The role of lens in early refractive development: evidence from a large cohort of Chinese children

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Abbreviations: LP = lens power; CP = corneal power; SER = spherical equivalent refraction; SD = standard deviation; AL = axial length; D = diopter; ANOVA = analysis of variance; RESC = Refractive Error Study in Children, COMET = Correction of Myopia Evaluation Trial; CLEERE = Collaborative Longitudinal Evaluation of Ethnicity and Refractive Error Study; SCORM = Singapore Cohort of the Risk Factors for Myopia.

Synopsis

The endpoint of early refractive development was mild hyperopia instead of emmetropia. Achievement and maintenance of the mild hyperopic status were largely determined by a push-back mechanism between the axial elongation and lens power loss.

Abstract

Aims: To document longitudinal changes in spherical equivalent refraction (SER) and related biometric factors during early refractive development.

Methods: This was a prospective cohort study of Chinese children, starting in 2018 with annual follow-ups. At each visit, children received cycloplegic autorefraction and ocular biometry measurements. Lens power (LP) was calculated using Bennett's formula. Children were divided into eight groups based on baseline age: the 3-year-old (n=426, 49.77% girls), 4-year-old (n=834, 47.36% girls), 6-year-old (n=292, 46.58% girls), 7-year-old (n=964, 43.46% girls), 9-year-old (n=981, 46.18% girls), 10-year-old (n=1181, 46.32% girls), 12-year-old (n=504, 49.01%), and 13-year-old (n=644, 42.70%) age groups.

Results: This study included right-eye data from 5826 children. The 3- and 4-year-olds demonstrated an inflection point in longitudinal SER changes at a mild hyperopic baseline SER (+1 to +2 D), with children with more myopic SER showing hyperopic refractive shifts while those with more hyperopic SER showing myopic shifts. The hyperopic shift in SER was mainly attributed to rapid LP loss, and were rarely seen in the older age groups. Axial elongation accelerated in the premyopia stage, accompanied by a partially counter-balancing acceleration of LP loss. For children aged 3 to 7 years, those with annual SER changes <0.25 D were all mildly hyperopic at baseline (mean: 1.23 D, 95%CI: 1.20 to 1.27 D).

Conclusion: Our findings suggest that during early refractive development, refractions cluster around or above +1.00 D. There is a pushback process in which increases in the rate of LP occur in parallel with increases in axial elongation.

Key Words: lens, axial length, myopia, emmetropization, children.

What is already known on this topic

Emmetropization refers to the process from neonatal hyperopia to emmetropia during childhood, which involves a complex interaction between different components of the eye. The lens undergoes complex morphological and power changes during this process.

What this study adds

Based on a large prospective cohort study of Chinese children, we found that early refractive development targeted mild hyperopia, which was achieved and maintained by a push-back mechanism between the axial elongation and lens power loss.

How this study might affect research, practice or policy

Our study findings provide important evidence that the lens plays an important role in early refractive development, and the crucial timepoint for myopia prevention is from a hyperopic reserve to premyopia, rather than from emmetropia to myopia.

Introduction

The term "emmetropization" was coined in the early 20th century to describe the process by which children transition from neonatal hyperopia to emmetropia as they grow older.[1 2] Population studies from different parts of the world, including the Refractive Error Study in Children (RESC) series, mostly reported that mild hyperopia is the most common type of refraction among children and young adults free of myopia.[3-6] Even in countries with a high prevalence of myopia, mild hyperopia is still the preferred state of refraction among preschool children.[6-8] This evidence has led to revived interest in the concept of a hyperopic reserve as the normal end-point for refractive development.

An endpoint of refractive error could only be achieved and maintained if all the major refractive components reach a balance in their growth rates, but it remains inconclusive how this was accomplished. The corneal power changes rapidly before stabilizing after 2 or 3 year of ages, while the axial length keeps increasing though with difference rates at different ages, leading to continuous myopic shifts in refraction.[9] The lens, on the other hand, reveals more complex morphological and power changes throughout the childhood, which collectively result in hyperopic shifts in refraction.[10] We speculate that the lens may act as a balance weight to compensate for the myopic shifts associated with axial elongation, resembling an active control underlying emmetropization. And myopia, from this perspective, represents a failure of the lens to compensate for axial elongation. A recent study by Ma et al. also provided evidence of a 'push-back' mechanism for the eye to maintain mild hyperopia around and above +1.00 D among Chinese children aged 3 to 5 years.[11]

To further clarify these issues, we assessed the longitudinal changes in refraction and related biometric factors based on a large prospective cohort of Chinese children aged 3 to 13 years.

Materials and Methods

Study population

The Zengcheng schOOl Myopia study (ZOOM) is a prospective longitudinal study which recruited children from four different grades (first-year kindergarten, first- and fourth-year primary school, and first-year junior high school) from the Zengcheng and Huadu Districts of Guangzhou, China. Written informed consents were obtained from children' parents or legal guardians at baseline in 2018, and follow-up examinations were performed annually. Details of the study population and methodology had been published previously.[10 12]

Examinations and measurements

Height (to the nearest 0.1cm) and weight (to the nearest 0.1kg) were measured using a height and weight monitor (RGZ-120-RT, SUHONG, China). Ocular biometry was measured using non-contact partial-coherence laser interferometry (IOLMaster 700; Carl Zeiss Meditec, Oberkochen, Germany) before cycloplegia, and the average of five measurements were recorded. Two drops of 1% cyclopentolate were administered 5 minutes apart, and after approximately 20 minutes, a third drop was administered. The pupil size and light reflex were examined by ophthalmologists and cycloplegia was deemed complete if the pupil was dilated to at least 6 mm and the pupillary light reflex was absent. Otherwise, an additional drop of cyclopentolate was administered and the pupil size and light reflex were re-examined 20 minutes later. Cycloplegic autorefraction (KR8800, Topcon, Tokyo, Japan) was performed, and three successive readings with a standard error of <5% were obtained. Slit-lamp examination was performed by an ophthalmologist, and the same equipment and protocol were followed throughout the study.

Statistical analysis

Children who participated in the baseline and at least one follow-up examinations were included, the exclusion criteria included: (1) unavailable data on spherical equivalent refraction (SER) or ocular biometry at baseline, (2) history of orthokeratology treatment or myopia corrective surgery, (3) history of ocular diseases or ocular trauma, (4) severe astigmatism (cylinder power ≤ -5 D), (5) severe hyperopia (SER > 5 D), (6) high myopia (SER < -5 D) at first grade, (7) unable to satisfy cycloplegia requirements. Only data from the right eye were used. The SER was calculated as the spherical power (D) plus half of the cylinder power (D). The corneal power (CP) was calculated as the average of the steepest and flattest meridian. The lens power (LP) was calculated using Bennett's equation.[13 14]

Children were divided into eight age groups based on their baseline age, as follows: 3-year-old, 4-year-old, 6-year-old, 7-year-old, 9-year-old, 10-year-old, 12-year-old, and 13-year-old age groups. Children aged 5, 8, and 11 years were further excluded from the analysis due to a very small sample size. The difference across age groups was assessed using the Chi-square test. The trend across different age groups was assessed by the Kruskal-Wallis test for baseline SER, and by linear regression for baseline AL, CP, and LP.

Multiple linear regression models were fitted to assess the associations between longitudinal SER changes and gender, baseline height, baseline SER as well as the longitudinal change in CP, AL, and LP during the follow-up. For children in each age group, lowess plots, fitted separately for myopic and non-myopic children, were presented to show the mean annual changes in SER, AL, and LP with baseline SER. Children with an annual SER change of less than 0.25 D were deemed stable in refractive status, and the corresponding observed mean and 95% confidence interval (CI) baseline SER for these children aged between 3 and 7 years were calculated. The 95%CI under bootstrapping 100,000 times was calculated. All analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

Of the 7050 children recruited, we excluded 553 children (7.84%) with no data on SER or ocular biometry measurement at baseline, 258 children (3.66%) with a history of orthokeratology treatment or myopia corrective surgery, 310 children (4.40%) with history of ocular diseases or trauma, 8 children (0.11%) with severe astigmatism, 14 children (0.20%) with severe hyperopia, 8 (0.11%) with high myopia at first grade, 38 children (0.54%) unable to satisfy cycloplegia requirements, and 35 children (0.50%) with baseline ages of 5, 8, or 11 years. As a result, a total of 5826 (82.64%) children aged 3-13 years at baseline were included in the final analysis.

Table 1 shows the baseline characteristics of children in each age group. The 3-year-old age group included 426 children (49.77% girls), the corresponding sample size in the 4-, 6-, 7-, 9-, 10-, 12- and 13-year-old age group was 834 (47.36% girls), 292 (46.58% girls), 964 (43.46% girls), 981 (46.18% girls), 1181 (46.32% girls), 504 (49.01% girls), and 644 (42.70% girls), respectively. No significant difference was observed for gender distribution across age groups, but children in the older age group showed significantly more myopic SER, longer AL, lower CP, and lower LP (all with P<0.001).

Table 2 and Figure 1 show the changes in SER, AL, CP, and LP during the follow-up for children in each age group. At the first-year follow-up, the mean (SD) change in SER in the 3-, 4-, 6-, 7-, 9-, 10-, 12- and 13-year-old age group was -0.04 (0.34), -0.05 (0.35), -0.23 (0.32), -0.24 (0.34), -0.48 (0.45), -0.52 (0.47), -0.47 (0.41) and -0.43 (0.39) D, respectively. The corresponding values during the second-year follow-up was 0.04 (0.38), -0.006 (0.37), -0.11 (0.37), -0.17 (0.39), -0.46 (0.49), -0.46 (0.46), -0.28 (0.38) and -0.26 (0.35) D, respectively. Overall, children in the older age group at baseline tended to have larger myopia shifts in refraction, with faster AL increase and smaller LP reduction (all with P<0.001). Changes in CP were very small though statistically significant for all children at both follow-ups (P<0.001).

Table 1. Baseline characteristics of the study participants (N=5826)

	3-year-old	4-year-old	6-year-old	7-year-old	9-year-old	10-year-old	12-year-old	13-year-old	P value*
Number, (%)	426 (7.31)	834 (11.83)	292 (4.14)	964 (13.67)	981 (13.91)	1181 (16.75)	504 (7.15)	644 (9.13)	/
Girls, n (%)	212 (49.77)	395 (47.36)	136 (46.58)	419 (43.46)	453 (46.18)	547 (46.32)	247 (49.01)	275 (42.70)	0.17
SER, diopters, Median (IQR)	1.375 (1.00, 1.75)	1.375 (1.125, 1.75)	1.25 (0.875, 1.50)	1.25 (0.875, 1.625)	0.625 (0.25, 1.00)	0.625 (-0.125, 0.875)	-0.625 (-2.25, 0.375)	-0.50 (-2.25, 0.50)	<0.001
AL, mm, Mean (SD)	21.96 (0.61)	22.10 (0.62)	22.56 (0.73)	22.64 (0.65)	23.15 (0.79)	23.42 (0.82)	24.07 (0.95)	24.10 (1.02)	<0.001
CP, diopters, Mean (SD)	43.43 (1.52)	43.43 (1.36)	43.40 (1.56)	43.42 (1.38)	43.37 (1.45)	43.16 (1.43)	43.24 (1.40)	43.22 (1.42)	<0.001
LP, diopters, Mean (SD)	27.12 (1.52)	26.50 (1.43)	24.60 (1.40)	24.13 (1.35)	23.16 (1.49)	22.78 (1.45)	21.90 (1.41)	21.77 (1.46)	<0.001

SER: spherical equivalent refraction, AL: axial length, CP: corneal power, LP: lens power, IQR: inter-quartile range, SD: standard deviation

* Chi-square test for comparing the distribution of sex by age group; The trend across age groups was testing by Kruskal-Wallis test for SER due to non-normality, and linear regression for AL, CP and LP.

Table 2. Changes of ocular biometric factors during the follow-up

	3-year-old	4-year-old	6-year-old	7-year-old	9-year-old	10-year-old	12-year-old	13-year-old	P value*
First-year follow-up									
n	406	804	278	911	876	966	427	546	/
SER, diopters	1.375 (1.00, 1.75)	1.375 (1.00, 1.75)	1.00 (0.625, 1.375)	1.00 (0.625, 1.375)	0.375 (-0.50, 0.75)	0.125 (-1.00, 0.75)	-1.125 (-2.625, 0.125)	-1.250 (-2.875, 0.125)	<0.001
ΔSER, diopters	-0.04 (0.34)	-0.05 (0.35)	-0.23 (0.32)	-0.24 (0.34)	-0.48 (0.45)	-0.52 (0.47)	-0.47 (0.41)	-0.43 (0.39)	<0.001
AL, mm	22.07 (0.65)	22.27 (0.65)	22.71 (0.73)	22.82 (0.67)	23.45 (0.84)	23.72 (0.89)	24.25 (1.04)	24.36 (1.08)	<0.001
ΔAL, mm	0.24 (0.07)	0.19 (0.09)	0.17 (0.08)	0.16 (0.10)	0.29 (0.17)	0.31 (0.19)	0.24 (0.15)	0.22 (0.15)	<0.001
CP, diopters	43.60 (1.49)	43.46 (1.38)	43.47 (1.55)	43.44 (1.38)	43.38 (1.46)	43.11 (1.44)	43.17 (1.40)	43.15 (1.39)	<0.001
ΔCP, diopters	-0.001 (0.15)	0.02 (0.14)	0.03 (0.12)	0.03 (0.16)	-0.02 (0.14)	-0.03 (0.21)	-0.05 (0.13)	-0.05 (0.12)	<0.001
LP, diopters	26.22 (1.41)	25.63 (1.41)	24.15 (1.34)	23.67 (1.35)	22.64 (1.48)	22.30 (1.44)	21.75 (1.37)	21.59 (1.45)	<0.001
ΔLP, diopters	-1.16 (0.48)	-0.90 (0.63)	-0.49 (0.49)	-0.43 (0.47)	-0.53 (0.46)	-0.50 (0.42)	-0.20 (0.37)	-0.19 (0.38)	<0.001
Second-year follow-up									
n	341	717	274	896	857	927	410	540	/
SER, diopters	1.375 (1.00, 1.75)	1.375 (1.00, 1.625)	1.00 (0.625, 1.25)	1.00 (0.50, 1.25)	0.00 (-1.25, 0.625)	-0.25 (-1.625, 0.50)	-1.50 (-3.125, 0.00)	-1.50 (-3.25, -0.125)	<0.001
ΔSER, diopters	0.04 (0.38)	-0.006 (0.37)	-0.11 (0.37)	-0.17 (0.39)	-0.46 (0.49)	-0.46 (0.46)	-0.28 (0.38)	-0.26 (0.35)	<0.001
AL, mm	22.27 (0.67)	22.43 (0.68)	22.90 (0.77)	23.01 (0.72)	23.65 (0.90)	23.93 (0.97)	24.46 (1.08)	24.51 (1.09)	<0.001
ΔAL, mm	0.18 (0.07)	0.17 (0.09)	0.20 (0.12)	0.19 (0.13)	0.25 (0.18)	0.24 (0.16)	0.16 (0.13)	0.15 (0.11)	0.658
CP, diopters	43.56 (1.46)	43.47 (1.42)	43.39 (1.58)	43.39 (1.39)	43.40 (1.46)	43.11 (1.41)	43.15 (1.43)	43.15 (1.38)	<0.001
ΔCP, diopters	-0.03 (0.15)	-0.02 (0.23)	-0.06 (0.11)	-0.04 (0.25)	-0.002 (0.23)	-0.02 (0.21)	0.03 (0.15)	0.03 (0.14)	<0.001
LP, diopters	25.29 (1.31)	24.79 (1.40)	23.54 (1.40)	23.16 (1.40)	22.33 (1.47)	22.07 (1.49)	21.46 (1.38)	21.31 (1.45)	<0.001
ΔLP, diopters	-0.92 (0.64)	-0.79 (0.60)	-0.64 (0.44)	-0.55 (0.54)	-0.34 (0.44)	-0.29 (0.39)	-0.29 (0.44)	-0.25 (0.38)	<0.001

SER: spherical equivalent refraction, AL: axial length, CP: corneal power, LP: lens power

Data was presented as median (inter quartile range) for SER and mean (standard deviation) for other variables. Δ was calculated as the value at baseline or 1-year follow-up subtracted from the corresponding value in the next year.

* The trend across age groups was testing by Kruskal-Wallis test for SER due to non-normality, and linear regression for AL, CP, LP and all Δs.

Annual change in SER, AL and LP by baseline SER among children in each age group are shown in Figure 2 and supplement figures 1-3. Children in the 3-year-old and 4-year-old age group demonstrated similar changing patterns of SER and a large number of hyperopic shifts in refraction were seen for the 3- and 4-year-old children (Supplement Figure 1). Given that the annual shifts are small, and within experimental measurement error, this could be attributed to random measurement errors, except that there was a systematic relationship between baseline refraction and change, where hyperopic shifts in refraction predominated for the less hyperopic baseline refractions, with myopic shifts in refraction predominating for more hyperopic baseline refractions. The x-axis of the inflection point was between +1.00 to 2.00 D.

Similar changing patterns were observed for children in the 6- and 7-year-old age groups, as well as those in the 9- and 10-year-old age groups and the 12- and 13-year-old age groups (Supplement Figure 1). At ages 6 and 7, a much lower percentage of hyperopic refractive shifts was observed, with the slope of the regression line almost reaching 0. These results confirm the findings of Ma et al.[11] However, unlike Ma et al., who applied linear regression to their data, we found that the scatter plots of our data were not a good fit for linear regression. We believe this should better reveal the underlying trend of changes (Figure 2 & Supplement Figure 4). At later ages, for baseline hyperopic refractions, the more expected pattern of myopic shifts in refraction was observed, with the magnitude of those shifts increasing as baseline refractions become less hyperopic/more myopic. As the number of myopic baseline refractions increased with age, the myopic shift in refraction decreased with age, and was largely constant with baseline refraction in older ages (Figure 2 & SFigure 1).

Changes in AL were not significantly related to baseline SER for children in the 3- (P=0.76) and 4-year-old group (P=0.94), while children in the other older age groups tended to experience a larger AL increase with more myopic baseline SER (Figure 2 & Supplement Figure 2). It could be seen that axial growth accelerated between 0 and 2D of baseline SER, and then for the myopic range of baseline refractions, a trend toward an age-specific rate of axial elongation that declined with age was observed, matching the pattern of an age-specific rate of change in SER that declined with age.

Increased rates of loss of LP that help to offset the impact of increased axial elongation are shown in Figure 2 and Supplement Figure 3. The LP estimates are subject to considerable error, since LP cannot be directly measured, but had to be calculated from other refractive and biometric measurements using Bennett's equations. Nevertheless, a clear pattern emerged. Overall, the annual rate of LP loss declined with age, from close to 1 D per year in the 3- and 4-year-olds to 0.1-0.2 D per year in the 12- and 13-year-olds, which can be seen most clearly for myopic baseline refractions (Table 2 and Figure 2). Over the same range of baseline refractions where axial elongation accelerated, namely between 0 D and 2 D, elevated rates of LP loss were seen over this range of up to 1.50 D/year (Figure 2 & Supplement Figure 3).

As shown in Table 3, the 3- and 4-year-old age groups were grouped together for the regression analyses due to similar changing patterns. This was also the case for those in the 6- and 7-year-old age groups, 9- and 10-year-old age groups, 12- and 13-year-old age groups. The longitudinal SER changes could be well explained by gender, baseline height, baseline SER, as well as changes in AL, CP, and LP (R square=0.99 for all children at the second-year follow-up). It could also be seen based on the standardized regression coefficient that the LP contributed more to the SE change than AL in the 3- and 4-year-old age group, while in older age groups, the AL become the biggest contributor to SE change.

The number of children with annual SER changes of less than 0.25 D was 40 (9.39%) in the 3-year-old group, 143 (17.15%) in the 4-year-old group, 156 (53.42%) in the 6-year-old group and 514 (53.32%) in the 7-year-old group. All these children showed a baseline SER in a mild hyperopic range (mean: 1.21 D, 95%CI: 1.16 to 1.26 D, Supplement Table).

Table 3. Multiple regression analyses of potential factors for SER change during the follow-up

	3 & 4 year-old*		6 & 7 year-old*		9 & 10 year-old*		12 & 13 year-old*	
	β (95%CI)	P value	β (95%CI)	P value	β (95%CI)	P value	β (95%CI)	P value
First-year follow-up	Adjusted R^2=0.98		Adjusted R^2=0.99		Adjusted R^2=0.98		Adjusted R^2=0.99	
Gender								
Boy	Ref.		Ref.		Ref.		Ref.	
Girl	-0.05 (-0.07, -0.04)	<0.001	-0.04 (-0.04, -0.03)	<0.001	-0.05 (-0.06, -0.05)	<0.001	-0.03 (-0.04, -0.02)	<0.001
Baseline height, cm	0.02 (0.006, 0.04)	0.007	0.02 (0.01, 0.02)	<0.001	0.03 (0.02, 0.04)	<0.001	0.02 (0.01, 0.03)	<0.001
Baseline SER, diopters	-0.06 (-0.07, -0.04)	<0.001	-0.02 (-0.03, -0.02)	<0.001	-0.04 (-0.05, -0.03)	<0.001	-0.04 (-0.05, -0.03)	<0.001
Change in CP, diopters	-0.39 (-0.40, -0.37)	<0.001	-0.42 (-0.43, -0.41)	<0.001	-0.40 (-0.41, -0.39)	<0.001	-0.31 (-0.32, -0.30)	<0.001
Change in AL, mm	-0.71 (-0.73, -0.70)	<0.001	-0.84 (-0.84, -0.83)	<0.001	-1.11 (-1.12, -1.10)	<0.001	-1.00 (-1.01, -0.99)	<0.001
Change in LP, diopters	-1.09 (-1.11, -1.07)	<0.001	-0.89 (-0.89, -0.88)	<0.001	-0.61 (-0.62, -0.60)	<0.001	-0.63 (-0.64, -0.62)	<0.001
Second-year follow-up	Adjusted R^2=0.99		Adjusted R^2=0.99		Adjusted R^2=0.99		Adjusted R^2=0.99	
Gender								
Boy	Ref.		Ref.		Ref.		Ref.	
Girl	-0.03 (-0.04, -0.03)	<0.001	-0.03 (-0.04, -0.03)	<0.001	-0.05 (-0.05, -0.04)	<0.001	-0.02 (-0.03, -0.01)	<0.001
Baseline height, cm	0.02 (0.02, 0.03)	<0.001	0.01 (0.007, 0.02)	<0.001	0.03 (0.02, 0.03)	<0.001	0.02 (0.008, 0.03)	<0.001
Baseline SER, diopters	-0.04 (-0.05, -0.03)	<0.001	-0.03 (-0.04, -0.02)	<0.001	-0.02 (-0.03, -0.02)	<0.001	-0.04 (-0.05, -0.04)	<0.001
Change in CP, diopters	-0.4 (-0.5, -0.3)	<0.001	-0.71 (-0.72, -0.70)	<0.001	-0.55 (-0.56, -0.54)	<0.001	-0.41 (-0.42, -0.40)	<0.001
Change in AL, mm	-0.85 (-0.86, -0.84)	<0.001	-1.08 (-1.09, -1.07)	<0.001	-1.17 (-1.18, -1.17)	<0.001	-0.85 (-0.86, -0.84)	<0.001
Change in LP, diopters	-1.03 (-1.04, -1.02)	<0.001	-0.88 (-0.89, -0.87)	<0.001	-0.71 (-0.72, -0.71)	<0.001	-0.75 (-0.76, -0.74)	<0.001

SER: spherical equivalent refraction, AL: axial length, CP: corneal power, LP: lens power, *β:* Standardized parameter estimate, CI: confidence interval.

* These age groups were analyzed together due to similar changes (as shown in figure 1).

Discussion

Our study demonstrated significantly different longitudinal refractive changing patterns for children at different ages, which collectively suggested that the endpoint of early refractive development was mild hyperopia. Achievement and maintenance of the mild hyperopic status were largely determined by a push-back mechanism between the axial elongation and LP loss. Specifically, mild hyperopes and emmetropes showed hyperopic shifts in refraction while more significant hyperopes showing myopic shifts in the 3- and 4-year-olds. The exact inflection point differed for children in these two age groups, but fell in the range of +1 to +2 D.

Mutti and other researchers reported that the mean value of refraction does not change significantly in children between 1.5 and 6.5 years of age.[11 15 16] Similar finding were observed in our study, we showed that the longitudinal SER changes could be well explained by gender, baseline height, baseline SER and changes in CP, AL, and LP (Table 3). Given that the change in CP was minimal after 2 years of age, the longitudinal SER changes could be attributed to the interplay between axial elongation and LP loss. Assuming an 1mm axial elongation could result in 0.27 to 0.33D myopic shifts in refraction, the average 1-year myopic shift in the youngest cohort (3-year-olds) in our study was 0.65 to 0.79 D, while the LP loss was -1.16 D, forming an overall hyperopic shift (Table 2). Meanwhile, the average 1-year myopic shift of the oldest cohort (13-year-olds) in our study was 0.59 to 0.73 D, while the LP loss was only -0.19 D, forming an overall myopic shift. The inflection point occurred around 6 years of age. Similar to Ma et al's findings, we observed that despite a significant association between longitudinal SER changes and baseline SER, the extent of axial elongation during the follow-up was not significantly associated with baseline refraction in the 3- and 4-year-olds. In contrast, loss of LP was significantly associated with baseline SER. The standardized regression coefficient also showed that LP loss contributed more to the overall SE changes than AL in the 3- and 4-year-olds, which was reversed after 6 years of age. The above findings collectively indicate an increased loss of LP to maintain a hyperopic reserve during early refractive development.

Ma et al. found that for 3- and 4-year-old children with a baseline SER of approximately +1.25 D, the mean 1-year SER change was about 0 D.[11] Our study provided further evidence that for children aged between 3 and 7 years, a baseline SER in a mild hyperopic range (1.21 D on average, STable) could lead to negligible SER changes during a two-year follow-up, suggesting the possibility for maintaining a mild hyperopic status. The mean baseline SER among children with relatively stable refractive status was similar to the inflection point identified in this study (slightly above +1.00 D), providing further evidence that the natural endpoint of early refractive development was more likely to be mild hyperopia instead of 0 D, maintained by a push-back mechanism. The reason we did not include children aged above 9 years in this analysis is that many children already developed myopia after this age in China.[17]

The 'push-back' mechanism could be clearly seen in the 3- and 4-year-olds in our study (Figure 2), similar to Ma et al's findings.[11] This fits with the idea that when refractions are too hyperopic, the system is producing myopic shifts in order to clear excessive hyperopia, but when refractions start to drop out of the preferred hyperopic range, hyperopic shifts in refraction are generated to try to bring them back. We further found that the hyperopic shifts in refraction are no longer visible at older ages. There could be two reasons for this. One is that the ability to generate hyperopic shifts in refraction get weaker with age. The other is that increasing environmental exposures to near work and limited time outdoors simply overwhelm this tendency.

The fact that early refractive development targets mild hyperopia instead of emmetropia may also explain why SER and AL change rapidly during the year before myopia onset.[14 18 19] It is likely that child's refraction first drops out of the preferred hyperopic range into the premyopic range in the year or so before myopia onset, driven by rapid AL changes. Our study showed an acceleration in axial elongation in children with baseline SER of 0 to +2 D, and an opposing acceleration of LP loss was also seen, suggesting an active role of the lens as a balance weight to offset, at least partially, the myopic shifts associated with axial elongation during early refractive development. The exact mechanism underlying these changes is unknown and warrants further investigation. Nevertheless, this suggests that the transition from the hyperopic reserve into the premyopia stage is of significance, supporting the idea that the crucial timepoint for myopia prevention is from a hyperopic reserve to premyopia, rather than from emmetropia to myopia.

This study has some limitations. First, children aged 5, 8, and 11 years were not included, hindering us from providing a complete picture of the refractive development for children of all ages. Second, the follow-up time was relatively short. Third, we only included children from China, caution should be taken when extrapolating the study conclusions to other populations. However, since the RESC and many other studies all reported a clustering refraction at mild hyperopia, the conclusion that refractive development targets mild hyperopia is likely to apply to all children, but the exact endpoint of hyperopia may differ by ethnicity, gender, and other environmental factors.

In conclusion, our study demonstrated that the eye tended to grow towards mild hyperopia and further maintain this status during early refractive development. This ability is largely determined by the speed and extent of LP loss in relation to axial elongation, and the push-back mechanism was clearly seen in 3- and 4-year-olds but not at older ages. Our findings indicate that the premyopia stage is a critical period for myopia prevention, and more attention should be paid to the kindergarten children whose push-back mechanism are still maintained. Future studies are needed to gain a deeper insight into the biological processes that drive the push-back mechanism, and to investigate why this mechanism fades with increasing age and how its disappearance relates to the risk of myopia development and progression.

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Declarations

Data access and sharing statement

Data will be shared upon reasonable request to pursue additional studies or for replication.

Author contributions

Study concept and design: YZ, XH; Acquisition, analyses, or interpretation: all authors; Drafting of the manuscript: XH; Critical revision of the manuscript for important intellectual content: all authors; Statistical analyses: LJ; Obtained funding: YZ, XH; Administrative, technical, or material support: XC, YQ, WL; Study supervision: YZ. YZ had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Ethics approval

This study adhered to the tenets of the Declaration of Helsinki and was approved by the Institutional Review Board of Zhongshan Ophthalmic Center, Guangzhou, China (2018KYPJ079). Participants or their legal guardians gave informed consent to participate in the study before taking part.

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The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

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