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Changes in choroidal thickness in pre-myopic children after repeated low-level red-light therapy and their role in predicting myopia prevention and controlling myopic shift

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ABSTRACT

Purpose: To investigate longitudinal changes in choroidal thickness (ChT) after 1-year treatment of repeated low-level red-light (RLRL) and their predictive value in efficacy on myopia prevention and myopic shift among pre-myopic children.

Methods: 278 pre-myopic (-0.50 D < spherical equivalent refraction, SER ≤ 0.50 D) participants were assigned to the RLRL group and control group randomly and evenly. The OCT, visual acuity, AL, SER and other parameters were measured before enrollment and every 3 months after intervention. The data from both eyes of the included participants were analyzed.

Results: A total of 463 eyes were analyzed. Due to the COVID-19 pandemic, 176 participants in the RLRL group had treatment interrupted. The continued RLRL group, interrupted RLRL group and control group were well balanced in baseline characteristics. In the continued and interrupted RLRL group, the average ChT increased significantly at 3-month visit (all $P < 0.001$) and the subfoveal ChT thickened evidently. The area under the curve (AUC) for the models including gender and 3-month change in ChT to predict satisfactory myopia prevention at 12 months was 0.983. The efficacy of the models that also used the combined indicators of baseline age, gender and the 3-month change in ChT to predict AL progression control over 12 months reached 0.944.

Conclusions: Continued RLRL intervention induced notable thickening of ChT in premyopic population, especially at the subfoveal sector. For participants received RLRL treatment, the 3-month change in ChT combined with other baseline factors have acceptable predictive discrimination of myopia prevention efficacy.

Introduction

Myopia, a refractive disorder characterized by optical myopic defocus and blurred vision, has emerged as the most prevalent ocular condition globally, especially prevalent in East Asia.[1,2] Furthermore, an earlier myopia onset and prolonged progression of myopia significantly increase the risk of macular degeneration and vision impairment, which is often associated with a decrease in the choroidal thickness (ChT).[3]

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Consequently, myopia prevention is a critical area of focus in the refractive development of children and adolescents. International Myopia Institute defined pre-myopia as a refractive state in which the spherical equivalent refraction (SER) is in the range of −0.50–0.75 diopter (D) inclusive in children and adolescents. This condition, when assessed alongside baseline SER, age, and other measurable risk factors, indicates a substantial likelihood of myopia onset, thereby warranting preventative interventions.[4]

Recent advances have introduced repeated low-level red-light (RLRL) as a promising intervention to control the myopic shift by slowing axial length (AL) elongation and controlling refraction.[5,6] Our previous randomized controlled trial (RCT) provided evidence that RLRL controlled myopic shift and effectively prevented the development of myopia in pre-myopic children.[7] In addition, our RCT showed that subfoveal ChT increased in the intervention group which was consistent with prior studies.[8,9]

A vital role in emmetropization is played by the choroid, which thickens or attenuates itself to enable external light to focus accurately on the retina and influences the synthesis and degradation of the scleral extracellular matrix.[10,11] Furthermore, short-term variations in subfoveal ChT have been linked to long-term changes in AL among myopic children undergoing treatments such as atropine eye drops and orthokeratology.[12,13] Xiong et al. reported a rapid increase in subfoveal ChT among children with myopia exposed to RLRL and it could predict long-term myopia control efficacy.[8] We speculate this predictive efficacy could extend to pre-myopic children and provide reference to clinical practice. In addition, changes across different choroidal regions post-RLRL treatment and the possible predictive value of other regions other than the central sector remain unexplored.

To test this hypothesis, we investigated the changes in different regions of the choroid after RLRL treatment and the predictive value of myopia prevention and control efficacy.

Methods

Study design

This study is a secondary analysis of data from a RCT.[7] In brief, the RCT was a 12-month, two-group, single-blind, school-based study conducted in Shanghai, China (ClinicalTrials.gov identifier: NCT04825769). This trial evaluates the efficacy and safety of this novel intervention for preventing myopia onset and controlling myopic shift among pre-myopic children aged 6–10 years.

We conducted screenings of students in grades 1 through 4 across 10 primary schools, enrolling those identified as pre-myopia (-0.50 D $<$ cycloplegic SER $\leq$ 0.75 D for at least one eye) and with one parent at least having a SER $\leq$ -3.00 D in either eye. Given the −1.00 D decrease in SER during the one year before myopia onset,[14] the inclusion criteria were established as −0.50 D $<$ SER $\leq$ 0.50 D for at least one eye. This was intended to select participants who were at a higher risk of developing myopia within the subsequent year. Children were excluded from the study if they had astigmatism $\geq$ 1.50 D, anisometropia $\geq$ 1.50 D, strabismus, or other ocular abnormalities. Additionally, those with systemic diseases or prior myopia interventions were also not eligible for inclusion.

After enrollment, children were assigned to the RLRL group and control groups randomly and evenly. Children in the RLRL group were exposed to the red light twice daily, five days per week, with each session having a duration of three minutes. Each session was conducted with a minimum interval of four hours between them. If a child was eligible for enrollment with only one eye, we sealed the laser beam hole on the opposite side of the instrument (Supplementary Figure 1). Initial treatment was supervised on-site by the research team, while subsequent treatments were conducted under the supervision of school teachers.

During the last three months of the trial, due to the COVID-19 pandemic, a subset of subjects in the RLRL group continued to receive the intervention at home, while others did not take the machine home and had their treatment interrupted. Therefore, we further subdivided the participants into the continued intervention group, the interrupted intervention group, and the control group (group A, B, C, respectively). In addition, a dedicated information system recorded the actual number of interventions received by the children in real-time to evaluate compliance. During the trial period, no interventions were applied to the participants in the control group.

This trial received approval from the Shanghai General Hospital Ethics Committee ([2021]022) and conducted in accordance with the ethical guidelines proposed by the Declaration of Helsinki.[15]

Ophthalmic examinations

Ophthalmic data collection during the five visits were obtained by the same examiner, utilizing consistent criteria and protocols throughout the study.[7] Before the trial began, researchers and project implementation staff underwent and completed relevant training and assessments.

Uncorrected visual acuity (UCVA) was assessed using the Early Treatment Diabetic Retinopathy Study (ETDRS) logMAR chart (Wehen 06, Guangzhou Xieyi Weishikang). AL was measured using the IOL-Master (Carl Zeiss 500, Meditec) before cycloplegia. The final recorded results were the averages of five readings, with the maximum difference between readings being less than 0.05 mm. 1 % cyclopentolate (Alcon) was administered as two drops, separated by a five-minute interval, to induce cycloplegia. Pupillary light reflex and pupil size were checked 30 minutes after the administration of the eye drops. SER after cycloplegic were measured by optometrist using an autorefractor (KR8900, Topcon). The subsequent optometrist verified that the maximum difference among the three readings of spherical or cylindrical $\leq$ 0.25 D, of axis $\leq$ 5 degrees. Anterior segment indicators were captured using a Scheimpflug camera (Pentacam HR, Oculus Optikgeräte GmbH).

OCT imaging and analysis

Fundus imaging was obtained with a swept-source optical coherence tomography (OCT) instrument (DRI-OCT Triton, Topcon). Before performing OCT scanning, it is essential to reconfirm cycloplegia completed to optimize image quality.[16] Additionally, to minimize the impact of diurnal rhythm on ChT measurements, OCT scans were taken between 10 AM and 3 PM.[17]

The fundus images, collected under a 12-line radial 9 mm scan pattern, were analyzed using the OCT's built-in software to segment the fundus layers. All images were reviewed by a specialized and experienced technician (B.Z.). Image quality was scored by the built-in software, while images with a score lower than 90 were excluded from the analysis. Choroidal thickness was defined as the vertical distance between the choroid-sclera interface and Bruch's membrane.

An ETDRS grid was applied to all OCT images, defining the regions of subfovea, parafovea, and fovea with diameters of 1 mm, 3 mm, and 6 mm, respectively. These circles were further divided into superior, inferior, temporal, and nasal quadrants. The average ChT of all nine sectors and ChT in each grid sector were calculated using the built-in software.

Statistical analysis

Data from both eyes of the participants were analyzed, except in cases where only one eye met the inclusion criteria. Missing values were not imputed. This analysis included only SER data that confirmed full cycloplegia to ensure the accuracy of the results. All P values were derived from two-sided tests, with statistical significance set at $P < 0.05$. Statistical analyses were conducted using SAS, version 9.4 (SAS Institute, Inc.).

The distribution of the data was examined by the

Kolmogorov–Smirnov test. Baseline characteristics were described as means with standard deviations or counts with percentages. Comparison of baseline data was performed using chi-square tests for gender and analysis of variance (ANOVA) tests for other characteristics. Univariate regression models were conducted to explore the correlation between each possible indicator and SER at 12 months or 12-month changes in AL. Mixed-effects models were employed to further evaluate the association while adjusting for intraclass correlation between bilateral data, allowing for a comparison with the results from the univariate analysis. To facilitate visualization of the results, baseline central corneal thickness (CCT) and changes in ChT were rescaled and divided by 10 to avoid overly small β values. Factors with P values < 0.10, including age, gender, UCVA, SER, and AL at baseline and 3-month changes in ChT, were included and examined in the consequent analysis. Stepwise regression models were then established using these potential associated covariates to predict myopia prevention and control effect over 12 months in group A. To compare and evaluate the predictive performance of various models, receiver operating characteristic (ROC) curves were utilized, and the area under the curve (AUC) was calculated. According to previous reports, a satisfactory myopic shift control threshold was defined as SER at 12-month not less than −0.50 D and annual progression rates of AL no more than 0.15 mm.[18,19]

Result

Baseline characteristics

This study enrolled 287 subjects. Among these, 111 of the 574 eyes did not meet the criteria for pre-myopic status, leaving 463 eyes for inclusion in this analysis. There were 55 (11.88 %) eyes in group A, 176 (38.01 %) in group B and 232 (50.11 %) in group C. The baseline characteristics are described in Table 1. The distribution of most indicators was well balanced among the three groups ($P > 0.05$). Only baseline CCT among groups were distributed statistically different ($P = 0.036$) but without clinical significance.

Topographic longitudinal changes in ChT

To intuitively visualize the changes in the choroid, we divided the macular-centered choroid into nine sectors based on the ETDRS grid (Fig. 1). In group A and B, ChT changes increased horizontally from the temporal to the central sector, then decreased toward the nasal quadrant. A similar trend was observed vertically from the superior to the inferior quadrant. Of note, in group B, the 3-month changes in ChT across the nine sectors were all significantly different from their adjacent sectors (all $P < 0.05$), with the most evidence increase in the subfoveal sector (21.36 ± 21.56 μm). Over time, fewer sectors showed significant differences in ChT changes from neighboring sectors. In group C, the trend was the opposite; the three-month ChT changes remained consistent across most sectors. However, by the 12th month, significant differences emerged between most sectors and their adjacent sectors, with the subfoveal sector showing the most significant changes in ChT.

To better compare ChT changes among the three groups at each follow-up, we standardized the scale at 4 time points. The topographic maps of participants in group A were similar to those in group B during the first 9 months (3-month: 17.22 ± 21.95 μm vs 16.44 ± 17.81 μm, $P = 0.839$; 6-month: 10.94 ± 24.25 μm vs 12.29 ± 19.97 μm, $P = 0.747$; 9-month: 11.92 ± 21.79 μm vs 14.99 ± 19.08 μm, $P = 0.577$). At the 3-month, 6-month and 9-month visits, the changes in average ChT in group C were statistically different from those in the other two groups (3-month: 3.64 ± 17.65 μm, 6-month: −6.95 ± 17.28 μm, 9-month: −7.74 ± 16.82 μm; all $P < 0.001$). However, by the 12-month visit, cumulative ChT changes in groups A and B had thinned rapidly over the three months, approaching those of group C (A: −0.94 ± 27.87 μm, B: −5.19 ± 26.38 μm, C: −6.16 ± 21.42 μm; all $P > 0.05$).

Additionally, ChT changes were compared every three months within each group. In groups A and B, there was a substantial increase in average ChT at the 3-month visit (all $P < 0.001$). The second 3-month changes in average ChT decreased (-8.72 ± 18.91 μm, $P < 0.010$; −5.68 ± 19.27 μm, $P < 0.010$, respectively), and remained unchanged afterwards in both groups (0.15 ± 20.97 μm, $P = 0.977$; 2.44 ± 15.00 μm, $P = 0.156$, respectively). The average ChT exhibited a decrease at the 12-month follow-up compared to that at 9 months. (-19.63 ± 24.07 μm, $P < 0.010$; −21.14 ± 21.73 μm, $P < 0.001$, respectively). In group C, average ChT initially increased at the first 3-month visit ($P = 0.01$), followed by a significant decrease at the second 3-month visit (-11.01 ± 20.66 μm, $P < 0.001$), and remained stable during the next two 3-month visits (-0.70 ± 15.20 μm, $P = 0.666$; −0.46 ± 22.63 μm, $P = 0.855$, respectively).

Table 1
Demographic and biometric characteristics measured at baseline.

	Included			
	Group A	Group B	Group C	*P* value
Age, years	8.27 (1.10)	8.30 (1.11)	8.32 (1.09)	0.730
Male, %	26 (47.27 %)	99 (56.25 %)	113 (48.71 %)	0.259
Height, cm	131.54 (7.95)	133.43 (9.41)	132.41 (8.02)	0.979
Weight, kg	29.23 (6.16)	30.68 (8.11)	29.97 (7.55)	0.938
UCVA, logMAR	0.08 (0.09)	0.09 (0.08)	0.08 (0.08)	0.408
SER, D	0.20 (0.28)	0.16 (0.28)	0.21 (0.27)	0.427
Corneal Radius, mm	7.87 (0.24)	7.88 (0.24)	7.83 (0.25)	0.099
AL, mm	23.30 (0.56)	23.42 (0.68)	23.29 (0.67)	0.341
Pupil diameter, mm	6.27 (0.83)	6.50 (0.85)	6.31 (0.96)	0.453
Central corneal thickness, μm	553.31 (34.59)	552.09 (36.53)	560.79 (29.39)	0.036*
Anterior chamber depth, mm	3.69 (0.21)	3.72 (0.22)	3.71 (0.20)	0.766
Lens thickness, mm	3.61 (0.20)	3.67 (0.19)	3.64 (0.22)	0.965
Subfoveal ChT, μm	265.80 (64.71)	278.06 (57.73)	278.63 (55.98)	0.338
Para temporal ChT, μm	279.00 (62.01)	288.42 (54.50)	294.18 (53.04)	0.107
Para superior ChT, μm	266.62 (59.72)	276.21 (55.30)	274.40 (53.93)	0.664
Para nosal ChT, μm	233.06 (62.84)	242.33 (55.74)	240.53 (55.45)	0.687
Para inferior ChT, μm	263.19 (66.34)	273.55 (59.30)	279.71 (55.93)	0.103
Peri temporal ChT, μm	280.20 (55.55)	285.27 (46.99)	294.14 (50.18)	0.052
Peri superior ChT, μm	260.95 (54.31)	269.11 (51.24)	266.15 (51.96)	0.875
Peri nosal ChT, μm	186.15 (56.26)	189.58 (49.24)	189.42 (49.33)	0.799
Peri inferior ChT, μm	249.01 (56.18)	257.21 (51.78)	264.23 (51.31)	0.072
Average ChT, μm	248.27 (54.35)	255.43 (48.07)	258.33 (48.08)	0.266

Data are presented as mean (standard deviation) or number (%).
Group A: continued intervention group; group B: interrupted intervention group; group C: control group.
UCVA = uncorrected visual acuity; SER = spherical equivalent refraction; AL= axial length; ChT = choroidal thickness; para = parafoveal; peri = perifoveal.
LogMAR = logarithm of minimum angle of resolution; D = diopter; cm = centimeter; mm = millimeter; μm = micrometer.
P values were calculated on the basis of ANOVA tests for continuous data and χ^2 tests for categorical data.
* for $P < 0.05$.

Factors associated with SER at 12 months and AL Elongation over 12 months

Considering that participants in group B did not complete the RLRL intervention after 9-month visit, only data from group A were included for subsequent analysis. Table 2 presents various factors that may be

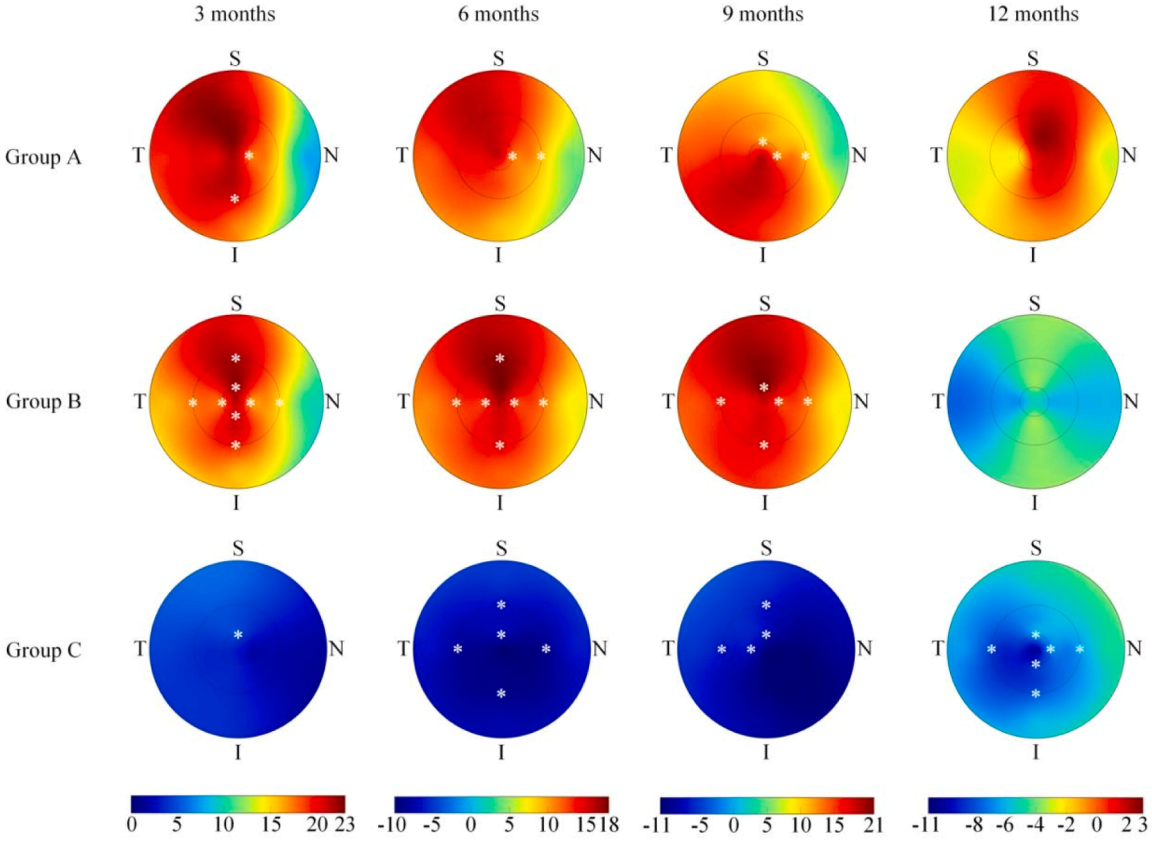

Fig. 1. Cumulative mean changes in ChT across different macular regions of participants over the 12 months. Group A: continued intervention group; group B: interrupted intervention group; group C: control group. T: temporal; S: superior; N: nasal; I: inferior. * $P < 0.05$ for comparison between the two adjacent sect.

Table 2
Univariate regression analysis for relationships between each associated factor and SER at 12 months, changes in AL over 12 months in the group A.

	SER at 12 months			12-month changes in AL		
	Estimated β (95 % CI)	*P*	R^2	Estimated β (95 % CI)	*P*	R2
Age, years	0.08 (−0.08, 0.25)	0.319	0.000	−0.06 (−0.11, −0.01)	0.027*	0.027
Male vs. female	−0.65 (−0.96, −0.34)	< 0.001*	0.233	0.17 (0.06, 0.28)	0.003*	0.138
Height, cm	0.01 (−0.01, 0.04)	0.269	0.005	−0.01 (−0.01, 0.00)	0.073	0.042
Weight, kg	−0.01 (−0.04, 0.02)	0.449	−0.008	0.00 (−0.01, 0.01)	0.837	−0.018
UCVA, logMAR	−3.32 (−5.09, −1.55)	< 0.001*	0.196	0.77 (0.13, 1.40)	0.019*	0.082
SER, D	1.38 (0.86, 1.89)	< 0.001*	0.339	−0.26 (−0.46, −0.06)	0.013*	0.095
Corneal radius, mm	−0.35 (−1.10, 0.39)	0.348	−0.002	0.12 (−0.13, 0.37)	0.355	−0.002
AL, mm	−0.31 (−0.62, 0.01)	0.055	0.050	0.07 (−0.04, 0.18)	0.196	0.013
Pupil diameter, mm	−0.19 (−0.47, 0.10)	0.194	0.021	0.04 (−0.06, 0.13)	0.428	−0.010
Central corneal thickness, μm	0.00 (−0.08, 0.07)	0.896	−0.029	−0.01 (−0.03, 0.01)	0.430	−0.011
Anterior chamber depth, mm	−0.23 (−1.37,0.90)	0.677	−0.024	0.01 (−0.37, 0.38)	0.977	−0.029
Lens thickness, mm	0.95 (−0.28, 2.17)	0.127	0.045	−0.44 (−0.84, −0.04)	0.031*	0.117
3-month change in Subfoveal ChT, 10 μm	0.12 (0.02, 0.22)	0.020*	0.153	−0.04 (−0.07, −0.01)	0.010*	0.166
3-month change in Para temporal ChT, 10 μm	0.12 (0.03, 0.22)	0.012*	0.181	−0.05 (−0.08, −0.02)	0.003*	0.254
3-month change in Para superior ChT, 10 μm	0.12 (0.03, 0.21)	0.013*	0.180	−0.04 (−0.07, −0.01)	0.011*	0.186
3-month change in Para nosal ChT, 10 μm	0.11 (0.01, 0.22)	0.039*	0.117	−0.04 (−0.08, −0.01)	0.014*	0.175
3-month change in Para inferior ChT, 10 μm	0.13 (0.03, 0.24)	0.014*	0.174	−0.04 (−0.08, −0.01)	0.020*	0.155
3-month change in Peri temporal ChT, 10 μm	0.15 (0.05, 0.24)	0.004*	0.242	−0.06 (−0.09, −0.03)	< 0.001*	0.352
3-month change in Peri superior ChT, 10 μm	0.10 (0.02, 0.19)	0.022*	0.149	−0.04 (−0.07, −0.01)	0.009*	0.200
3-month change in Peri nosal ChT, 10 μm	0.08 (−0.05, 0.20)	0.243	0.015	−0.04 (−0.08, 0.00)	0.065	0.088
3-month change in Peri inferior ChT, 10 μm	0.13 (0.02, 0.24)	0.018*	0.161	−0.04 (−0.08, −0.01)	0.014*	0.176
3-month change in Average ChT, 10 μm	0.14 (0.03, 0.25)	0.013*	0.177	−0.05 (−0.09, −0.02)	0.004*	0.243

Group A: continued intervention group.
UCVA = uncorrected visual acuity; SER = spherical equivalent refraction; AL= axial length; ChT = choroidal thickness; para = parafoveal; peri = perifoveal.
LogMAR = logarithm of minimum angle of resolution; D = diopter; cm = centimeter; mm = millimeter; μm = micrometer.
* for $P < 0.05$.

associated with SER at 12 months and 12-month changes in AL. In group A, each 10 μm increase in the 3-month change in subfoveal ChT was associated with a 0.12 D increase in 12-month SER (P = 0.020) and a 0.04 mm decrease in the change in AL ($P = 0.010$). Similarly, 3-month changes in ChT in other sectors and average ChT exhibited a negative correlation with the 12-month change in AL, while demonstrating a

positive correlation with SER at the 12-month. (all $P < 0.10$). Notably, the R^2 value of the regression models reached 0.242 and 0.352 when the change in perifoveal temporal ChT was included as the independent variable, the highest compared with other sectors. SER at 12 months were also associated with gender, UCVA and SER at baseline ($\beta = -0.65$, $\beta = -3.32$, $\beta = 1.38$, respectively; all $P < 0.001$). Other baseline factors, including age, UCVA, SER, lens thickness at baseline and gender were associated with AL change over 12 months ($\beta = -0.06$, 0.77, −0.26, −0.44, 0.17, respectively; all $P < 0.05$). The mixed-effects model, after adjusting for the correlation between binocular data, also revealed statistically significant associations between the aforementioned indicators and the outcomes (Supplementary Table 1).

Initial ChT changes with myopia prevention and control efficacy

A stepwise regression model was established, and factors with *P* values < 0.10 in Table 2 and e Table 1 were entered to identify independent factors associated with SER at 12 months and the 12-month change in AL. Among all nine sectors of the choroid, the models selected and included 3-month changes in subfoveal and perifoveal temporal ChT. The results in Table 3 showed that only gender and the 3-month change in subfoveal or perifoveal temporal ChT were associated with 12-month SER (all $P < 0.01$). Meanwhile, baseline age, gender and the 3-month change in subfoveal or perifoveal temporal ChT were all negatively associated with AL change in group A (all P < 0.05, except for age).

Fig. 2 presents the ROC curves of different models for predicting myopia control and prevention efficacy in group A. Models that included the 3-month change in perifoveal temporal or subfoveal ChT had AUCs of 0.833 and 0.800, respectively, for predicting satisfactory AL elongation under the thresholds of 0.15 mm/yr (model 1 in A, C respectively). The combination of baseline age, gender, 3-month changes in subfoveal or perifoveal temporal ChT, and gender achieved AUCs of 0.956 for both (model 2 in A, C respectively). In addition, ROC curves were established for predicting effective myopia prevention outcomes at the 12-month pre-myopia after RLRL treatment. The AUCs of models using only the 3-month change in perifoveal temporal or subfoveal ChT were 0.858 and 0.825 (model 1 in B, D respectively). Multivariate models that also included gender demonstrated satisfactory predictive discrimination for successful myopia prevention over a 12-month period, with AUCs of 0.983 for both (model 3 in B and, D respectively).

Discussion

To the best of our knowledge, this study represents the first investigation into the longitudinal changes in ChT across different ETDRS sectors and the independent factors associated with myopia prevention among Chinese pre-myopic children following 12 months of RLRL therapy. ChT thickening was observed after 3 months of RLRL therapy, with the magnitude decreasing at the 6-month visit and stabilizing at 9 months. Moreover, among participants who received continuous RLRL intervention, 3-month ChT changes were associated with long-term myopia prevention and control efficacy significantly.

In this study, we observed significant differences in the changes in ChT between adjacent sectors in group B at 3 months, with these differences decreasing over time. Similarly, Xiong et al. reported that ChT first increased, then decreased, and finally stabilized in subjects over 12 months of RLRL treatment.[8] We hypothesized that the gradual stabilization of the RLRL effect on the choroid represents the adaptation of the visual system to RLRL. This suggests that children should be carefully monitored for responses for RLRL within the first three months of RLRL and that RLRL is safe and stable for at least one year. However, we did not observe a similar phenomenon in group A which might be due to the much smaller sample size.

Due to the COVID-2019 pandemic in Shanghai, the RLRL intervention was interrupted for most participants in the intervention group after 9-month visit. This resulted in a rapid thinning of their choroid, which eventually approached that of group C eventually. This suggests that the effect of RLRL may diminish after 3 months of discontinuation, and longer discontinuation may increase the risk of rebound. Notably, subjects who continued using RLRL in group A ended up with only a non-significant increase in ChT changes compared to those in group B. We speculate that during pandemic isolation at home, increased risk factors for myopia such as lack of outdoor activity[20], and increased screen time[21] may have counteracted the effect of RLRL on ChT.

Previous researches have demonstrated a correlation between ChT and the progression of myopia[22–24], indicating that ChT could be a potential factor in the mechanism of myopia. However, the role of initial ChT changes in myopia prevention efficacy have not been fully demonstrated. Therefore, this study investigated the associations between 3-month ChT changes and 12-month axial elongation or SER at 12 months after RLRL treatment. We found that in the control group, the 12-month changes in AL and SER correlated with ChT at baseline (Supplementary Table 2). In contrast, in the continuous intervention group, the changes in refractive status were associated with the 3-month

Table 3
Stepwise regression analysis for association between potential factors and SER at 12 months, changes in AL over 12 months in group A.

	Multivariate Model 1			Multivariate Model 2		
	Estimated β (95 % CI)	*P*	Adjusted R^2	Estimated β (95 % CI)	*P*	Adjusted R^2
SER at 12 months						
Male vs. female	−0.81 (−1.19, −0.43)	< 0.001*	0.494	−0.77 (−1.13, −0.41)	< 0.001*	0.552
UCVA, logMAR						
SER, D						
AL, mm						
3-month change in Subfovel ChT, 10 μm	0.12 (0.04, 0.20)	0.004*				
3-month change in Peri temporal ChT, 10 μm				0.14 (0.06, 0.21)	< 0.001*	
12-month changes in AL						
Age, years	−0.06 (−0.12, 0.00)	0.064	0.352	−0.04 (−0.10,0.01)	0.100	0.488
Male vs. female	0.19 (0.05, 0.33)	0.012*		0.17 (0.04, 0.30)	0.011*	
UCVA, logMAR						
3-month change in Subfovel ChT, 10 μm	−0.04 (−0.07, 0.00)	0.016*				
3-month change in Peri temporal ChT, 10 μm				−0.05 (−0.08,−0.02)	< 0.001*	

Group A: continued intervention group.
UCVA = uncorrected visual acuity; SER = spherical equivalent refraction; AL= axial length; ChT = choroidal thickness; peri = perifoveal.
LogMAR = logarithm of minimum angle of resolution; D = diopter; mm = millimeter; μm = micrometer.
Multivariate Model 1 including 3-month changes in subfoveal ChT and other covariates.
Multivariate Model 2 including 3-month changes in perifoveal temporal ChT and other covariates.
* for $P < 0.05$.

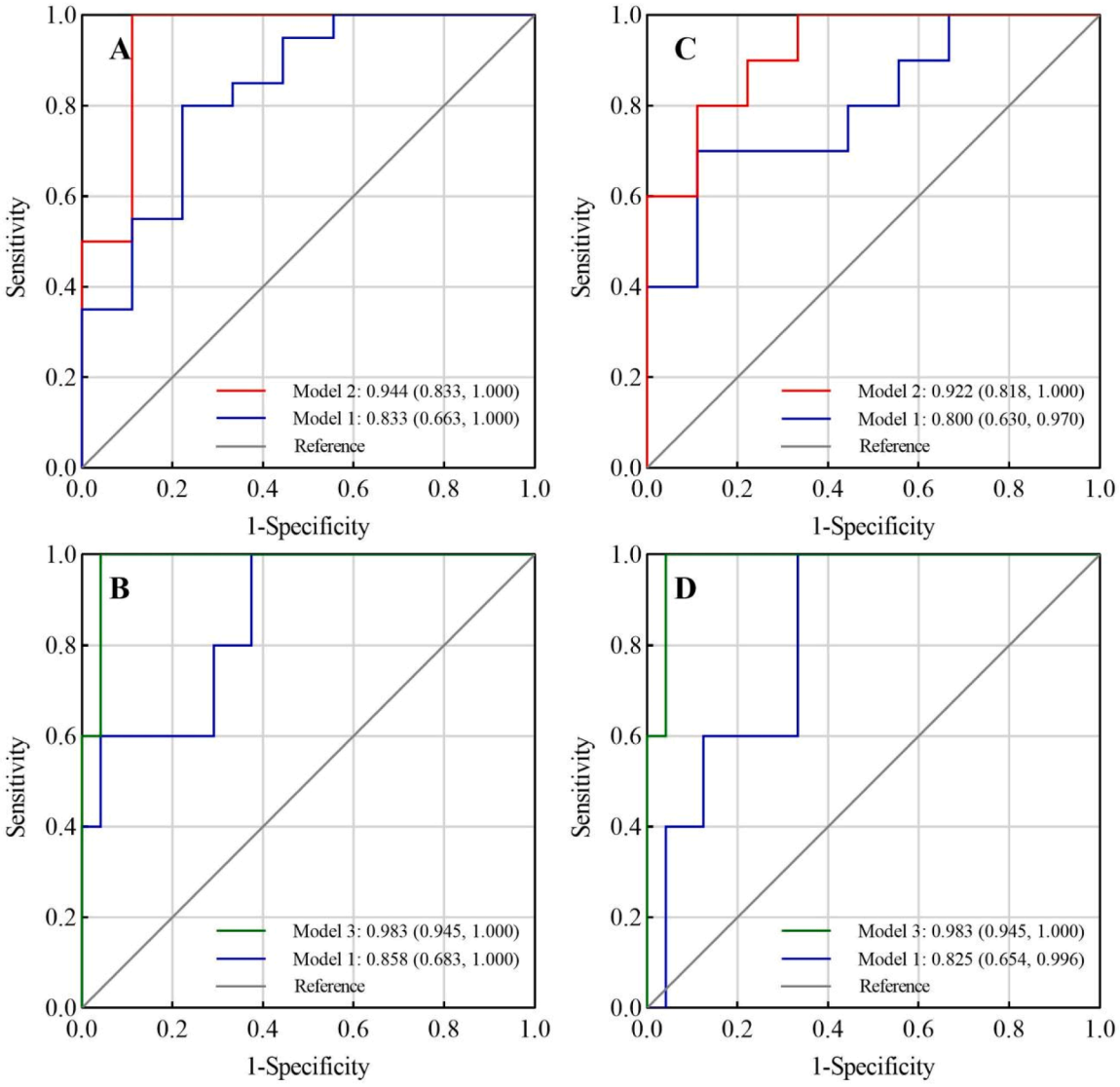

Fig. 2. Receiver operating characteristic (ROC) curves for the prediction of a satisfactory prevention and control effect on myopia in group A. A/C: AL elongation $\leq$ 0.15 mm/year; B/D: SER at 12 months $\geq$ -0.50 D. Group A: continued intervention group. Model 1 included 3-month change in ChT (A, B: perifoveal temporal ChT; C, D: subfoveal ChT); Model 2 included age, gender and 3-month change in ChT (A: perifoveal temporal ChT; C: subfoveal ChT); Model 3 included gender and 3-month change in ChT (B: perifoveal emporal ChT; D: subfoveal ChT).

changes in ChT, instead of baseline ChT. The choroidal thickening partially contributed to the impact of RLRL treatment on AL elongation (R^2 in Table 2: 0.155–0.352). These results indicate that the increase in ChT may mediate ocular growth pathways, possibly by affecting the choroidal blood flow,[25–27] and thus be involved in scleral hypoxia and remodeling.[28]

Both vertically and horizontally in topographic maps, changes in ChT in the subfoveal sector were more evident compared to other regions. This is because the macular fovea centralis is densely populated with cone cells[29,30] and is more sensitive to visual stimuli. Therefore, we believe that there may be an association between changes in subfoveal ChT and subsequent changes in the refractive system. However, several studies have reported changes in temporal ChT were significantly different from other regions after stimulation.[31–33] In addition, the change in perifoveal temporal ChT achieved the highest R^2 among all sectors in the univariate regression analysis.

Therefore, the subsequent models included changes in both subfoveal and perifoveal temporal ChT as a sensitivity analysis to test whether different sectors would affect the predictive efficacy on myopia. By combining gender and three-month ChT changes, both models could discriminate myopia at 12-month with an AUC of 0.983. Meanwhile, models established based on the combination of baseline age, SER, lens thickness and three-month ChT change could predict satisfactory AL elongation control efficacy with an AUC of 0.944 in this study. Given the small difference in effects between models constructed based on 3-month changes in central and perifoveal temporal ChT, we consider the association between the short-term changes in ChT after RLRL and myopia progression to be robust.

Our research has several limitations that should be recognized. Firstly, this trial has only gathered data for one year so far, and children with pre-myopia require longer interventions. The predictive efficacy of short-term ChT change for longer-term AL growth control effects also needs further examination. Secondly, only 55 eyes received continuous RLRL intervention, resulting in a smaller sample size than anticipated. This may partially explain why the ROC analysis, which included changes in ChT in different sectors separately, achieved the exact same AUC. Future studies should consider expanding the sample size and comparing the two sectors to determine which one provides better predictive efficacy. Thirdly, the study did not include other critical confounding factors such as time spent outdoors, screen time, and

genetic predisposition for myopia, which may influence the effect of RLRL on myopia prevention. These factors might interfere with the analysis for precise difference and association.

Conclusion

Our study suggests that RLRL can increase ChT, especially in the subfoveal sector, and control the development and progression of myopia among pre-myopic children. For participants receiving RLRL, a 3-month thickening in ChT was associated with myopia prevention and control efficacy. The combination of other baseline indicators shows promise for clinical application to predict long-term satisfactory RLRL treatment efficacy with high accuracy.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.apjo.2024.100115.

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