

Prevalence and Associations of Anisometropia in Children

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PURPOSE. To describe prevalence and associations of anisometropia in children.

METHODS. The cross-sectional school-based study included children aged 4 to 18 years.

RESULTS. The study included 6025 (94.7%) of 6364 eligible children. Mean refractive anisometropia was 0.37 ± 0.57 diopters (median: 0.25 diopters; range: 0-7.88 diopters; prevalence $[\geq 1$ diopter]: $7.0\% \pm 0.3\%$). In multivariate analysis (regression coefficient r : 0.66), higher refractive anisometropia was associated with older age ($P < 0.001$; β : 0.07; B : 0.01; 95% CI: 0.01-0.02), higher maternal education level ($P < 0.001$; β : 0.04; B : 0.02; 95% CI: 0.01-0.03), more total time spent indoors reading or writing ($P = 0.001$; β : 0.04; B : 0.01; 95% CI: 0.01-0.02), larger intereye difference in axial length ($P < 0.001$; β : 0.57; B : 1.20; 95% CI: 1.15-1.24), shorter mean axial length of both eyes ($P = 0.03$; β : -0.03; B : -0.02; 95% CI: -0.03 to -0.001), larger intereye difference in best corrected visual acuity (BCVA) ($P < 0.001$; β : 0.14; B : 1.83; 95% CI: 1.54-2.12), and lower stereoacuity ($P < 0.001$; β : 0.08; B : 0.31; 95% CI: 0.22-0.39). Refractive anisometropia showed a U-shaped correlation with refractive error. Higher anisomyopia was associated (r : 0.57) with older age ($P = 0.001$; β : 0.05; B : 0.006; 95% CI: 0.002-0.009), higher level of paternal education ($P = 0.001$; β : 0.01; B : 0.01; 95% CI: 0.01-0.02), more total time spent indoors reading or writing ($P = 0.01$; β : 0.03; B : 0.01; 95% CI: 0.00-0.01), larger intereye difference in axial length ($P < 0.001$; β : 0.22; B : 0.26; 95% CI: 0.23-0.29), greater myopic refractive error ($P < 0.001$; β : -0.46; B : -0.07; 95% CI: -0.08 to -0.07), and lower corneal astigmatism ($P < 0.001$; β : -0.10; B : -0.06; 95% CI: -0.08 to -0.05). In the same multivariate model, hyperopic anisometropia was not significantly associated with time spent indoors with reading ($P = 0.18$). Cylindrical anisometropia (mean: 0.30 ± 0.32 diopters; prevalence $[\geq 1$ diopter]: $3.7\% \pm 0.2\%$) increased with higher refractive anisometropia ($P < 0.001$; β : 0.16; B : 0.09; 95% CI: 0.08-0.11), greater myopic refractive error ($P < 0.001$; β : -0.06; B : -0.01; 95% CI: -0.01 to -0.01), higher corneal astigmatism ($P < 0.001$; β : -0.22; B : -0.15; 95% CI: -0.17 to -0.13), and lower mean BCVA ($P < 0.001$; β : 0.11; B : 0.90; 95% CI: 0.68-1.17).

CONCLUSIONS. In 4- to 18-year-old children, refractive anisometropia and anisomyopia increased with systemic parameters such as age, parental education level, and lifestyle of the children, for example, more time spent indoors reading or writing. In contrast, hyperopic anisometropia and cylindrical anisometropia were not related with lifestyle parameters.

Keywords: anisometropia, myopia, epidemiology, population-based study, Shandong children eye study

Anisometropia is an intereye asymmetry in the refractive status of an individual and can be associated with strabismus, amblyopia, aniseikonia, and spectacle intolerance, to mention only a few sequelae.¹⁻⁵ Anisometropia has already been examined in children in previous population-based studies such as the Multi-Ethnic Pediatric Eye Disease Study and the Sydney Childhood Eye Study and other investigations.^{3,6-11} While most of the previous investigations have examined individuals from Western countries, studies focused on children from mainland China, the most populous country

worldwide, have been scarce so far.^{10,12-14} In addition, most of the previous studies have not measured or correlated axial length and other ocular biometric data or data on the socioeconomic background and children's lifestyle with the presence and amount of anisometropia. To differentiate between refractive and cylindrical anisometropia, we conducted the present study to measure the prevalence and amount of anisometropia in a population-based study, in both a rural and urban region of the Eastern Chinese province of Shandong, to



assess associations of anisometropia with general and ocular parameters including visual acuity and stereoacuity.

METHODS

The Shandong Children Eye Study was a school-based, cross-sectional study on children in the East Chinese province of Shandong. According to the Declaration of Helsinki, the Ethics Committee of the Eye Institute of the Shandong University of Traditional Chinese Medicine and the local Administration of the Education and School Board approved the study, and the parents or guardians of the children gave written informed consent. The study participants were recruited by a stratified cluster sampling method in the city of Weihai in the Eastern part of Shandong and in the rural areas of Guanxian in the Western region of Shandong. The schools were randomly selected. Based on the inclusion criterion of age between 4 to 18 years, 6364 children were eligible to take part in the study, as described in detail recently.^{15,16}

In the school houses, the children underwent a series of examinations including an interview with a standardized questionnaire similar to the one used in the RESC (Refractive Error Study in Children) studies, cycloplegic refractometry, measurement of presenting visual acuity, uncorrected visual acuity, and best corrected visual acuity (BCVA), noncontact tonometry (Topcon CT80; Topcon Corp., Tokyo, Japan), slit-lamp-based biomicroscopy of the anterior and posterior ocular segments, and laser interferometry-based ocular biometry (IOL-Master, V5.0; Carl Zeiss Meditec AG, Jena, Germany). Cycloplegia was induced by instilling 1% cyclopentolate eye drops (Alcon, Fort Worth, TX, USA) at least three times into each eye, except for eyes with diseases.¹⁷ Stereoacuity was assessed by using the Titmus stereo test (Stereo Optical Co., Inc., Chicago, IL, USA). The Titmus test possesses disparities ranging from 800 to 40 arc-seconds. Through a pair of polarizing glasses, subjects viewed the stereogram at a distance of 40 cm and were asked to seize the wings of the fly. If the participant tried to seize the wings of the fly, the participant was asked to point to the circle that seemed to “jump” out of the book. If a mistake occurred, the preceding target was reassessed. If an accurate response was repeatedly obtained on the preceding target, the target's disparity was regarded as the measurement value. Testing started with the largest disparity, and inability to correctly identify the target with the largest disparity was recorded as “nil” stereo. Sensory status was assessed with the Worth 4-dot test at both distance and near conditions (2 m and 40 cm). The results of the Worth 4-dot test were classified as fusion, suppression, and alternate suppression or as diplopia.

Refractive anisometropia was defined as the intereye difference in refractive error (spherical equivalent). Anisomyopia was defined as an unequal amount of myopia in both eyes, with myopia defined as refractive error ≤ -0.5 diopters. Hyperopic anisometropia (or anisohyperopia or anisometropic hyperopia) was defined as an unequal amount of hyperopia in both eyes, with hyperopia defined as refractive error of ≥ 0.5 diopters. Cylindrical anisometropia was the difference between both eyes of the same individual in cylindrical refractive error. Differences in the angle of the cylindrical refractive error were not taken into account. To assess the effect of anisometropia on stereoacuity, poor stereoacuity was defined as stereoacuity of more than 100 seconds of arc.^{5,18}

Inclusion criterion for the present study was the availability of bilateral refractometric measurements. The statistical analysis was carried out by using a commercially available software package (SPSS for Windows, version 22.0; IBM-SPSS, Chicago, IL, USA). In a first step, we examined the mean values

(presented as mean \pm standard deviation) of the measured parameters. Frequencies were presented as mean \pm standard error with the 95% confidence intervals (CIs). In a second step, we performed a univariate regression analysis to examine the associations between the amount of anisometropia and other ocular and nonocular parameters. In a third step, a multivariate analysis was conducted with the amount of anisometropia as dependent variable, and as independent variables all parameters for which the *P* value in the univariate analysis was < 0.05 . Step by step, we first dropped those parameters for which the variance inflation factor (VIF) of the analysis of collinearity was higher than 4. We then dropped, through a combination of stepwise, forward, and backward regression analyses, all those parameters which were no longer significantly associated with anisometropia in the multivariate analysis. The standardized regression coefficient β , the nonstandardized regression coefficient *B*, and the 95% CIs were calculated. Logistic regression was used to analyze association between the prevalence of anisometropia and other parameters. Odds ratios (ORs) were calculated. All *P* values were two sided and were considered statistically significant when the values were less than 0.05.

RESULTS

Of 6364 eligible participants, bilateral cycloplegic measurements of refractive error were available for 6025 children (3186 [52.9%] boys) without optically important opacities of cornea and lens, fundus disorders, and optic nerve damage. The participation rate was 94.7%. The mean age was 10.0 ± 3.3 years (median: 10.0 years; range: 4–18 years), and the mean axial length was 23.4 ± 1.2 mm (range: 18.95–28.59 mm). Mean corneal radius of curvature was 7.84 ± 0.27 mm (range: 6.98–9.61 mm), and mean horizontal corneal diameter was 12.0 ± 0.38 mm (median: 12.00 mm; range: 10.1–15.0 mm). Intraocular pressure was 17.6 ± 2.7 mm Hg (median: 18.0 mm Hg; range: 8–28 mm Hg).

Mean refractive anisometropia was 0.37 ± 0.57 diopters (median: 0.25 diopters; range: 0–7.88 diopters). If defined as a refractive anisometropia ≥ 1 diopter, prevalence of refractive anisometropia was $7.0\% \pm 0.3\%$ (95% CI: 6.3%–7.6%). It increased significantly with older age. In univariate analysis, presence of refractive anisometropia (≥ 1 diopter) increased the risk of poor stereoacuity by a factor of 6.73 (95% CI: 4.78–9.47) (χ^2 test).

In univariate analysis, the amount of refractive anisometropia increased significantly with older age ($P < 0.001$; β : 0.16; equation of the regression line: Anisometropia (diopters) = $0.03 \times \text{Age [years]} + 0.09$). Refractive anisometropia was significantly higher in girls than in boys (0.38 ± 0.57 diopters versus 0.35 ± 0.56 diopters, $P < 0.001$; Fig. 1). Higher refractive anisometropia was further associated with the systemic parameters of taller body height ($P < 0.001$), heavier body weight ($P < 0.001$), older paternal age ($P < 0.001$), older maternal age ($P < 0.001$), higher education of father ($P < 0.001$) and mother ($P < 0.001$), more time spent indoors reading and writing in a weekday ($P = 0.002$) or during a weekend ($P = 0.002$), more time spent indoors playing handheld computer games in a weekday ($P = 0.03$) or during the weekend ($P = 0.001$), less time spent outdoors in a week (total) ($P = 0.001$), and shorter sleeping duration time ($P < 0.001$) (Table 1). Higher refractive anisometropia was associated with the ocular parameters of longer axial length ($P < 0.001$) and larger intereye difference in axial length ($P < 0.001$), greater myopic refractive error ($P < 0.001$) (Fig. 2), longer corneal curvature radius (left eye) ($P = 0.007$) and higher intereye difference in corneal curvature radius ($P <$

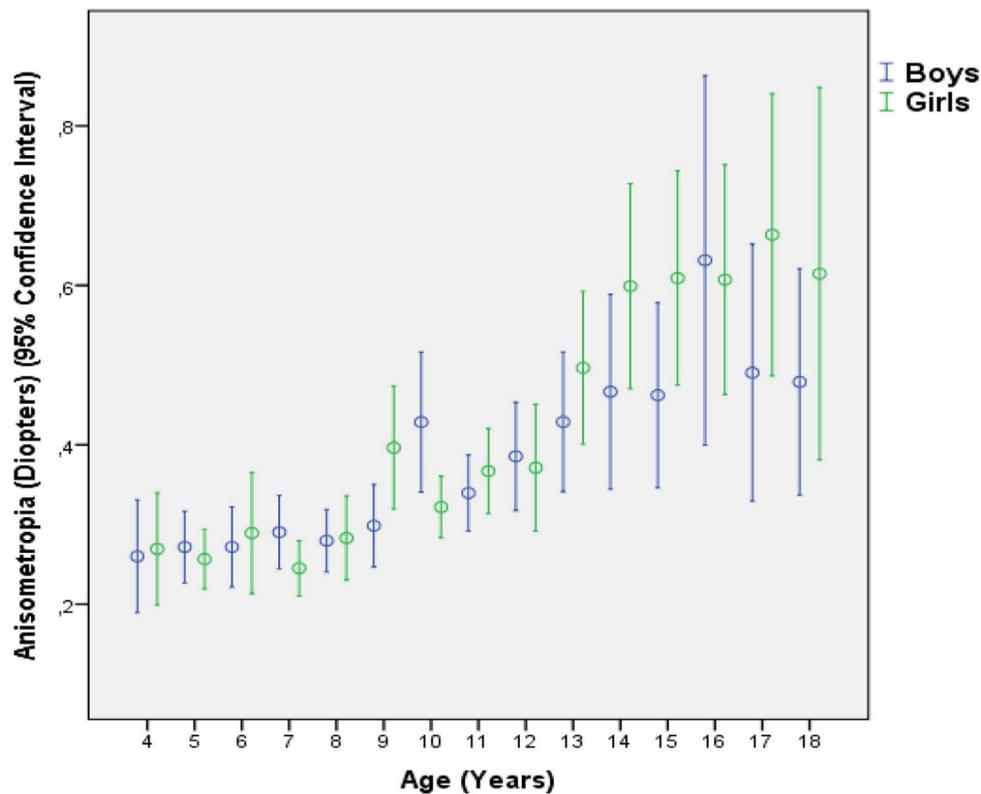


FIGURE 1. Graph showing the distribution of refractive anisometropia stratified by age and sex in the Shandong Children Eye Study.

0.001), lower corneal astigmatism ($P < 0.001$) and higher intereye difference in corneal astigmatism ($P < 0.001$) (Fig. 3), lower BCVA ($P < 0.001$), lower stereoacuity ($P < 0.001$) (Fig. 4), higher prevalence of an abnormal Worth 4-dot test ($P < 0.001$), and higher intraocular pressure ($P = 0.008$) (Table 1). Refractive anisometropia was not significantly associated with region of habitation ($P = 0.10$), birth length ($P = 0.80$) and birth weight ($P = 0.69$), perinatal oxygen therapy ($P = 0.48$), paternal myopia ($P = 0.18$) and maternal myopia ($P = 0.14$), writing posture ($P = 0.92$), distance between the eyes and book when reading or writing ($P = 0.09$), way of holding the pen during writing ($P = 0.92$), axis of the corneal astigmatism of the right eye ($P = 0.95$) and left eye ($P = 0.12$), corneal diameter of right eye ($P = 0.89$) and left eye ($P = 0.99$), intraocular pressure of the right eye ($P = 0.23$), and intereye difference in intraocular pressure ($P = 0.95$).

The multivariate analysis included ametropia as dependent variable and all parameters as independent variables, which were significantly associated with refractive anisometropia in the univariate analysis. Owing to collinearity, we dropped the intereye difference in refractive error (VIF: 7.1). Owing to missing statistical significance we dropped step by step the parameters of paternal educational level ($P = 0.99$), mean sleeping duration ($P = 0.97$), time spent indoors playing handheld computer games during the week ($P = 0.99$), Worth 4-dot test results ($P = 0.95$), left corneal astigmatism ($P = 0.94$), paternal age ($P = 0.93$), body height ($P = 0.84$), corneal curvature radius (left eye) ($P = 0.94$), total time spent indoors ($P = 0.89$), BCVA (right eye) ($P = 0.72$), time spent indoors playing handheld computer games during a weekend ($P = 0.43$), maternal age ($P = 0.55$), time spent reading during the weekend ($P = 0.45$), intereye difference in corneal astigmatism ($P = 0.46$), time spent reading during the week ($P = 0.39$), body weight ($P = 0.28$), sex ($P = 0.27$), intereye difference in corneal curvature radius ($P = 0.11$), total time spent outdoors

($P = 0.10$), intraocular pressure ($P = 0.09$), and corneal astigmatism (right eye) ($P = 0.06$).

In the final model (regression coefficient r : 0.66), higher refractive anisometropia was associated with older age ($P < 0.001$), higher level of maternal education ($P < 0.001$), more total time spent indoors reading or writing ($P = 0.001$), larger intereye difference in axial length ($P < 0.001$), shorter mean axial length of both eyes ($P = 0.03$), larger intereye difference in BCVA ($P < 0.001$), and lower stereoacuity ($P < 0.001$) (Table 2).

If one dropped stereoacuity and visual acuity from the model (since both parameters were the sequelae and not the causes of refractive anisometropia), similar results were obtained: higher refractive anisometropia was associated (r : 0.67) with older age ($P < 0.001$; β : 0.06; B : 0.01; 95% CI: 0.01–0.02), higher maternal education level ($P = 0.01$; β : 0.03; B : 0.01; 95% CI: 0.003–0.03), more time spent indoors reading or writing ($P = 0.003$; β : 0.04; B : 0.01; 95% CI: 0.003–0.02), shorter mean axial length of both eyes ($P = 0.001$; β : –0.05; B : –0.02; 95% CI: –0.04 to –0.01), larger intereye difference in axial length ($P < 0.001$; β : 0.65; B : 1.38; 95% CI: 1.34–1.43), and lower right corneal astigmatism ($P < 0.001$; β : –0.04; B : –0.05; 95% CI: –0.07 to –0.02).

The prevalence of refractive anisometropia as defined by an intereye difference in refractive error of ≥ 1 diopter was associated with similar parameters as was the amount of ametropia. In a binary regression analysis, prevalence of refractive anisometropia was associated with older age ($P < 0.001$), higher maternal level of education ($P = 0.004$), longer total reading time indoors ($P = 0.002$), higher intereye difference in axial length ($P < 0.001$), lower corneal astigmatism ($P < 0.001$), and lower stereoacuity ($P < 0.001$) (Table 3).

Mean anisomyopia was 0.12 ± 0.32 diopters (median: 0.00 diopters; range: 0–6.75 diopters) with a prevalence of $26.1\% \pm$

TABLE 1. Associations (Univariate Analysis) Between the Amount of Refractive Anisometropia (Spherical Equivalent; Diopters) and Ocular and Nonocular Parameters in the Shandong Children Eye Study

| Parameter | P Value | Standardized Correlation Coefficient β | Standardized Regression Coefficient B | 95% Confidence Interval of B |
|--|---------|--|---------------------------------------|------------------------------|
| Nonocular parameters | | | | |
| Age | <0.001 | 0.16 | 0.03 | 0.02 to 0.03 |
| Sex | <0.001 | | | |
| Body height, cm | <0.001 | 0.16 | 0.005 | 0.004 to 0.006 |
| Body weight, kg | <0.001 | 0.15 | 0.006 | 0.005 to 0.007 |
| Paternal age, y | <0.001 | 0.09 | 0.012 | 0.008 to 0.015 |
| Maternal age, y | <0.001 | 0.07 | 0.009 | 0.006 to 0.013 |
| Paternal educational level | <0.001 | 0.07 | 0.03 | 0.02 to 0.05 |
| Maternal education level | <0.001 | 0.06 | 0.03 | 0.02 to 0.04 |
| Time spent indoors reading and writing in a weekend, h | <0.001 | 0.10 | 0.05 | 0.04 to 0.06 |
| Time spent indoors reading and writing, total, h | <0.001 | 0.11 | 0.03 | 0.02 to 0.04 |
| Time spent indoors playing handheld computer games in a weekday, h | 0.03 | 0.03 | 0.03 | 0.003 to 0.05 |
| Time spent indoors playing handheld computer games during a weekend, h | 0.001 | 0.05 | 0.03 | 0.01 to 0.05 |
| Time spent indoors, total, h | 0.002 | 0.05 | 0.01 | 0.003 to 0.01 |
| Time spent outdoors in a week, total, h | 0.001 | -0.05 | -0.02 | -0.03 to -0.01 |
| Sleeping duration, h | <0.001 | -0.08 | -0.07 | -0.09 to -0.04 |
| Ocular parameters | | | | |
| Axial length, mean of right eye and left eye, mm | <0.001 | 0.08 | 0.04 | 0.02 to 0.05 |
| Axial length right eye minus left eye, amount, mm | <0.001 | 0.66 | 1.43 | 1.39 to 1.47 |
| Refractive error, mean of right eye and left eye, D | <0.001 | -0.06 | | |
| Corneal curvature, anterior radius, right eye, mm | | 0.14 | | |
| Corneal curvature, anterior radius, left eye, mm | 0.007 | 0.04 | 0.07 | 0.02 to 0.13 |
| Corneal curvature, anterior radius, right eye minus left eye, amount, mm | <0.001 | 0.05 | 0.43 | 0.22 to 0.65 |
| Corneal astigmatism, right eye, D | <0.001 | -0.07 | -0.06 | -0.09 to -0.04 |
| Corneal astigmatism, left eye, D | <0.001 | -0.13 | -0.14 | -0.16 to -0.11 |
| Corneal astigmatism, right eye minus left eye, amount, D | <0.001 | 0.05 | 0.01 | 0.004 to 0.011 |
| Best corrected visual acuity, right eye, logMAR | <0.001 | 0.24 | 2.78 | 2.50 to 3.07 |
| Best corrected visual acuity, left eye, logMAR | <0.001 | 0.18 | 2.13 | 1.84 to 2.42 |
| Best corrected visual acuity, right eye minus left eye, amount, logMAR | <0.001 | 0.36 | 3.61 | 3.37 to 3.85 |
| Stereoacuity, logarithmic, arc-s | <0.001 | 0.24 | 0.89 | 0.80 to 0.98 |
| Worth 4-dot test, abnormal | <0.001 | 0.16 | 0.81 | 0.64 to 0.98 |
| Intraocular pressure, right eye, mm Hg | 0.008 | 0.03 | 0.01 | 0.001 to 0.01 |

D, diopter.

0.6% (95% CI: 25.0%-27.2%). If only individuals with anisomyopia were included, mean anisomyopia was 0.46 ± 0.48 diopters (median: 0.38 diopters; range: 0.13-6.75 diopters). If defined as an anisomyopia of ≥ 1 diopter, prevalence of anisomyopia was $2.7\% \pm 0.2\%$ (95% CI: 2.3%-3.1%). It increased significantly ($P < 0.001$) with older age. In univariate analysis, presence of anisomyopia (≥ 1 diopter) increased the risk of poor stereoacuity by a factor of 2.79 (95% CI: 1.52-5.12).

In univariate analysis, the amount of anisomyopia increased significantly with older age ($P < 0.001$; β : 0.33; equation of the regression line: Anisometropia (diopters) = $0.03 \times \text{Age (years)} - 0.20$). Anisomyopia was significantly higher in girls than in boys (0.14 ± 0.35 diopters versus 0.11 ± 0.28 diopters; $P < 0.001$). Higher anisomyopia was further associated with the systemic parameters of taller body height ($P < 0.001$), heavier body weight ($P < 0.001$), older paternal age ($P < 0.001$), older maternal age ($P < 0.001$), higher education of father ($P < 0.001$) and mother ($P < 0.001$), more time spent indoors reading and writing in a weekday ($P = 0.002$) or during a weekend ($P = 0.002$), more time spent indoors playing handheld computer games in a weekday ($P = 0.03$) or during the weekend ($P = 0.001$), and shorter sleeping duration time ($P < 0.001$). Higher anisomyopia was associated with the ocular parameters of longer axial length ($P < 0.001$) and larger intereye difference in axial length ($P < 0.001$), greater myopic

refractive error ($P < 0.001$), longer corneal curvature radius (right eye: $P = 0.048$; left eye: $P = 0.02$), lower corneal astigmatism ($P < 0.001$) and higher intereye difference in corneal astigmatism ($P = 0.02$), lower stereoacuity ($P = 0.03$), and higher intraocular pressure ($P = 0.001$). In contrast to refractive anisometropia, anisomyopia was significantly associated with urban region of habitation ($P < 0.001$), perinatal oxygen therapy ($P = 0.009$), paternal myopia ($P < 0.001$) and maternal myopia ($P < 0.001$), writing posture ($P < 0.001$), shorter distance between the eyes and book when reading or writing ($P < 0.001$), way of holding the pen during writing ($P < 0.001$), and axis of the corneal astigmatism of the left eye ($P = 0.005$). In contrast to refractive anisometropia, anisomyopia was not significantly associated with time spent outdoors in a week (total) ($P = 0.48$), intereye difference in corneal curvature radius ($P = 0.49$), and BCVA ($P = 0.26$). As with refractive anisometropia, anisomyopia was not significantly associated with birth length ($P = 0.53$) and birth weight ($P = 0.06$), axis of the corneal astigmatism of the right eye ($P = 0.20$), and corneal diameter of right eye ($P = 0.69$) and left eye ($P = 0.65$).

In the multivariate analysis with anisomyopia as dependent variable and all parameters as independent variables—which were significantly associated with anisomyopia in the univariate analysis—we first dropped, owing to collinearity, the corneal curvature (right eye) (VIF: 12.8), mean axial length

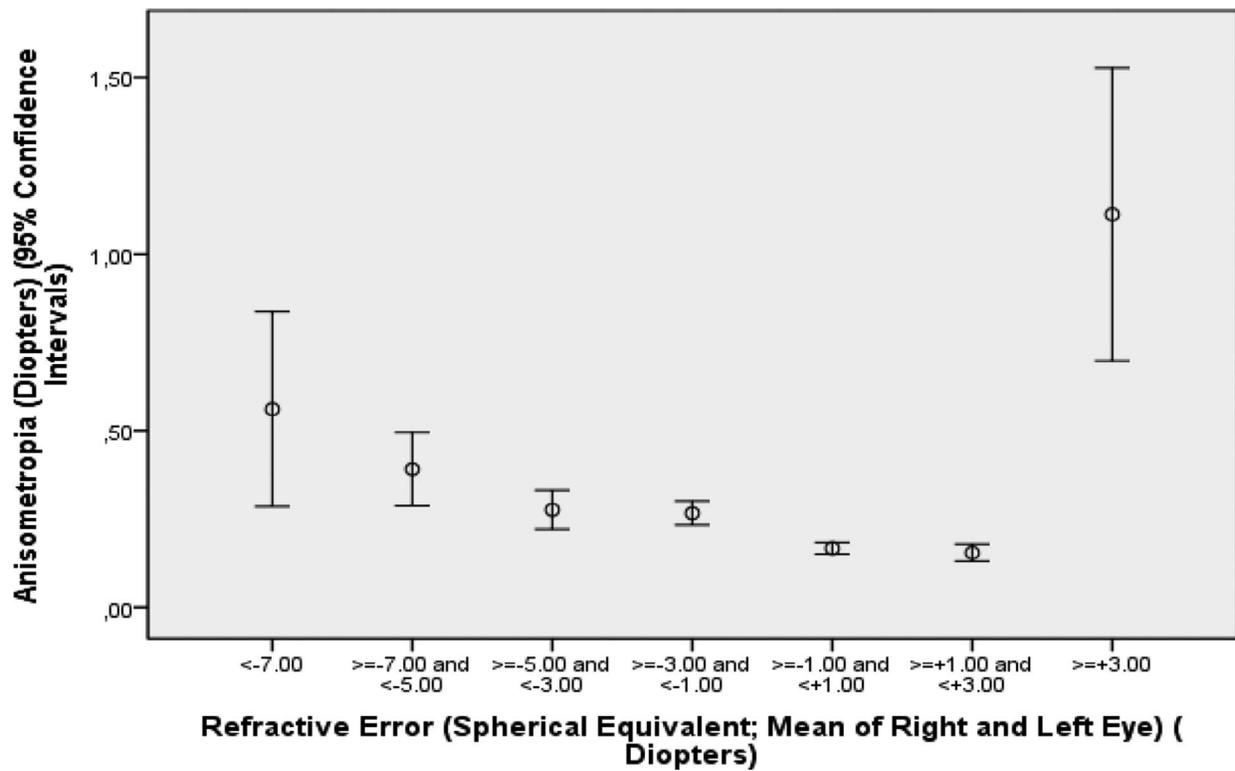


Figure 2. Graph showing the distribution of refractive anisometropia stratified by refractive error in the Shandong Children Eye Study.

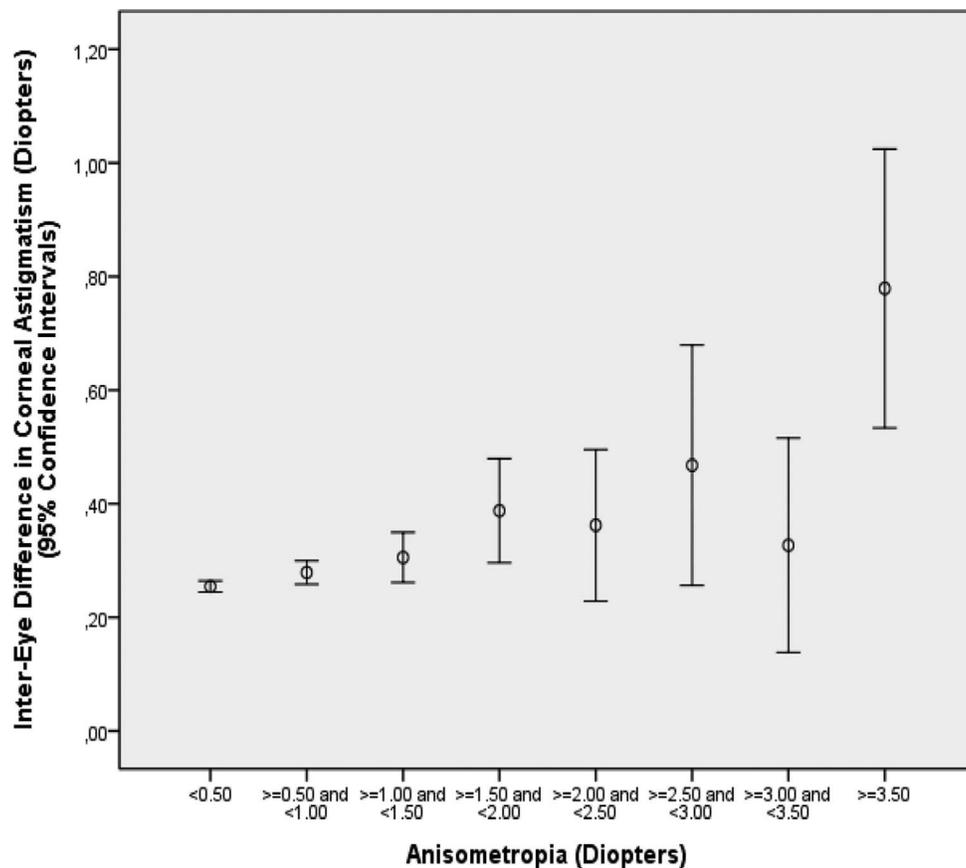


Figure 3. Graph showing the distribution of the intereye difference in corneal astigmatism stratified by refractive ametropia in the Shandong Children Eye Study.

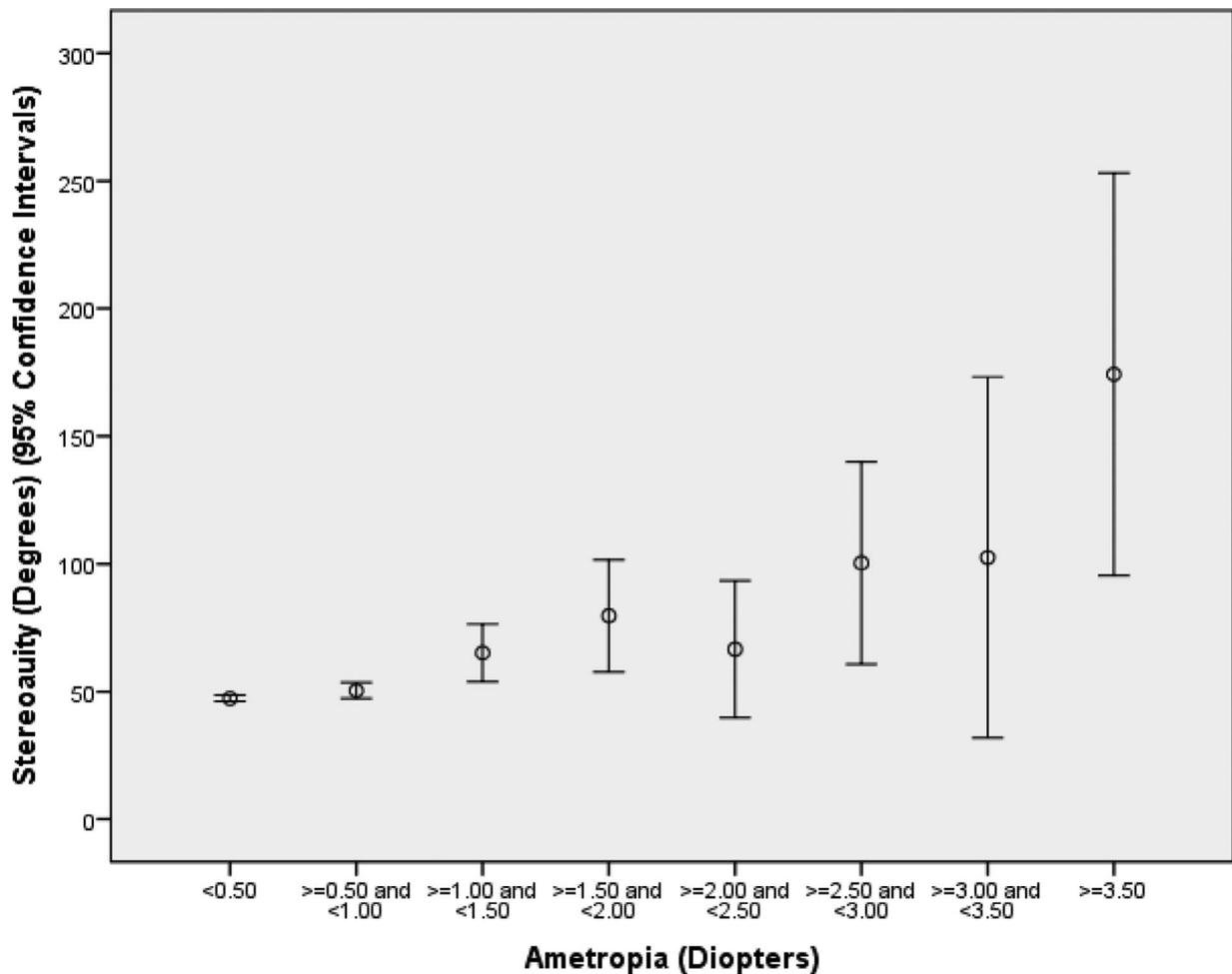


FIGURE 4. Graph showing the distribution of stereoacuity stratified by refractive ametropia in the Shandong Children Eye Study.

(VIF: 10.4), body height (VIF: 7.6), time spent indoors reading and writing during the week (VIF: 4.8) and weekend (VIF: 21.2), and body weight (VIF: 2.7). Owing to missing statistical significance we then dropped step by step the parameters of paternal age ($P = 0.97$), distance between the eyes and book when reading or writing ($P = 0.97$), maternal age ($P = 0.99$), time spent indoors playing handheld computer games during the weekend ($P = 0.99$), writing posture ($P = 0.76$), axis of corneal astigmatism ($P = 0.66$), intereye difference in corneal astigmatism ($P = 0.95$), paternal myopia ($P = 0.61$), mean sleeping duration ($P = 0.30$), maternal education ($P = 0.46$), stereoacuity ($P = 0.87$), sex ($P = 0.54$), corneal astigmatism

(left eye) ($P = 0.26$), intraocular pressure left eye ($P = 0.24$) and right eye ($P = 0.24$), region of habitation ($P = 0.14$), maternal myopia ($P = 0.14$), time spent indoors playing games ($P = 0.21$), corneal curvature (left eye) ($P = 0.13$), perinatal oxygen therapy ($P = 0.13$), and way of holding the pen during writing ($P = 0.22$).

In the final model ($r: 0.57$), higher anisomyopia was associated with older age ($P = 0.001$), higher level of paternal education ($P = 0.001$), more total time spent indoors reading or writing ($P = 0.01$), larger intereye difference in axial length ($P < 0.001$), more myopic refractive error ($P < 0.001$), and lower right corneal astigmatism ($P < 0.001$) (Table 4). If intereye

TABLE 2. Associations (Multivariate Analysis) Between the Amount of Refractive Anisometropia (Spherical Equivalent; Diopters) and Ocular and Nonocular Parameters in the Shandong Children Eye Study

| Parameter | P Value | Standardized Correlation Coefficient β | Standardized Regression Coefficient B | 95% Confidence Interval of B | Variance Inflation Factor |
|---|---------|--|---------------------------------------|------------------------------|---------------------------|
| Age | <0.001 | 0.07 | 0.01 | 0.01 to 0.02 | 1.70 |
| Maternal education level | <0.001 | 0.04 | 0.02 | 0.01 to 0.03 | 1.12 |
| Time spent indoors reading or writing, h | 0.001 | 0.04 | 0.01 | 0.01 to 0.02 | 1.22 |
| Axial length intereye difference, mm | <0.001 | 0.57 | 1.20 | 1.15 to 1.24 | 1.13 |
| Axial length mean of both eyes, mm | 0.02 | -0.03 | -0.02 | -0.03 to -0.001 | 1.48 |
| Best corrected visual acuity, intereye difference, logMAR | <0.001 | 0.14 | 1.83 | 1.54 to 2.12 | 1.10 |
| Stereoacuity, arc-s | <0.001 | 0.08 | 0.31 | 0.22 to 0.39 | 1.06 |

TABLE 3. Associations (Binary Regression Analysis) Between the Prevalence of Refractive Anisometropia and Ocular and Nonocular Parameters in the Shandong Children Eye Study

| Parameter | P Value | Odds Ratio | 95% Confidence Interval |
|--|---------|------------|-------------------------|
| Age | <0.001 | 1.13 | 1.08-1.19 |
| Maternal education level | 0.004 | 1.17 | 1.01-1.31 |
| Time spent indoors reading or writing, h | 0.002 | 1.12 | 1.04-1.20 |
| Axial length intereye difference, mm | <0.001 | 81.5 | 50.3-132 |
| Corneal astigmatism right eye, D | 0.01 | 0.75 | 0.60-0.94 |
| Stereoacuity, arc-s | <0.001 | 7.89 | 4.15-15.0 |

difference in corneal astigmatism was added to the model, it was not significantly associated ($P = 0.82$), nor was stereoacuity ($P = 0.49$).

If hyperopic anisometropia was defined as an unequal amount of hyperopia in both eyes, with hyperopia defined as refractive error of ≥ 0.5 diopters, the amount of hyperopic anisometropia increased significantly with higher intereye difference in axial length ($P < 0.001$; β : 0.54; B : 1.04; 95% CI: 0.97-1.12), shorter mean axial length ($P < 0.001$; β : -0.08; B : -0.05; 95% CI: -0.07 to -0.03), lower stereoacuity ($P < 0.001$; β : 0.07; B : 0.21; 95% CI: 0.09-0.32), and higher intereye difference in BCVA ($P < 0.001$; β : 0.17; B : 1.77; 95% CI: 1.37-2.17), while time spent indoors with reading ($P = 0.18$), maternal education ($P = 0.88$), and age ($P = 0.09$) were no longer significantly associated in the multivariate model.

Mean cylindrical anisometropia was 0.30 ± 0.32 diopters (median: 0.25 diopters; range: 0-5.50 diopters). It increased with older age ($P < 0.001$). If defined as a cylindrical anisometropia of ≥ 1 diopter, prevalence of cylindrical anisometropia was $3.7\% \pm 0.2\%$ (95% CI: 3.2%-4.2%). In univariate analysis, each diopter in cylindrical anisometropia increased the risk of poor stereoacuity by a factor of 2.65 (95% CI: 1.98-3.55). Presence of a cylindrical astigmatism of ≥ 1 diopter increased the risk of poor stereoacuity by a factor of 4.69 (95% CI: 2.97-7.39) (χ^2 test).

In univariate analysis, the amount of cylindrical anisometropia increased significantly with older age ($P < 0.001$) (Fig. 5), lower birth weight ($P = 0.01$), taller body height ($P < 0.001$), heavier body weight ($P < 0.001$), older maternal and paternal age ($P = 0.048$), more time spent indoors reading and writing in a weekday ($P = 0.008$) or during a weekend ($P = 0.009$) and more total time spent indoors reading and writing ($P = 0.004$), more time spent indoors playing handheld computer games in a weekday ($P = 0.008$) or during the weekend ($P = 0.002$), shorter mean sleeping duration ($P < 0.001$), higher refractive ametropia ($P < 0.001$), higher intereye difference in axial length ($P < 0.001$), longer mean axial length ($P = 0.04$), greater myopic mean refractive error ($P < 0.001$), smaller mean corneal curvature radius ($P = 0.04$), larger intereye difference in corneal curvature radius ($P < 0.001$), higher mean corneal astigmatism ($P < 0.001$), lower

mean BCVA ($P < 0.001$) and higher intereye difference in BCVA ($P < 0.001$), lower stereoacuity ($P < 0.001$), and negative Worth 4-dot test ($P = 0.03$).

In multivariate analysis, we dropped body height (VIF: 6.7) and mean axial length (VIF: 8.0), and mean corneal curvature radius ($P = 0.85$), mean sleeping duration ($P = 0.82$), results of the Worth 4-dot test ($P = 0.99$), time spent indoors playing handheld computer games during the week ($P = 0.89$), paternal age ($P = 0.83$), maternal age ($P = 0.86$), stereoacuity ($P = 0.85$), intereye difference in BCVA ($P = 0.73$), time spent indoors playing handheld computer games during the week ($P = 0.56$), time spent indoors reading and writing in a weekday ($P = 0.43$) and during the week ($P = 0.80$), intereye difference in axial length ($P = 0.37$), age ($P = 0.21$), birth weight ($P = 0.08$), body weight ($P = 0.15$), total time spent indoors reading and writing ($P = 0.61$), and intereye difference in corneal curvature radius ($P = 0.18$).

In the final model (r : 0.34), higher cylindrical anisometropia was associated with higher refractive anisometropia ($P < 0.001$; β : 0.16; B : 0.09, 95% CI: 0.08-0.11), greater myopic refractive error (mean of both eyes) ($P < 0.001$; β : -0.06; B : -0.01, 95% CI: -0.01 to -0.01), higher corneal astigmatism (mean of both eyes) ($P < 0.001$; β : -0.22; B : -0.15, 95% CI: -0.17 to -0.13), and lower mean BCVA (logMAR) (mean of both eyes) ($P < 0.001$; β : 0.11; B : 0.90, 95% CI: 0.68-1.17).

DISCUSSION

In 4- to 18-year-old children of our study population, refractive anisometropia increased with older age, higher level of maternal education, more total time spent indoors reading or writing, larger intereye difference in axial length, shorter mean axial length of both eyes, larger intereye difference in BCVA, and lower stereoacuity. Anisometropia showed a U-shaped correlation with refractive error. Prevalence of anisometropia (defined as an anisometropia ≥ 1 diopter) was $7.0\% \pm 0.3\%$ (95% CI: 6.3%-7.6%) and increased with older age ($P < 0.001$), higher maternal level of education ($P = 0.004$), longer total reading time indoors ($P = 0.002$), higher intereye difference in axial length ($P < 0.001$), lower corneal astigmatism ($P <$

TABLE 4. Associations (Multivariate Analysis) Between the Amount of Anisomyopia (Spherical Equivalent; Diopters) and Ocular and Nonocular Parameters in the Shandong Children Eye Study

| Parameter | P Value | Standardized Correlation Coefficient β | Standardized Regression Coefficient B | 95% Confidence Interval of B | Variance Inflation Factor |
|--|---------|--|---|--------------------------------|---------------------------|
| Age | 0.001 | 0.05 | 0.006 | 0.002 to 0.009 | 1.67 |
| Paternal education level | 0.001 | 0.04 | 0.01 | 0.01 to 0.02 | 1.08 |
| Time spent indoors reading or writing, h | 0.03 | 0.03 | 0.01 | 0.00 to 0.01 | 1.24 |
| Axial length intereye difference, mm | <0.001 | 0.22 | 0.26 | 0.23 to 0.29 | 1.05 |
| Refractive error, D | <0.001 | -0.46 | -0.07 | -0.08 to -0.07 | 1.49 |
| Corneal astigmatism right eye, D | <0.001 | -0.10 | -0.06 | -0.08 to -0.05 | 1.02 |

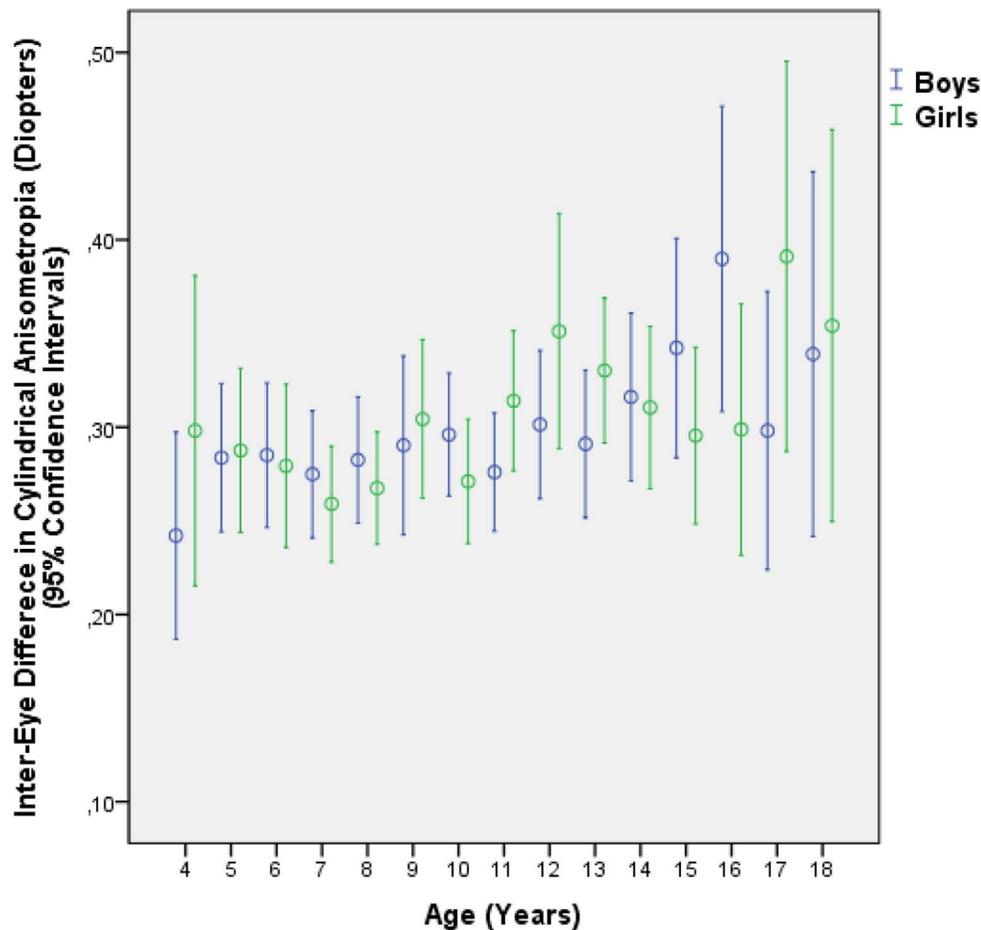


FIGURE 5. Graph showing the distribution of cylindrical anisometropia stratified by age and sex in the Shandong Children Eye Study.

0.001), and lower stereoacuity ($P < 0.001$). In univariate analysis, presence of anisometropia (≥ 1 diopter) increased the risk of poor stereoacuity by a factor of 6.73 (95% CI: 4.78–9.47).

The results of our study agree with findings obtained in previous investigations such as the Northern Ireland Childhood Errors of Refraction Study (prevalence of anisometropia [≥ 1 diopters] in 6- to 7-year-old children: 8.5%; in 12- to 13-year-old children: 9.4%).^{11,19–21} In contrast to our study, prevalence of anisometropia does not increase with older age in the Northern Ireland study. In the Californian Multi-Ethnic Pediatric Eye Disease Study on children aged 6 to 72 months, the prevalence of anisometropia (≥ 1 diopter) is 4.3% for Hispanics and 4.2% for African Americans.⁸ In the Sydney Pediatric Eye Disease Study on children aged 6 to 72 months, the overall prevalence of anisometropia (≥ 1 diopter) is 2.7%.²¹ The difference in the prevalence of anisometropia between these studies and our investigation may be explained by the difference in age. In the Multi-Country Refractive Error Study on 39,500 children aged 5 to 15 years, the most common cause of amblyopia is anisometropia, with an overall prevalence of amblyopia of 0.74%.¹⁰ The surrogate for amblyopia in our study was the intereye difference in BCVA, which, after the intereye difference in axial length, was the parameter with the second strongest association with anisometropia. Anisometropia has previously also been examined in teenager and adult study populations such as in the Singapore Longitudinal Aging Study and the Central India Eye and Medical Study.^{22,23} However,

since developing asymmetric cataract with asymmetric secondary cataract-induced myopization is a main cause for anisometropia in the adult population, causative factors for anisometropia in the adult population are different from those in children. The findings obtained in adult study populations may therefore not be helpful for the discussion on ametropia in children.

Interestingly, higher refractive anisometropia as well as higher anisomyopia were associated with more total time spent indoors reading or writing after adjusting for age, sex, intereye difference in axial length, mean axial length of both eyes, and other parameters (Tables 2–4). Confirming other observational investigations, He and colleagues²⁴ have shown in a recent landmark study that more time spent outdoors during school time is associated with a significantly lower incidence of myopia.^{25,26} The results of our study extended the findings by He and colleagues²⁴ and suggested that the development of axial myopia, and potentially also the development and increase in refractive anisometropia, and in particular in anisomyopia, may depend on the lifestyle of the school children. It fits with the findings in our study that the amount of hyperopic anisometropia, as well as of cylindrical anisometropia, was not significantly related with lifestyle parameters in the multivariate model. The finding of the potential influence of lifestyle on anisomyopia may a priori be astonishing since the influence of systemic parameters such as lifestyle should be equal for both eyes. Future studies may address which intraocular parameters in association with lifestyle parameters

influence the development of myopia including anisometropia and anisomyopia.

The finding that refractive anisometropia and anisomyopia were strongly associated with the intereye difference in axial length but not with the intereye difference in corneal curvature radius, a finding which was in agreement with other studies, suggests that the development of refractive anisometropia and of anisomyopia in children mainly occurs through the influence of changes in the posterior segment of the eye, including lengthening of the vitreous cavity.^{27,28} It also fits with animal studies in which induction of axial myopia by various means—such as wearing a monocularly depriving face mask, lid suture, or wearing myopia-inducing goggles—is associated with axial elongation, mainly a lengthening of the vitreous cavity, and in which the experimental axial elongation decreases with increasing ambient light intensity.^{29–33} Correspondingly, cylindrical anisometropia, in contrast to refractive anisometropia and anisomyopia, was not significantly associated with the lifestyle of the school children. It fits with histologic and population-based studies that primary myopia is mainly associated with changes in the posterior segment of the globe.^{34,35}

Mean cylindrical anisometropia in our study was 0.30 ± 0.32 diopters and it increased with older age (Fig. 5). Prevalence of cylindrical anisometropia (≥ 1 diopter) was $3.7\% \pm 0.2\%$ (95% CI: 3.2%–4.2%). A similar figure was reported in the Multi-Ethnic Pediatric Eye Disease Study of Hispanic and African American children aged 6 to 72 months in which the prevalence of cylindrical anisometropia of ≥ 1 diopter was 5.6% and 4.5%, respectively.⁸ As in our study, prevalence of cylindrical anisometropia is not associated with age after age 1 year. As in our study, Huynh and colleagues²⁷ have reported that cylindrical anisometropia mainly results from an intereye difference in corneal astigmatism.

Stereoacuity was strongly influenced by the presence and amount of refractive anisometropia and of hyperopic anisometropia, while anisomyopia was not significantly associated with stereoacuity (Tables 1–4). In univariate analysis, presence of a cylindrical astigmatism ≥ 1 diopter increased the risk of poor stereoacuity by a factor of 4.69; in multivariate analysis, however, cylindrical astigmatism was no longer significantly associated with stereoacuity. It suggested that the main parameters associated with lower stereoacuity were refractive anisometropia in general and hyperopic anisometropia in particular. It may indicate that the marked increase in the prevalence of myopia in the young generation in East Asia may lead to a decrease in the prevalence of poor stereoacuity.³⁶

Potential limitations of our study should be mentioned. First, our study had a cross-sectional recruitment of participants. As in any cross-sectional study in comparison to a longitudinal investigation, we could not examine causal relationships between anisometropia as the main outcome parameter and other parameters. Second, as for any population-based study or school-based investigation, nonparticipation might have led to a bias. The participation rate of 94.7% in our study was relatively high; despite this, however, the group of nonparticipants and the group of children included into the study differed significantly in age and refractive error. Third, the data obtained by the interview based on the standardized questionnaire were self-reported and might have been due to a bias.

In conclusion, in 4- to 18-year-old Chinese school children from a rural region and from an urban region in East China, refractive anisometropia and anisomyopia increased with systemic parameters such as age, parental education level, and lifestyle of the children, for example, more time spent indoors reading or writing. In contrast, cylindrical anisometropia was not related with lifestyle parameters.

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