Acceleration of Myopic Shifts in Refraction and Axial Elongation Begins in the Premyopia Stage

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Purpose. To investigate the dependence of age-specific annual changes in refraction and axial elongation on starting refraction (refraction at the first of two yearly examinations).

Methods. Children (2259 participants) from the Guangzhou Twin Eye Study, with baseline ages from 7 to 15 years and 12 annual follow-ups, were included. Validation samples were drawn from the Guangzhou Longitudinal Outdoor Activity Study (GOALS). Refractions were categorized into three groups based on starting spherical equivalent (SE): myopia (SE ≤ -0.5 D), premyopia ($-0.5 <$ SE $\leq +0.75$ D), and hyperopia (SE $> +0.75$ D). Within each category, we divided data into different bins. Locally estimated scatterplot smoothing (LOWESS) lines were drawn to determine where myopic shifts in refraction and axial elongation begin to accelerate.

Results. In the hyperopic category, the annual change in SE was similar across all age groups. In the premyopic category, the annual change in SE increased as the starting SE decreased. Increases were particularly clear before age 12. In the established myopes, the annual change in SE was highest, up to approximately -1.0 D in those under 10 years, but remained relatively stable across all myopic bins at a given age. The LOWESS lines show that the trend of gradual increase in annual change in SE with decreasing starting SE begins at a starting SE of approximately $+1.00$ D. The trends in axial length were similar. Similar results were seen in the GOALS.

Conclusions. Myopia acceleration starts in mild hyperopia. Public health interventions should aim to keep refractions over $+1.00$ D to delay entry into the premyopic range.

Keywords: myopia, premyopia, emmetropia

It is now generally accepted that there is an epidemic of myopia in most parts of East Asia and some parts of Southeast Asia, characterized by the prevalence of myopia reaching approximately 80% by the end of 12 years of schooling.[1–3] In parallel, there has been a disproportionate increase in the prevalence of sight-threatening high myopia up to 10% to 30% of children, depending on the location.[4,5] The argument that this epidemic cannot be due to genetic change has now been generally accepted,[6] including by molecular geneticists.[7,8] However, some people continue to argue that genetic variation is the major cause of variation in the severity of myopia or underpins ethnic differences in prevalence and the impact of having myopic parents on myopia in children.[9] The main causal factors driving these increases in prevalence appear to be intense education from an early age[3,10–12] and limited amounts of time outdoors.[13–16] The emergence of these epidemics has led to an explosion of interest in methods for slowing the onset and progression of myopia.

One of the characteristics of the development of myopia is that rapid myopic shifts in refraction appear quite abruptly after a period of relatively slow myopic shifts.[17] This leads to a new phase during which myopic shifts in refraction in developing myopes appear to be higher, age-for-age, than in children who are not yet myopic. Unfortunately, the studies from the COMET (Correction of Myopia Evaluation Trial) Group[17] were based on noncycloplegic refractions, and thus, when this acceleration occurs during development relative to baseline refractive error was not precisely established. Mutti et al.,[18] had earlier shown, using data from the US-based The Collaborative Longitudinal Evaluation of Ethnicity and Refractive Error (CLEERE) study, that myopic shifts in refraction accelerated as many as 3 to 4 years before the onset of myopia, reached a peak in the year that myopia was first observed, and then declined subsequently, in all the ethnic groups examined. They also showed that there was a parallel acceleration of the rate of axial elongation before the onset of myopia. This finding has since been

confirmed in studies on children from Singapore[19,20] and China.[21] Overall, these results demonstrate that there are fundamental changes in the rates of axial elongation and myopic shift in refraction before the onset of myopia across ethnic groups, but they do not define the range of baseline refractions over which these accelerations appear. Understanding these changes in greater detail is likely to be crucial for the use of interventions to prevent the onset of myopia.

In 2019, Flitcroft et al.,[22] defined premyopia, a refractive state covering a range from +0.75 D to −0.50 D, which represents a slightly larger range of refractions (+0.5 D to −0.5 D) than that normally defined as emmetropic. Flitcroft et al defined this range as "a refractive state of an eye … in children where a combination of baseline refraction, age and other quantifiable risk factors provide a sufficient likelihood of the future development of myopia to merit preventative interventions."

This definition was developed based on other results from the CLEERE Study. The results showed that grade-specific cut-off refractions for prediction of subsequent development of myopia by grade 8 for children from grade 3 was around 0.75 D. It was also the best cut-off for prediction of myopia onset in younger children.[23] This definition of a premyopia has generated considerable interest, but it has largely been used as a range in which there is a high risk of subsequent development of myopia, without taking into account the need for additional indicators of high risk. Given previous work that has indicated that acceleration of myopic shifts in refraction occur before the onset of myopia, it seems possible that this acceleration occurs during the premyopia range.

In this article, we use data from the Guangzhou Twin Eye Study (GTES)[24,25] and the Guangzhou Outdoor Activity Longitudinal Study (GOALS)[16] to establish how rates of myopic shift in refraction and axial elongation vary with age and background refractive status and to more precisely define the age-specific range of refractions over which increased rates of myopic shift in refraction and axial elongation appear before the onset of myopia.

Methods

Recruitment of Participants

In brief, all twins aged 7 to 15 years living in Guangzhou were invited for annual follow-up examinations from 2006 to 2018 for the GTES. In the current analysis, only participants who participated in a particular visit and attended the subsequent year's follow-up were included. Only records obtained between the ages of 7 and 18 were used. For the GOALS, students from 12 schools who were 6 years old and in the first grade of primary school at baseline were included. The trial was initiated in 2009 and followed for 3 years, with data collection taking place four times, over the age range of 6 to 9 years old. Participants with manifest strabismus, nystagmus, ocular trauma, congenital cataract, retinopathy of prematurity, or participants with intellectual disabilities who were uncooperative in the examination were excluded.

All participants or their legal guardians were asked for informed consent after an in-depth explanation of the study. The Zhongshan University Ethics Review Board and Ethics Committee of Zhongshan Ophthalmic Center approved of the study, which was conducted in accordance with the tenets of the Declaration of Helsinki.

Measurement of Refraction and Axial Length (AL)

In the GTES, after arriving at the Zhongshan Ophthalmic Center, the identity of all twins was verified. After that, they were given examination forms and questionnaires to complete. The ophthalmic examination began with the assessment of uncorrected visual acuity, utilizing a retroilluminated LogMAR chart featuring tumbling E optotypes (Precision Vision, La Salle, IL, USA). Ocular biometric parameters, including AL and anterior chamber depth were measured using noncontact partial-coherence laser interferometry (IOLMaster, Carl Zeiss Meditec, German), or optical low-coherence reflectometer Lenstar LS 900 (Haag-Streit AG, Koeniz, Switzerland). Measurements were taken five times. If the difference of any two measurements was greater than 0.05 mm, the outlier was deleted and a repeated measurement was conducted. Furthermore, We used the longitudinal data results to recheck and clean the data.

Cycloplegia refraction was then measured for all participants. Cycloplegia was induced using cyclopentolate 1% solution (Alcon, Fort Worth, TX, USA). The first two drops of cyclopentolate were administered 5 minutes apart and a third drop was given 20 minutes later. Refraction measurements were conducted at least 15 minutes after the last administration of cyclopentolate eyedrops to make sure complete cycloplegia (determined by the absence of light reflex and a dilated pupil ≥6 mm in diameter) was achieved. If the light reflex was still present, after an additional 15 minutes a final measurement was taken), regardless of the persistence of the light reflex. All measurements were taken using an autorefractor (Topcon KR8800, Japan). Three readings were taken per eye. If the difference of any two readings was greater than 0.5 D, the outlier was deleted and an additional reading was acquired. Then, the best-corrected visual acuity was assessed using the same visual chart used for the uncorrected visual acuity test. For GOALS, all examinations were performed at the schools. The examination procedure was the same as GTES and was conducted by the same team.

Definition and Statistical Methods

Right eyes were used arbitrarily for analysis. Spherical equivalent (SE) was defined as the sum of 1/2 cylinder power and sphere. The refractive status was classified into three categories: myopia (SE ≤ −0.5 D), premyopia (−0.5 < SE ≤ +0.75 D), and hyperopia (SE > 0.75 D) (including mild, moderate, and high hyperopia).

In the analysis of the GOALS data, we pooled students by grade and treated each grade as an age cohort; for example, all first-grade pupils were assigned an age of 6 years, even though 8.2% were slightly older than 7 years at the time of testing. The same convention was applied to the higher grades

We restricted the analysis to participants with two sequential annual follow-up visits. Bar plots were used to investigate the annual SE change and AL elongation over the subsequent year against starting refraction, which is defined as the refraction recorded at the first of the two visits. Within each refractive category, we used varying increments to segment each category into different bins, 0.50 D bins for the myopia and hyperopia categories and 0.25 D for the premyopia category, thereby facilitating a more granular evaluation of the data in the premyopia range. Scatter plots

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and locally estimated scatterplot smoothing (LOWESS) lines were then used to examine the annual changes in SE and AL over the subsequent year against starting refraction as a continuous variable. Data from the GTES and GOALS were analyzed similarly. Statistical analyses were performed using a commercial statistical software package (STATA, version 16.0; Stata Corp., College Station, TX, USA). A P value of less than 0.05 was defined as statistically significant.

Results

For the GTES study, a total of 2259 participants, with 48.2% males (1088), were eligible and enrolled in the current analysis. The age-specific numbers of participants and distribution of annual change in SE and AL in the next year by different starting refraction are presented in Table. Within each age group, the annual change in SE and AL increased progressively from the hyperopia to myopia categories (P for trend test, all $P < 0.05$).

The annual change in SE against starting refraction is shown in Figure 1. In the hyperopic range, the annual change in SE was similar across all age groups, with most values being around −0.2 D/year. In the premyopic category, the annual change in SE gradually increased as the starting SE decreased from the +0.75 to +0.5 D bin to the −0.25 to −0.5 D bin. This trend was particularly evident before the age of 12. After 12 years of age, this age-related trend gradually decreased and a significant change was not visible for ages over 15 years. In the established myopes, the annual change in SE was the highest among the three categories, reaching around −1.0 D in participants younger than

Table. The Age-Specific Annual Change in SE (D) and AL (mm) Over the Next Year by Starting Refractive Category

		Starting SE: SE >0.75 D (Hyperopia)			Starting SE: −0.5 < SE ≤ 0.75 D (Premyopia)			Starting SE: SE ≤ −0.5 D (Myopia)		
Baseline Age	Sex (Male/Female)	No	Annual SE Change in the Next Year (D)	Annual Change in AL Over the Next Year (mm)	No	Annual SE Change in the Next Year (D)	Annual AL Change in the Next Year (mm)	No	Annual SE Change in the Next Year (D)	Annual AL Change in the Next Year (mm)
7	70/56	77	−0.19 ± 0.31	0.19 ± 0.12	36	−0.33 ± 0.53	0.29 ± 0.32	13	−0.89 ± 0.44	0.46 ± 0.18
8	214/196	194	−0.23 ± 0.36	0.21 ± 0.16	138	−0.54 ± 0.55	0.36 ± 0.22	78	−0.82 ± 0.60	0.45 ± 0.21
9	352/339	277	−0.33 ± 0.37	0.21 ± 0.13	218	−0.52 ± 0.55	0.34 ± 0.21	196	−0.82 ± 0.51	0.43 ± 0.21
10	441/456	233	−0.27 ± 0.31	0.17 ± 0.11	310	−0.48 ± 0.48	0.31 ± 0.18	354	−0.82 ± 0.43	0.41 ± 0.16
11	516/509	187	−0.36 ± 0.34	0.16 ± 0.13	300	−0.44 ± 0.44	0.26 ± 0.16	538	−0.71 ± 0.44	0.35 ± 0.15
12	623/646	168	−0.24 ± 0.33	0.13 ± 0.12	338	−0.34 ± 0.44	0.21 ± 0.17	763	−0.57 ± 0.44	0.29 ± 0.17
13	675/699	135	−0.16 ± 0.32	0.09 ± 0.10	311	−0.25 ± 0.40	0.14 ± 0.13	928	−0.48 ± 0.40	0.23 ± 0.13
14	684/760	116	−0.09 ± 0.33	0.06 ± 0.07	247	−0.22 ± 0.38	0.13 ± 0.13	1081	−0.38 ± 0.37	0.18 ± 0.12
15	721/769	110	−0.15 ± 0.34	0.05 ± 0.07	240	−0.14 ± 0.08	0.08 ± 0.11	1140	−0.29 ± 0.42	0.14 ± 0.14
16	659/768	99	−0.08 ± 0.36	0.04 ± 0.08	208	−0.04 ± 0.35	0.05 ± 0.10	1120	−0.20 ± 0.37	0.10 ± 0.12
17	569/682	80	−0.14 ± 0.36	0.02 ± 0.06	172	−0.14 ± 0.35	0.06 ± 0.08	999	−0.18 ± 0.35	0.09 ± 0.10

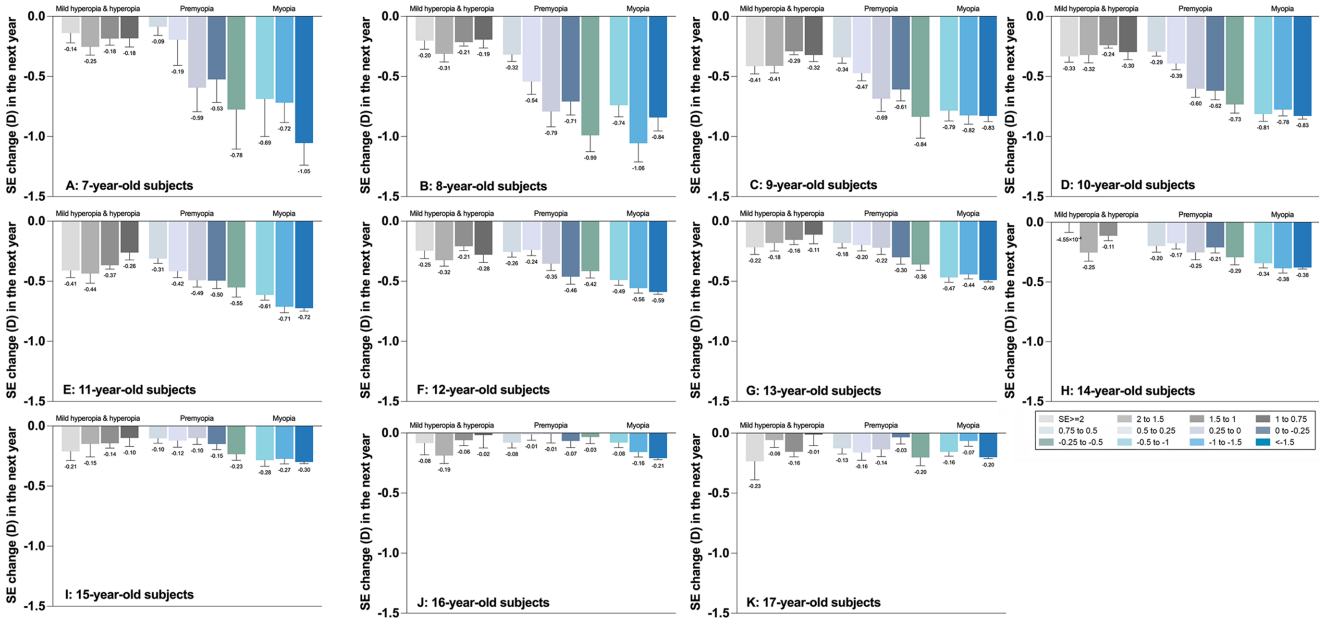

Figure 1. Annual changes in SE against starting refraction by age. (**A**) Annual change in SE from baseline at age 7 in children aged 7 to 8 years. (**B–K**) Corresponding changes for ages 8 to 17 years. Data are expressed as mean ± standard error).

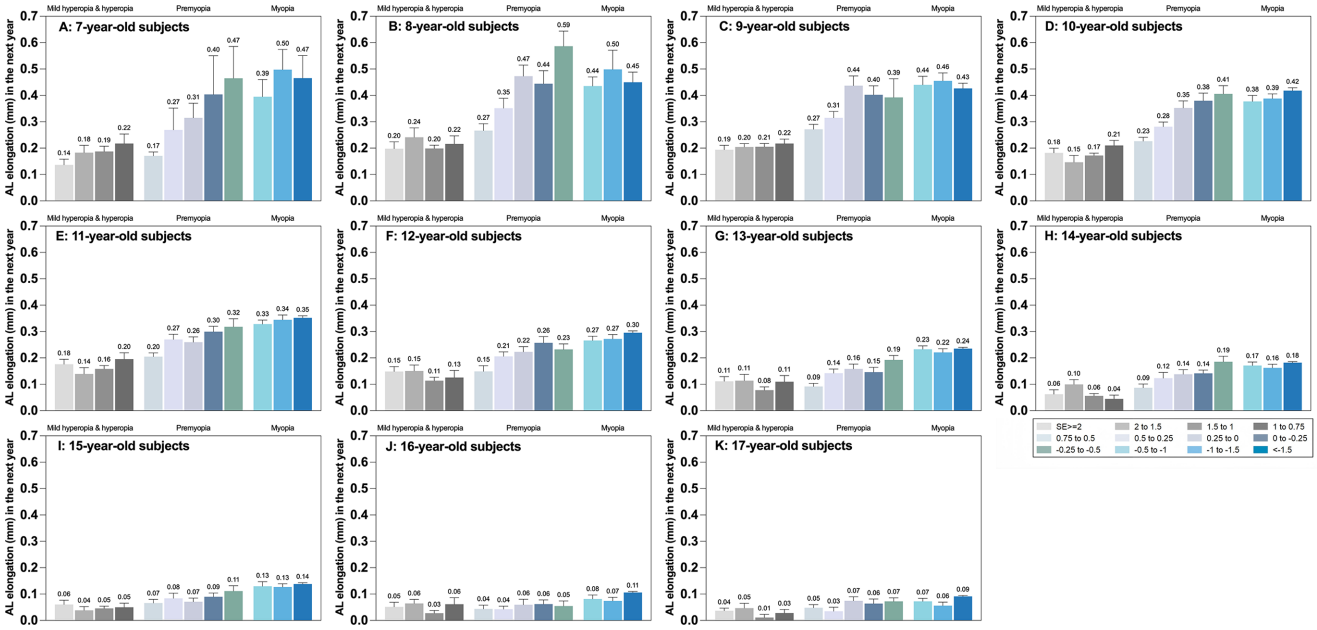

Figure 2. Annual increases in AL against starting refraction by age. (**A**) Annual AL change from baseline at age 7 in children aged 7 to 8 years. (**B–K**) Corresponding changes for ages 8 to 17 years. Data are expressed as mean ± standard error).

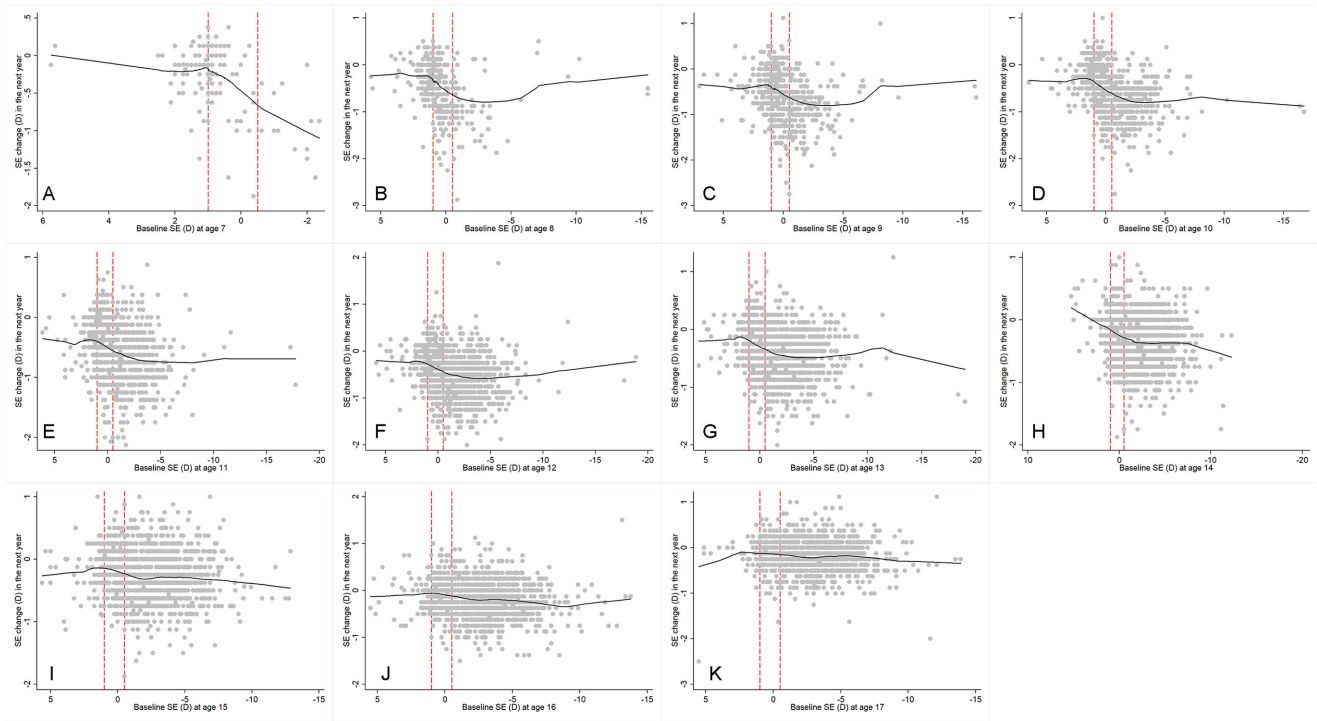

Figure 3. Scatter plots and LOWESS lines for annual change in SE against starting refraction by age. (**A**) Annual SE change from baseline at age 7 in children aged 7 to 8 years. (**B–K**) Corresponding changes for ages 8 to 17. *Solid line*, LOWESS line. *Dotted vertical line*, reference values of +1.0 (*left*) and −0.5 (*right*).

10 years old. However, across all bins, the annual change in SE remained relatively stable.

Similar results were obtained for the rates of annual increase in AL against starting refraction (Fig. 2). In the hyperopic category, before the age of 12, the annual AL elongation was in the range of 0.20 to 0.25 mm; between the ages of 12 and 15, it was around 0.15 mm; and after the age of 15, it was less than 0.10 mm. In the premyopic category, the annual increase in AL gradually increased as the starting SE decreased from +0.75 to +0.50 D bin to the −0.25 to −0.50 D bin. This trend is particularly evident before the age of 12. After 13 years of age, this trend almost disappears. In

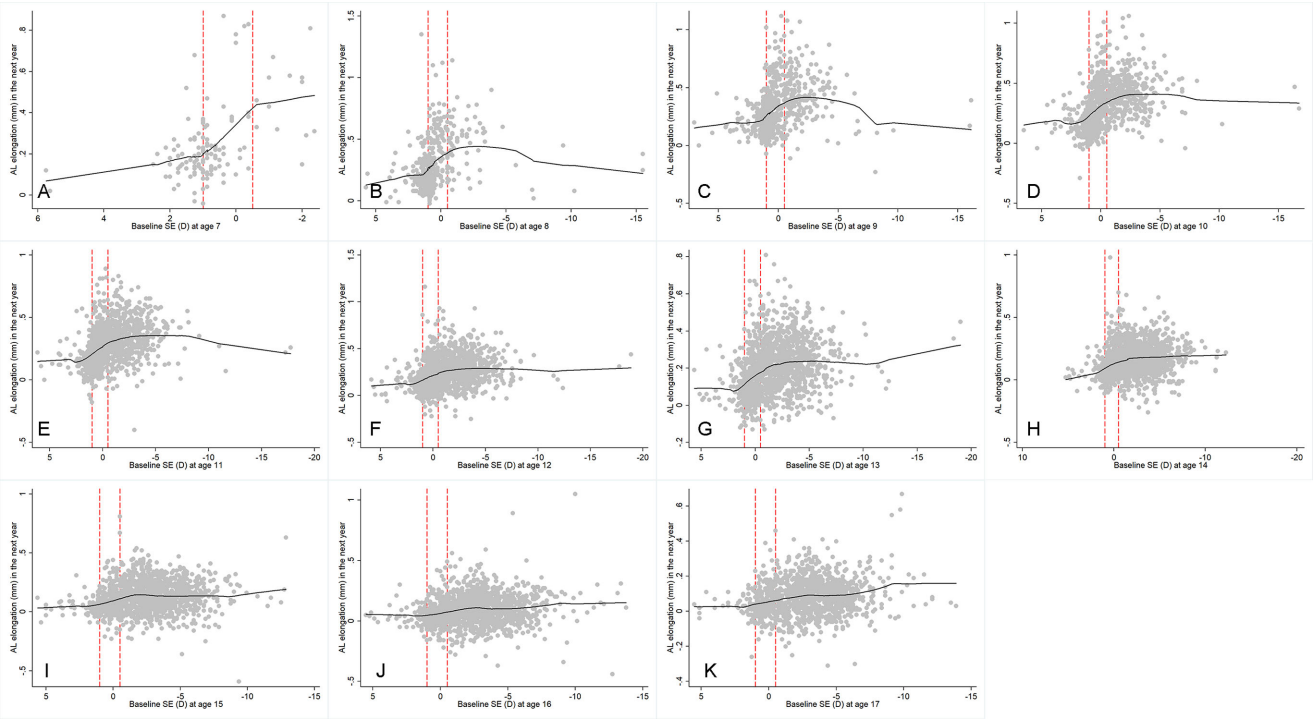

Figure 4. Scatter plots and LOWESS lines for annual change in SE against starting refraction by age. (**A**) Annual SE change from baseline at age 7 in children aged 7 to 8 years. (**B–K**) Corresponding changes for ages 8 to 17 years. *Solid line*, LOWESS line. *Dotted vertical line*, reference values of +1.0 (*left*) and −0.5 (*right*).

established myopes, the annual increase in AL is the highest of all three refractive categories, reaching up to over 0.5 mm in participants younger than 10 years old. For each age, the annual increase in AL elongation is similar as the starting SE decreases toward more severe myopia

The scatter plots and LOWESS lines for the annual change in SE and AL against starting refraction are presented in Figures 3 and 4, respectively. The LOWESS lines indicate that the annual changes in SE do not vary significantly with starting refraction in both the hyperopic and myopic range, whereas they show a continuous increase in the premyopic range. Correspondingly, the annual changes in AL show a continuous decrease as starting refractions become more myopic in the premyopic group.

The GOALS dataset gave similar results. A total of 1415 participants, with 54.1% male (766), were eligible and enrolled in the current analysis. The age-specific numbers of participants and distribution of annual change in SE and AL by starting refraction are presented in Supplementary Table S1. Within each age group, the annual changes in SE and AL increase in absolute magnitude from the hyperopia category to established myopes (P for trend test, all $P < 0.05$). The bar plots illustrating the annual changes in SE and AL against starting refraction, from ages 6 to 9 years, are presented in Supplementary Figures S1 and S2. The scatter and LOWESS plots are shown in Supplementary Figures S3 and S4.

Discussion

These results confirm that the rates of change in SE and AL are systematically higher in established myopes compared with hyperopes. These higher rates first become apparent in the premyopia range. They do not occur abruptly when the cut-off for myopia (−0.5 D) or emmetropia (0 D, or a range from +0.5 to −0.5 D) is reached, but appear to increase in magnitude across the entire premyopic range, as myopic shifts in refraction bring refractions closer to the cut-off for myopia. There is some evidence that rapid rates of change may start as early as around +1.00 D, with little evidence of accelerated rates at more hyperopic refractions, and little further acceleration once myopia has been achieved.

The results also suggest that a tendency to increased rates of change can be seen in the range from +1.00 D to +0.75 D, but that rates of change are more stable with starting refraction for more hyperopic refractions. This tendency is more obvious in younger children. Given that measurements of refraction are subject to an instrument error of ±0.25 D, which is significant relative to the magnitude of annual changes in refraction of 1.00 D or less, the results on changes in SE are inherently noisy, but LOWESS analysis should average out underlying random measurement errors, revealing the underlying trend. Measurements of AL are more precise, but essentially the same pattern is seen. This finding suggests that the regulation of axial elongation, which is the basis of myopic shifts in refraction, changes significantly when starting refractions drop below approximately 1.00 D and enter the premyopia range, before the onset of myopia, consistent with earlier evidence of changes occurring before the onset of myopia.[19–21]

Premyopia has so far been defined as a range of refractions where the risk of rapid development of myopia is increased.[22] At one level, this must be true because premyopic refractions are, by definition closer to the cut-off for myopia than more hyperopic refractions, and thus the cumulative change required to establish myopia is less. Thus, even

if axial elongation did not accelerate, a higher risk associated with starting premyopia compared with starting hyperopia would be expected. These results show that, in addition, the premyopic range is also a range in which rates of change in SE and AL start to accelerate in magnitude, which would further increase the likelihood of rapid development of myopia at these starting refractions. These results are consistent with previous studies that have demonstrated that the acceleration of axial elongation and myopia progression appears before the onset of myopia, but more precisely delineate that the changes appear over a range of refractions that covers the premyopia range. It is interesting that these changes appear to be similar across ethnic groups,[18–21] suggesting that the changes in regulation of ocular growth taking place over the premyopia range are common to all ethnic groups and appear to be a fundamental feature of the eye growth control mechanisms. It is, however, important to note that the overall risk of developing myopia is much higher in East Asia and Singapore than in Western countries, despite the similar changes occurring in the premyopia range.

There is other evidence of substantial changes in regulation of axial elongation in the transition from hyperopia to myopia. Schaeffel and Swiatczak et al.,[26–28] have reported that the myopic eye loses the ability to respond to defocused red or blue light by changing choroidal thickness seen in hyperopic/emmetropic eyes. In addition, significant simplification of the ERG responses of myopic eyes compared with nonmyopic eyes, which would suggest considerable changes to retinal processing has been reported.[29] Whether all of these changes occur in parallel over the premyopia range and are based on the same changes in retinal processing is an important question to resolve. It is also important to determine whether these changes in processing affect the ability of myopia prevention and control techniques to work in the premyopia range.

We pooled data from two Guangzhou-based cohorts, GTES and GOALS. Although the overall trajectories were parallel, myopia conversion in premyopes and annual changes in SE and AL were consistently larger in GOALS than in GTES, most clearly at ages 7 to 8 years. This discrepancy likely reflects differences in sampling: GTES enrolled twins from both urban and suburban districts, whereas GOALS recruited predominantly from city-center key primary schools, where myopia prevalence and development have been shown to exceed those in less urbanized areas.[30–32]

Although our sample is a population-based sample of twins, previous reports have demonstrated that there is no significant difference in refraction between twins and a general population-based samples.[33] In addition, twin studies from Australia[34] have demonstrated that there is no significant difference in refraction between their twin populations and the general population.

The strengths of this study are the unique collection of longitudinal data on the development of refraction and AL in Chinese children of school age, based on annual measurements, using the gold standard, cycloplegic refraction. One of the limitations of the study is that numbers are limited for younger children aged 7 years, owing to the initial recruitment protocol. The study is also limited to children of Chinese ancestry growing up in one city in China; however, results indicating acceleration before the onset of myopia have been reported for children of Chinese ancestry growing up in Singapore and in the United States, where acceleration before the onset of myopia was seen in a population of predominantly European ancestry.

In summary, these results suggest that the transition from hyperopia to myopia, which is undergone by any child who is born hyperopic and who becomes myopic later in life, that is, the vast majority of myopic children, is a complex process during which the eye loses control over eye growth, with high rates of myopic shift in refraction contributing to the rapid onset of myopia. Ultimately, particularly in children who are young when this change takes place, this would lead to the disproportionate development of high myopia. The changes in retinal processing to produce this acceleration of rates of axial elongation and related shifts in SE are currently unclear, but understanding this process in detail is important, because of the current interest in targeting children with premyopic refractions for myopia prevention. The evidence that axial elongation accelerates during the transition from mildly hyperopic refractions to myopia underlines the importance of early intervention at this stage, to limit the deleterious effects of the current epidemic. Furthermore, this phenomenon also provides a new clinical clue that may inform future etiological research into myopia onset. Given that the development of myopia is a cumulative process, largely based on cumulative axial elongation, the public health target should be to maintain refractive status in the mild hyperopic range and to prevent children entering the premyopic range of refractions, by increasing time outdoors and decreasing early educational pressures, rather than waiting to apply clinical interventions at this stage.

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