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Age of onset of myopia predicts risk of high myopia in later childhood in myopic Singapore children

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Abstract

Purpose: To investigate the effect of age of myopia onset on the severity of myopia later in life among myopic children.

Methods: In this prospective study, school children aged 7–9 years from the Singapore Cohort Of the Risk factors for Myopia (SCORM) were followed up till 11 years (n = 928). Age of myopia onset was defined either through questionnaire at baseline (age 7–9 years) or subsequent annual follow-up visits. Age of onset of myopia was a surrogate indicator of duration of myopia progression till age 11 years. Cycloplegic refraction and axial length were measured at every annual eye examination. High myopia was defined as spherical equivalent of ≤−5.0 D. A questionnaire determined the other risk factors.

Results: In multivariable regression models, younger age of myopia onset (per year decrease) or longer duration of myopia progression was associated with high myopia (odds ratio (OR) = 2.86; 95% CI: 2.39 to 3.43), more myopic spherical equivalent (regression coefficient (β) = −0.86 D; 95% CI: −0.93 to −0.80) and longer axial length (β = 0.28 mm; 95% CI: 0.24 to 0.32) at aged 11 years, after adjusting for gender, race, school, books per week and parental myopia. In Receiver Operating Curve (ROC) analyses, age of myopia onset alone predicted high myopia by 85% (area under the curve = 0.85), while the addition of other factors including gender, race, school, books per week and parental myopia only marginally improved this prediction (area under the curve = 0.87).

Conclusions: Age of myopia onset or duration of myopia progression was the most important predictor of high myopia in later childhood in myopic children. Future trials to retard the progression of myopia to high myopia could focus on children with younger age of myopia onset or with longer duration of myopia progression.

Introduction

Myopia is a common ocular condition that affects over 80% of young adults in Asia, of which 15–20% have high myopia. Myopia may develop in early childhood, late teens or in adulthood.[1] Early onset of myopia has been reported to lead to more myopic refractive error or high myopia later in life.[2,3] High myopia, defined by a refractive error of at least −5.00 dioptres (D) or −6.00 D is associated with sight threatening complications such as retinal detachment, myopic retinopathy and glaucoma.[4–8] Myopia is influenced by both genetic and environmental factors[9] and precision

medicine takes into account individual variations in genes, environment, and lifestyle. This may allow better assessment of myopes at risk of progressing to high myopia, thus allowing the development of targeted treatment strategies to prevent the onset of high myopia.

A small number of studies in children[10] and adults[2,3] have found early onset of myopia leading to higher levels of myopia. A study of 159 Danish children aged 9–12 years showed that among those with age of onset less than 7 years, 54.5% of children developed high myopia. [10] In a British twin cohort of 1465 myopic adults aged 16–85 years, over 90% of high myopes were found to have worn glasses before 17 years of age.[2]

We aim to evaluate the effect of the age of onset of myopia on the severity of myopia in later childhood among myopic Singapore children aged 11 years in the Singapore Cohort Of the Risk factors for Myopia (SCORM) cohort. Age of onset of myopia was a surrogate indicator of duration of myopia progression till age 11 years.

Methods

SCORM cohort

The SCORM study was initiated in three schools in Singapore and the methodology has been described previously.[11–14] The total number of eligible students was 2913. Of the 2913, children from an eastern school (n = 660) and a northern school (n = 1023) were invited to participate in November 1999, while children from a western school (n = 1230) were invited to participate in May 2001. Of the 2913, 1979 children aged 7–9 years agreed to participate at baseline (participation rate = 67.9%): children from the eastern school (n = 313), northern school (n = 705) and western school (n = 961). There were four follow-up visits from 2000 to 2005. Of the 1979 participants, 345 children (17.4%) were lost to follow-up and 1634 children (82.6%) returned for ocular examination at age 11 years. Of the 1634 children, we further excluded those that were non-myopic (n = 585), with missing data on age of onset of myopia (n = 14) and those with age of onset of myopia at age 11 (n = 107). Thus, the final sample size for the current analysis was 928 (n = 761 Chinese, n = 113 Malays and n = 54 Indians and others). Informed written consent was obtained after the nature of the study was explained to the parents. The tenets of the Declaration of Helsinki were observed and approved by the Singapore Eye Research Institute Ethnics Committee.

Age of onset of myopia

At baseline (age 7–9 years), age of onset of myopia was determined through a questionnaire, as the reported age at which spectacles was first prescribed to correct myopia (352/928; 37.9%). For children who developed myopia at or after the baseline visit, the age of onset of myopia was determined via annual eye examinations at baseline or subsequent follow up visits (576/928; 62.1%).

Ocular measurements

Cycloplegia was induced in each eye by the instillation of three drops of 1% cyclopentolate hydrochloride (Cyclogyl; www.alcon.com) 5 min apart. At least 30 min after the last drop, five consecutive measurements of refractive error were obtained by using a table-mounted autorefractor (Model RK5; www.canon.com). Myopia was defined as spherical equivalent (S.E.) of at least −0.50 D. Axial length (AL) measurements were obtained using contact ultrasound biometry (Echoscan model US-800; www.usa.nidek.com). The average of six AL values was taken if the standard deviation (S.D.) of the six measurements was less than 0.12 mm. If the S.D. was 0.12 mm or greater, the measurements were repeated until S.D. was less than 0.12 mm. Ocular measurements were performed annually during the follow-up visits. Children were categorised into three groups according to their refractive error. Mild myopia was defined as S.E. between −0.50 to −2.99 D (n = 463), moderate myopia as S.E. between −3.00 to −4.99 D (n = 299) and high myopia as S.E. of at least −5.00 D (n = 166). Based on the World Health Organization (WHO) definition, we defined high myopia as ≤−5.00 D. This was also the cut-off point used in previous studies to identify people at greater risk of pathologic myopia.[15,16] As the outcome, S.E., was determined at the same age of 11 years for all children, the age of onset is also the interval of progression calculated as the number of years from age of onset till 11 years.

Questionnaires and measurement

During the baseline visit, a parent-administered questionnaire was completed to obtain information about demographic data such as race or type of school; and risk factors. Parents were considered to be myopic if they reported that they were currently wearing spectacles or contact lenses to see far distances. The number of myopic parents was classified into three categories (none, one or two). Near work activity was defined by the number of books read per week and was classified into two categories (≤2 books per week vs >2 books per week). Height was measured with children standing and without shoes.

Statistical methods

Data for the right and left eyes were highly correlated (Pearson correlation coefficient (r) = 0.92 for S.E. and

$r = 0.91$ for AL, respectively), thus only the right eye results were presented. Statistical analyses were performed on 928 children with available S.E. data and 927 children with available AL data. We compared the baseline characteristics of children who were present at the eye examination ($n = 1634$) to those who were lost to follow-up ($n = 345$) from the visit at age 11 years, using chi square or *t*-test as appropriate for the variable. As we did not have myopia data on children who were lost to follow up, we were not able to compare children lost to follow-up and children who remain in the study amongst myopic children. We then examined the distribution of the different types of myopia severity and S.E. by age of onset of myopia. As there were a smaller number of children who developed myopia between the ages of 3–6 years, these age categories were combined into one group ($n = 105$). Third, we examined the association of age of onset of myopia (explanatory or independent variable) with high myopia (dependent variable) using two multivariate logistic regression models; model 1 adjusted for gender, race and school (surrogate of education intensity in the Singapore setting); and model 2 additionally adjusted for number of books per week and parental myopia. For this analysis, mild and moderate myopia were combined into one category (−0.50 to −4.99 D) and used as the reference category. Fourth, we examined the association of age of onset of myopia with S.E. and AL at 11 years using multivariate linear regression models adjusted for the same variables. Height was additionally adjusted if AL was the outcome variable. Finally, to examine the predictive ability of age of myopia onset, we constructed receiver operating characteristic (ROC) curves separately and in combination with parental myopia and books per week, and compared the area under the curve (AUC) among the different models. The age of myopia onset is an indicator of duration of myopia progression till age 11 years. Statistical significance was set at $p < 0.05$. Data analysis was performed with STATA (StataCorp. 2009. Stata Statistical Software: Release 11, www.stata.com).

Results

Table 1 shows a comparison of children present at the eye examination that was conducted at age 11 years, compared to those who dropped out before or at this visit. In comparison to children who were lost to follow-up at age 11 years ($n = 345$), children who were present for eye examination at aged 11 years ($n = 1634$) were slightly older at baseline,

Table 1. Characteristics of children present at the eye examination compared to those who were lost to follow-up from the eye examination at age 11 years ($n = 1634$)

	Children present at the eye examination at 11 years ($n = 1634$)			Children dropped out from the eye examination at 11 years ($n = 345$)			
	N	Mean (S.D.)†	%†	*N*	Mean (S.D.)†	%†	P value‡
Age at baseline, years	1634	7.9 (0.8)		345	7.6 (0.8)		<0.001
Gender							
Male	824		50.4	177		51.3	
Female	810		49.6	168		48.7	0.77
Race							
Chinese	1220		74.6	259		75.1	
Malay	292		17.9	57		16.5	
Indian and others	122		7.5	29		8.4	0.73
Type of school							
School 1	238		14.6	75		21.7	
School 2	579		35.4	126		36.5	
School 3	817		50.0	144		41.8	0.001
Age of onset of myopia, years	1178	8.8 (2.2)		201	8.0 (1.9)		<0.001
Books read per week							
≤2	1054		66.0	200		59.5	
>2	543		34.0	136		40.5	0.02
Height, cm	1627	127.2 (7.6)		344	126.0 (7.5)		0.01
Parents with myopia							
No	676		41.4	90		26.3	
Either	626		38.4	150		43.9	
Both	330		20.2	102		29.8	<0.001

S.D., standard deviation.

†Mean (S.D.) for continuous variables and percentages for categorical variables.

‡Student *t*-test or Chi square test where appropriate (2-sided).

had a higher proportion of children from School 3, were myopic at an older age, had a higher proportion of children who read two books or less per week, were slightly taller and had a larger proportion of non-myopic parents. There were no significant differences by gender and race between the two groups.

Among the 928 children included in the study, the mean S.E. of the right eye was −3.32 ± 1.84 (S.D.) D and the mean AL was 24.68 ± 0.97 (S.D.) mm at aged 11 years. The mean age of onset of myopia was 8.0 ± 1.4 (S.D.) years old with 63.4% developing myopia at or after the age of 8. The distribution of S.E. and AL of children age 11 years across the various age of myopia onset categories were explored in *Figure 1*. Children with an earlier age of onset of myopia or longer duration of myopia progression showed a decreasing trend towards a more myopic S.E. (*Figure 2a*; $P_{trend} < 0.001$) and an increasing trend towards a longer AL (*Figure 2b*; $P_{trend} < 0.001$) at aged 11 years. *Figure 2* reveals the annual myopia progression rate between age of myopia onset to the follow-up at age 11 years, across the various myopia onset categories. The progression rates across all ages appears to be similar. However, it is evident that children with a longer duration of myopia progression show a more myopic refractive error. The final S.E. at aged 11 years was −5.48 D among children with age of onset of myopia from 3 to 6 years old or a duration of myopia progression of 5 years or more, while the S.E. at aged 11 years was −1.53 D among children with age of onset of myopia at 10 years old or a duration of myopia progression of 1 year.

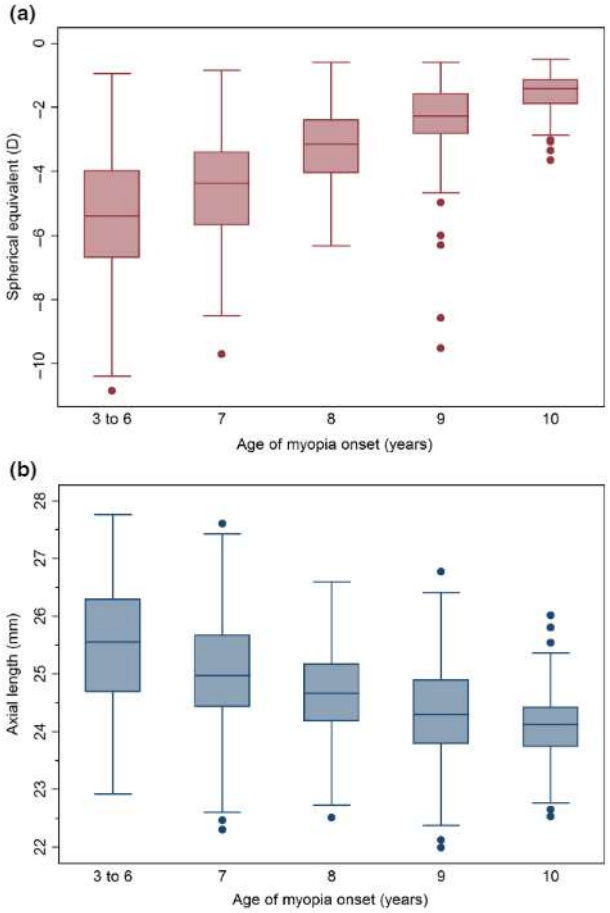

Figure 1. (a) Boxplots of spherical equivalent (D) among myopic children at age 11 years, stratified by age of myopia onset (n = 928). (b) Boxplot of axial length (mm) among myopic children at age 11 years, stratified by age of myopia onset (n = 928).

Table 2 shows the multivariate-adjusted associations of age of onset of myopia with high myopia, S.E. and AL after adjusting for gender, race, school, books per week and parental myopia. In multivariable model 2, every year younger in age of onset of myopia was associated with a higher odds of high myopia (OR, 2.86; 95% CI 2.39 to 3.43), more myopic S.E. (regression coefficient, −0.86; 95% CI −0.93 to −0.80) and longer AL (regression coefficient, 0.28; 95% CI 0.24 to 0.32). This finding demonstrates that children with a longer period of myopia progression were more likely to have more myopic refractive error, longer axial length and a higher risk of high myopia. In addition, a non-linear age of myopia onset model was also fitted as an exploratory analysis and this gave a better fit than the linear age model ($p < 0.001$; data not shown). Despite the statistical significance, the difference in the two trajectories had little practical significance except for the lower end of the age range where the sample size was very small. Thus, the linear final model was used for the age of myopia onset model.

After adjusting for gender, race, school, books per week and age of onset of myopia, children with two myopic parents were associated with higher odds of high myopia (OR, 1.82; 95% CI 1.03 to 3.21), more myopic S.E. (regression coefficient, −0.39; 95% CI −0.63 to −0.15) and longer AL (regression coefficient, 0.24; 95% CI 0.09 to 0.38) when compared to children with no myopic parents. However, no statistically significant association was observed between children with one myopic parent and high myopia (p = 0.16), S.E. (p = 0.06) or AL (p = 0.09). Longer AL was associated with children who read more than two books per week (regression coefficient = 0.11; 95% CI 0.002 to 0.22). However, children who read more than two books per week was not statistically significantly associated with high myopia (p = 0.38) or S.E. (p = 0.09; data not shown).

The AUC of risk factors predictive of high myopia were examined in univariate logistic regression analysis. Age of myopia onset was the strongest predictor of high myopia, with an AUC of 0.85, parental myopia had an AUC of 0.61 and books per week had an AUC of 0.56. *Figure 3* shows the ROC curves of age of myopia onset alone and in

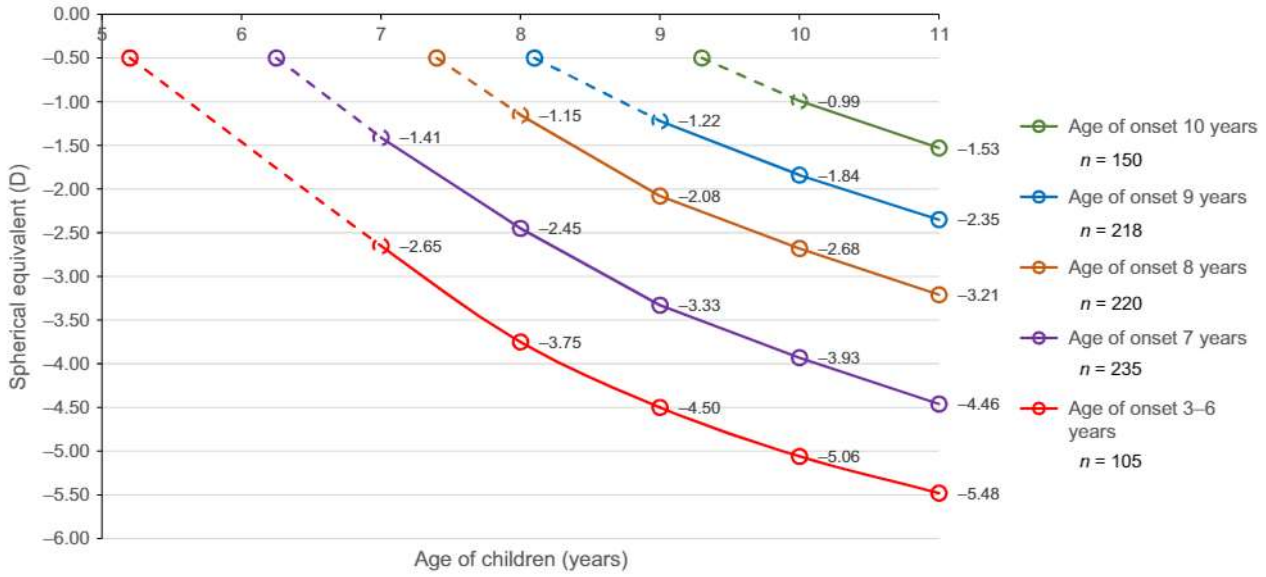

Figure 2. Yearly changes in spherical equivalent (D) of myopic children from age 7–11 years, stratified by age of myopia onset (n = 928). D, dioptres.

Table 2. Association of age of myopia onset with high myopia, spherical equivalent and axial length among 11-year old children (n = 910)

	High Myopia (≤−5.0 D) vs mild or moderate myopia (−0.50 to −4.9 D)			Spherical equivalent refraction (D)			Axial length (mm)		
Variable	***N***	**Multivariate logistic regression OR (95% CI)**	**P value**	***N***	**Multivariate regression coefficient β (95% CI)**	**P value**	***N***	**Multivariate regression coefficient β (95% CI)**	**P value**
Age of onset of myopia (per year decrease)									
Model 1[†]	910	2.93 (2.44 to 3.51)	<0.001	910	−0.88 (−0.94 to −0.82)	<0.001	905	0.29 (0.25 to 0.33)	<0.001
Model 2[‡,§]	910	2.86 (2.39 to 3.43)	<0.001	910	−0.86 (−0.93 to −0.80)	<0.001	905	0.28 (0.24 to 0.32)	<0.001

OR, odds ratio; D, dioptres; mm, millimetre.

[†]For the outcomes high myopia, spherical equivalent and axial length, the model 1 is adjusted for gender, race and school.

[‡]For the outcomes high myopia and spherical equivalent, the model 2 is adjusted for gender, race, school, books per week and parental myopia.

[§]For the outcome axial length, the model 2 is adjusted for gender, race, school, books per week, parental myopia and height.

combination with other variables. The addition of gender, race, school and parental myopia to age of myopia onset only improved the predictive ability of the model slightly (AUC = 0.87). The sensitivities and specificities were determined for each age of myopia onset cut-off from 3 to 10 years. The best combination of sensitivity and specificity was identified at the age of myopia onset at 7 years or younger or a duration of myopia progression of at least 4 years or more. Among those without high myopia (with mild/moderate myopia), there was a 74.3% probability that the child had an age of onset older than 7 years old or a duration of myopia progression of 3 years or less (specificity). Of those with high myopia, there was an 86.8% probability that the child had an age of onset at 7 years or younger or a duration of myopia progression of 4 years or more (sensitivity).

Discussion

In our SCORM cohort, an earlier age of onset of myopia or longer duration of myopia progression was the most significant predictor of high myopia at aged 11 years. In addition, younger age of onset or longer duration of myopia progression was also significantly associated with more myopic S.E. and longer AL at aged 11 years. The addition of other factors including parental myopia did not improve the prediction model.

Myopia typically develops at approximately 8 years of age, progresses over the next 10–15 years and may stabilize during teenage years[17] or early adulthood.[1] As the final eye examination was performed on children at age 11 years, the age of myopia onset till age 11 years may be a surrogate indicator of duration of myopia progression. In contrast, age of

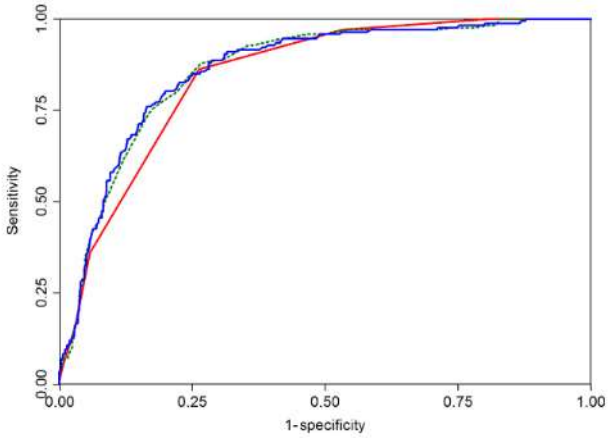

Figure 3. Receiver operating curves for prediction of high myopia in myopic children at age 11 years. (n = 910) AUC for model age of myopia onset (red line) 0.85; AUC for model age of myopia onset, gender, race and school (dashed green line) 0.87; AUC for model age of myopia onset, gender, race, school, books per week and parental myopia (blue line) 0.87.

onset may not represent the duration of myopia progression for most children. This is because differences in genetics, lifestyle and environmental factors among individuals influences the onset, progression rate and duration of myopia progression.[9] The age of myopia cessation varies for each child. Our results were in agreement with previous studies showing younger age of myopia onset and associations with more severe myopic S.E. in later life.[2,3,10] In 1995, a small cohort of 159 Danish children aged 9–12 years showed that children with age of myopia onset younger than 7 years were found to have more myopic S.E. compared to children with age of myopia onset older than 10 years.[10] However, this study was conducted more than 20 years ago and was limited by a small sample size. Similar findings were reported in a British cohort of 1465 subjects aged 16–85 years,[2] and in a cross-sectional study among 397 Argentinian office workers with a mean age of 43 years.[3] Both studies required subjects to recall age of myopia onset that may have occurred more than 20 years ago, which may result in recall bias.[2,3]

Age of onset of myopia could be the single best predictor for high myopia and a simple model with just age of onset of myopia may be sufficient to predict high myopia. Firstly, age of onset may already be a surrogate of genes or environmental factors before the onset of myopia, thus adding parental myopia and books per week again to the prediction of age of onset on high myopia only improved it minimally. Secondly, it is plausible that individuals diagnosed with early-onset myopia will have a longer duration for myopia to progress and are at higher risk of high myopia.[2] Thirdly, the progression rates may be greater in younger aged children compared to older aged children.[11,18] Our findings are particularly relevant to the epidemic of myopia in Asian countries. We showed that early-onset myopes (age 7 years or younger) may have increased likelihood of developing high myopia compared to school-onset myopes (age 8 years or older). This has important implications due to increased risk of pathological eye diseases associated with high myopia.[4] Thus, it is vital for clinicians to assess and manage myopes accordingly. A simple measure of age of onset alone is cost-effective and far less time-consuming than administering detailed questionnaires to evaluate the child's near work activities and parental myopia status.

Strengths of the study include the availability of age of myopia onset data and eye measurements in a prospective longitudinal cohort, which allows us to establish the temporal sequence of association. There was a reasonable proportion of high myopes (17.8%) at age 11 years to establish the association of age of onset and high myopia. Limitations of the study include eye measurements performed at a relatively young age of 11 years. At age 11 years, the refractive error of these children will continue to progress and may stabilize during early adulthood. Thus, our study may have low myopes who have not yet converted to high myopes. The final refractive error will depend on the rate of progression from age 11 years till early adulthood. As the rate of progression differs between people, individuals with the most severe myopic refraction at adulthood may not be the same group of children with high myopia at age 11 years. Despite the limitation that the final follow-up was at an early age of 11 years old, age of myopia onset emerged as a robust risk factor for predicting high myopia. Age of onset of myopia was obtained from both questionnaire and via eye examinations. Information collected through questionnaire may be subjected to misclassification bias as the parents had to recall the age of the child's first prescription. However, this was minimal among those who answered through questionnaire, as the length of recall at the baseline age of 7–9 years was not long. Moreover, questionnaires are a valid tool to identify myopic refractive status.[19] Of the 397 non-myopic children at baseline, 35 children (8.8%) reported to be myopes before baseline and prescribed with spectacles, but did not have myopia at the baseline examination. Of the 531 myopic children at baseline, 179 children (33.7%) reported to be non-myopic before the baseline visit. Thus, there might be 19.2% of children (179/928) who may have had myopia at an earlier age. Among the 179 children, the age of onset was between ages 7–9 years, with a S.E. of between −1.15 to −1.43 D at baseline. Moreover, the Health Promotion Board in Singapore conducts yearly eye tests for preschoolers and school children,[20] thus the difference between the actual age of onset and diagnosed age of onset may be small. As age of myopia onset was defined prospectively, the direction of the association should still remain.

Selection bias may exists as this study was a school-based sample rather than population-based. The overall non-

participation rate was 32.1% at baseline and the 11-year-lost to follow up rates was 17.4%. From the original cohort examined at baseline, 345 children (17.4%) dropped out at age 11 years, of which 82 had age of onset of myopia at or before the age of 7. The children who remained in the study tend to have a slightly older age of onset of myopia (8.8 vs 8.0 years) and a larger percentage of non-myopic parents (41.4% vs 26.3%), compared to children who dropped out of the study at age 11 years. This may have reduced the proportion of high myopes within our sample and may have underestimated the observed association. Other limitations may include misclassifications of parent-reported near work and parental myopia. Finally, lack of genetic data limits our ability to identify those who may be genetically predisposed to early-onset myopia and also at higher risk for high myopia.

In conclusion, this cohort showed that myopic Asian children who developed myopia at a younger age have a higher risk of high myopia, more myopic S.E. and longer AL. Age of onset of myopia or duration of myopia progression till 11 years emerged as the strongest predictor of high myopia in later childhood, more than other factors. Our findings suggest that information on the age of onset of myopia or duration of myopia progression alone may be sufficient to identify at risk patients of high myopia, which may be useful for targeted treatments (e.g., atropine eye drops) to retard the progression of myopia to high myopia. Further large studies should be conducted to evaluate age of onset or duration of myopia progression as a single predictor of high myopia in early adulthood.

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Disclosures

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