

# Role of Parental Refractive Status in Myopia Progression: 12-Year Annual Observation From the Guangzhou Twin Eye Study

Chimei Liao,<sup>1</sup> Xiaohu Ding,<sup>1</sup> Xiaotong Han,<sup>1</sup> Yu Jiang,<sup>1</sup> Jian Zhang,<sup>1</sup> Jane Scheetz,<sup>2</sup> and Mingguang He<sup>1</sup>

<sup>1</sup>State Key Laboratory of Ophthalmology, Zhongshan Ophthalmic Center, Sun Yat-sen University, Guangzhou, China

<sup>2</sup>Centre for Eye Research Australia, Royal Victorian Eye and Ear Hospital, Melbourne, Australia

Correspondence: Mingguang He, Zhongshan Ophthalmic Center, Sun Yat-sen University, no. 54 Xianlie Road, Guangzhou 510060, China; mingguang\_he@yahoo.com.

CL and XD are joint first authors.

Submitted: March 25, 2019

Accepted: July 15, 2019

Citation: Liao C, Ding X, Han X, et al. Role of parental refractive status in myopia progression: 12-year annual observation from the Guangzhou twin eye study. *Invest Ophthalmol Vis Sci.* 2019;60:3499–3506. <https://doi.org/10.1167/iops.19-27164>

**PURPOSE.** We investigate the impact of parental myopia on spherical equivalent (SE) progression and axial length (AL) elongation.

**METHODS.** Children and their parents were invited for annual examinations from 2006 (baseline). Cycloplegic autorefractometry and AL were measured at each visit. Parental refractive status was determined using refraction data from their baseline visit. Children were classified into five groups: no myopic parents (non-non), only one moderately myopic parent (non-moderate), only one highly myopic parent (non-high), two moderately myopic parents (moderate-moderate), and one moderately myopic or more severe and one highly myopic parent (moderate-high/high-high). The relationship between progression of SE and AL with parental refractive status was estimated by linear mixed-effects models. Data from 2006 to 2017 were analyzed in the current study.

**RESULTS.** A total of 1831 children were enrolled (mean age,  $11 \pm 2.7$  years; mean standard error,  $-0.49 \pm 2.16$  diopters [D] at baseline). Myopia progressed faster for children with parental myopia (non-non group as reference, all  $P < 0.05$ ), while AL elongation mirrored the change in SE (all  $P < 0.001$  except for non-mod group  $P = 0.12$ ). As for the age-specific change in SE and AL, children in the mod-high/high-high group presented with the fastest progression. Children with highly myopic parents were at higher risks of being highly myopic during adulthood (odds ratio = 13.98 and 25.71 for non-high and mod-high/high-high groups; both  $P < 0.001$ ).

**CONCLUSIONS.** SE progresses and AL elongates at a faster rate at an earlier age in children with parental myopia. Children with highly-myopic parents have higher risks of being highly myopic during adulthood.

Keywords: parental myopia, myopia progression, axial length

Myopia has become a public health concern due to its increasing global prevalence. The prevalence of myopia is estimated to increase to 50% by 2050,<sup>1</sup> resulting in a tremendous global economic burden and loss of productivity.<sup>2</sup> High myopia has the potential to create additional visual challenges for patients due to an increased risk of ocular diseases, such as glaucoma,<sup>3</sup> retinal detachment,<sup>4</sup> and myopic macular degeneration.<sup>5</sup> Identifying risk factors for myopia progression and eye growth will help target at risk populations and implement early intervention strategies.

It is well recognized that myopia is a complex disease with multiple risk factors, among which family history has drawn much attention in the etiology of myopia.<sup>6</sup> The association between family history and refractive error has been established in cross-sectional studies.<sup>7–9</sup> Several longitudinal studies have shown that a myopic shift and eye growth occurs more rapidly among children with a stronger parental history of myopia.<sup>10–13</sup> However, drawing conclusions from previous epidemiologic studies has been difficult due to various limitations, such as the recruitment of only myopic children

at baseline.<sup>14,15</sup> Consequently, parental influence in the general population has not been able to be addressed fully. Other studies have been population-based and findings were calculated based on relatively small sample sizes or short follow-ups.<sup>12,13,16</sup> In addition, questionnaire data were used to determine parental refraction, which can lead to inaccuracies due to recall bias.<sup>13,17</sup>

Furthermore, myopia and high myopia seem to have different familial patterns of inheritance,<sup>18</sup> with a previous study finding that more severe myopia in one parent resulted in an increased risk of myopia in their children.<sup>19</sup> A strong association also has been found between having one or more parents who are highly myopic and the axial length (AL) of children.<sup>20</sup> However, to our knowledge, how the severity of parental myopia influences refraction development and AL elongation of offspring has not been reported. Therefore, we explored the impact of parental myopia on spherical equivalent (SE) progression and AL elongation in Chinese children using data from a 12-year annual follow-up of twins.



## METHOD

### Study Population

Participants in this study were recruited from the Guangzhou Twin Eye study, which has been described in detail previously.<sup>21,22</sup> Briefly, the Guangzhou Twin Eye study is a population-based registry established in Guangzhou, China. All twins born between 1987 and 2000 were identified using the official Household Registry of Guangzhou. Those living in two districts adjacent to the Zhongshan Ophthalmic Center were invited for baseline data collection in 2006, with a response rate of 82.3%. Since then, participating twins and their biological parents were invited to attend for annual follow-up examination.

This study was conducted in accordance with the tenets of the World Medical Association's Declaration of Helsinki. Ethics approval was obtained from the Sun Yat-sen University ethical review board and the ethics committee of the Zhongshan Ophthalmic Center. Written informed consent was obtained for all participants from parents or their legal guardian.

### Eye Examinations

At each annual visit, AL was measured in children by noninvasive partial-coherence laser interferometry (IOLMaster; Carl Zeiss Meditec, Oberkochen, Germany) in a dark room before pupil dilation. At least five consecutive measurements were taken for each eye. Refraction was measured under cycloplegia for children and without cycloplegia for parents. Cycloplegia was induced with two drops of cyclopentolate 1% administered to each eye 5 minutes apart, followed by a third drop administered after 20 minutes. Complete cycloplegia was defined as pupil dilation of  $\geq 6$  mm with an absent light reflex. The refraction of children and adults were measured using an autorefractor (KR8800; Topcon Corp., Tokyo, Japan) with three measurements taken for each eye.

The presence of myopia was defined as a SE of at least  $-0.50$  diopter (D). Those with a SE less than  $-6.0$  D were categorized as having moderate myopia and  $\geq -6.0$  D were categorized as having high myopia. Parental refractive status was determined using refraction data obtained from their baseline visit, and was classified into six categories as follows: neither parent was myopic (non-non), one parent was nonmyopic and the other moderately myopic (non-mod), one parent was nonmyopic and the other highly myopic (non-high), both parents were moderately myopic (mod-mod), one parent was moderately myopic and the other highly myopic (mod-high), and both parents were highly myopic (high-high). Because the sample size of the high-high group was small ( $n = 28$ ), it was combined into the moderate-high group in our analysis. Children with ocular disease, such as manifest strabismus, amblyopia, and nystagmus, were excluded as these diseases have the potential to affect the natural growth of the eye. Only those with successful cycloplegia in the right eye and complete parental data were included in the study.

### Statistical Analysis

Annual examination data of twins from 2006 to 2017 were analyzed in current study. The right eye was arbitrarily selected for analysis due to the high correlation between eyes (Pearson correlation coefficient = 0.92;  $P < 0.001$ ).

The longitudinal change in SE and AL among children and its relationship to parental refractive status were analyzed. To achieve an accurate estimation accounting for repeated measurements within the same individual and clustering of observations within families, multilevel mixed-effects models using the individual as the first level and family as the second

level were used. The time factor used in the model was age at each visit, and was centralized before regression. Interaction between parental refractive status and age was included to explore the effect of parental myopia over time. Age-specific SE progression and AL elongation were plotted to visualize the longitudinal changes in children with different parental refractive status using Lowess smoothing. In addition, the rate of annual change in SE and AL (defined as the difference between the visit and the last year) was calculated and graphed as a function of each age-interval using Lowess smoothing. The Lowess curves were generated using all true values of SE or AL from the 12-year data. Multilevel ordinal regression was used to estimate the influence of parental myopia on refractive status in adulthood.

Statistical analyses were performed using STATA version 14.0 (StataCorp, College Station, TX, USA). For the linear mixed models, the "mixed" procedure of Stata was used.  $P < 0.05$  was considered statistically significant.

## RESULTS

Among 2616 children enrolled at baseline, 1831 participants with complete parental refraction data were included in the analysis. Compared to the participants excluded, those included were significantly older at baseline (11.7 vs. 11.0 years;  $P < 0.001$ ), had a greater myopic SE ( $-0.73$  vs.  $-0.49$  D;  $P = 0.02$ ), and a similar AL (23.62 vs. 23.50 mm;  $P = 0.08$ ). Baseline characteristics of included participants by different parental refractive status are shown in Table 1. Children in the non-non group were the oldest, but were the least myopic (mean SE,  $-0.09$  D, as reference), followed by the non-mod ( $-0.52$  D;  $P = 0.01$ ), mod-mod ( $-0.73$  D;  $P = 0.01$ ), non-high ( $-1.25$  D;  $P = 0.001$ ), and mod-high/high-high ( $-1.31$  D;  $P < 0.001$ ) groups. Axial length was shortest among children in the non-non group (mean, 23.36 mm, as reference), followed by the non-mod (mean, 23.51 mm;  $P = 0.07$ ), mod-mod (mean, 23.63 mm;  $P = 0.02$ ), non-high (mean, 23.68 mm;  $P = 0.06$ ), and mod-high/high-high (mean, 23.76 mm;  $P = 0.03$ ) groups.

The trend of SE progression and AL elongation among children in different groups is plotted in Figures 1 and 2 using Lowess smoothed methods. Overall, myopic shift occurred in all groups. SE showed an initial rapid decrease with increasing age, followed by stability around adulthood. Among groups, children without myopic parents were more hyperopic, while children in the mod-high/high-high group were more myopic from childhood to adulthood. AL increased with age during childhood and stabilized around adulthood. Children without myopic parents showed slower AL elongation from childhood to adulthood. Generally, the elongation of AL was consistent with the progression of SE, except that the non-high group was on average more myopic than the mod-mod group, but with a shorter AL.

The association between SE and AL with parental refractive status was estimated using linear mixed-effect models (Table 2). Parental education level and maximum family income were excluded from the model due to their insignificant correlation with SE (paternal education level,  $P = 0.39$ ; maternal education level,  $P = 0.22$ ; maximum income,  $P = 0.80$ ) and AL (paternal education level;  $P = 0.54$ ; maternal education level;  $P = 0.67$ ; maximum income;  $P = 0.68$ ) in the multiple regression. Only sex was adjusted for in the final mixed model. The negative slope for age ( $-0.63$ ,  $P < 0.001$ ) and the positive slope for age<sup>2</sup> ( $0.02$ ,  $P < 0.001$ ) suggest that the decline in SE decelerated as participants got older. The parental effect was strongly significant, with children having parental myopia being more myopic on average at the age of 7 ( $P < 0.001$ ). The coefficients for the interaction between parental refractive status and age

TABLE 1. Characteristics of Participants at Baseline by Different Parental Refractive Status

Characteristics	Non-Non	Non-Mod	Non-High	Moderate-Mod	Mod-High / High-High	Total
<i>n</i>	609	724	101	301	96	1831
Follow-up visit times, median, (1st-3rd quartile)	8 (5-10)	8 (6-10)	9 (6-10)	9 (6-10)	9 (7-11)	9 (6-10)
Male, <i>n</i> (%)	306 (50.3)	353 (48.8)	50 (49.5)	154 (51.2)	47 (49.0)	910 (49.7)
Age, years, mean ± SD	11.7 ± 2.7	10.9 ± 2.6	10.7 ± 3.1	10.3 ± 2.5	10.0 ± 2.6	11.0 ± 2.7
SE, D, mean ± SD	-0.09 ± 1.92	-0.52 ± 2.17	-1.25 ± 2.73	-0.73 ± 2.18	-1.31 ± 0.29	-0.49 ± 2.16
AL, mm, mean ± SD	23.36 ± 1.13	23.51 ± 1.11	23.68 ± 1.38	23.63 ± 1.17	23.76 ± 0.97	23.50 ± 1.14
Paternal SE, D, mean ± SD	0.49 ± 0.83	-0.74 ± 1.56	-3.59 ± 5.12	-2.33 ± 1.51	-5.31 ± 3.52	-0.99 ± 2.46
Maternal SE, D, mean ± SD	0.26 ± 0.56	-0.96 ± 1.58	-5.35 ± 5.65	-2.23 ± 1.50	-7.19 ± 5.04	-1.33 ± 2.87
Paternal education level*						
Less than high school, <i>n</i> (%)	166 (39.3)	116 (22.0)	10 (14.3)	26 (13.5)	6 (8.6)	324 (25.3)
High school or above, <i>n</i> (%)	256 (60.7)	411 (78.0)	60 (85.7)	167 (86.5)	64 (91.4)	958 (74.7)
Maternal education level†						
Less than high school, <i>n</i> (%)	203 (44.6)	168 (29.5)	12 (16.0)	28 (12.6)	2 (2.7)	413 (29.6)
High school or above, <i>n</i> (%)	252 (55.4)	401 (70.5)	63 (84.0)	195 (87.4)	72 (97.3)	983 (70.4)
Maximum income, RMB/month, <i>n</i> (%)‡						
≤5000	315 (63.4)	308 (49.5)	28 (31.5)	64 (27.2)	26 (31.7)	741 (48.6)
≤10,000	116 (23.3)	183 (29.5)	37 (41.6)	84 (35.7)	14 (17.1)	434 (28.5)
≤20,000	48 (9.7)	98 (15.8)	20 (22.5)	69 (29.4)	34 (41.5)	269 (17.7)
>20,000	18 (3.6)	32 (5.2)	4 (4.5)	18 (7.7)	8 (9.8)	80 (5.2)

\* Number with paternal education level data = 1282.  
 † Number with maternal education level data = 1396.  
 ‡ Number with income data = 1524.

was significant, indicating that the rate of decline in SE with age differed across different groups. The more negative coefficient suggested that the rate of myopia progression was on average faster for children with parental myopia (non-mod group,  $\beta = -0.03$ ,  $P = 0.01$ ; non-high group,  $\beta = -0.1$ ,  $P < 0.001$ ; mod-mod group,  $\beta = -0.1$ ,  $P < 0.001$ ; mod-high/high-high group,  $\beta = -0.15$ ,  $P < 0.001$ ). Similarly, AL elongation also showed a curved pattern that the increase in AL decelerated

with age. At the age of 7, children with parental myopia showed a longer AL compared to children without (all  $P < 0.05$ ). Axial elongation was on average faster for children with parental myopia (non-high group,  $\beta = 0.05$ ,  $P < 0.001$ ; mod-mod group,  $\beta = 0.03$ ,  $P < 0.001$ ; mod-high/high-high group,  $\beta = 0.05$ ,  $P < 0.001$ ), except for children in the non-mod group ( $\beta = 0.01$ ,  $P = 0.118$ ).

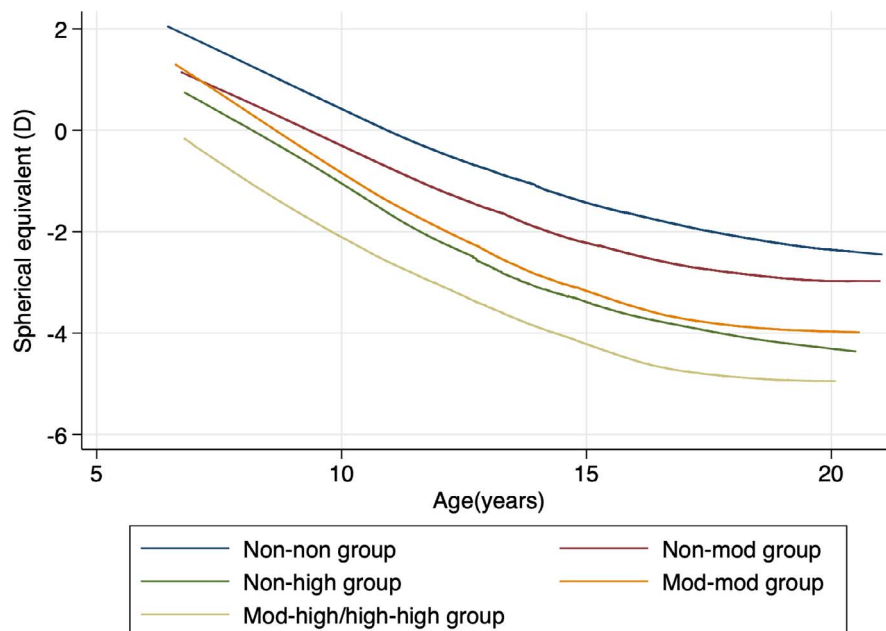
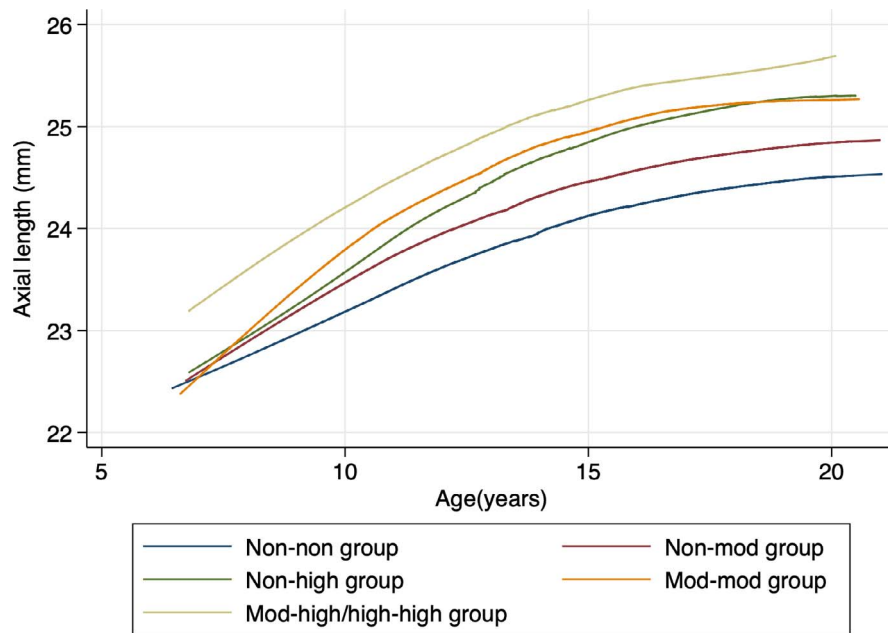


FIGURE 1. Lowess-smoothed spherical equivalent progression by different parental refractive status. Profile of spherical equivalent progression of children categorized into five groups according to their parental status of myopia: none of the parents was myopic (non-non), one parent was nonmyopic and the other was moderately myopic (non-moderate), one parent was nonmyopic and the other was highly myopic (non-high), both parents were moderately myopic (mod-mod), and one of the parents was moderately myopic and the other was highly myopic or both parents were highly myopic (mod-high/high-high).



**FIGURE 2.** Lowess-smoothed axial length elongation by different parental refractive status. Profile of axial length elongation of children categorized into five groups according to their parental status of myopia: none of the parents was myopic (non-non), one parent was nonmyopic and the other was moderately myopic (non-moderate), one parent was nonmyopic and the other was highly myopic (non-high), both parents were moderately myopic (mod-mod), and one parent was moderately myopic and the other was highly myopic or both parents were highly myopic (mod-high/high-high).

Age-specific annual rate of change of SE using Lowess smoothed methods is plotted in Figure 3. The true values without smoothing are listed in Supplementary Table S2. Generally, a pattern of decrease in SE started with an accelerated progression before the age of around 10, followed by a diminishing progression after a peak rate. The magnitude of SE change rate was smallest among children in the non-non group when compared to other groups. The peak rate of progression emerged earliest in the mod-high/high-high group at 7 to 9 years old, but appeared latest in the non-non group at approximately age 11. Children in the non-high and mod-mod groups displayed a similar trend in the annual change rate of SE from childhood to adulthood. Like SE

progression, AL elongated most rapidly at approximately 8 to 12 years of age and stabilized at approximately adulthood (Fig. 4; Supplementary Table S3). Change of AL mirrored the change of SE in each group.

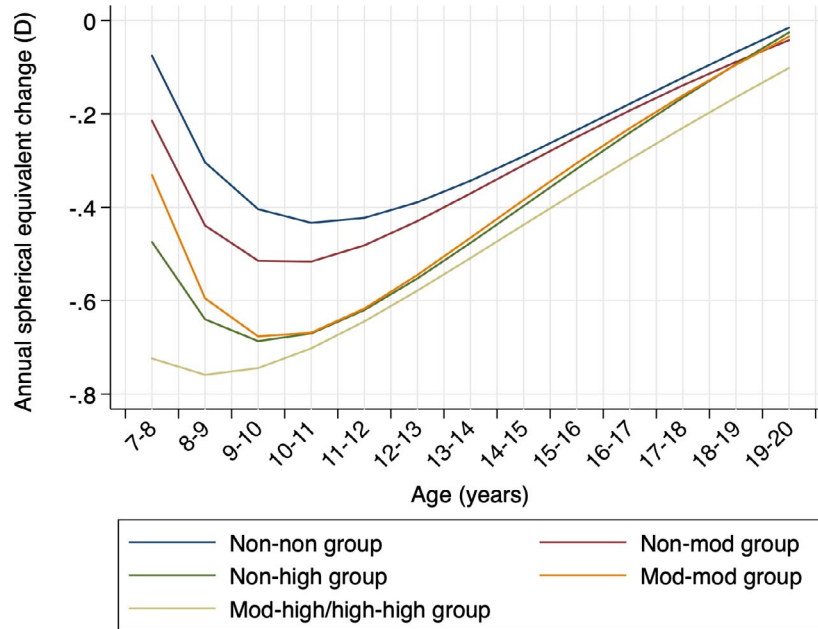
The refractive error status after age 16 was available in 1502 participants and the results are listed in Table 3. More than 30% of children with one or both highly myopic parents had high myopia in adulthood. Nearly 30% of children without myopic parents tended to remain emmetropic after 16 years of age. Children with highly myopic parents were at a significantly higher risk of being myopic in adulthood (odds ratio [OR] = 13.98 and 25.71 for non-high and mod-high/high-high groups, respectively; both  $P < 0.001$ ).

**TABLE 2.** Linear Mixed-effect Models for Associations of the SE and AL with Sex, Age, and Parental Refractive Status

Predictors	SE		AL	
	Adjusted $\beta$ (95% CI)	Adjusted $P$ Value	Adjusted $\beta$ (95% CI)	Adjusted $P$ Value
Female	-0.11 (-0.27, 0.06)	0.21	-0.51 (-0.60, -0.43)	<0.001
Age	-0.63 (-0.66, -0.60)	<0.001	0.38 (0.36, 0.39)	<0.001
Age <sup>2</sup>	0.02 (0.02, 0.03)	<0.001	-0.02 (-0.02, -0.01)	<0.001
Parental refractive status				
Non-non	Reference	-	Reference	-
Non-mod	-0.57 (-0.84, -0.30)	<0.001	0.28 (0.14, 0.42)	<0.001
Non-high	-1.20 (-1.73, -0.68)	<0.001	0.41 (0.13, 0.69)	0.004
Mod-mod	-0.73 (-1.07, -0.39)	<0.001	0.42 (0.24, 0.60)	<0.001
Mod-high/high-high	-1.40 (-1.93, -0.88)	<0.001	0.58 (0.30, 0.87)	<0.001
Parental refractive status $\times$ Age				
Non-non	Reference	-	Reference	-
Non-mod	-0.03 (-0.06, -0.01)	0.01	0.01 (-0.002, 0.02)	0.118
Non-high	-0.10 (-0.15, -0.05)	<0.001	0.05 (0.02, 0.07)	<0.001
Mod-mod	-0.10 (-0.14, -0.07)	<0.001	0.03 (0.02, 0.05)	<0.001
Mod-high/high-high	-0.15 (-0.20, -0.10)	<0.001	0.05 (0.03, 0.08)	<0.001

Age was centralized at 7 years (minimum age at baseline). Age<sup>2</sup> was calculated as age  $\times$  age.





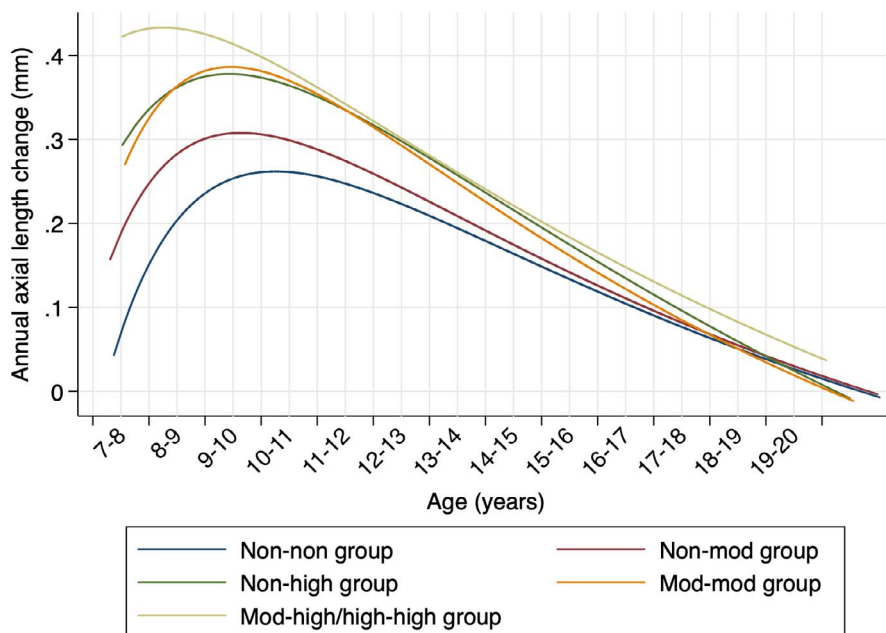
**FIGURE 3.** Lowess smoothed rate of annual change in spherical equivalent at each age-interval. Age-specific annual rate of change of spherical equivalent among five groups using Lowess smoothed methods. Children were categorized into five groups according to their parental status of myopia: none of the parents was myopic (non-non), one parent was nonmyopic and the other was moderately myopic (non-moderate), one parent was nonmyopic and the other was highly myopic (non-high), both parents were moderately myopic (mod-mod), and one parent was moderately myopic and the other was highly myopic or both parents were highly myopic (mod-high/high-high).

**DISCUSSION**

Using data from 12-year annual follow-up examinations and parental refraction measurements from the Guangzhou Twin Eye Study, our study investigated parental influence on refraction development and AL elongation in their offspring. The results showed that children with myopic parents had

more rapid myopia progression and AL elongation. This parental influence took effect more significantly at an earlier age.

The correlation between family and refractive error has been well established through a number of cross-sectional studies, in which a significant positive association was identified between parental myopia and a child’s risk of being



**FIGURE 4.** Lowess smoothed rate of annual change in axial length at each age-interval. Age-specific annual rate of change of axial length among five groups using Lowess smoothed methods. Children were categorized into five groups according to their parental status of myopia: none of the parents was myopic (non-non), one parent was nonmyopic and the other was moderately myopic (non-moderate), one parent was nonmyopic and the other was highly myopic (non-high), both parents were moderately myopic (mod-mod), and one parent was moderately myopic and the other was highly myopic or both parents were highly myopic (mod-high/high-high).

TABLE 3. Multilevel Ordinal Regression Model for Predicting Refractive Errors Status of Participants after 16 Years of Age

Groups	Emmetropia, <i>n</i> (%)	Moderate Myopia, <i>n</i> (%)	High Myopia, <i>n</i> (%)	OR (95%CI)	<i>P</i> Value
Non-non ( <i>n</i> = 519)	149 (28.7)	333 (64.2)	37 (7.1)	Reference	-
Non-mod ( <i>n</i> = 602)	107 (17.8)	433 (71.9)	62 (10.3)	2.60 (1.60, 4.21)	<0.001
Non-high ( <i>n</i> = 75)	8 (10.7)	44 (58.7)	23 (30.7)	13.98 (5.40, 36.18)	<0.001
Mod-mod ( <i>n</i> = 224)	20 (8.9)	152 (67.9)	52 (23.2)	10.13 (5.29, 19.41)	<0.001
Mod-high/high-high ( <i>n</i> = 82)	3 (3.7)	52 (63.4)	27 (32.9)	25.71 (9.71, 68.04)	<0.001

This model is adjusted for sex.

myopic.<sup>23</sup> Whether and how parental myopia influences refraction development cannot be fully addressed through cross-sectional study designs. In this longitudinal study, greater myopic shift was observed in children with myopic parents through preschool to adulthood ( $-0.47$  vs.  $-0.38$  vs.  $-0.38$  vs.  $-0.28$  vs.  $-0.22$  D/yr in mod-high/high, mod-mod, non-high, non-moderate, and non-non groups, respectively), indicating a significant parental influence on a child's refractive progression. Consistent with our study, Saw et al.<sup>24</sup> observed that children with a parental history of myopia showed a higher rate of myopia progression than those without ( $-0.63$  vs.  $-0.42$  D/yr). The same phenomenon was observed in the Correction of Myopia Evaluation Trial (COMET) study (5-year progression,  $-2.59$  vs.  $-2.04$  vs.  $-1.81$  D in two-, one-, and nonmyopic parents groups)<sup>14</sup> as well as in a 22-year follow-up study (23-year progression,  $-4.21$  vs.  $-1.9$  D in children with and without parental myopia).<sup>15</sup> Unlike the aforementioned studies that enrolled myopic children at baseline, a school-based study also found that family correlation was associated with myopia progression ( $-0.22$  vs.  $-0.07$  vs.  $-0.02$  D in two-, one-, and nonmyopic parent groups),<sup>13</sup> although observation lasted for 1 year only. Overall, it is difficult to make comparisons to the magnitude of SE change rate among these studies due to differing recruitment protocols, follow-up time, and recall bias. However, they all indicated a positive correlation between parental myopia and change in refractive error.

In the current study, changes in AL mirrored the changes in SE, with greater AL elongation and SE progression seen in children with myopic parents. These findings are consistent with studies conducted in Chinese students aged 5 to 16 years in Hong Kong (annual growth,  $0.37$  vs.  $0.26$  vs.  $0.20$  mm in two-, one-, and nonmyopic parent group)<sup>13</sup> and multiethnic children aged 6 to 11 in the COMET trial (5-year elongation,  $1.18$  vs.  $0.93$  vs.  $0.89$  mm in two-, one-, and nonmyopic parent group).<sup>14</sup> In contrast, a 22-year follow-up study found no significant difference between AL elongation and parental myopia in myopic children.<sup>15</sup> However, because the study was conducted in Finland, the findings are less generalizable to other populations due to the genetically homogenous study sample.

Our finding that children with highly myopic parents have a longer AL and a more myopic SE at the age of 7 suggested that the influence of parental myopia takes effect at an early age. Given that the majority of emmetropization takes place during preschool years, it is reasonable to postulate that parental myopia influences the process of emmetropization. Emmetropization is a developmental process that matches eye length to optical power, which is characterized by the continuous loss of intraocular compensation to neutralize the impact of axial elongation. Therefore, decreases in intraocular compensation will induce the myopic shift that normally would be associated with increases in AL.<sup>25</sup> In the current population at the age of 7 to 8, an increase in AL of  $0.13$  mm was accompanied with  $-0.06$  D of myopic shift in the non-non group. This was comparable to previous studies where a  $1$  mm increase in AL

was associated with a  $-0.38$  to  $-0.45$  change in SE in preschool children.<sup>25,26</sup> However, the SE and AL ratio was significantly larger for children in the mod-high/high-high group: an increase of  $1$  mm in AL was associated with an approximate  $-1.69$  D change in SE at the age of 7 to 8. This rate was approximate to the value in adulthood ( $-2$  D/mm) when most participants had become myopic, indicating that the potential intraocular compensation for this group was nearly "used up" at an early age. Therefore, it can be suggested that parental myopia may accelerate the emmetropization process, resulting in a higher risk of their offspring suffering myopia.<sup>27</sup> However, it is not clear whether the acceleration of emmetropization is a result of intrinsic ocular structures being less able to compensate for these changes, or a higher sensitivity and effectiveness brought on by the influence of parental myopia. Further studies are required to address this gap in the literature.

Another interesting finding is that the difference in SE progression rate among groups gradually reduced after the rapid growth stage and faded away at approximately adulthood. At this stage, the counterbalance from changes in lens power tends to be constant after myopia onset and AL acts as the primary determinant of refractive error.<sup>28</sup> The decreasing difference in progression among groups suggested a declining effect of parental myopia on AL elongation after late teenage years. This finding contradicts findings from some previous studies in which familial predisposition was associated with the occurrence and progression of adult-onset myopia.<sup>16,29,30</sup> In fact, parental myopia is a complex measure including the influence of genes, environment, and gene-environment interaction. We believe the reduction of familial influence in late teens might be partially attributed to greater changes in familial environment, especially for those children who live alone or do not share their environment with biological parents. Another hypothesis is that the environmental effect becomes dominant in this period. Moreover, the maturation of ocular structures may limit the plasticity of the globe and suppress parental influence. Overall, the relationship between parental myopia and myopia progression in adulthood remains up for debate. Our study depicted how parental myopia influences refraction development and found that parental myopia accelerates the process of emmetropization and myopia onset, but is of limited effect in the late teens. A possible explanation for parental influence in the early stages of myopia development is genetics, with the general belief that diseases caused mainly by genetic factors tend to have an earlier onset and more severe clinical presentation. However, only few loci of small effect have been successfully characterized to date.<sup>31</sup> Another possible interpretation is the effect of the environment, evidenced by the result that myopia still occurred in children without myopic parents. This phenomenon indicates that the environment has an influence on myopia development.

Unlike other studies relying on questionnaire data to ascertain parental refractive status,<sup>13,17</sup> we collected parental refraction data via noncycloplegia autorefractometry, which

enabled us to subdivide parental refractive status by different severity accurately. An interesting finding from our study is that children with only one highly myopic parent (non-high group) showed similar myopic progression and eye growth trend to children having two moderately myopic parents (mod-mod group). This is inconsistent with previous reports that greater myopia progression is associated with the greater number myopic parents.<sup>14</sup> This finding provided an important implication that parental influence is not just a simple relationship that depends on the number of myopic parents, but also relates to the severity of parental myopia. Moreover, children with one highly-myopic parent have a higher risk of also being highly myopic as an adult compared to those with one moderately-myopic parent, indicating the importance of familial pattern of inheritance in high myopia.

Another strength of the current study is that refraction and AL data of participants were collected annually over 12 years in the Guangzhou Twin Eye Study. Standardized examinations were conducted at baseline and each follow-up. By far, to our knowledge, this is the largest and longest follow-up study reporting parental influence on refraction development and eye growth. However, several limitations should be noted. Firstly, due to the enrolling age at baseline or loss to follow-up, not every participant had complete data from age 7 to 20. Therefore, we adopted a linear mixed model to avoid bias caused by missing values and take full advantage of data from each visit. Secondly, we did not adjust sociodemographic and environmental factors, such as parental education level, outdoor activity time, and reading time. Therefore, familial correlation in our study may include genetic factors and unmeasured shared environmental factors. Furthermore, we only analyzed parental influence on biometric parameters of AL. The inconsistency of SE and AL progression between the non-high and mod-mod groups indicated the influence of other biometrics on SE. Parental effects on other biometrics, such as anterior chamber depth and vitreous chamber depth and their contribution to refraction progression requires further study.

In conclusion, children with a parental history of myopia progress at a faster rate and have an earlier onset of myopia. Parental myopia is suggested to influence refraction development by accelerating the process of emmetropization and myopia onset. Children with highly myopic parents are at higher risk of being highly myopic in adulthood.

### Acknowledgments

Supported by the Fundamental Research Funds of the State Key Laboratory in Ophthalmology, National Natural Science Foundation of China (No. 81125007) National Natural Science Foundation of China (No. 81300795), and Fundamental Research Funds of the State Key Laboratory. The sponsor or funding organization had no role in the design or conduct of this research.

Disclosure: **C. Liao**, None; **X. Ding**, None; **X. Han**, None; **Y. Jiang**, None; **J. Zhang**, None; **J. Scheetz**, None; **M. He**, None

### References

- Holden BA, Fricke TR, Wilson DA, et al. Global prevalence of myopia and high myopia and temporal trends from 2000 through 2050. *Ophthalmology*. 2016;123:1036-1042.
- Naidoo KS, Fricke TR, Frick KD, et al. Potential lost productivity resulting from the global burden of myopia: systematic review, meta-analysis and modelling. *Ophthalmology*. 2019;126:338-346.
- Marcus MW, de Vries MM, Junoy Montolio FG, Jansonius NM. Myopia as a risk factor for open-angle glaucoma: a systematic review and meta-analysis. *Ophthalmology*. 2011;118:1989-1994.
- Daïen V, Le Pape A, Heve D, Carriere I, Villain M. Incidence, risk factors, and impact of age on retinal detachment after cataract surgery in France: a national population study. *Ophthalmology*. 2015;122:2179-2185.
- Wong Y, Sabanayagam C, Ding Y, et al. Prevalence, risk factors, and impact of myopic macular degeneration on visual impairment and functioning among adults in Singapore. *Invest Ophthalmol Vis Sci*. 2018;59:4603-4613.
- Zadnik K. The effect of parental history of myopia on children's eye size. *JAMA*. 1994;271:1323-1327.
- Harrington SC, Stack J, O'Dwyer V. Risk factors associated with myopia in schoolchildren in Ireland [published online ahead of print February 11, 2019]. *Br J Ophthalmol*. doi:10.1136/bjophthalmol-2018-313325.
- Lim DH, Han J, Chung TY, Kang S, Yim HW; Epidemiologic Survey Committee of the Korean Ophthalmologic Society. The high prevalence of myopia in Korean children with influence of parental refractive errors: the 2008-2012 Korean National Health and Nutrition Examination Survey. *PLoS One*. 2018;13:e0207690.
- Lin Z, Gao TY, Vasudevan B, et al. Generational difference of refractive error and risk factors in the Handan Offspring Myopia Study. *Invest Ophthalmol Vis Sci*. 2014;55:5711-5717.
- Jones LA, Sinnott LT, Mutti DO, Mitchell GL, Moeschberger ML, Zadnik K. Parental history of myopia, sports and outdoor activities, and future myopia. *Invest Ophthalmol Vis Sci*. 2007;48:3524-3532.
- French AN, Morgan IG, Mitchell P, Rose KA. Risk factors for incident myopia in Australian schoolchildren: the Sydney adolescent vascular and eye study. *Ophthalmology*. 2013;120:2100-2108.
- Saw SM, Shankar A, Tan SB, et al. A cohort study of incident myopia in Singaporean children. *Invest Ophthalmol Vis Sci*. 2006;47:1839-1844.
- Lam DSC, Fan DSP, Lam RF, et al. The effect of parental history of myopia on children's eye size and growth: results of a longitudinal study. *Invest Ophthalmol Vis Sci*. 2008;49:873-876.
- Kurtz D, Hyman L, Gwiazda JE, et al. Role of parental myopia in the progression of myopia and its interaction with treatment in COMET children. *Invest Ophthalmol Vis Sci*. 2007;48:562-570.
- Pärssinen O, Kauppinen M. What is the influence of parents' myopia on their children's myopic progression? A 22-year follow-up study. *Acta Ophthalmol*. 2016;94:579-585.
- Onal S, Toker E, Akingol Z, et al. Refractive errors of medical students in Turkey: one year follow-up of refraction and biometry. *Optom Vis Sci*. 2007;84:175-180.
- Pärssinen O, Kauppinen M, Viljanen A. The progression of myopia from its onset at age 8-12 to adulthood and the influence of heredity and external factors on myopic progression. A 23-year follow-up study. *Acta Ophthalmol*. 2014;92:730-739.
- Morgan I, Rose K. How genetic is school myopia? *Prog Retin Eye Res*. 2005;24:1-38.
- Xiang F, He M, Morgan IG. The impact of severity of parental myopia on myopia in Chinese children. *Optom Vis Sci*. 2012;89:884-891.
- Liang CL, Yen E, Su JY, et al. Impact of family history of high myopia on level and onset of myopia. *Invest Ophthalmol Vis Sci*. 2004;45:3446-3452.
- He M, Ge J, Zheng Y, Huang W, Zeng J. The Guangzhou Twin Project. *Twin Res Hum Genet*. 2006;9:753-757.

22. Zheng Y, Ding X, Chen Y, He M. The Guangzhou Twin Project: an update. *Twin Res Hum Genet.* 2013;16:73–78.
23. Zhang X, Qu X, Zhou X. Association between parental myopia and the risk of myopia in a child. *Exp Ther Med.* 2015;9:2420–2428.
24. Saw S-M, Javier Nieto F, Katz J, Schein OD, Levy B, Chew S-J. Familial clustering and myopia progression in Singapore school children. *Ophthalmol Epidemiol.* 2001;8:227–236.
25. Guo X, Fu M, Ding X, Morgan IG, Zeng Y, He M. Significant axial elongation with minimal change in refraction in 3- to 6-year-old Chinese preschoolers: the Shenzhen Kindergarten Eye Study. *Ophthalmology.* 2017;124:1826–1838.
26. Ip JM, Huynh SC, Kifley A, et al. Variation of the contribution from axial length and other ophthalmometric parameters to refraction by age and ethnicity. *Invest Ophthalmol Vis Sci.* 2007;48:4846–4853.
27. Morgan IG, Rose KA, Ellwein LB; Refractive Error Study in Children Survey Group. Is emmetropia the natural endpoint for human refractive development? An analysis of population-based data from the refractive error study in children (RESC). *Acta Ophthalmol.* 2010;88:877–884.
28. Hou W, Norton TT, Hyman L, Gwiazda J; COMET Group. Axial elongation in myopic children and its association with myopia progression in the correction of myopia evaluation trial. *Eye Contact Lens.* 2018;44:248–259.
29. Lee Y-Y, Lo C-T, Sheu S-J, Yin L-T. Risk factors for and progression of myopia in young Taiwanese men. *Ophthalmol Epidemiol.* 2014;22:66–73.
30. Dirani M, Shekar SN, Baird PN. Adult-onset myopia: the Genes in Myopia (GEM) twin study. *Invest Ophthalmol Vis Sci.* 2008;49:3324–3327.
31. Verhoeven VJ, Hysi PG, Wojciechowski R, et al. Genome-wide meta-analyses of multi-ancestry cohorts identify multiple new susceptibility loci for refractive error and myopia. *Nat Genet.* 2013;45:314–318.