Peripheral Refractive Changes Associated with Myopia Progression

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Purpose. To evaluate the changes in peripheral refraction profiles associated with myopia progression and treatment modalities used in the Cambridge Anti-Myopia Study.

Methods. One hundred and seventy-seven myopes in the age range of 14 to 22 years were enrolled in the study. The mean spherical equivalent refractive error was –3.12 ± 1.87 diopters (D) and the refractive error of each participant was corrected with contact lenses. The participants were randomly assigned to one of four treatment groups, which included: altered spherical aberration and vision training, altered spherical aberration only, vision training only, and control. Peripheral refractive error was measured using an open field autorefractor in the central 60° of the retina in 10° steps. The refractive error was measured using cycloplegic autorefraction. Two-year refractive progression data and initial peripheral refraction measurements were available in 113 participants. Measurements of peripheral refraction and cycloplegic refraction were obtained at three visits over 2 years in 12-month intervals for 92 participants.

Results. All subjects showed a relative peripheral hyperopia, especially in the nasal retina. A limited magnitude of myopia progression of –0.34 ± 0.36 D over 2 years was found in each of the four groups on average. There were no significant differences in the rate of progression between any of the treatment groups ($P > 0.05$). Initial peripheral J45 astigmatic refractive error at 20° and 30° in the nasal retina was weakly correlated with progression of myopia over 2 years ($r = -0.27$, $P = 0.004$ and $r = -0.20$, $P = 0.040$, respectively; $n = 113$). The change in spherical equivalent peripheral refractive error at 30° nasal retina over time was also significantly correlated with progression of myopia especially at 24 months ($r = -0.24$, $P = 0.017$, $n = 92$).

Conclusions. Relative peripheral hyperopia is associated with myopia. Myopia progression may be weakly linked to changes in the peripheral refraction profiles in the nasal retina. However, a causative link between peripheral refractive error and myopia progression could not be established. (*Invest Ophthalmol Vis Sci.* 2013;54:1573–1581) DOI:10.1167/iovs.12-10278

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Peripheral refractive error has been considered as a possible factor influencing myopia development and progression since the 1970s when Hoogerheide et al.[1] showed that individuals with certain types of peripheral refraction profiles were more likely to develop myopia than others. Several subsequent studies have found characteristic differences in peripheral refraction between different refractive groups (see Charman and Radhakrishnan[2] for a review).

Millodot[3] showed that myopic subjects exhibited a relative hyperopic refractive error in the peripheral retina, whereas emmetropes tended to have a relative peripheral myopic refractive error. Similar results have been shown by several other studies.[4–7] Calver et al.[8] and Mathur et al.[9] studied the changes in peripheral refraction with accommodation in myopes and emmetropes and found no strong differences between refractive groups. Both the studies showed no significant changes in relative peripheral refractive error (RPRE) with accommodation in myopes and emmetropes. These characteristic peripheral refraction profiles in myopes and emmetropes might merely be associated with the refractive error rather than playing a causative role in refractive changes.

Animal studies have provided evidence for the hypothesis that eye growth can be regulated by different local regions of the retina, rather than just by foveal vision.[10–13] More recently, studies on infant monkeys suggest that the peripheral retina can play an important role in modulating overall eye growth.[14–19] In contrast, Schippert and Schaeffel[20] found that chicks reared with lenses having clear central apertures remained emmetropic, showing no evidence of failure of emmetropization when peripheral refraction was artificially changed. It may be that these apparently conflicting results reflect interspecies differences—in particular, visual resolution declines much more rapidly with field angle in primates than in birds.[21] The differences between the studies could also arise from the variations in the extent of visual field restriction caused by pinholes in the studies.

Following the study of Hoogerheide et al.[1] on late onset myopes, Mutti et al.[22] studied approximately 1000 children between the ages of 6 and 14 years measuring RPRE at 30° temporal retina and the axial refraction. They found that children who became myopic had more hyperopic relative peripheral refractive errors than did emmetropes from 2 years before onset through 5 years after onset of myopia. However, peripheral refraction at 30° temporal retina did not change significantly in the postmyopia onset visits. This study shows a potential link between peripheral refractive error and myopia development. The peripheral refraction profiles across the

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retina were not assessed in this study. Therefore, changes in peripheral refraction profiles associated with myopia development and progression still remain unclear. In a further study, Mutti et al.[23] studied peripheral refraction at 30° temporal retina in 2043 nonmyopic children and followed up 774 children for a period of 1 to 8 years. They found that relative peripheral refraction does not have a consistent effect on the risk of myopia onset. Sng et al.[24] studied peripheral refraction up to 30° eccentricity in the nasal and the temporal retina at 15° intervals in 187 children. They showed that baseline peripheral refractive error was not predictive of myopia development/progression. The potential link between peripheral refraction and refractive error in these studies has led to experiments in which spectacle lenses or contact lenses alter the peripheral refraction.[25–27] It has been found that such lenses may reduce myopia progression over a 1-year period in some studies.[26]

The Cambridge Anti-Myopia Study (CAMS) is designed to evaluate a dual treatment modality for myopia on myopia progression rates. The present study aims to investigate the changes in peripheral refraction profiles associated with myopia progression. The results will help in assessing whether the initial peripheral refraction profiles in myopes support earlier work, whether some features of the peripheral refraction profiles are predictive of subsequent myopic changes, and whether the changes in peripheral refraction profiles accompany progression of myopia. It assesses the peripheral refraction profiles in the central 60° of the retina in a subset of the participants enrolled on the CAMS trial in order to evaluate the changes in peripheral refraction profiles associated with myopia progression and treatment modalities.

Methods

One hundred and seventy-seven myopes in the age range of 14 to 22 years were enrolled in the study. This cohort included a subset of the participants who took part in the CAMS trial. The study design for the CAMS trial is described in detail by Allen et al.[28] In summary, the Cambridge Anti-Myopia Study is a double-masked clinical trial that employs custom designed contact lenses that control spherical aberration in an attempt to optimize static accommodation responses during near-work, and a vision-training program to improve accommodation dynamics. A factorial trial design was used to test the efficacy of the two independent treatments simultaneously. There were four treatment groups: altered spherical aberration and vision training; altered spherical aberration only; vision training only; and control (no vision training or alteration of spherical aberration, the control group contact lenses were designed to have zero spherical aberration regardless of the measured spherical aberration level of the eye).

The spherical equivalent cycloplegic refractive error of the participants ranged between –0.75 to –10.00 diopters (D), with astigmatism of 0.75 D or less. All participants had logMAR visual acuity of 0.00 or better in each eye with spectacle correction. One hundred and seventy seven participants were suitable to commence the trial and to take part in the peripheral refraction measurements. Participants gave informed consent for taking part in the study, which followed the tenets of the Declaration of Helsinki and was approved by the Anglia Ruskin University Ethical Committee.

The blocking variables for the randomization procedure were age, sex, and cylindrical refractive error, and participants were stratified for spherical refractive error. Unlike the CAMS trial, individuals with negative spherical aberration were not excluded from the present study. One experimenter, who was unmasked, allocated participants to groups. This experimenter did not participate in any of the masked measurements, and was available to look at treatment regimes with Vision Training, and clinical issues relating to contact lens aftercare. The masked experimenters had no information about the allocation of individual participants to treatment groups. Figure 1 shows a flow diagram depicting the passage of participants through the study. One of the participants in the contact lens treatment group who completed the 12-month visit did not complete the 24-month visit. Hence, peripheral refraction measurements at all three visits were available only for 92 participants. The Table shows the baseline characteristics of participants in each group. There were no significant differences in baseline refractive error and age between the four subject groups ($P > 0.05$). No significant differences were found between the baseline characteristics in the initial cohort ($n = 177$), those who completed the study ($n = 113$) and the cohort that took part in all three measurements ($n = 92$) of peripheral refraction ($P > 0.05$).

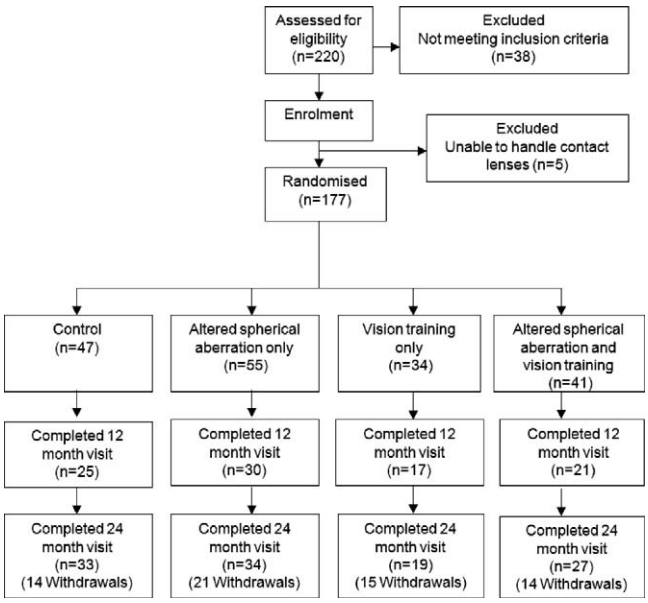

Figure 1. Flow diagram of participants in the present study.

Soft contact lenses were designed to alter ocular spherical aberration in addition to correcting the spherical equivalent axial refractive error. The front surface curvature was calculated using paraxial optics to correct the axial refractive error. The spherical aberration of the lens was manipulated by altering the eccentricity value of the front surface of the lens. The contact lenses were designed to alter the existing fourth-order spherical aberration of the patient to –0.1 μm (referenced to a 5-mm diameter pupil) while maintaining the appropriate paraxial correction. Theagarayan et al.[29] demonstrated that altered spherical aberration can influence the slope of the accommodation response curve. The spherical aberration of the control group lenses was designed to have zero spherical aberration in the contact lenses regardless of the measured spherical aberration level of the eye. Spherical aberration of –0.1 microns for a 5-mm pupil diameter equates to –0.137 D/mm^2 and, therefore, approximately –0.55 D at the edge of a 4-mm pupil. In equivalent dioptric terms, the spherical defocus required to produce the same wavefront variance as –0.1 μm SA equates to –0.11 D. Both the treatment and control group participants were asked to wear contact lenses for at least 10 hours per day.

Customized contact lenses for each participant were manufactured by UltraVision CLPL (Leighton Buzzard, UK) specifically for this study. All lenses were made of 58% HEMA-based material. The contact lenses were fitted such that the movement on blink was approximately 0.25 mm.

The vision training regime consisted of lens flipper exercises[30] using a +2.00 D/–2.00 D flipper at 40 cm. The exercises were performed for 18 minutes per day for up to 6 weeks. There was a wide range of baseline accommodative facility values, hence a goal-orientated approach was used. Participants were to continue with the vision training until a minimum value of 25 cycles per minute was

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Table. Demographic and Clinical Characteristics of the Participants at Baseline Visit

Blocking Variable	Altered Spherical Aberration and Vision Training	Vision Training Only	Altered Spherical Aberration Only	Control	All
Demographic data at randomization, $n = 177$					
Age, y	17.43 + 2.28	17.74 + 2.36	16.89 + 2.21	17.15 + 2.23	17.24 + 2.26
Sex, % female	52	56	53	55	54
Spherical equivalent, D	−2.93 + 1.74	−2.98 + 1.92	−3.31 + 1.76	−3.23 + 1.80	−3.06 + 1.91
Astigmatism, D	−0.43 + 0.31	−0.44 + 0.31	−0.42 + 0.29	−0.47 + 0.27	−0.44 + 0.29
Participants, *n*	41	34	55	47	177
Demographic data for those who completed the study at 24 months, $n = 113$					
Age, y	17.03 + 1.80	17.09 + 2.55	16.40 + 1.99	16.70 + 2.03	16.75 + 2.05
Sex, % female	51	59	56	53	56
Spherical equivalent, D	−3.82 + 2.10	−2.98 + 2.00	−3.24 + 1.76	−3.38 + 1.73	−3.37 + 1.84
Astigmatism, D	−0.45 + 0.33	−0.42 + 0.29	−0.36 + 0.31	−0.44 + 0.28	−0.45 + 0.30
Participants, *n*	27	19	34	33	113
Demographic data for those who completed all three visits, $n = 92$					
Age, y	16.92 + 2.05	17.16 + 2.10	16.71 + 2.13	16.89 + 2.11	16.89 + 2.09
Sex, % female	52	57	58	55	57
Spherical equivalent, D	−3.18 + 2.19	−2.87 + 1.72	−3.25 + 1.74	−3.31 + 1.77	−3.14 + 1.81
Astigmatism, D	−0.44 + 0.28	−0.44 + 0.28	−0.33 + 0.32	−0.43 + 0.23	−0.45 + 0.28
Participants, *n*	21	17	29	25	92

achieved; this is consistent with established normal values for dynamic accommodation responses.[31] Participants were given verbal and written instruction for the vision training and were to keep a log of training sessions and achievement. The training was conducted at home with the log books randomly checked for training compliance by the unmasked examiner.

Peripheral refraction measurements were taken on the right eye with an autorefractor (Shin-Nippon SRW-500; Ajinomoto Trading, Inc., Tokyo, Japan) aligned with the center of the pupil with the target viewing distance of 2.5 m. This instrument has been shown to produce valid and reliable measurements of refraction.[32] Contact lenses were removed. Measurements were taken under cycloplegia with two drops of tropicamide hydrochloride 1% (Minims; Chauvin Pharmaceuticals, London, UK) instilled at least 30 minutes prior to the measurements being taken. The participant fixated a high contrast letter target subtending a visual angle of 1.5 minutes of arc mounted on a screen at the appropriate distance from the cornea. Targets were positioned on the screen so that they were separated by 10, 20, and 30 degrees with respect to the line of sight in primary gaze, in both temporal and nasal meridians. Three refraction measurements were taken at each eccentricity and were averaged. Each spherocylindrical refractive error measurement was decomposed into vector components using the following equations derived by Thibos et al.[33]:

$$J_{180} = \frac{-C\cos 2\theta}{2} \quad (1)$$

$$J_{45} = \frac{-C\sin 2\theta}{2} \quad (2)$$

$$M = S + \frac{C}{2} \quad (3)$$

where S is the sphere, C the cylinder, θ the cylinder axis, M the spherical equivalent, and J_{180} and J_{45} are the powers of two Jackson crossed-cylinder components. All averaging was done in terms of these power vectors.

Axial refractive error of both eyes was determined following cycloplegia with two drops of tropicamide hydrochloride 1% (Chauvin Pharmaceuticals) in each eye at 5-minute intervals.[34] Objective measurement of axial refractive error was made with an autorefractor (Nidek AR600-A; Nidek, Gamagori, Japan) using a series of five readings per eye according to the protocol for the CAMS trial. The autorefractor (Nidek) has been shown to have good repeatability and validity.[35] The cycloplegic refraction data were used to determine myopia progression.

Peripheral refraction and refractive error were measured under cycloplegia at the baseline, 12-, and 24-month visits. A number of participants were lost to follow-up and refractive progression data was available at 24 months for 113 participants who took part in the initial peripheral refraction measurements. However, the 12-month data were not available on 21 of these participants (i.e., peripheral refraction measurements were only available at baseline and 24 months for this cohort). Therefore, changes in peripheral refraction over time were studied in this subgroup of 92 participants. Over the course of the trial, 36% of participants dropped out of the study. Reasons for dropping out included dislike of the contact lens wearing modality (e.g., the lenses were not daily disposable); difficulty in traveling to data collection appointments; and moving away from the trial center. Some participants did not respond to invitations to follow-up appointments. There was no significant difference in the number of subjects who dropped out of the study from each treatment group (χ^2 $P = 0.81$) or in the sex of participants who dropped out (χ^2 $P = 0.49$).

Data Analysis

Baseline refractive errors were compared using an analysis of variance performed on the M, J_{45}, and J_{180} refractive error components, with the treatment group as the between-groups variable and retinal eccentricity as the within-groups variable. Posthoc analysis was performed with Tukey's HSD test. Changes in these refractive errors at each visit were examined using repeated measures ANOVAs. Pearson correlation coefficients were used to examine the relationship between refractive error components and myopia progression.

Results

Peripheral Refractive Error Profile at Baseline

The peripheral refractive error profile at baseline in the central 60° of the retina in all four treatment groups is shown in Figure 2. The spherical equivalent peripheral refractive error in all four groups shows a similar pattern (Fig. 2A), with the nasal retina exhibiting a slightly higher level of relative peripheral

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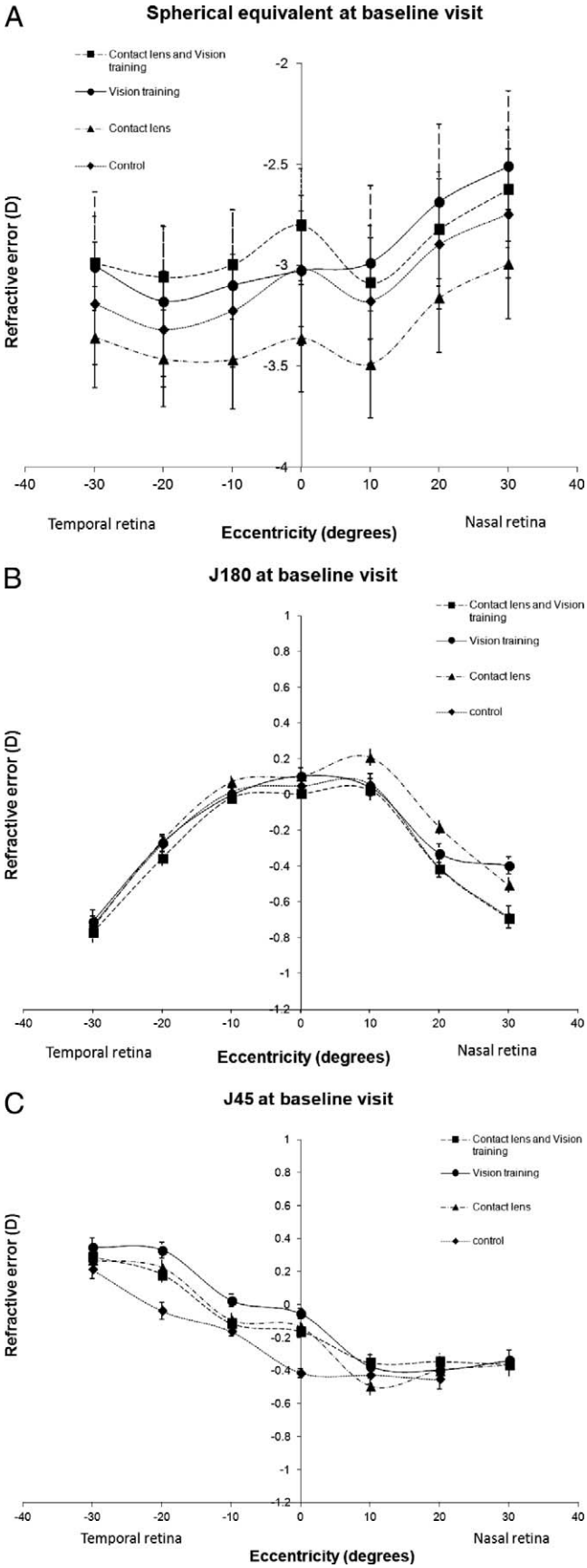

hyperopia than the temporal retina. The relative peripheral hyperopia was only found to be statistically significant at 30° in the nasal retina (Tukey's post hoc test, $P < 0.05$). The baseline axial refractive error in the contact lens group was slightly higher than the baseline axial refractive error in the other three groups, although the differences were not statistically significant with analysis of variance ($P > 0.05$). The astigmatic components in the peripheral retina show a similar pattern in all four groups (Figs. 2B, 2C). The mean J_{180} component was found to be close to zero on axis, changing to more negative values at peripheral eccentricities. The J_{45} astigmatic component was found to be more positive in the temporal retina when compared with the nasal retina. Analysis of variance showed no significant difference in spherical equivalent and astigmatic components at all eccentricities between the four groups ($P > 0.05$).

All participants reported at least 10 hours of contact lens wear per day. All participants in the vision training treatment group reported that they completed the scheduled program of vision training and achieved their target facility rates; where our measurements in the clinic revealed that their facility was below the target rate, they were asked to repeat the exercise regime again until their facility was again at the target rate.

Myopia in each of the four groups showed a limited magnitude of progression of –0.34 ± 0.36 D (over 2 years) on average. There were no significant difference in the rate of progression between any of the treatment groups with analysis of variance ($P > 0.05$).

Correlation between peripheral refractive error at the baseline visit and myopia progression (spherical equivalent refractive error and the astigmatic components) at the 24-month visit ($n = 113$) was studied to assess if any aspect of the initial peripheral refractive error profile could be used as a predictor for myopia progression. Significant correlation was only found between J_{45} astigmatic components in the nasal retina at 20° (Pearson correlation coefficient = –0.27; $P = 0.004$) and 30° (Pearson correlation coefficient = –0.20; $P = 0.040$; Fig. 3) and myopia progression. However, only the correlation between J_{45} astigmatic components in the nasal retina at 20° would remain significant after Bonferroni correction. A considerable number of participants had a negative J_{45} astigmatic component. No significant correlation was found between all other peripheral refraction components and the 24-month myopia progression.

Changes in Peripheral Refraction over Time

Peripheral refractive error under cycloplegia was measured at the baseline, 12-month, and 24-month visits. We analyzed a subgroup of 92 subjects for whom data were available at all three visits. For all other participants, data from either the 12-month or 24-month visit was unavailable. The changes in spherical equivalent and astigmatic component relative peripheral refractive error over time are shown in Figure 4. The overall pattern of spherical equivalent peripheral refraction appears to remain broadly similar over the 2-year timescale, although considerable reduction in peripheral refraction is seen in the nasal retina after the baseline visit. Analysis of variance showed no significant effect of treatment group on the peripheral refractive error at all three visits ($P > 0.05$). Significant changes in relative peripheral refraction were found

FIGURE 2. Components of the four treatment groups as a function of retinal eccentricity. (**A**) Spherical equivalent. (**B**) J_{180}. (**C**) J_{45} astigmatic component. Negative eccentricity values indicate temporal retina (nasal visual field) and positive values indicate nasal retina (temporal visual field). The *error bars* represent ±1 standard error of mean.

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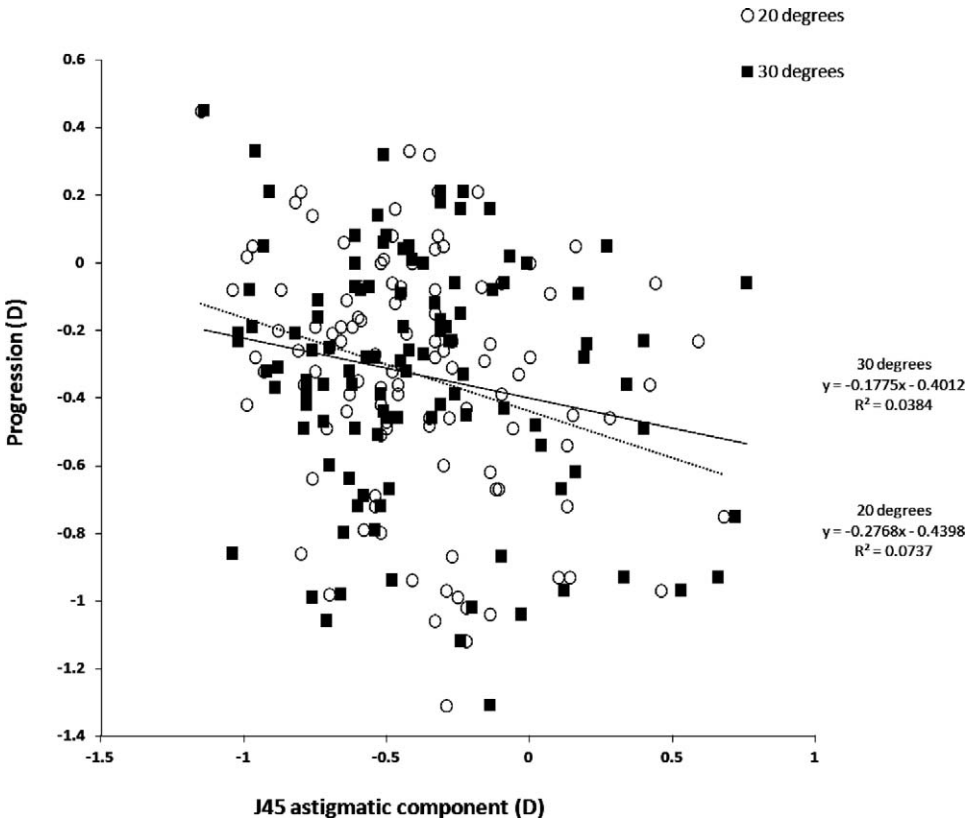

Figure 3. Progression at 24-month as a function of baseline J_{45} astigmatic component at 20° and 30° in the nasal retina.

with repeated measures analysis of variance at 20° ($F_{2,192}$ = 11.08; P = 0.001) and 30° ($F_{2,192}$ = 11.38; P = 0.001) nasal retina between the three visits. No significant interaction was found with treatment groups at both of these eccentricities (20°: $F_{6,192}$ = 1.27; P = 0.274 and 30°: $F_{6,192}$ = 0.82; P = 0.558). Repeated measures analysis of variance showed no significant changes in the astigmatic components (J_{180} and J_{45}) of peripheral refractive error between the three visits at all eccentricities tested ($P > 0.05$). The changes in the J_{180} and J_{45} astigmatic components over the three visits were not significantly correlated with the changes in spherical equivalent refractive error both at 12 months (J_{180}: r^2 = 0.064; P = 0.630 and J_{45}: r^2 = 0.254; P = 0.307) and 24 months (J_{180}: r^2 = 0.081; P = 0.584 and J_{45}: r^2 = 0.096; P = 0.550).

The correlation between refractive error progression at 12 and 24 months and changes in peripheral refraction at each eccentricity at the follow-up visits was assessed to further understand any links that might exist between these factors. No significant correlations were found for peripheral refractive changes in the temporal retina and for changes at 10° eccentricity in the nasal retina ($P > 0.05$). Refractive error progression at the 12-month visit was found to be significantly correlated with the change in spherical equivalent (M) refractive error at 30° nasal retina (Pearson correlation coefficient for change in RPRE at 12-month visit: –0.28 [r^2 = 0.078; P = 0.005] and at 24 months: –0.21 [r^2 = 0.044; P = 0.035]). The change in RPRE at the 12-month visit for 30° nasal retina remains significantly correlated with the progression at the 12-month visit even after Bonferroni correction ($P <$ 0.008). This indicates that the changes in RPRE at the 12-month visit are significantly associated with myopia progression at 12 months.

The relationship between refractive error progression at the 24-month visit and the change in spherical equivalent RPRE at 30° nasal retina at the 12- and 24-month visit is shown in Figure 5. The correlation between myopia progression at 24 months and the change in spherical equivalent RPRE at 30° nasal retina at the 12- and 24-month visits was found to be significant (Pearson correlation coefficient for change in refraction at the 12-month visit: –0.20 (P = 0.048) and at 24 months: –0.24 (P = 0.017). However, these did not remain significant after Bonferroni correction ($P > 0.008$). Also, it should be noted that there is wide scatter in the data and in some cases, the change in spherical equivalent peripheral refraction becomes more positive with refractive progression.

Discussion

The results show that myopic eyes tend to have relative peripheral hyperopia, especially in the nasal retina. Several other studies have also shown that myopes have prolate-shaped eyes with the refractive error tending to be relatively hyperopic in the periphery.[3,5,7,36,37] The variability of the peripheral refraction measurements from the mean in the present study appear to be similar to those reported in previous literature.[23,24,38]

A marked reduction (of the order of 0.2 D) in relative peripheral refraction in the nasal retina was found following the baseline visit. The cause of such change is unclear, but it could have perhaps been due to changes in the corneal curvature following contact lens wear. However, it is unlikely that contact lenses would alter corneal curvature only affecting one-half of the retina as the participants were fitted with spherical soft lenses. Participants in the contact lens treatment group and the contact lens and vision therapy treatment group were fitted with spherical aberration altering lenses and the other participants were fitted with contact lenses with zero

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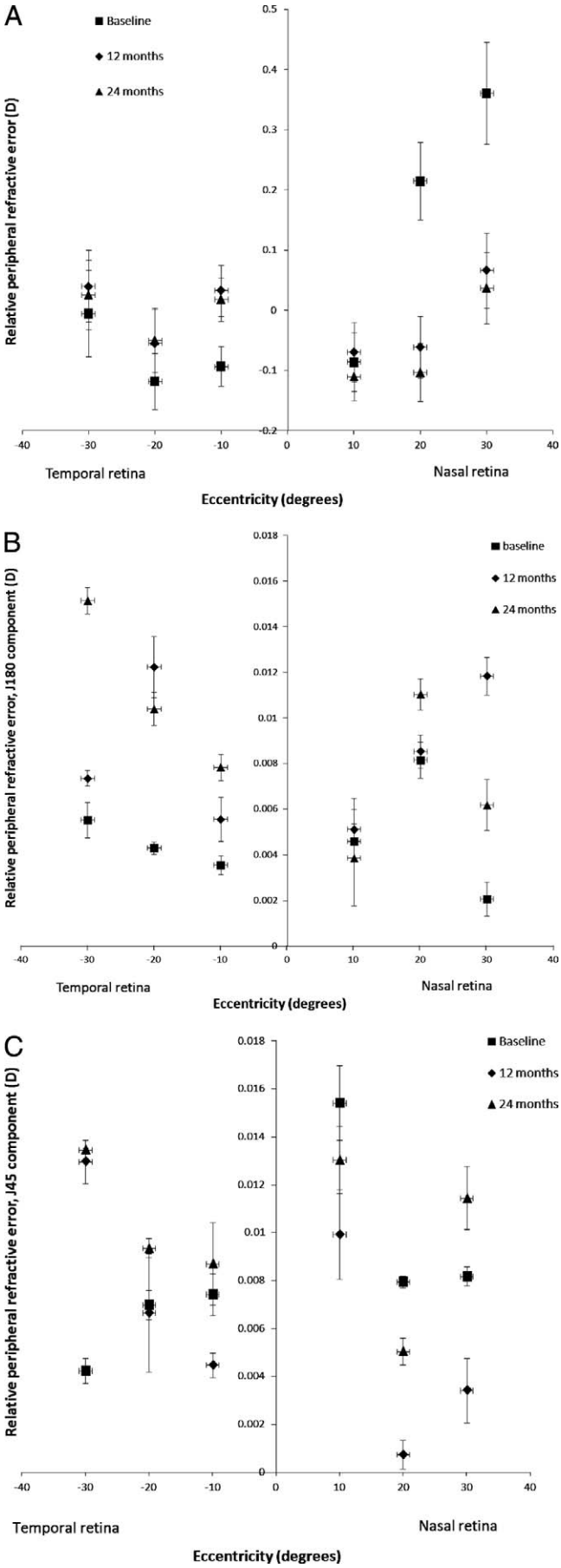

Figure 4. RPRE at the baseline, 12-month, and 24-month visits in a cohort of 92 subjects. (**A**) Spherical equivalent. (**B**) Astigmatic component J_{180}. (**C**) J_{45} component. The *error bars* represent ± 1 standard error of mean.

spherical aberration. It is therefore possible that wearing these contact lenses could have altered the peripheral refraction profiles of the participants. However, all measurements of peripheral refractive error were obtained without the contact lenses. The fact that no significant effect of treatment group was found on changes in peripheral refraction between the follow-up visits indicates that the use of contact lenses is unlikely to have caused any substantial changes to the peripheral refraction. Although many studies have examined the effects of soft contact lens wear on corneal curvature, few have looked at the effect on corneal shape, which would impact peripheral astigmatism. Santodomingo-Rubido et al.[39] found that 18 months of soft contact lens wear had no effect on corneal peripheral flattening, but their finding was based only on measurement of the anterior corneal surface. Moezzi et al.[40] measured corneal swelling resulting from contact lens wear. They found that soft lenses caused greater corneal swelling centrally than peripherally, flattening the posterior surface of the cornea. Changes to corneal shape might therefore affect the peripheral refraction of the eye through changes to the posterior corneal surface, although this would produce a much smaller effect than changes to the anterior surface. In a recent study, Miranda et al. (Miranda MA, et al. *IOVS* 2010;51:ARVO E-Abstract 2011) assessed the effect of contact lens design and material on peripheral refractive error in healthy young adults and showed that most commercially available contact lenses are unlikely to significantly alter the peripheral refraction profiles. The present study showed that the changes in the J_{180} and J_{45} astigmatic components over the three visits were not significantly correlated with the changes in spherical equivalent refractive error at these visits. This indicates that the changes in spherical equivalent refractive error are unlikely to be due to the changes in corneal curvature.

None of the treatment modalities used in our study had much effect on peripheral refraction. One would expect peripheral refraction to change slightly when participants were wearing contact lenses that induced negative spherical aberration. Previous work has shown that peripheral refraction measurements remain valid when eyes are corrected with conventional soft contact lenses.[41,42] Lenses with aspherical surfaces would, however, induce different amounts of peripheral astigmatism. Our contact lenses induced relatively low levels of spherical aberration (0.1 μm over a 5-mm pupil diameter) and all peripheral refraction measurements in the present study were obtained without contact lenses. Therefore, inherent changes in peripheral refraction produced by the contact lenses are unlikely to have affected the results of the present study.

The mean J_{45} component was slightly negative in many participants when measured on axis. This component depends on the magnitude and axis direction of the cylindrical component of the refractive error. It will be negative if the negative cylinder axis lies between 90° and 180°, and its highest negative value is reached when the cylinder axis is 135°. This indicates that many of our participants had oblique astigmatism rather than with- or against-the-rule astigmatism. The source of this oblique astigmatism is unclear, but it may have resulted from misalignments of the eye's optical structures. For example, theoretical studies have shown that small displacements of the eye's optical axis can affect the J_{180}

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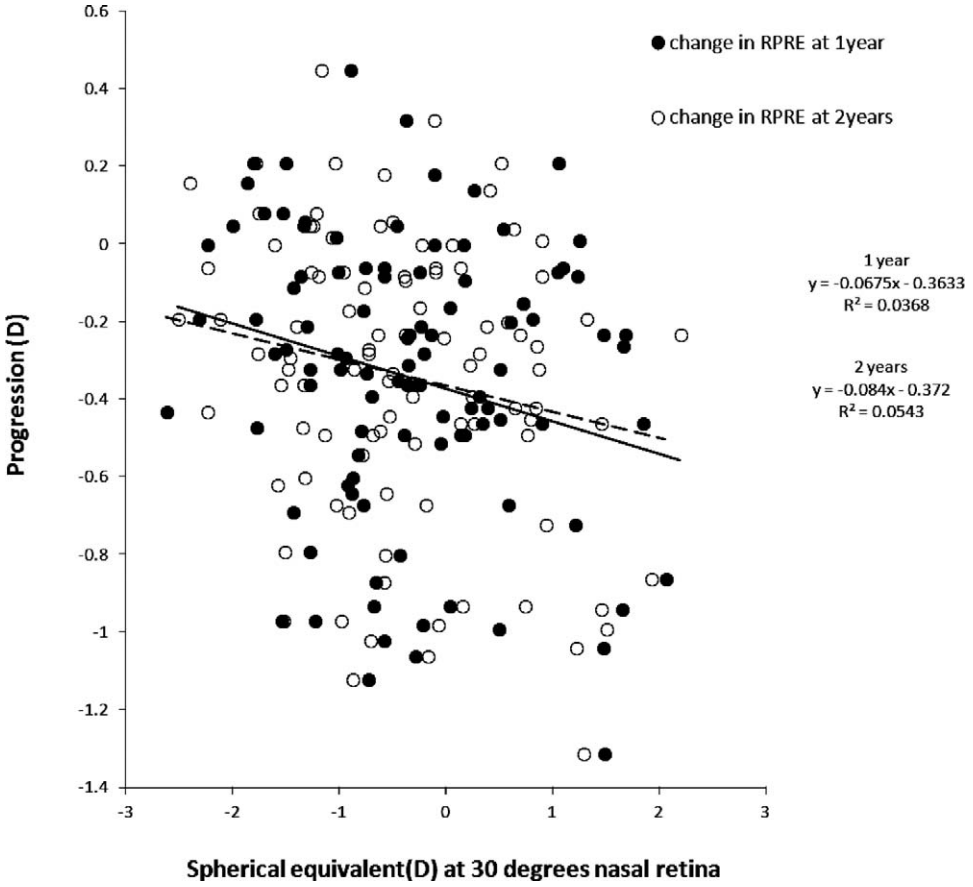

Figure 5. Refractive error progression at 24 months as a function of changes in spherical equivalent RPRE at 30° in the nasal retina.

and J_{45} components.[43] There is a trend for the J_{45} component to become more positive with increasing eccentricity in the temporal retina (nasal visual field), and for the J_{180} component to become more negative with increasing eccentricity in both the temporal and nasal retina. These trends agree with previous studies that measured peripheral refractive errors in myopic participants.[6,42,44]

Figure 3 shows that the only baseline parameters to have a statistically significant, although low (3%–7%), predictive effect for myopia progression were the J_{45} values at 20° and 30° nasal field. Therefore, it is possible that the initial relative peripheral refraction over a more limited area of the peripheral field may be more important, rather than the overall peripheral refractive error profile. This hypothesis is further supported by animal studies.[45,46] The apparent importance of the J_{45} component suggests that orientation of astigmatism might be important in predicting progression, and that nonzero J_{45} values are important (i.e., astigmatism other than with-the-rule or against-the-rule). Some animal studies have assessed the effect of applying cylindrical lenses to the central retina of developing animals and produced mixed results. Irving et al.[47] found evidence for a partial compensatory astigmatic growth in chick eyes; the effectiveness of the compensation varied with the orientation of the axis of the cylinder. In contrast, Schmid and Wildsoet[48] found no astigmatic compensation in the growing chick eye: rather chicks appeared to "emmetropize" to the meridian with the greater myopic defocus, irrespective of the cylinder axis. In monkeys, application of 1.50DS/−3.00DC crossed-cylinder lenses resulted in "emmetropization" to one of the two focal planes associated with the two principal meridians of the astigmatism, rather than the circle of least confusion[49]; most animals in their study became more hyperopic. All these studies show that variation between animals is greater with the application of cylindrical lenses than when spherical lenses are used. No previous study has applied cylindrical error in the peripheral retina and studied its effect on axial growth.

The temporal changes in the peripheral refractive error profile with age have been found to be minimal. Atchison et al.[44] showed that peripheral refractive errors are similar in younger and older patients with the same magnitude of axial refractive error. Charman and Jennings[50] studied changes in peripheral refraction over a time interval of 26 years in two individuals and showed that the peripheral refractive error profile does not change by any considerable magnitude over time. Mutti et al.[22] showed results similar to the present study where after myopia onset, the peripheral refraction at 30° in the temporal retina did not change significantly over time. The only significant changes in the peripheral refractive error profiles of the participants in the present study over the 2 years of follow up occurred at 20° and 30° in the nasal retina. These changes, although small, were significantly correlated with myopia progression (Fig. 5), suggesting perhaps that the eyeball might be undergoing a more localized distortion rather than a simple axial elongation. This could indicate that the changes in peripheral refraction in the nasal retina may either precede or be associated with myopia progression. Given that posterior staphyloma associated with high myopia often occur in nasal regions of retina near the optic nerve, it is possible that the changes in nasal retina may relate to the structural changes in the globe during myopic eye growth.

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The limitations of the present study must be acknowledged. As with all cohort studies, some participants may not remain throughout the entire duration of the study and may be lost to follow-up. The 2-year loss to follow-up rate was quite high (64/117; 36%) and may reflect the very transient nature of this age range of the Cambridge population—many were either studying in Cambridge or moved away to study during the period of CAMS. Secondly, contact lens centration was not quantified during data collection. In the fitting assessment of contact lenses, the lenses were assessed using qualitative measures. Any lens not achieving a "good centration" rating was altered until that rating was achieved. Some contact lens decentration could potentially result in asymmetric corneal changes that could contribute to asymmetric changes in peripheral refraction. Thirdly, since pupil size varies throughout the day due to different ambient lighting and the various tasks undertaken by the individual, the aberration correction provided by the contact lenses in the contact lens treatment groups is unlikely to have remained consistent throughout the day. Nevertheless, it is expected that the participants would have experienced negative spherical aberration of variable amounts depending on the pupil size and this negative spherical aberration was expected to produce more accurate accommodation in these individuals. Lastly, the participants' mean age of approximately 16 years may explain the small myopic progression found in our study. Many studies select younger participants whose refractive errors are likely to change more rapidly.

In summary, most subjects exhibited relative peripheral hyperopia, especially in the nasal retina. Initial peripheral astigmatic refractive error in the nasal retina was correlated with myopia progression over 2 years. The change in peripheral refractive error at 30° nasal retina was also significantly correlated with progression of myopia. The type of treatment had no effect on changes in peripheral refractive error over time. Relative peripheral hyperopia is associated with myopia progression. However, a causative link between peripheral refractive error and myopia progression could not be established.

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References

1. Hoogerheide J, Rempt F, Hoogenboom WP. Acquired myopia in young pilots. *Ophthalmologica*. 1971;163:209–215.
2. Charman WN, Radhakrishnan H. Peripheral refraction and the development of refractive error: a review. *Ophthalmic Physiol Opt*. 2010;30:321–338.
3. Millodot M. Effect of ametropia on peripheral refraction. *Am J Optom Physiol Opt*. 1981;58:691–695.
4. Mutti DO, Sholtz RI, Friedman NE, Zadnik K. Peripheral refraction and ocular shape in children. *Invest Ophthalmol Vis Sci*. 2000;41:1022–1030.
5. 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;19:2363–2373.
6. Atchison DA, Pritchard N, Schmid KL. Peripheral refraction along the horizontal and vertical visual fields in myopia. *Vision Res*. 2006;46:1450–1458.
7. 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;46:2698–2707.
8. Calver R, Radhakrishnan H, Osuobeni E, O'Leary D. Peripheral refraction for distance and near vision in emmetropes and myopes. *Ophthalmic Physiol Opt*. 2007;27:584–593.
9. Mathur A, Atchison DA, Charman WN. Myopia and peripheral ocular aberrations. *J Vis*. 2009;915:11–12.
10. Wallman J, Gottlieb MD, Rajaram V, Fugatewentzek LA. Local retinal regions control local eye growth and myopia. *Science*. 1987;237:73–77.
11. Diether S, Schaeffel F. Local changes in eye growth induced by imposed local refractive error despite active accommodation. *Vision Res*. 1997;37:659–668.
12. Hodos W. Avian models of experimental myopia: environmental factors in the regulation of eye growth. *Ciba Found Symp*. 1990;155:149–156; discussion 156–159.
13. Miles FA, Wallman J. Local ocular compensation for imposed local refractive error. *Vision Res*. 1990;30:339–349.
14. Smith EL III, Kee CS, Ramamirtham R, Qiao-Grider Y, Hung LF. Peripheral vision can influence eye growth and refractive development in infant monkeys. *Invest Ophthalmol Vis Sci*. 2005;46:3965–3972.
15. Smith EL III, Ramamirtham R, Qiao-Grider Y, et al. Effects of foveal ablation on emmetropization and form-deprivation myopia. *Invest Ophthalmol Vis Sci*. 2007;48:3914–3922.
16. Huang J, Hung LF, Ramamirtham R, et al. Effects of form deprivation on peripheral refractions and ocular shape in infant rhesus monkeys (Macaca mulatta). *Invest Ophthalmol Vis Sci*. 2009;50:4033–4044.
17. Hung LF, Ramamirtham R, Huang J, Qiao-Grider Y, Smith EL III. Peripheral refraction in normal infant rhesus monkeys. *Invest Ophthalmol Vis Sci*. 2008;49:3747–3757.
18. Smith EL III, 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;50:5057–5069.
19. Smith EL III, Hung LF, Huang J. Relative peripheral hyperopic defocus alters central refractive development in infant monkeys. *Vision Res*. 2009;49:2386–2392.
20. Schippert R, Schaeffel F. Peripheral defocus does not necessarily affect central refractive development. *Vision Res*. 2006;46:3935–3940.
21. Hodos W, Erichsen JT. Lower-field myopia in birds: an adaptation that keeps the ground in focus. *Vision Res*. 1990;30:653–657.
22. 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;48:2510–2519.
23. 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;52:199–205.
24. Sng CC, Lin XY, Gazzard G, et al. Change in peripheral refraction over time in Singapore Chinese children. *Invest Ophthalmol Vis Sci*. 2011;52:7880–7887.
25. Sankaridurg P, Donovan L, Varnas S, et al. Spectacle lenses designed to reduce progression of myopia: 12-month results. *Optom Vis Sci*. 2010;87:1–11.
26. Holden BA, Sankaridurg P, Ho A, et al. Impact of novel contact lenses on progression of myopia. Paper presented at: 13th Annual International Myopia Conference; 2010; Tübingen, Germany.
27. Lopes-Ferreira D, Ribeiro C, Maia R, et al. Peripheral myopization using dominant design multifocal contact lens. *J Optom*. 2011;4:14–21.
28. Allen PM, Radhakrishnan H, Rae S, et al. Aberration control and vision training as an effective means of improving

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accommodation in individuals with myopia. *Invest Ophthalmol Vis Sci*. 2009;50:5120–5129.

29. Theagarayan B, Radhakrishnan H, Allen PM, Calver RI, Rae SM, O'Leary DJ. The effect of altering spherical aberration on the static accommodative response. *Ophthalmic Physiol Opt*. 2009;29:65–71.
30. Sterner B, Abrahamsson M, Sjostrom A. The effects of accommodative facility training on a group of children with impaired relative accommodation–a comparison between dioptric treatment and sham treatment. *Ophthalmic Physiol Opt*. 2001;21:470–476.
31. Griffin J, Grisham J. *Binocular Anomalies: Diagnosis and Vision Therapy*. Oxford, UK: Butterworth-Heineman; 2002.
32. Mallen EA, Wolffsohn JS, Gilmartin B, Tsujimura S. Clinical evaluation of the Shin-Nippon SRW-5000 autorefractor in adults. *Ophthalmic Physiol Opt*. 2001;21:101–107.
33. Thibos LN, Wheeler W, Horner D. Power vectors: an application of Fourier analysis to the description and statistical analysis of refractive error. *Optom Vis Sci*. 1997;74:367–375.
34. Manny RE, Hussein M, Scheiman M, Kurtz D, Niemann K, Zinzer K. Tropicamide (1%): an effective cycloplegic agent for myopic children. *Invest Ophthalmol Vis Sci*. 2001;42:1728–1735.
35. Allen PM, Radhakrishnan H, O'Leary DJ. Repeatability and validity of the PowerRefractor and the Nidek AR600-A in an adult population with healthy eyes. *Optom Vis Sci*. 2003;80:245–251.
36. Charman WN. Aberrations and myopia. *Ophthalmic Physiol Opt*. 2005;25:285–301.
37. Stone RA, Flitcroft DI. Ocular shape and myopia. *Ann Acad Med Singapore*. 2004;33:7–15.
38. Berntsen DA, Mutti DO, Zadnik K. Validation of aberrometry-based relative peripheral refraction measurements. *Ophthalmic Physiol Opt*. 2008;28:83–90.
39. Santodomingo-Rubido J, Gilmartin B, Wolffsohn J. Refractive and biometric changes with silicone hydrogel contact lenses. *Optom Vis Sci*. 2005;82:481–489.
40. Moezzi AM, Fonn D, Simpson TL, Sorbara L. Contact lens-induced corneal swelling and surface changes measured with the Orbscan II corneal topographer. *Optom Vis Sci*. 2004;81:189–193.
41. Artal P, Derrington AM, Colombo E. Refraction, aliasing, and the absence of motion reversals in peripheral vision. *Vision Res*. 1995;35:939–947.
42. Davies LN, Mallen EA. Influence of accommodation and refractive status on the peripheral refractive profile. *Br J Ophthalmol*. 2009;93:1186–1190.
43. Charman WN, Atchison DA. Decentred optical axes and aberrations along principal visual field meridians. *Vision Res*. 2009;49:1869–1876.
44. Atchison DA, Pritchard N, White SD, Griffiths AM. Influence of age on peripheral refraction. *Vision Res*. 2005;45:715–720.
45. Chu CH, Deng L, Kee CS. Effects of hemiretinal form deprivation on central refractive development and posterior eye shape in chicks. *Vision Res*. 2012;55:24–31.
46. Stone RA, Pendrak K, Sugimoto R, et al. Local patterns of image degradation differentially affect refraction and eye shape in chick. *Current Eye Res*. 2006;31:91–105.
47. Irving EL, Callender MG, Sivak JG. Inducing ametropias in hatchling chicks by defocus–aperture effects and cylindrical lenses. *Vision Res*. 1995;35:1165–1174.
48. Schmid K, Wildsoet CF. Natural and imposed astigmatism and their relation to emmetropization in the chick. *Exp Eye Res*. 1997;64:837–847.
49. Kee CS, Hung LF, Qiao-Grider Y, Roorda A, Smith EL III. Effects of optically imposed astigmatism on emmetropization in infant monkeys. *Invest Ophthalmol Vis Sci*. 2004;45:1647–1659.
50. Charman WN, Jennings JA. Longitudinal changes in peripheral refraction with age. *Ophthalmic Physiol Opt*. 2006;26:447–455.

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