Relative Myopic Defocus in the Superior Retina as an Indicator of Myopia Development in Children

Zhenghua Lin,[1,2] Xiaoyun Xi,[1] Longbo Wen,[1] Zhiwei Luo,[1] Pablo Artal,[1,2] Zhikuan Yang,[1,3–5] and Weizhong Lan[1,3–5]

[1]Aier School of Ophthalmology, Central South University, Changsha, Hunan, China
[2]Laboratorio de Óptica, Universidad de Murcia, Campus de Espinardo, Murcia, Spain
[3]School of Stomatology and Ophthalmology, Xianning Medical College, Hubei University of Science and Technology, Xianning, Hubei, China
[4]Hunan Province Optometry Engineering and Technology Research Center, Changsha, Hunan, China
[5]Hunan Province International Cooperation Base for Optometry Science and Technology, Changsha, Hunan, China

Correspondence: Pablo Artal, Laboratorio de Óptica, Universidad de Murcia, Campus Universitario de Espinardo, Edificio 34, Murcia 30100, Spain; pablo@um.es.
Zhikuan Yang, Aier School of Ophthalmology, Central South University, No. 188, Furong South Rd, Changsha 410000, Hunan, China; yangzhikuan@aierchina.com.
Weizhong Lan, Aier School of Ophthalmology, Central South University, No. 188, Furong South Rd, Changsha 410000, Hunan, China; lanweizhong@aierchina.com.

Received: January 30, 2023
Accepted: March 17, 2023
Published: April 14, 2023

Citation: Lin Z, Xi X, Wen L, et al. Relative myopic defocus in the superior retina as an indicator of myopia development in children. *Invest Ophthalmol Vis Sci.* 2023;64(4):16. https://doi.org/10.1167/iovs.64.4.16

Purpose. To investigate the role of peripheral refraction in children's myopization.

Methods. This 2-year study included 214 children (8–15 years old). Refraction across the retina (field of view: 60° × 36°) was measured with a custom-made aberrometer every year. Three datasets were established: dataset 1, 214 subjects from baseline to the first-year visit; dataset 2, 152 subjects from baseline to the second-year visit; and dataset 3, 59 initial emmetropes from baseline to the second-year visit. The baseline refraction of different retina regions was correlated with the central myopic shift, and was compared among groups with different levels of myopic shift.

Results. In datasets 1 and 2, the refraction distribution across the retina was significantly different among the subjects who were initially emmetropes but not among those who were initially hyperopic or myopic. Refraction in the central vertical retina, especially in the superior retina ($r = -0.5$, $P < 0.001$), was significantly correlated with the myopic shift for emmetropes in that subjects with more relative myopia in the superior retina manifested greater central myopic shifts. In dataset 3, 21 subjects remained emmetropic after 2 years, 15 subjects became myopic at the 1-year visit, and 23 subjects became myopic at the 2-year visit. No difference was found for the relative peripheral refraction in all of the peripheral regions between the stage prior to and after the onset of myopia.

Conclusions. Relative myopic defocus in the superior retina could be a predictor of central myopia shift. Changes in relative peripheral refraction are more likely a consequence of myopia progression rather than a cause.

Keywords: myopia, myopization, emmetropia, peripheral retinal refraction, peripheral defocus

Myopia, or nearsightedness, is a common ocular condition that develops in children and young adults, whose eyes become relatively larger, resulting in retinal images that are out of focus and consequently blurred without proper optical correction. Despite increasing research on myopia over the past 40 years, myopia is still on the rise in most countries. In several Asian cities such as Singapore, Hong Kong, and Shanghai, myopia rates have reached 95%. The "high myopias" (those with refractive errors larger than 6 diopters [D]) carry a severe risk of blindness and represent 20% of young Asian people today.[1] In the United States and Europe, the incidence is lower, but still 51% of persons graduating from high school are myopic.[2] This is double the prevalence of half a century ago. Although myopia can be corrected with spectacles, contact lenses, or refractive surgery, the increasing proportion of people suffering from this condition is becoming a severe health problem worldwide.[3]

There are several theories regarding the causes and prevalence of myopia. Genetics is a long-time recognized factor; however, genetics cannot be the reason for the ongoing increase in cases. A recent study with twins suggested that refractive error is mostly affected by a shared environment rather than heritability.[4] Other often-mentioned risk factors for myopia development include extensive near work,[5] insufficient outdoor activities in children,[6] and low luminance conditions.[7]

For years, conventional wisdom attributed myopia primarily to accommodation errors associated with near work. Although the relationship between myopia development and accommodation has been intensively investigated, the relationship is still uncertain.[8,9] Accommodative lag, or an insufficient amount of accommodation, causes hyperopic defocus on the retina, which, if sustained over long periods of time, might prompt axial elongation in the eye and therefore stimulate the onset of myopia during childhood.[10] Some

studies have shown a relationship between the lag of accommodation and myopia,[11,12] whereas others have not found such a connection.[8,13] Hence, it is still unclear if accommodation affects myopia, much less whether the lag of accommodation can be either a cause or an effect of myopia.

Another possible cause that has been suggested for myopia progression is the specific refractive patterns in the periphery of the retina. The best visual performance is obtained for the fovea, which exhibits the largest concentration of cone photoreceptors; consequently, standard eye refraction is accomplished for foveal or central vision. Vision outside the fovea is known as peripheral vision. Myopes are known to have a posterior eye shape that differs from that of emmetropic eyes, affecting the morphology of the retina.[14,15] Whether the differences in retinal shape and their impact on peripheral refraction (PR) relative to the central fovea are a cause or a consequence of myopia progression remains controversial.[16–20] It is, however, important to confirm if interventions affecting PR[21] are truly useful to controlling myopia.

There are two main obstacles regarding the accessibility of data for peripheral optics. The first obstacle is the lack of adequate instrumentation to easily and comfortably obtain measurements in subjects, including children. Although various methods and instruments have been developed to study peripheral optics and refraction in the eye, none of them is ready for continuous and extensive use. However, a scanning Hartmann–Shack (HS) wavefront sensor[22] has been developed that is based on local estimation of an incoming wavefront slope by sampling it through an array of microlenses. From the set of local slope values, reconstruction of the wavefront can be accomplished. The relay containing the sensor is mechanically rotated around the subject's eye, who is only required to maintain a steady fixation. Refraction and optical aberrations along the horizontal meridian can be estimated in less than 2 seconds.[23,24] This type of instrument allows peripheral measurements to be easily made in a larger group of subjects.

The second obstacle is related to insufficient investigation regarding longitudinal changes in PR, especially with high spatial resolution. Several longitudinal studies have aimed to address this issue.[17–20] But, due to the lack of high spatial resolution in the peripheral field or to limited samples of underaged subjects, the results have been difficult to apply. An earlier study by Mutti et al.[20] found that PR at 30° temporal might be useful for predicting the onset of myopia. Even though this measured point is important, it is unlikely that the remainder of the periphery retina makes no contribution to myopia development. Thus, deeper insight into the global evolution of PR is necessary to address this gap in knowledge. In addition, most existing data are based on adults with differing refractive errors, but the current study followed peripheral optics in children during the critical period when they are likely to become myopic.

In this context, we set up a 2-year longitudinal study for a relatively large group of children from 2018 to 2021 to measure their two-dimensional (2D) PR map together with other optical and anatomical ocular data. To distinguish confounding factors, the subjects' visual behavior and possible parental myopia were also investigated during the first year of the study.

Materials and Methods

Subjects

The study was conducted in a primary–middle school from October 2018 to May 2021 in the rural area of Zhuzhou, Hunan, China. The two groups of participants had similar demographic characteristics. The collection for baseline started in October 2018 for the first group and in March 2019 for the second group. For the next 2 years, two follow-up visits were made at an interval of 12 months for each group. The baseline, first-year, and second-year data from the two groups were combined for analysis. Prescription glasses were fitted in children requiring them, and refraction was re-evaluated every 6 months. All experimental protocols complied with the tenets of the Declaration of Helsinki and were approved by the institutional review board of Aier Eye Hospital. Both participants and their parents/guardians were fully informed and provided signed consent prior to initiation of the trial.

The inclusion criteria included astigmatism < 1.5 D, best-corrected visual acuity of 20/20 or better, no historical eye disease, no systemic disease, no functional vision problems, or no history of any myopia control treatment, including orthokeratology contact lenses, multifocal spectacles, or eye drops. The exclusion criteria included intraocular pressure > 21 mmHg, strong corneal reflection in the HS images, or problems with monocular fixation during the peripheral measurements.

A total of 260 children were initially recruited; of these, 231 subjects were able to participate in the first visit, 155 completed the second visit, and 29 children missed the first visit but completed the second one. Data from 16 subjects for the first-year visit and three subjects from the second-year visit were removed due to poor quality of the peripheral measurements. Data for 214 children were available for analysis for the first-year visit (baseline to the first follow-up visit) and for 152 children for the second-year visit (baseline to the second follow-up visit; note that some subjects missed the first-year visit). The mean age at baseline was 12.2 ± 1.4 years (range, 8–15) for those children completing the first-year visit (214 subjects) and 11.5 ± 1.2 years (range, 8–14) for those completing the second-year visit (152 subjects). The mean central refraction of children at the beginning of the study (baseline) was -0.66 ± 1.4 D for those completing the first-year visit (214 subjects) but changed to -1.03 ± 1.63 D after 1 year. For the group completing the second-year visit (152 subjects), the mean refraction at baseline was -0.42 ± 1.18 D, which changed to -1.26 ± 1.6 D after 2 years. Figure 1 presents the distribution of refractive changes in the first and second year of the study (see caption for additional details).

Only 114 subjects completed all measures over the course of the study. The baseline included 14 hyperopes (spherical equivalent error [SER] $= 0.67 \pm 0.16$ D), 63 emmetropes (SER $= 0.00 \pm 0.28$ D), and 37 myopes (-1.80 ± 1.44 D). The first-year visit included nine hyperopes (SER $= 0.61 \pm 0.06$ D), 44 emmetropes (SER $= -0.04 \pm 0.28$ D), and 61 myopes (-1.86 ± 1.46 D). The second-year visit included seven hyperopes (SER $= 0.66 \pm 0.11$ D), 31 emmetropes (SER $= -0.02 \pm 0.27$ D), and 76 myopes (-2.23 ± 1.49 D). We analyzed these subjects separately to allow a more continuous evaluation of the progression. See Figure 2 for more information.

Investigative Ophthalmology & Visual Science

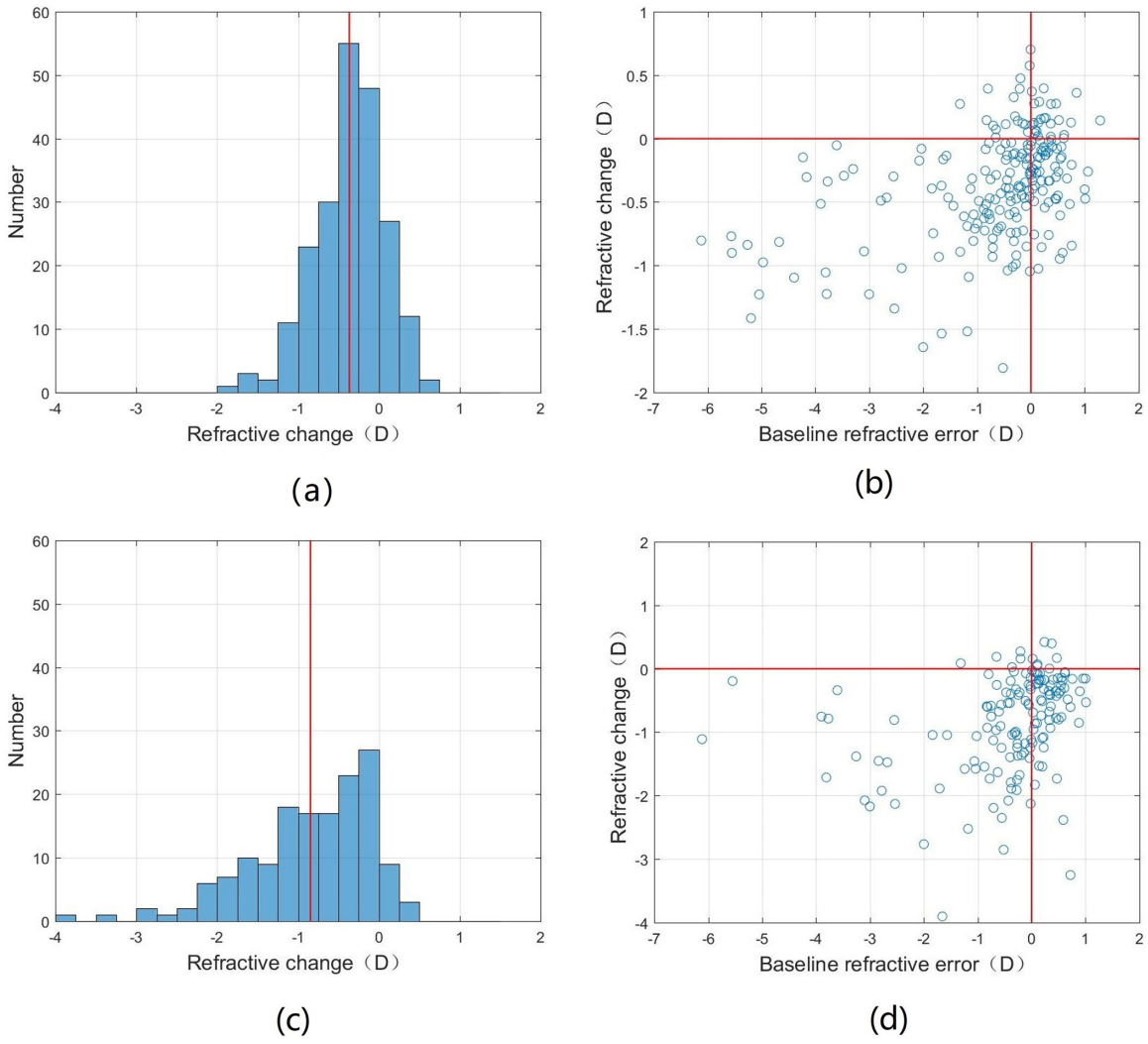

Figure 1. Demographics. (**a**, **c**) Histograms of the change in refractive error at 1 year and 2 years, respectively. The *red lines* indicate the median of the progression. (**b**, **d**) Refractive errors at baseline versus refraction progression at 1 year and 2 years, respectively.

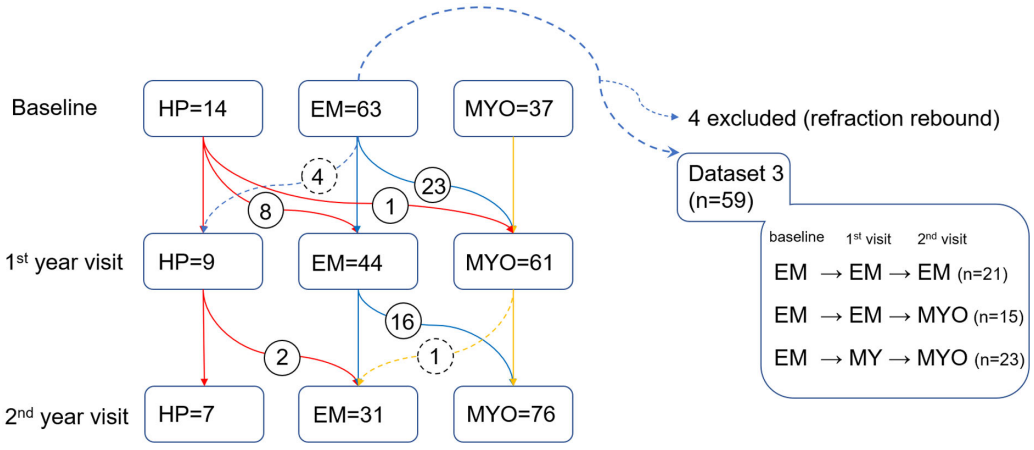

Figure 2. Number of subjects for each visit during the 2-year period. HP, hyperopes (SER > +0.5 D); EM, emmetropes (−0.5 D ≤ SER ≤ 0.5 D); MYO, myopes (SER < −0.5 D). The values in the *boxes* represent the number of participants at each visit. The values in the *solid circles* indicate the number of participants whose refractive status shifted from one group to a more myopic group. Four emmetropes at baseline and one myope at the first-year visit (*dashed circles*) were found to have refraction rebound (i.e., hyperopic shift from one group to another). For the four emmetropes, the mean change was +0.38 ± 0.14 D; for the one myope, the change was +0.18 D. Note that the data for the four subjects who had shifted from the EM group to the HP group at the first-year follow-up visit were excluded from analysis of the refractive status changes of the emmetropes (dataset 3).

Investigative Ophthalmology & Visual Science

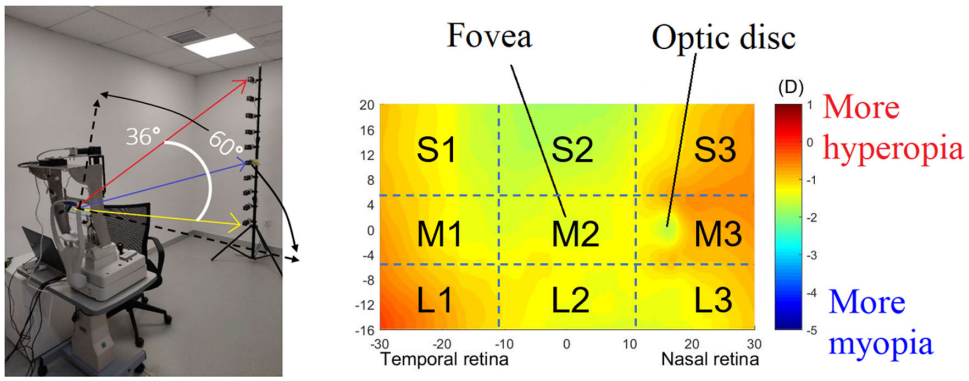

Figure 3. (**a**) Peripheral refractor with the arrangement of fixation targets in the vertical direction. Data covering a visual field of 60° × 35° were recorded. (**b**) Example of a 2D PR map. The origin of the coordinates corresponds to the fovea of the subject, and the optical nerve is approximately located 17° to the nasal side. The map is color coded, with *red* indicating greater hyperopia and *blue* indicating greater myopia.

Instruments and Procedure

The two-dimensional retinal refraction maps were measured with a custom open-view HS wavefront sensor (VPR; Voptica SL, Murcia, Spain). Details about the instrument and measurement procedures have been published elsewhere.[23,24] In brief, the instrument has a motorized optical arm that scans 60° of the horizontal visual field in steps of 1° in 1.3 seconds. For each measurement, four scans were necessary, and the mean was used to establish a refractive map. To measure refraction in the vertical direction, we set a series of fixation targets 2.5 meters away from the subjects. In total, 10 cross-shaped lighting targets, manually controlled by the operator, were placed in front of the subjects, with the top target corresponding to the superior 20° and the lowest one corresponding to the inferior 16°. The interval was 4° for adjacent targets. Thus, 2D refractive maps were retrieved from 10 horizontal scans, including 610 data collection points (resolution = 61 × 10). A spline-based interpolation was used to produce the final 2D maps. The refraction and higher-order aberrations were analyzed within the central 4-mm pupil area. Only the right eye was measured with the given device to avoid the problem of left–right mirror symmetry of aberrations; the left eye was occluded during the measure. Figure 3a shows a picture of the instrument, and an example of the obtained 2D PR maps is provided in Figure 3b.

In addition to PR, axial length (LENSTAR LS 900; Haag-Streit AG, Köniz, Switzerland), multimodal fundus imaging (DRI OCT Triton; Topcon Healthcare, Oakland, NJ, USA), intraocular pressure, and subjective refraction were obtained for each subject at each visit. All measurements were performed under paralyzed accommodation after instilling one drop of Alcaine (Alcon, Geneva, Switzerland) followed by two drops of 1% cyclopentolate (Alcon).

Visual Behavior Information

Visual behavior information was retrieved using a commercially available wearable device (Clouclip; Glasson Technology, Hangzhou, China).[25] The device was worn on the right arm of the glasses frame to record viewing distance (measurement range, 0–204 cm; frequency, 5 seconds per measure) and ambient light intensity (measurement range, 1–65,336 lux; frequency, 2 minuets per measure) along the line of sight. The recordings were performed over the course of 1 week (beginning at 8:30 AM on Monday and continuing to the next Monday). All participants were encouraged to wear the device for the entire day from the time they received the device, except while in the shower or sleeping. Pairs of glasses frames without lenses were assigned to the emmetropic subjects. The device is imbedded with a three-axis accelerometer (*x*-, *y*-, and *z*-axes). When a static condition was detected for more than 40 seconds, the Clouclip turned to "sleeping mode" and stopped recording until the angular speed changed again. The data collected between 7:00 AM and 20:00 PM were verified, and only the data with more than 80% availability were exported for analysis. The visual behavior of each subject was quantified with the following parameters: (1) the mean viewing distance in a week (mean distance), (2) the mean ambient light intensity in a week (mean lux), (3) the mean viewing distance for near work in a week (mean near distance, viewing distance less than 60 cm), (4) the mean duration of near-work activity (near-distance time), and (5) the average duration of exposure to more than 1000 lux (time over 1000 lux, equal to outdoor activities).

Data Analysis

We performed two different types of analyses: (1) all subjects and (2) only subjects who completed all visits. In the first case, based on the initial central refractive error, subjects were classified into three categories: hyperopes (SER $>$ 0.5 D), emmetropes (-0.5 D $\leq$ SER $\leq$ 0.5 D) and myopes (SER $<$ -0.5 D). For each group, subjects were further divided equally into three groups based on the change of central refraction over time, including those with slow progression (33.3% with the slowest myopia progression), moderate progression (33% with moderate myopia progression), and fast progression (33.3% with the fastest myopia progression).

To compare the differences in PR between each group, the 2D maps were divided into 3 × 3 regions, and the mean value in each zone was used for statistical analysis. The zones were labeled with S, M, or L to represent superior, middle, and lower parts of the map, respectively, followed by the number 1, 2, or 3 to indicate nasal, central, or temporal side of the map, respectively. The segmentation was based on two horizontal lines on the superior 5.5° and inferior

5.5° and two vertical lines on the nasal 10.5° and temporal 10.5°. The data points around the optic nerve head ($13.5 < x < 21.5$, $3.5 < y < 5.5$) were excluded.

All data are expressed as mean ± 1 SD or otherwise stated separately. Two-tailed *t*-tests were used to compare differences between the fast progress group and the moderate progress group. One-way ANOVA was used to compare the PR differences in the three progress groups. If the data did not fit a normal distribution, the Kruskal–Wallis test was used to compare the differences. The relationship between PR in each zone and myopic change, or the increase of axial length, was evaluated with Pearson correlation coefficient analysis, and *P* values were corrected using the false discovery rate method. The second analysis was limited to those subjects with two complete follow-up visits. Three categories based on refractive errors at each visit rather than the progression of central myopia at 1 year or 2 years were created. Category 1 (EM-EM-EM) included subjects that remained emmetropic during the whole period. Category 2 (EM-EM-MY) included subjects who were emmetropic at baseline and at the first follow-up but had developed myopia at the second follow-up. Category 3 (EM-MY-MY) included subjects who were emmetropic at baseline but had developed myopia at the first follow-up visit. Similar statistics were adopted for each visit for lateral comparisons of relative PR among three categories. The repeated-measures ANOVA test was used to evaluate the progression of relative peripheral refraction (RPR) at three longitudinal time points. Bonferroni correction was applied for post hoc comparisons in the repeated-measures ANOVA.

Results

2D PR Maps and Myopia Progression

The average 2D refraction maps for the different groups and measurement times are presented from baseline to the first-year visit in Figure 4a and from baseline to the second-year visit in Figure 4b. Supplementary Tables S1 to S4 present the statistical results for the different cases where the retinal maps were divided into nine regions. As expected, the hyperopic children, regardless of the levels of myopic shift during the observation period, had more relative hyperopic defocus in the central retina, with a distribution of refraction in the superior–nasal to inferior–temporal direction. No statistical difference in the average baseline refraction for each of the nine regions was found among the three progression groups. For emmetropic children, the average distribution patterns in all groups were quite like each other and similar to those of hyperopes but with less relative hyperopia in the whole map. The differences among the progression groups were larger in the superior retina; the PR means at 1 year in the superior retina in the slow-, moderate-, and fast-progression groups were −0.14 ± 0.41 D, −0.27 ± 0.35 D, and −0.44 ± 0.38 D, respectively ($P = 0.041$, ANOVA). The mean refraction in the central region

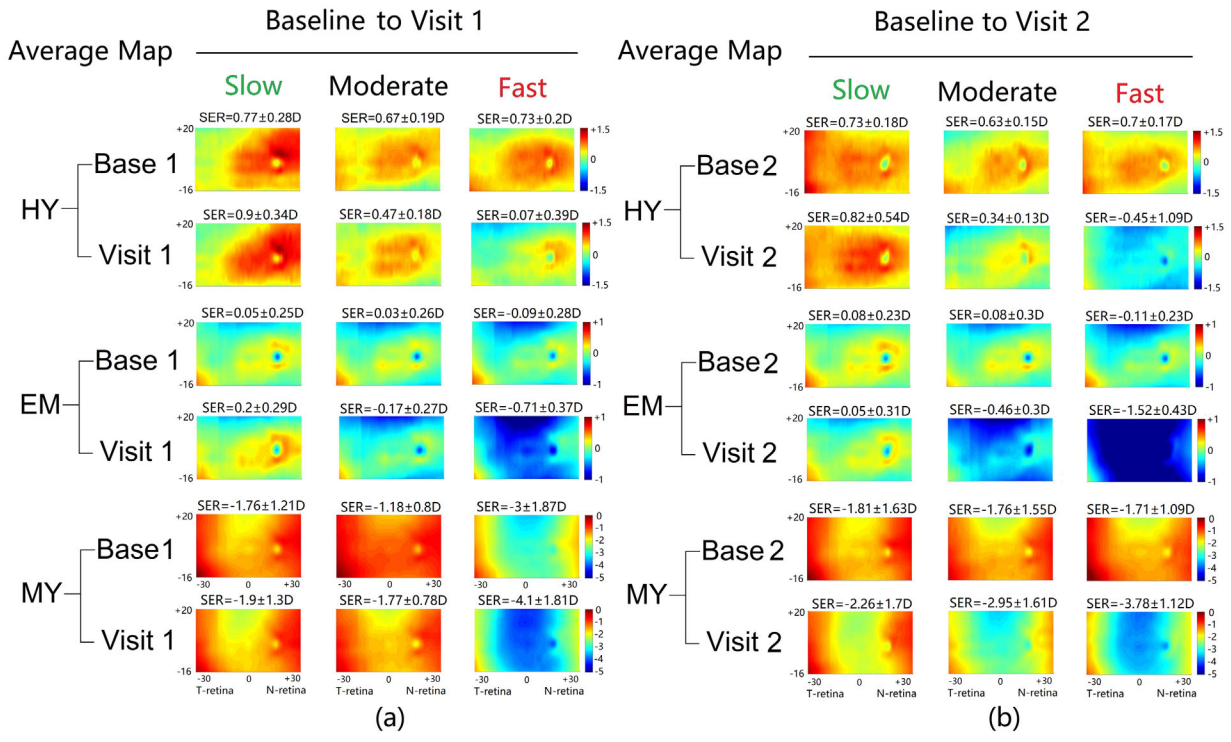

Figure 4. Average 2D PR maps for the different subgroups. (**a**) One-year visit. (**b**) Two-year visits. Subjects were classified into three refractive groups according to their initial refraction at baseline visit: HP (SER > +0.5 D), EM (−0.5 D ≤ SER ≤ 0.5 D), or MYO (SER < −0.5 D). At the first- and second-year visits (**b**), these groups were further divided based on their refractive changes into slight-, moderate-, and fast-progression groups. Spherical refraction values are color coded, with *red* indicating relatively hyperopia, *blue* indicating relative myopia, and *yellow–green* indicating zero defocus. Map coordinates on the *x*-axis show the horizontal meridian, with positive values being the nasal retina (temporal visual field) and negative values the temporal retina (nasal visual field). For the *y*-axis, positive values indicate the superior retina and negative values the inferior retina.

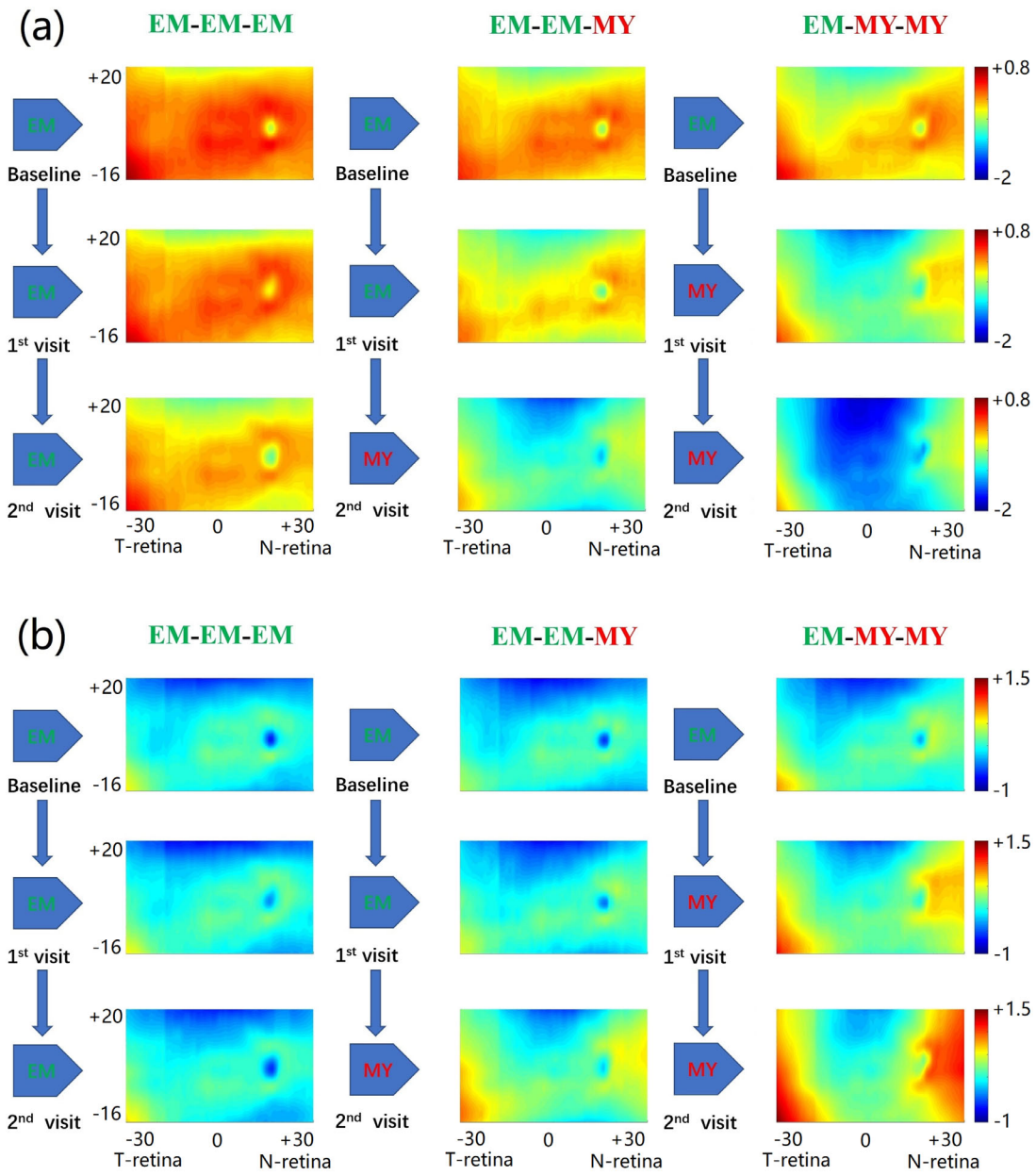

Figure 5. Average 2D PR maps, relative (**a**) and absolute (**b**), for emmetropic children from baseline to the second follow-up visit. Subjects were assigned to three categories based on the status of their central refractive error over the 2 years. Category 1 (EM-EM-EM) corresponds to the group that remained emmetropic during the entire period. Category 2 (EM-EM-MY) corresponds to the group that was emmetropic at baseline and at the first follow-up but had developed myopia by the second follow-up visit. Category 3 (EM-MY-MY) corresponds to the group that was emmetropic at baseline but had developed myopia by the first follow-up visit. Spherical equivalent refraction values are color coded, with *red* indicating relatively hyperopia, *blue* indicating relative myopia, and *yellow–green* indicating zero defocus. Map coordinates on the *x*-axis show the horizontal meridian, with positive values being the nasal retina (temporal visual field) and negative values the temporal retina (nasal visual field). For the *y*-axis, positive value indicate the superior retina and negative value indicate the inferior retina.

of the fast-progression group was slightly but significantly more myopic than in both the moderate- and the slow-progression groups; the PR means in the central region in the slow-, moderate-, and fast-progression groups were 0.13 ± 0.23 D, 0.1 ± 0.27 D, and −0.04 ± 0.27 D, respectively ($P = 0.046$, ANOVA). The same trend was found in the central location; the refraction means for the slow-, moderate-, and fast-progression groups were 0.05 ± 0.25 D, 0.03 ± 0.26 D, and −0.09 ± 0.28 D, respectively ($P = 0.043$, ANOVA). A significant correlation between PR and myopia progression was found in the middle column of the regions in emmetropes. The correlation was gradually weakened from the superior region to the inferior region (r values for refraction changes at the first-year visit were 0.308, 0.256, and 0.243 for the superior, central, and inferior regions, respectively; r values for axial length change at the first-year visit were −0.385, −0.379, and −0.31 for the superior, central, and inferior regions, respectively). In the group of myopic children, PR had the tendency to become more relatively hyperopic in the peripheral retina in the horizontal meridian (for this study, the averaged relative peripheral hyperopia for 30° eccentricity was less than 2 D), in both

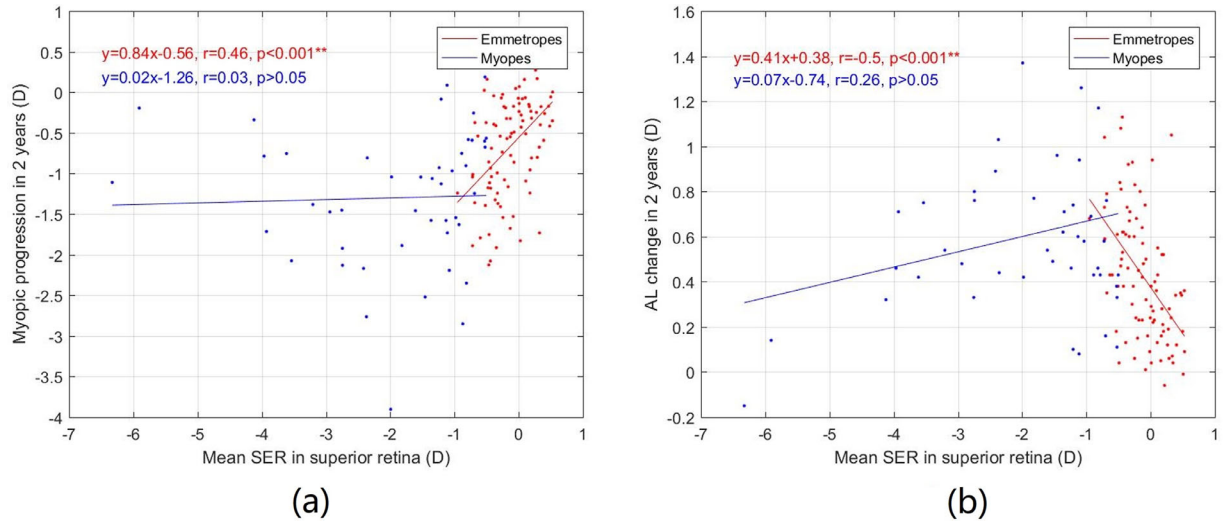

Figure 6. Correlation analysis for refraction in the superior retina and myopia progression in 2 years. (**a**) The change of central refraction as a function of superior SER over the 2 years. (**b**) The change of axial length as a function of superior SER over the 2 years. The superior refraction was calculated as the average from a representative region: ($-3 \leq x \leq 3$) and ($8 \leq y \leq 12$), for a total of 35 data points. Data from emmetropes and myopes are presented as *red* and *blue* dots, respectively, and as the corresponding fit line. The data for hyperopes were excluded from the figures due to the limited sample size.

the superior and inferior regions. For the 1-year visit, the fast-progression group had significantly more myopia in the central retina compared to the slow-progression group and the moderate group; for the 1-year study, central refractions in the slow, moderate, and fast groups were -1.76 ± 1.21 D, -1.18 ± 0.8 D, and -3 ± 1.87 D, respectively ($\chi^2 = 14.996$, $P < 0.001$). Nevertheless, in the 2-year study, no significant differences were found for central refraction; central refractions in the slow, moderate, and fast groups were -1.81 ± 1.63 D, -1.76 ± 1.55 D, and -1.71 ± 1.09 D, respectively ($F = 0.019$, $P = 0.981$). The refraction means in all subdivided regions were significantly correlated with central myopic progression.

Figure 5a shows the evolution of RPR in the subjects who completed all of the measurements over the 2 years. Those subjects were divided into three categories: category 1, those who remained emmetropes over the 2 years (EM-EM-EM); category 2, those who had become myopes at year 2 (EM-EM-MY); and category 3, those who had already become myopes at 1 year (EM-MY-MY). At baseline, although all three groups were emmetropes, there was a minor, but significant, difference in central refractive error ($F = 22.266$, $P < 0.001$). On average, category 3 (EM-MY-MY) was 0.43 D more myopic than category 1 (EM-EM-EM) and 0.25 D more myopic than category 2 (EM-EM-MY). Two-dimensional maps at baseline for category 3 show greater relatively hyperopic defocus than category 1 in regions S1, S3, M1, M3, L1, L2, and L3 (two-tailed *t*-test), but no difference was found among the three categories in all peripheral regions. At the first follow-up visit, similar two-tailed *t*-test results were found when comparing category 1 with category 3. One-way ANOVA found significant differences in S3, M1, M3, L1, and L3 among the three groups. At the second follow-up visit, all peripheral regions, except for S2, showed significant differences among the categories. Figure 5b shows the 2D maps for absolute PR for the three categories at baseline and at the first- and second-year visits. The effect of myopia progression in the 2D maps can first be observed in the superior retina and slightly close to the temporal direction. This progression continued to the central–vertical regions. Figure 5 shows a remarkable temporal evolution of PR through myopia progress and its effects were gradually extended to central retina. Supplementary Tables S5, S6, S7, and S8 presents the results for relative PR and absolute PR. In addition, a two-tailed *t*-test was conducted to compare RPR for the stage prior to the first follow-up in category 2 versus baseline in category 3, as well as after the onset of myopia at the second follow-up in category 2 versus the first follow-up in category 3, but no significant differences were found between the groups.

Local Retinal Values of PR and Myopia Progression

Supplementary Table S1 shows a statistical analysis of the PR values for each group and retinal areas for the 1-year study, and Supplementary Table S2 shows the correlations between the local values of PR and myopia progression for the 1-year study. Supplementary Tables S3 and S4 present the same results for the 2-year study. Figure 6 shows the correlation between the mean PR values in the region that includes the superior 8°, superior 12°, nasal 3°, and temporal 3° and central myopia progression (Fig. 6a) and axial length change (Fig. 6b) over 2 years. In the emmetropic group (Fig. 6, red symbols), children with more peripheral myopia in the superior retina had greater myopia progression. At the 2-year follow-up, superior defocus could explain 21.2% of the myopic change ($r = 0.46$, $P < 0.001$) or 25% of the axial elongation ($r = 0.5$, $P < 0.001$).

Analysis of Confounding Factors

An analysis of possible confounding factors related to visual behavior or heritability was also carried out. The main results are presented in Supplementary Table S9. We did not find any differences in the hyperopic group at the 1-year study baseline in any of the biological parameters (age, gender, height, central refraction, axial length), visual behaviors, or number of myopic parents. For the group of emmetropic

children, we found statistical differences in their baseline age and baseline central refraction, but they were not significant (mean difference in age, ~0.5 years; mean difference in base refraction, 0.1 D). The mean value for viewing distance over a 1-week period in the fast-progression group was significantly longer than in the slow-progression and moderate-progression groups (59.62 ± 32.74 cm, 58.27 ± 30.96 cm, and 77.21 ± 25.5 cm for the slow-, moderate-, and fast-progression groups, respectively; $F = 4.753$, $P < 0.01$). The same trend was found in the mean value of near viewing distance (16.19 ± 8.86 cm, 15.02 ± 8.91 cm, and 19.94 ± 6.66 cm for the slow-, moderate-, and fast-progression groups, respectively; $F = 3.723$, $P < 0.05$). For the group of myopes, the baseline axial length in the fast-progression group was significantly longer than in the slow- and moderate-progression groups (axial lengths for the slow-, moderate-, and fast-progression groups were 23.72 ± 0.81, 23.49 ± 0.7, and 24.62 ± 0.93, respectively; $F = 13.712$, $P < 0.001$).

Discussion

Relative Peripheral Defocus

This was a longitudinal study investigating the evolution of 2D PR in children during the critical age of myopia progression. We found that the baseline peripheral defocus in the whole central vertical field was positively related with myopic shift and negatively related with an increase in axial length in the group of emmetropic children. This finding was pronounced for the superior retina, where greater myopia was associated with greater myopic shift. This result is relevant after considering that the potential confounding factors analyzed were not significantly different among the groups with differing levels of refractive change.

The 2D relative PR patterns were similar in emmetropes and hyperopes. The baseline refractive patterns in the myopic group were similar for the three different progression subgroups. Myopic subjects had relative peripheral hyperopia in nasal and temporal retina beyond 15° of eccentricity (Fig. 4b, maps for MY–Base2). An interesting finding was that the 2D maps were not radially symmetrical across the retina, especially in the emmetropes. This asymmetric feature was closely related with refractive error status and central myopia progression over the 2 years of the study. Our findings are consistent with those of previous studies reporting that asymmetries were observed in horizontal and vertical meridians,[26–30] usually with greater myopic refraction in the superior retina. At least one two-dimensional study (42° × 32° visual field, 38 fixation targets) has found considerable superior–inferior asymmetry in hyperopes (age around 29 years) but not in emmetropes.[28] This asymmetry could be attributed to differences in ages and ethnicities among studies. In any case, those findings suggest that ocular dimensions do not change equally across the retina, and, as a consequence, commonly performed measurements across the horizontal meridian or vertical meridian to represent the overall PR are not sufficient.

To maintain comparable experimental conditions among different studies, it has been suggested that subjects who are emmetropes should have no optical intervention but the central refraction in both myopes and hyperopes should be corrected. For this reason, in this study we provided free single-vision glasses for the myopic children, and they underwent eye exams every 6 months to maintain good visual acuity.

A careful statistical analysis of the local PR values did not show any relationship with myopia progression in the groups of both hyperopes and myopes (see Supplementary Tables S2 and S4). However, in the emmetropic group, we found that children with greater relative peripheral myopia in the superior retina had greater myopia progression. This was indeed a surprising result, as it appears to be contrary to previous findings in animal studies or clinical trials using optical interventions based on the assumption that larger relative peripheral myopia should be related with less myopia progression.

Relative Myopia in the Superior Retina as a Cause of Myopia?

One assumption would be that, among children who are initially emmetropic, having a superior retina with greater relative myopia is a precursor of myopia development. In our study, the average difference between the children with fast and slow myopia progression was around 0.3 D ($P = 0.017$). Although this value would induce a modest blur in the retinal image, it could be sufficient to stimulate axial length growth. Thus, keeping the peripheral retina emmetropic might be the best option to prevent central myopia in emmetropes due to the different reaction mechanisms for retinal defocus among emmetropes and myopes. For example, it was recently found that the ability to detect defocus in emmetropic eyes differs from that in myopes.[31]

Another possibility is that school-aged Chinese children spend more time on near-work tasks in indoor environments than they do on outdoor activities.[32] Near-work tasks such as reading usually require the eye to look down, which would result in greater relative peripheral myopia in the inferior retina as the convergence of light from the ceiling or the sky would be close to 0 D. By comparison, the superior retina would be much more relatively hyperopic, as near tasks usually take place at around 16 to 20 cm (the average of viewing distance for near-work tasks recorded in the present study) and produce accommodative stimuli of approximately 5 D. If there is a lag of accommodation in emmetropic eyes, the peripheral hyperopia would be dominant in the superior retina and perhaps accelerate the local extension. Such a local response to defocus in the periphery has been demonstrated in animal studies.[33,34] In addition, children with early-onset myopia present a greater accommodative variability than emmetropic children.[35] Gwiazda et al.[36] found that a sustained accommodative lag of only 0.5 D might be sufficient to promote myopia in emmetropes.

Relative Myopia in the Superior Retina as a Consequence of Myopia?

Another possible explanation of our results would be to consider the relative myopia in the superior retina as a consequence of ocular growth during myopia development. The development of myopia may occur first in the superior retina when children begin myopization and would gradually grow and expand to the posterior eyeball followed by the nasal or temporal regions. This process would be determined by genetics, not defocus from the visual environment. Supporting evidence is that the change of ocular shape is more prominent in height than in width when emmetropes

first become myopes.[37] Other evidence could be inferred from our previous study on the four most common types of peripheral refractive patterns among 82 emmetropic children.[23] In our previous study, the fast-progression group was most closely similar to category 2 of this study (bilateral hyperopia pattern, accounting for 14% of all subjects).

Conclusions

The main strength of this study is that we carried out a longitudinal evaluation of the PR in the 2D field with high-resolution sampling. We also investigated other possible confounding factors that may affect the results, but found no significant effects. The homogeneous genetics and growth environment of the study group make our findings comparable among the various progression groups. We found that emmetropic children with greater relative myopia in the superior retina may experience faster central myopia progression; however, no particular PR maps were found to have an impact on myopic shifts for those subjects who were still hyperopes or already myopes. This myopic defocus in the superior retina around 10° was therefore a predictor of myopia development. These results could be used in future devices to keep the superior retina relatively emmetropic to prevent myopia in children.

Acknowledgments

Supported by grants from the Key Research and Development Project of Science & Technology Department of Hunan Province (2019SK2051); Key Research and Development Project of Science & Technology, Ministry of Science and Technology, China (2022YFE0124600); Aier Eye Hospital Group (AR1903D2); and Agencia Estatal de Investigación, Spain (PID2019-105684RB-I00/AEI/10.13039/501100011033).

Disclosure: **Z. Lin**, None; **X. Xi**, None; **L. Wen**, None; **Z. Luo**, None; **P. Artal**, None; **Z. Yang**, None; **W. Lan**, None

References

1. Sun J, Zhou J, Zhao P, et al. High prevalence of myopia and high myopia in 5060 Chinese university students in Shanghai. *Invest Ophthalmol Vis Sci*. 2012;53(12):7504–7509.
2. Mirshahi A, Ponto KA, Hoehn R, et al. Myopia and level of education: Results from the Gutenberg Health Study. *Ophthalmology*. 2014;121(10):2047–2052.
3. Wildsoet CF, Chia A, Cho P, et al. IMI – Interventions Myopia Institute: Interventions for controlling myopia onset and progression report. *Invest Ophthalmol Vis Sci*. 2019;60(3):M106–M131.
4. Pusti D, Benito A, Madrid-Valero JJ, Ordoñana JR, Artal P. Inheritance of refractive error in millennials. *Sci Rep*. 2020;10(1):8173.
5. Jiang BC, White JM. Effect of accommodative adaptation on static and dynamic accommodation in emmetropia and late-onset myopia. *Optom Vis Sci*. 1999;76(5):295–302.
6. Saw SM. A synopsis of the prevalence rates and environmental risk factors for myopia. *Clin Exp Optom*. 2003;86(5):289–294.
7. Norton TT, Siegwart JT. Light levels, refractive development, and myopia – A speculative review. *Exp Eye Res*. 2013;114:48–57.
8. Mutti DO, Mitchell GL, Hayes JR, et al. Accommodative lag before and after the onset of myopia. *Invest Ophthalmol Vis Sci*. 2006;47(3):837–846.
9. Gwiazda JE, Hyman L, Norton TT, et al. Accommodation and related risk factors associated with myopia progression and their interaction with treatment in COMET children. *Invest Ophthalmol Vis Sci*. 2004;45(7):2143–2151.
10. Wolffsohn JS, Flitcroft DI, Gifford KL, et al. IMI – Myopia control reports overview and introduction. *Invest Ophthalmol Vis Sci*. 2019;60(3):M1–M19.
11. Maddock RJ, Millodot M, Leat S, Johnson CA. Accommodation responses and refractive error. *Invest Ophthalmol Vis Sci*. 1981;20(3):387–391.
12. Ding C, Chen Y, Li X, Huang Y, Chen H, Bao J. The associations of accommodation and aberrations in myopia control with orthokeratology. *Ophthalmic Physiol Opt*. 2022;42(2):327–334.
13. Weizhong L, Zhikuan Y, Wen L, Xiang C, Jian G. A longitudinal study on the relationship between myopia development and near accommodation lag in myopic children. *Ophthalmic Physiol Opt*. 2008;28(1):57–61.
14. Pope JM, Verkicharla PK, Sepehrband F, Suheimat M, Schmid KL, Atchison DA. Three-dimensional MRI study of the relationship between eye dimensions, retinal shape and myopia. *Biomed Opt Express*. 2017;8(5):2386–2395.
15. Atchison DA, Pritchard N, Schmid KL, Scott DH, Jones CE, Pope JM. Shape of the retinal surface in emmetropia and myopia. *Invest Ophthalmol Vis Sci*. 2005;46(8):2698–2707.
16. Atchison DA. The possible role of peripheral refraction in development of myopia. *Optom Vis Sci*. 2016;93(9):1042–1044.
17. Atchison DA, Li SM, Li H, et al. Relative peripheral hyperopia does not predict development and progression of myopia in children. *Invest Ophthalmol Vis Sci*. 2015;56(10):6162–6170.
18. Rotolo M, Montani G, Martin R. Myopia onset and role of peripheral refraction. *Clin Optom (Auckl)*. 2017;9:105–111.
19. Hartwig A, Charman WN, Radhakrishnan H. Baseline peripheral refractive error and changes in axial refraction during one year in a young adult population. *J Optom*. 2016;9(1):32–39.
20. Mutti DO, Hayes JR, Mitchell GL, et al. Refractive error, axial length, and relative peripheral refractive error before and after the onset of myopia. *Invest Ophthalmol Vis Sci*. 2007;48(6):2510–2519.
21. Mutti DO, Sinnott LT, Mitchell GL, et al. Relative peripheral refractive error and the risk of onset and progression of myopia in children. *Invest Ophthalmol Vis Sci*. 2011;52(1):199–205.
22. Prieto PM, Vargas-Martín F, Goelz S, Artal P. Analysis of the performance of the Hartmann-Shack sensor in the human eye. *J Opt Soc Am A Opt Image Sci Vis*. 2000;17(8):1388–1398.
23. Lan W, Lin Z, Yang Z, Artal P. Two-dimensional peripheral refraction and retinal image quality in emmetropic children. *Sci Rep*. 2019;9(1):16203.
24. Jaeken B, Lundström L, Artal P. Fast scanning peripheral wave-front sensor for the human eye. *Opt Express*. 2011;19(8):7903–7913.
25. Li L, Wen L, Lan W, Zhu H, Yang Z. A novel approach to quantify environmental risk factors of myopia: Combination of wearable devices and big data science. *Transl Vis Sci Technol*. 2020;9(13):17.
26. Chen X, Sankaridurg P, Donovan L, et al. Characteristics of peripheral refractive errors of myopic and non-myopic Chinese eyes. *Vision Res*. 2010;50(1):31–35.
27. Atchison DA, Pritchard N, Schmid KL. Peripheral refraction along the horizontal and vertical visual fields in myopia. *Vision Res*. 2006;46(8-9):1450–1458.
28. Osuagwu UL, Suheimat M, Atchison DA. Peripheral aberrations in adult hyperopes, emmetropes and myopes. *Ophthalmic Physiol Opt*. 2017;37(2):151–159.
29. Ehsaei A, Mallen EA, Chisholm CM, Pacey IE. Cross-sectional sample of peripheral refraction in four meridians

in myopes and emmetropes. *Invest Ophthalmol Vis Sci*. 2011;52(10):7574–7585.

30. Seidemann A, Schaeffel F, Guirao A, Lopez-Gil N, Artal P. Peripheral refractive errors in myopic, emmetropic, and hyperopic young subjects. *J Opt Soc Am A Opt Image Sci Vis*. 2002;19(12):2363–2373.
31. Swiatczak B, Schaeffel F. Emmetropic, but not myopic human eyes distinguish positive defocus from calculated blur. *Invest Ophthalmol Vis Sci*. 2021;62(3):14.
32. Wen L, Cao Y, Cheng Q, et al. Objectively measured near work, outdoor exposure and myopia in children. *Br J Ophthalmol*. 2020;104(11):1542–1547.
33. Smith EL, Huang J, Hung LF, Blasdel TL, Humbird TL, Bockhorst KH. Hemiretinal form deprivation: Evidence for local control of eye growth and refractive development in infant monkeys. *Invest Ophthalmol Vis Sci*. 2009;50(11):5057–5069.
34. Wallman J, Gottlieb MD, Rajaram V, Fugate-Wentzek LA. Local retinal regions control local eye growth and myopia. *Science*. 1987;237(4810):73–77.
35. Langaas T, Riddell PM, Svarverud E, Ystenaes AE, Langeggen I, Bruenech JR. Variability of the accommodation response in early onset myopia. *Optom Vis Sci*. 2008;85(1):37–48.
36. Gwiazda J, Thorn F, Held R. Accommodation, accommodative convergence, and response AC/A ratios before and at the onset of myopia in children. *Optom Vis Sci*. 2005;82(4):273–278.
37. Atchison DA, Jones CE, Schmid KL, et al. Eye shape in emmetropia and myopia. *Invest Ophthalmol Vis Sci*. 2004;45(10):3380–3386.

Investigative Ophthalmology & Visual Science