Title: Axial Elongation Trajectories in Chinese Children and Adults with High Myopia: An Eight-year Prospective Cohort Study

Running title: axial elongation trajectories in high myopes

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Abbreviations and Acronyms: ZOC-BHVI=Zhongshan Ophthalmic Centre-Brien Holden Vision Institute; D=diopters; META-PM=meta-analyses of pathologic myopia; UCVA=Uncorrected visual acuity; BCVA=best corrected visual acuity; LogMAR= Logarithm of the Minimum Angle of Resolution; IOP=Intraocular pressure; SER=Spherical equivalent refraction; ETDRS=Early Treatment Diabetic Retinopathy Study; MMD=myopic macular degeneration; PAM = portioning around medoids; CI=confidence interval, SD=standard deviation.

Key points

Question: What are the axial elongation trajectories and related visual outcomes in Chinese high myopes?

Findings: High myopes exhibited continued axial elongation into late adulthood with three trajectories: stable (0.017 mm/y), moderate (0.12 mm/y) and rapid (0.38 mm/y) progression. The rapid progression trajectory exhibited a 6.92 times higher risk of developing pathological macular degeneration, and associated with a slight mean decrease in best-corrected visual acuity compared with the stable progression trajectory at the 8^{th}-year follow-up.

Meaning: The rapid progression trajectory carried a higher risk of poorer visual prognosis.

Abstract

Importance: In high myopes, excessive axial elongation continued into adulthood. Understanding the long-term axial elongation trajectory is important to prevent blindness but it remains unknown.

Objective: To evaluate the axial elongation trajectories and related visual outcomes in highly myopic children and adults.

Design, setting and participants: This was a prospective cohort study. Participants from the Zhongshan Ophthalmic Centre-Brien Holden Vision Institute (ZOC-BHVI) high myopia cohort were followed up every other year for eight years, and those with available axial length (AL) measurement at baseline (2011) and at least one follow-up visit were included.

Exposure: High myopia **(**spherical power ≤ -6.00 diopters).

Main outcomes and Measures: Longitudinal axial elongation trajectories identified by clustering analysis, and axial elongation rates calculated by linear mixed models.

Results: A total of 793 participants (median age, 17.8 years, range, 6.76 to 69.7; 52.7% female; including 1586 eyes) were included. Axial elongation rates were 0.46 (95% confidence interval [CI], 0.44 to 0.48), 0.072 (95% CI, 0.055 to 0.089), and 0.13 (95% CI, 0.065 to 0.19) mm/y for children and adolescents (7 ≤ baseline age < 18 years), young adults (18 ≤ baseline age ≤ 40 years) and older adults (40 < baseline age ≤ 70 years), respectively. Using cluster analysis, three axial elongation trajectories were identified, with the stable, moderate, and rapid progression trajectory having an axial elongation rate of 0.017 (95% CI, 0.011 to 0.024), 0.12 (95% CI, 0.11 to 0.13) and 0.38 (95% CI, 0.35 to 0.42) mm/y, respectively. The rapid progression trajectory had a 6.92 times higher risk of developing pathological myopic macular degeneration (OR, 6.92, 95% CI, 1.07 to 44.6, P = .04), and it was associated with a 0.032 LogMAR decrease in best-corrected visual acuity (β, 0.032, 95% CI, 0.001 to 0.063, P = .04) compared with the stable progression trajectory at the end of 8th-year follow-up.

Conclusions and relevance: These data support substantial heterogeneity in axial elongation trajectories from childhood to late adulthood in high myopia. The rapid progression trajectories identified suggest a higher risk of poor visual prognosis and support the need for future studies regarding early identification and intervention.

Introduction

High myopia-related maculopathy is emerging as a major cause of blindness among individuals of working age.[1] It is projected by 2050, one in every ten people globally will suffer from high myopia, and up to 18.5 million people will be blind due to myopic maculopathy.[2] High myopia mostly develops from excessive axial elongation, which is directly associated with a higher risk of visually-threatening ocular pathology.[3-5] High myopes with axial length (AL) ≥ 30 mm had 25 to 94 times higher risks of vision impairment compared to those with AL < 24 mm.[6] Furthermore, unlike mild or moderate myopia, high myopes tends to progress into adulthood.[7]

Given the continued axial elongation across decades of life, long-term follow-up data is warranted to reveal the whole picture of AL changes in high myopes. However, existing knowledge regarding the axial elongation trajectories in high myopes are limited, to our knowledge and are from relatively small sample sizes, short follow-up duration, and retrospective designs.[8,9] Two prospective longitudinal studies assessed the AL changes in highly myopic adults.[10 7] Moreover, existing studies mostly only reported the average rates of axial elongation without illustrating the axial elongation trajectory. The ability to discern if high myopes will remain stable or undergo rapid progression has implications for clinical management, including determining follow-up frequency, deciding on aggressive clinical interventions, and optimizing visual outcomes. Nevertheless, the axial elongation trajectory in high myopes has never been reported.

Thus, this study aimed to assess the axial elongation trajectories in Chinese high myopes using the Zhongshan Ophthalmic Centre-Brien Holden Vision Institute (ZOC-BHVI) high myopia cohort, which included 890 high myopes and followed up for 8 years.[11] Clustering analysis was used to identify different axial elongation trajectories, and their impact on visual outcomes was also investigated.

Methods

Study population

The ZOC-BHVI high myopia cohort is an ongoing prospective cohort study in Guangzhou, China. Participants with high myopia were recruited between November 2011 and October 2012 and followed up every other year, with no monetary stipend provided. The methodology has been detailed elsewhere.[11] In brief, participants with binocular high myopia (defined as spherical power ≤ -6.00 diopters [D]) and aged 7–70 years, without secondary myopia or history of ocular surgery, and without severe systemic conditions were enrolled. Eyes with available data on AL at baseline and at least one follow-up visit, and gradable fundus images based on the meta-analyses of pathologic myopia (META-PM) criteria at both baseline and participant's last follow-up visit were included in the current analysis (**Supplemental Figure 1**). Eyes were excluded if they received ocular surgeries during follow-up, or had staphyloma (considering the possible effect on accurate AL measurement[12]) based on the fundus images, or received specific treatments for myopia (i.e. corneal laser surgery for myopia, progressive lenses, orthokeratology lenses, eyedrops of atropine, tropicamide or anisodamine, acupuncture treatment for myopia) during the follow-up. Written informed consent was obtained from adults and from parents or guardians for participant under 18 years of age. The study conformed to the principles of the Declaration of Helsinki and was approved by the ZOC Ethics Committee. The reporting of this study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines.

Ophthalmic examinations and questionnaire

At baseline and each visit, standardized ophthalmic examinations were performed by qualified ophthalmologists and optometrists. Before cycloplegia, ocular biometric parameters including AL were measured using partial coherence interferometry with the Lenstar LS900 (Haag-Streit AG, Koeniz, Switzerland). IOL Master 500 (Carl Zeiss Meditec, Oberkochen, Germany) was used if the participant's AL exceeded the measurement range of Lenstar (up to 32 mm). High agreement between the two devices had been consistently proved in previous studies.[13,14] Best-corrected visual acuity (BCVA) were assessed using an ETDRS LogMAR tumbling E visual chart (Precision Vision, Villa Park, Illinois, USA) at a distance of 4 meters. Intraocular pressure (IOP) was measured under topical

anesthesia using a Goldman applanation tonometer. An autorefractor (Topcon KR8800; Topcon Corp., Tokyo, Japan) was used to assess cycloplegic refraction after complete pupil dilation (≥ 6 mm pupil diameter and absent light reflex) with 2 drops of 0.5% tropicamide (5 minutes apart). Spherical equivalent refraction (SER) was calculated by sphere power plus half of the cylinder power. Additionally, two 45° color fundus photographs of completely dilated eyes were obtained with a Canon camera (Canon CX-1, Tokyo, Japan), of which one was centered on the macula and the other on the optic disc. Family history of myopia was collected by uniformed questionnaire.

Based on fundus photographs and META-PM classification, myopic macular degeneration (MMD) was graded by trained graders (S.Z., Y.C.) independently into five categories: normal fundus (Category 0, C0), tessellated fundus only (Category 1, C1), diffuse chorioretinal atrophy (Category 2, C2), patchy chorioretinal atrophy (Category 3, C3), and macular atrophy (Category 4, C4). Disagreement between the two graders was adjudicated by a third grader (X.H.).[15] Pathological MMD was defined as a category of C2 or above, namely C2/3/4.

Statistical analysis

Data from the both eyes were used for analyses if eligible. Baseline characteristics were presented as means (standard deviations [SD]) or median (interquartile range [IQR]) for quantitative variables and numbers (percentages) for categorical variables. For comparison between individuals, the unpaired Student's t-test or Wilcoxon test or one-way analysis of variance or Kruskal–Wallis test was used for continuous variables, and the Pearson chi-squared test or Fisher's exact test was used for categorical variables. For comparison between eyes, mixed effect analyses were conducted.

To quantify the axial elongation rate (mm/y) over eight years and related risk factors, a three-level nested mixed model was utilized, with eyes nested within each individual, baseline age, sex, baseline AL, IOP, MMD category and family history of myopia treated as fixed effects, age and age*age treated as fixed and random effects. Based on baseline age, we further divided the participants into three age groups: the children and adolescents (< 18 years), early adulthood (18-40 years) and late

adulthood (>40 years) group. In each age group, the axial elongation rates were stratified by sex (male vs. female), baseline AL (< 27, 27–29, and > 29 mm), and presence of pathological MMD (C2/3/4 vs. C0/1).

To identify possible axial elongation trajectories during the 8-year follow-up, clustering analysis was performed with the partitioning around medoids (PAM) method in R with specific packages including "dplyr" and "cluster". PAM was based on searching for representative points, namely medoids, in the dataset.[16-18] Herein, the medoids were determined by subtracting the average AL of five different visits from the AL at each visit. Participants with available AL measurements at both baseline and the 8th-year follow-up visit, and no more than one loss to follow-up visit in between were included in this analysis. For those with one loss to follow-up visit, the missing data on AL were imputed using the individual longitudinal regression imputation method.[19] After axial elongation trajectories were determined, mixed logistic regression was applied to investigate risk factors for different trajectories with eye treated as a random effect. Mixed logistic/linear regression analysis was used to investigate the association between different trajectories and pathological MMD as well as BCVA at the 8th year, respectively. All *P* values were two-sided but not adjusted for multiple analyses. All statistical analyses were conducted using Stata 17 (StataCorp LP, College Station, TX, USA) and R 4.0.4 (R Foundation for Statistical Computing, www.R-project.org).

Results

Participants and baseline characteristics

A total of 793 participants (1586 eyes) with available AL measurements at both baseline and at least one follow-up were included (**Supplemental Figure 2**). Baseline characteristics between participants included and not included are demonstrated in **Supplemental Table 1.** At baseline, participants had a median age of 17.8 (range: 6.76 to 69.7, IQR, 13.9 to 26.2) years, and 52.7% of them were female. Mean SER was -9.69 (SD, 3.19) D and mean AL was 27.3 (SD, 1.42) mm. Baseline characteristics of the children and adolescents group (N=407, median, 14.0 years; IQR, 11.9 to 15.7), early adulthood

group (N=320, median, 24.7 years; IQR, 21.3 to 29.8) and late adulthood group (N=66, median, 48.0 years; IQR, 43.3 to 56.1) are shown in **Supplemental Table 2.**

Axial elongation rates and risk factors

The axial elongation rate was 0.46 (95% confidence interval [CI], 0.44 to 0.48, $P < .001$) mm/y in the children and adolescents group, 0.072 (95% CI, 0.055 to 0.089, $P < .001$) mm/y in the early adulthood group and 0.13 (95% CI, 0.065 to 0.19, $P < .001$) mm/y in the late adulthood group. As shown in **Table 1**, younger baseline age was associated with faster axial growth during the following up in all participants (per 1 year, β, 0.12, 95% CI, 0.114 to 0.122, $P < .001$), as well as in the children and adolescents group (per 1 year, β, 0.22, 95% CI, 0.21 to 0.23, $P < .001$), the early adulthood group (per 1 year, β, 0.059, 95% CI, 0.054 to 0.064, $P < .001$) and the late adulthood group (per 1 year, β, 0.061, 95% CI, 0.048 to 0.075, $P < .001$). Longer baseline AL was associated with faster axial growth in all participants (per 1 mm, β, 0.98, 95% CI, 0.96 to 0.99, $P < .001$), as well as the children and adolescents group (per 1 mm, β, 0.99, 95% CI, 0.98 to 1.01, $P < .001$), the early adulthood group (per 1 mm, β, 1.01, 95% CI, 1.00 to 1.03, $P < .001$) and the late adulthood group (per 1 mm, β, 0.93, 95% CI, 0.88 to 0.99, $P < .001$). In the late adulthood group, presence of pathological MMD at baseline was linked to a 0.21 mm/y faster axial growth (β, 0.21, 95% CI, 0.003 to 0.42, $P = .047$) compared with no pathological MMD; female sex was associated with a 0.15 mm/y slower growth in AL compared with male (β, -0.15, 95% CI, -0.30 to -0.01, $P = .03$) (**Table 1; Supplemental Figure 3**).

Axial elongation trajectories and risk factors

A total of 469 eyes from 240 participants were included in the clustering analysis (**Supplemental Table 3**). Three clusters of axial elongation trajectories were identified (**Figure 1**). Clusters 1 and 3 were characterized as progressing steadily and rapidly over time with the slowest and steepest slope, respectively. Cluster 2 had a progression speed and slope in between. The mean axial elongation rate was 0.017 (95% CI, 0.011 to 0.024), 0.12 (95% CI, 0.11 to 0.13) and 0.38 (95% CI, 0.35 to 0.42) mm/y in Cluster 1, 2 and 3, respectively. Therefore, we considered the Cluster 1, 2 and 3 as the stable, moderate and rapid progression trajectory, respectively. The axial elongation trajectory of each

participant in the three clusters is depicted in **Figure 2**. The stable, moderate, and rapid progression trajectory was observed in 29.3%, 41.4% and 29.3% of participants in the children and adolescents group; 61.2%, 31.2% and 7.64% in the early adulthood group; as well as 67.4 %, 23.9% and 8.70% in the late adulthood group, respectively (**Supplemental Table 3**).

Younger baseline age (per 1 year, Model 1, Odds Ratio [OR], 1.09, 95% CI, 1.06 to 1.10, $P < .001$; Model 2, OR, 1.09, 95% CI, 1.06 to 1.11, $P < .001$), longer baseline AL (per 1 mm, OR, 1.55, 95% CI, 1.29 to 1.86, $P < .001$), pathological MMD at baseline (yes vs. no, OR, 5.94, 95% CI, 2.82 to 12.5, $P < .001$) and family history of myopia (yes vs. no, Model 1, OR, 1.70, 95% CI, 1.13 to 2.57, $P = .01$; Model 2, OR, 1.60, 95% CI, 1.06 to 2.40, $P = .02$) were associated with higher risk of being in a faster progression trajectory (**Table 2**).

Visual outcomes related to different trajectories

Compared to the stable progression trajectory, the rapid progression trajectory had a 6.92 times higher risk of developing pathological MMD (OR, 6.92, 95% CI, 1.07 to 44.6, $P = .04$), and it was associated with a decrease of 0.032 LogMAR in BCVA (β, 0.032, 95% CI, 0.001 to 0.063, $P = .04$) at the end of 8^{th}-year follow-up (**Table 3**).

Discussion

We identified three different axial elongation trajectories from childhood to late adulthood using a hypothesis-free approach, based on an 8-year follow-up of a large high myopia cohort comprising participants across various age groups. Furthermore, a rapid progression trajectory was associated with an almost seven times higher point estimate risk for pathological MMD and a slight mean LogMAR decrease of 0.032 in BCVA. We believe these findings are of considerable importance because understanding lifetime AL changes and related risk factors is crucial in guiding the clinical management of high myopia.

In our study, the highest axial elongation rates were in the children and adolescents group (0.46 mm/y), in comparation to the early (0.072 mm/y) and late adulthood group (0.13 mm/y). A retrospective study of 8 Australian studies reported that in mild myopic eyes, the most rapid AL progression occurred before the age of 18 years.[20] Previous studies regarding longitudinal AL changes in children mainly focused on mild to moderate myopia, with reported rates of 0.2 to 0.5mm/y and follow-up periods of 1-3 years.[21-24] Few studies, mostly with a short follow-up duration, documented axial elongation rates in highly myopic adults, showing a rate of 0.05 to 0.07 mm/y in early adulthood and 0.03 to 0.07 mm/y in late adulthood,[7,8,10,25] similar to our findings.

Leveraging PAM, a type of unsupervised machine learning that can help identify hidden patterns and structures within data,[17] three axial elongation trajectories were identified in high myopes. A similar method had been adopted by Chen et al. who identified three SER progression patterns for children mostly with emmetropia and mild myopia from the Guangzhou Twin Eye Study.[16] To our knowledge, different axial elongation trajectories in high myopia have never been reported. More importantly, after adjusting for baseline AL, eyes with rapid progression trajectory had a 6.92 times higher risk for pathological maculopathy and a decrease of 0.032 LogMAR in BCVA at the 8th-year follow-up. These findings suggest that axial elongation trajectory could be a potential indicator regarding risk assessment for high myopes. Additionally, pre-identification of the axial elongation trajectory had pragmatic importance. Participants in the stable progression trajectory might be assured of having a relatively good quality of life and less frequent clinic visits. In contrast, those in the rapid progression group might be better candidates to consider more aggressive intervention and more frequent screening to improve visual prognosis. Nevertheless, more studies are needed in the future to better understand the axial elongation trajectory of high myopes for personalized risk prediction and management.

In the current study, younger age and longer baseline AL were risk factors for faster axial growth and being in a faster progression trajectory. Both factors were consistently reported as risk factors for axial elongation in previous studies.[7,10,25] Longer AL and MMD are associated with thinner choroid

and sclera and defects of the Bruch membrane, which makes the eyeball prone to prolong.[7] However, pathological MMD was associated with faster axial growth only in late adulthood. The exact reason is unknown, one possible explanation could be the greater severity of MMD in older participants.

Specifically, a family history of myopia was related with a 1.60 to 1.70 times higher risk of being in a faster progression trajectory, indicating a potential genetic contribution to the different axial elongation trajectories in high myopia. The Consortium for Refractive Error and Myopia recently reported that high myopes inherited a higher number of variants compared with mild myopes.[26] It might be of interest to investigate whether certain genes or variants were related to the axial elongation trajectory, to better understand the underlying mechanism and help with early risk prediction. Environmental factors (i.e., education, near work, outdoor time) are also risk factors that might contribute to high myopia.[27] Whether specific environmental factors, as well as the interaction between the genetic and environmental factors, could affect the axial elongation trajectory in high myopes may warrant future research.

The study has several strengths. First, participants with high myopia included in our study had varying age spectrum and received multiple examinations during multiple study visits scheduled every other year. Additionally, we utilized a hypothesis-free method for analyzing different axial elongation trajectories.

However, there are limitations. First, this study was not a population-based study and included only Chinese participants. Since the axial elongation rates in myopic populations have shown variations across studies,[7,9,10,28-30] regardless of ethnicities, the precise numerical rates in our study may not be directly applicable to other populations. However, we are confident that the observed trajectories and associations can serve as valuable references for future research. Second, there is a high loss to follow-up rate in the 6^{th}- and 8^{th}-year follow-up due to the COVID-19 pandemic. Third, this cohort consisted of a relatively large proportion of the young population. Future studies with larger sample sizes, longer follow-ups, more diverse populations, and other analysis methods for trajectory analysis

are recommended to better understand this issue. In addition, one point worth mentioning is that the current study was a cohort study, but it did not include a distinct unexposed or control group. The reason for this is that an unexposed or control group would not be necessarily appropriate in our study since we were looking at a very specific population of high myopes and testing was done in a hypothesis-free manner.

Conclusions

In our study of Chinese high myopes, AL continued to grow from childhood to late adulthood, following three distinct trajectories. The rapid progression trajectory exhibited an almost seven times higher point estimate risk of developing pathological MMD, associated with a slight LogMAR decrease of 0.032 in BCVA compared with the stable progression trajectory at the 8^{th}-year follow-up. These distinct axial elongation trajectories could prove valuable for early identification and intervention for high-risk individuals. These findings support the possibility that lifetime management could be considered in individuals with high myopia, and support consideration of more research on AL growth patterns and associated factors.

Declarations

Competing interest

The authors have no proprietary interest in any aspect of this study.

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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: SZ, XH; Acquisition, analyses, or interpretation: all authors; Drafting of the manuscript: SZ, XH, YC, MH; Critical revision of the manuscript for important intellectual content: all authors; Statistical analyses: SZ, JZ, YH, YC; Obtained funding: MH, XH; Administrative, technical, or material support: YZ, QY; Study supervision: XH, MH. XH and MH 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.

Role of funder/sponsor statement

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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Figure legends

Figure 1. Partitioning clustering analysis of longitudinal axial length in high myopes (469 eyes). Three clusters of axial elongation trajectory were identified. Cluster 1, 2, 3 refer to stable progression, moderate progression, rapid progression, respectively.

Figure 2. Axial elongation trajectories over 8 years stratified by different clusters identified by partitioning clustering analysis. Mean axial elongation rate in Cluster 1 (stable progression), Cluster 2 (moderate progression), Cluster 3 (rapid progression) was 0.017 (95% CI, 0.011 to 0.024), 0.12 (95% CI, 0.11 to 0.13) and 0.38 (95% CI, 0.35 to 0.42) mm/y, respectively.

437 **Table 1.** Factors associated with axial growth during the 8-year follow-up.

			Multivariable linear mixed effect model*					
	Total β (95% CI)	***P* value**	**[7, 18) years#**		**[18, 40] years#**		**(40, 70] years#**	
			β (95% CI)	***P* value**	**β (95% CI)**	***P* value**	**β (95% CI)**	***P* value**
Baseline age, per 1 year younger	0.12 (0.114, 0.122)	< .001	0.22 (0.21, 0.23)	< .001	0.059 (0.054, 0.064)	< .001	0.061 (0.048, 0.075)	< .001
Female, vs male	-0.035 (-0.070, -0.001)	.04	-0.024 (-0.058, 0.010)	.17	0.004 (-0.030, 0.038)	.83	-0.15 (-0.30, -0.01)	.03
AL, per 1 mm longer	0.98 (0.96, 0.99)	< .001	0.99 (0.98, 1.01)	< .001	1.01 (1.00, 1.03)	< .001	0.93 (0.88, 0.99)	< .001
IOP, per 1 mmHg higher	0.003 (-0.003, 0.01)	.36	0.002 (-0.005, 0.009)	.61	0.002 (-0.004, 0.009)	.44	0.002 (-0.026, 0.030)	.89
MMD								
C0	Ref.		Ref.		Ref.		Ref.	
C1	-0.018 (-0.05, 0.019)	.35	-0.010 (-0.050, 0.029)	.61	0.031 (-0.006, 0.068)	.10	0.12 (-0.071, 0.30)	.22
C2/3/4	0.056 (0.004, 0.11)	.03	-0.039 (-0.090, 0.013)	.14	0.055 (-0.001, 0.11)	.05	0.21 (0.003, 0.42)	.047
Family history of myopia, yes vs. no	0.032 (-0.002, 0.065)	.07	0.012 (-0.022, 0.046)	.50	0.032 (-0.002, 0.065)	.06	0.011 (-0.16, 0.18)	.90

438 * In the multivariable linear mixed effect model, baseline age, sex, baseline AL, BCVA, IOP, MMD category and family history of myopia were
439 treated as fixed effects; age and age*age were treated as fixed and random effects; eyes were nested within each individual (three-level nested
440 model).
441 # [7, 18) referred to the children and adolescent group, [18, 40] referred to the early adulthood group, (40, 70] referred to the late adulthood
442 group.
443 AL=axial length; IOP=intraocular pressure; MMD=myopic macular degeneration; C=category. C2/3/4 was defined as pathological MMD;
444 CI=confidence interval.

Table 2. Factors associated with different axial elongation trajectories using mixed logistic regression analysis.

	Model 1 *		Model 2 #	
	OR (95% CI)	***P* value**	**β (95% CI)**	***P* value**
Baseline age, per 1 year younger	1.09 (1.06 to 1.10)	< .001	1.09 (1.06, 1.11)	< .001
Baseline AL, per 1 mm longer	/	/	1.55 (1.29, 1.86)	< .001
MMD				
C0	Ref.		/	/
C1	0.87 (0.56, 1.36)	.54	/	/
C2/3/4	5.94 (2.82, 12.5)	< .001	/	/
Family history of myopia	1.70 (1.13, 2.57)	.01	1.60 (1.06, 2.40)	.02

AL=axial length; MMD=myopic macular degeneration; C=category; OR=odds ratio; CI=confidence interval. C2/3/4 was defined as pathological MMD.

* Model 1 was adjusted for baseline age, baseline category of myopic macular degeneration and family history of myopia, with eye treated as a random effect.

Model 2 was adjusted for baseline age, baseline axial length, and family history of myopia with eye treated as a random effect.

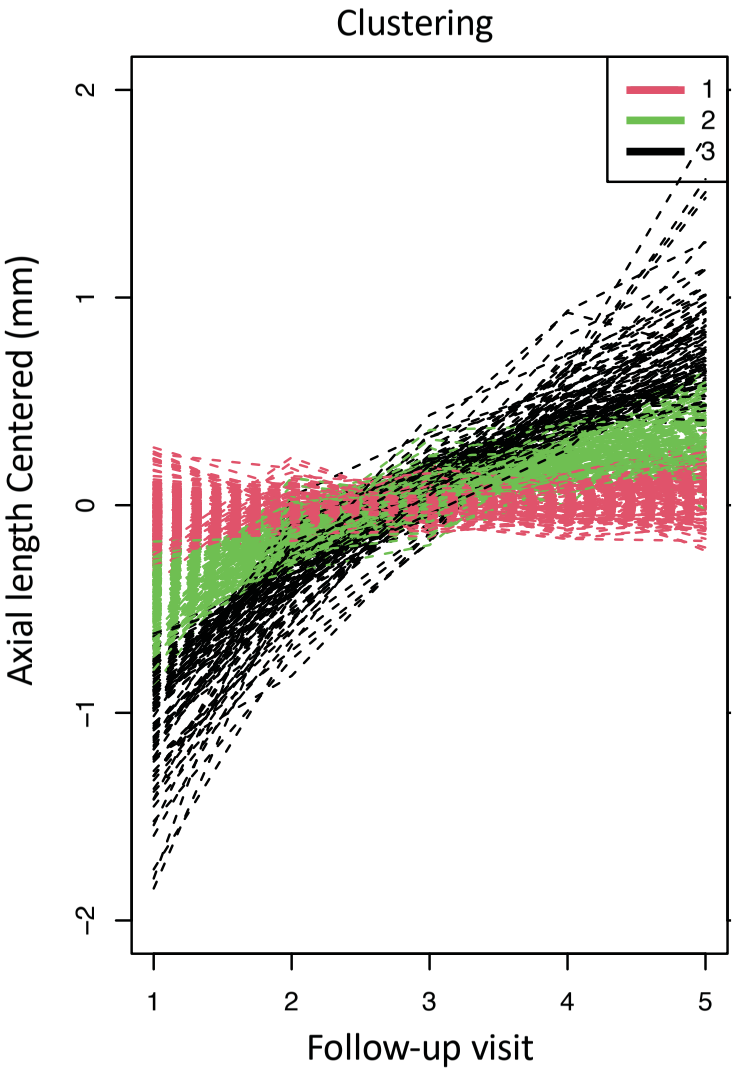
Table 3. Associations between different axial elongation trajectories and visual outcomes at the end of 8th-year follow-up.

Cluster (Progression trajectory)	Pathological MMD (Category 2 or above) *		Best-corrected visual acuity (LogMAR) #	
	OR (95% CI)	*P* value	β (95% CI)	*P* value
1 (steady progression)	Ref.		Ref.	
2 (moderate progression)	5.33 (0.96, 29.5)	.06	0.017 (-0.008, 0.042)	.19
3 (rapid progression)	6.92 (1.07, 44.6)	.04	0.032 (0.001, 0.063)	.04

MMD=myopic macular degeneration; LogMAR= Logarithm of the Minimum Angle of Resolution; OR=odds ratio; CI=confidence interval.

* Analyzed by mixed logistic regression model, in which baseline age, sex, baseline axial length, baseline category of myopic macular degeneration, intraocular pressure, best-corrected visual acuity and family history of myopia were adjusted and treated as fixed effect; eye was treated as a random effect.

Analyzed by mixed linear regression model, in which baseline age, sex, baseline axial length, baseline category of myopic macular degeneration, intraocular pressure, best-corrected visual acuity and family history of myopia were adjusted and treated as fixed effect; eye was treated as a random effect.


Clustering
Axial length Centered (mm)
Follow-up visit
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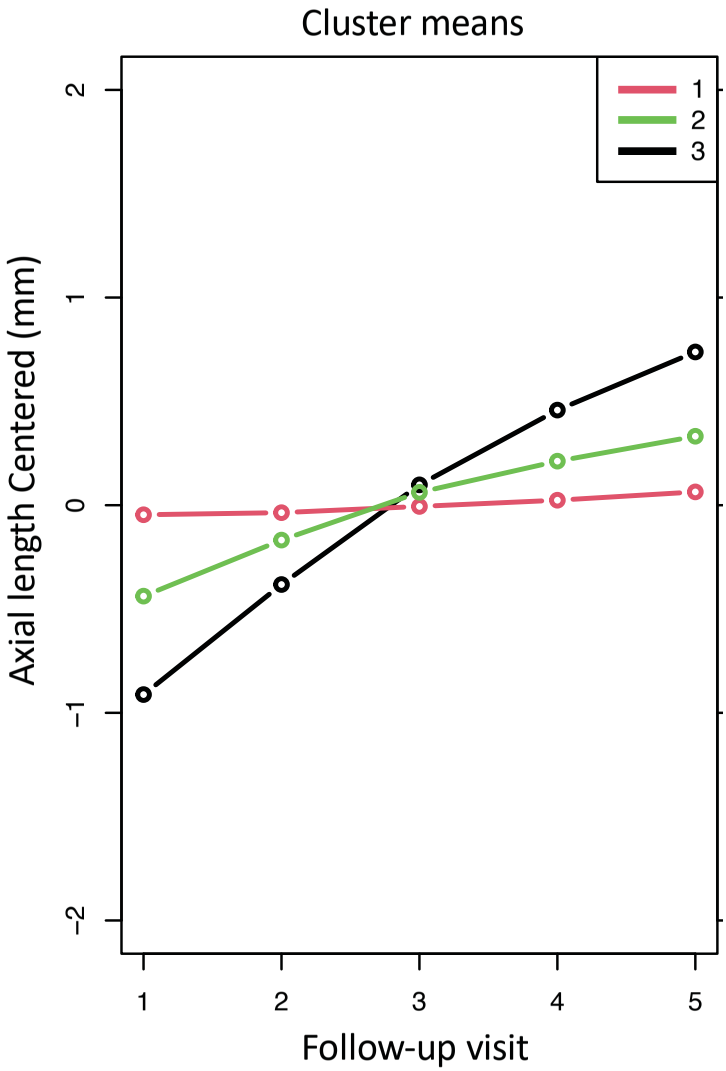
Cluster means
Axial length Centered (mm)
Follow-up visit
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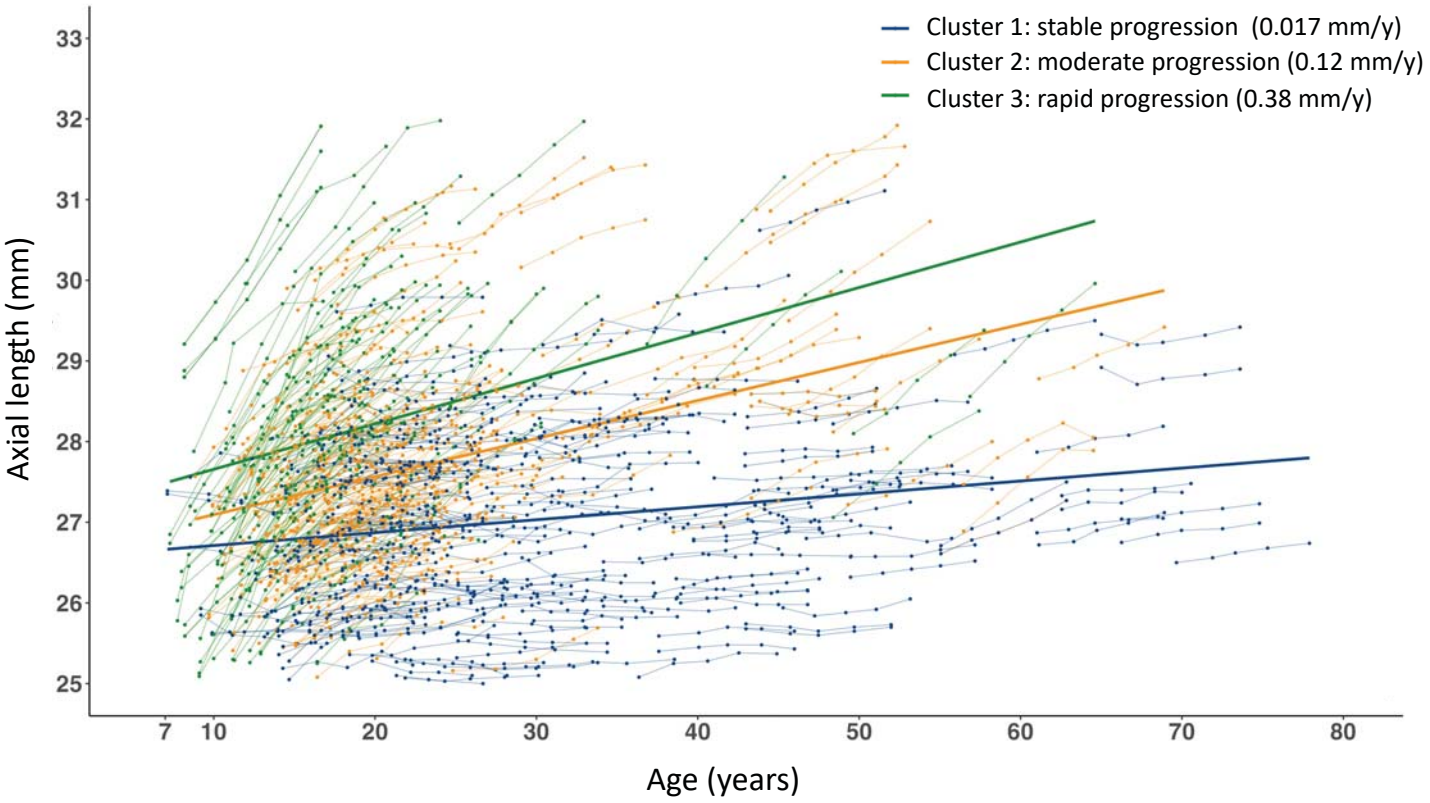
Cluster 1: stable progression (0.017 mm/y)
Cluster 2: moderate progression (0.12 mm/y)
Cluster 3: rapid progression (0.38 mm/y)
Axial length (mm)
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80
Age (years)