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Prediction for Cycloplegic Refractive Error in Chinese School Students: Model Development and Validation

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Purpose: To predict cycloplegic refractive error using measurements obtained under noncycloplegic conditions.

Method: Refractive error was measured in 5- to 18-year-old Chinese students using a NIDEK autorefractor before and after administration of 0.5% tropicamide. Spherical equivalent (SER) in diopters (D) was calculated as sphere plus half cylinder. A multivariable prediction model for cycloplegic SER was developed using data from students in Jinyun ($n = 1938$) and was validated using data from students in Hangzhou ($n = 1498$). The performance of the prediction model was evaluated using R^2, mean difference between predicted and measured cycloplegic SER, and sensitivity and specificity for predicting myopia (cycloplegic SER ≤ -0.5 D).

Results: Among 3436 students (mean age, 9.7 years; 51% female), the mean (SD) noncycloplegic and cycloplegic SER values were −1.12 (1.97) D and −0.20 (2.19) D, respectively. The prediction model that included demographics, noncycloplegic SER, axial length/corneal curvature radius ratio, uncorrected visual acuity (UCVA), and intraocular pressure predicted cycloplegic SER with R^2 of 0.93 in the development dataset and 0.92 in the validation dataset. The mean (SD) differences between predicted and measured cycloplegic SER were 0.0 (0.55) D in the development dataset and 0.06 (0.64) D in the validation dataset. In both the development and validation datasets, the combination of predicted SER and UCVA yielded high sensitivity (91.4% and 91.9%, respectively) and specificity (95.0% and 90.1%, respectively) for detecting myopia.

Conclusions: Cycloplegic refractive error can be predicted using measurements obtained under noncycloplegic conditions. The prediction model could potentially be used to correct the myopia prevalence in epidemiological studies in which administering cycloplegic agent on all participants is not feasible.

Translational Relevance: The prediction model may provide a tool for correcting the overestimation of myopia from noncycloplegic refractive error in future epidemiological studies in which administering cycloplegic agent on all participants is not feasible.

translational vision science & technology

Introduction

The prevalence of myopia is growing throughout the world, particularly among the younger generations of East and Southeast Asia.[1] The number of individuals with myopia was estimated as 1.4 billion in 2020, and it is predicted to increase to 4.8 billion by 2050.[1] The risk of myopia increases dramatically after approximately 6 years of age, likely linked with the start of intense primary school education.[2] Myopia rate increases with age until the age of 18 years, with myopia rates as high as 80% for the urban Han population in China.[3] Because myopia is associated with many ophthalmic diseases, including retinal detachment, glaucoma, and maculopathy,[4] epidemiology studies for monitoring myopia prevalence and determining the protective or risk factors of myopia for timely intervention are crucial from the public health perspective.

Measuring refractive error under relaxed ocular accommodation is the gold standard for the detection of myopia.[5] However, because of the wide range of accommodation in children, cycloplegic agents, such as atropine, cyclopentolate, or tropicamide, must be administered to paralyze the accommodative system.[6,7] When cycloplegic agents are withheld, the prevalence and severity of myopia are overestimated.[7,8] Cycloplegic agents can have adverse effects, including blurred vision, photophobia, and glare.[9] As a result, it sometimes can be challenging to administer cycloplegic eyedrops to children in a large-scale epidemiology study, particularly when the study is limited in resources for cycloplegic refraction. Although previous studies[10–12] have demonstrated that, with great effort and resources, it is possible to take cycloplegic measures in a large pediatric refractive error study, noncycloplegic refractive error is still used for determining the presence or severity of myopia in some population-based epidemiological studies of pediatric myopia.[13–15] Not only does the use of noncycloplegic refractive error in these studies overestimate myopia prevalence and severity, but also the misclassification of myopia status due to using noncycloplegic refractive error could also bias the evaluation of associations between protective/risk factors and myopia.

Attempts to improve the estimate of myopia prevalence and the determination of their associated risk factors in children without the application of cycloplegic eyedrops have included the development of prediction models for cycloplegic refractive error using the measures obtained under noncycloplegic conditions.[16–22] Previous studies have explored the prediction of cycloplegic refractive error using various predictors, including demographics, ocular biometric measures,[20] noncycloplegic refractive error, and uncorrected visual acuity.[22] These predictive models have yielded mixed results, with R^2 ranging from 0.26 to 0.92, likely due to the variations in the selected predictors, children's ages, and their refractive error.[16–22]

In this cross-sectional, school-based study of myopia in Chinese school students 5 to 18 years old from two cities in China, we aimed to develop and validate a multivariable prediction model for predicting cycloplegic refractive error using more easily obtainable measures under noncycloplegic conditions, including demographics, noncycloplegic refractive error, uncorrected visual acuity (UCVA) and ocular biometric measures (e.g., axial length, corneal curvature radius, anterior chamber depth). We hypothesized that the developed prediction model may be able to accurately predict the cycloplegic refractive error, thus potentially providing a tool for correcting the overestimation of myopia due to the use of noncycloplegic refractive error in children. We hope the developed prediction model can potentially be used in future epidemiology studies of myopia prevalence and risk factors in which administering cycloplegic agents on children is not feasible.

Methods

This is a cross-sectional, school-based study of myopia conducted in two cities, Jinyun and Hangzhou, in central Zhejiang Province, People's Republic of China. Hanzhou is a large capital city of Zhejiang with a population of approximately 12 million, and Jinyun is a smaller, county-level city with a population of 0.5 million. From October 2020 to January 2021, school students between 5 and 18 years of age were enrolled in the study from Jinyun ($n = 1938$) and Hangzhou ($n = 1498$). In both cities, three kindergartens, one elementary school (grades 1–6), one middle school (grade 7–9), and one high school (grades 10–12) were randomly selected. From the selected schools, a random sample of classes from each grade was selected, and all students from the selected classes were invited to participate in the study. Human subject research approval was obtained from Zhejiang University and the local administration of the Education and School Board. Written informed consent was obtained from legal parents or guardians. The study followed the tenets of the Declaration of Helsinki.

Demographic information, including age, gender, and grade, was obtained from the roster of the selected classes. All students underwent comprehensive eye examination by trained eyecare

professionals (optometrists or ophthalmologists) following the standard study protocol, which included testing for distance visual acuity using retro-illuminated logMAR charts with tumbling-E optotypes and the assessment of ocular biometrics under noncycloplegic conditions (e.g., axial length, corneal curvature index, central corneal thickness, anterior chamber depth) using a NIDEK A-scan (NIDEK, Tokyo, Japan). A table-mounted NIDEK ARK-510A autorefractor was used to take measurements of refractive error from each eye before and after cycloplegia using 0.5% tropicamide eyedrops by the same eyecare professional. For cycloplegic autorefraction, one drop of 0.5% tropicamide was instilled in each eye. A second, third, and fourth drop of 0.5% tropicamide was instilled in each eye every 5 minutes. Thirty minutes after the fourth drop of 0.5% tropicamide was instilled, cycloplegic refractive error was taken from each eye.

For both noncycloplegic and cycloplegic refractive error, three readings of refractive error (sphere, cylinder, and axis) were taken from each eye. If the difference between any of two readings from an eye was greater than 0.5 diopters (D), refractive error for that eye was retaken. For every eye, the average of three readings of refractive error was entered into the database for statistical analysis. Students were asked whether they wear glasses, contact lens, or orthokeratology contact lens. For the students not wearing glasses, the UCVA was measured for each eye. For those wearing glasses, both UCVA and best-corrected visual acuity (BCVA) were measured.

For quality assurance, 5% of students were randomly selected to repeat the assessment of refraction, visual acuity, and ocular biometrics. If the mean difference between the initial testing and retesting was above the allowed threshold (0.5 D in refractive error, 0.1 logMAR in visual acuity, or 0.1 mm in axial length), then corrective measures (e.g., additional training) were taken to improve the quality of measurements. The data were double entered into Excel sheets (Microsoft Corporation, Redmond, WA), and any discrepancies were resolved by checking the source data.

Statistical Analyses

Cycloplegic and noncycloplegic spherical equivalent refraction (SER) values were calculated as sphere plus half of the cylinder for each eye. Myopia was defined as cycloplegic SER −0.5 D or worse, and high myopia was defined as cycloplegic SER −6.0 D or worse. We used the data for the students from Jinyun ($n = 1938$) for model development (i.e., development dataset), and we used the data for the students from Hangzhou ($n = 1498$) for validation (i.e., validation dataset). To develop a multivariable prediction model for the cycloplegic refractive error, we first performed univariable regression analysis to determine the factors associated with cycloplegic refractive error. Factors analyzed included age, gender, glasses-wearing status, noncycloplegic SER, UCVA, BCVA, axial length (AL), corneal curvature radius (CR), AL/CR ratio, anterior chamber length, central corneal thickness, and intraocular pressure (IOP). All significant predictors ($P < 0.05$) from univariable analyses were included into the initial multivariable regression model. Two-way interaction terms were also included in the initial multivariable model. The multivariable model went through stepwise selection of predictors, and the final multivariable regression model retained only the predictors and interaction terms with $P < 0.05$ in the final prediction model. In these regression models, the cycloplegic SER in each eye was modeled as the outcome variable, and inter-eye correlation was accounted for using generalized estimating equations.

We evaluated the performance of the prediction model using the mean (SD) of differences between predicted and measured cycloplegic SER, R^2 for correlation between predicted and observed cycloplegic SER, and agreement in the predicted and observed rate of myopia. In addition, we evaluated the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of the model with and without consideration of UVCA. Predicted myopia positive was defined as predicted SER −0.5 D or worse and/or UCVA 20/40 or worse in either eye. The performance of our predictive model was assessed independently in the development dataset and the validation dataset, as well as in a combined dataset containing all study subjects. All statistical analyses were performed in SAS 9.4 (SAS Institute, Cary, NC), and two-sided $P < 0.05$ was considered to be statistically significant.

Results

The study included 3436 school-aged students, with1938 students coming from Jinyun for model development and 1498 students from Hangzhou for model validation. Student characteristics in the development and validation datasets are shown in Table 1. The two groups were similar in age, gender, and most of the biometric measures. Among all 3436 children, the age ranged from 5 to 18 years, with a mean (SD) of 9.7 (3.6) years. Females (1740) accounted for 50.6% of the study population. Elementary school students

Table 1. Characteristics of School Students From Two Cities ($N = 3436$)

Characteristics	Jinyun ($n = 1938$)	Hangzhou ($n = 1498$)	All ($N = 3436$)
Age (y), *n* (%)			
5	35 (1.8)	23 (1.5)	58 (1.7)
6	429 (22.1)	227 (15.2)	656 (19.1)
7	317 (16.4)	269 (18.0)	586 (17.1)
8	210 (10.8)	218 (14.6)	428 (12.5)
9	148 (7.6)	151 (10.1)	299 (8.7)
10	132 (6.8)	70 (4.7)	202 (5.9)
11	148 (7.6)	91 (6.1)	239 (7.0)
12	109 (5.6)	82 (5.5)	191 (5.6)
13	82 (4.2)	83 (5.5)	165 (4.8)
14	69 (3.6)	57 (3.8)	126 (3.7)
15	65 (3.4)	56 (3.7)	121 (3.5)
16	72 (3.7)	59 (3.9)	131 (3.8)
17	61 (3.2)	58 (3.9)	119 (3.5)
18	61 (3.2)	54 (3.6)	115 (3.4)
Mean (SD)	9.6 (3.6)	9.9 (3.6)	9.7 (3.6)
Female gender, *n* (%)	999 (51.2)	741 (49.5)	1740 (50.6)
Grade in school, *n* (%)			
Kindergarten	414 (21.4)	199 (13.3)	613 (17.8)
Elementary school	1105 (57.0)	920 (61.4)	2025 (58.9)
Middle school	223 (11.5)	201 (13.4)	424 (12.3)
High school	196 (10.1)	178 (11.9)	374 (10.9)
Wearing glasses (yes), *n* (%)	439 (22.7)	309 (20.6)	748 (21.8)
Myopia in either eye (yes), *n* (%)	652 (33.6)	617 (41.2)	1269 (36.9)
High myopia in either eye (yes), *n* (%)	40 (2.1)	51 (3.4)	91 (2.7)
Cycloplegic SER in each eye (D), *n* (%)			
≤ -6.0	67 (1.7)	77 (2.6)	144 (2.1)
> -6.0 to ≤ -3.0	371 (9.6)	326 (10.9)	697 (10.1)
> -3.0 to ≤ -0.5	711 (18.3)	698 (23.3)	1409 (20.5)
> -0.5 to ≤ 0.5	739 (19.1)	568 (19.0)	1307 (19.0)
>0.5 to ≤ 3.0	1930 (49.8)	1282(42.8)	3212 (46.7)
>3.0	58 (1.5)	45 (1.5)	103 (1.5)
Mean (SD)	−0.07 (2.11)	−0.37 (2.27)	−0.20 (2.19)
Noncycloplegic SER in each eye (D), *n* (%)			
≤ -6.0	97 (2.5)	99 (3.3)	196 (2.9)
> -6.0 to ≤ -3.0	499 (12.9)	414 (13.8)	913 (13.3)
> -3.0 to ≤ -0.5	1386 (35.8)	1100 (36.7)	2486 (36.2)
> -0.5 to ≤ 0.5	1480 (38.2)	1024 (34.2)	2504 (36.4)
>0.5 to ≤ 3.0	390 (10.1)	348 (11.6)	738 (10.7)
>3.0	24 (0.6)	11 (0.4)	35 (0.5)
Mean (SD)	−1.1 (1.92)	−1.2 (2.06)	−1.1 (1.98)
Uncorrected visual acuity, *n* (%)			
20/200 or worse	206 (5.3)	246 (8.2)	452 (6.6)
>20/200 to 20/100	272 (7.0)	265 (8.9)	537 (7.8)
>20/100 to 20/50	356 (9.2)	369 (12.3)	725 (10.6)
20/40	148 (3.8)	158 (5.3)	306 (4.5)
20/33	214 (5.5)	261 (8.7)	475 (6.9)
20/25	367 (9.5)	603 (20.2)	970 (14.1)
20/20 or better	2313 (59.8)	1088 (36.4)	3401 (49.5)
Axial length (mm), mean (SD)	23.5 (1.3)	23.6 (1.3)	23.5 (1.3)
Corneal curvature radius (mm), mean (SD)	7.83 (0.25)	7.84 (0.26)	7.84 (0.26)
AL/CR ratio, mean (SD)	3.00 (0.14)	3.01 (0.16)	3.00 (0.15)
Anterior chamber depth (mm), mean (SD)	3.61 (0.3)	3.56 (0.3)	3.59 (0.3)
Central corneal thickness (μm), mean (SD)	555 (31)	549 (31)	553 (31)
IOP (mmHg), mean (SD)	17.2 (2.8)	17.6 (2.9)	17.4 (2.9)

(2025) accounted for 59% of the study population; 613 students (17.8%) were from kindergarten; 424 students (12.3%) were from middle schools; and 374 students (10.9%) were from high schools. The mean (SD) cycloplegic SER was −0.20 (2.19) D, with a range of −14.1 to 8.4 D. Of the 3436 students, 1269 had myopia in one or two eyes (36.9%), 91 had high myopia (2.7%), and 748 wore glasses (21.8%). The mean (SD) noncycloplegic SER was −1.12 (1.98) D; more than half of the eyes (52.9%) had noncycloplegic SER of −0.5 D or

Table 2. Multivariable Regression Model for Predicting Cycloplegic Refractive Error Using Demographics, Noncycloplegic Refractive Error, UCVA, and Ocular Biometric Measures in the Development Data From Jinyun ($N = 1938$ children)

Predictors	Regression Coefficient (SE)	*P*
Intercept	22.4 (2.48)	<0.0001
Age (y)	−0.54 (0.23)	0.02
Female	−0.07 (0.02)	0.003
Noncycloplegic SER	1.58 (0.31)	0.002
UCVA	1.44 (0.24)	<0.0001
AL/CR ratio	−9.54 (0.60)	<0.0001
Wearing glass	−0.22 (0.07)	0.002
IOP	−0.02 (0.004)	<0.0001
Interaction terms		
Age × noncycloplegic SER	0.05 (0.006)	<0.0001
Age × UCVA	−0.08 (0.02)	0.0002
Age × AL/CR ratio	0.32 (0.06)	<0.0001
Noncycloplegic SER × UCVA	−0.13 (0.03)	0.002
Noncycloplegic SER × AL/CR ratio	−0.23 (0.07)	0.01
Noncycloplegic SER × wearing glasses	−0.26 (0.03)	<0.0001

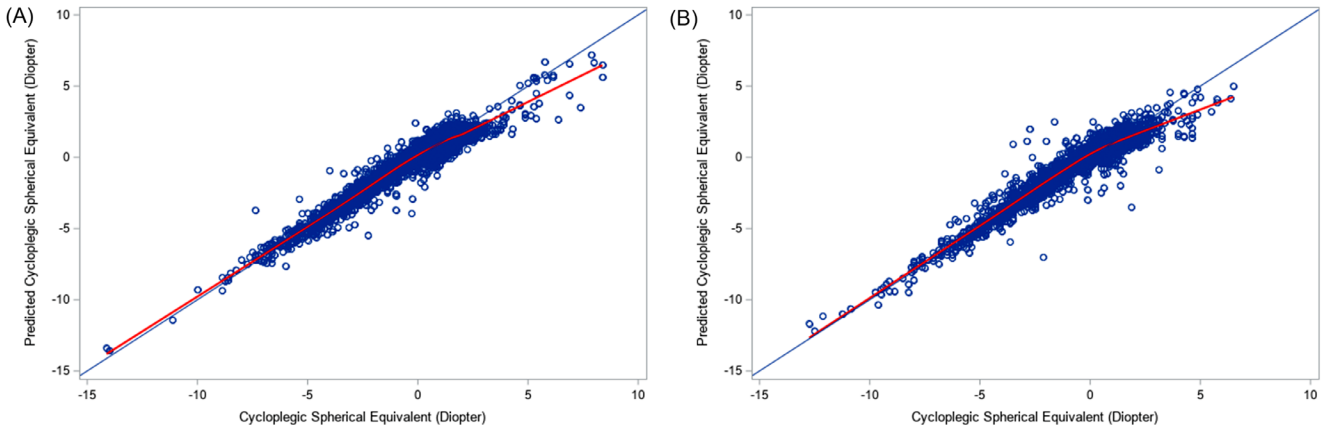

Figure 1. (**A**) Scatterplot with the locally estimated scatterplot smoothing (LOESS) line for the predicted versus observed cycloplegic spherical equivalent in the development dataset ($n = 3876$ eyes from 1938 children). The *diagonal line* represents the line of equality. (**B**) The scatterplot with LOESS line for the predicted versus observed cycloplegic spherical equivalent in the validation dataset ($n = 2996$ eyes from 1498 children). The *diagonal line* represents the line of equality.

worse. Visual acuity measurements showed that 6.6% of eyes had UCVA of 20/200 or worse, and half of the eyes had UCVA 20/20 or better (49.5%). The mean (SD) of biometric measures was 23.5 (1.3) mm for axial length, 7.84 (0.26) mm for corneal curvature radius, 3.00 (0.15) for AL/CR ratio, 553 (31) µm for central corneal thickness, 3.59 (0.32) mm for anterior chamber depth, and 17.4 (2.85) mmHg for intraocular pressure. The validation dataset had a higher rate of myopia (41.2% vs. 33.6%; $P < 0.0001$) and a lower percent of eyes with UCVA of 20/20 or better (36.4% vs. 59.8%; $P < 0.0001$) compared with the development dataset.

Using the development dataset, a multivariable prediction model for cycloplegic SER was developed as presented in Table 2. The prediction model included age ($P = 0.02$), gender ($P = 0.003$), glasses-wearing status ($P = 0.002$), noncycloplegic SER ($P = 0.002$), AL/CR ratio ($P < 0.0001$), UCVA ($P < 0.0001$), and IOP ($P < 0.0001$). The prediction model also included significant two-way interaction terms, including

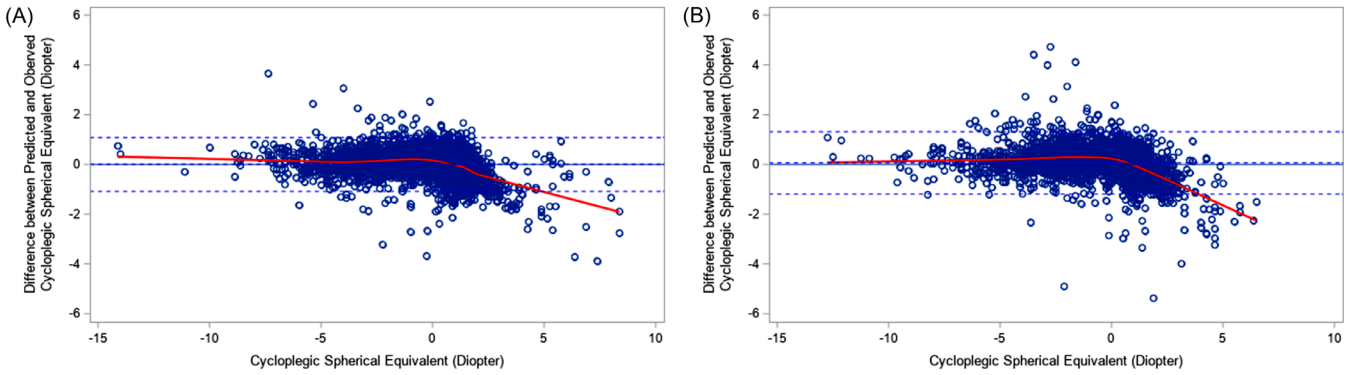

Figure 2. (**A**) Scatterplot for the difference between the predicted and observed cycloplegic spherical versus true cycloplegic spherical equivalents in the development dataset ($n = 3876$ eyes from 1938 children). The *dashed lines* represent the mean difference and upper and lower limits for the 95% limits of agreement. The *red line* represents the LOESS line. (**B**) Scatterplot for the difference between the predicted and observed cycloplegic spherical versus true cycloplegic spherical equivalents in the validation dataset ($n = 2996$ eyes from 1498 children). The *dashed lines* represent the mean difference and upper and lower limits for the 95% limits of agreement. The *red line* represents the LOESS line.

Table 3. Differences Between Noncycloplegic and Cycloplegic Spherical Equivalent and Differences Between Predicted and Measured Cycloplegic Spherical Equivalents in the Development Dataset and the Validation Dataset by Age Group and by Cycloplegic Refractive Error Group

	Jinyun Development Dataset ($N = 1938$)		Hangzhou Validation Dataset ($N = 1498$)	
	Difference Between Noncycloplegic and Cycloplegic SER, Mean (SD)	Difference Between Predicted and Observed Cycloplegic SER, Mean (SD)	Difference Between Noncycloplegic and Cycloplegic SER, Mean (SD)	Difference Between Predicted and Observed Cycloplegic SER, Mean (SD)
Overall	−1.00 (0.99)	0.00 (0.55)	−0.82 (0.88)	0.06 (0.64)
By age (y)				
5	−2.12 (1.60)	−0.09 (0.68)	−1.25 (1.13)	0.05 (0.64)
6	−1.43 (1.02)	−0.01 (0.56)	−1.14 (1.02)	0.02 (0.73)
7	−1.24 (1.11)	0.01 (0.55)	−1.03 (0.90)	0.05 (0.62)
8	−1.11 (1.01)	−0.05 (0.52)	−0.88 (0.95)	0.05 (0.59)
9	−0.86 (0.82)	0.07 (0.49)	−0.78 (0.76)	0.08 (0.65)
10	−0.65 (0.67)	0.02 (0.59)	−0.72 (0.75)	0.08 (0.71)
11	−0.74 (0.76)	−0.03 (0.54)	−0.63 (0.80)	0.14 (0.65)
12	−0.52 (0.66)	0.08 (0.59)	−0.50 (0.79)	0.12 (0.68)
13	−0.55 (0.59)	0.01 (0.49)	−0.65 (0.62)	−0.10 (0.52)
14	−0.71 (0.77)	0.01 (0.53)	−0.53 (0.61)	0.13 (0.64)
15	−0.52 (0.66)	0.07 (0.63)	−0.41 (0.74)	0.10 (0.70)
16	−0.49 (0.66)	0.13 (0.53)	−0.48 (0.63)	0.04 (0.48)
17	−0.65 (0.62)	−0.12 (0.52)	−0.41 (0.57)	0.22 (0.60)
18	−0.74 (0.80)	−0.16 (0.63)	−0.70 (0.84)	−0.07 (0.68)
By cycloplegic SER				
≤ −6.0	−0.41 (0.94)	0.25 (0.62)	−0.34 (0.42)	0.18 (0.54)
> −6.0 to ≤ −3.0	−0.37 (0.44)	0.05 (0.51)	−0.31 (0.42)	0.19 (0.63)
> −3.0 to ≤ −0.5	−0.49 (0.57)	0.20 (0.52)	−0.40 (0.62)	0.32 (0.64)
> −0.5 to ≤0.5	−0.79 (0.89)	0.14 (0.52)	−0.63 (0.72)	0.24 (0.51)
>0.5 to ≤3.0	−1.37 (0.99)	−0.11 (0.49)	−1.23 (0.91)	−0.15 (0.55)
>3.0	−2.32 (1.74)	−1.20 (0.99)	−2.24 (1.36)	−1.54 (1.07)

age × noncycloplegic SER ($P < 0.0001$), age × UCVA ($P = 0.0002$), age × AL/CR ratio ($P < 0.0001$), noncycloplegic SER × UCVA ($P < 0.0001$), noncycloplegic SER × AL/CR ratio ($P = 0.01$), and noncycloplegic SER × glasses-wearing status ($P < 0.0001$). This prediction model predicted cycloplegic SER with R^2 of 0.93 in the development dataset (Fig. 1A) and 0.92 in the validation dataset (Fig. 1B), values that are much higher than the R^2 obtained from the prediction model that used only the

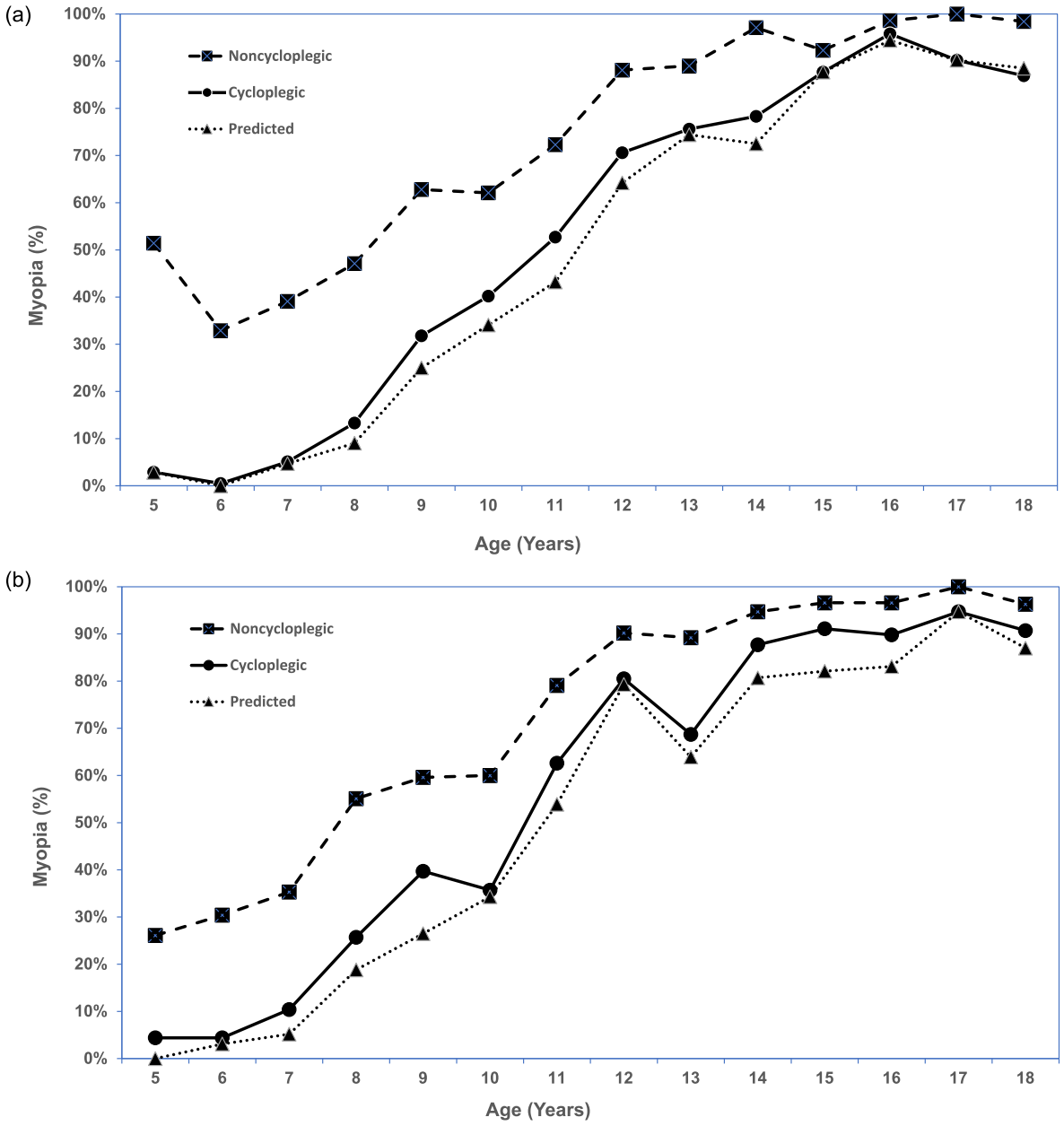

Figure 3. (**A**) Myopia rate by age based on the noncycloplegic, cycloplegic, and predicted cycloplegic spherical equivalents in the development dataset ($n = 1938$ children). (**B**) Myopia rate by age based on the noncycloplegic, cycloplegic, and predicted cycloplegic spherical equivalents in the validation dataset ($n = 1498$ children).

noncycloplegic refractive error as the predictor in the development dataset ($R^2 = 0.78$) and the validation dataset ($R^2 = 0.85$).

The scatterplot for the differences between predicted and measured cycloplegic SER (calculated as predicted – measured) is shown in Figure 2A for the development dataset and Figure 2B for the validation dataset. Their differences are all around 0 when cycloplegic refractive error measures are myopic, and most of differences are negative when cycloplegic refractive error measures are hyperopic. The overall mean differences (SD) between predicted and measured cycloplegic SER were 0.00 (0.55) D in the development dataset and 0.06 (0.64) D in the validation dataset, values that are much smaller than the mean (SD) difference of −1.00 (0.99) in the development dataset and −0.82 (0.88) in the validation dataset between measured noncycloplegic SER and cycloplegic SER (Table 3). When analyses of these differences were stratified by student age, the mean difference between predicted and measured

Table 4. Sensitivity, Specificity, and Positive and Negative Predictive Values Using Various Methods to Define Myopia Positive Versus Myopia Defined Using Cycloplegic Refractive Error

Measures Used to Define Myopia Positive	Myopia Positive Definition	Statistics	Development Dataset ($n = 1938$)	Validation Dataset ($n = 1498$)
Noncycloplegic SER	SER ≤ -0.5D in either eye	Sensitivity (95% CI)	100 (99.4–100)	99.2 (98.2–99.7)
		Specificity (95% CI)	61.1 (58.4–63.8)	65.5 (62.2–68.6)
		PPV (95% CI)	56.6 (53.7–59.5)	66.8 (63.7–69.9)
		NPV (95% CI)	100 (99.5–100)	99.1 (98.0–99.7)
Predicted SER	SER ≤ -0.5D in either eye	Sensitivity (95% CI)	87.3 (84.5–89.7)	83.6 (80.5–86.5)
		Specificity (95% CI)	97.9 (97.2–98.7)	97.8 (96.9–98.8)
		PPV (95% CI)	95.4 (93.5–97.0)	96.5 (94.5–97.8)
		NPV (95% CI)	93.8 (92.4–95.0)	89.5 (87.6–91.4)
Predicted SER + UCVA	SER ≤ -0.5D or UCVA 20/40 or worse in either eye	Sensitivity (95% CI)	91.4 (89.3–93.6)	91.9 (89.5–93.9)
		Specificity (95% CI)	95.0 (93.6–96.1)	90.1 (88.0–92.0)
		PPV (95% CI)	90.2 (87.6–92.3)	86.7 (83.8–89.2)
		NPV (95% CI)	95.6 (94.3–96.7)	94.1 (92.3–95.6)

cycloplegic SER for each age group was within 0.17 D in both the development dataset and validation dataset (Table 3).

When differences were stratified by level of measured cycloplegic SER, the mean difference between predicted and measured cycloplegic SER for each cycloplegic SER group was within 0.25 D in both the development dataset and the validation dataset, except when the cycloplegic SER was 3.0 D or greater, in which case the mean difference between the predicted and measured cycloplegic SER was larger (−1.20 D in the development dataset and −1.30 D in the validation dataset).

We further evaluated the performance of the prediction model by calculating the myopia rate using the predicted cycloplegic SER and measured cycloplegic SER using the same cutpoint of SER (−0.5 D). In the development dataset, the overall myopia rate was 30.8% (95% confidence interval [CI], 28.7–32.9) based on the predicted cycloplegic SER, and 33.6% (95% CI, 31.4–35.8) using measured cycloplegic SER. Both are much lower than the myopia rate based on the noncycloplegic SER (59.4%; 95% CI, 57.2–61.6). In the validation dataset, the overall myopia rates were 35.7% (95% CI, 33.4–38.2) based on the predicted cycloplegic SER and 41.2% (95% CI, 38.7–43.7) based on the measured cycloplegic SER, which are much lower than the myopia rate of 61.2% (95% CI, 58.7–63.7) based on the noncycloplegic SER. Age-specific myopia rates using predicted cycloplegic SER, measured cycloplegic SER, and noncycloplegic SER are shown in Figure 3A for the development dataset and Figure 3B for the validation dataset. Overall, the age-specific myopia rates from the predicted and measured cycloplegic SER are very similar and increase with age, and they are much lower than the rate from noncycloplegic refractive error.

When myopic positive was defined as predicted cycloplegic SER of −0.5 D or less, the prediction model has sensitivity of 87.3% (95% CI, 84.5–89.7), specificity of 97.9% (95% CI, 97.2–98.7), PPV of 95.4% (95% CI, 93.5–97.0), and NPV of 93.8% (95% CI, 92.4–95.0) in the development dataset. Similar model performance was found in the validation dataset with sensitivity of 83.6% (95% CI, 80.5–86.5), specificity of 97.8% (95% CI, 96.9–98.8), PPV of 96.5% (95% CI, 94.5–97.8), and NPV of 89.5% (95% CI, 87.6–91.4).

We further improved the prediction of myopia by considering the combination of predicted cycloplegic SER and measured UCVA (Table 4). When myopia positive was defined as predicted cycloplegic SER $\leq$ −0.5 D or UCVA of 20/40 or worse in either eye, the combination yielded sensitivity of 91.4% (95% CI, 89.3–93.6), specificity of 95.0% (95% CI, 93.6–96.1), PPV of 90.2% (95% CI, 87.6–92.3), and NPV of 95.6% (95% CI, 94.3–96.7) in the development dataset. The validation dataset had sensitivity of 91.9% (95% CI, 89.5–93.9), specificity of 90.1% (95% CI, 88.0–92.0), PPV of 86.7% (95% CI, 83.8–89.2), and NPV of 94.1% (95% CI, 92.3–95.6).

Discussion

In this large school-based study, we developed and validated a prediction model for predicting cycloplegic refractive error based on the noncycloplegic refractive error from a NIDEK autorefractor, demographics, BCVA, and ocular biometric measures taken under noncycloplegic conditions. In both the development and validation datasets from school-age children enrolled from two cities, our model predicted cycloplegic refractive error moderately well, showing no clinically significant deviation from measured

cycloplegic SER (e.g., mean difference less than 0.25 D) when the cycloplegic refractive error was myopic. Applying the predicted cycloplegic refractive error for detecting myopia yielded good sensitivity (87% in the development dataset and 84% in the validation dataset) and excellent specificity (98% in both the development and validation datasets).The combination of predicted cycloplegic refractive error and UCVA further improved the detection of myopia, with sensitivity of approximately 92% in both the development and validation datasets, and specificity of 95% in the development dataset and 90% in the validation dataset. Our prediction model significantly improved the detection of myopia when comparing to the noncycloplegic refractive error, which has high sensitivity of 99.6% yet very low specificity of 62.9%. Our prediction model provided similar prevalence rates of myopia as using cycloplegic refractive error across all age groups in both the development dataset and validation dataset. Thus, our prediction model could potentially be used to correct the myopia prevalence in epidemiological studies in which administering cycloplegic agents on all participants is not feasible.

For predicting cycloplegic refractive error, we considered ocular biometric measures (axial length, corneal curvature radius, central corneal thickness, and anterior chamber depth) that can be reliably measured under noncycloplegic conditions. Although axial length and cycloplegic refractive error were highly correlated in previous studies[17,23] and in our study (Pearson correlation coefficient of 0.82), we did not use the axial length for prediction. Instead, we used the AL/CR ratio as a predictor, because many previous studies and our study have found that the AL/CR ratio is more strongly correlated with cycloplegic refractive error than the axial length.[17–19,21,23–25] Because currently there is no readily portable and affordable biometric device available for measuring axial length and corneal curvature radius, the use of our prediction model can be limited for national myopia surveys in which biometric measures from every participants may not be easily obtained. With further development of the technology, portable and affordable biometric devices may be available in the future for providing accurate biometric measurements, and our prediction model may be more widely used for predicting the cycloplegic refractive error using measurements obtained under noncycloplegic conditions.

Attempts to detect significant refractive errors in children without the application of cycloplegic eyedrops have included the development prediction models for cycloplegic refraction. Previous studies have explored the prediction of cycloplegic refractive error using ocular biometric measures obtained under noncycloplegic conditions,[20] noncycloplegic refractive error, and UCVA,[22] yielding mixed results. Magome et al.[20] developed and validated prediction models for cycloplegic spherical and cylinder refraction in 2- to 9-year-old Japanese children ($n = 1040$) using demographics (age and gender) and ocular biometric measures (axial length, anterior chamber depth, corneal refractive power, and corneal astigmatism). Their prediction models were found to be precise with mean differences of −0.12 D for sphere and −0.05 D for cylinder between predicted and measured cycloplegic refraction, and the correlations between predicted and measured refraction were 0.96 for sphere and 0.89 for cylinder. Our prediction model differs from their model in that our model was developed to predict the spherical equivalent, a measure commonly used to define the myopia, and that our model included noncycloplegic autorefraction measures, which can be easily obtained using an autorefractor. Similar to our study, Sankaridurg et al.[22] developed prediction models for cycloplegic refractive error based on 6017 Chinese children ages 4 to 15 years by using age, noncycloplegic refractive error, and UCVA. Their prediction model yielded R^2 of 0.91, with sensitivity of 89.3% and specificity of 97.6% for myopia, which is slightly worse than our model, likely because their prediction model did not include the ocular biometric measures that were included in our prediction model. The other previous prediction models for the cycloplegic refractive error used axial length, corneal curvature radius, or the AL/CR ratio and yielded correlations of 0.53 to 0.81 between predicted and measured cycloplegic refractive error in children 3 to 13 years of age.[16–19,21] In comparison to these previous studies, our prediction model used the most comprehensive predictors, including demographics, noncycloplegic refractive error, UCVA, and ocular biometric measures, all of which are obtainable under noncycloplegic conditions. All these factors contributed to the precise prediction of refractive error in our study. Because our prediction model was developed in a large sample and independently validated in another large sample of children with a wide range of ages (5 to 18 years old) and refractive error status (cycloplegic spherical equivalent −14.1 to 8.4 D), our model has the potential to be applicable to population-based myopia research when measuring cycloplegic refractive error in all children is not feasible.

In young children, precise measurement of refractive error requires the use of cycloplegia to control for their wide range of accommodation. However, use of cycloplegia in children sometimes can be challenging in large studies because (1) development of the cycloplegic effect requires at least 30 minutes or

longer, and the associated photophobia can persist for several hours, resulting in disturbance to daily life during accommodation paralysis; (2) children receiving cycloplegic eyedrops may experience ocular irritation, which may result in a lack of cooperation from the children or their parents; and (3) cycloplegic agents are reported to be associated with the risk for the development of mental disorders or toxicity due to central nervous system or cardiovascular disease.[26–28] Although previous large-scale studies (e.g., Refractive Error Study in Children,[12] Sydney Myopia Study,[10] Singapore Cohort Study of the Risk Factors[11]) have demonstrated some success in obtaining cycloplegic refractive error measures in children, some large population-based epidemiological studies may not have sufficient resources to obtain the cycloplegic refractive error measures in all children. Our prediction model can potentially be applied to correct the well-known overestimation of myopia prevalence and severity due to noncycloplegic refractive error measurements.

Although noncycloplegic refractive error measures can be used operationally for myopia screening and surveillance, the noncycloplegic refractive error overestimates the prevalence and severity of myopia in children as a result of the wide range of accommodation and resulting myopic shift errors.[7,20,29,30] Previous studies differed in the use of cycloplegic agents, autorefractors for measuring refractive error, age ranges of participants, and status of their refractive errors, but these studies consistently demonstrated substantial differences between cycloplegic and noncycloplegic refractive error measurements, with mean SER differences ranging from 0.60 to 1.23 D. Using our prediction model, the overestimation of myopic shift can be largely corrected, as our study found overall mean (SD) differences between the predicted and measured spherical equivalent of 0.0 (0.55) D in the development dataset and 0.06 (0.64) D in the validation dataset. Our prediction model allows for the reasonably accurate detection of myopia (sensitivity of 86% and specificity of 98% in the development and validation datasets combined) using the predicted cycloplegic spherical equivalent (≤ -0.5 D) as myopia positive. Combining the predicted cycloplegic spherical equivalent (≤ -0.5 D) with BCVA (20/40 or worse) further improved the detection of myopia (sensitivity of 92% and specificity of 93% in the development and validation datasets combined). Thus, our prediction model has the potential to be used for providing accurate estimates of myopia prevalence in children based on measures taken under noncycloplegic condition.

In this study, we developed and validated a prediction model using the measures that are available from noncycloplegic conditions. The predicted value of spherical equivalent from our model was close to the measured cycloplegic spherical equivalent, and the prevalence rate of myopia estimated from using the predicted cycloplegic refractive error was also similar to that estimated from the measured cycloplegic refractive error in both the large development dataset and validation dataset. Thus, the application of our prediction model may provide good assessment of refractive error in children while avoiding the possible side-effects of cycloplegic eyedrops. Our prediction model has potential for use in future population-based studies of myopia when administering cycloplegic agents on all participants is not feasible.

Some limitations of our study should be noted. First, this study used 0.5% tropicamide instead of the gold-standard cyclopentolate as the cycloplegic agent, because tropicamide has less toxicity and fewer side-effects than cyclopentolate.[31] Although a few previous studies found that tropicamide offered an adequate cycloplegic effect in myopic children,[31,32] other studies have suggested that full cycloplegic refraction from tropicamide might not be achieved in some children.[33–39] Several studies have compared the cycloplegic effects of cyclopentolate and tropicamide in children and adults and reported mean refractive error differences ranging from −0.08 D to 0.54 D.[33–38] Meta-analyses of these studies[33–38] indicated that the cycloplegic effect of cyclopentolate was stronger than that of tropicamide with an insignificant mean refractive error difference of 0.175 D; however, the cycloplegic effect difference was statistically significant in children with a mean refractive error of 0.215 D (95% CI, 0.082–0.348) or more from cyclopentolate than from tropicamide.[40] Thus, the cycloplegic refractive error from using tropicamide in our study can be underestimated, thus bias the assessment of our prediction model. The validity of our prediction model for correcting the noncycloplegic refractive error must be further assessed in future studies in which more rigorous cycloplegia is administered, and pupil dilation and light reflex are closely monitored to provide valid refractive error measures for comparison. Second, our study used a NIDEK autorefractor in Chinese children; thus, our findings may not be directly generalizable to different types of autorefractors or children of other races or ethnicities. Our prediction model may have to be calibrated and further validated before its use in settings different from those in our study. Finally, our prediction model did not perform well for predicting hyperopic refractive error, so our prediction model should not be used to predict such refractive errors.

In conclusion, we developed and validated a multivariable prediction model for predicting cycloplegic

refractive error using the available demographics, noncycloplegic refractive error, UCVA, and ocular biometric measures taken under noncycloplegic conditions. The prediction model has been demonstrated to provide reasonably accurate estimates of myopic refractive error and estimates of myopia prevalence rates while avoiding the possible side effects or patient refusal associated with the use of cycloplegic eyedrops. Although cycloplegic refractive error using cyclopentolate is the gold standard for determining the prevalence or incidence of myopia, and previous large epidemiological studies have demonstrated the success of taking cycloplegic measures in children, noncycloplegic refractive error is still sometimes used to determine the prevalence or incidence of myopia even though it is known to overestimate myopia rate and severity. Although our prediction model cannot completely replace the cycloplegic refractive error measures, our model could potentially be used to correct myopia prevalence in epidemiological studies in which it is not feasible to administer a cycloplegic agent in all participants.

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