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ORIGINAL ARTICLE



Relative peripheral hyperopia leads to greater short-term axial length growth in White children with myopia

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Abstract

Purpose: Controversy exists regarding the influence of peripheral visual experience on the onset and progression of childhood myopia. This longitudinal, observational study evaluated the relationship between relative peripheral refraction (RPR) and changes in refractive error and axial length (AL) over 12 months in White children aged 6–7 and 12–13 years with a range of baseline refractive errors.

Methods: Cycloplegic baseline autorefraction at horizontal retinal eccentricities of 0° and ±30° were recorded with the Shin-Nippon NVision-K 5001 while AL was measured using the Zeiss IOLMaster 700. Measurements were repeated after 12 months on a subgroup. Refractive data were transposed into power vectors as mean spherical equivalent (M), J_o and J₄₅. RPR was calculated by subtracting central from peripheral measurements. Participants were defined as myopic ($M \le -0.50 \text{ D}$), premyopic ($-0.50 \text{ D} < \text{M} \le +0.75 \text{ D}$), emmetropic (+0.75 D < M < +2.00 D) or hyperopic (M \ge +2.00 D).

Results: Data were collected from 222 and 245 participants aged 6-7 and 12-13 years, respectively. Myopic eyes demonstrated, on average, more hyperopic RPR. Emmetropes and premyopes displayed emmetropic RPR, and hyperopes showed a myopic RPR. Fifty-six 6- to 7-year-olds and seventy 12- to 13-year-olds contributed 12-month repeated measures. Longitudinal data demonstrated a significant relationship between a more hyperopic RPR in the nasal retina and greater short-term axial elongation in teens with myopia at baseline ($\beta = 0.69$; p = 0.04). Each dioptre of relative peripheral hyperopia in the nasal retina was associated with an additional 0.10 mm (95% CI: 0.02–0.18 mm) annual increase in AL.

Conclusions: Hyperopic RPR in the nasal retina of myopic children is indicative of increased risk for rapid axial elongation and may be a useful metric to support decision-making in myopia management.

KEYWORDS

axial length, myopia, peripheral refraction, refractive error, relative peripheral hyperopia, relative peripheral refraction

INTRODUCTION

The worldwide prevalence of myopia and high myopia has increased significantly over recent decades,^{1–5} now reaching epidemic proportions in East Asia.^{6–10} Myopia

develops due to a disparity between the axial length (AL) and the focal length of the ocular media, most commonly caused by excessive axial elongation. This abnormal eye growth also increases the risk of developing myopic macular degeneration, retinal detachment and glaucoma,¹¹

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all of which may lead to visual impairment in later life.¹² With the prevalence of myopia projected to affect half of the world's population by 2050,¹³ a concurrent increase in visual impairment can also be expected unless myopia interventions are put in place.¹² Hence, the majority of modern myopia research is aimed at establishing efficacious myopia control strategies to both delay the onset and slow the progression of myopia.^{14–19} The World Council of Optometry have defined a standard of care for myopia management that optometrists are advised to incorporate into their clinical practice.²⁰ Emerging studies suggest that the number of eye care practitioners offering more active management strategies for childhood myopia is increasing^{21,22}; however, clearer guidance still needs to be established to promote the more widespread uptake of these practices.^{23–27}

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Myopia is heterogenous in nature, with a combination of genetic and environmental factors playing a role in its onset and progression.²⁸ The visual experience of the peripheral retina is also speculated to influence eye growth, with animal experiments demonstrating that the eye will grow to compensate for lens-induced defocus²⁹⁻³¹ even when the optic nerve is surgically severed or pharmacologically blocked.³²⁻³⁴ Furthermore, the phenomenon of lens compensation remains despite the photoablation or occlusion of the fovea in rhesus monkeys.²⁹ Studies on mice have established that the rod photoreceptors, primarily located in the mid-peripheral retina, are critical in signalling normal refractive development and form deprivation myopia.³⁵ These findings indicate that the vision-dependent mechanism directing eye growth is local (within the eye) at retinal level and is particularly sensitive to signals from the peripheral retina.³⁶

Clinical observations further support this theory, with patients who have natural or treatment-induced peripheral retinal abnormalities, for example, in cases of retinitis pigmentosa or cryotherapy-treated retinopathy of prematurity, frequently exhibiting extreme refractive error.^{37,38} Likewise, children with ocular pathology primarily affecting the peripheral retina exhibit greater refractive errors than those with central retinal pathology.³⁹

Central and peripheral vision can be characterised by an image shell that falls in front of, on or behind the retina. When the peripheral image shell falls in front of the retina, the eye is considered to have relative peripheral myopia. Conversely, when the peripheral image shell falls behind the retina, this results in relative peripheral hyperopia. Previous studies have proposed that the presence of relative peripheral hyperopia promotes axial eye growth as the eye attempts to bring the retinal surface into concordance with the image shell.^{29,40–42} Due to the anatomical constraints on eye growth imposed by the orbital socket, a myopic eye develops a more prolate shape, with the retina becoming flatter vertically than horizontally. This reduces the tendency for relative hyperopic shifts in the

Key points

- A more hyperopic relative peripheral refraction in the nasal retina is associated with accelerated axial growth over 12 months in White teenage myopes.
- Eye care clinicians identifying the presence of relative peripheral hyperopia in the nasal retina of myopic patients may use these data to prioritise the application of optical myopia control strategies.
- Greater magnitudes of relative 'against-therule' astigmatism in the nasal retina conferred significantly larger short-term myopic shifts in refractive error in premyopic and emmetropic children. These data may help refine the risk of future childhood myopia.

vertical meridian and promotes greater relative peripheral hyperopia across the horizontal retina in myopic eyes.⁴³ Conversely, emmetropic and hyperopic eyes typically present with relatively emmetropic or myopic peripheral refractions along the horizontal retina.^{44,45}

In the context of the outcomes from animal studies and clinical observations, it is reasonable to hypothesise that peripheral hyperopic defocus promotes the development and progression of childhood myopia. The notion of manipulating relative peripheral refraction (RPR) has informed the design of contemporary management strategies aimed at slowing the progression of myopia^{15,46,47}; many of which have demonstrated good efficacy among myopic children.^{14–17} However, the supporting evidence from human studies is inconsistent. The Collaborative Longitudinal Evaluation of Ethnicity and Refractive Error (CLEERE) study established that compared with children who remained emmetropic, those who developed myopia had more relative peripheral hyperopia in the temporal retina (nasal visual field) from 2 years before myopia onset through 5 years after onset.⁴⁸ Similarly, Radhakrishnan et al.⁴⁹ found that an increase in relative peripheral hyperopia in the nasal retina (temporal visual field) was associated with myopia progression in adolescent myopes (aged 14-22 years) over a 2-year period, although the study was not able to establish a causal link.⁴⁹ By contrast, Atchison et al.⁵⁰ concluded that relative peripheral hyperopia along the horizontal retina was not predictive of the development nor the progression of myopia in Chinese children aged 7 and 14 years examined over a 2year period. A 2-year randomised controlled trial of 8- to 13-year-old myopes in Hong Kong established that the Defocus Incorporated Multiple Segments (DIMS) spectacle lens, which imposed myopic defocus on the peripheral retina, had a significant myopia control effect compared with single-vision spectacle lens wear.⁴¹ Interestingly,

there were no significant changes in horizontal RPR observed in the DIMS spectacle lens-wearing group over the study period, whereas the group wearing single-vision lenses (control group) exhibited significant increases in relative peripheral hyperopia in the nasal retina. It could be speculated that greater hyperopic defocus in the nasal retina was promoting myopia progression in the control group; however, it may also be argued that relative peripheral hyperopia is a consequence rather than a cause of axial elongation.

To the knowledge of the authors, only two longitudinal studies to date have explored the relationship between RPR and the development and progression of myopia using AL measures in a White paediatric population.^{48,51} Mutti et al.⁴⁸ found that children with a more hyperopic RPR were more likely to develop myopia. However, peripheral refraction was measured in only one location in the temporal retina, thus limiting this study's findings. More recently, Rotolo et al.⁵¹ concluded that RPR cannot predict the development nor the progression of myopia in White Mediterranean children. However, the relationship between RPR and changes in central AL were not evaluated and the investigation was also limited by a noncycloplegic protocol and small sample size. Compared with refractive measures, AL measurements are more precise and, therefore, able to detect smaller changes in myopic eye growth.⁵² Furthermore, AL measurement is arguably the more relevant measure relating to ocular health status than refractive findings alone.

Hence, the present study examined two cohorts of White children and evaluated the following:

- The relationship between RPR measured at two locations along the horizontal retina and cycloplegic refractive error in children with a range of ametropias.
- Whether the magnitude and type of RPR is associated with short-term changes in refractive error and central AL measured using swept-source optical coherence tomography (IOLMaster 700; Carl Zeiss Meditec AG, zeiss. com/meditec).⁵³

METHODS

Participants

Participants were recruited from the Northern Ireland Childhood Errors of Refraction (NICER) study,⁵⁴ a crosssectional, epidemiological study of UK children's refractive error which commenced in 2006 and was relaunched in 2018 to re-evaluate the prevalence of refractive error among contemporary children (NICER 2.0). All children participating in NICER 2.0 between March 2019 and March 2020 were included in the cross-sectional aspect of the present study, and a subgroup was invited for repeat measures 12 months after their initial participation. The subgroup was selected in a manner that ensured a range of ametropia was included in the study analysis. Exclusion criteria included the presence of ocular pathology, manifest strabismus and astigmatism ≥1.50 DC as measured by

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Informed written parental consent and participant assent were obtained prior to data collection. The study was approved by Ulster University Research Ethics Committee and adhered to the tenets of the Declaration of Helsinki.

Examination procedures

cycloplegic autorefraction.

Baseline visits took place on school premises during the school day. Twelve months (±2 months) after baseline, repeat measures were undertaken using identical instrumentation and measurement protocols and conducted by the same examiner. Testing for 12-month follow-up took place at Ulster University.

It is recommended that peripheral refraction is measured with accommodation paralysed to avoid changes to the refractive profile.⁵² Hence, cycloplegia was achieved by instilling one drop of proxymetacaine hydrochloride 0.5% followed by one drop of cyclopentolate 1% to both eyes. Autorefraction and ocular biometry were performed at least 20 min after the instillation of the cycloplegic agent, and cycloplegia was confirmed by dilated pupils that were nonresponsive to light.

An open-field autorefractor (Shin-Nippon NVision-K 5001; Rexxam Co. Ltd., rexxam.co.jp) measured central and peripheral refractions.^{55–57} Participants fixated centrally on three targets (Maltese crosses) positioned along the horizontal midline at angles of 0° and ±30° retinal eccentricities, as recommended by the International Myopia Institute.⁵² Both central and peripheral refractions were measured without correction. Participants rested their head against the instrument headrests, kept their head stationary and turned their eyes to fixate the peripheral targets.^{58,59} A minimum of five consecutive measurements were taken at each retinal eccentricity, with the internally calculated representative value used in subsequent data analysis. For the right eye, fixating on the temporal target (to the participant's right side) corresponded with a measurement of the temporal retina (nasal visual field). RPR was defined in terms of retinal eccentricity.

Mutti et al.⁴⁸ used A-Scan ultrasonography for AL measures. In the present study, ocular biometric parameters (AL and lens thickness [LT]) were measured using a more modern biometer, the IOLMaster 700 (Carl Zeiss Meditec AG, zeiss.com/meditec).⁵³ All study instrumentation was calibrated daily prior to data collection.

Definitions

Right eye spherocylindrical refractive data (negative cylinder), in terms of spherical power (S), cylindrical power (C) and axis (θ), were transposed into power vectors for reporting as mean spherical equivalent (M), J₀ (cylindrical power at 90° and 180° axes) and J₄₅ (cylindrical power at 45° and 135° axes) astigmatism using the following conventional formulae:

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$$M = S + \left(\frac{C}{2}\right)$$
$$J_0 = \frac{-C\cos(2\vartheta)}{2}$$
$$J_{45} = \frac{-C\sin(2\vartheta)}{2}$$

Relative peripheral refraction (RPR) refers to M, J₀ or J₄₅ in the nasal or temporal retina relative to the central refractive measures. Hence, RPR M/J₀/J₄₅ was calculated by subtracting central M/J₀/J₄₅ from peripheral M/J₀/J₄₅. Positive and negative M values indicate relative peripheral

Baseline Group

hyperopia and relative peripheral myopia, respectively. Positive and negative J_0 values represent with-the-rule (WTR) and against-the-rule (ATR) astigmatism, respectively. The J_{45} value represents oblique astigmatism.

Participants were divided into refractive groups according to their baseline refractive error⁶⁰:

Myopia	M≤-0.50 D
Premyopia	$-0.50 \text{ D} < \text{M} \le +0.75 \text{ D}$
Emmetropia	+0.75 D < M < +2.00 D
Hyperopia	M≥+2.00 D

Statistical analysis

Statistical analysis was performed using SPSS (version 25; ibm.com). Descriptive statistics were used to describe the data and Shapiro–Wilk tests to explore their distribution.

6–7 years	Ν	222
		(1 myope, 20 pre-myopes, 114 emmetropes, 87 hyperopes)
	Sex	43% male
	Central M	+1.69 ± 1.00, -3.00 to +10.13
12–13 years	Ν	245
		(36 myopes, 72 pre-myopes, 111 emmetropes, 26 hyperopes)
	Sex	54% male
	Central M	+1.25 ± 0.50, -6.50 to +6.25
Longitudinal G	roup	
6–7 years	Ν	56
		(7 pre-myopes, 31 emmetropes, 18 hyperopes)
	Sex	28.6% male
	Central M	+1.63 ± 0.97, +0.25 to +8.75
12–13 years	Ν	70
		(18 myopes, 23 pre-myopes, 24 emmetropes, 5 hyperopes)
	Sex	42.9% male
	Central M	+0.63 ± 1.81, -6.50 to +5.00

FIGURE 1 Flowchart showing the number, refractive group, sex and baseline refractive error of participants seen at baseline (baseline group) and those followed up 12 months later (longitudinal group). There were significant differences in baseline refractive error between baseline and longitudinal groups of both ages (both $p \le 0.003$). N, number; M, mean spherical equivalent in dioptres in terms of median ± IQR, range.

Pearson's/Spearman's correlations were applied to evaluate the relationships between all baseline measures, including central refractive error, RPR and AL, as well as the relationships between baseline RPR and changes in refractive error, AL and LT over 12 months. The relationships between baseline RPR (independent variable) and change in refractive error and axial elongation were determined using multiple linear regression analyses, adjusting for gender, baseline refractive error and AL.

Paired-sample *t*-tests/Wilcoxon signed-rank tests were used to investigate differences between baseline and follow-up measurements of all parameters measured (refractive error, nasal and temporal RPR, AL and LT). A *p*-value < 0.05 was considered significant.

RESULTS

Participant information is described in Figure 1.

Baseline data

Relative peripheral refraction, spherical equivalent (M)

As depicted in Figure 2, myopic participants demonstrated, on average, more hyperopic RPR in the nasal and temporal retina. This contrasts with emmetropic and premyopic participants who displayed, on average, emmetropic RPR and hyperopes who displayed myopic RPR along the horizontal retina.

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An asymmetrical RPR profile, that is, differences between the nasal and temporal RPR, was found in emmetropic (median±IQR difference+0.13±0.12 D) and premyopic (median±IQR difference+0.25±0.13 D) children aged 12–13 years, with the nasal retina exhibiting a more hyperopic RPR (both $p \le 0.03$). All other refractive groups of both ages had symmetrical patterns of RPR (all $p \ge 0.09$).

When baseline AL and RPR were explored as continuous data, a more hyperopic RPR in the nasal ($\rho = 0.22$, p < 0.001) and temporal ($\rho = 0.38$, p < 0.001) retina was significantly associated with longer AL in children aged 12–13 years. Likewise, there was a significant negative correlation found between temporal RPR and AL in 6- to 7-year-old children ($\rho = -0.36$, p < 0.0001). There was no significant relationship between nasal RPR and AL in these younger children ($\rho = 0.07$, p = 0.30).

Relative peripheral refraction, J_0 and J_{45}

Relative to central values, J_0 astigmatism became more ATR with greater retinal eccentricity (Figure S1). The temporal retina showed significantly greater ATR astigmatism than the nasal retina in all refractive groups and ages studied (all $p \le 0.007$). Six- to seven-year-old myopes had insufficient sample size and, therefore, were not included in this analysis. Conversely, J_{45} astigmatism showed little change



FIGURE 2 Mean RPR M in the nasal (N) and temporal (T) retina according to refractive group in children aged 6–7 and 12–13 years. Where sufficient sample size allowed, error bars represent 95% confidence intervals of the means. D, dioptres; M, mean spherical equivalent; RPR, relative peripheral refraction.

over the horizontal retina in all refractive groups and ages studied (all $p \ge 0.06$) (Figure S2).

Longitudinal data

Twelve-month changes in refractive and biometric measures

Baseline and follow-up measures for central M, RPR and ocular biometric parameters are summarised for children aged 6–7 and 12–13 years in Tables 1 and 2, respectively. The single myopic child in the younger baseline cohort did not consent to follow-up; hence, no myopes were prospectively monitored in the younger cohort. One child aged 6–7 years and two aged 12–13 years developed myopia over the 12-month follow-up period (Figures 2 and 3).

Relationship between baseline relative peripheral refraction and myopia progression

There was a significant relationship between RPR M in the nasal retina and axial elongation over 12 months among myopes aged 12–13 years, with greater magnitudes of relative peripheral hyperopia at baseline associated with greater axial growth (p=0.04) (Table 3). There was no significant relationship between RPR J₀ or J₄₅ and myopia progression nor axial elongation in these children (all $p \ge 0.23$).

Myopic children aged 12–13 years were further grouped into those who displayed 'faster' axial elongation over 12 months (\geq 0.20 mm/year)⁶¹ and those who displayed 'slower' axial elongation (<0.20 mm/year). Myopic children who exhibited 'faster' axial elongation had significantly more hyperopic nasal RPR at baseline than those who displayed 'slower' axial change (t=-2.02, p=0.03). There was no significant difference in baseline temporal RPR M between these groups.

Each dioptre of hyperopic RPR in the nasal retina was associated with an additional annual axial elongation of 0.10 mm (95% CI: 0.02–0.17 mm) in 12- to 13-year-olds with myopia (ρ =0.53, p=0.02) (Figure 3).

Relationship between baseline relative peripheral refraction and changes in refractive error and axial length in emmetropes and pre-myopes

Data from children with emmetropic and premyopic refractive errors at baseline were grouped together by age for this analysis (Table 4). A more myopic RPR M in the nasal retina showed a significant correlation with axial growth over 12 months in 6- to 7-year-olds with emmetropia and premyopia (p=0.03). In addition, a more negative RPR J₀ in the nasal retina at baseline was a significant predictor for myopic shift in this cohort (p=0.02) (Figure S5).

In the 12- to 13-year-old children with emmetropia and premyopia at baseline, a more myopic nasal RPR M was significantly associated with a greater negative shift in refractive error over the 12-month period (p=0.04). However, there was no association found between RPR J₀ or J₄₅ and change in refractive error nor AL in these older children (all p > 0.39).

DISCUSSION

Consistent with previous reports, ^{44,62–66} the present study established that myopia is associated with a more hyperopic RPR, emmetropia and premyopia with an emmetropic RPR and hyperopia with a more myopic RPR.

TABLE 1 Baseline and follow-up parameter measures for children aged 6–7 years according to their baseline refractive group.

	Refractive group at baseline											
Premyopia (7)			Emmetropia	(31)		Hyperopia (1	8)					
Parameter	Baseline	Follow-up	р	Baseline	Follow-up	p	Baseline	Follow-up	p			
Central M (D)	+0.63 (0.25)	+0.25 (0.51)	0.03*	+1.50 (0.38)	+1.25 (0.50)	0.004*	+2.69 (1.25)	+2.50 (1.29)	0.04*			
Nas RPR M (D)	-0.38 (0.63)	+0.13 (0.76)	0.02*	0.00 (0.63)	0.00 (088)	0.34	-0.38 (0.87)	-0.32 (1.38)	0.12			
Nas RPR J ₀ (D)	-0.82 (0.69)	-0.49 (0.72)	0.02*	-0.43 (0.39)	-0.53 (0.40)	0.09	-0.41 (0.44)	-0.48 (0.40)	0.02			
Nas RPR J ₄₅ (D)	+0.08 (0.45)	+0.10 (0.41)	0.61	-0.07 (0.25)	0.00 (0.31)	0.65	+0.09 (0.31)	-0.02 (0.40)	0.10			
Temp RPR M (D)	-0.25 (1.12)	0.00 (1.88)	0.06	-0.13 (0.75)	0.00 (1.13)	0.43	-0.82 (1.23)	-0.44 (0.84)	0.08			
Temp RPR J ₀ (D)	-1.49 (0.54)	-1.20 (0.75)	0.25	-1.06 (0.47)	-0.96 (0.50)	0.35	-1.04 (0.65)	-1.09 (0.41)	0.71			
Temp RPR J ₄₅ (D)	-0.06 (0.40)	-0.08 (0.61)	0.87	+0.08 (0.34)	+0.01 (0.46)	0.27	+0.19 (0.41)	-0.05 (0.39)	0.004*			
AL (mm)	22.65 (1.58)	22.92 (1.66)	0.02*	22.88 (1.01)	23.06 (1.13)	<0.0001*	21.74 (1.52)	21.92 (1.68)	<0.0001*			
LT (mm)	3.37 (0.15) ^a	3.32 (0.17) ^a	0.01*	3.46 (0.14) ^a	3.42 (0.15) ^a	<0.0001*	3.47 (0.15) ^a	3.44 (0.16) ^a	<0.0001*			

Note: J₀ and J₄₅ indicate with/against the rule and oblique astigmatism, respectively. *p*-Values from paired sample *t*-tests/Wilcoxon signed-rank tests show the presence of significant differences in baseline and follow-up measures.

Abbreviations: AL, axial length; D, dioptres; LT, lens thickness; M, mean spherical equivalent; Nas, nasal; RPR, relative peripheral refraction; Temp, temporal.

^aMean (standard deviation) presented for parametric data, otherwise median (interquartile range) presented.

*Significant values.

					Refr	active gro	up at baseline					
	Myopia (18)			Premyopia (23	(Emmetropia ((24)		Hyperopia (5)		
Parameter	Baseline	Follow-up	ď	Baseline	Follow-up	р	Baseline	Follow-up	d	Baseline	Follow-up	р
Central M (D)	–1.57 (1.59) ^a	–2.00 (1.69) ^a	0.01*	+0.50 (0.50) ^a	+0.38 (0.75) ^a	0.74	+1.25 (0.47) ^a	+1.32 (0.50) ^a	0.66	+3.38 (2.25) ^a	+3.50 (2.62) ^a	0.29
Nas RPR M (D)	+0.85 (0.64)	+0.67 (0.77)	0.11	+0.32 (0.79)	+0.23 (0.64)	0.43	-0.10 (0.59)	-0.10 (0.72)	1.00	-0.03 (0.94)	+0.02 (0.84)	0.67
Nas RPR J ₀ (D)	-0.60 (0.55)	-0.72 (0.30)	0.23	-0.48 (0.42)	-0.44 (0.32)	0.54	-0.65 (0.38)	-0.74 (0.42)	0.34	-0.62 (0.25)	-0.62 (0.42)	0.69
Nas RPR J ₄₅ (D)	-0.01 (0.34)	-0.13 (35)	0.45	+0.01 (0.46)	-0.02 (0.36)	0.92	+0.05 (0.43)	+0.05 (0.31)	0.33	+0.10 (0.54)	+0.09 (0.30)	0.35
Temp RPR M (D)	+0.84 (0.77)	+0.88 (0.84)	0.74	-0.15 (0.62)	-0.19 (0.67)	0.67	-0.16 (0.64)	-0.35 (0.65)	0.04*	-0.50 (0.62)	-0.68 (0.21)	0.55
Temp RPR J ₀ (D)	-0.97 (0.65)	-0.92 (0.38)	0.66	-1.17 (0.32)	-1.12 (0.47)	0.23	-1.08 (0.43)	-1.10 (0.60)	0.94	-1.22 (0.82)	-1.29 (0.58)	0.50
Temp RPR J ₄₅ (D)	+0.06 (0.43)	-0.08 (0.41)	0.04*	-0.07 (0.27)	-0.07 (0.29)	0.37	-0.10 (0.41)	-0.09 (0.43)	0.94	-0.09 (0.73)	0.00 (0.44)	0.14
AL (mm)	24.50 (0.99)	24.68 (0.99)	<0.0001*	23.59 (0.67)	23.64 (0.68)	0.02*	23.42 (0.82)	23.49 (0.81)	<0.0001*	22.32 (0.82)	22.37 (0.83)	0.12
LT (mm)	3.34 (0.13)	3.35 (0.13)	0.01*	3.44 (0.13)	3.45 (0.13)	0.004*	3.40 (0.21)	3.41 (0.22)	0.03*	3.41 (0.12)	3.43 (0.12)	0.003*
<i>Note</i> : J ₀ and J ₄₅ indicate Abbreviations: AL, axial I ^a Median (interguartile ra	with/against the ru ength; D, dioptres; inge) presented for	le and oblique asti LT, lens thickness; r nonparametric da	gmatism, respe [.] M, mean spheri. ta, otherwise m	ctively. <i>p</i> -Values froi cal equivalent; Nas, ean (standard devia	m paired-sample t- nasal; RPR, relative ition) presented.	tests/Wilcox peripheral ru	on signed-rank tes efraction; Temp, te	sts show the presentimporal.	ce of significan	t differences in base	eline and follow-up	measures.

Findings from animal studies and some clinical observations have led to the hypothesis that peripheral refractive error has a role in driving the development and progression of childhood myopia.^{29,39} The present study found that in established myopes, children with greater magnitudes of relative peripheral hyperopia showed significantly more axial elongation over a 12-month period. Furthermore, in the myopic eyes of teenagers aged 12-13 years old, each dioptre of relative peripheral hyperopia was associated with an additional 0.10 mm of axial elongation over 12 months. This was slightly more than the expected average annual change in AL for White children of this age with progressing myopia (0.07 mm).^{61,67} Assessing the presence and magnitude of relative peripheral hyperopia could be a valuable clinical tool to aid clinicians in identifying myopic children at risk for faster-than-average progression and for whom modification of the image shell using interventions, which add peripheral myopic defocus, are potentially the most applicable myopia control strategy. The data of Zhang et al.⁶⁸ suggest that such children are likely to gain more benefit from optical myopia control strategies. However, the repeatability of cycloplegic autorefraction has been demonstrated to be the greatest centrally and decrease as retinal eccentricity increases.⁶⁹ This greater variability is an important limitation to consider when using autorefraction to measure peripheral refractive errors.

Contrary to the present study findings, Rotolo et al.⁵¹ established that RPR could not predict the progression of myopia in White children. However, unlike the current study, Rotolo et al. did not investigate the relationship between RPR at baseline and change in AL over time.

The relationship between relative peripheral hyperopia and myopia progression was most strongly evidenced through AL rather than refractive measures over the 12month period of the present study. Previous paediatric studies, which reported no association between baseline RPR and myopia progression in Chinese children over similar time frames, have characterised progression using refractive measures alone.^{40,50,70} The greater precision offered by AL measurement is a valuable addition to investigations evaluating predictive factors associated with myopia progression.

Although the nasal retina appears to exert the greatest influence over myopic eye growth, both the nasal and temporal retina of the teenagers included in the present study exhibited comparable magnitudes of relative peripheral hyperopia. Considering that animal studies have demonstrated the retina to respond in a regionally selective manner, it has been speculated that because the nasal retina is exposed to a wider visual field, it may be more sensitive to peripheral defocus and thus be more influential in regulating ocular growth.⁷¹

The relationship between RPR, refractive error change and ocular growth in eyes which were classed as premyopic or emmetropic at the start of the study period contrasted to that seen in established myopes. In the premyopic and emmetropic eyes of children aged 6–7 and 12–13 years, a

*Significant values.

Baseline and follow-up parameter measures for children aged 12–13 years according to their baseline refractive group.

TABLE 2



FIGURE 3 Correlation between baseline RPR M and 12-month change in central M and axial elongation among 12- to 13-year-old children with myopia at baseline. Linear regression lines have been added for 30 degrees nasal and temporal RPR M. AL, axial length; D, dioptres; M, mean spherical equivalent; RPR, relative peripheral refraction.

more myopic RPR in the nasal retina was associated with accelerated axial growth in the younger cohort and a greater negative shift in refractive error in the older cohort over the subsequent 12 months. In contrast, Mutti et al.⁴⁸ established that children who became myopic had more hyperopic RPR than those remaining emmetropic from 2 years prior to onset. However, other reports from studies of children of Chinese and White ethnicities are consistent with the present findings that relative peripheral hyperopia does not precede myopia onset but rather occurs after its development.^{40,50,51,70} It may be postulated that relative peripheral hyperopia is a consequence of the eye changing from an oblate to a relatively more prolate shape.

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In contrast to previous studies conducted in East Asian paediatric cohorts,^{40,70} the present study determined that greater magnitudes of relative ATR astigmatism (J_0) in the nasal retina conferred a significantly increased risk of larger myopic shifts in refractive error among 6- to 7-year-old children with emmetropia or premyopia at baseline. Previous studies involving both children and animal models of myopia have shown an association between ATR astigmatism and the development of childhood myopia.^{72,73} The mechanisms underlying this association are not yet well understood. However, it is suggested that astigmatism may reduce a child's sensitivity to focusing cues leading to a lag in accommodation



TABLE 3 Multiple linear regressions between independent variables RPR M/J₀/J₄₅ and dependent variables 12-month change in central M and AL among children aged 12–13 years with myopia at baseline.

	Муоріа	progression	(D)			Axial elongation (mm)				
Pasalina DDD	Regress coeffici	ion ent	95% CI fo	or B		Regression	coefficient	95% CI fo	or B	p
(D)	Beta	В	Lower	Upper	p	Beta	В	Lower	Upper	
Adjusting for age	, gender an	d baseline M				Adjusting fo	r age, gender an	d baseline AL		
Nas M	-0.74	-0.46	-0.99	0.08	0.08	0.69	0.13	0.01	0.25	0.04*
Nas J _o	0.00	0.00	-0.91	0.91	0.99	-0.12	-0.04	-0.26	0.19	0.73
Nas J ₄₅	-0.53	-0.64	-1.98	0.70	0.30	0.04	0.02	-0.34	0.37	0.92
Temp M	-0.47	-0.24	-0.69	0.21	0.25	0.41	0.06	-0.05	0.17	0.23
Temp J ₀	-0.20	-0.17	-0.84	0.51	0.58	-0.06	-0.01	-0.18	0.15	0.85
Temp J.	-0.53	-0.61	-1.89	0.67	0.31	-0.18	-0.06	-0.36	0.23	0.64

Note: J₀ and J₄₅ indicate with/against the rule and oblique astigmatism, respectively.

Abbreviations: AL, axial length; Cl, confidence intervals; D, dioptres; M, mean spherical equivalent; Nas, nasal; RPR, relative peripheral refraction; Temp, temporal. *Significant values.

TABLE 4 Multiple linear regressions between independent variables RPR $M/J_0/J_{45}$ and the dependent variables change in central M and AL for children with emmetropia and premyopia at baseline.

	Change in central M (D)					Axial elongation (mm)					
Baseline	Regress coefficie	Regression coefficient		95% CI for B		Regression coefficient		95% Cl for B			
RPR (D)	Beta	В	Lower	Upper	р	Beta	В	Lower	Upper	p	
Adjusting for	age, gender	and baseline	e M			Adjusting f	or age, gender and	baseline AL			
6–7 years											
Nas M	0.23	0.13	-0.11	0.37	0.28	-0.47	-0.09	-0.17	-0.01	0.03*	
Nas J _o	0.46	0.49	0.09	0.89	0.02*	-0.35	-0.13	-0.26	0.01	0.07	
Nas J ₄₅	-0.22	-0.31	-0.88	0.26	0.27	0.20	0.10	-0.07	0.26	0.26	
Temp M	0.07	0.04	-0.26	0.35	0.79	0.21	0.04	-0.06	0.14	0.39	
Temp J ₀	-0.30	-0.29	-0.73	0.15	0.19	-0.05	-0.02	-0.16	0.13	0.84	
Temp J ₄₅	0.01	0.02	-0.50	0.54	0.94	0.21	0.10	-0.06	0.26	0.22	
12–13 years											
Nas M	0.37	0.16	0.01	0.32	0.04*	-0.22	-0.02	-0.06	0.01	0.21	
Nas J_0	-0.01	-0.01	-0.35	0.34	0.97	-0.16	-0.04	-0.13	0.05	0.39	
Nas J_{45}	0.07	0.07	-0.34	0.48	0.73	-0.13	-0.03	-0.14	0.07	0.50	
Temp M	-0.22	-0.11	-0.30	0.08	0.23	-0.22	-0.03	-0.08	0.02	0.28	
Temp J ₀	-0.03	-0.03	-0.38	0.32	0.87	0.15	0.03	-0.05	0.12	0.44	
Temp J ₄₅	-0.04	-0.05	-0.56	0.47	0.86	0.05	0.01	-0.11	0.14	0.83	

Note: J₀ and J₄₅ indicate with/against the rule and oblique astigmatism, respectively.

Abbreviations: AL, axial length; CI, confidence intervals; D, dioptres; M, mean spherical equivalent; Nas, nasal; RPR, relative peripheral refraction; Temp, temporal. *Significant values.

and the development of myopia to compensate for hyperopic defocus.⁷³

These data may help to further refine the risk of future myopia in White children whose central refractive error (i.e., emmetropic or premyopic) is already established as a risk factor if a practical method for assessing J_0 in the nasal retina could be applied in clinical practice.⁷⁴ The use of ocular biometrics and family history of myopia data to stratify

patients for future risk of myopia is becoming increasingly attractive as mitigation against future myopia is identified as a core responsibility of eye care practitioners^{20,26} and as novel 'prophylactic' myopia interventions are proposed.¹⁸

The strength of the present study is the longitudinal evaluation of peripheral refraction in relation to ocular growth and refractive change in White children. The use of cycloplegia ensured robust measurement of central

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and peripheral refractive errors, while AL measurements were achieved using swept-source optical coherence tomography to provide precise biometric data with which to identify change. Furthermore, peripheral refraction was measured in two retinal quadrants along the horizontal meridian to facilitate comparisons between nasal and temporal asymmetry, as well as their independent influence on the changes in refractive error and AL.

Common with the limitations of previous reports, the sample size of the present study is relatively small. In line with the prevalence and incidence of myopia within the population studied,³ there was a single myope at baseline in the younger age group and this child did not consent to follow-up. Hence, the longitudinal aspect of the study contained no 6- to 7-year-old myopes at baseline and the number of participants who developed myopia over the study period was limited. Therefore, the investigation of the relationship between RPR and myopia progression was constrained in the younger age group. The present study assessed the peripheral profile only in the horizontal plane. While this could be considered a limitation, this methodology was chosen because previous reports suggest that relative ametropia is limited in the vertical meridian.^{62,64,75} The present study measured uncorrected peripheral refraction, rather than investigating the relative peripheral defocus habitually experienced by those children who were spectacle or contact lens wearers. A moderate (approximately -3.00 D) myopic single-vision spectacle correction has been reported to increase relative peripheral hyperopia by 0.75 D or more, compared with uncorrected measures, depending on the retinal eccentricity measured.^{76,77} This would be expected to exacerbate further the hyperopic defocus experienced by myopic participants in the present study, strengthening growth-promoting signals to the peripheral retina.

Conclusion

A more hyperopic RPR in the nasal retina was associated with accelerated short-term eye growth in White teenage myopes. Eye care clinicians identifying the presence of a hyperopic RPR in the nasal retina of myopic patients may use these data to support the application of optical myopia control strategies. Given that higher magnitudes of relative hyperopia in the periphery indicate risk for faster axial growth, these measures can also inform management decisions relating to retest frequency and how proactively myopia control interventions are applied.

By contrast, in premyopic and emmetropic children, myopic RPR was associated with accelerated eye growth, suggesting that prophylactic application of peripheral myopic defocus to nonmyopes may be counterproductive. However, given the potential of other interventions, which may delay myopia onset in at-risk children, RPR measures provide an opportunity to stratify further premyopic children's risk for future myopia through the evaluation of relative 'against-the-rule' astigmatism.

AUTHOR CONTRIBUTIONS

Rebecca E. Leighton: Conceptualization (equal); data curation (equal); formal analysis (equal); investigation (lead); methodology (equal); project administration (lead); resources (equal); validation (equal); visualization (equal); writing - original draft (lead); writing - review and editing (lead). Karen M. Breslin: Conceptualization (equal); formal analysis (supporting); funding acquisition (equal); investigation (supporting); methodology (equal); project administration (supporting); supervision (equal); visualization (supporting); writing - original draft (supporting). Patrick Richardson: Conceptualization (equal); formal analysis (supporting); methodology (supporting); resources (equal); software (supporting); visualization (supporting); writing - original draft (supporting). Lesley Doyle: Formal analysis (equal); visualization (equal); writing - original draft (equal); writing - review and editing (equal). Sara J. McCullough: Conceptualization (equal); formal analysis (equal); funding acquisition (equal); methodology (equal); project administration (supporting); resources (equal); supervision (equal); validation (equal); visualization (equal); writing - original draft (equal); writing - review and editing (equal). Kathryn J. Saunders: Conceptualization (lead); formal analysis (equal); funding acquisition (lead); methodology (equal); project administration (supporting); resources (equal); supervision (lead); visualization (equal); writing - original draft (equal); writing - review and editing (equal).

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CONFLICT OF INTEREST STATEMENT

The authors report no conflicts of interest and have no proprietary interest in any of the materials mentioned in this article.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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