Longitudinal Changes in Spherical Equivalent Refractive Error Among Children With Preschool Myopia

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PURPOSE. Preschool myopia generally indicated a high risk of progression to high myopia. However, no previous study has reported its longitudinal evolution. This study aimed to investigate the longitudinal changes in preschool myopia and explore the associated key determinants.

METHODS. Medical records of patients seeking refractions at Zhongshan Ophthalmic Center between 2009 and 2017 were retrospectively reviewed. Mean rates of change in spherical equivalent (SE) refractive errors were evaluated in patients with preschool myopia. Association between the rate of change in SE and patient characteristics at the initial visit were examined using linear mixed-effect regression models.

RESULTS. A total of 495 cases (median initial age: 5.12 years, interquartile range [IQR], 4.12–5.76 years) were assessed with at least 2-year follow-up. The initial median SE was −3.00 D (IQR, −5.25 to −1.75 D) and the median duration of follow-up was 3.69 years (IQR, 2.89–4.99 years). On average, myopia progressed by −0.59 ± 0.47 D/year. A total of 312 (63.0%) children demonstrated myopia progression (mean rate of change in SE ≤ −0.50 D/year in either eye) and 177 (35.8%) children demonstrated refraction stability (mean rate of change < ±0.50 D/year in both eyes). Older age (β = −0.06, $P = 0.003$), female sex (β = −0.09, $P = 0.035$), and initial lower myopic SE (β = −0.07, $P < 0.001$) were associated with faster myopia progression.

CONCLUSIONS. Preschool myopia on average progresses, although considerable proportion of subjects demonstrates longitudinal refraction stability. The rate of myopia progression is associated with initial patient characteristics.

Keywords: preschool myopia, risk factor, progression

Myopia is one of the most prevalent ocular conditions and has become a significant public health problem worldwide. The disease is prevalent among school-aged (usually 6 years and older) children,[1] while the prevalence of myopia is relatively low in children aged less than 6 years.[2-5] Myopia that occurs before 6 years of age is defined as "preschool myopia" to differentiate it from "school myopia". Apart from the difference in prevalence, myopia in preschool[3,4,6-8] and school-aged children[9-12] also shows distinct risk factors.

Compared to school myopia, preschool myopia is considered to be associated with a greater risk of progression to high myopia and subsequent high myopia-related irreversible blinding complications. However, this assumption is mainly based on longitudinal observations in school children, among whom myopia mostly progresses after its onset; younger children and children with greater initial myopic refractive errors are at a greater risk of myopia progression.[13-17]

Regarding preschool myopia, little is known about its longitudinal evolution and the factors related to these longitudinal changes. A report on 57 preschool highly myopic (−5.0 D or greater) children demonstrated a longitudinally stable refraction (change in spherical equivalent [SE] ≤ ±0.50 D over the follow-up period) or even myopia regression (change in SE ≥ +0.75 D over the follow-up period) in around 55% of study participants, with the tendency toward regression appearing to be related to higher initial myopia.[18] The results indicated that the clinical course of preschool myopia and its related factors may be somewhat different from that of myopia in school-aged children. However, considering the high refractive errors of study participants and the relatively small sample size, the conclusions of that study cannot be fully generalized to preschool myopia.

In the present study, we investigated the longitudinal changes in SE in Chinese preschool children with myopia and explored key determinants related to these longitudinal changes.

METHODS

Study Population

We retrospectively and inclusively reviewed the clinical records of patients seeking refractive error corrections at Zhongshan Ophthalmic Center between 2009 and 2017. "Myopia" was defined as a spherical power ≤ −0.50 D in all meridians in cycloplegic subjective refraction assessments. Children in whom binocular myopia was first detected before 6 years of age were categorized as having preschool myopia. The initial visit was identified as the first visit when preschool myopia was detected and visits thereafter were defined as follow-up visits.

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Preschool myopic children with at least 2 years of follow-up data since the initial visit and at least three cycloplegic refractive error evaluations were included. Exclusion criteria were as follows: (1) presence of any ocular or systemic disease that is potentially associated with preschool myopia, such as primary congenital glaucoma, Marfan syndrome, or history of prematurity; (2) presence of any other ocular condition that would potentially influence refraction evolution, such as tropia, nystagmus, or amblyopia; and (3) a history of orthokeratology or atropine treatment for control of myopia progression. A total of 495 patients were found to be eligible. The study was approved by the Ethics Committee of Zhongshan Ophthalmic Center, Sun Yat-sen University, Guangzhou and conducted in accordance with the Declaration of Helsinki.

Measurement of Refraction

The results of cycloplegic subjective refraction assessments were documented at every visit. Cycloplegia was achieved with 1% atropine ointment administered every night for three consecutive days or three successive 1% cyclopentolate or tropicamide eye drops instilled 5 minutes apart. Subjective refraction measurements were performed at least 30 minutes after the last administration of cycloplegic drugs. Complete cycloplegia (determined by the absence of light reflex and a dilated pupil at least 6 mm in diameter) was achieved before assessments of subjective refraction. Of the 495 eligible patients, 198 received the same cycloplegic agent throughout the follow-up period. Another 35 received the same cycloplegic agent at the initial and final visits but received different agents in some interim visits. The remaining 262 subjects received different cycloplegic agents at the initial and final visits. Among these, 249 received 1% atropine at the initial visit (and some consecutive following visits) and 1% cyclopentolate or tropicamide at the final visit.

Subjective refraction measurements were obtained by 23 optometrists trained to perform assessments with a standardized protocol. Before examination, children were first evaluated for their cooperation in the visual acuity (VA) test. If the cooperation was assessed as poor, a teaching session was held in which optometrists taught the children how to cooperate during the test. Cycloplegic retinoscopy was performed before measurements of subjective refraction. The starting point of the subjective refraction assessments was the result of retinoscopy and the endpoint was the least myopic spherical power providing best VA. The power and axis of astigmatism were taken from the results of retinoscopy among children younger than 8 years. Jackson cross-cylinder technique was applied to determine the astigmatism among children aged 8 years or older. Refraction was checked and determined by one of two senior optometrists in charge when the examining optometrist was uncertain about the result. Refractions were recorded in increments of 0.25 D. The SE (spherical power plus 1/2 cylindrical power) and astigmatism in vector notation (J_0 [Jackson cross-cylinder with axes at 180° and 90°] and J_{45} [Jackson cross-cylinder with axes at 45° and 135°])[19] were calculated.

Definitions

The primary outcome of the current study was the rate of change in SE. The mean rate of change in SE over the follow-up period (defined as the difference between the final and initial SE refractive errors divided by the follow-up duration in years) was calculated to represent the raw rate of change in refraction of each child. Children demonstrating myopia progression were identified as subjects with a mean rate of change in SE $\leq$ −0.50 D/year in either eye; those demonstrating refraction stability were identified as individuals showing mean rates of change less than $\pm$0.50 D/year in both eyes; and children demonstrating myopia regression were identified as those with at least one eye showing a mean rate of change $\geq$ +0.50 D/year and the other eye showing a mean rate of change < $\pm$0.50 D/year.

Statistical Analysis

The correlation between the right and left eye SE refractive errors measured at the initial visit was 0.87 and it was 0.88 for the final visit (both $P < 0.0001$, pairwise Pearson correlation test). Therefore, refractive error data were reported for the right eyes only, with the exception in reporting the interocular SE difference and proportions of children demonstrating myopia progression, refraction stability, and myopia regression. Descriptive statistics were applied, with means and standard deviations (SDs), medians and interquartile ranges (IQRs), or numbers and percentages reported where appropriate. Considering the confounding impact of the use of different cycloplegic agents on the assessments of longitudinal SE changes, additional analyses were conducted in a subgroup of 233 patients who used the same cycloplegic agents at the initial and final visits. The mean rate of change in SE and percentages of children demonstrating myopia regression, stability, and progression were calculated in this group of patients and compared with the corresponding values for the remaining 262 patients by using the unpaired *t*-test and chi-squared test where appropriate.

The mean rate of change in SE was compared among children with different initial age, sex, SE, J_0, J_{45}, and interocular SE difference by using unpaired *t*-test or trend analysis. To visualize differences in longitudinal evolution among children with these different initial characteristics, linear mixed-effect models were further applied. Individual patient profiles, as well as the regression lines, relating SE refractive errors with the time since the initial visit, were plotted. The time factor used in the modeling was the time since the initial visit.

To evaluate whether age, sex, SE, J_0, J_{45}, and interocular SE difference at the initial visit affected the rate of change in SE, the interaction terms of these characteristics with time since the initial visit were added to the linear mixed-effect models. A statistically significant coefficient of the interactions would indicate that the characteristic had an effect on the rate of change in SE. The method of cycloplegia at each visit was also included in regression models to adjust for its confounding impact on refraction measurements.

Statistical analyses were performed using STATA version 12.0 (Stata Corporation, College Station, TX, USA) and R (https://www.r-project.org/). A *P* value < 0.05 was considered statistically significant.

RESULTS

A total of 495 patients were identified. Their median age at the initial visit was 5.12 years (IQR, 4.12–5.76 years), and approximately 59.6% of the participants were boys. Study participants were followed up for a median of 3.69 years (IQR, 2.89–4.99 years), with a maximum of 15 cycloplegic refractive error measurements (median, 5 measurements; IQR, 4–6 measurements). Median initial SE was −3.00 D (IQR, −5.25 to −1.75 D) and median initial J_0, J_{45}, and interocular SE difference were +0.57 D (IQR, +0.19 to +1.13 D), 0.00 D (IQR, −0.16 to +0.29 D), and 0.50 D (IQR, 0.25–1.13 D), respectively.

TABLE 1. Mean Rate of Change in SE Categorized by Age, Sex, and Ocular Refractions at the Initial Visit

| Characteristics	Number	Mean Rate of Change in SE (D/year)
Age at initial visit (years)		
<3	29	−0.42 ± 0.53
≥3 and <5	198	−0.49 ± 0.46
≥5 and <6	268	−0.68 ± 0.45
P for trend		<0.001
Sex		
Boys	295	−0.55 ± 0.46
Girls	200	−0.64 ± 0.48
P		0.0387
Initial SE (D)		
>−2 and ≤−0.5	149	−0.85 ± 0.44
>−4 and ≤−2	153	−0.66 ± 0.42
>−6 and ≤−4	93	−0.34 ± 0.42
≤−6	100	−0.32 ± 0.37
P for trend		<0.001
Initial J_0 (D)		
≤−0.5	10	−0.29 ± 0.22
>−0.5 and <+0.5	228	−0.66 ± 0.49
≥+0.5	257	−0.54 ± 0.45
P for trend		0.108
Initial J_{45} (D)		
≤−0.5	22	−0.63 ± 0.49
>−0.5 and <+0.5	413	−0.62 ± 0.47
≥+0.5	60	−0.37 ± 0.44
P for trend		0.001
Initial interocular SE difference (D)		
<1	349	−0.64 ± 0.46
≥1	146	−0.48 ± 0.47
P		0.0004

Data are presented as mean ± standard deviation unless otherwise indicated.

For all 495 participants, the mean rate of change in SE was −0.59 ± 0.47 D/year. A total of 6 (1.2%) children demonstrated myopia regression over the follow-up period. One hundred and seventy-seven (35.8%) children showed stable refractions, and 312 (63.0%) children demonstrated myopia progression. Subgroup analyses of the 233 individuals who received the same cycloplegic agents at the initial and final visits showed similar results. Their mean rate of change in SE was −0.57 ± 0.44 D/year. The numbers of children demonstrating myopia regression, stability, and progression were 2 (0.9%), 90 (38.6%), and 141 (60.5%), respectively. The mean rate of change in SE and percentages of children demonstrating myopia regression, stability, and progression among these 233 patients were not significantly different from the corresponding values for the remaining 262 individuals (all *P* > 0.1).

Table 1 shows the mean rate of change in SE based on the initial demographic and refractive error characteristics of participants. Older children and female sex showed a greater mean myopia progression rate. Children with lower myopic SE, J_{45} smaller than +0.50 D, and interocular SE difference <1 D at the initial visit showed greater rates of myopia progression. Individual SE change with time and linear mixed-effect regressions based on the participant characteristics at the initial visit are demonstrated in Figures 1 through 5.

To explore the key determinants of the rate of change in SE, multivariate linear mixed-effect models were fitted and the impacts of demographic and refractive error characteristics at the initial visit were examined (Table 2). Older age (β = −0.06,
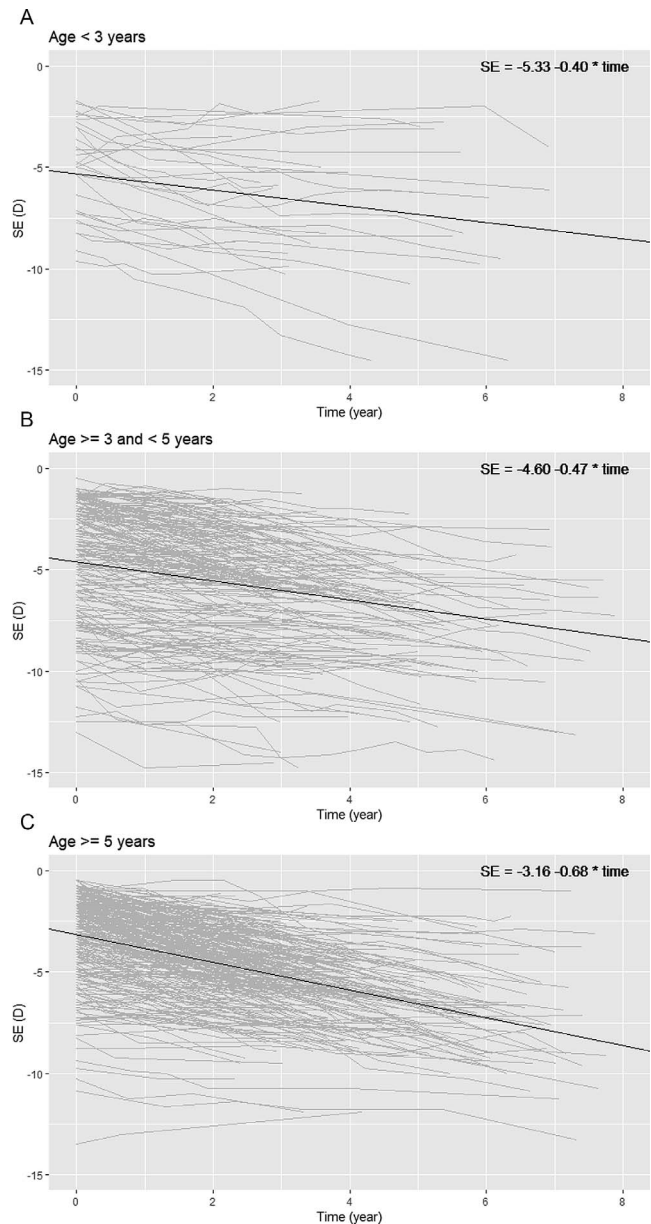
FIGURE 1. Individual refraction evolutions and estimated linear regression lines of preschool myopes aged <3 (**A**), ≥3 and <5 (**B**), and ≥5 years (**C**) at the initial visit.

P = 0.003) and lower myopic SE (β = −0.07, *P* < 0.001) at the initial visit were associated with a greater rate of myopia progression. The association between female sex and faster myopia progression (β = −0.09, *P* = 0.035) was of borderline significance.

DISCUSSION

In the current study, we reported longitudinal changes in the SE refractive errors in Chinese preschoolers with myopia. The mean rate of change in SE was −0.59 ± 0.47 D per year. Most preschool myopes (63.0%) demonstrated myopia progression and approximately 35.8% of the children showed stable refractive errors. The myopia progression rate was greater among older children, girls, and children with lower myopic SE at the initial visit.
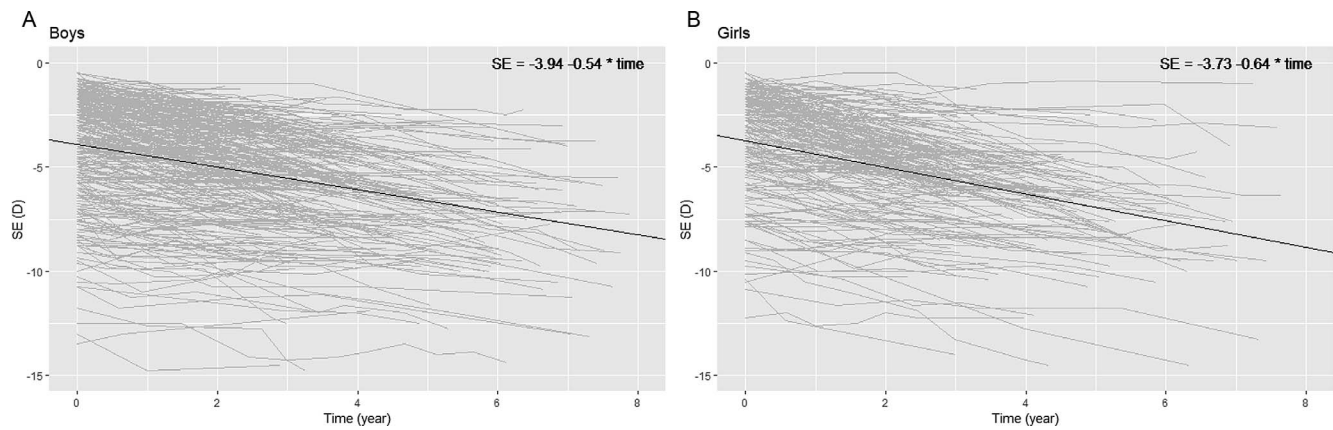
FIGURE 2. Individual refraction evolutions and estimated linear regression lines of boys (**A**) and girls (**B**) with preschool myopia.

Previous longitudinal studies have reported that the myopia progression rate in school-aged children ranges from −0.39 to −0.68 D/year.[9,14,20] While most cases of myopia in school-aged children showed myopia progression after disease onset, about 37% of our preschool participants demonstrated longitudinally stable myopia or even reductions in their myopia. A previous study reported that the proportion of long-term stable refraction (longitudinal SE change equal to or less than ±0.50 D) or myopia regression (longitudinal SE change ≥ +0.75 D) was about 55% in a group of preschool children with myopia of −5.0 D or more.[18] These results may not be exactly comparable to our study findings because the age and

refraction distributions of the study populations were different. However, the results do indicate that preschool myopia is likely to demonstrate its own course of evolution.

Currently available information regarding the mechanisms underlying the stability or regression of preschool myopia is speculative. Among preschool children with high myopia, despite that some individuals demonstrated longitudinally stable or regressive myopia, their axial lengths were documented to show some increase (0.14 mm/year and 0.05 mm/year for those demonstrating refraction stability and myopia regression, respectively).[18] Thus, it is most likely that the decreasing lens thickness and power during early childhood
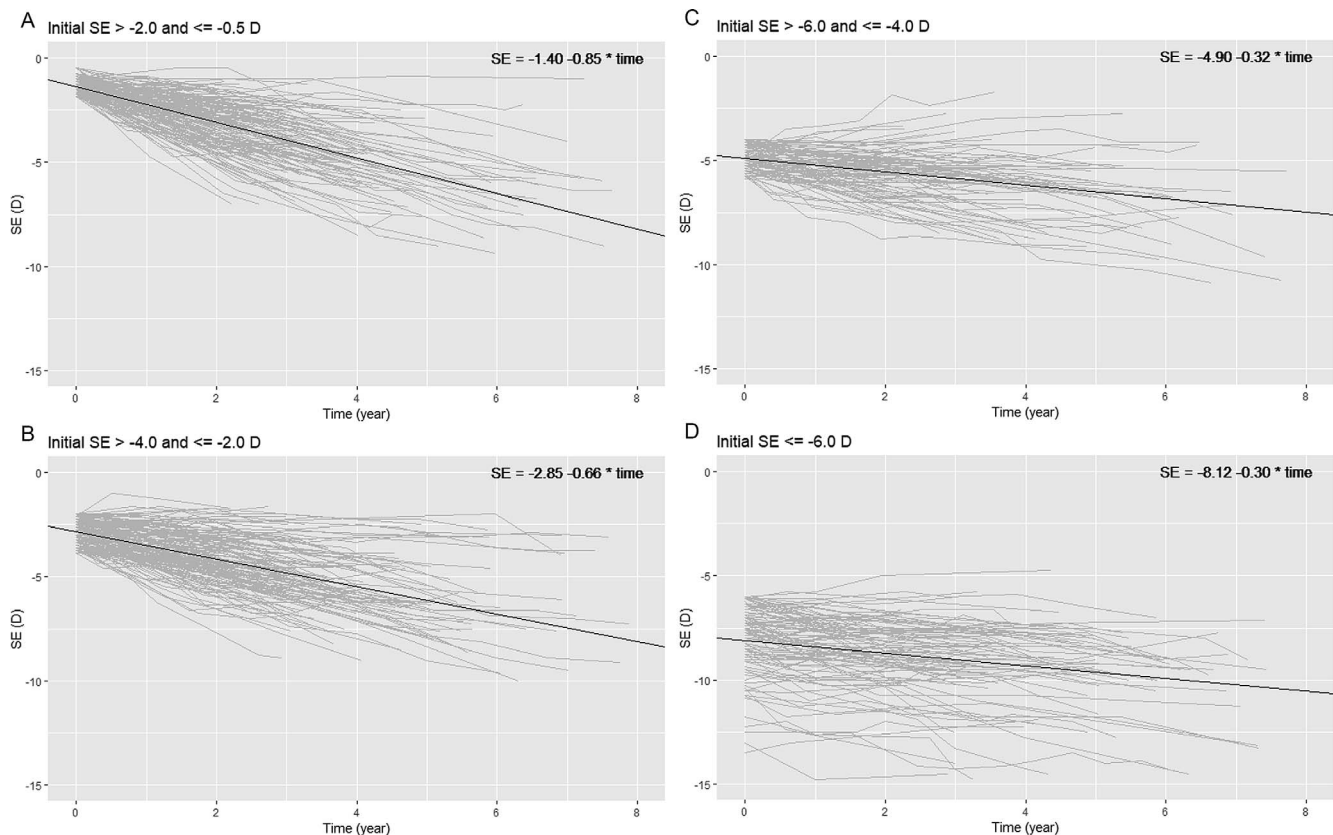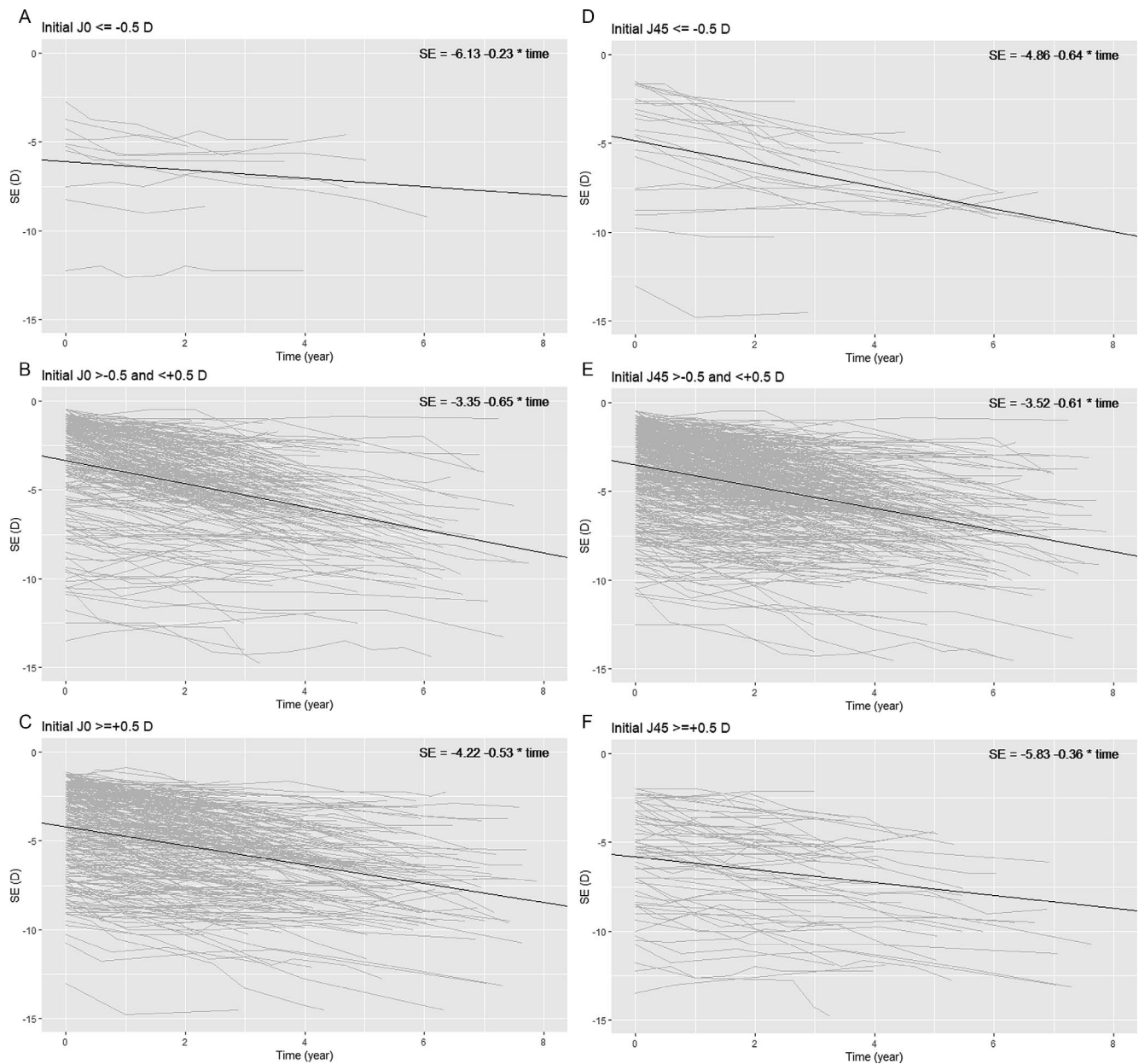

FIGURE 3. Individual refraction evolutions and estimated linear regression lines of preschool myopes with initial SE (**A**) > −2.0 and ≤−0.5, (**B**) > −4.0 and ≤ −2.0, (**C**) > −6.0 and ≤ −4.0, and (**D**) ≤ −6.0 D.

FIGURE 4. Individual refraction evolutions and estimated linear regression lines of preschool myopes with different initial astigmatism. *A, B,* and *C* evolutions of children with initial J_0 (A) $\leq$ −0.5, (B) > −0.5 and < +0.5, and (C) $\geq$ +0.5 D. *D, E,* and *F* evolutions of children with initial J_{45} (D) $\leq$ −0.5, (E) > −0.5 and < +0.5, and (F) $\geq$ +0.5 D. J_0, Jackson cross-cylinder with axes at 180° and 90°; J_{45}, Jackson cross-cylinder with axes at 45° and 135°.

would compensate for the growing globe and maintain ocular refraction or cause myopia regression.[2,21,22] Further studies investigating longitudinal changes in the ocular biometric parameters, as well as refraction, are warranted to comprehensively understand the mechanisms.

In our study, older preschool children and children with lower myopic SE at the initial visit showed greater rates of myopia progression. Shih et al.[18] have also reported a relationship between lower initial myopia and greater progression among preschool children with high myopia. These findings are opposite to those found in school myopia, in which older age and lower initial myopic refractive errors are found to be associated with slower rate of myopia progression.[14–17] These differences indicate that the factors related to myopia progression are different in preschool and school-aged

children. The underlying mechanisms need to be explored in more detail.

The limitations of the current study include its retrospective nature and the unavailability of the ocular biometric data. Refractions were examined using different methods for cycloplegia, which might have confounded the estimations of the mean rate of change in SE. However, subgroup analyses comparing patients receiving the same and different cycloplegic agents at the initial and final visits did not reveal statistically significant difference in the mean rate of change. For this reason, we reported data for all the 495 patients combined. Information on factors that may relate to the progression of preschool myopia—such as parental refractive errors and near work and outdoor activities—was not collected. The follow-up periods of the current study were relatively short. Further
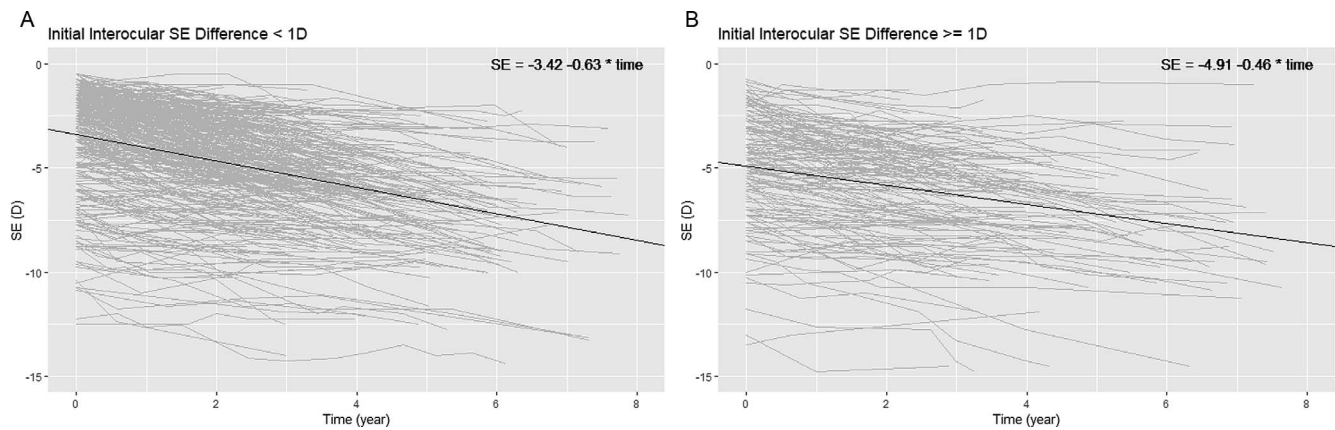
FIGURE 5. Individual refraction evolutions and estimated linear regression lines of preschool myopes with initial interocular SE difference (**A**) <1 and (**B**) ≥1 D.

TABLE 2. Linear Mixed-effect Models for Associations of the Rate of Change in SE With Age, Sex, and Ocular Refractions at the Initial Visit

	Rate of Change in SE (D/year)					
	Model 1*		Model 2†		Model 3‡	
Characteristics	β (95%CI)	P	β (95%CI)	P	β (95%CI)	P
Age (y) at the initial visit	−0.06 (−0.10, −0.02)	0.004	−0.06 (−0.10, −0.02)	0.004	−0.06 (−0.10, −0.02)	0.003
Sex	−0.08 (−0.16, 0.00)	0.039	−0.08 (−0.16, 0.00)	0.049	−0.09 (−0.16, −0.01)	0.035
Initial SE (D)	−0.08 (−0.09, −0.06)	<0.001	−0.07 (−0.09, −0.06)	<0.001	−0.07 (−0.09, −0.05)	<0.001
Initial astigmatism (D)						
J_0			0.03 (−0.03, 0.08)	0.386	0.03 (−0.03, 0.08)	0.382
J_{45}			0.04 (−0.07, 0.14)	0.513	0.03 (−0.08, 0.13)	0.623
Initial interocular SE difference (D)					0.03 (−0.01, 0.07)	0.161

* Model 1 adjusted for method of cycloplegia, initial age, sex (boys as reference), and SE (log likelihood = −2125.5, $P < 0.0001$).
† Model 2 adjusted for method of cycloplegia, initial age, sex (boys as reference), SE, and astigmatism (log likelihood = −2124.9, $P < 0.0001$).
‡ Model 3 adjusted for method of cycloplegia, initial age, sex (boys as reference), SE, astigmatism, and interocular SE difference (log likelihood = −2123.9, $P < 0.0001$).

studies with longer follow-up periods extending into adolescence and early adulthood are needed to fully characterize the evolution of preschool myopia.

In summary, myopic refractive errors typically progressed in patients with preschool myopia, although about 37% of these children demonstrated stability or regression of myopia. Older children, female sex, and children with lower myopic SE at the initial visit showed faster myopia progression. Further studies are warranted to illuminate the longitudinal changes in the ocular biometric parameters and the additional factors related to the evolution of preschool myopia.

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