Glaucoma

Intraocular Pressure and Associated Factors in Children: The Shandong Children Eye Study

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Purpose. We examined the distribution of intraocular pressure (IOP) and its associated factors in children.

Methods. Using a random cluster sampling from kindergartens, primary schools, and junior and senior high schools from rural Guanxian County and the city of Weihai, the school-based cross-sectional Shandong Children Eye Study included children aged 4 to 18 years. All participants underwent an ocular examination, including ocular biometry, cycloplegic refractometry, and noncontact tonometry.

Results. Mean IOP was 17.6 ± 2.7 mm Hg (range, 10–28 mm Hg). The IOP increased up to an age of 10 years and subsequently decreased with older age. In multivariate regression analysis, higher IOP was associated with female sex ($P < 0.001$; standardized correlation coefficient β, 0.06; regression coefficient β, 0.34; 95% confidence interval [CI], 0.18, 0.50), higher body mass index ($P < 0.001$; correlation coefficient β, 0.09; regression coefficient β, 0.07; 95% CI, 0.04,0.09), younger age ($P < 0.001$; correlation coefficient β, −0.15; regression coefficient β, −0.13; 95% CI, −0.17,−0.10), maternal myopia ($P < 0.001$; correlation coefficient β, 0.05; regression coefficient β, 0.34; 95% CI, 0.15,0.53), and more time spent indoors with reading/writing ($P = 0.002$; correlation coefficient β, 0.05; regression coefficient β, 0.07; 95% CI, 0.03,0.11), and with the ocular parameters of longer axial length ($P < 0.001$; correlation coefficient β, 0.14; regression coefficient β, 0.29; 95% CI, 0.21,0.37) and smaller corneal horizontal diameter ($P < 0.001$; correlation coefficient β, −0.06; regression coefficient β, −0.31; 95% CI, −0.46,–0.15).

Conclusions. In children aged 4 to 18 years, IOP showed an M-shaped association with age. Higher IOP was associated with the nonocular parameters of female sex ($P < 0.001$), higher body mass index ($P < 0.001$), younger age ($P < 0.001$), maternal myopia ($P < 0.001$), and more time spent indoors with reading/writing ($P = 0.002$), and with the ocular parameters of longer axial length ($P < 0.001$) and smaller corneal horizontal diameter ($P < 0.001$).

Keywords: intraocular pressure, ocular hypertension, epidemiology, population-based study, shandong children eye study

Ocular physiology and pathophysiology is connected strongly with the intraocular pressure (IOP), which has been defined as the transcorneal pressure difference.[1] Numerous previous studies have addressed the distribution of IOP in the adult population of various ethnicities, the parameters associated with IOP measurements, and the factors associated with IOP.[2–7] Relatively little information, however, has been available on the IOP in children, IOP distribution in relation to age and growing eye size in the children, dependence of the IOP measurements on various variables, and definition of abnormally low or abnormally high IOP values.[8–16] Most of these previous studies on IOP in children were hospital-based investigations on a relatively small number of children, and often, a multivariate analysis was not performed or did not contain the majority of known factors associated with IOP. We, therefore, conducted this school-based study on children for a rural region and an urban region, measured the IOP, and correlated the measurements with general demographic variables, data on the development of myopia, and ocular biometric data.

Methods

The Shandong Children Eye Study was a school-based cross-sectional study performed in Shandong province in coastal Eastern China. 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 consent, according to the Declaration of Helsinki. The study was conducted 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 Shandong is a relatively

TABLE 1. IOP (Mean ± SD) in the Shandong Children Eye Study Stratified by Age, Sex, and Region of Habitation

Age, y	N	IOP, mm Hg Right Eyes	IOP, mm Hg Left Eyes	Mean Interocular Difference in IOP, mm Hg Absolute Amount
4	105	17.2 ± 2.3	17.3 ± 2.5	1.4 ± 1.2
5	347	16.6 ± 2.6	16.9 ± 2.8	1.4 ± 1.3
6	434	17.4 ± 2.6	17.6 ± 2.8	1.5 ± 1.4
7	620	17.8 ± 2.6	18.0 ± 2.7	1.4 ± 1.3
8	730	17.8 ± 2.6	17.8 ± 2.6	1.4 ± 1.2
9	546	18.0 ± 2.5	17.9 ± 2.6	1.4 ± 1.2
10	699	18.1 ± 2.7	18.0 ± 2.8	1.4 ± 1.2
11	587	17.6 ± 2.9	17.8 ± 2.9	1.5 ± 1.4
12	483	17.6 ± 2.7	17.7 ± 2.6	1.3 ± 1.2
13	434	17.8 ± 2.8	17.7 ± 2.8	1.3 ± 1.3
14	339	17.9 ± 2.6	17.9 ± 2.6	1.4 ± 1.2
15	228	17.9 ± 2.4	17.9 ± 2.6	1.5 ± 1.3
16	134	17.5 ± 2.7	17.6 ± 2.6	1.2 ± 1.3
17	128	17.1 ± 2.7	17.5 ± 2.8	1.5 ± 1.3
18	105	16.3 ± 2.5	16.4 ± 2.7	1.5 ± 1.4
Sex				
Boys	3118	17.5 ± 2.7	17.6 ± 2.8	1.4 ± 1.3
Girls	2801	17.8 ± 2.6	17.9 ± 2.7	1.4 ± 1.2
Region of habitation				
Rural	3050	16.8 ± 2.5	17.0 ± 2.6	1.5 ± 1.3
Urban	2869	18.5 ± 2.6	18.6 ± 2.6	1.3 ± 1.2
Total	5919	17.7 ± 2.7	17.8 ± 2.7	1.4 ± 1.3

highly developed province. All schools in Weihai and Guanxian were selected randomly to be sampled in our study, and were stratified by grade and classes from each level. Based on the inclusion criterion of an age between 4 years to 18 years, 6364 children were eligible to take part in the study. The study has been described in detail recently.[17]

The series of examinations started with a standardized questionnaire that was similar to the one used previously in the Refractive Error Study in Children (RESC) studies, and consisted of questions on the children's family history, time spent doing outdoor and indoor activities, study intensity, lifestyle, and so forth.[18] We measured uncorrected and best

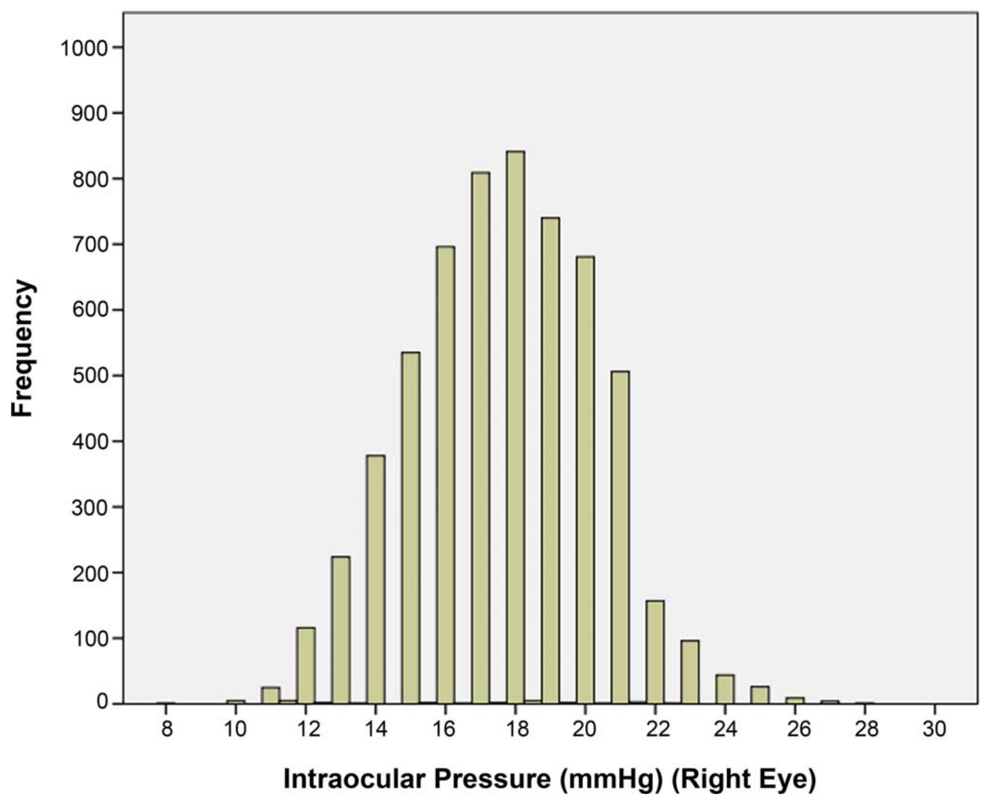

FIGURE 1. Histogram showing the distribution of IOP in the Shandong Children Eye Study.

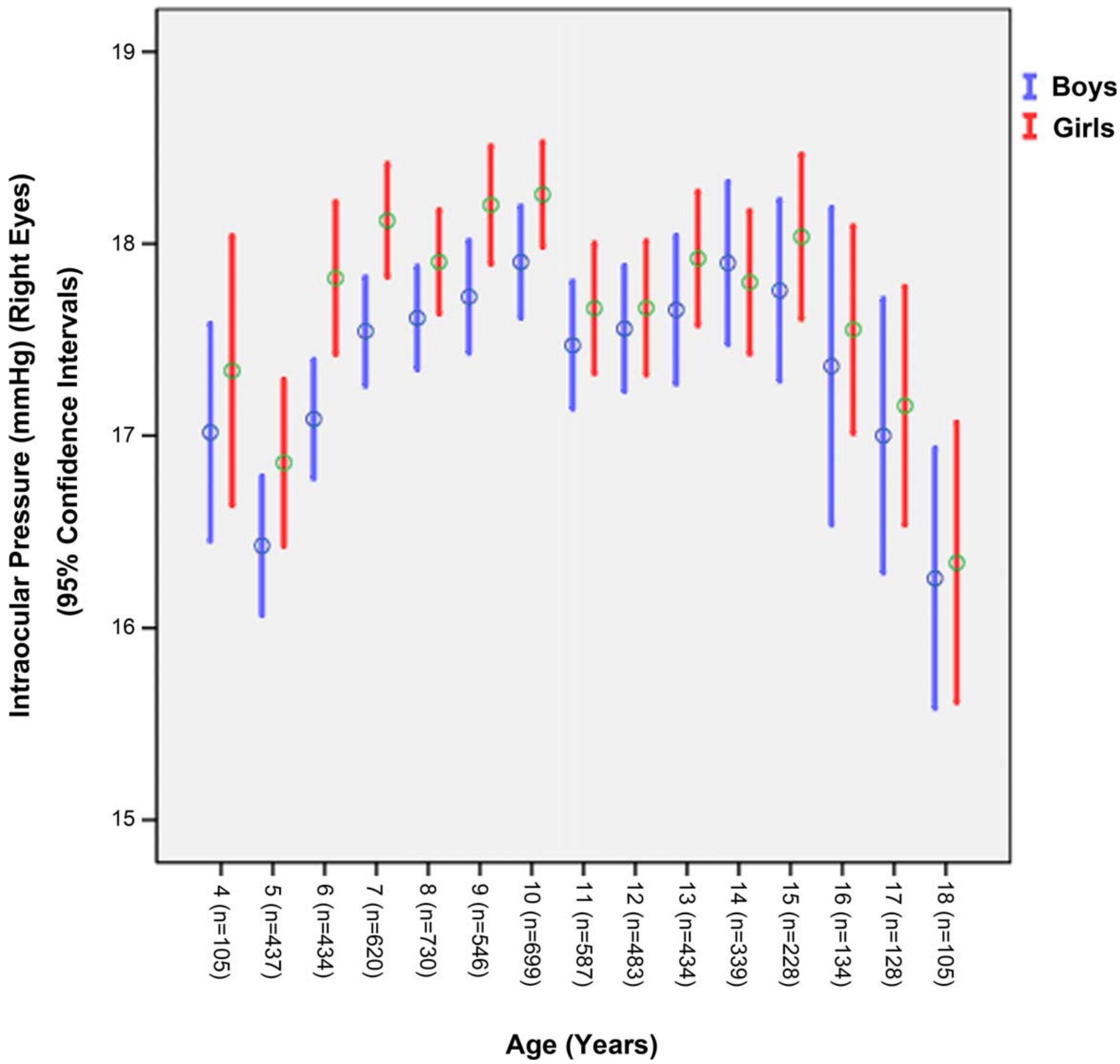

FIGURE 2. Distribution of IOP stratified by age and sex in the Shandong Children Eye Study.

corrected visual acuity using the tumbling "E" chart (#600722; Good-Lite Co., Elgin, IL, USA). The IOP was determined by a noncontact tonometer (Topcon CT80; Topcon Co., Tokyo, Japan). Each eye was measured at least four times to get four valid readings. For further analysis, the mean of these four readings was taken. We calculated the interocular difference in IOP as the square root of the square of the difference of IOP of the right eye minus IOP of the left eye. This calculation resulted in the absolute amount of the interocular difference in IOP. Using the slit-lamp, an ophthalmologist examined the anterior and posterior ocular segments, and noted any abnormality. After instilling 1% cyclopentolate eye drops (Alcon, Ft. Worth, TX, USA) at least three times, cycloplegia was achieved and autorefractometry was performed (KR-8900; Topcon Co.). Each eye was measured at least 3 times. The difference between the maximum and minimum value of the measurements of spherical refractive error and cylindrical refractive error had to be less than 0.5 diopters (D), otherwise the measurements had to be repeated. The spherical equivalent of the refractive error was defined as the spherical value of refractive error plus one-half of the cylindrical value. Ocular biometry for measurement of axial length and corneal horizontal diameter was performed using laser interferometry (IOL-Master, V5.0; Carl Zeiss Meditec AG, Jena, Germany). The axial length–to–corneal curvature radius ratio was calculated as the axial length value plus corneal curvature radius.

Inclusion criterion for the present study was the availability of bilateral IOP measurements. Statistical analysis was performed using SPSS for Windows, version 21.0 (IBM-SPSS, Chicago, IL, USA). In a first step, we examined the mean values (presented as mean ± SD) of IOP. In a second step, we performed a univariate regression analysis to examine the associations between IOP, and the nonocular and ocular parameters. In a third step, a multivariate analysis was conducted with IOP as dependent variable, and as independent variables all parameters for which the P value in the univariate analysis was ≤ 0.10. 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 analysis, all those parameters that were no longer significantly associated with IOP in the multivariate analysis. In case of doubt we deleted those parameters that were considered to be secondarily associated with IOP; for example, we dropped region of habitation and kept axial length, since myopia was significantly more common in the urban region than in the rural region and since IOP was considered to be closer related to axial length than to location

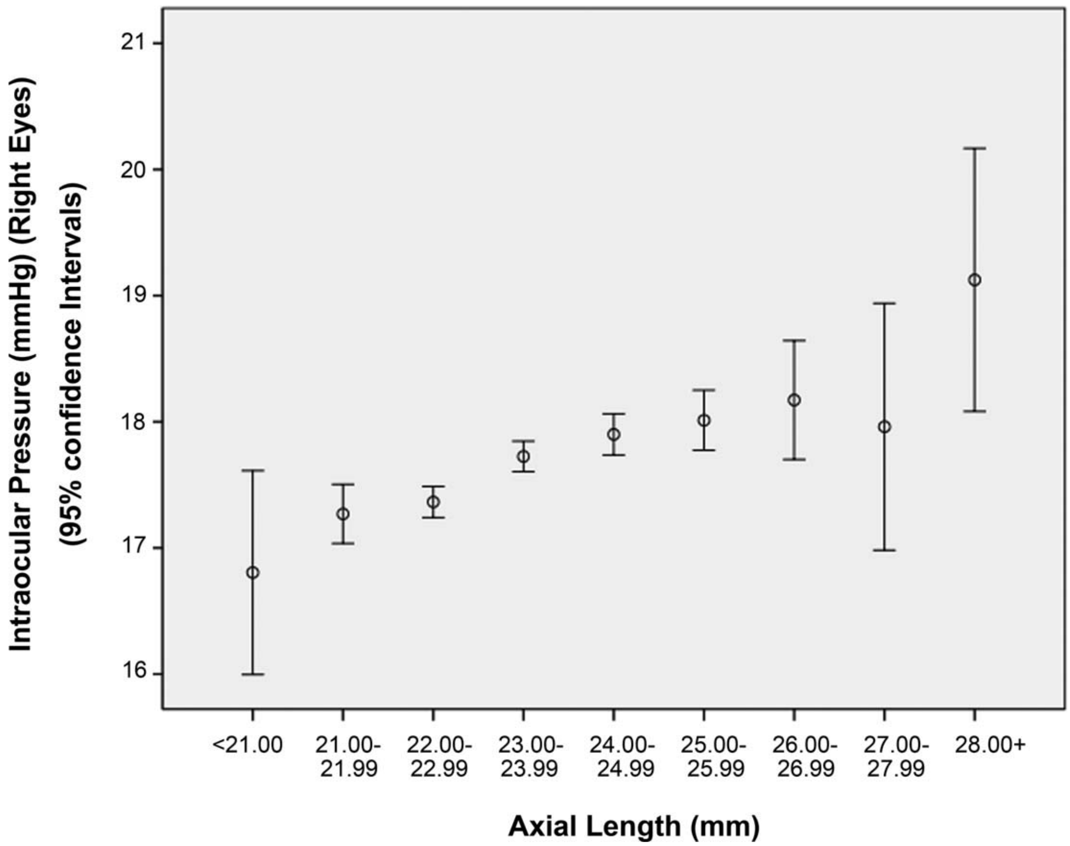

FIGURE 3. Diagram showing the distribution of IOP stratified by axial length in the Shandong Children Eye Study.

of the school. Standardized correlation coefficients and regression coefficients with their 95% confidence intervals (95% CI) were calculated. All P values were 2-sided and were considered statistically significant when the values were less than 0.05.

RESULTS

Of 6364 eligible children, 328 (5.2%) children refused the examination and for 117 (1.8%) children, the general and ophthalmic examination was not complete or it was not possible to obtain reliable IOP measurements. The study eventually included 5919 (93.0%) children (2801 girls, 47.3%). The mean age was 10.0 ± 3.3 years (median, 10.0 years; range, 4–18 years). Mean refractive error (spherical equivalent) was −0.21 ± 2.10 D (median, 0.50 D; range, −11.75–10.50 D) for the right eyes and −0.13 ± 2.08 D (median, 0.50 D; range, −11.75–11.00 D) for the left eyes.

The mean IOP of the right eye was 17.7 ± 2.7 mm Hg (median, 18 mm Hg; range, 8–28 mm Hg; Table 1; Fig. 1). Mean IOP of the left eyes was 17.8 ± 2.7 mm Hg (median, 18 mm Hg; range, 8–29 mm Hg, Table 1). The IOP measurements were significantly ($P < 0.001$) higher in the left eyes than in the right eyes (17.8 ± 2.7 vs. 17.7 ± 2.7 mm Hg). The mean absolute amount of the interocular difference was 1.4 ± 1.3 mm Hg. For both eyes, the IOP was not normally distributed (Kolmogorov-Smirnov test, $P < 0.001$). The histograms showed approximately a Gaussian distribution curve with a minor skew to the right (Fig. 1).

In univariate linear analysis, IOP was not significantly associated with age (right eye, $P = 0.23$; left eye, $P = 0.68$), but showed an M-like curve (Fig. 2). The graph showing the distribution of IOP with age revealed a significant ($P < 0.001$) increase in IOP from the age of 4 to 10 years, a significant ($P < 0.001$) decline from the age of 10 years to a plateau-like phase of the age between 11 and 16 years, followed by a sustained ($P < 0.001$) downward trend toward the age of 18 years (Fig. 2). The IOP values in the age groups from 11 to 16 years did not differ significantly (all $P > 0.05$).

In univariate analysis, IOP (right eye) was significantly or marginally significantly ($P \leq 0.10$) associated with the nonocular parameters of female sex ($P < 0.001$), urban region of habitation (P < 0.001), higher body height ($P < 0.001$), greater body weight ($P < 0.001$), higher body mass index (BMI; $P < 0.001$), higher paternal ($P < 0.001$) and maternal ($P < 0.001$) education, paternal and maternal myopia ($P < 0.001$), more time spent indoors reading or writing ($P < 0.001$) and less time spent outdoors ($P = 0.002$), higher birth weight ($P = 0.06$), number of days with postnatal oxygen supply ($P = 0.01$), and breastfeeding as infant ($P = 0.008$). The IOP was associated with the ocular parameters of more myopic refractive error ($P < 0.001$), longer axial length ($P < 0.001$, Fig. 3), higher axial length–to–corneal curvature radius ratio ($P < 0.001$), shorter horizontal corneal diameter ($P < 0.001$), and longer corneal curvature radius ($P = 0.09$, Table 2).

In the multivariate linear regression analysis, we first dropped body weight due to the collinearity with BMI (VIF, 60), axial length–to–corneal curvature (VIF, 595), body height (VIF, 6.3), and refractive error (VIF, 3.6). We then dropped, through a combination of stepwise, forward and backward regression analysis, all those parameters that were no longer significantly associated with IOP in the multivariate analysis. In the final model, higher IOP of the right eye was significantly associated with the nonocular parameters of younger age ($P < 0.001$), female sex ($P < 0.001$), higher BMI ($P < 0.001$),

Table 2. Univariate Analysis of Associations Between IOP (Right Eyes), and Nonocular and Ocular Parameters in the Shandong Children Eye Study

Parameter	*P* Value	Standardized Correlation Coefficient	Steepness of the Regression Line	95% CI of the Steepness of Regression Line
Nonocular parameters				
Sex, boys/girls	<0.001	0.06	0.34	0.21, 0.48
Region of habitation, rural/urban	<0.001	0.32	1.62	1.56, 1.82
Body height, cm	<0.001	0.072	0.011	0.007, 0.015
Body weight, kg	<0.001	0.084	0.015	0.010, 0.019
BMI, kg/m^2	<0.001	0.089	0.067	0.048, 0.086
Paternal education	<0.001	0.098	0.23	0.16, 0.29
Maternal education	<0.001	0.10	0.24	0.17, 0.30
Paternal myopia	<0.001	0.08	0.55	0.37, 0.73
Maternal myopia	<0.001	0.09	0.58	0.40, 0.76
Time spent indoors reading/writing	<0.001	0.051	0.067	0.031, 0.102
Time spent outdoors, total	0.002	−0.08	−0.06	−0.09, −0.02
Birth weight, kg	0.06	0.03	0.02	−0.001, 0.045
Oxygen supply after birth, days	0.01	−0.04	−0.09	-0.16, −0.02
Breastfeeding as infant	0.008	0.04	0.13	0.03, 0.22
Ocular parameters				
Refractive error, spherical equivalent, diopters	<0.001	−0.09	−0.12	−0.15, −0.09
Axial length, mm	<0.001	0.10	0.20	0.15, 0.26
Horizontal corneal diameter, mm	<0.001	−0.05	−0.30	−0.45, −0.16
Corneal curvature radius, mm	0.09	0.02	0.20	−0.03, 0.43
Axial length to corneal curvature radius ratio	<0.001	0.05	0.33	0.15, 0.50
Statistically nonsignificant parameters				
Age, y	0.23			
Body length at birth, cm	0.86			
Time total spent indoors	0.87			
Cylindrical refractive error, diopters	0.80			

maternal myopia ($P < 0.001$), and more time spent indoors with reading/writing ($P = 0.002$), and with the ocular parameters of longer axial length ($P < 0.001$) and smaller corneal horizontal diameter ($P < 0.001$, Table 3). If the IOP of the left eyes was included into the multivariate analysis, similar results were obtained: Higher IOP of the right eye was significantly associated with the nonocular parameters of female sex ($P < 0.001$), higher BMI ($P < 0.001$), younger age ($P < 0.001$), maternal myopia ($P < 0.001$), and more time spent indoors with reading/writing ($P = 0.007$), and with the ocular parameters of longer axial length ($P < 0.001$), while IOP was no longer significantly associated with corneal horizontal diameter ($P = 0.10$, Table 4).

Discussion

In our school-based cross-sectional study on 5919 children, IOP increased from the age of 4 to 10 years, and decreased toward an age of 11 years, from which it remained mostly unchanged till the age of 16 years, after which it declined toward the age group of 18 years (Fig. 1). In multivariate regression analysis, higher IOP was associated significantly with female sex (Fig. 1), higher BMI, younger age, maternal myopia, more time spent indoors with reading/writing, longer axial length, and smaller corneal horizontal diameter. These results agreed with findings of previous studies. An increase in IOP with increasing age for 405 children up to an age of 12 years was reported by Sihota et al.[19] In contrast to our study, Sihota et al.[19] reported on an association between higher IOP, and hyperopic refractive error and shorter axial length, while in our study IOP increased with longer axial length. An increase in IOP with older age for children aged less than 10 years also was reported by other studies.[9] In the study by Yildrim et al.[15] on 602 healthy schoolchildren with a mean age of 10.1 ± 1.6 years, mean IOP was 16.7 ± 2 mm Hg using a noncontact tonometer. This value was similar to the readings obtained in our study. As in our study, the corneal curvature radius had no significant relationship with the IOP readings in the study by Yildirim et

Table 3. Multivariate Linear Regression Analysis of Associations Between IOP (Right Eye), and Nonocular and Ocular Parameters in the Shandong Children Eye Study

Parameter	*P* Value	Standardized Regression Coefficient β	Regression Coefficient β	95% CI of β	Variance Inflation Factor
Age, y	<0.001	−0.15	−0.13	−0.17, −0.10	1.76
Boys/girls	<0.001	0.06	0.34	0.18, 0.50	1.10
BMI, kg/m^2	<0.001	0.09	0.07	0.04, 0.09	1.26
Maternal myopia	<0.001	0.05	0.34	0.15, 0.53	1.08
Indoors time spent with reading/writing	0.002	0.05	0.07	0.03. 0.11	1.23
Axial length, mm	<0.001	0.14	0.29	0.21, 0.37	1.59
Horizontal corneal diameter, mm	<0.001	−0.06	−0.31	−0.46, −0.15	1.06

TABLE 4. Multivariate Linear Regression Analysis of Associations Between IOP (Left Eye), and Nonocular and Ocular Parameters in the Shandong Children Eye Study

Parameter	*P* Value	Standardized Regression Coefficient *β*	Regression Coefficient *β*	95% CI of *β*	Variance Inflation Factor
Age, y	<0.001	−0.10	−0.09	−0.12, −0.05	1.60
Boys/girls	<0.001	0.06	0.30	0.14, 0.46	1.06
BMI, kg/m^2	<0.001	0.08	0.06	0.04, 0.08	1.24
Maternal myopia	<0.001	0.06	0.39	0.20, 0.58	1.05
Indoors time spent with reading/writing	0.007	0.04	0.06	0.02. 0.10	1.22
Axial length, mm	<0.001	0.07	0.11	0.06, 0.17	1.28
Horizontal corneal diameter, mm	0.10	−0.02	−0.08	−0.17, 0.02	1.02

al.[15] In an investigation by Sahin et al.[16] on 165 healthy school children with an age ranging between 7 to 12 years, mean IOP was 16.8 ± 3.1 mm Hg.[16] As in our study, the investigators did not detect an association between the IOP readings and corneal curvature readings.

The association between higher IOP and longer axial length or more myopic refractive error also has been found in studies on adults, such as in the Japanese Beaver Dam Study, the Tajimi Study, and the Central India Eye and Medical Study.[7,20,21] It is not in agreement with findings from the Los Angeles Latino Eye Study.[22] The relationship between higher IOP with longer axial length or more marked myopic refractive error raises the question whether a higher IOP in childhood may lead to an axial elongation of the globe.[23] In a study by Edwards and Brown,[24] IOP was measured at yearly intervals in 106 children from age 7 to 9 years. During the follow-up, 13 children became myopic, with no significant difference in baseline IOP between the incident myopic children and the remaining children. Interestingly, the IOP during the follow-up in the myopic incident group was higher after onset of myopia than it was at baseline, so that the investigators concluded that a high IOP followed the onset of myopia and did not cause the onset of myopia. A similar result was reported by Goss and Caffey,[25] who did not find a difference in baseline IOP between incident myopic children and nonmyopic children.

The association between higher IOP and higher BMI in children also has been reported for adults in whom higher BMI was associated with higher IOP and higher cerebrospinal fluid pressure, which by itself was associated with higher IOP.[26,27] In the studies on adult subjects, higher IOP additionally was associated with higher arterial blood pressure, which was not measured in our study.[3,6] The relationship between higher IOP and female sex as found in our study generally has not been reported in previous pediatric eye studies.

The relationship between higher IOP and maternal myopia, and with more time spent indoors with reading/writing may be related to the association between higher IOP and more myopic refractive error or longer axial length, since presence and development of axial myopia in children was associated with more time spent indoors and with maternal myopia.[17] Interestingly, IOP was not related with birth weight or birth height in the multivariate analysis. It is in contrast to an association between smaller birth size and narrower retinal arterioles in early adolescence as reported by Gopinath et al.[28]

Potential limitations of our study should be discussed. First, corneal pachymetry to measure central corneal thickness was not performed so that the IOP readings could not be corrected for their dependence on central corneal thickness. In a similar manner, blood pressure was not determined, so that the association between IOP and blood pressure as reported in adults could not be assessed in our pediatric study population.[3,6] Second, IOP was measured by noncontact tonometry rather than by Goldmann applanation tonometry, potentially leading to higher readings of IOP in our study than as if the IOP had been measured by applanation tonometry.[29] It has remained unclear how results might have differed had Goldmann tonometry been used. Third, relatively small differences in IOP were associated with various independent variables, with some of these differences being so small that the practical impact of the association was rather limited. This finding held true for all associations for which the standardized correlation coefficient was lower than 0.10, such as the associations between IOP and sex, maternal myopia, or time spent indoors with reading or writing (Tables 3, 4). Therefore, future studies may address whether the statistical significance of these associations also had an equivalent clinical significance. Fourth, the data of Shandong province may be not representative for the whole of China in view of the heterogeneity of the country.

In conclusion, in children aged 4 to 18 years, IOP showed an M-shaped association with age. Higher IOP was associated with female sex, higher BMI, younger age, maternal myopia, more time spent indoors with reading/writing, longer axial length, and smaller corneal horizontal diameter.

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