135/42.6%                                                     | 10/3.1%                                           | -0.58±0.59                               | 0.51±0.67                                 | 23.96±1.02        | 557±33                          | 43.21±1.37                           | 3.54±0.21            | 3.07±0.13                             |
| 15 to <16   | 416      | 189/227          | -1.56±2.20                   | 220/55.3%                                                         | 18/4.3%                                                | 187/47.9%                                                     | 26/6.3%                                           | -0.60±0.66                               | 0.50±0.68                                 | 24.13±1.09        | 558±34                          | 43.02±1.45                           | 3.57±0.26            | 3.07±0.14                             |
| 16 to <17   | 313      | 136/177          | -1.71±1.95                   | 192/63.6%                                                         | 11/3.5%                                                | 146/50.0%                                                     | 21/6.7%                                           | -0.59±0.62                               | 0.51±0.71                                 | 24.15±1.09        | 557±31                          | 43.18±1.33                           | 3.56±0.19            | 3.09±0.12                             |
| 17+         | 255      | 112/143          | -1.84±2.37                   | 149/61.6%                                                         | 13/5.1%                                                | 120/50.0%                                                     | 15/5.9%                                           | -0.61±0.62                               | 0.54±0.78                                 | 24.16±1.17        | 552±33                          | 43.05±1.59                           | 3.56±0.25            | 3.08±0.14                             |
| All         | 4406     | 2159/2247        | -0.87±1.73                   | 1742/40.1%                                                        | 66/1.5%                                                | 1441/33.5%                                                    | 101/2.3%                                          | -0.52±0.56                               | 0.42±0.61                                 | 23.67±1.03        | 557±32                          | 43.11±1.42                           | 3.53±0.23            | 3.02±0.12                             |





**FIGURE 1** Graph showing the distribution of refractive error stratified by age and sex in the Ural Children Eye Study (equation of the regression line: Refractive Error (Diopters) =  $-0.18$  (95% CI:  $-0.19, -0.16$ )  $\times$  Age (Years) +  $1.25$ ;  $p < 0.001$ ).



**FIGURE 2** Graph showing the distribution of refractive error in dependence of axial length in the Ural Children Eye Study, stratified by sex (equation of the regression line: Refractive Error (Diopters) =  $-1.14$  (95% CI:  $-1.17, -1.10$ )  $\times$  Axial Length (mm) +  $26.0$ ;  $p < 0.001$ ).

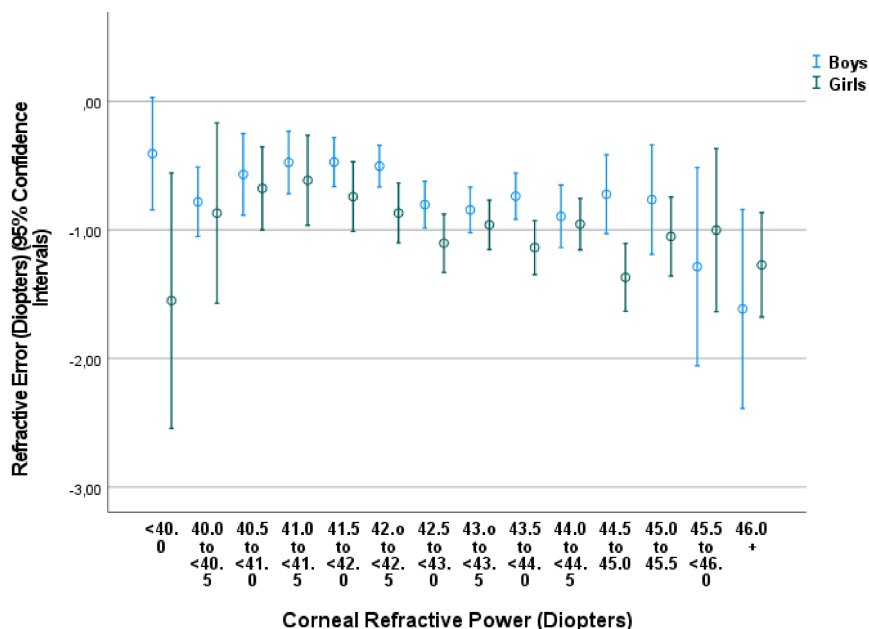
Corneal refractive power slightly ( $p = 0.02$ ) decreased with older age in the univariate analysis (Table 2; Figure 5). In multivariable analysis (regression coefficient  $r^2 = 0.33$ ), corneal refractive power decreased mostly with longer axial length (Figure 6), thicker lens thickness, and thinner central corneal thickness and increased with older age and female sex (Table 3). It was not significantly correlated with the ethnic background in that model ( $p = 0.75$ ).

The AL/CR ratio increased until the age of 14 years ( $\beta$ : 0.34;  $B$ : 0.017; 95% CI: 0.016, 0.019;  $p < 0.001$ ), and then became independent of age ( $\beta$ : 0.04;  $B$ : 0.005; 95% CI:  $-0.001, 0.011$ ;  $p = 0.13$ ). In multivariable analysis (regression coefficient  $r^2 = 0.78$ ), the AL/CR ratio increased

mostly with higher corneal refractive power, lower refractive error and thinner lens thickness and older age (Table 3). The parameter of axial length was excluded from the multivariable model due to collinearity (VIF: 5.41). It was not significantly correlated with the ethnic background in that model ( $p = 0.62$ ).

Lens thickness increased in multivariable analysis (regression coefficient  $r = 0.27$ ) with age and decreased with longer axial length and higher corneal refractive error (Table 3). It was not significantly correlated with the ethnic background in that model ( $p = 0.16$ ).

Central corneal thickness was independent of age in the univariate analysis (Table 2). In multivariable analysis, central corneal thickness decreased with higher



**FIGURE 3** Graph showing the distribution of refractive error in dependence of corneal refractive power in the Ural Children Eye Study, stratified by sex (equation of the regression line: Refractive Error (Diopters) =  $-0.12$  (95% CI:  $-0.15, -0.08$ )  $\times$  Corneal Refractive Power (Diopters) +  $4.11$ ;  $p < 0.001$ ).

**TABLE 2** Associations (univariate analysis) between age and ocular biometric parameters in the Ural Children Eye Study.

| Parameter                               | Standardized regression coefficient $\beta$ | Non-standardized regression coefficient $B$ | 95% confidence interval of $B$ | $p$ -value |
|-----------------------------------------|---------------------------------------------|---------------------------------------------|--------------------------------|------------|
| Refractive error (diopters)             | -0.32                                       | -0.18                                       | -0.19, -0.16                   | <0.001     |
| Cylindrical refractive error (diopters) | -0.10                                       | -0.02                                       | -0.02, -0.01                   | <0.001     |
| Anisometropia (diopters)                | 0.14                                        | 0.03                                        | 0.02, 0.03                     | <0.001     |
| Axial length (mm)                       | 0.37                                        | 0.12                                        | 0.11, 0.13                     | <0.001     |
| Central corneal thickness ( $\mu$ m)    | -0.003                                      | -0.03                                       | -0.33, 0.28                    | 0.86       |
| Corneal refractive power (diopters)     | -0.04                                       | -0.02                                       | -0.03, -0.002                  | 0.03       |
| Lens thickness (mm)                     | 0.03                                        | 0.002                                       | -0.001, 0.005                  | 0.20       |
| Corneal refractive power/axial length   | -0.26                                       | -0.01                                       | -0.11, -0.009                  | <0.001     |

corneal refractive power ( $p < 0.001$ ) and, slightly, with shorter axial length ( $p = 0.02$ ) (Table 3).

## 4 | DISCUSSION

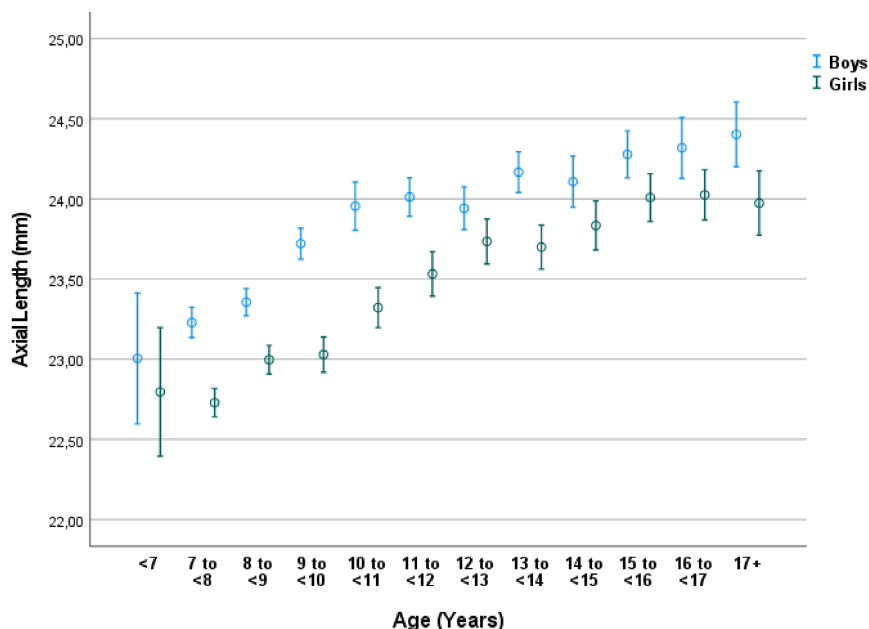
In this school-based study, the main determinants of higher myopic refractive error were longer axial length and higher corneal refractive power, in addition to lower cylindrical refractive error, thicker lens thickness and female sex. In univariate analysis, the increase in myopic refractive error with older age was more significant and steeper in girls than in boys, particularly for the age group of 11+ years. Axial length increased in univariate analysis with older age (steeper for age  $< 11$  years than for age  $\geq 11$  years). In multivariable analysis, axial length increased mostly with lower refractive error and lower corneal refractive power, in addition to older age, male sex, higher cylindrical refractive error and thinner lens thickness, while it was not significantly correlated with central corneal thickness. Corneal refractive power decreased mostly with longer axial length, thicker lens thickness and thicker central corneal thickness and increased with older age and female sex. The AL/CR ratio

increased until the age of 14 years, and it was then independent of age. In multivariable analysis, the AL/CR ratio increased mostly with higher corneal refractive power, lower refractive error and thinner lens thickness and older age.

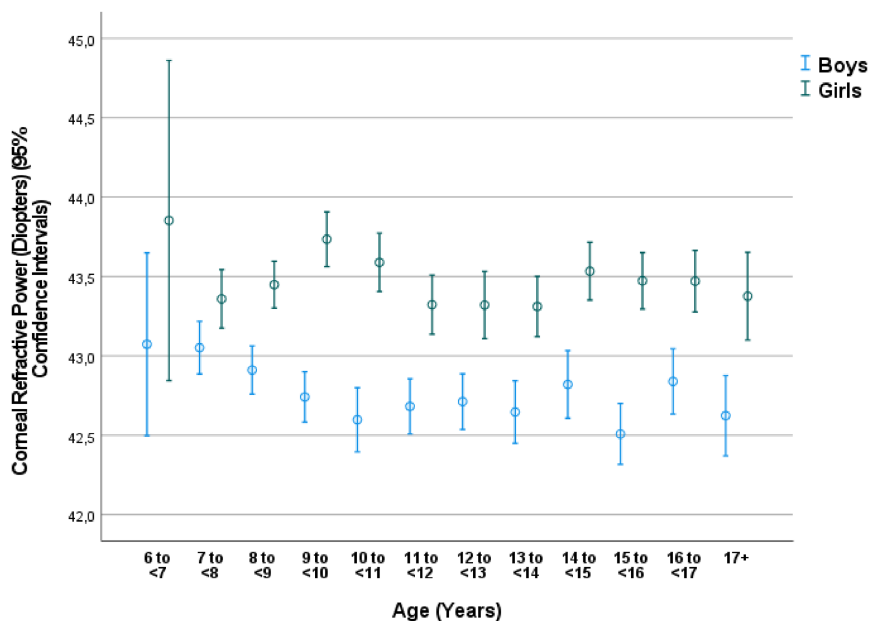
The findings obtained in our study population agree with observations made in previous investigations, including those conducted by the Collaborative Longitudinal Evaluation of Ethnicity and Refractive Error (CLEERE) Study Group (Gwiazda et al., 2002; He et al., 2021; Iribarren, Morgan, Chan, et al., 2012; Iribarren, Morgan, Nangia, et al., 2012; Kleinstei et al., 2021; Li et al., 2012; Morgan et al., 2012; Mutti et al., 2005, 2007; Ojaimi et al., 2005; Olsen et al., 2007; Omoto et al., 2020; Saw et al., 2002; Shih et al., 2009; Twelker et al., 2009; Wang et al., 2021; Wu et al., 2013; Zadnik et al., 2003; Zhang et al., 2022). In the Chinese Anyang Childhood Eye Study, myopic refractive error increased with longer axial length, and girls as compared to boys, as in our study population, had steeper corneas and shorter eyes (Li et al., 2012). Also as in our study, lens thickness was not associated with sex in the Chinese Anyang Childhood Eye Study and it decreased with more myopic refractive error (Li et al., 2012). Mutti

**TABLE 3** Associations (multivariable analysis) between various biometric ocular parameters and age and sex.

| Parameter                                                                                                                                                         | Standardized regression coefficient $\beta$ | Non-standardized regression coefficient $B$ | 95% confidence interval of $B$ | $p$ -value | Variance inflation factor |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------|---------------------------------------------|--------------------------------|------------|---------------------------|
| Refractive error (diopters) associated with ( $r^2=0.73$ )                                                                                                        |                                             |                                             |                                |            |                           |
| Age (years)                                                                                                                                                       | 0.05                                        | 0.02                                        | 0.01, 0.04                     | <0.001     | 1.25                      |
| Sex (boys/girls)                                                                                                                                                  | -0.15                                       | -0.50                                       | -0.57, -0.42                   | <0.001     | 1.10                      |
| Cylindrical refractive error (diopters)                                                                                                                           | 0.10                                        | 0.34                                        | 0.27, 0.41                     | <0.001     | 1.03                      |
| Axial length (mm)                                                                                                                                                 | -0.99                                       | -1.64                                       | -1.68, -1.59                   | <0.001     | 1.77                      |
| Corneal refractive power (diopters)                                                                                                                               | -0.55                                       | -0.67                                       | -0.70, -0.64                   | <0.001     | 1.47                      |
| Lens thickness (mm)                                                                                                                                               | -0.11                                       | -0.85                                       | -1.02, -0.69                   | <0.001     | 1.08                      |
| Cylindrical refractive error (diopters) associated with: (due to collinearity with axial length, the parameter of axial length was dropped)                       |                                             |                                             |                                |            |                           |
| Age (years)                                                                                                                                                       | -0.05                                       | -0.01                                       | -0.01, -0.003                  | 0.002      | 1.13                      |
| Sex (boys/girls)                                                                                                                                                  | 0.05                                        | 0.06                                        | 0.03, 0.09                     | 0.001      | 1.07                      |
| Refractive error (diopters)                                                                                                                                       | 0.19                                        | 0.06                                        | 0.05, 0.07                     | <0.001     | 1.14                      |
| Corneal refractive power (diopters)                                                                                                                               | -0.07                                       | -0.03                                       | -0.04, -0.02                   | <0.001     | 1.07                      |
| Axial length (mm) associated with                                                                                                                                 |                                             |                                             |                                |            |                           |
| Age (years)                                                                                                                                                       | 0.14                                        | 0.05                                        | 0.04, 0.05                     | <0.001     | 1.05                      |
| Sex (boys/girls)                                                                                                                                                  | -0.13                                       | -0.27                                       | -0.31, -0.23                   | <0.001     | 1.09                      |
| Refractive error (diopters)                                                                                                                                       | -0.68                                       | -0.41                                       | -0.42, -0.40                   | <0.001     | 1.15                      |
| Cylindrical refractive error (diopters)                                                                                                                           | 0.04                                        | 0.08                                        | 0.05, 0.12                     | <0.001     | 1.07                      |
| Lens thickness (mm)                                                                                                                                               | -0.15                                       | -0.67                                       | -0.75, -0.59                   | <0.001     | 1.03                      |
| Corneal refractive power (diopters)                                                                                                                               | -0.53                                       | -0.39                                       | -0.40, -0.37                   | <0.001     | 1.08                      |
| Corneal refractive power (diopters) associated with: (due to collinearity with axial length, the parameter of refractive error was dropped)                       |                                             |                                             |                                |            |                           |
| Age (years)                                                                                                                                                       | 0.15                                        | 0.06                                        | 0.05, 0.08                     | <0.001     | 1.22                      |
| Sex (boys/girls)                                                                                                                                                  | 0.14                                        | 0.40                                        | 0.30, 0.49                     | <0.001     | 1.07                      |
| Cylindrical refractive error (diopters)                                                                                                                           | -0.08                                       | -0.21                                       | -0.30, -0.13                   | <0.001     | 1.03                      |
| Axial length (mm)                                                                                                                                                 | -0.56                                       | -0.76                                       | -0.82, -0.71                   | <0.001     | 1.30                      |
| Lens thickness (mm)                                                                                                                                               | -0.13                                       | -0.80                                       | -1.01, -0.59                   | <0.001     | 1.06                      |
| Central corneal thickness ( $\mu\text{m}$ )                                                                                                                       | -0.09                                       | -0.004                                      | -0.006, -0.003                 | <0.001     | 1.01                      |
| Ratio of axial length divided by corneal curvature radius associated with: (due to collinearity with refractive error, the parameter of axial length was dropped) |                                             |                                             |                                |            |                           |
| Age (years)                                                                                                                                                       | 0.16                                        | 0.006                                       | 0.005, 0.007                   | <0.001     | 1.14                      |
| Sex (boys/girls)                                                                                                                                                  | -0.14                                       | -0.03                                       | -0.04, -0.03                   | <0.001     | 1.09                      |
| Refractive error (diopters)                                                                                                                                       | -0.75                                       | -0.05                                       | -0.05, -0.05                   | <0.001     | 1.20                      |
| Cylindrical refractive error (diopters)                                                                                                                           | 0.05                                        | 0.011                                       | 0.007, 0.016                   | <0.001     | 1.07                      |
| Cornea refractive power (diopters)                                                                                                                                | 0.25                                        | 0.02                                        | 0.02, 0.02                     | <0.001     | 1.10                      |
| Lens thickness (mm)                                                                                                                                               | -0.16                                       | -0.09                                       | -0.10, -0.08                   | <0.001     | 1.01                      |
| Central corneal thickness ( $\mu\text{m}$ )                                                                                                                       | -0.02                                       | -0.00001                                    | 0.000, 0.000                   | <0.001     | 1.02                      |
| Lens thickness (mm) associated with                                                                                                                               |                                             |                                             |                                |            |                           |
| Age (years)                                                                                                                                                       | 0.15                                        | 0.01                                        | 0.01, 0.01                     | <0.001     | 1.20                      |
| Axial length (mm)                                                                                                                                                 | -0.34                                       | -0.08                                       | -0.09, -0.06                   | <0.001     | 1.59                      |
| Corneal refractive power (diopters)                                                                                                                               | -0.18                                       | -0.03                                       | -0.04, -0.02                   | <0.001     | 1.38                      |
| Central corneal thickness associated with                                                                                                                         |                                             |                                             |                                |            |                           |
| Axial length (mm)                                                                                                                                                 | -0.04                                       | -1.30                                       | -2.36, -0.25                   | 0.02       | 1.33                      |
| Cornea refractive power (diopters)                                                                                                                                | -0.17                                       | -3.78                                       | -4.55, -3.01                   | <0.001     | 1.33                      |



**FIGURE 4** Graph showing the distribution of axial length stratified by age and sex in the Ural Children Eye Study (equation of the regression line: Axial Length (mm)=0.12 (95% CI: 0.11, 0.13) × Age (Years)+22.2;  $p<0.001$ ).

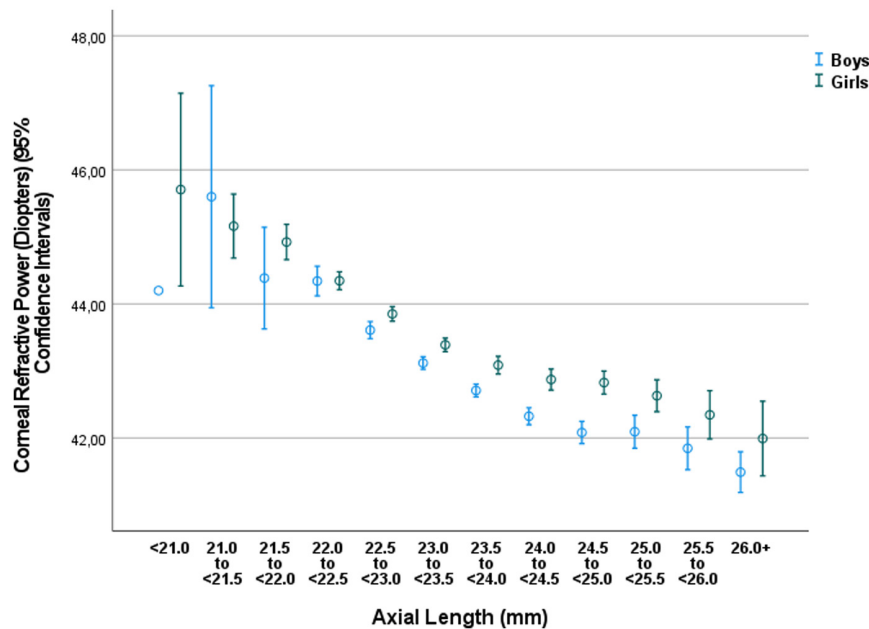


**FIGURE 5** Graph showing the distribution of corneal refractive power in dependence of age in the Ural Children Eye Study, stratified by sex (equation of the regression line: Corneal refractive Power (Diopters)=−0.02 (95% CI: −0.03, −0.002) × Age (Years)+43.3;  $p=0.02$ ).

et al. (2005) examined the ocular components in their relationship to emmetropization in human infants between 3 and 9 months of age. In the study period, refractive error decreased from +2.16 D to +1.36 D, in association with axial elongation, thinning and flattening of the lens, increases in lens equivalent refractive index and decreases in the refractive power of the cornea and lens. The decrease in hyperopic refractive error was associated with axial elongation but not with changes in refractive power of the corneal or lens (Mutti et al., 2005). Axial elongation correlated with a reduction in corneal refractive power. In the Collaborative Longitudinal Evaluation of Ethnicity and Refractive Error (CLEERE) Study, myopic refractive error increased with older age, without

a sex-related difference (Zadnik et al., 2003). Girls had steeper corneas than boys, and corneal refractive power was not significantly associated with age. Lens thickness decreased with older age, without a sex-related difference in lens thickness. As myopic refractive error, axial length increased with older age and male gender, with girls having an axial length 0.32 mm shorter than those of boys (Zadnik et al., 2003). In the Central India Eye and Medical Study on individuals aged 50+ years, myopic refractive error increased most markedly (i.e. highest  $\beta$  coefficient) with longer axial length, followed by higher refractive lens power and higher corneal refractive power, taking into account that the study population included also individuals with nuclear cataract (Iribarren,





**FIGURE 6** Graph showing the distribution of corneal refractive power stratified by axial length and sex in the Ural Children Eye Study sex (equation of the regression line: Corneal refractive Power (Diopters) =  $-0.68$  (95% CI:  $-0.72, -0.65$ )  $\times$  Axial Length (mm) + 59.3;  $p < 0.001$ ).

Morgan, Nangia, et al., 2012). In the Reykjavik Eye Study on citizens aged 55+ years, refractive error decreased predominantly with longer axial length ( $\beta$ :  $-0.59$ ), lower refractive lens power ( $\beta$ :  $-0.26$ ) and lower refractive corneal power ( $\beta$ :  $-0.16$ ) (Olsen et al., 2007). Longer axial length correlated with lower corneal refractive power. As in our study, the boys as compared to the girls in the investigation conducted by Saw et al. (2002) and in the Correction of Myopia Evaluation Trial (COMET) had a longer axial length in a multivariable analysis (Gwiazda et al., 2002). In contrast to our study, in the study performed by Omoto et al. (2020), refractive error was not correlated with corneal refractive power.

The AL/CR ratio increased in our study with older age until the age of 14 years in our study population and then remained constant. In multivariable analysis, it decreased with higher refractive error and thicker lens thickness after adjusting for corneal refractive power, cylindrical refractive error, lens thickness and age (Table 3). Grosvenor and Scott (1994) defined the parameter of the AL/CR ratio and found in adults aged 18–30 years a ratio of 2.60 for highly hyperopic eyes, of 3.00 in emmetropic eyes and of 4.10 in highly myopic eyes. The ratio was strongly associated with refractive error ( $\beta$ : 0.84). In our study population, the AL/CR ratio showed a slightly lower  $\beta$  value in its association with refractive error ( $\beta$ : 0.75) (Table 3). The reason for the slight discrepancy may be differences in the list of independent variables included into the multivariable analysis. In the population-based study conducted by Hashemi et al. (2013) in Sharoud/Iran on individuals aged 40–64 years, the AL/CR ratio (mean: 3.03) was strongly correlated with refractive error, and the correlation between refractive error was significantly stronger with the ratio than with axial length or corneal curvature radius and corneal curvature radius alone.

In our study population, cylindrical refractive error increased mostly with higher refractive error and lower

corneal refractive power, in addition to male sex and younger age. The results agree with the observations made by other researchers, such as Linke et al. (2011), who examined refractive surgery candidates and did not find an association between cylindrical refractive error and ametropia (Afsari et al., 2013; Dandona et al., 1999; Ferraz et al., 2015; Qin et al., 2005; Sawada et al., 2008). In a population-based study from Brazil, cylindrical refractive error increased with older age (Ferraz et al., 2015). In the study performed by Qin et al. (2005) on individuals aged 20–40 years showed that cylindrical refractive error and spherical refractive error astigmatism were independently associated with anisometropia. In the Sydney Pediatric Eye Disease Study, an increasing risk of anisometropia with higher cylindrical refractive error (Afsari et al., 2013).

While the findings shown and discussed above mostly confirm the observations made in previous investigations, the novelty of the results of our study is to supply data for the world region of Russia and Central Asia for which almost no relevant information about the topics addressed in this study had been available before, and to provide general information about the levels of correlations between the various biometric parameters of the eye in childhood and adolescence. It also includes the relationships between higher myopia and parameters such as lower cylindrical refractive error, thicker lens and female sex. It agrees with observations made in studies on adults, in which highly myopic eyes and non-highly myopic eyes did not differ markedly in cylindrical refractive error, and in which female sex was associated with myopic refractive error and was a risk for the development and progression of myopic maculopathy (Fang et al., 2018; Liu et al., 2010; Xu et al., 2005; Yan et al., 2018).

When the results of our study are discussed, its limitations should be considered. First, for cycloplegia, we did not use cyclopentolate but one eye drop of tropicamide, so that hyperopic children might still have partially

accommodated during refractometry. It might have led to a falsely low prevalence of hyperopia and a falsely high rate of emmetropia and low myopia (Fotedar et al., 2007; Wang et al., 2018). Correspondingly, the Shandong Children Eye Study revealed that the difference between non-cycloplegic refractometry and complete cycloplegic refractometry increased mainly with higher cycloplegic refractive error (Hu et al., 2015). It is not likely, that, if the cycloplegic effect was not complete, it may have affected the measurement of refractive error in the highly myopic range and thus the prevalence and associations of high myopia. In addition, we measured axial length as a surrogate for refractive error for myopia. In view of a potential bias in the prevalence of low refractive myopia, we used as definition of low refractive myopia a cut-off value of a myopic refractive error of  $>-0.75$  D. This is 0.25 D more than suggested in the myopia definition given by Flitcroft et al. (2019) from International Myopia Institute. In addition, we measured axial length as a surrogate for refractive error for myopia, and we calculated the AL/CR ratio, which is not affected by poor cycloplegia and correlates highly with cycloplegic refractive error. Second, we did not assess the refractive power of the lens as an additional component of the ocular optical system (Iribarren, 2015). Third, our study was started before the outbreak of the COVID-19 pandemics and underwent a break due to the COVID-19-related lockdown of schools (Bikbov et al., 2023). In a subgroup of children undergoing refractometry before and after the lockdown, the school lockdown was associated however only with a relatively minor increase in axial elongation, detected only in children aged  $<9.6$  years. In the latter age group, the annual axial elongation during the study period was larger than the mean annual increase in axial length at baseline (0.29 vs. 0.21 mm). One may discuss that the school lockdown did not have a major effect on the results of the present study, in particular since it was not focused on the prevalence of myopia but on the relationship between the various biometric parameters.

In conclusion, in this ethnically mixed urban school children population from Russia, the main determinants of higher myopic refractive error were longer axial length and higher corneal refractive power, in addition to lower cylindrical refractive error, thicker lens thickness and female sex. Increase in myopic refractive error with older age was more significant and steeper in girls, particularly for the age group of 11+ years. The relationships between the various ocular biometric parameters in children and adolescents may be helpful to further elucidate the process of emmetropization.

## DISCLOSURES

Jost B. Jonas: Patent holder with Biocompatibles UK Ltd. (Farnham, Surrey, UK) (Title: Treatment of eye diseases using encapsulated cells encoding and secreting neuroprotective factor and/or anti-angiogenic factor) (Patent number: 20120263794); Patent application: European patent application 16720043.5 and US patent application US 2019 0085065 A1 'Agents for use in the therapeutic or prophylactic treatment of myopia or hyperopia'; Patent application: Agents for the use in the therapeutic or prophylactic treatment of retinal pigment

epithelium associated diseases. Other authors: No financial disclosures.

## ORCID

Jost B. Jonas  <https://orcid.org/0000-0003-2972-5227>

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