Does Past Myopia Progression Predict Future Progression?

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Received: October 16, 2025
Accepted: December 19, 2025
Published: January 16, 2026

Citation: Beaulieu WT, Repka MX, Pineles SL, et al. Does past myopia progression predict future progression? *Invest Ophthalmol Vis Sci.* 2026;67(1):38. https://doi.org/10.1167/iovs.67.1.38

Purpose. To quantify the value of using prior changes in spherical equivalent refractive error (SER) and axial length (AL) to predict future myopia progression.

Methods. For this post hoc analysis of a randomized controlled trial, we used data from children ages 5 to 12 years with SER −1.00 to −6.00 D who had been randomized 2:1 to 0.01% atropine or placebo eye drops for 24 months. Multivariable linear regression evaluated the association of baseline-to-12-month change in SER and AL versus 12-to-24-month change while controlling for age and SER or AL at 12 months. Treatment groups were pooled for analyses; sensitivity analyses were conducted using only the placebo group.

Results. Among 187 children, 136 (73%) with complete data were included. For predicting a 0.50-D-or-more SER increase of myopia in the second 12 months based on observing a 0.50-D-or-more increase of myopia in the first 12 months, the positive predictive value was 42% (19 of 45; 95% confidence interval [CI], 29%–57%). Greater baseline-to-12-month SER change was weakly associated with greater 12-to-24-month SER change (0.20 D per additional 1.00 D; 95% CI, 0.02 to 0.39; $P = 0.03$; partial $R^2 = 0.03$). The 95% prediction interval half-width for 12-to-24-month change was ±0.66 D with prior change versus ±0.67 D without (difference = 0.01 D; 95% CI, −0.05 to 0.07). Analyses of AL and sensitivity analyses limited to the placebo group were qualitatively similar.

Conclusions. Changes in SER and AL of children in the prior 12 months were poor predictors of future myopia progression, limiting their usefulness for clinical decision-making or selecting participants for clinical trials.

Keywords: myopia progression, spherical equivalent refractive error (SER), axial length (AL), predictive modeling, pediatric myopia control

Investigators and clinicians have long sought to determine which demographic and clinical factors predict the likelihood and magnitude of future myopia progression, as well as a child's eventual refractive error in adulthood.[1] The initial interest was to help clinicians target treatments to the children at highest risk of myopia progression and avoid the cost and burden of treatment in those with little anticipated benefit. Identifying predictive factors for myopia progression is also of interest to those who design clinical trials involving potential treatments for slowing myopia progression. Some have suggested that identifying so-called "fast progressors" would enrich the study cohort with those most likely to have the greatest treatment response, thereby reducing sample size.[2]

Our previous randomized trial, Low-Dose Atropine for Treatment of Myopia (Myopia Treatment Study 1 [MTS1]; NCT03334253, ClinicalTrials.gov), compared 0.01% atropine with placebo eye drops for the control of myopia progression but found no differences in spherical equivalent refractive error (SER) progression or axial length (AL) elongation

between the atropine and placebo groups after 12 or 24 months of treatment.[3] In an effort to target children most likely to benefit from myopia control strategies, some clinicians have considered prior rate of progression as a key criterion.[4] We therefore conducted a post hoc analysis of data from our recent randomized, placebo-controlled trial[3] to evaluate whether prior SER myopia progression and AL elongation over a 12-month period predict future change over the next 12-month period.

Methods

This research was supported by the National Eye Institute and carried out in compliance with the tenets of the Declaration of Helsinki by the Pediatric Eye Disease Investigator Group across 12 clinical centers in the United States. Institutional review boards approved the study protocol and the informed consent documents, which were compliant with the Health Insurance Portability and Accountability Act (HIPAA). Written consent was obtained from a parent or guardian, and children provided written assent when applicable. The trial was conducted under an investigational new drug application (#137441) authorized by the U.S. Food and Drug Administration (FDA). An independent data and safety monitoring committee maintained oversight.

Methods for the MTS1 randomized controlled trial have been reported previously.[3] Briefly, children ages 5 to 12 years with SER −1.00 diopters (D) to −6.00 D were randomized 2:1 to nightly 0.01% atropine or placebo eye drops. Prior myopia control treatment was exclusionary. Follow-up visits occurred at 6, 12, 18, and 24 months after randomization. Study visits occurred from 2018 to 2022. At each visit, SER was calculated as the average of three cycloplegic autorefraction measurements per eye, taken 30 minutes after two drops of 1% cyclopentolate, spaced 5 minutes apart. AL was calculated as the average of three measurements per eye performed following cycloplegia.

Analyses were restricted to data from children who completed the 12- and 24-month visits with measurements of SER and AL. For analysis, we classified participants as progressor or non-progressor based on whether they met a threshold for myopia progression defined as ≤−0.50 D change in SER or ≥0.25 mm change in AL (note that a *negative* SER change indicates myopia progression, whereas a *positive* AL change indicates myopia progression). The predictive value of a ≤−0.50 D change in SER and ≥0.25 mm change in AL in the first 12 months was assessed by cross-tabulating with the same change thresholds in the second 12 months and calculating sensitivity (recall), specificity, positive predictive value (precision), negative predictive value, and misclassification with 95% confidence intervals (CIs) calculated using the Wilson (score) method.[5] The initial choice of 0.50 D SER and 0.25 mm AL thresholds was somewhat arbitrary, in part due to the clinical convenience of a 0.50 D value. The approximate relationship between a 0.50 D SER change and a 0.25 mm AL change is supported by data from the current study and previous literature,[6] but additional sensitivity analyses were conducted with different thresholds based on median values. To quantify agreement between 1- and 2-year classifications, we used Cohen's kappa[7] with 95% CIs. For Cohen's kappa, a value of 0 indicates agreement that is no better than chance, and a value of 1 indicates perfect agreement.

To quantify the ability of prior progression of myopia to predict future change, we fit a multivariable linear regression model with a dependent variable of change in SER from 12 to 24 months with and without change in SER from baseline to 12 months as an independent variable while controlling for age and SER at 12 months. The mean absolute error, root mean square error, and 95% prediction interval half-width (calculated as 1.96× root mean square error) were calculated by 10-fold cross-validation with 10,000 replications. Parallel analyses were conducted for change in AL from 12 to 24 months. Sex, race, number of myopic parents, and eye color were not included as independent variables because previous analyses from the same cohort found no significant association between these factors and changes in SER or AL between baseline and 30 months.[8]

The atropine and placebo groups were pooled for analysis because there was no significant mean difference in SER or AL changes at 24 months.[3] To rule out an effect of atropine, sensitivity analyses limited to the placebo group were conducted. Nominal *P* values and 95% CIs are two sided without adjustment for multiplicity. Analyses were conducted using SAS 9.4 (SAS Institute, Cary, NC, USA).

Results

Study Cohort

Inclusion criteria for these analyses were met by 136 of 187 randomized participants (73%). Incomplete data were primarily due to virtual 12-month visits required during the COVID-19 pandemic (37/187, 20%), which precluded the collection of AL and SER in those participants. Mean ± SD age at 12 months was 10.2 ± 1.8 years, 75 were female (55%), 86 were White (63%), and 20 were Hispanic or Latino (15%) (Table 1). Mean changes in SER were −0.40 ± 0.35 D in the first 12 months and −0.35 ± 0.38 D in the second 12 months (difference = −0.05 D; 95% CI, −0.13 to 0.02). Mean changes in AL over the first and second 12 months were 0.23 ± 0.17 mm and 0.18 ± 0.16 mm (difference = 0.05 mm; 95% CI, 0.03–0.08). The correlations between changes in SER and AL were −0.87 (95% CI, −0.90 to −0.82) over the first 12 months and −0.90 (95% CI, −0.92 to −0.86) over the second 12 months.

Prediction of Future Progression Based on Classification of Prior Change

For predicting a myopic increase of 0.50 D or more SER in the second 12 months based on a myopic increase of 0.50 D or more SER in the first 12 months (Supplementary Table S1), the positive predictive value (precision) was 42% (19/45; 95% CI, 29%–57%); other performance metrics are listed in Table 2. Using the median 12-month change in SER (−0.32 D) as the threshold value, the positive predictive value was 56% (38/68; 95% CI, 44%–67%).

For predicting axial elongation of 0.25 mm or more in the second 12 months based on axial elongation of 0.25 mm or more in the first 12 months (Supplementary Table S2), the positive predictive value (precision) was 46% (25/54; 95% CI, 34%–59%) (Table 2). Using the median 12-month change in AL (0.21 mm) as the threshold value, the positive predictive value was 51% (35/68; 95% CI, 40%–63%).

Prediction of Future Progression Based on Regression of Prior Change

Controlling for age and SER at 12 months, greater change in SER from baseline to 12 months was very weakly associated with change in SER from 12 to 24 months (0.20 D

Table 1. Characteristics of the Study Cohort

Characteristic	
Subjects, *n*	136
Age (y), *n* (%)	
5 to 6	7 (5)
7 to 8	28 (21)
9 to 10	47 (35)
11 to 12	54 (40)
Mean ± SD	10.2 ± 1.8
Sex, *n* (%)	
Female	75 (55)
Male	61 (45)
Race, *n* (%)	
White	86 (63)
Black/African American	18 (13)
East Asian	15 (11)
West Asian/Indian	4 (3)
More than one race	12 (9)
Unknown/not reported	1 (1)
Ethnicity, *n* (%)	
Hispanic or Latino	20 (15)
Not Hispanic or Latino	116 (85)
Treatment group, *n* (%)	
Atropine	88 (65)
Placebo	48 (35)
AL (mm), mean ± SD	
At 12 mo	24.7 ± 0.8
Change from 0 to 12 mo	0.23 ± 0.17
Change from 12 to 24 mo	0.18 ± 0.16
SER (mm), mean ± SD	
At 12 mo	−3.23 ± 1.20
Change from 0 to 12 mo	−0.40 ± 0.35
Change from 12 to 24 mo	−0.35 ± 0.38

AL, axial length; mo, months; SD, standard deviation; SER, spherical equivalent refractive error.

per additional 1.00 D change; 95% CI, 0.02–0.39; $P = 0.03$; partial $R^2 = 0.03$) (Fig. part A). Estimated using 10-fold cross validation, the half-width of the 95% prediction interval including prior change was ±0.66 D versus ±0.67 D without prior change (difference = 0.01 D; 95% CI, −0.05 to 0.07). Mean absolute error and root mean square error values are shown in Table 3. In a sensitivity analysis limited to placebo participants ($n = 48$), the 95% prediction interval half width was ±0.64 D with prior change and ±0.64 D without prior change (difference = 0.00 D; 95% CI, −0.09 to 0.06).

Controlling for age and AL at 12 months, greater change in AL from baseline to 12 months was very weakly associated with greater change in AL from 12 to 24 months (0.28 mm per additional 1 mm prior change; 95% CI, 0.13–0.43; $P < 0.001$; partial $R^2 = 0.06$) (Fig. part B). Estimated using 10-fold cross validation, the 95% prediction interval half width including prior change was ±0.23 mm versus ±0.24 mm without prior change (difference = 0.01 mm; 95% CI, −0.03 to 0.05). Mean absolute error and root mean square error values are shown in Table 3. In a sensitivity analysis limited to placebo participants ($n = 48$), the 95% prediction interval half width was ±0.20 mm with prior change and ±0.22 without prior change (difference = 0.02 mm; 95% CI, −0.04 to 0.12).

Discussion

In this post hoc analysis of a randomized controlled trial, we compared myopia progression in the first 12 months with progression in the second 12 months. For both SER and AL, the magnitude of progression in the preceding 12 months was a poor predictor of future change. Similar results were found when analyses were limited to the placebo group. Evaluating prior progression as a possible predictor of subsequent progression in the Collaborative Longitudinal Evaluation of Ethnicity and Refractive Error (CLEERE) study, Mutti et al.,[9] concluded that prior-year progression of AL or SER was not useful as a predictive factor. They commented that the CLEERE study used ultrasound to measure AL and questioned whether the AL result might have differed if optical biometry had been available. In the present study, we used optical biometry to measure AL and also found that a past increase in AL was a poor predictor of myopia progression. Brennan et al.,[10] in a large review of myopia control studies, concluded that there is insufficient evidence to assert that faster progressors, typically younger children, experience greater treatment efficacy and called for more data. Similarly, Matsumura et al.,[11] found that annual myopia progression was associated with future progression but that it did not substantially improve prediction. Taken together with prior studies, the results of the present study suggest that past progression of myopia is a poor predictor of future progression.

There are perils in assuming that identifying fast progressors will be helpful for future clinical trials of treatments for myopia progression. For example, regression to the mean occurs when a continuous measure (e.g., prior progression in SER), which has inherent measurement error, is used as both an enrollment criterion with a threshold cut point and as an outcome. Mutti et al.,[9] noted that, when a clinician attempts to identify fast progressors and assumes they will continue to progress as rapidly in the subsequent time interval, a regression-to-the mean effect results in slower progression, on average, in the following year at the cohort level.

Even if past progression were a reasonable predictor of future progression, it may be impractical to use in clinical care or as an eligibility criterion for future random-

Table 2. Performance of SER Myopia Increase and Axial Elongation in Prior 12 Months as Binary Classifiers

	SER Myopia Increase ≥ 0.50 D		SER Myopia Increase ≥ 0.32 D		Axial Elongation ≥ 0.25 mm		Axial Elongation ≥ 0.21 mm	
	n	% (95% CI)	*n*	% (95% CI)	*n*	% (95% CI)	*n*	% (95% CI)
Sensitivity (recall)	19/40	48 (33–63)	38/67	57 (45–68)	25/34	74 (57–85)	35/48	73 (59–83)
Specificity	70/96	73 (63–81)	39/69	57 (45–68)	73/102	72 (62–79)	55/88	63 (52–72)
Positive predictive value (precision)	19/45	42 (29–57)	38/68	56 (44–67)	25/54	46 (34–59)	35/68	51 (40–63)
Negative predictive value	70/91	77 (67–84)	39/68	57 (46–68)	73/82	89 (80–94)	55/68	81 (70–88)
Misclassification	47/136	35 (27–43)	47/136	35 (27–43)	38/136	28 (21–36)	38/136	28 (21–36)
Cohen's kappa (95% CI)	0.20 (0.03–0.37)		0.13 (−0.03–0.30)		0.38 (0.22–0.53)		0.32 (0.17–0.48)	

CI, confidence interval; SER, spherical equivalent refractive error.

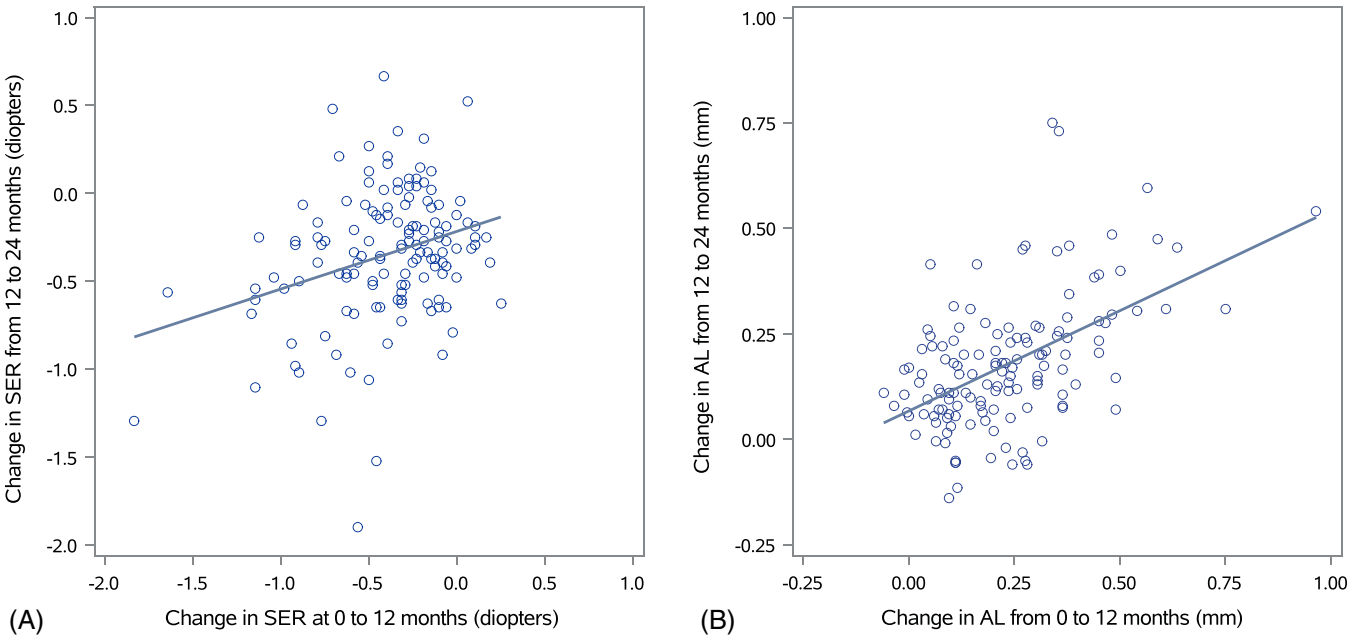

Figure. (**A**, **B**) Scatterplots of change in SER (**A**) and AL (**B**) from 0 to 12 months versus change from 12 to 24 months. Bivariate least-squares regression lines are shown.

Table 3. Performance Metrics for Predicting Future Change With and Without Prior Change

	With Prior Change (95% CI)*	Without Prior Change (95% CI)*	Difference (95% CI)*
Change in SER (D) from 12 to 24 mo			
Mean absolute error	0.26 (0.16, 0.39)	0.27 (0.17, 0.39)	0.00 (−0.03, 0.03)
Root mean square error	0.34 (0.20, 0.54)	0.34 (0.21, 0.54)	0.01 (−0.03, 0.04)
Prediction interval half-width†	0.66 (0.40, 1.05)	0.67 (0.41, 1.05)	0.01 (−0.05, 0.07)
Change in AL (mm) from 12 to 24 mo			
Mean absolute error	0.09 (0.05, 0.14)	0.09 (0.06, 0.14)	0.01 (−0.01, 0.02)
Root mean square error	0.12 (0.06, 0.19)	0.12 (0.07, 0.20)	0.01 (−0.01, 0.03)
Prediction interval half-width†	0.23 (0.12, 0.37)	0.24 (0.14, 0.39)	0.01 (−0.03, 0.05)

* Point estimates and 95% CIs were estimated as the mean, 2.5th percentile, and 97.5th percentiles from the distribution of 10,000 replications.

† Calculated as root mean square error multiplied by 1.96.

ized controlled trials of myopia treatments. Summarizing results from a workshop involving the FDA and several ophthalmologic and optometric organizations, Walline et al.,[12] concluded that prior progression is difficult to use in practice due to seasonal variation and differences in how refraction has been measured before study enrollment (e.g., less rigorous methods), both of which may result in less progression observed when a child has been enrolled in a study.

To demonstrate the pitfalls of prior progression, consider an example using data from the present study. The mean axial elongation in year 1 was 0.23 mm. What would happen if the children had been followed for 1 year and then enrolled into the randomized controlled trial based on axial elongation in year 1? Among children with axial elongation greater than or equal to the median value of 0.21 mm in year 1, mean axial elongation in year 2 was 0.24 mm, essentially the same as the full cohort in year 1 (mean, 0.23 mm). Although it is true that children with below-median axial elongation in year 1 had lower mean axial elongation in year 2 (0.12 mm), overall myopia progression slowed in year 2 in part due to the fact that the children were a year older. A recent meta-regression suggested an annual 15% slowing in the rate of axial elongation[13]; in this study, we observed approximately 22% slowing in year 2. Thus, if planning sample size for a study, there is no meaningful gain in power by following the children for a year before enrolling to select for the so-called fast progressors. However, there are added financial costs and complexity, as well as an opportunity cost to the children who miss out on a year of potential treatment earlier in their disease course.

Limitations

Our present study has limitations. First, data from the atropine and placebo groups were combined for analysis, based on our previous finding that 0.01% atropine had no significant treatment effect on change in AL or SER at 12 or 24 months. Nevertheless, sensitivity analyses limited to the placebo group yielded similar results, albeit with a smaller sample size. Second, only 73% of the randomized trial cohort contributed to this analysis, largely due to missing 12-month

data related to the COVID-19 pandemic; however, we expect those omitted to be at random and unrelated to risk for myopia progression.

Conclusions

Among U.S. children 5 to 12 years of age at enrollment with mild to moderate myopia, changes in AL and SER in the prior year were poor predictors of future change, limiting the usefulness of those measures for clinical decision-making or selecting participants for clinical trials. Further study is necessary to identify factors that can help determine which children could benefit most from myopia control therapy.

Acknowledgments

Supported by a grant from the National Eye Institute, National Institutes of Health (EY011751). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Disclosure: **W.T. Beaulieu**, None; **M.X. Repka**, None; **S.L. Pineles**, None; **D.L. Chandler**, None; **Y. Pang**, None; **L.A.F. Kehler**, None; **C.O. Jordan**, None; **K.A. Lee**, None; **D.B. Petersen**, None; **S.R. Hatt**, None; **S.A. Cotter**, None; **R.T. Kraker**, None; **K.K. Weise**, None; **J.M. Holmes**, None

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