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Association of Age at Myopia Onset With Risk of High Myopia in Adulthood in a 12-Year Follow-up of a Chinese Cohort

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➕ Supplemental content

IMPORTANCE Early-onset myopia is well known to progress to high myopia in adulthood. However, no accurate estimation of how a specific age at myopia onset is associated with the probability of developing high myopia in adulthood is available, and a very-long-term follow-up study with data from annual visits is needed.

OBJECTIVE To estimate the risk of developing high myopia in adulthood associated with a specific age at myopia onset from a data set with a 12-year annual follow-up.

DESIGN, SETTING, AND PARTICIPANTS This ongoing, population-based prospective cohort study of twins was conducted in Guangzhou, China, on July 11, 2006. Data from baseline to August 31, 2018, were analyzed. The first-born twins completed follow-up until 17 years or older, and the 443 participants (after exclusions) who developed myopia were included in the analysis. Data were analyzed from September 1, 2018, to January 20, 2020.

MAIN OUTCOMES AND MEASURES Age at myopia onset was determined by prospective annual cycloplegic refractions (365 participants [82.4%]) or with a questionnaire. Refraction in adulthood was defined as the cycloplegic refraction measured at the last follow-up visit.

RESULTS Among the 443 eligible participants (247 [55.8%] female; mean [SD] age at myopia onset, 11.7 [2.0] years), 54 (12.2%) developed high myopia (spherical equivalent, −6.00 diopters or worse determined by cycloplegic refractions) in adulthood. Among participants with age at myopia onset of 7 or 8 years, 14 of 26 (53.9%; 95% CI, 33.4%-73.4%) developed high myopia in adulthood; among those with onset at 9 years of age, 12 of 37 (32.4%; 95% CI, 18.0%-49.8%); among those with onset at 10 years of age, 14 of 72 (19.4%; 95% CI, 11.1%-30.5%); among those with onset at 11 years of age, 11 of 78 (14.1%; 95% CI, 7.3%-23.8%); and among those with onset at 12 years or older, 3 of 230 (1.3%; 95% CI, 0.2%-3.8%). Results of multivariate logistic regression analysis suggested that the risk of developing high myopia in adulthood decreased significantly with delay in the age at myopia onset (odds ratio, 0.44; 95% CI, 0.36-0.55; *P* < .001), from greater than 50% for 7 or 8 years of age to approximately 30% for 9 years of age and 20% for 10 years of age.

CONCLUSIONS AND RELEVANCE These findings suggest that the risk of high myopia is relatively high in children with myopia onset during the early school ages. Each year of delay in the age at onset substantially reduces the chance of developing high myopia in adulthood, highlighting the importance of identifying effective prevention strategies under investigation, such as increasing outdoor time.

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Myopia is a common ocular condition and has been recognized as an important public health issue worldwide.[1] A significant concern of myopia is its progression to high myopia.[1-3] High myopia carries great risks of irreversible blinding complications, such as glaucoma, retinal detachment, and myopic maculopathy.[1,4-6]

In the past few decades, an earlier onset of myopia has been reported in East and Southeast Asia.[7,8] It is widely acknowledged that the earlier the age at onset, the greater the percentage of the population with high myopia.[9-12] An epidemic of early-onset myopia might suggest an impending epidemic of high myopia.

Despite existing knowledge on the association between early myopia onset and increased risk of high myopia, to the best of our knowledge, the exact level of risk of developing high myopia in adulthood for a given age of onset is currently unclear. Similarly, questions such as how much benefit an individual would gain by each 1-year delay in onset and after what age of myopia onset the risk decreases to an insignificant level remain unanswered. The answers to these questions require a prospective, long-term follow-up study with annual visit data.

The primary objective of this study was to determine the risk of developing high myopia in adulthood in association with specific ages at myopia onset using data from a population-based Chinese twin cohort that was followed up annually for 12 years. The secondary objective was to identify the underlying factors mediating the association between early myopia onset and increased risk of developing high myopia in adulthood besides the well-known period of myopia progression. Onset age-specific changes in ocular refractions and axial length (AL) were described and compared. The association of age at myopia onset with the rate of myopia progression was examined. The information provided in this study could help to determine whether myopia prevention strategies, such as increasing outdoor time, can be used as the first line of defense against high myopia as well as in setting the targets for conducting such strategies.

Methods

Study Population

This ongoing, population-based prospective cohort study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline. Data for the current study analysis were extracted from the Guangzhou Twin Eye Study. Details of this study have been described previously.[13,14] Briefly, the Guangzhou Twin Eye Study is a population-based ongoing longitudinal study that commenced in 2006. At baseline, twins aged 7 to 15 years who lived in 2 districts adjacent to the Zhongshan Ophthalmic Center, Guangzhou, China, were recruited, and follow-up visits were scheduled annually. The refractions and ALs of participants in the Guangzhou Twin Eye Study were similar to those in the population-based Guangzhou Refractive Error Study in Children.[14,15] The study was conducted in accordance with the tenets of the World Medical Association's Declaration of Helsinki[16] and approved by the ethical review board of Sun Yat-Sen University and the ethics committee of Zhongshan Ophthalmic Center. Written informed consent was obtained for all participants from their parents or legal guardians. Free glasses were offered to the participants who needed refractive corrections throughout the study period.

The present study analyzed annual examination data from July 11, 2006, to August 31, 2018. First-born twins with myopia (cycloplegic spherical equivalent [SE] −0.50 diopters [D] or less) and 17 years or older at their last follow-up visits were included in the analysis. Participants with ocular disorders such as strabismus and amblyopia, a history of orthokeratology treatment, or a history of refractive surgery were excluded. Individuals with myopia onset at 16 years or older were not included because they were considered to have late-onset myopia.

Data Collection

Cycloplegic refraction assessment was performed at each annual follow-up visit. Cycloplegia was induced by 2 drops of cyclopentolate hydrochloride, 1%, instilled 5 minutes apart, followed by a third drop instilled 20 minutes later. Refractions were measured by an autorefractor (KR-8800; Topcon Corp) after complete cycloplegia (determined by the absence of light reflex and a dilated pupil at least 6 mm in diameter). Axial length was measured at each follow-up visit before pupil dilation using noninvasive partial-coherence laser interferometry (IOLMaster; Carl Zeiss Meditec AG). An interviewer-administered questionnaire survey was performed to collect data on participants' medical history, including age at myopia onset for those who developed myopia before the study baseline, hours of near work and outdoor activity per day, and information on refractive corrections. Parental refractions were measured using noncycloplegic autorefraction at baseline.

Definitions

The age at myopia onset was prospectively determined using annual examination data for participants who developed myopia at baseline or during the follow-up visits (365 [82.4%] of the cohort). This was determined as the age at the visit when an SE of −0.50 D or less was first detected, which was verified by refractions measured at subsequent follow-up visits. Alternatively, the age at myopia onset was determined by the questionnaire data.

Key Points

Question What is the risk of developing high myopia in adulthood in association with a specific age at myopia onset?

Findings In this cohort study of 443 individuals with myopia, the risk of developing high myopia was greater than 50% for those with myopia onset at 7 or 8 years of age. The risk substantially decreased to approximately 30% for onset at 9 years of age, 20% for onset at 10 years of age, and less than 5% for onset at 12 years or older.

Meaning These data suggest that early onset is strongly associated with high myopia risk in adulthood and that a delay in each year of onset substantially reduces this risk, supporting the need for prompt myopia prevention strategies.

The SE and AL measured at the last follow-up visit (at age ≥17 years) were defined as the SE and AL in adulthood. High myopia in adulthood was defined as an SE of at least −6.00 D in adulthood.

Statistical Analysis

Data were analyzed from September 1, 2018, to January 20, 2020. Only the data of the right eye were used in the present analysis because of the high correlation between the right and left eye measurements. The age at myopia onset was rounded and categorized into groups with 1-year intervals. The groups of children with onset at 7 and 8 years of age were combined because of the relatively small sample sizes.

Spherical equivalent and AL in adulthood by age at myopia onset are presented as boxplots. Changes in myopic SE and AL in adulthood with delayed onset of myopia from 7 or 8 years of age were estimated using multivariate linear regression models. The percentage of participants with high myopia in adulthood was calculated for specific ages of myopia onset and is presented in bar graph format. Risks of developing high myopia in adulthood, stratified by sex and onset ages, were determined using a multivariate logistic regression model. Sex was adjusted in all regression models. Other potential confounding variables, including near work activity, time outdoors, and number of parents with high myopia, were first examined using univariate regression analyses. Variables with $P < .10$ were further examined in multivariate models, and those with $P < .05$ were included in the final models. Variables included in the final model for SE in adulthood were sex, age at myopia onset, and number of parents with high myopia. Those included in the final models for AL and risk of high myopia in adulthood were sex and age at myopia onset.

Mixed-effect regression models were established to describe the evolutions of SE and AL specific to age at onset. The time since myopia onset was used as the variable time factor in these models. An interaction of onset age with time since myopia onset was included in these models to examine the association of age at myopia onset with the rate of SE progression or AL elongation. Interactions of age and sex with time since myopia onset were also included to adjust for the effects of these factors on the rate of myopia progression. For each specific age of onset, the annual changes in SE and AL were estimated using the established models, and the changes in SE and AL were plotted. Statistical analyses were performed using STATA, version 15.0 (StataCorp LLC) and R, version 3.4.4 (R Project for Statistical Computing). All P values were 2 sided, and no adjustments were made to the P values for the analyses undertaken. Unless otherwise indicated, data are expressed as mean (SD).

Results

Figure 1 shows the flowchart for participant inclusion in the present study. Of the 1303 first-born twins who participated in the Guangzhou Twin Eye Study at baseline, 53 (4.1%) had

Figure 1. Flowchart Depicting Inclusion of Participants Assessed in This Study
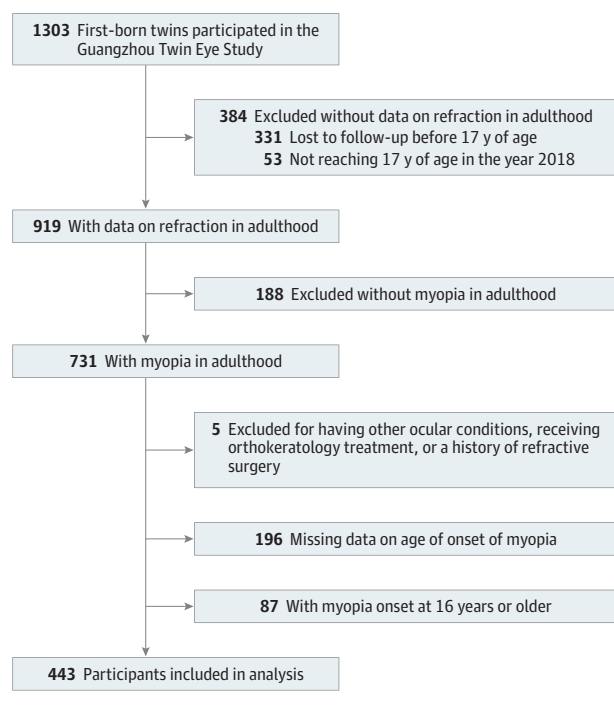
not reached 17 years of age in 2018 and 331 (25.4%) missed follow-up before 17 years of age; thus, 919 participants had data of refraction measurements in adulthood. Among these, 731 (79.5%) had myopia. Of these participants, 288 were excluded because they had other ocular conditions, history of orthokeratology or refractive surgery, missing age at myopia onset, or late-onset myopia. The final analysis therefore included data for the remaining 443 individuals, among whom 196 (44.2%) were male and 247 (55.8%) were female. Characteristics of the included participants are shown in eTable 1 in the Supplement. Their mean (SD) age at myopia onset was 11.7 (2.0) years; at the last follow-up visit, 20.4 (2.6) years. The mean (SD) SE in adulthood was −3.86 (1.85) D, and the mean (SD) AL in adulthood was 25.2 (1.0) mm.

Figure 2 shows the SE and AL in adulthood categorized by age at myopia onset. In participants with age of onset of 7 or 8 years, the mean (SD) cycloplegic SE in adulthood was −6.28 (1.84) D, and the mean (SD) AL in adulthood was 26.4 (0.9) mm. A relatively less myopic SE (−5.53 [1.31] D among those with onset at 9 years of age and −4.94 [1.62] D among those with onset at 10 years of age) and shorter AL (26.0 [0.8] mm among those with onset at 9 years of age and 25.5 [0.9] mm among those with onset at 10 years of age) in adulthood were observed among participants with older ages at myopia onset ($P < .001$ for trend for both SE and AL in adulthood). The estimated reductions in myopic SE and AL in adulthood with a delay in myopia onset from 7 or 8 years of age are shown in eTable 2 in the Supplement.
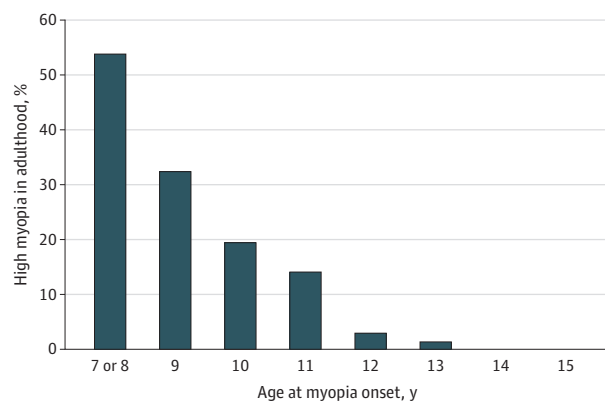
Among the 443 participants, 54 (12.2%) had high myopia in adulthood. Percentage of high myopia in adulthood stratified by age at myopia onset is presented in **Figure 3**.

Figure 2. Boxplots of Spherical Equivalent (SE) and Axial Length (AL) in Adulthood, Stratified by Age at Myopia Onset

A Spherical equivalent

B Axial length
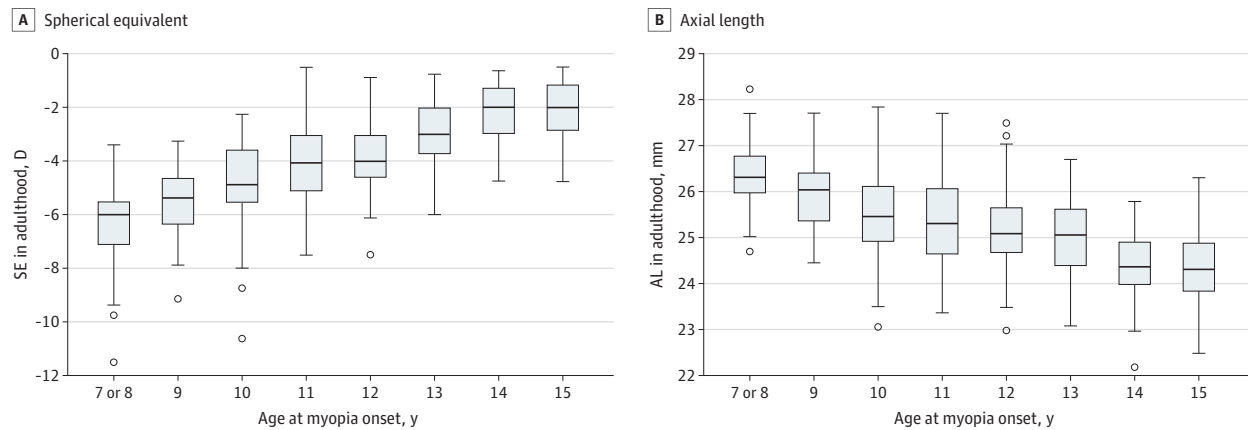
The center lines in the boxes represent the median, the lower and upper ends of the boxes represent the 25th and 75th percentiles, error bars represent adjacent values, and data points represent outliers. D indicates diopter.

Figure 3. Percentage of Patients With High Myopia in Adulthood, Stratified by Age at Myopia Onset

Table. Risk of High Myopia in Adulthood, Stratified by Sex and Age at Myopia Onset

Age at myopia onset, y	Risk of high myopia in adulthood, % (95% CI)[a]	
	Men	Women
7 or 8	52.9 (33.4-71.7)	55.3 (35.5-73.5)
9	31.5 (11.4-56.4)	33.6 (12.4-58.7)
10	18.6 (6.3-37.7)	20.0 (6.9-40.0)
11	13.5 (4.3-29.9)	14.6 (4.7-31.9)
12	2.8 (0.5-12.7)	3.1 (0.5-13.8)
13	1.3 (0.1-10.2)	1.5 (0.1-11.1)

[a] Estimated using a multivariate logistic regression model including sex and age at myopia onset.

Among participants with age at myopia onset of 7 or 8 years, 14 of 26 (53.9%; 95% CI, 33.4%-73.4%) developed high myopia in adulthood; among those with onset at 9 years of age, 12 of 37 (32.4%; 95% CI, 18.0%-49.8%); among those with onset at 10 years of age, 14 of 72 (19.4%; 95% CI, 11.1%-30.5%); among those with onset at 11 years of age, 11 of 78 (14.1%; 95% CI, 7.3%-23.8%); among those with onset at 12 years of age, 2 of 67 (3.0%; 95% CI, 0.4%-10.4%); among those with onset at 13 years of age, 1 of 71 (1.4%; 95% CI, 0.0%-7.6%); and among those with onset at 14 or 15 years of age, 0 of 92. The **Table** shows the risk of developing high myopia in adulthood for specific ages at myopia onset, determined by multivariate logistic regression model (odds ratio, 0.44; 95% CI, 0.36-0.55; $P < .001$). Among men with myopia onset at 7 or 8 years of age, the risk of developing high myopia was 52.9% (95% CI, 33.4%-71.7%). The risk was 55.3% (95% CI, 35.5%-73.5%) for women with the same age at myopia onset. With a delay in the age at onset to 9 years, the risk decreased to approximately 30%. The risk further decreased to approximately 20% with a delay in the age at
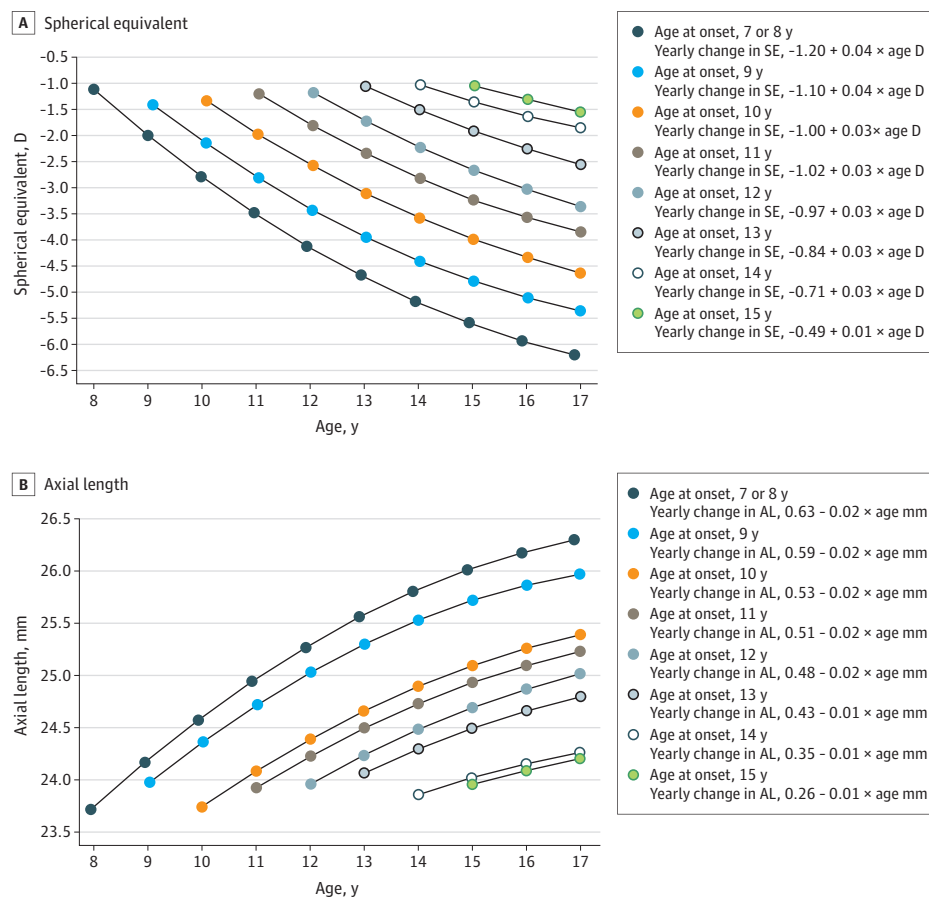
myopia onset to 10 years. With myopia onset after age 12 years, the risk of developing high myopia in adulthood was less than 5%.

Figure 4 shows the evolutions of SE and AL for different ages of myopia onset. After adjusting for the effects of age and sex, an earlier onset was associated with a faster rate of myopic SE progression (β, 0.03; 95% CI, 0.02-0.04; $P < .001$) and AL elongation (β, −0.02; 95% CI, −0.02 to −0.01; $P < .001$).

Discussion

The present study provides data on the exact risk of developing high myopia in adulthood for specific ages at myopia onset. The risk was relatively high for children with myopia onset in the early school ages (>50% for 7 or 8 years of age and approximately 30% for 9 years of age) but decreased substantially with a delay in each year of myopia onset. The study results highlight the immense importance of implementing myopia prevention strategies, such as increasing outdoor time, to reduce or delay the early onset of myopia. Studies aimed at devising new strategies could refer to the data provided herein to develop effective methods to definitely alleviate the burden of high myopia.

Figure 4. Evolution of Spherical Equivalent and Axial Length, Stratified by Age at Myopia Onset

A Spherical equivalent

Age at onset, 7 or 8 y
Yearly change in SE, −1.20 + 0.04 × age D
Age at onset, 9 y
Yearly change in SE, −1.10 + 0.04 × age D
Age at onset, 10 y
Yearly change in SE, −1.00 + 0.03× age D
Age at onset, 11 y
Yearly change in SE, −1.02 + 0.03 × age D
Age at onset, 12 y
Yearly change in SE, −0.97 + 0.03 × age D
Age at onset, 13 y
Yearly change in SE, −0.84 + 0.03 × age D
Age at onset, 14 y
Yearly change in SE, −0.71 + 0.03 × age D
Age at onset, 15 y
Yearly change in SE, −0.49 + 0.01 × age D

B Axial length

Age at onset, 7 or 8 y
Yearly change in AL, 0.63 − 0.02 × age mm
Age at onset, 9 y
Yearly change in AL, 0.59 − 0.02 × age mm
Age at onset, 10 y
Yearly change in AL, 0.53 − 0.02 × age mm
Age at onset, 11 y
Yearly change in AL, 0.51 − 0.02 × age mm
Age at onset, 12 y
Yearly change in AL, 0.48 − 0.02 × age mm
Age at onset, 13 y
Yearly change in AL, 0.43 − 0.01 × age mm
Age at onset, 14 y
Yearly change in AL, 0.35 − 0.01 × age mm
Age at onset, 15 y
Yearly change in AL, 0.26 − 0.01 × age mm

Data were estimated using mixed-effect regression models. D indicates diopter.

Compared with previous studies that reported the association of early myopia onset with great risk of high myopia,[9-12] the present study results are strengthened by the availability of annual eye examination data in a prospective cohort with a long follow-up. In a retrospective study conducted in Denmark,[11] 32.5% of participants who had myopia onset at 7 to 8 years of age had high myopia in adulthood. Their mean cycloplegic SE was −5.31 D. Among participants with age at myopia onset from 9 to 10 years, 17.0% developed high myopia in adulthood, with a mean cycloplegic SE of −4.66 D; and among participants with age at myopia onset from 11 to 12 years, none had high myopia, and they had a mean SE of −3.72 D.[11] In the present study, more myopic SE and a greater percentage of participants with high myopia were reported than those in the Danish study despite similar ages at onset. This difference might be due to ethnic and cultural differences between the 2 populations. Change in educational intensity during the past decades could be another reason because the Danish study was conducted more than 20 years ago.

As the secondary objective, we examined evolutions of refractions and AL for specific ages at myopia onset. Compared with participants with myopia onset at older ages, those with earlier onset presented a faster rate of myopia progression. This outcome could be another reason for the greater risk of developing high myopia in participants with an earlier age of myo-

pia onset besides the well-known period of myopia progression. The underlying mechanism for this observed association is speculative. It is plausible that genes and environmental factors before myopia onset, which determine the age of myopia onset, probably influence the participants in later life, affecting the rate of myopia progression. Age at onset, although a surrogate risk factor before myopia onset, could also be a surrogate risk factor for myopia progression.

Limitations

The main study limitation is the relatively small sample size, especially of the participants with age at myopia onset of 7 and 8 years. Future studies with a larger sample size might be needed to validate or modify the risks established herein. Another potential limitation is the generalizability of the study results to other populations. The risk of developing high myopia might vary depending on the sample ethnicity, culture, and educational intensity.

Conclusions

More than half of the Chinese study participants with myopia onset at 7 or 8 years of age developed high myopia in adulthood. This risk substantially decreases with a delay in

each year of myopia onset. The findings suggest the significance of prevention or delay of myopia onset at early school ages using strategies such as increasing outdoor time.

Future studies with a larger sample size may be needed to validate or modify the risks established in the present study.

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