Relative Peripheral Hyperopia Does Not Predict Development and Progression of Myopia in Children

David A. Atchison,1,2 Shi-Ming Li,1 He Li,3 Si-Yuan Li,1 Luo-Ru Liu,3 Meng-Tian Kang,1 Bo Meng,4 Yun-Yun Sun,1 Si-Yan Zhan,4 Paul Mitchell,5 and Ningli Wang1

1Beijing Tongren Eye Center, Beijing Tongren Hospital, Beijing Ophthalmology & Visual Science Key Lab, Beijing Institute of Ophthalmology, Capital Medical University, Beijing, China
2School of Optometry & Vision Science and Institute of Health & Biomedical Innovation, Queensland University of Technology, Kelvin Grove Q, Australia
3Anyang Eye Hospital, Henan Province, China
4Department of Epidemiology and Health Statistics, Peking University School of Public Health, Beijing, China
5Centre for Vision Research, Department of Ophthalmology and Westmead Millennium Institute, University of Sydney, Sydney, Australia

Correspondence: Ningli Wang, Beijing Tongren Eye Center, Beijing Tongren Hospital, Beijing Ophthalmology & Visual Science Key Lab, Beijing Institute of Ophthalmology, Capital Medical University, Beijing, China 100730; wningli@vip.163.com.

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PURPOSE. To test the hypothesis that relative peripheral hyperopia predicts development and progression of myopia.

METHODS. Refraction along the horizontal visual field was measured under cycloplegia at visual field angles of 0°, ±15°, and ±30° at baseline, 1 and 2 years in over 1700 initially 7-year-old Chinese children, and at baseline and 1 year in over 1000 initially 14-year olds. One refraction classification for central refraction was “nonmyopia, myopia” (nM, M), consisting of nM greater than −0.50 diopters (D; spherical equivalent) and M less than or equal to −0.50 D. A second classification was “hyperopia, emmetropia, low myopia, and moderate/high myopia” (H, E, LM, MM) with H greater than or equal to +1.00 D, E, −0.49 to +0.99 D, LM, −2.99 to −0.50 D, and MM less than or equal to −3.00 D. Subclassifications were made on the basis of development and progression of myopia over the 2 years. Changes in central refraction over time were determined for different subgroups, and relative peripheral refraction over time was compared between different subgroups.

RESULTS. Simple linear regression of central refraction as a function of relative peripheral refraction did not predict myopia progression as relative peripheral refraction became more hyperopic: relative peripheral hyperopia and relative peripheral myopia predicted significant myopia progression for 0% and 35% of group/visual field angle combinations, respectively. Subgroups who developed myopia did not have more initial relative peripheral hyperopia than subgroups who did not develop myopia.

CONCLUSIONS. Relative peripheral hyperopia does not predict development nor progression of myopia in children. This calls into question the efficacy of treatments that aim to slow progression of myopia in children by “treating” relative peripheral hyperopia.

Keywords: Chinese children, myopia progression, peripheral refraction, relative peripheral hyperopia

In the early 1970s, Rempt, Hoogerheide, and Hoogenboom1 recognized five patterns of peripheral refraction across the horizontal visual field. The type IV pattern was the typical pattern in emmetropes and hypermetropes, with light refracted in the vertical pupil meridian showing a hyperopic shift into the periphery and light refracted in the horizontal pupil meridian showing a considerable myopic shift. The type I pattern was typically found in myopes, with light refracted in both pupil meridians showing hyperopic shifts into the periphery. Another way of considering this is that there was a change from a relative peripheral myopia (mean refraction in the periphery is myopic relative to the central refraction) in emmetropes and hypermetropes, to a relative peripheral hyperopia in myopes. Many cross-sectional studies since have supported this trend, at least for the horizontal visual field.2–6

Hoogerheide et al.7 claimed that peripheral refraction pattern influences the development of myopia, with people with type I more likely to develop myopia than those with type IV. This study was largely forgotten for 30 years, when the idea of peripheral refraction driving myopia rearose, along with the possibility of preventing or slowing myopia progression by manipulating the pattern in susceptible people.8–11

It has been believed widely that the Hoogerheide et al.7 peripheral refractions were taken at the time of the baseline eye examination. However, Rosén et al.12 reasoned that the peripheral refractions were taken at a later examination, after myopia did or did not occur, and that the refraction data from the baseline examination were retrieved from medical archives. Thus, the Hoogerheide et al.7 study does not provide evidence that relative peripheral hyperopia predicts the development of myopia.
However, there is evidence of peripheral refraction’s role in myopia development. The Smith13 work with monkeys indicates that peripheral retina is important to emmetropization and myopia development. If the central retina is blocked or ablated by a laser, young monkeys can still emmetropize,14 but if there is interference with the peripheral retina, myopia can result,15–17 for example, partial occlusion at the front of the eye leads to elongation in the corresponding part of the retina17 and lens-induced relative peripheral hyperopia produces central myopia.16 There have been clinical studies with spectacle lenses,18 contact lenses,19,20 and orthokeratology,21–26 that treat relative peripheral hyperopia, with limited success in slowing myopia progression.18,19 It is possible that any success may be due to other mechanisms.

The opposing view to the peripheral refraction pattern driving myopia development and progression is that the peripheral refraction pattern is a merely an accompaniment, rather than a cause, of myopia. The Charman and Jennings27 modeling showed that elongating an emmetropic eye to produce myopia, without changing equatorial size nor any other optics, changes the refraction pattern. Refraction must remain the same at the equator in such a model regardless of the axial refraction, so a peripheral myopic pattern for an emmetrope eventually becomes a relative hyperopic refraction pattern for some degree of myopia. While myopic eyes are bigger overall than emmetropic eyes in adults, this model appears to be reasonable for the horizontal meridian of the retina in which the additional growth is limited.28

Mutti et al.29 found that relative peripheral hyperopia measured at 30° nasal visual field in 9-year-old children had little consistent influence on risk of myopia onset within the following 5 years. Sng et al.30 conducted a longitudinal study of peripheral refraction in 187 7-year-old Singaporean Chinese children. A group of emmetropic children who did not become myopic had peripheral myopia at both a baseline visit and at a follow-up visit approximately 15 months later, whereas the group of emmetropic children who became myopic also had peripheral myopia at baseline, but by follow-up had developed relative peripheral hyperopia. Lee and Cho31 conducted a similar study in 58 6- to 9-year-old Chinese children with a baseline visit and follow-up visits at 6 and 12 months, and also found that baseline relative peripheral refraction did not correlate significantly with myopic shift.

To summarize the above, there is strong animal evidence that the peripheral retina, including its refractive status, is important to driving myopia development and this is backed weakly by peripheral “antimyopia” clinical studies, while longitudinal studies of peripheral refraction indicate that peripheral refraction is not predictive of the development of myopia. Following on from Sng et al.30 and Lee and Cho,31 we investigate this further with a large scale longitudinal study of peripheral refraction in Chinese children. The hypothesis to be

<table>
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<th>Classification Type</th>
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<th>No. of 7 Year Olds</th>
<th>Subclassification Older Children</th>
<th>No. of 14 Year Olds</th>
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<td>Nonmyopic, myopic</td>
<td>nM0- nM1- nM2</td>
<td>972 (52.7%)</td>
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<td>107 (10.5%)</td>
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<td>215 (11.7%)</td>
<td>M0-M1</td>
<td>855 (83.5%)</td>
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<td>185 (9.9%)</td>
<td>M0-M1</td>
<td>56 (5.5%)</td>
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<tr>
<td></td>
<td>Missed 2-year</td>
<td>164 (8.9%)</td>
<td>M0-M1</td>
<td>855 (83.5%)</td>
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<td>Other groups*</td>
<td>37 (2.0%)</td>
<td>Other groups*</td>
<td>6 (0.6%)</td>
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<tr>
<td></td>
<td>Total</td>
<td>1845</td>
<td>Total</td>
<td>1024</td>
</tr>
<tr>
<td>H, E, LM, MM</td>
<td>H0-H1</td>
<td>288 (15.6%)</td>
<td>H0-H1</td>
<td>10 (1.0%)</td>
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<tr>
<td></td>
<td>H0-E1</td>
<td>298 (16.2%)</td>
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<td>11 (1.1%)</td>
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<td>E0-E1</td>
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<td>45 (2.3%)</td>
<td>Other groups*†</td>
<td>19 (1.9%)</td>
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<td>Total</td>
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<td>Total</td>
<td>1024</td>
</tr>
<tr>
<td>H1-H2</td>
<td>135 (7.3%)</td>
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<td>138 (7.5%)</td>
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<td>696 (37.7%)</td>
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<td>E1-LM1</td>
<td>275 (14.9%)</td>
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<td>LM1-LM2</td>
<td>308 (16.2%)</td>
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<tr>
<td>LM1-MM2</td>
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<td>MM1-MM2</td>
<td>22 (1.2%)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Missed 2-year</td>
<td>164 (8.9%)</td>
<td></td>
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</tr>
<tr>
<td>Other groups†</td>
<td>39 (2.1%)</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Total</td>
<td>1845</td>
<td></td>
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</tbody>
</table>

* “Regressed” to a less myopic/more hyperopic group between visits (young: nM0-M1-nM2 19, M0-nM1-M2 9, M0-nM1-M2 6, M0-M1-M2 3; older M0-M1-M2 6).
† “Regressed” to a less myopic/more hyperopic group between visits (young: E0-H1 19, LM0-H1 2, LM0-E1 16; older: E0-H1 2, LM0-E1 6, MM0-LM1 10) or progressed by two refraction groups between visits (young: H0-LM1 6; older: H0-LM1 1).
‡ “Regressed” to a less myopic/more hyperopic group between visits (E1-H2 12, LM1-E2 22) or progressed by two refraction groups between visits (H1-LM2 5).
FIGURE 1. Change in central refraction between baseline and 1 year for the young children, who were not myopic at baseline, as a function of relative peripheral refraction at 30° temporal visual field angle. The regression fit is $y = 0.17x - 0.46$, $R^2 = 0.051$, $P < 0.001$. Lines are the regression fit and its 95% confidence limits.

**METHODS**

**Study Population**

The Anyang Childhood Eye Study (ACES) is measuring parameters in two cohorts of schoolchildren in Anyang urban areas, Henan Province, Central China in order to observe prevalence, incidence, and risk factors for myopia. Detailed methodology of the study has been described elsewhere. Briefly, 2893 7-year-old children and 2267 14-year-old children were examined at baseline. Ethics approval was obtained from the institutional review board of Beijing Tongren Hospital, Capital Medical University (Beijing, China), and followed the tenets of the declaration of Helsinki. Informed written consent was obtained from at least one parent. Verbal assent was obtained from each child.

At baseline, 2154 7-year-old children and 1780 14-year-old children had data of peripheral refraction. During the follow-up periods, some children were reluctant to use cycloplegia and were absent for peripheral refraction measurement. At 12 months there were 1845 young children (86%) and 1024 older children (60%) with peripheral refraction data, and at 24 months 1685 young children (79%) had peripheral refraction data.

**Measurement**

Peripheral refraction was performed with an open-field autorefractor (WAM5500; Grand Seiko, Hiroshima, Japan) on right eyes after cyclogpa was produced with 1 drop topical anesthetic agent (Alcaine; Alcon, Fort Worth, TX, USA), 2 drops 1% cyclopentolate and 1 drop tropicamide, administered at 5-minute intervals. Thirty minutes after the last drop, a third drop of cyclopentolate was administrated if pupillary light reflex was still present or pupil size was less than 6.0 mm. A horizontal arc of 35-cm radius with fixation targets at 0°, ±15°, and ±30° angles was attached to the instrument’s extension rod. Children were instructed to keep their heads stationary, occlude the left eye with their hand, and fixate the central target first and then nasal and temporal targets. Children who had ocular pathology or
who could not fixate the targets monocularly were excluded. Means of five measurements were recorded for each angle. Other details were given by Li et al.2

Classification

One refraction classification for central refraction was “nonmyopia, myopia” (nM, M), consisting of nM greater than –0.50 diopters (D; spherical equivalent) and M less than or equal to –0.50 D. A second classification was “hyperopia, emmetropia, low myopia, and moderate/high myopia” (H, E, LM, MM) with H greater than or equal to +1.00 D, E, –0.49 to +0.99 D, LM, –2.99 to –0.50 D, and MM less than or equal to –3.00 D (note that incorrect limits were given previously for hyperopia [> +1.00 D] and the upper limit of emmetropia [+1.00D]2). The two classification systems represented two different levels of complexity. The nM, M classification gave large numbers in each group, but did not give the finer distinctions as shown for the other classification, such as distinguishing between hyperopes and emmetropes or between magnitudes of myopia.

Subclassifications were made on the basis of development and progression of myopia over the 2 years. For the “nM, M” classification, the young children were divided into those who did not become myopic over 2 years (nM0–nM1–nM2), children who were nonmyopic at baseline and at 1 year but were myopic at 2 years (nM0–nM1–M2), children who were nonmyopic at baseline but were myopic at 1 year and 2 years (nM0–M1–M2), and children who remained myopic during the 2 years (M0–M1–M2).

The “H, E, LM, MM” subclassification for the young children included examples such as H0–H1–H2 and H0–E1–LM2, where subscripts 0, 1, and 2 again refer to baseline, 1 and 2 year visits, respectively. The large number of possible comparisons was reduced by considering only consecutive visits (e.g. H0–H1, H1–E2).

The older children were subclassified similarly as for the younger children, except that results were available only at baseline and at 1 year. The “nM, M” subclassification was thus restricted to nM0–nM1, nM0–M1 and M0–M1.

Statistics

Linear regressions were conducted at each visual field angle to determine whether relative peripheral refraction was a predictor of changes in central refraction after 1 and 2 years for various groups. The unpaired Student t-test was used to compare relative peripheral refraction of some subgroups who had the same refraction classification at a given time but who had different refraction classification at a later time: nM0–nM1–nM2 and nM0–nM1–M2 at baseline, nM0–nM1–nM2 and nM0–M1–M2 at baseline and 1 year, nM0–nM1–nM2 and nM0–M1–M2 at baseline, H0–H1 and H0–E1 at baseline, E0–E1 and LM0–LM1 at baseline, H1–H2 and H1–E2 at 1 year, and E1–E2 and E0–LM2 at 1 year. Statistical significance was set at 0.0125, incorporating a Bonferroni correction because there were four visual angles. In t-tests comparing groups, 98.75% confidence intervals (CI) were used rather than 95% CIs.

RESULTS

Table 1 shows classifications and subclassification of children, and includes the numbers in each subgroup. There were considerable differences in refraction distributions between the young and older children: the former were mainly...
hyperopic and emmetropic (85% at baseline), whereas the latter were mainly myopic (84% at baseline). There were only a few young moderate/high myopes (0.4% at baseline) and older hyperopes (2.1% at baseline), making statistical comparisons with these groups difficult.

Regression of Central Refraction Shift as a Function of Relative Peripheral Refraction

Table 2 shows results of linear regressions conducted at each visual field angle to determine whether relative peripheral refraction was a predictor of changes in central refraction after 1 and 2 years for various groups. Figure 1 gives the example for the young nonmyopic group (nM0) between baseline and 1 year for 30° temporal visual field angle. The correlation was low ($R^2 = 0.051$), but highly significant ($P < 0.001$) because of the large number of children. The hypothesis that relative peripheral hyperopia predicts myopic progression indicates a negative relationship should occur, but the relationship was in the opposite direction to this. There were several cases (40% and 25% for young and older children, respectively) with significant positive slopes for which $R^2$ values were between 0.013 and 0.150, but there was no example of a significant negative slope (Table 2).

Comparison of Relative Peripheral Refraction Between Different Subgroups

Figure 2 shows results for the young children for the “nonmyopia, myopia” classification, with the top row showing peripheral refraction at baseline, 1 and 2 years and the second row showing the corresponding relative peripheral refractions. Only the major subgroups are included, so the children who “regressed” between visits from the myopic group to the hyperopic group are omitted. The errors bars are 95% CIs of means. In many cases in this and the following figures, the error bars are too small to be distinguished. At baseline, the subgroups that were nonmyopic showed relative peripheral myopia, while the subgroup that was already myopic showed relative peripheral hyperopia at ±30° (bottom, left). The subgroup nM0-nM1-M2 that did not become myopic at any stage retained relative peripheral myopia, while as subgroups progressed they developed relative peripheral hyperopia: nM0-nM1-M2 at 1-year (bottom, middle) and nM0-nM1-M2 at 2-years (bottom, right). The M0-M1-M2 subgroup showed increasing relative peripheral hyperopia as its myopia increases from baseline to 1 year and then to 2 years.

Figure 3 shows results for the younger children with the “H, E, LM, MM, HM” classification, with the top row showing peripheral refrations of major subgroups at baseline and 1 year. Error bars are 95% confidence limits about means; some are too small to be distinguished. Only subgroups who were nonmyopic at baseline are included at bottom left; only subgroups who were nonmyopic at 1 year are included at bottom right. The asterisks indicate significant differences in relative peripheral refraction between subgroups H1-H2 and H1-E2 at 30° T and 30° N.
refraction for the subgroups that have hyperopia or emmetropia at these visits. All groups in the bottom row had relative peripheral myopia.

Figures 4 and 5 are the equivalents of Figure 1 and Figure 2 for the older children. As for the young children, with the nM0-nM1 classification the older subgroups that were nonmyopic at any particular visit showed relative peripheral myopia (Fig. 4, bottom, left and bottom, right) and the subgroup that was myopic at baseline showed relative peripheral hyperopia at 330° (Fig. 4, bottom, left). The group nM0-nM1 that did not become myopic at any stage retained relative peripheral myopia, while the group nM0-M1 that became myopic at 1-year developed relative peripheral hyperopia. The M0-M1 group showed increasing relative peripheral hyperopia as its myopia increased from baseline to 1 year. For the H, E, LM, MM classification scheme in Figure 5, all the subgroups shown in the bottom row, which had hyperopia or emmetropia at baseline, had either relative peripheral myopia or no relative peripheral hyperopia at baseline.

There were 6 of possible 44 cases in the figures where subgroups with the same refraction status (nonmyopia, H or E) at a particular time, but not at a later time, showed significances differences in relative peripheral refraction that suggest that relative peripheral hyperopia predicts development of myopia (asterisks in Figs. 2 and 3). These affected only the young children. The most obvious of these were nM0-nM1-nM2 versus nM0-M1-M2 at baseline at 30° N (Fig. 2 bottom, left, mean difference and 98.7% CI 0.25 ± 0.20 D) and H1-H2 versus H1-E2 at 30° T and 30° N (Fig. 2 bottom, right, 0.29 ± 0.24 D and 0.40 ± 0.20 D, respectively). For these significant comparisons, the mean central refractions of the subgroups were considerably different at the visit of interest, for example, the mean difference between the subgroups nM0-nM1-nM2 and nM0-M1-M2 was 1.1 D at baseline (Fig. 2, bottom, left). In order to reduce the central refraction variation between the subgroups, if the upper limit for central refraction at the first of the two corresponding visits is lowered to +1.63 D for nM0 or to +2.90 D for H1, the statistical significances disappear.

DISCUSSION

This study has tested the hypothesis that relative peripheral hyperopia predicts the development and progression of myopia. Figure 6 gives an idealized summary of our results. The left figure shows change in central refraction between two visits as a function of relative peripheral refraction at the first of the visits. The hypothesis implies that central refraction change should become more negative (more myopic) as relative peripheral refraction become more positive (more hyperopic), as is represented by the red thick dotted line. However, this did not occur in the study, and for over one-third of group/visual field combinations there were significant results in the opposite direction as represented by the thin black dotted line (also see Table 2 and Fig. 1). The right figure shows relative peripheral refraction of two subgroups who had nonmyopia initially. The subgroup that remained nonmyopia had relative peripheral refraction that was negative (i.e., it had relative peripheral myopia). The subgroup that developed myopia was predicted to have relative positive peripheral refraction (relative peripheral hyperopia) as represented by the thick red dotted line, but in fact had negative relative peripheral refraction, as represented by the thin black line, that was similar to that of the other subgroup (Figs. 2-5).

For the last decade, it has been widely accepted that a pattern of relative peripheral hyperopia refraction predicts...
development of myopia. However, in support of longitudinal studies of Sng et al.30 and Lee and Cho31 with smaller groups of Chinese children, this large scale longitudinal study with Chinese children along the horizontal visual field does not support this. This finding suggests that attempts to reduce rate of progression of myopia using ophthalmic lenses that induce relative peripheral myopia will not be successful.

We should note that Lee and Cho31 anticipated our findings. Their initially hyperopic, emmetropic and myopic groups were divided into slow and fast progressing subgroups. The emmetropic and myopic subgroups with the faster progressions showed less relative peripheral hyperopia than the subgroups with the slower progressions, although the differences were not significant.

The understanding that a pattern of relative peripheral hyperopia refraction predicts development of myopia arose from interpretation of the Hoogerheide et al.7 However, as mentioned in the Introduction, Rosén et al.12 argued that the Hoogerheide et al.7 study did not provide evidence for this:

1. Hoogerheide et al.7 did not state that peripheral refractions were measured before the changes in refraction were monitored;
2. If peripheral refractions were obtained at a baseline examination and given the likely rates of recruitment and successful completion of training, the study must have taken place during a period of 10 to 15 years. It is much more likely that Hoogerheide et al.7 measured peripheral refractions in a shorter time-period; and
3. Despite there being many more emmetropes and hyperopes in the Rempt et al.1 paper than there are in the following Hoogerheide et al.7 paper, the number of people in the type I and II “at risk” patterns was greater in the latter, which is consistent with the central refraction status being reported from an earlier time by Hoogerheide et al.7 than by Rempt et al.1

There are problems with why the peripheral optics might be relevant to progression of myopia. Firstly, resolution in the peripheral retina is poor and insensitive to refraction manipulation.32 If we disregard this, it is not reasonable to think that a hyperopic periphery might stimulate myopia by providing an “on-signal” to ocular growth. However, while relative peripheral hyperopia may be present along the
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horizontal visual field, it is not usually found along the much less tested vertical visual field, and no one has explained why the retina/visual system should ignore the vertical and possibly other fields concerning eye growth. There are also the aberrations of astigmatism and transverse chromatic aberrations that make the peripheral retinal image very blurred. Finally, if relative peripheral hyperopia were to promote development of myopia, this would cease to have an influence in the uncorrected state once central myopia have developed sufficiently so that the peripheral refraction was also myopic.

Our findings do not lead to the firm conclusion that the peripheral retina is irrelevant in development of central refraction. For example, the retinal shape may play a role (e.g. steep retinas may predispose to the progression of myopia). While it might be expected that there is a correlation between retinal shape and peripheral refraction, with a steeper/flatter retina corresponding to relative peripheral hyperopia/myopia, this has been little explored, with retinal shape (or overall eye shape) usually being inferred from the relative peripheral refraction or relative peripheral refraction being inferred from estimates of retinal shape.

Detailed description of peripheral refraction results at baseline has been given in our previous paper. This, along with our results here, are in line with other studies of peripheral refraction along the horizontal visual field that show a change from relative peripheral myopia, to hyperopia and emmetropia, to relative peripheral hyperopia in myopia, 3-5,8,57,58. This pattern is consistent across a range of ages, 4,5 showing more relative peripheral hyperopia and more central myopia.

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