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Environmental Risk Factors Can Reduce Axial Length Elongation and Myopia Incidence in 6- to 9-Year-Old Children

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Purpose: To identify risk factors for axial length (AL) elongation and incident school myopia.

Design: Population-based prospective birth-cohort study.

Participants: Four thousand seven hundred thirty-four children examined at 6 and 9 years of age from the Generation R Study in Rotterdam, The Netherlands.

Methods: Axial length and corneal radius (CR) were measured with an IOLMaster 500 and daily life activities and demographic characteristics were obtained by questionnaire. Three thousand three hundred sixty-two children (71%) were eligible for cycloplegic refractive error measurements. Linear regression models on AL elongation were used to create a risk score based on the regression coefficients resulting from environmental and ocular factors. The predictive value of the prediction score for myopia (≤ -0.5 diopter) was estimated using receiver operating characteristic curves. To test if regression coefficients differed for baseline AL-to-CR ratio, interaction terms were calculated with baseline AL-to-CR ratio and environmental factors.

Main Outcome Measures: Axial length elongation and incident myopia.

Results: From 6 to 9 years of age, average AL elongation was 0.21 ± 0.009 mm/year and myopia developed in 223 of 2136 children (10.4%), leading to a myopia prevalence at 9 years of age of 12.0%. Seven parameters were associated independently ($P < 0.05$) with faster AL elongation: parental myopia, 1 or more books read per week, time spent reading, no participation in sports, non-European ethnicity, less time spent outdoors, and baseline AL-to-CR ratio. The discriminative accuracy for incident myopia based on these risk factors was 0.78. Axial length-to-CR ratio at baseline showed statistically significant interaction with number of books read per week ($P < 0.01$) and parental myopia ($P < 0.01$). Almost all predictors showed the highest association with AL elongation in the highest quartile of AL-to-CR ratio; incidental myopia in this group was 24% (124/513).

Conclusions: Determination of a risk score can help to identify school children at high risk of myopia. Our results suggest that behavioral changes can offer protection particularly in these children. *Ophthalmology 2019;126:127-136 © 2018 by the American Academy of Ophthalmology*

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Myopia (nearsightedness) is a common refractive error that is reaching epidemic proportions worldwide.[1−6] Concomitantly with the myopia boom, high myopia (spherical equivalent [SE], ≤ -6 diopters [D]) also has burgeoned,[2−4,7] which is worrisome because the underlying excessive axial elongation increases the risk of maculopathy, glaucoma, and other myopia-related complications that lead to blindness later in life.[8,9] Current prevalence estimates of high myopia already are reaching 7% to 10% among 14- to 16-year-olds in East Asia, and the onset of myopia in these children often occurs at school age or before.[7,10,11] Identifying risk factors for eye growth at a young age may help to characterize children at risk for whom lifestyle advice and interventions could be beneficial.[12−14]

Many studies have identified risk factors that are associated with an increased risk of myopia in children.[15−19] Several follow-up studies have investigated risk factors prospectively to assess their contribution to the onset of myopia and have found the best predictive value for baseline SE and ocular biometry.[20,21] Up to now, lifestyle factors such as time spent outdoors did not seem to have additional predictive value, potentially because differences in SE are the result of previous behavioral patterns. In addition, the number of environmental risk factors studied was limited.[22] Nonetheless, this is remarkable because it is becoming more and more clear that an important cause of the myopia rise in the world is the changing lifestyles of school children.[15−19] This is also unfortunate, because in contrast to baseline ocular parameters, lifestyle factors can be modified.

In this study, we investigated the effect of a large set of variables measured in children at 6 years of age on axial length (AL) eye growth, refractive error, and onset of myopia at 9 years of age. We calculated the predictive value

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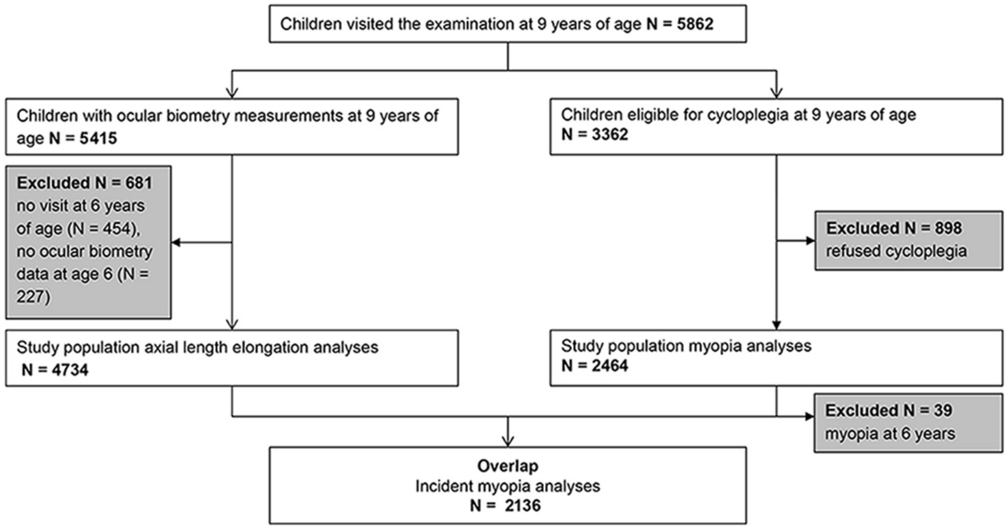

Figure 1. Flowchart showing distribution of study population.

of ocular and nonocular factors and evaluated the risk of incident myopia for various risk profiles.

Methods

This study was embedded in the Generation R Study, a population-based prospective cohort study of pregnant women and their children in Rotterdam, The Netherlands. The complete methodology has been described elsewhere.[23,24] Briefly, 9778 pregnant women were included in the study, and children were born between April 2002 and January 2006. The children were invited at 6 and 9 years of age for examination at the research center. Of the initial cohort, 6690 children (68.4%) participated in the physical examination at 6 years of age and 5862 children (60.0%) participated at 9 years of age. The study protocol was approved by the Medical Ethical Committee of the Erasmus Medical Centre, Rotterdam (MEC 217.595/2002/20), and written informed consent was obtained from all participants. Research was conducted according to the tenets of the Declaration of Helsinki.

Ocular biometry at 6 and 9 years of age was measured by Zeiss IOLMaster 500 (Carl Zeiss Meditec, Jena, Germany). For AL, 5 measurements per eye were averaged to a mean AL. Three measurements of corneal curvature (K1 and K2) were obtained from the right and left eyes and were averaged to a mean corneal radius (CR) of curvature. The AL-to-CR ratio, a measurement highly related to SE, was calculated by dividing the AL (in millimeters) by the CR (in millimeters).[25] Axial elongation was calculated in millimeters per year: (AL 9 years − AL 6 years) / (age at 9 years − age at 6 years). At 9 years, 1.5 years after the start of this follow-up round, the institutional review board approved the installation of cycloplegic eye drops, and automated cycloplegic refractive error was introduced (Topcon auto refractor KR8900; Topcon, Tokyo, Japan). Two drops (3 in patients with dark irises) of cyclopentolate 1% with a 5-minute interval were administered at least 30 minutes before refractive error measurement. Pupil diameter was 6 mm or more at the time of the measurement. Spherical equivalent was calculated as the sum of the full spherical value and half of the cylindrical value in accordance with standard practice. Myopia was defined as SE of −0.5 D or less.

At 6 years of age, the method of automated cycloplegic refractive error was performed in children with a visual acuity of more than 0.1 logarithm of the minimum angle of resolution with logarithm of the minimum angle of resolution−based LEA charts at a 3-m distance by means of the Early Treatment Diabetic Retinopathy Study method[26] in at least 1 eye or in children with an ophthalmologic history to identify children with myopia. Children with visual acuity of 0.1 logarithm of the minimum angle of resolution or less or no glasses or ophthalmic history were classified as nonmyopic at 6 years of age.[27,28] Incident myopia was the proportion of all new cases of myopia in children who underwent cycloplegic refractive error at 9 years of age and underwent AL measurement at both ages.

Predictor Variables

Each mother completed a questionnaire when her child was 6 years of age regarding the daily life activities of her child. Time spent playing outdoors was obtained using questions such as “How much time does your child spend outdoors?” separately for the morning, afternoon, and evening for both weekdays and weekend days. Answers were multiple choice: never, 0−0.5 hour, 0.5−1 hour, 1−2 hours, 2−3 hours, and 3−4 hours. Total time spent in a week was summed and divided by 7 to make an average number of hours per day. Computer and television use was processed likewise as time spent outdoors. Maternal education was defined according to Statistics Netherlands and categorized in primary and secondary or higher education. Income was obtained using the questionnaire and was clustered in low income (lowest tertile, <€2400/month) and higher income. As a proxy for ethnicity, the parents’ country of birth was obtained and grouped into European and non-European. At 6 years of age, reading habits were not assessed; at 9 years of age, questions about number of books read per week (<1 or ≥1 per week), time spent reading (>5 hours/week), interval duration of reading (≥30 minutes), reading distance (<30 cm or ≥30 cm), and parental myopia were determined. Child height and weight were measured at 6 years of age without shoes and heavy clothing, body mass index (kg/m^2) of children was calculated. 25-Hydroxy vitamin D was measured using the gold standard liquid chromatography−tandem mass spectrometry method. Birth parameters and gestational age were obtained using medical records and hospital registries. Standard deviation score (SDS) for weight for gestational age were calculated according to Northern European Growth Standards.[29]

Table 1. Demographic Characteristics of the Study Population and the Risk of Myopia at 9 Years of Age

Characteristics	All Children with Refractive Error Data (n = 2464)	Myopia at 9 Years of Age (n = 287)	Odds Ratio (95% Confidence Interval) of School Myopia	*P* Value*
Age (yrs)	6.00 (0.32)	6.02 (0.37)	1.45 (0.99–2.11)	0.05
Female gender, no. (%)	50 (1236)	53 (152)	1.14 (0.89–1.45)	0.31
BMI (kg/m^2)	16.2 (2.0)	16.3 (2.1)	1.05 (0.98–1.12)	0.18
Low family income, no. (%)	31 (762)	45 (129)	2.00 (1.47–2.72)	<0.001
Low education mother, no. (%)	45 (1106)	56 (159)	1.62 (1.23–2.13)	0.001
Vitamin D (nmol/l)	68 (29)	60 (28)	0.99 (0.98–0.99)	<0.001
Myopic parents (0–2), no. (%)				
0	41 (1017)	31 (88)	Reference	—
1	38 (938)	40 (115)	1.51 (0.98–2.32)	0.06
2	21 (509)	29 (84)	2.18 (1.38–3.44)	0.002
Gestational age (wks)	39.8 (2)	39.6 (2)	0.94 (0.89–1.00)	0.06
Birth weight (kg)	3.4 (0.6)	3.4 (0.6)	0.83 (0.67–1.03)	0.09
Weight for gestational age (SD)	−0.06 (1.0)	−0.09 (1.0)	0.95 (0.84–1.08)	0.46
Activities daily life				
Time spent outdoors (hrs/d)	1.6 (1.1)	1.3 (0.95)	0.78 (0.64–0.95)	0.02
Watching television (hrs/d)	1.4 (1.0)	1.6 (1.1)	1.16 (1.02–1.31)	0.02
Computer use (hrs/d)	0.3 (0.4)	0.4 (0.5)	1.29 (0.95–1.74)	0.10
No participating in sports, no. (%)	57 (1394)	64 (183)	1.40 (1.05–1.88)	0.03
Books read (≥1/wk)	43 (1066)	50 (144)	1.38 (1.00–1.90)	0.05
Time spent reading (>5 hrs/wk)	37 (923)	40 (115)	1.13 (0.80–1.59)	0.48
Continuous near work (>30 minutes)	16 (382)	21 (61)	1.54 (1.03–2.31)	0.04
Reading distance (<30 cm)	47 (1175)	56 (160)	1.44 (1.12–1.68)	0.01
Ocular biometry at 6 yrs of age				
Axial length (mm)	22.3 (0.72)	22.7 (0.78)	2.18 (1.81–2.64)	<0.001
AL-to-CR ratio (per 0.01 increase)	2.87 (0.07)	2.94 (0.08)	1.21 (1.18–1.24)	<0.001
Ethnicity, no. (%)				
Non-European	30 (749)	53 (151)	2.95 (2.30–3.80)	<0.001

AL = axial length; BMI = body mass index; CR = corneal radius; SD = standard deviation.
Values are means (SD) unless otherwise indicated. All numbers and odds ratios refer to the imputed dataset in children with cycloplegic refractive error available (n =2464). All variables were measured at 6 years of age except number of books read, time spent reading, continues near work, and reading distance.
*Unadjusted logistic regression models.

Statistical Methods

Univariate associations between candidate predictors and myopia were tested using logistic regression. Univariate and multivariate associations between candidate predictors and axial elongation were tested using linear regression models. A relatively high proportion of the environmental determinants had missing values. Parental myopia (39%), reading habits (32%), and 25-hydroxy vitamin D levels (36%) had the highest rate of missing values. Time spent outdoors was missing for 24% of the cohort. Other predictors had less than 20% missing values. To avoid any bias because of missing candidate predictors, fully conditional specification, an iterative of the Markov chain Monte Carlo approach, was used for imputation. Multivariate linear regression was performed with backward selection to select combinations of predictor variables. All variables with a *P* value of less than 0.05 in univariate analysis were tested in a multivariate analysis. All variables with a *P* value of less than 0.05 in the multivariate analysis were added to the prediction model. The AL-to-CR ratio and time spent outdoors were categorized in the prediction model. We tested interaction effect with the AL-to-CR ratio at baseline by adding multiplicative interaction terms with the environmental risk factors. The AL-to-CR ratio was divided into 4 quartiles to compare regression coefficients between groups with increasing myopic SE. To identify the predictive value of the risk factors, independent of the ocular measurements at baseline, we used the quartile-specific βs of the significant associated factors in the complete sample to calculate a prediction score in the 2 highest quartiles.

A prediction score was created by multiplying regression coefficients by 100. Calibration of the model was evaluated with the Hosmer-Lemeshow chi-square statistic, and the final model's ability to discriminate between myopic and nonmyopic children was assessed by using the area under the receiver operating characteristic curve (AUC). Analyses were performed with SPSS software version 21.0 (IBM Corp., Armonk, NY).

Results

General Characteristics

A total of 4734 children, 50.7% girls, underwent ocular biometry measurements at both 6.0±0.5 years of age and 9.8±0.3 years of age (Fig 1). Despite a difference in eye size, the increase in AL was not different between boys and girls ($P = 0.95$) and averaged 0.21 mm/year (SD, 0.09 mm/year). Children with myopia at the last visit demonstrated significantly greater axial elongation compared with nonmyopic participants (0.34 mm/year vs. 0.19 mm/year; $P < 0.001$).

Cycloplegic measurements of refractive error were introduced 1.5 years after the start of the examinations at 9 years of age. After that time point, 2464 of 3362 children (73%) had reliable

Table 2. Univariate and Multivariate Regression Analysis of the Coefficients (Standard Deviations) between Axial Elongation between 6 and 9 Years of Age and Potential Predictors

Characteristics at 6 Years of Age	Model 1: Association of Axial Elongation (mm/year)	Model 1: P Value	Model 2: Association of Axial Elongation (mm/year)	Model 2: P Value
Age (yrs)	**−0.010 (0.003)**	**<0.001**	**−0.021 (0.003)**	**<0.001**
Female gender	0.000 (0.002)	0.95	0.002 (0.002)	0.35
BMI (kg/m^2)	0.001 (0.001)	0.88	—	—
Low family income	**0.008 (0.003)**	**0.006**	0.001 (0.004)	0.82
Mother with low education	0.001 (0.003)	0.71	—	—
Vitamin D (/20 nmol/l)	**−0.002 (0.001)**	**0.006**	0.000 (0.000)	0.77
Myopic parents (0−2)				
0	Reference		Reference	—
1	**0.014 (0.003)**	**0.001**	**0.11 (0.003)**	**0.002**
2	**0.026 (0.005)**	**<0.001**	**0.19 (0.004)**	**<0.001**
Gestational age (wks)	−0.001 (0.001)	0.17	—	—
Birthweight (g)	0.000 (0.000)	0.52	—	—
Size for gestation (SDS)	0.000 (0.001)	0.98	—	—
Environmental risk factors				
Time spent outdoors (hrs/d)	**−0.005 (0.001)**	**0.004**	**−0.003 (0.001)**	**0.007**
Watching television (hrs/d)	0.002 (0.001)	0.10	—	—
Computer use (hrs/d)	**0.007 (0.003)**	**0.03**	0.002 (0.003)	0.46
No sports participation	**0.010 (0.003)**	**<0.001**	**0.008 (0.002)**	**0.001**
Books read per week (>1)	**0.021 (0.003)**	**<0.001**	**0.013 (0.003)**	**<0.001**
Time reading at 9 yrs of age (>5 hrs)	**0.017 (0.003)**	**<0.001**	**0.012 (0.003)**	**0.001**
Continuous reading at 9 yrs of age (≥30 minutes)	0.008 (0.005)	0.12	—	—
Reading distance at 9 yrs of age (<30 cm)	0.007 (0.003)	0.08	—	—
Ocular biometry at 6 yrs of age				
AL (mm)	**0.024 (0.002)**	**<0.001**	—	—
AL/CR ratio (mm/mm)	**0.332 (0.016)**	**<0.001**	**0.32 (0.016)**	**<0.001**
Ethnicity (%)				
Non-European	**0.015 (0.003)**	**<0.001**	**0.010 (0.03)**	**0.001**

AL = axial length; BMI = body mass index; CR = corneal radius; SDS = standard deviation score; — = not significant in model 1.
Boldface indicates statistically significant $P < 0.05$.
Model 1 is adjusted only for age and gender; model 2 is also adjusted for significant variables from model 1.

measurements of SE at 9 years of age (Fig 1); they did not differ significantly in AL-to-CR ratio from children who declined cycloplegia (2.970 vs. 2.966; $P = 0.32$). Spherical equivalent at 9 years of age was +0.73 D (SD, 1.29 D) on average. Myopic children at 9 years of age were more often from low socioeconomic families, of non-European descent, more often had parents who were myopic, spent less time outdoors, read more books, and had higher ALs and AL-to-CR ratios at 6 years (Table 1).

Children with at least 1 predictor variable missing (n = 3192) were less likely to be of European descent (67% vs. 81%), to have a mother with high education (56% vs. 66%), and to come from high-income families (69% vs. 78%). To prevent results based on selection bias, we imputed data to the total cohort of 4734 children. No large differences in regression coefficients were found between the results for AL elongation in the imputed and nonimputed dataset (Table S1, available at www.aaojournal.org).

Risk Factors for Axial Eye Growth

In the univariate analysis, greater axial elongation was associated with a younger age of the participant, low family income, non-European descent, lower 25-hydroxy vitamin D levels, 1 or 2 myopic parents, less time spent outdoors and sports participation, more computer use and time spent reading, and increased AL or AL-to-CR ratio at 6 years of age. In the multivariate analyses, the predictors 1 or 2 myopic parents, less time spent outdoors, no participation in sports, more books read per week, more time spent reading, an increased AL-to-CR ratio at baseline, and ethnicity remained associated significantly with increased axial elongation (Table 2). Axial length at baseline was not taken into account in the multivariate model because this measure was correlated highly with the AL-to-CR ratio. The regression coefficients of the predictors were not significantly different in a model with and without AL-to-CR ratio in the model (Table S2, available at www.aaojournal.org).

Prediction of Myopia

A total of 2175 children had complete ocular biometry data at 9 years of age and cycloplegic refractive error. At baseline, 39 children (1.8%) were diagnosed with myopia at 6 years of age and were excluded from further risk analyses. Myopia incidence was 223 of 2136 children (10.4%) between the 2 visits. The total of 2136 children were included in the prediction analyses. A prediction score for each child was calculated by the sum of the βs of the multivariate association multiplied by 100 (Table 3). The score ranged from 0 to 19.4, with a mean of 5.5 (SD, 3.0). Total prediction score was associated with axial elongation (β, 0.010; SD, 0.0004; $P < 0.001$). Each 1-point increase in the score had an odds ratio of 1.43 (95% confidence interval, 1.35−1.52) of

Table 3. Multivariate Prediction Model for Axial Elongation

Predictor Variables	Complete Model, β (95% Confidence Interval)	Assigned Points for Prediction Score
Characteristics at 6 yrs of age		
Myopic parents (0–2)		
0	Reference	0
1	0.012 (0.005–0.019)	1.2
2	0.019 (0.010–0.028)	1.9
Environmental factors		
Time spent outdoors (<2 hrs/d)	0.005 (0.000–0.011)	0.5
No sports participation	0.008 (0.003–0.013)	0.8
No. of books read per wk	0.012 (0.006–0.018)	1.2
Time spent reading at 9 yrs of age (>5 hrs)	0.012 (0.006–0.018)	1.2
Ocular biometry at 6 yrs of age		
AL-to-CR ratio		
≤2.80	Reference	0
2.80–2.85	0.008 (0.000–0.016)	0.8
2.85–2.90	0.019 (0.011–0.027)	1.9
2.90–2.95	0.034 (0.026–0.042)	3.4
2.95–3.00	0.055 (0.046–0.065)	5.6
>3.00	0.128 (0.114–0.142)	12.8
Ethnicity (%)		
Non-European	0.010 (0.004–0.016)	1.0
Total		19.4
Hosmer-Lemeshow (*P* value)		0.67
Area under the receiver operating characteristic curve		0.78

AL = axial length; CR = corneal radius.
Model is adjusted for potential confounding effects of age and gender. Points calculated based on regression coefficients (regression coefficient multiplied by a factor of 100). Individual prediction score can be calculated by using the following equation: individual score = 1.2 × 1 myopic parent (1 myopic parent = 1, 0 or 2 myopic parents = 0) + 1.9 × 2 myopic parents (2 myopic parents = 1, 0 or 1 myopic parent = 0) + 0.5 × time spent outdoors (<2 hrs/day = 1, ≥2 hrs/day = 0) + 0.8 × sport participation (no = 1, yes = 0) + 1.2 × no. of books read per wk (1 = ≥1/wk, 0 = <1/wk) + 1.2 × time spent reading (1 = ≥5 hrs/wk, 0 = <5 hrs/wk) + 0 to 12.8 × AL-to-CR ratio category (1 = category, 0 = other category) + 1.0 × ethnicity (1 = non-European, 0 = European).

incident myopia. The AUC of the uncategorized prediction score was 0.78; without ocular biometry, this was 0.65 (Fig 2). The model was well calibrated according to the Hosmer-Lemeshow *P* value of 0.67. Table S3 (available at www.aaojournal.org) reports sensitivity, specificity, positive predictive values, and negative predictive values at the different cutoff values. Of the 571 children with a predictor score of 3.5 or less, myopia developed in only 8 (1.4%) between 6 and 9 years of age. In contrast, myopia developed in 54% (27/50) of the children with a score of 11 or more at this age (Fig 3). The prediction score (AUC, 0.79) in study participants with complete data (83 patients and 959 control participants) was comparable with the data set including imputed data (AUC, 0.78). The prediction of axial eye growth between 6 and 9 years of age for incident myopia was highest with an AUC of 0.85.

Effects in Children with High Values of Axial Length-to-Corneal Radius Ratio at Baseline

To test if predictors were independent of the AL-to-CR ratio at baseline, we tested multiplicative interaction terms. The AL-to-CR ratio at baseline showed statistically significant interaction with parental myopia ($P < 0.01$), number of books read per week ($P < 0.01$), reading distance ($P = 0.04$), ethnicity ($P < 0.01$), and the environmental risk score ($P < 0.001$; Fig 4). The multivariate analyses were repeated in a stratified analysis of the 4 quartiles of baseline AL-to-CR ratio (Table 4). All predictors except for sports participation showed the highest association with AL elongation in the highest quartile of the AL-to-CR ratio; incidental myopia in this group was 24% (124/513).

Discussion

In this study, we identified ocular as well as environmental risk factors for axial eye growth. By combining these risk factors, we calculated a prediction score for myopia onset between 6 and 9 years of age and found a predictive value of 0.78. Axial length elongation had the highest predictive value for onset of myopia with an AUC of 0.85. Environmental factors were associated significantly with both increase in AL and incident myopia and had the greatest effect in children with the highest quartile of AL-to-CR ratio at baseline, suggesting that this group of children may benefit the most from behavioral and lifestyle interventions.

Previous Studies

The values for eye growth are lower in the current European study than those estimated in Singapore with children of comparable age. Average eye growth in Singapore was 0.30 mm/year, and likewise, myopia had a higher incidence.[30] Algorithms to predict the development of myopia have been reported previously, predominantly in young children.[22,31] These previous studies report that those with low values of refractive error, but still emmetropic values, showed the highest risk of incident myopia. Our predictive value of AL growth was comparable with their predictive value of baseline refractive error, as well as the predictive

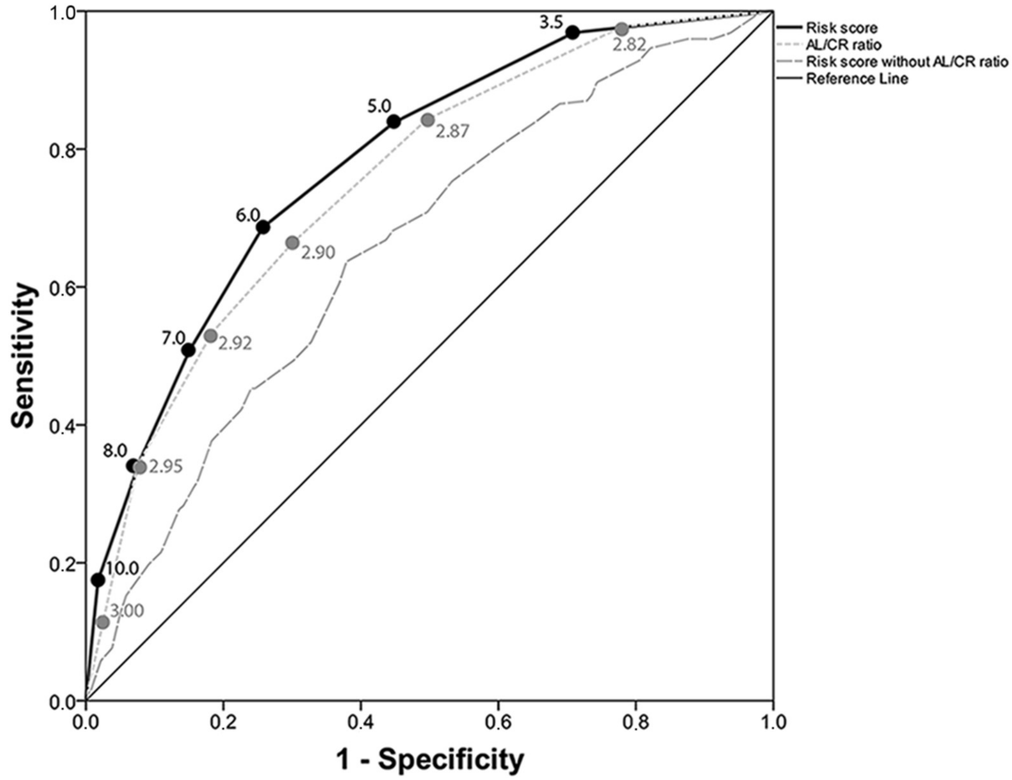

Figure 2. Graph showing the receiver operating characteristic (ROC) curve for prediction of incident myopia between 6 and 9 years of age. Cutoff values of prediction score are reported as dots in the curve. The area under the ROC curve (C-index) for the categorized score is 0.78 for the prediction score, 0.75 for the axial length (AL)-to-corneal radius (CR) ratio only and 0.63 for the risk score without ocular biometry.

value of a model including only nonocular data, resulting in an AUC of 0.63 compared with the model of the Collaborative Longitudinal Evaluation of Ethnicity and Refractive Error (CLEERE) study,[22] which included only nonocular factors (AUC, 0.58−0.68). However, the other studies did not find an additional effect for environmental factors. In this study, the highest effect of environmental factors was found for those children with the highest risk of myopia. Based on these factors, the AUC was almost 0.70 in this group, suggesting that these children have the most benefit of lifestyle changes.

Strengths and Limitations

Strengths of this study are the large sample size, longitudinal nature of the data, the homogeneous group of children, and the wide variety of predictors in this study. Using AL growth allowed us to study a continuous phenotype and the entire spectrum of the trait and to detect more subtle changes than merely the dichotomous myopia, but some limitations have to be discussed. There is a potential selection bias in response to cycloplegia. Children with dark irises more often were nonresponders to cyclopentolate (1%) and more often were non-European. This response was probably not related to the current SE within this group, and therefore affected only power to detect an association with non-European ethnicities. Another limitation is that baseline ocular biometry and refractive error as a predictor of incident myopia have the disadvantage that these factors are not only a result of genetic variation or susceptibility for eye growth, but also reflect previous risk behavior. This may result in an underestimation of the profit that can be gained by behavioral change. Ideally, the same participants were used for the axial elongation analysis as well as for the myopia analysis, but because of later implementation of cycloplegia, this was not possible. The reading habit measurements were not measured at baseline, but are important behavioral factors, and for this reason, we added them to the model.

Interpretation of the Results

This prediction score has the highest validity in urban children with AL and refractive error in the normal range before 10 years of age. Eye growth is highest in the first years of life. At birth, the average AL is 17.3 mm, which increases to 22.3 mm at 6 years of age, 23.1 mm at 9 years of age, and 23.5 mm in the current adult population, which may become higher as a result of the cohort effect.[32,33] Nonetheless, the decrease in eye growth rate with

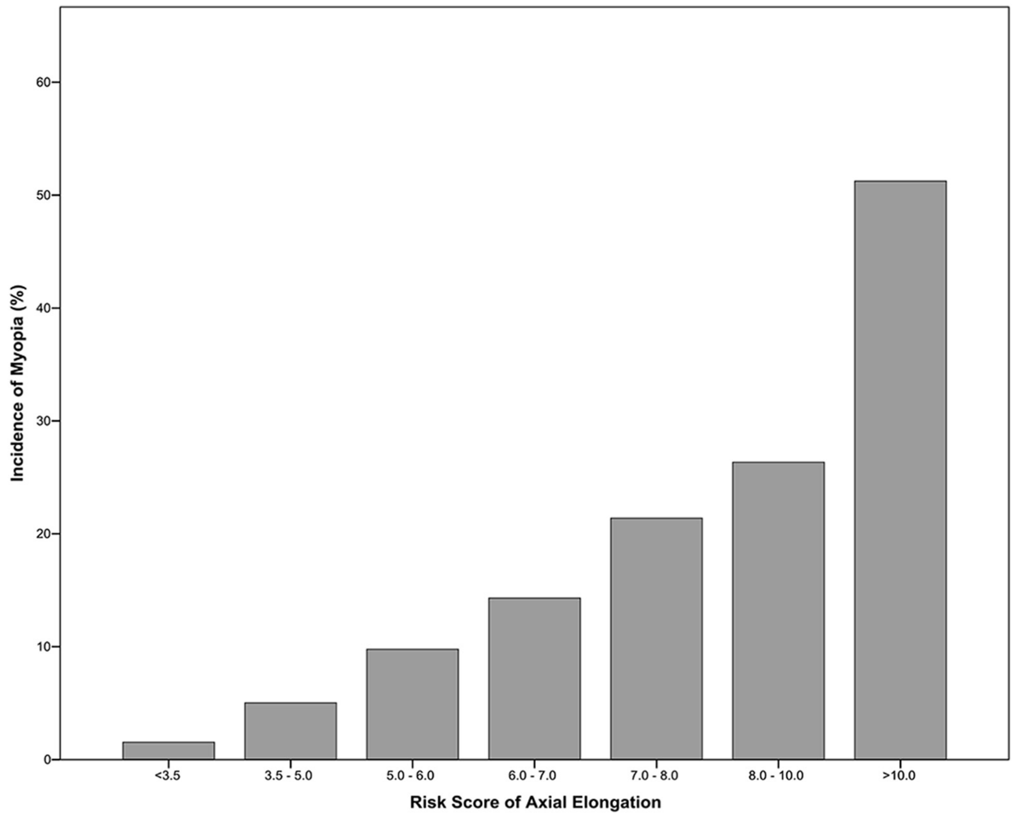

Figure 3. Bar graph showing the proportions of children with incident myopia and children who remained nonmyopic based on the risk score for axial length elongation.

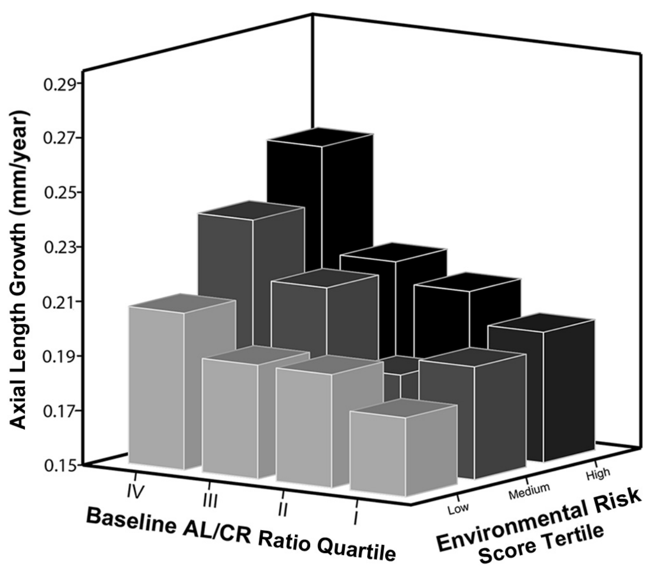

Figure 4. Three-dimensional bar graph showing axial length (AL) elongation in relation to baseline AL-to-corneal radius (CR) ratio and environmental risk factors. Baseline AL-to-CR ratios were divided into quartiles. Environmental prediction scores were based on βs of time spent outdoors, sports participation, number of books read per week, and time spent reading in Table 3 and divided into tertiles.

increasing age will lower the validity of the prediction score in children younger than 6 years or older than 10 years.

Hence, the prediction score is most suitable for primary or secondary prevention by detecting children at risk of high myopia developing. Two studies described the effect of time spent outdoors on myopia development. More time spent outdoors during class recess has a positive effect in a 2-school comparison as well as in a randomized controlled trial.[34,12] Furthermore, an experimental glass classroom has been developed to investigate the effect of more light during school hours, but results are pending.[35] According to our results, interventions are especially beneficial for the high-risk group. Based on the expected eye growth, additional other options for secondary prevention are available for inhibiting progression of myopia.[36] Orthokeratology decreases eye growth by 30% to 50%, and atropine 1% can decrease progression by as much as 75%.[37,38]

In conclusion, the risk score developed by this study helps to identify schoolchildren at high risk of myopia. Future applications in school children may initiate behavioral changes and other interventions that delay myopia onset and reduce the risk of high myopia.

Table 4. Multivariate Prediction Models for Axial Elongation per Quartile of Axial Length-to-Corneal Radius Ratio at Baseline

Quartile of Axial Length-to-Corneal Radius Ratio at Baseline	**High**	**Medium High**	**Medium Low**	**Low**
Predictor variables	β	β	β	β
Characteristics at 6 yrs of age				
Myopic parents (0–2)				
0	Reference	Reference	Reference	Reference
1	**0.019 (0.002–0.036)**	**0.013 (0.002–0.024)**	0.010 (−0.005 to 0.025)	0.005 (−0.006 to 0.015)
2	**0.037 (0.019–0.054)**	**0.024 (0.011–0.037)**	0.010 (−0.004 to 0.024)	0.007 (−0.015 to 0.028)
Activities daily life				
Time spent outdoors (<2 hrs/d)	0.010 (−0.010 to 0.030)	0.004 (−0.006 to 0.015)	−0.003 (−0.012 to 0.006)	0.008 (−0.001 to 0.018)
No sports participation	0.009 (−0.003 to 0.022)	**0.012 (0.003–0.022)**	**0.011 (0.002–0.019)**	0.002 (−0.006 to 0.015)
No. of books read per week (>1/wk)	**0.023 (0.008–0.0038)**	**0.011 (0.001–0.022)**	0.007 (−0.005 to 0.018)	0.006 (−0.006 to 0.018)
Time spent reading (>5 hrs/wk)	0.013 (−0.003 to 0.029)	0.010 (−0.001 to 0.021)	**0.016 (0.003–0.023)**	0.009 (−0.001 to 0.018)
Reading distance (<30 cm)	**0.026 (0.008–0.044)**	0.002 (−0.008 to 0.012)	−0.003 (−0.005 to 0.012)	−0.004 (−0.020 to 0.011)
Ethnicity (%)				
Non-European	**0.025 (0.011–0.038)**	0.004 (−0.006 to 0.015)	0.006 (−0.004 to 0.015)	0.009 (−0.001 to 0.018)
Incidental myopia, % (n)	24 (124/513)	11 (60/546)	6 (31/540)	1 (8/537)
Hosmer-Lemeshow (*P* value)	0.48	0.39	—	—
Area under the receiver operating characteristic curve*	0.66	0.64	—	—

– = medium low Hosmer Lemeshow 0.38 and AUC 0.64 and low Hosemer Lemeshow 0.77 and 0.59.
Boldface indicates statistical significance.
*Calculated based on the prediction score with quartile-specific regression coefficients. The axial length-to-corneal radius ratio in the high group was >2.916, in the medium high group was 2.876–2.916, in the medium low group was 2.833–2.876, and in the low group was <2.833.

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Abbreviations and Acronyms:
AL = axial length; **AUC** = area under the receiver operating characteristic curve; **CR** = corneal radius; **D** = diopter; **SDS** = standard deviation score; **SES** = socioeconomic status; **VA** = visual acuity; **SD** = standard deviation; **SE** = spherical equivalent.

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