

# Axial Growth and Lens Power Loss at Myopia Onset in Singaporean Children

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**PURPOSE.** We studied biometry changes before and after myopia onset in a cohort of Singaporean children.

**METHODS.** All data were taken from the Singapore Cohort Study of the Risk Factors for Myopia (SCORM). Participants underwent refraction and biometry measurements with a follow-up of 3 to 6 years. The longitudinal ocular biometry (spherical equivalent refraction, axial length, and lens power) changes were compared between children who suffered myopia during the study ( $N = 303$ ), emmetropic children ( $N = 490$ ), and children myopic at baseline ( $N = 509$ ).

**RESULTS.** At myopia onset, the myopic shift increased to 0.50 diopters (D)/y or more in new myopes compared to the minor changes in emmetropes of the same age. New myopes had higher axial growth rates than emmetropes, even years before myopia onset (0.37 and 0.14 mm/y, respectively; ANOVA with Bonferroni post hoc test,  $P < 0.001$ ). After onset, the change in both parameters slowed down gradually, but significantly ( $P < 0.05$ ). In new myopes, lens power loss ( $-0.71$  D/y) was significantly higher up to 1 year before myopia onset compared to emmetropes ( $-0.46$  D/y), after which lens power loss slows down rapidly. At age 7 years, (future) new myopes had lens power values close to those of emmetropes (25.12 and 25.23 D, respectively), while later these values approached those of children who were myopic at baseline (23.06 and 22.79 D, respectively, compared to 23.71 D for emmetropes;  $P < 0.001$ ).

**CONCLUSIONS.** New myopes have higher axial growth rates and lens power loss before myopia onset than persistent emmetropes.

Keywords: myopia, myopia onset, crystalline lens, biometry, SCORM

The power of the crystalline lens changes throughout life and seems to have a pivotal role in determining the refractive status. Recently, it has been suggested that myopia may be the result of a failure in homeostasis,<sup>1</sup> a process that preserves the delicate balance between the optical power of the eye and the retinal position to keep the ocular refraction close to low hyperopia during eye growth. The growing eye does this by balancing passive, somatic eye growth with more active mechanisms, such as accommodation, retinal circuits, choroidal thickness changes, and scleral growth.<sup>2</sup> This process is best studied longitudinally by prospectively enrolling a large group of young schoolchildren and following their changing ocular biometry until adolescence. Since some of these children would eventually suffer myopia, this would form an ideal platform to investigate the biometric changes associated with the onset of myopia. Such studies have shown that in children the ocular dimensions undergo considerable changes at the time of myopia onset, such as a rapid decrease in spherical equivalent refraction (SER),<sup>3</sup> a corresponding increase in axial growth rate,<sup>3,4</sup> and a sudden stop in crystalline lens power loss.<sup>5</sup> During normal eye growth the development of the crystalline lens is characterized

by thinning, flattening, and decreasing power to maintain emmetropia by compensating for eye growth.<sup>5</sup> Longitudinal data from before and after myopia onset, however, show that this compensating response is disrupted at onset, as if the lens had reached some limit at which it can no longer neutralize the effect of the increased rate of axial elongation.<sup>6</sup>

Xiang et al.<sup>5</sup> examined Chinese twins aged 7 to 15 years and did not find significant lens power changes at onset.<sup>3</sup> This may be due to their use of the Bennett-Rabbetts formula in their calculations,<sup>7</sup> which is relatively inaccurate compared to the lens power values of the CLEERE study, which were determined directly by phakometry.<sup>5</sup> This relative inaccuracy is the result of the fact that Bennett-Rabbetts does not consider any lens parameters in its calculations, requiring additional assumptions for its estimates. Therefore, the normal course of lenticular changes around myopia onset, as well as their explanation, remains unclear. Likewise, it is not clear why myopic eyes have a lower lens power than emmetropes and why there is a sudden cessation in lens power loss at myopia onset. To understand this development in detail, there is the need to collect data before and after myopia onset.



This study aims to analyze how the ocular and lenticular dimensions changes around the time of myopia onset in a large cohort of Singaporean children. Developing myopes were grouped according to age at myopia onset. The myopic groups were compared by changes in the ocular components of refraction with persistent emmetropes (those that remained emmetropic during the study) and persistent myopes (those that were already myopic at baseline). These comparisons may help to resolve previous conflicting findings on biometric changes around myopia onset.

## METHODS

### Subjects

This work involves data of the Singapore Cohort Study of the Risk Factors for Myopia (SCORM). These data contained the biometry of children aged 6 to 9 years recruited from three Singaporean schools in 1999 and 2001. The detailed methodology has been reported previously.<sup>8,9</sup> The study was approved by the ethics committee of the Singapore Eye Research Institute and the study protocol adhered to the tenets of the Declaration of Helsinki. Only children with written informed consent from their parents participated in the study.

The children underwent yearly examinations in their schools by a trained team using standard methodology. After cycloplegia (0.5% proparacaine, followed by three drops of 1% cyclopentolate solution at 5-minute intervals), refraction and corneal radius were measured using an autokeratorefractor (model RK5; Canon, Inc., Ltd., Tochigiken, Japan). An Echoscanner model US-800 (Nidek Co., Ltd., Tokyo, Japan) was used to measure axial length, vitreous chamber depth, anterior chamber depth, and lens thickness.

### Calculations

The SER of the randomly selected eye was calculated as sphere power + 0.5-cylinder power. A child was deemed emmetropic throughout the study if its SER remained between  $-0.50$  and  $+1.00$ . A child who started out with emmetropia at the first visit and suffered a SER equal to or below  $-0.75$  D later in the study was classified as having newly developed myopia. All children with newly developed myopia and at least three visits were included in the analysis. A third subset was included containing children who were already myopic (i.e., SER  $\leq -0.75$  D) at baseline, and either stabilized or progressed further during follow-up.

Corneal power, in diopters (D), was calculated from the corneal radius of curvature with a refractive index of 1.328, as proposed by Olsen<sup>10</sup> and Manns et al. (IOVS 2014;55:ARVO E-Abstract 3785).<sup>10</sup> The crystalline lens power was calculated based on distance cycloplegic autorefraction, corneal power, anterior chamber depth, lens thickness, and axial length using the formula proposed by Bennett.<sup>11</sup>

### Progression Analysis

Previous studies<sup>3,5</sup> analyzed myopia development by sorting follow-up visits according to the age at myopia onset, assigning that moment  $t = 0$ . Years before onset were indicated by negative numbers ( $t = -1, -2, \dots$ ) and years after onset by positive numbers ( $t = +1, +2$ ). In our study, to avoid mixing subjects of different ages and ocular growth stages, children were grouped according to age at myopia onset. This allowed comparisons between subjects of the same age who remained emmetropic, were myopic at baseline, or had myopia during the study. The yearly changes in the main ocular components were calculated by subtracting the value of the previous year.

Children with myopia onset at ages 8 and 9 years were excluded from the analysis due to insufficient data before onset.

### Statistical Analysis

The mean values for SER and the main ocular components were calculated with 95% confidence intervals. Comparisons were performed using ANOVA and Bonferroni post hoc tests, which corrects for  $\alpha$ -inflation due to the large number of repeated tests. Data analyses were performed with SPSS (version 15.0; SPSS, Inc., Chicago, IL, USA).

## RESULTS

### Demographics

The cohort consisted of 1302 Singaporean children aged  $8.02 \pm 0.86$  years at first visit (51.7% boys, 48.3% girls), of whom 490 were myopic at baseline and 303 remained emmetropic throughout the study. The remaining 509 children suffered myopia during the study, at a mean age at onset of  $9.57 \pm 1.03$  years (range, 8–11 years).

### Changes in Spherical Equivalent Refraction With Age

In emmetropes, the mean SER changes very slowly, but significantly with age (ANOVA with Bonferroni post hoc tests,  $P < 0.05$ ; Fig. 1a; Table 1; full Table available as Supplementary Table S1). Children who were myopic at baseline had rapid progression, albeit at a rate that decreased with age ( $P < 0.05$ ). The refractive error changes in newly developed myopes remained in-between these two groups. For example, children with an onset at age 8 years already experienced an accelerated decrease in SER compared to emmetropes at baseline ( $P < 0.001$ ). Meanwhile, those with an onset age of 11 years experienced a far more gradual process, with a slow initial decrease in SER early on, an accelerated decrease right before onset, followed by a gradual stabilization of the refraction after onset ( $P < 0.001$ ; Fig. 1a). Initially, the mean SER in these later-onset children remained close to that of emmetropes (i.e., between 0 and  $+0.5$  D), but significant differences in the refractive error already appeared up to 3 years before onset. For example, children with myopia onset at age 10 years had a mean SER of 0.00 D at age 8 years, while children who remained emmetropic had a mean SER of  $+0.44$  D at the same age ( $P = 0.011$ ).

### Changes in Axial Length With Age

The axial growth rate appeared steady before and after myopia onset, and gradually flattened with age (Fig. 1b). Interestingly, myopia onset seemed to occur at approximately the same mean axial length in each onset age group ( $23.85 \pm 0.69$  mm, indicated by dots in Fig. 1b), which differed significantly between sexes (boys,  $24.08 \pm 0.67$  mm; girls,  $23.69 \pm 0.69$  mm;  $t$ -test  $P < 0.001$ ). Compared to emmetropes, all myopic groups had a higher axial growth rate in the years before onset (ANOVA with Bonferroni post hoc test,  $P < 0.001$ ). At age 8 years, for example, the yearly axial growth rate for children who remained emmetropic was  $0.12 \pm 0.24$  mm, while at the same age the growth rate in children with a myopia onset at age 10 years was  $0.35 \pm 0.29$  mm ( $P = 0.013$ ).

### Lenticular Changes With Age

Lens thickness changed with age according to a U curve and was generally thicker in emmetropes compared to early-onset

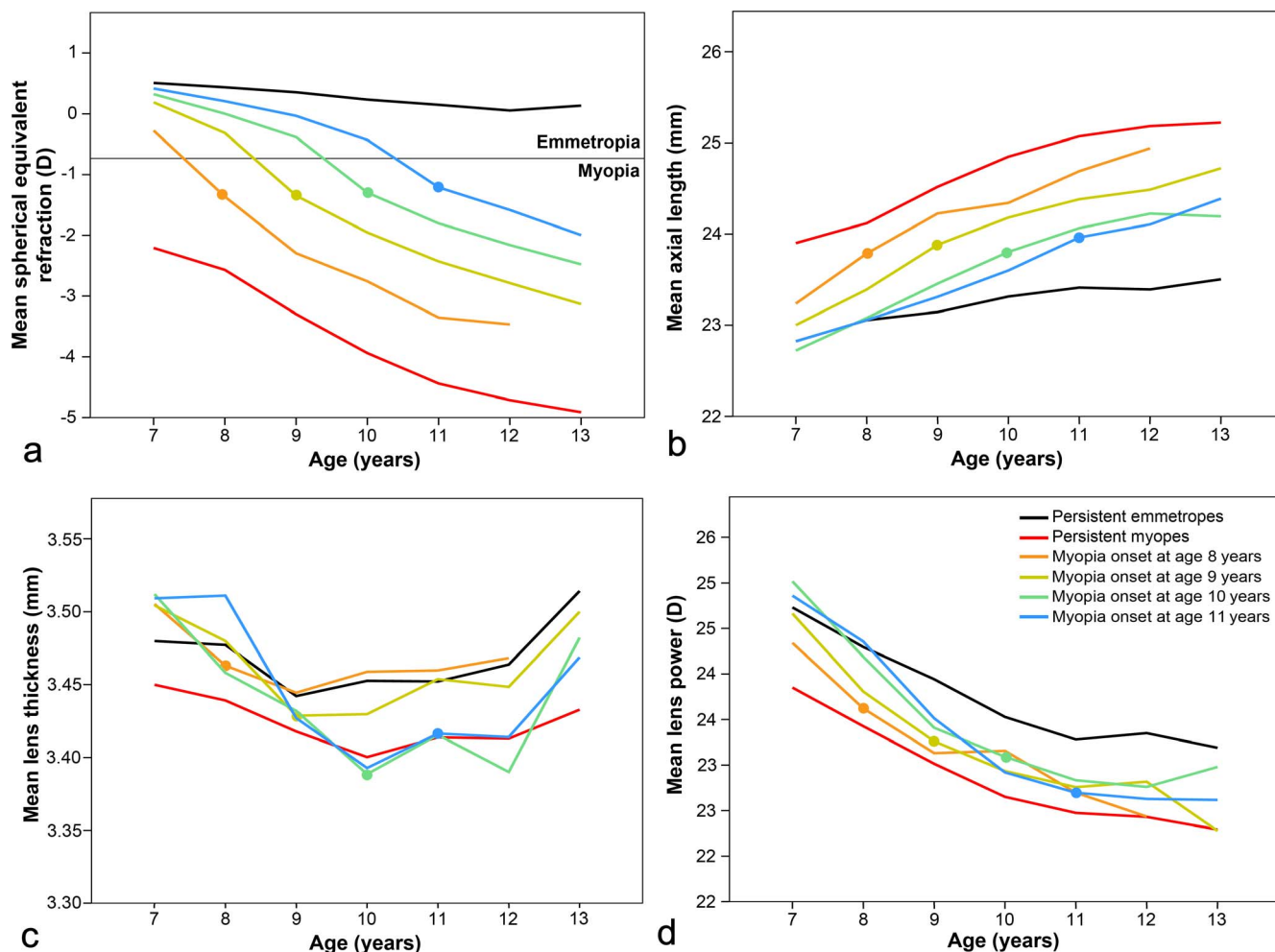


FIGURE 1. Mean spherical equivalent refraction and biometry data in right eyes according to age and split by ages of onset. (a) Spherical equivalent refraction, (b) axial length, (c) lens thickness, and (d) lens power. The dots represent the values at first myopic visit.

myopes. The age at onset groups showed the similar curve shape (Fig. 1c).

The lens power decreased in all onset groups. Emmetropes had lens powers approximately 1D higher than myopes throughout the study (ANOVA with Bonferroni post hoc test,  $P < 0.001$ ; Fig. 1d; Table 1). New myopes at age 7 years had lens power values close to those of emmetropes (25.12 and 25.23 D, respectively;  $t$ -test,  $P = 0.632$ ), which changed to power values close to those of persistent myopes at age 12 years (23.06 and 22.79 D, respectively, compared to 23.71 D for emmetropes;  $t$ -test,  $P < 0.001$ ). In children with a late onset of this change from emmetropic to myopic lens powers occurred later and at lower lens power at myopia onset than in early-onset children ( $24.23 \pm 1.63$  mm for onset at 8 years, compared to  $23.13 \pm 1.49$  mm for onset at 11 years;  $t$ -test,  $P < 0.001$ ; Fig. 1d; Table 2).

### Growth Rate Changes With Age

To better visualize growth rate changes, the yearly changes were analyzed for the most important components (Table 2; full table available as Supplementary Table S1). Children myopic at baseline had their greatest change in SER ( $-1$  D per year) at age 8 years, which slowed linearly to  $-0.25$  D per year at age 13 years (Fig. 2a). Simultaneously, axial growth and lens power loss rates also decreased linearly with age. Lens power loss seemed to stop at age 12 years (Fig. 1d), meaning

that the myopic change of 0.2 mm per year after this age is no longer compensated by the lens.

Children with myopia onset at age 10 years had a peak in refractive error change at onset, followed by a decrease in progression speed (Fig. 2b). At the same time axial growth increased at onset, after which it gradually decreased. Lens power loss was relatively high in developing myopes compared to persistent emmetropes until 1 year before myopia onset, when it rapidly and significantly decreased from  $-0.75$  D/y to no loss in just 3 years (ANOVA with Bonferroni post hoc test,  $P < 0.05$ ; Table 2). The same was found in children with onset at age 11 years, albeit at higher deceleration rates for axial growth and lens power loss (Fig. 2c). Both figures, therefore, suggest accelerated lens power loss up to 1 year before the peaks in refractive error and axial length change at myopia onset. In persistent emmetropes only very gradual changes were seen (Fig. 2d), with a minor, near-constant decrease in refractive error, a gradual deceleration in axial growth, and a gradual slowing in lens power loss. These ocular changes seem to stabilize at approximately age 12 years. The lens power loss in children who became myopic during the study (Figs. 2b, 2c) and that in baseline myopes (Fig. 2a) shows that at a point between ages 8 and 10 years there was a moment of significantly higher power loss (0.70–0.90 D/y) in new myopes compared to baseline myopes (0.40–0.50 D/y; Table 2).

TABLE 1. Biometric and Refractive Error Parameters as a Function of Age for Each Onset Group

Parameter	Age	Persistent Myopia			Myopia Onset at 10 y			Myopia Onset at 11 y			Persistent Emmetropia			Comparison Between Groups†				
		Mean ± SD	Change Over Past x Years*		Mean ± SD	Change Over Past x Years*		Mean ± SD	Change Over Past x Years*		Mean ± SD	Change Over Past x Years*		PM	O10	O11	PE	
			1	2		3	1		2	3		1	2					3
SER(D)	7	-2.22 ± 1.51	•	•	•	0.32 ± 0.32	•	•	•	0.42 ± 0.22	•	•	•	•	•	•	•	
	8	-2.57 ± 1.49	•	•	•	0.00 ± 0.32	•	•	•	0.21 ± 0.31	•	•	•	•	•	•	•	
	9	-3.30 ± 1.70	•	•	•	-0.38 ± 0.26	•	•	•	-0.03 ± 0.33	•	•	•	•	•	•	•	
	10	-3.94 ± 1.75	•	•	•	-1.29 ± 0.53	•	•	•	-0.43 ± 0.27	•	•	•	•	•	•	•	
	11	-4.44 ± 1.79	•	•	•	-1.80 ± 0.66	•	•	•	-1.21 ± 0.41	•	•	•	•	•	•	•	
	12	-4.71 ± 1.83	•	•	•	-2.15 ± 0.72	•	•	•	-1.58 ± 0.52	•	•	•	•	•	•	•	
	13	-4.91 ± 1.83	•	•	•	-2.48 ± 0.91	•	•	•	-2.00 ± 0.83	•	•	•	•	•	•	•	
	K <sub>mean</sub> (D)	7	43.15 ± 1.30	•	•	•	43.12 ± 1.26	•	•	•	42.82 ± 1.14	•	•	•	•	•	•	•
		8	43.12 ± 1.35	•	•	•	43.05 ± 1.34	•	•	•	42.76 ± 1.25	•	•	•	•	•	•	•
		9	43.01 ± 1.33	•	•	•	42.85 ± 1.35	•	•	•	42.77 ± 1.23	•	•	•	•	•	•	•
		10	43.00 ± 1.33	•	•	•	42.93 ± 1.35	•	•	•	42.79 ± 1.23	•	•	•	•	•	•	•
		11	43.01 ± 1.36	•	•	•	42.91 ± 1.34	•	•	•	42.74 ± 1.22	•	•	•	•	•	•	•
		12	42.94 ± 1.31	•	•	•	42.83 ± 1.37	•	•	•	42.68 ± 1.22	•	•	•	•	•	•	•
ACD(mm)	7	42.99 ± 1.32	•	•	•	43.07 ± 1.36	•	•	•	42.47 ± 1.21	•	•	•	•	•	•	•	
	8	3.68 ± 0.27	•	•	•	3.50 ± 0.24	•	•	•	3.50 ± 0.22	•	•	•	•	•	•	•	
	9	3.66 ± 0.28	•	•	•	3.62 ± 0.22	•	•	•	3.55 ± 0.28	•	•	•	•	•	•	•	
	10	3.68 ± 0.29	•	•	•	3.64 ± 0.27	•	•	•	3.59 ± 0.23	•	•	•	•	•	•	•	
	11	3.70 ± 0.28	•	•	•	3.64 ± 0.25	•	•	•	3.66 ± 0.26	•	•	•	•	•	•	•	
	12	3.66 ± 0.29	•	•	•	3.65 ± 0.26	•	•	•	3.67 ± 0.26	•	•	•	•	•	•	•	
	13	3.55 ± 0.34	•	•	•	3.64 ± 0.27	•	•	•	3.63 ± 0.27	•	•	•	•	•	•	•	
LT(mm)	7	3.45 ± 0.17	•	•	•	3.58 ± 0.29	•	•	•	3.68 ± 0.25	•	•	•	•	•	•	•	
	8	3.44 ± 0.17	•	•	•	3.51 ± 0.17	•	•	•	3.51 ± 0.16	•	•	•	•	•	•	•	
	9	3.42 ± 0.16	•	•	•	3.46 ± 0.16	•	•	•	3.43 ± 0.16	•	•	•	•	•	•	•	
	10	3.40 ± 0.17	•	•	•	3.39 ± 0.16	•	•	•	3.43 ± 0.16	•	•	•	•	•	•	•	
	11	3.41 ± 0.17	•	•	•	3.42 ± 0.17	•	•	•	3.39 ± 0.20	•	•	•	•	•	•	•	
	12	3.41 ± 0.17	•	•	•	3.39 ± 0.19	•	•	•	3.42 ± 0.19	•	•	•	•	•	•	•	
	13	3.43 ± 0.19	•	•	•	3.48 ± 0.13	•	•	•	3.47 ± 0.11	•	•	•	•	•	•	•	
	7	23.90 ± 0.91	•	•	•	22.72 ± 0.63	•	•	•	22.82 ± 0.53	•	•	•	•	•	•	•	
	8	24.12 ± 0.89	•	•	•	23.08 ± 0.61	•	•	•	23.06 ± 0.67	•	•	•	•	•	•	•	
	9	24.52 ± 0.93	•	•	•	23.46 ± 0.69	•	•	•	23.31 ± 0.65	•	•	•	•	•	•	•	
	10	24.86 ± 0.95	•	•	•	23.82 ± 0.68	•	•	•	23.61 ± 0.64	•	•	•	•	•	•	•	
	11	25.09 ± 0.95	•	•	•	24.08 ± 0.71	•	•	•	23.98 ± 0.64	•	•	•	•	•	•	•	
	12	25.23 ± 0.98	•	•	•	24.26 ± 0.81	•	•	•	24.14 ± 0.69	•	•	•	•	•	•	•	
13	25.28 ± 1.03	•	•	•	24.27 ± 0.90	•	•	•	24.43 ± 0.87	•	•	•	•	•	•	•		
P <sub>t</sub> (D)	7	24.36 ± 1.61	•	•	•	25.51 ± 1.42	•	•	•	25.36 ± 1.32	•	•	•	•	•	•	•	
	8	23.93 ± 1.49	•	•	•	24.69 ± 1.39	•	•	•	24.86 ± 1.64	•	•	•	•	•	•	•	
	9	23.52 ± 1.44	•	•	•	23.91 ± 1.57	•	•	•	24.01 ± 1.64	•	•	•	•	•	•	•	
	10	23.12 ± 1.49	•	•	•	23.53 ± 1.46	•	•	•	23.38 ± 1.69	•	•	•	•	•	•	•	
	11	22.93 ± 1.50	•	•	•	23.27 ± 1.46	•	•	•	23.13 ± 1.49	•	•	•	•	•	•	•	
	12	22.79 ± 1.61	•	•	•	23.14 ± 1.56	•	•	•	22.99 ± 1.66	•	•	•	•	•	•	•	
13	22.61 ± 1.36	•	•	•	23.18 ± 1.41	•	•	•	22.95 ± 1.54	•	•	•	•	•	•	•		

Full table available as Supplementary Table S1. K<sub>mean</sub>, mean keratometry; ACD, anterior chamber depth; LT, lens thickness; AL, axial length; P<sub>t</sub>, lens power; PM, persistent myopia; O10, myopia onset at age 10; O11, myopia onset at age 11; PE, persistent emmetropia  
 \* ANOVA with Bonferroni post hoc test to identify significant parameter changes over a period of x (1, 2, 3) years; P < 0.05 indicates a significant difference (marked by “•”).  
 † ANOVA with Bonferroni post hoc test to identify significant parameter differences between onset groups; P < 0.05 indicates a significant difference (marked by “•”).

TABLE 2. Changes in Biometric and Refractive Error Parameters as a Function of Age for Each Onset Group

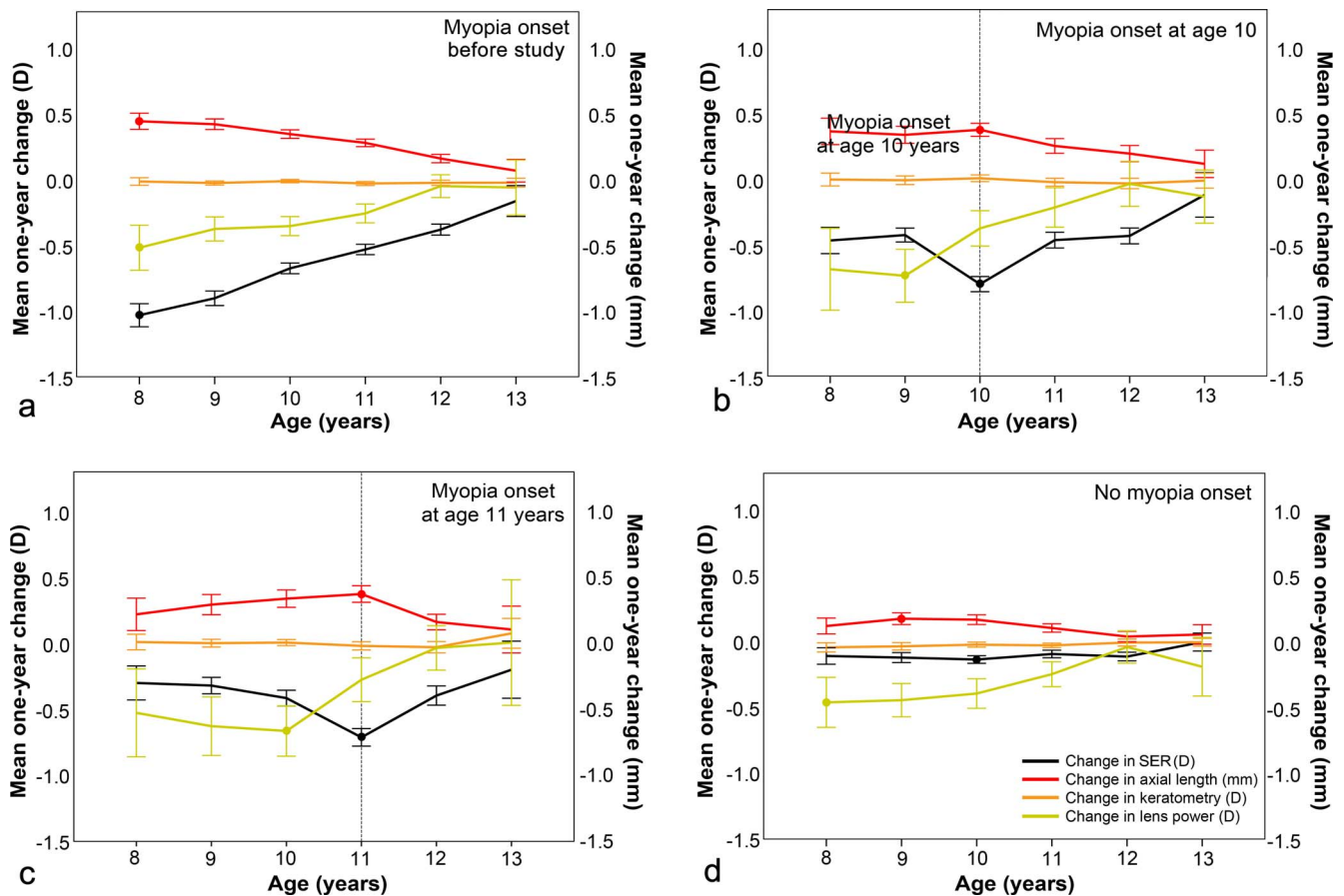
Parameter	Age	Persistent Myopia			Myopia Onset at 10 y			Myopia Onset at 11 y			Persistent Emmetropia			Comparison Between Groups†			
		Mean ± SD	Change Over Past x Years*		Mean ± SD	Change Over Past x Years*		Mean ± SD	Change Over Past x Years*		Mean ± SD	Change Over Past x Years*		PM	O10	O11	PE
			1	2		3	1		2	3		1	2				
dSER(D)	8	-1.03 ± 0.47			-0.47 ± 0.29			-0.31 ± 0.29			-0.11 ± 0.26						
	9	-0.90 ± 0.48			-0.43 ± 0.25			-0.33 ± 0.25			-0.12 ± 0.25						
	10	-0.68 ± 0.44			-0.80 ± 0.36			-0.42 ± 0.29			-0.14 ± 0.24						
	11	-0.53 ± 0.43			-0.47 ± 0.35			-0.72 ± 0.34			-0.09 ± 0.25						
	12	-0.38 ± 0.42			-0.44 ± 0.34			-0.40 ± 0.36			-0.11 ± 0.26						
dAL(mm)	8	0.44 ± 0.33			-0.13 ± 0.38			-0.21 ± 0.39			0.00 ± 0.26						
	9	0.42 ± 0.35			0.35 ± 0.30			0.21 ± 0.27			0.12 ± 0.24						
	10	0.35 ± 0.35			0.33 ± 0.30			0.28 ± 0.31			0.17 ± 0.29						
	11	0.28 ± 0.32			0.37 ± 0.31			0.32 ± 0.32			0.17 ± 0.30						
	12	0.16 ± 0.32			0.24 ± 0.33			0.36 ± 0.32			0.10 ± 0.27						
dK <sub>mean</sub> (D)	8	-0.01 ± 0.15			0.19 ± 0.34			0.15 ± 0.29			0.04 ± 0.32						
	9	-0.05 ± 0.14			0.11 ± 0.23			0.09 ± 0.32			0.05 ± 0.28						
	10	-0.01 ± 0.14			-0.01 ± 0.14			0.00 ± 0.13			-0.04 ± 0.14						
	11	-0.05 ± 0.17			-0.02 ± 0.15			-0.01 ± 0.12			-0.04 ± 0.19						
	12	-0.02 ± 0.20			0.00 ± 0.16			-0.01 ± 0.11			-0.02 ± 0.16						
dP <sub>L</sub> (D)	8	-0.52 ± 0.92			-0.05 ± 0.17			-0.03 ± 0.16			-0.03 ± 0.14						
	9	-0.38 ± 0.79			-0.04 ± 0.22			0.06 ± 0.20			-0.01 ± 0.11						
	10	-0.38 ± 0.78			-0.02 ± 0.13			-0.04 ± 0.21			-0.01 ± 0.11						
	11	-0.28 ± 0.77			-0.69 ± 0.92			-0.53 ± 0.74			-0.46 ± 0.77						
	12	-0.15 ± 0.88			-0.74 ± 0.95			-0.65 ± 0.89			-0.46 ± 0.85						
	13	-0.24 ± 0.88			-0.44 ± 0.84			-0.71 ± 0.94			-0.43 ± 0.94						
					-0.22 ± 0.86			-0.32 ± 0.86			-0.28 ± 0.82						
					-0.10 ± 0.96			-0.11 ± 0.92			-0.11 ± 1.01						
					-0.45 ± 0.48			-0.16 ± 0.95			-0.36 ± 0.91						

Full Table available as Supplementary Table S1. dSER, change in spherical equivalent refraction; dK<sub>mean</sub>, change in mean keratometry; dAL, change in axial length; dP<sub>L</sub>, change in lens power; PM, persistent myopia; O10, myopia onset at age 10; O11, myopia onset at age 11; PE, persistent emmetropia.

\* ANOVA with Bonferroni post hoc test to identify significant parameter changes over a period of x (1, 2, 3) years; P < 0.05 indicates a significant difference (marked by “•”).

† ANOVA with Bonferroni post hoc test to identify significant parameter differences between onset groups; P < 0.05 indicates a significant difference (marked by “•”).





**FIGURE 2.** Mean changes in spherical equivalent refraction and ocular biometry data over previous 12 months for children (a) with a myopia onset before the first visit, (b) a myopia onset at age 10 years, (c) a myopia onset at age 11 years, and (d) persistent emmetropes. Error bars: 95% confidence interval of the mean. Myopia onset age is indicated by the dashed line.

The refractive error change of each onset group followed similar patterns around the time of myopia onset (Fig. 3a), which is more pronounced in early onset individuals (ANOVA,  $P < 0.05$ ). Similar patterns are seen for the mean axial length and lens power changes, which show more axial growth and more rapid power loss in early-onset children (Figs. 3b, 3c). For the mean lens power changes this acceleration was significant ( $t$ -test,  $P < 0.001$ ) and takes place up to one year before onset.

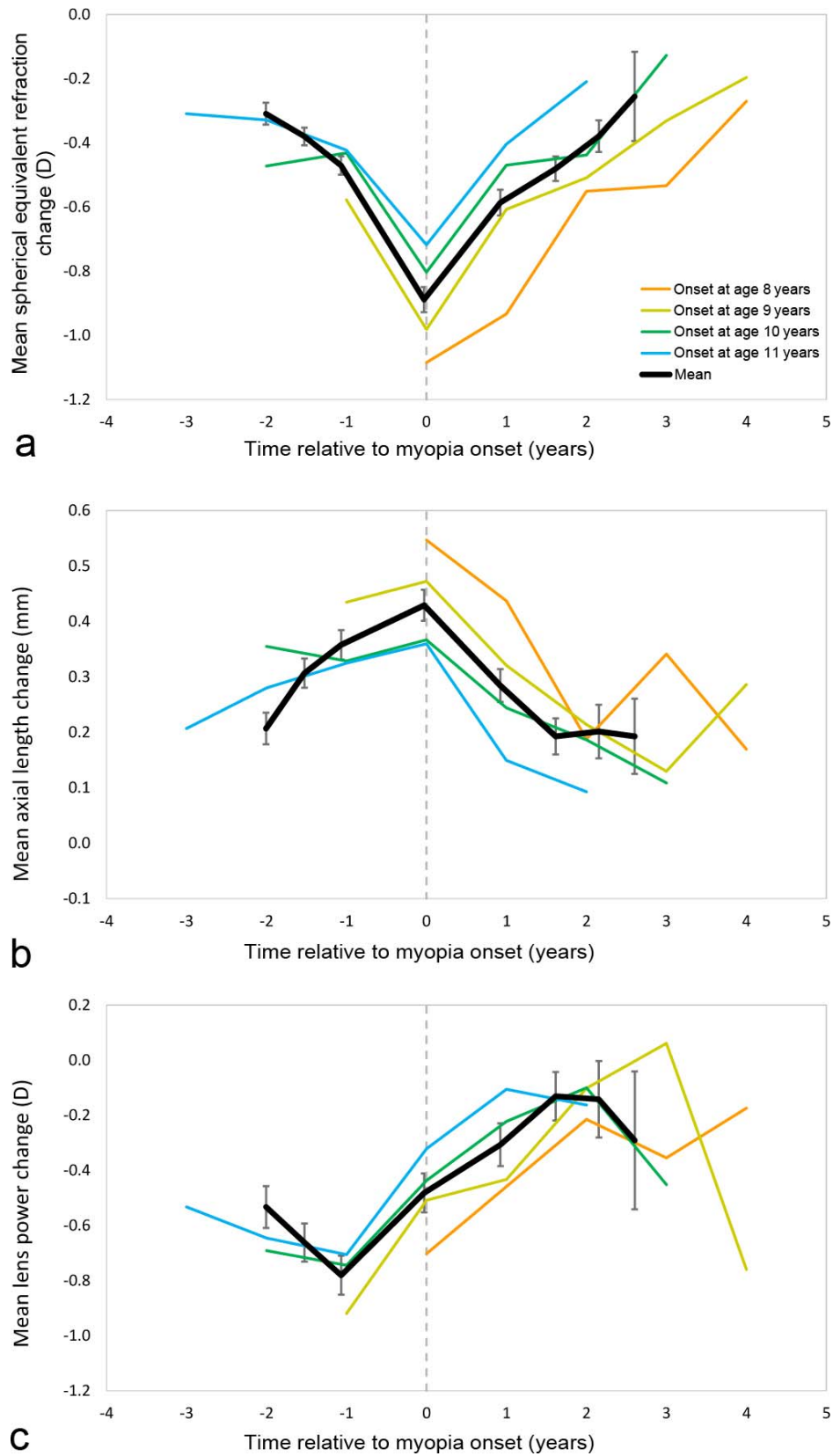
## DISCUSSION

The results above describe the ocular growth curves, separated by age at myopia onset, based on a longitudinal follow-up of a large cohort of school-age children. Children who later developed myopia already saw myopic shifts some years before onset, already differentiating them from emmetropic children. These new myopes experienced an accelerated myopic progression at onset that gradually slowed down in the following period. Simultaneously, new myopes had a faster axial growth compared to emmetropes and a rapid decrease in axial growth after onset, albeit still faster than emmetropes.

One finding of this work is that the deceleration in lens power loss precedes myopia onset by 1 year, rather than occurs simultaneously with onset as reported previously.<sup>12</sup> There also is a slight, but significant acceleration that appears to compensate for the higher axial elongation rate also present before onset, thus postponing myopia onset.

A considerable variation in biometric changes is observed between onset groups. For example, early-onset myopes

tended to have a faster and longer lasting refractive error progression compared to later-onset myopes,<sup>13</sup> leading to higher amounts of myopia by the end of the study. This also was seen in the acceleration of the myopia development, which was larger for early-onset individuals,<sup>13</sup> and may result from more intense environmental stimuli (e.g., lack of outdoor time or more near work). The main determining factor of this development was axial growth, which seemed remarkably parallel between onset groups (Fig. 1b). When changes in growth speed were considered, a subtler picture appeared where axial growth underwent a modest acceleration at onset, followed by a gradual deceleration in the years thereafter. This axial growth acceleration was concurrent with greater lens power loss before onset. This pattern was not found in persistent emmetropes, where lenticular changes remained modest at all times. This pattern is of paramount importance for homeostasis to succeed, while a breakdown in this balanced growth can lead to myopia.<sup>1</sup> Given that corneal power stabilizes early in life, at approximately age 2 to 3 years,<sup>14</sup> refractive homeostasis is mostly determined by the gradual changes in crystalline lens power and axial length. Based on animal studies, these lenticular changes are mostly passive in nature,<sup>15</sup> resulting from uncontrolled internal changes that gradually alter the lens thickness, curvature, and gradient index.<sup>12,16,17</sup> To explain lens thinning and associated power loss in ocular growth in humans, a theory implicating lens stretch by zonular traction has been proposed.<sup>6,18</sup> Axial length, on the other hand, undergoes a combination of somatic and regulated growth, and, therefore, can compensate for



**FIGURE 3.** Mean changes in (a) spherical equivalent refraction, (b) axial length, and (c) lens power with respect to the year of myopia onset. Colored lines correspond with the different onset ages; the black line represents the mean of all new myopes, with the age corrected for sampling artefacts. Error bars: 95% confidence interval of the mean.

variations in lens power loss,<sup>2</sup> leading, for example, to longer emmetropic eyes with lower lens power.<sup>16</sup>

Up to 3 years before myopia onset, future myopes still have a near-emmetropic refraction. Their axial growth rates, however, are faster than in emmetropes, most likely affected by known risk factors, such as large amounts of near work activities and time spent indoors.<sup>19,20</sup> At first, the high axial growth rate would be compensated by an increased lens power loss rate, which continues until 1 year before myopia onset. At this stage, as was originally postulated by Mutti et al.,<sup>5</sup> the lens seems to reach a physiologic limit below which it is unable to lose power efficiently,<sup>17</sup> causing a sudden deceleration in lens power loss. Meanwhile, axial growth is at a relatively high rate, which, combined with the abrupt change in lens power loss, leads to a rapid shift in SER that leads to the onset of myopia. After onset, the axial elongation slows down due to the myopic defocus or the age-related slowing in axial growth. As these growth rates are higher in younger children, this slowing would take longer in early-onset myopes, leading to higher amounts of myopia.<sup>3</sup> This combination of changes explains why myopes have lower lens power than emmetropic eyes in children and adults.<sup>16,21</sup>

The suggestion that changes in lens power loss have a role in myopia was previously reported for the CLEERE study, where lens power loss ceased immediately at myopia onset. The Guangzhou twin study,<sup>3</sup> on the other hand, found no such variations in lens power loss, while our results confirmed those of the CLEERE study, albeit with a more gradual transition. These discrepancies may originate from ethnic, environmental, or methodologic differences between studies, such as the use of phakometry, the Bennett-Rabbetts formula in the Guangzhou study, and the Bennett formula in our study. Another difference lies in the fact that the CLEERE and Guangzhou studies superimposed data from all onset ages, thereby averaging out the nuances between early-onset and later-onset myopes. This by itself would not be sufficient to explain the discrepancy, however, or further analysis with independently collected datasets and a wider range of myopia onset ages would be recommended to confirm the current results. It also would be interesting to extend these analyses to adolescent groups, but longitudinal biometric studies are not yet available for this important age group<sup>17,22</sup> when myopia incidence can peak in some low prevalence environments.<sup>23</sup>

Several theories have been proposed as to why the lens loses its power over time.<sup>16</sup> Based on the longitudinal Orinda study,<sup>6</sup> Mutti et al.<sup>18</sup> hypothesized that lens thinning was the result of zonular traction, mediated by ciliary muscle tension during ocular growth. Eventually lens thinning and power loss would reach a limit due to scleral expansion in myopic children, explaining their original observation of a slowing lens power loss at the age at 10 years, when myopia has a peak in incidence.<sup>23</sup> Meanwhile, an earlier analysis<sup>12</sup> of the current Singaporean cohort suggested that in theory school age lens power loss results from a loss in its surface power, combined with lens compacting and internal remodeling of the gradient refractive index. This internal remodeling might be the result of shape changes, which in turn could alter the curvatures of the isoindical surfaces of gradient index (i.e., surfaces of equal refractive index).<sup>16,24</sup> To simplify complex measurements, studies often use the equivalent index, which is the refractive index that a homogeneous lens must have to match the power of the lens surfaces and gradient index power. The CLEERE and Orinda<sup>6</sup> studies measured lens curvatures and lens equivalent index, finding decreasing values of both in school children.<sup>5,6</sup> Meanwhile, Mutti et al.<sup>5</sup> also reported an increased lens equivalent index in myopes after onset,<sup>5</sup> which is in contrast with the fact that myopes have lower lens power. Although,

the gradient index profile has not yet been measured for different refractive errors, there are some indirect indications that myopic eyes could have a steeper gradient, such as the fact that older, myopic eyes are less prone to lose lens power or to have hyperopic shifts in adult years,<sup>25</sup> as if they could have reached a limit of lens power loss in early ages. This leaves open the question of how increased axial elongation could be linked to more power loss before myopia onset.

Note that one clear indicator for future myopia seems to be a much faster axial growth rate, so the onset axial length of 23.80 mm in boys and  $\pm 23.71$  mm in girls;  $P < 0.001$ ) is reached long before most emmetropes would reach it (if at all). Interestingly, this is very similar to the mean axial length at onset reported by the CLEERE study.<sup>4</sup> Limitations of the study are related with the large interindividual variations and measurements of biometry in some young children might be difficult to collect. Also, variations can occur between different time points of the follow-up. Subject ethnicity was not considered, which is known to affect myopia.

The clinical applications of the current work will be limited at the current stage, as the reported changes are rather subtle and cannot be used to predict a patient's myopia risk. However, the observation that the increase in axial length growth and lens power loss precede the myopia onset shows that genetic and environmental factors act well before the eye officially becomes myopic, which may be of great use in defining or evaluating new approaches to myopia prevention.<sup>19</sup> Optical interventions to control myopia may be implemented during the phase of active changes before the onset of myopia and tested in premyopic children for prevention of myopia onset.

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