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Higher order aberrations, refractive error development and myopia control: a review

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Evidence from animal and human studies suggests that ocular growth is influenced by visual experience. Reduced retinal image quality and imposed optical defocus result in predictable changes in axial eye growth. Higher order aberrations are optical imperfections of the eye that alter retinal image quality despite optimal correction of spherical defocus and astigmatism. Since higher order aberrations reduce retinal image quality and produce variations in optical vergence across the entrance pupil of the eye, they may provide optical signals that contribute to the regulation and modulation of eye growth and refractive error development. The magnitude and type of higher order aberrations vary with age, refractive error, and during near work and accommodation. Furthermore, distinctive changes in higher order aberrations occur with various myopia control treatments, including atropine, near addition spectacle lenses, orthokeratology and soft multifocal and dual-focus contact lenses. Several plausible mechanisms have been proposed by which higher order aberrations may influence axial eye growth, the development of refractive error, and the treatment effect of myopia control interventions. Future studies of higher order aberrations, particularly during childhood, accommodation, and treatment with myopia control interventions are required to further our understanding of their potential role in refractive error development and eye growth.

Key words: eye growth, higher order aberrations, myopia control, refractive error development, visual experience

The prevalence of myopia has dramatically risen over the past 60 years[1] with significant regional variations in myopia prevalence across the world, from approximately 15 per cent of adults in Australia,[2] to 70–90 per cent in South East Asian countries such as China,[3] South Korea,[4] Singapore,[5] and Taiwan.[6] By 2050, it is estimated that 50 per cent of the global population will be myopic (> −0.50 D), with one-fifth of these being highly myopic (> −5.00 D).[7] The numerous sight-threatening ocular conditions that are associated with myopia, including retinal detachment,[8] myopic maculopathy,[9] glaucoma,[10] and cataract,[11] represent a significant public health concern both in terms of the global economy[12] and the visual consequences of these ocular pathologies.[13]

While the aetiology of refractive error is multifactorial,[14] evidence from animal studies suggest that visual experience is an important factor in eye growth regulation.[15] Higher order aberrations (HOAs), defined as optical aberrations that remain following the optimal correction of defocus and astigmatism with conventional spherocylindrical lenses, can significantly influence retinal image quality,[16] the accommodation response of the eye,[17] and the relative focal plane of different regions of the entrance pupil.[18] Therefore, there are various mechanisms through which they may play a role in guiding eye growth and the development of refractive errors. This review summarises the literature examining HOAs in animal models of refractive error development and changes in the HOA profile in humans with age, refractive error, abnormal visual development and various myopia control interventions. Additionally, possible mechanisms linking HOAs with refractive error development and the treatment effect of myopia control interventions are discussed in detail.

Visual regulation of eye growth

During infancy and childhood, structural changes occur within the eye to minimise refractive error. Axial length increases proportionately to a decrease in the dioptric power of the optical components of the eye, which suggests biological, passive regulation of eye growth,[19] a process termed emmetropisation.[20] Refractive errors are primarily determined by axial length changes[21] that are disproportionate to the change in the ocular refractive power, where a slowed and increased rate of axial eye growth results in hyperopia and myopia, respectively, due to a failure in emmetropisation.[22] Exposure of the eye to different visual experiences can disrupt emmetropisation, which suggests that the eye also uses visual input to actively influence eye growth in humans.[23]

A range of animal models have demonstrated that complete visual obscuration by lid suture (in chicks,[24] mice,[25] rabbits,[26] tree shrews,[27] marmosets[28] and rhesus monkeys[29]) or the deprivation of form vision using translucent filters (diffusers) (in fish,[30] mice,[31] guinea pigs[32] and rhesus monkeys[33]) typically results in excessive axial elongation and myopia. Similarly, humans with unilateral visual obstruction from congenital ptosis,[34,35] cataract,[35] corneal

opacity[36] or vitreous haemorrhage[37] also typically develop axial myopia due to form deprivation. First reported by Schaeffel et al.[38] in the chick model, imposed defocus also results in predictable bidirectional changes in eye growth in a variety of species.[39] Exposure to hyperopic defocus leads to an increased ocular growth rate to minimise the imposed refractive error, while the opposite occurs in response to myopic defocus, as demonstrated in chicks,[38,40] mice,[25] guinea pigs,[41] fish,[42] tree shrews,[43,44] marmosets[45,46] and rhesus monkeys.[47] Recently, short-term, transient, bidirectional axial length[48] and choroidal thickness[48–50] changes in response to defocus have also been reported in adult humans, but to a much smaller degree than in animal models. Insights from the chick model have shown that the response to imposed defocus occurs rapidly, within minutes of the visual stimuli being introduced.[51] Additionally, the sign-dependent responses to imposed defocus appear to be locally mediated,[52,53] which indicates that the eye can detect odd-error cues for eye growth within the retinal image. Temporal integration of these cues from the retinal image are thought to modulate scleral remodelling and axial eye growth.[54]

Evidence from animal studies

During normal visual development, chick,[55,56] marmoset[57] and rhesus monkey[58] eyes display a decrease in HOAs over time, similar to the reduction in neonatal refractive error. A myopigenic stimulus such as imposed hyperopic defocus[55,59] or form deprivation[56,57,59] results in significantly greater ocular HOAs associated with the development of significant ametropia compared to untreated eyes (Figure 1A); however, both the treated and untreated eyes show a reduction in HOAs over time (Figure 1B). The increase in ocular HOAs observed in chicks reared with monocularly imposed negative lenses[55] and diffusers[56] are predominantly due to changes in third order RMS (root mean square wavefront error), while fourth order[55] and spherical aberration[56] RMS were minimally affected. Similarly, the magnitude of coma and trefoil RMS (both third order terms) increased in monkeys who developed refractive errors from imposed defocus and form deprivation.[59] Coletta et al.[57] also showed strong interocular correlations for each radial order of HOAs, except third order RMS, in monocularly form-deprived marmosets.

Following removal of the visual stimuli in lens-treated and form-deprived eyes, the increase in HOAs generally reduced; however, the HOAs remained higher in the treated eyes than in the fellow untreated eyes.[57,59] Additionally, Ramamirtham et al.[59] found that some eyes showed no recovery from their experimentally induced ametropia, and in these eyes, an increase in total ocular HOAs during the recovery phase was observed, rather than a decrease. Interestingly, there was no difference in the HOA profile between the eyes that recovered and those that failed to recover from their acquired refractive errors prior to treatment (Figure 1C).

The findings of experimentally induced ametropia in animal models suggest that the changes in HOAs associated with refractive error development are predominated by an increase in the asymmetric aberrations of the third radial order.[55–57,59] Eyes with experimentally acquired ametropia show increased magnitudes of coma and trefoil, therefore such asymmetric HOAs may provide a signal that influences ocular growth, which has been hypothesised based on longitudinal data from human studies.[60–62] Additionally, Wildsoet and Schmid[63] demonstrated that the chick eye is able to modulate ocular growth on the basis of optical vergence, hence it may be possible that the eye uses vergence cues from these asymmetric HOAs to influence eye growth. Furthermore, monkey eyes that developed experimentally induced hyperopia or myopia, both exhibited an increase in magnitude and inter-subject variability of HOAs compared to emmetropic eyes.[59] While it remains possible that an increase in HOAs provides a form deprivation-like stimulus due to a reduction in retinal image quality, or that individual HOAs produce a visual signal that promotes or inhibits ocular growth, the overall trends observed in animal studies across various species suggest that an increase in HOAs occurs coincidentally with refractive error development.

The reduction of HOAs[55–58] and the time course of the increase in HOAs during the

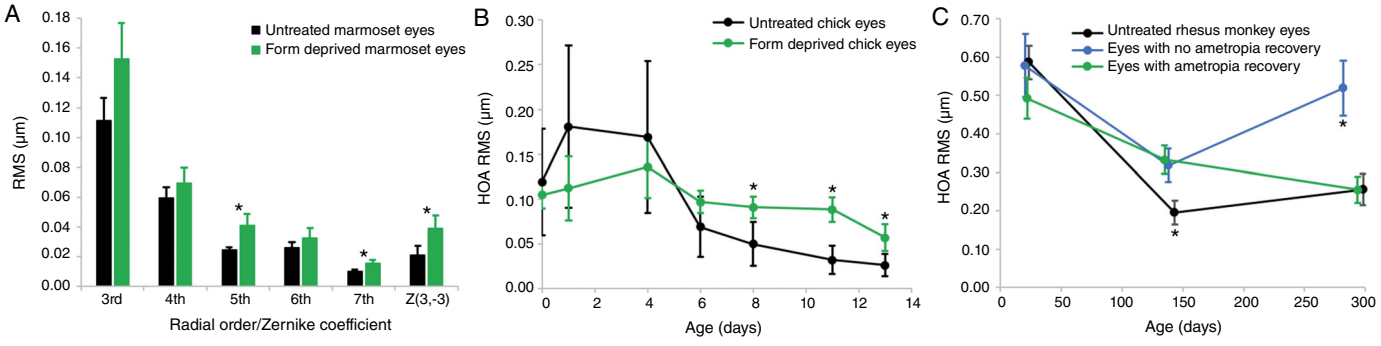

Figure 1. Higher order aberrations (HOAs) associated with animal models of experimental myopia showing A: the greater level of HOAs during or immediately following form deprivation compared to untreated fellow eyes in marmosets (reproduced from Coletta et al.[57]), B: the change in HOAs in chick eyes during treatment with form deprivation compared to untreated control eyes (reproduced from Garcia de la Cera et al.[56]), and C: the change in HOAs in treated rhesus monkey eyes that developed form deprivation or lens-induced ametropia compared to an untreated control group (reproduced from Ramamirtham et al.[59]), where the three time points represent pre-treatment, immediately post-treatment and following a period of recovery in rhesus monkeys. Note that the eyes that did not recover from their experimental ametropia showed increased HOAs compared to untreated eyes and treated eyes that exhibited recovery from induced ametropia. In A, B, and C, asterisks indicate statistically significant group differences. In A and B, error bars represent the standard deviation, and in C, the standard error of the mean.

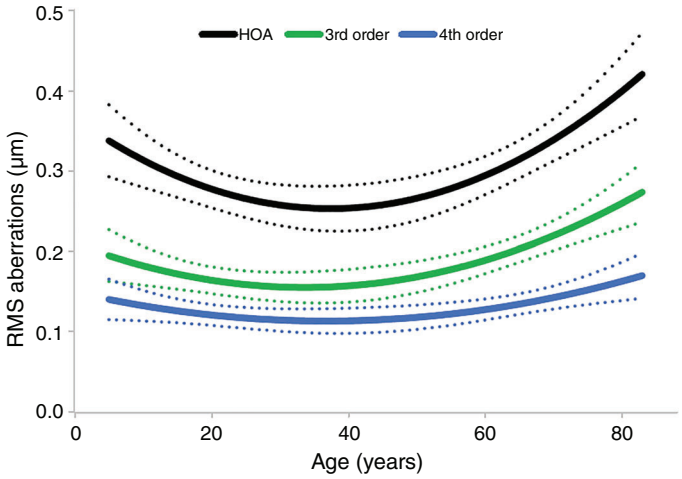

Figure 2. The change in higher order aberrations (HOAs), third order and fourth order root mean square wave front error (RMS) with age over a 5 mm pupil (polynomial regression functions adapted from Brunette et al.[69]). Dotted lines represent the 95% confidence intervals for the regression functions. HOA, third order and fourth order RMS varied in an approximate quadratic association with age, decreasing during childhood to a minimum between 30–40 years and subsequently increasing with age.

development of ametropia[55–57,59] suggests a passive scaling effect due to growth in ocular structures,[55–58] and that any increase in the level of HOAs is likely a consequence, rather than a cause, of refractive error development. However, modelling demonstrates that simple scaling of the optical components in chicks[55] and rhesus monkeys[58] cannot account for the total changes observed in HOAs, which may provide some evidence for visual, rather than entirely passive, regulation of HOAs.

HOAs and age

On-axis HOAs

Total ocular HOAs are influenced by the refractive elements within the eye, specifically the curvature, alignment, refractive index, and axial separation of the anterior and posterior surfaces of the cornea and crystalline lens. In humans, a partial compensatory balance exists between the anterior corneal and internal HOAs (the combination of the posterior cornea and crystalline lens), whereby the internal HOAs are of reduced magnitude and opposite in sign to the anterior corneal HOAs.[64]

Several studies have reported a linear increase in HOA RMS between the ages of 20 and 70 years.[65–68] In a cross-sectional analysis, Brunette et al.[69] demonstrated that across a lifetime (six to 82 years), the change in HOA RMS was best described by a second order polynomial, where the elderly (over 60 years) displayed greater HOA RMS values than those 20 to 60 years old, with a minimum at approximately 40 years (Figure 2). Similarly, other studies have found that HOA RMS remains stable between the ages of approximately 20 and 55 years.[70,71] Brunette et al.[69] also showed that coma and spherical aberration RMS vary with age in an approximate quadratic association, reaching a minimum between 20 to 30 years, and increasing with older age.[71,72] Primary horizontal coma (Z_3^1) and spherical aberration (Z_4^0) have shown negative[65] and positive associations with age,[71,72] respectively, between approximately 20 and 70 years.

Cataract development typically causes internal ocular HOAs to increase,[73–75] predominantly positive shifts in coma RMS and primary spherical aberration (Z_4^0) for cortical and nuclear cataracts, respectively.[73,75] Since anterior corneal HOAs exhibit negligible variation throughout adulthood[68,72,76] and with cataract formation,[75] it is likely that these age-related lenticular changes result in a breakdown of the partial internal compensation of HOAs and account for the reported changes in HOAs with age,[68] particularly over 60 years.[69]

The changes in HOAs observed during childhood are not consistent. A recent large cross-sectional study of Chinese children (n = 1,634) measured HOAs under cycloplegia and reported a trend of increasing HOA RMS from three to 17 years (Figure 3), primarily due to a negative shift in primary vertical coma (Z_3^{-1}), primary spherical aberration (Z_4^0), and secondary trefoil (Z_3^{-5}), and positive shifts in primary trefoil (Z_3^{-3}) and secondary astigmatism (Z_4^2).[77] Conversely, Brunette et al.[69] examined Canadian children under cycloplegia and demonstrated a reduction in HOA RMS during childhood and suggested that HOAs are regulated similarly to lower order aberrations (spherical and astigmatic refractive errors) during emmetropisation. While this finding is consistent with various animal models,[55–58] their sample included only 29 subjects under the age of 20 years whereas Zhang et al.[77] examined over 1,600 subjects in this age group. Significant differences in the refractive error range of the examined populations of Brunette et al.[69] and Zhang et al.[77] may explain the inconsistency in their results, with −3.50 to +3.50 D (across all included ages from six to 82 years) and −10.00 to +8.25 D, respectively, although Zhang et al.[77] reported no significant differences in HOAs between the myopes, emmetropes and hyperopes within each age group. Additionally, Caucasian and Asian adults,[78,79] and Chinese and Malay children,[80] have been reported to exhibit HOA profile differences, particularly for primary spherical aberration (Z_4^0); therefore, ethnic variation may also exist between the HOA profiles of Canadian and Chinese children. Given the cross-sectional designs of both studies, longitudinal studies are required to further the current understanding of the temporal variations in HOAs during childhood.

The studies of HOAs and age in adults show consistent trends in HOAs as a function of age; however, a factor which is typically neglected is the effect of natural pupil size. In adults, it is well-established that pupil size decreases with age.[81,82] Winn et al.[81] demonstrated that average pupil size at 20 years was ~4.5 mm and decreased by ~0.02 mm per year to ~3.2 mm at 85 years, under typical indoor room lighting (~263 lux). Contrary to adults, pupil size in indoor room lighting during childhood has been shown to increase from ~5 mm at birth to ~6.1 mm by late adolescence; however, the exact luminance during measurement was not reported.[83] Each of the studies examining age-related changes in HOAs report the

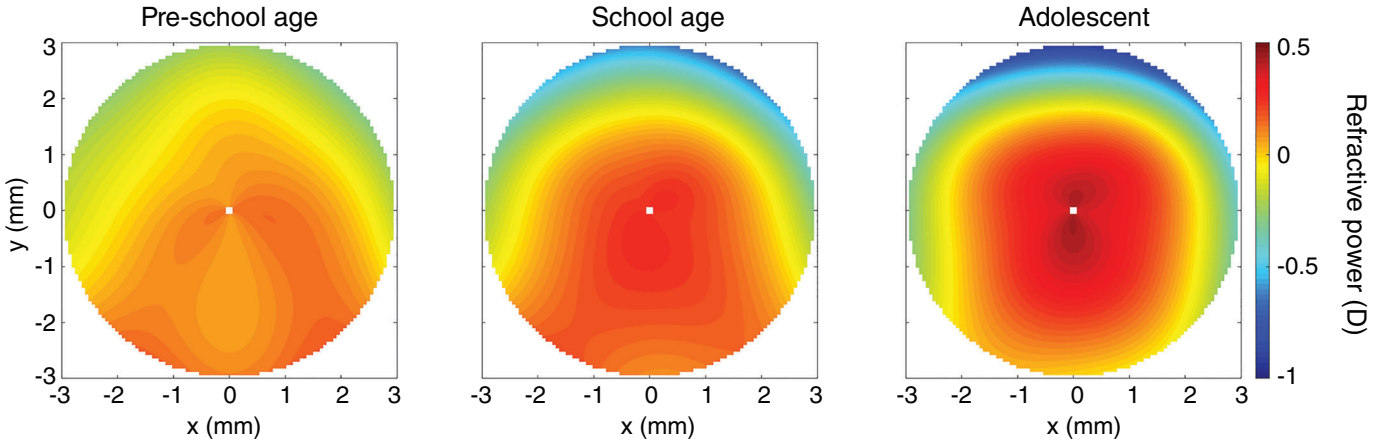

Figure 3. Refractive power maps generated from the higher order aberrations (HOAs) (third to fifth order) in pre-school age children, school age children, and adolescents (data from Zhang et al.[77]). The observed changes between age groups result from positive shifts in primary trefoil (Z_3^{-3}) and secondary astigmatism (Z_4^2), and negative shifts in primary vertical coma (Z_3^{-1}), primary spherical aberration (Z_4^0) and secondary trefoil (Z_5^{-3}), which produce the increase in positive and negative power at the centre and margin of the 6 mm pupil diameter, respectively.

HOAs over fixed pupil diameters of greater than 4.5 mm; however, the HOA profile through the natural pupil may have differed since pupil size varies with age. Furthermore, it is possible that the consistently observed increase in HOAs reported in older adults may be offset by the natural age-related pupillary miosis, since HOAs decrease with decreasing pupil size.[16]

Off-axis HOAs

Off-axis HOAs are typically of greater magnitude than on-axis HOAs, particularly for coma terms, likely as a result of the change in alignment and shape differences of the ocular refractive surfaces from off-axis incident light rays.[84–87] Changes in off-axis HOAs also occur with age. Emmetropic adolescents (11 to 14 years) show greater levels of off-axis HOA RMS compared to on-axis measurements,[88] with a magnitude similar to young adult emmetropes.[85] Primary vertical coma (Z_3^{-1}) and primary horizontal coma (Z_3^1) also increase off-axis, while primary spherical aberration (Z_4^0) remains stable across the visual field.[88]

In young (20 to 30 years) and old (50 to 71 years) emmetropes, HOA RMS also varies with eccentricity in an approximate quadratic association along the horizontal and vertical meridian; however, the rate of change with eccentricity is greater in older eyes.[85] Additionally, Mathur et al.[85] found an age by eccentricity interaction for all third and fourth order Zernike terms, except primary trefoil (Z_3^{-3}) and quadrafoil (Z_4^{-4}), which suggests a difference between age groups in the off-axis variation of these HOAs. However, on average, the magnitude of these HOAs across the visual field was reported to be minimal except for primary vertical (Z_3^{-1}) and horizontal (Z_3^1) coma, and spherical aberration (Z_4^0).[85] Most significantly, the combination of the coma terms increased approximately linearly across the visual field, and older eyes exhibited a greater rate of change than younger eyes,[85] where the orientation of the off-axis variation of the combined coma terms aligned with the axis of the term, as expected due to the change in alignment and shape of the cornea and crystalline lens. For example, vertical coma varied across the vertical meridian, horizontal coma varied across the horizontal meridian, and the combined terms varied along oblique visual field meridians being measured. Primary spherical aberration (Z_4^0) was stable across the visual field in each group; however, the older subjects displayed more positive values on average.[85] Studies of peripheral HOAs in children, in addition to longitudinal studies of off-axis HOAs, ocular biometry and refractive error are required to further examine changes in on- and off-axis HOAs with age and their potential role in eye growth and refractive error development.

HOAs and refractive error

Cross-sectional studies

Numerous cross-sectional studies have compared HOAs between subjects with established refractive errors; however, the results have not been consistent (Table 1). Several studies of adults have found that myopic eyes show significantly higher levels of ocular HOA RMS than emmetropic eyes,[89–91] but others have found no differences.[92,93] Llorente et al.[94] showed that hyperopic eyes exhibit greater HOA RMS than myopic eyes; however, this finding has not been duplicated.[92] Spherical aberration and coma RMS have been reported to increase with increasing levels of myopia.[90] Similarly, most studies have shown that third order, fourth order, and coma-like RMS values are higher in myopes than emmetropes and hyperopes,[89,91] but this is also not a universal finding.[94] While some studies have shown no trend,[92,94] a positive correlation between primary spherical aberration (Z_4^0) and refractive error has been observed, whereby spherical aberration becomes more negative with increasing myopia.[91,93]

Cross-sectional studies of off-axis HOAs in young adults have shown that HOA RMS increases more rapidly with visual field eccentricity in myopes than in emmetropes;[86] however, Osuagwu et al.[87]

Authors	Year	N	Ages (years)	N by refractive group and range (D)	Sex	Location (ethnicity)	Measurement technique	Accommodation control	PD (mm)	HOA	3rd	4th	SA	Coma
Carkeet et al.[80]	2002	273	7.9–12.7	138 M 36 HM (≤ –3.00) 102 LM (–3.00 ≤ –0.5) 123 E (–0.5 ≤ +1.00) 12 H (≥ +1.00)	147 female, 126 male	Singapore (Chinese, Malay, Indian)	Hartman-Shack	1% Cyclopentolate (3 drops)	5	M = E = H	M = E = H	HM < LM = E = H	HM < LM = E = H (same for Z_4^0)	M = E = H
He et al.[89]	2002	170	10–17	87 M (≤ –0.75) 83 E (±0.50)	NR	China, America	Psychophysical ray tracing	Badal	≥ 6	M > E	NR	NR	NR	NR
		146	18–29	92 M (≤ –0.75) 54 E (±0.50)						M > E	M > E	M > E	NR	NR
Paquin et al.[90]	2002	33	18–32	26 M 5 HM (≤ –6.00) 13 MM (–6.00 ≤ –3.00) 9 LM (–3.00 ≤ –1.00) 7 E (≥ –1.00)	NR	Canada	Hartman-Shack	1% Tropicamide; 2.5% Phenylephrine	5; 9	M > E	NR	NR	↑ M / ↑ SA	↑ M / ↑ coma
Cheng et al.[92]	2003	162	26.1 ± 5.6 (mean ± SD)	124 M (≤ –0.75) 19 E (–0.75 ≤ +0.75) 19 H (≥ +0.75)	NR	America	Hartman-Shack	0.5% Cyclopentolate	6	M = E = H	NR	NR	M = E = H	NR
Llorente et al.[94]	2004	46	23–40	24 M (≤ –0.8) 22 H (≥ +0.5)	NR	Spain	Laser ray tracing	1% Tropicamide	6.5	M < H	H > M	NR	H > M (Z_4^0)	H > M
Kirwan et al.[95]	2006	82 (162 eyes)	4–14	25 M (≤ –0.70) 137 H (≥ 0.06)	42 female, 40 male	Ireland	Hartman-Shack	1% Cyclopentolate	6	M > H	M = H	M > H	M = H	M > H (Z_3^{-1})
Kwan et al.[93]	2009	116	19–29	86 M 30 HM (≤ –5.00) 56 MM (–5.00 ≤ –0.50) 30 E (≥ –0.50)	62 female, 54 male	Hong Kong (Chinese)	Hartman-Shack	Internal instrument fixation target	5	M = E	E = M	E > M; ↑ M / ↓ 4th	E > M; ↑M / ↓SA; ↑M / ↓Z_4^0	E = M
Martinez et al.[101]	2009	771	5.7–7.9	53 E (–0.50 ≤ +0.50) 718 H (≥ +0.50)	368 female, 403 male	Australia (Caucasian)	Hartman-Shack	1% Cyclopentolate; 1% Tropicamide	5	E < H	E = H	E < H	E < H; ↓H / ↓Z_4^0	E = H
		643	11.2–13.9	150 E (–0.50 ≤ +0.50) 493 H (≥ +0.50)	318 female, 325 male									
Li et al.[97]	2012	86	7–13	64 M 21 MM (–6.00 ≤ –3.00) 43 LM (–3.00 ≤ –0.50) 22 E (–0.50 ≤ +0.50)	45 female, 41 male	China (Chinese)	Hartman-Shack	0.5% Tropicamide (5 drops); 1.50 D target fogging	5	M = E	M = E	M = E	M = E	Z_3^1 varied

Table 1. Summary of cross-sectional cohort studies examining on-axis higher order aberrations between refractive error groups

Authors	Year	N	Ages (years)	N by refractive group and range (D)	Sex	Location (ethnicity)	Measurement technique	Accommodation control	PD (mm)	HOA	3rd	4th	SA	Coma
Philip et al.[99]	2012	675	16–19	125 M 25 MM (< –3.00) 100 LM (–3.00 < –0.50) 197 E (–0.50 < –0.50) 353 H (≥ +0.50)	339 female, 336 male	Australia	Hartman-Shack	1% Cyclopentolate; 1% Tropicamide	5	MM = LM = E < H	M = E = H	MM = LM = E < H	MM = LM = E < H (same for Z_4^0)	M = E = H
Zhang et al.[96]	2013	148	6–16	99 PM (–4.25 ± 1.58) 49 SM (–3.79 ± 1.92)	NR	China (Chinese)	Hartman-Shack	1% Tropicamide	6	PM > SM	PM > SM	PM = SM	PM = SM	PM > SM (more -ve)
Little et al.[98]	2014	317	9–16	33 M (≤ –0.50) 85 E (–0.13 < +0.50) 199 H (≥ +0.50)	162 female, 156 male	Northern Ireland	Hartman-Shack	1% Cyclopentolate	5	M = E = H	M = E = H	M = E = H	M = E = H	M = E = H
Yazar et al.[91]	2014	1,034	18.3–22.1	217 M (≤ –0.50) 476 E (–0.50 < +0.50) 314 H (≥ +0.50)	477 female, 530 male	Australia (85% Caucasian)	Hartman-Shack	1% Tropicamide; 10% Phenylephrine	6	M > E; ↑ M / ↑ HOA	M > E > H	M > E > H	↑ M / ↓ Z_4^0	↑ M / ↑ coma
Papmastorakis et al.[100]	2015	557	10–15	320 M (≤ –0.50) 201 E (–0.50 < +0.50) 36 H (≥ +0.50)	266 female, 291 male	Greece	Hartman-Shack	Chart fixation (0.25 D demand)	5	NR	NR	NR	↑ M / ↓ Z_4^0	NR
Philip et al.[88]	2018	618	11.09–13.9	91 M (≤ –0.50) 166 E (–0.50 < +0.50) 361 H (≥ +0.50)	52 female, 39 male 77 female, 89 male 179 female, 182 male	Australia (Caucasian, Asian, Middle Eastern)	Hartman-Shack	1% Cyclopentolate; 1% Tropicamide	5	M = E < H	M = E = H	M = E M < H E < H	M < E < H	NR

Coma: coma RMS, E: emmetropia, H: hyperopia, HM: high myopia, HOA: higher order aberrations RMS, LM: low myopia, M: myopia, MM: moderate myopia, N: number of participants in sample/refractive group, NR: not reported, PD: pupil diameter for analysis, PM: progressive myopia, 3rd: third order RMS, 4th: fourth order RMS, SM: stable myopia, SA: spherical aberration RMS, Z_3^{-1}: primary vertical coma, Z_4^0: primary spherical aberration, Z_3^1: primary horizontal coma, ↑: increase, ↓: decrease.

Table 1. Continued

found no significant differences between refractive error groups. Consistent with the findings of on-axis HOA studies, myopes exhibit more negative primary spherical aberration (Z_4^0) than emmetropes,[86] and hyperopes display more positive primary spherical aberration (Z_4^0) than emmetropes and myopes on average across the visual field.[87] Coma varies with visual field eccentricity, with primary vertical coma (Z_3^{-1}) increasing from the superior to inferior field and primary horizontal coma (Z_3^1) increasing from the nasal to temporal field.[86,87] While Mathur et al.[86] reported that the rate of off-axis change in coma is double in myopes than in emmetropes, this finding was not confirmed by Osuagwu et al.[87] across the same visual field range. This may be due to study differences in the level of myopia between the two cohorts, since axial length and corneal and retinal shape are influenced by refractive error and may affect the rates of change of off-axis HOAs.

While each of these studies measured HOAs either under cycloplegia, or using a fixed distance target or the internal fixation target of the instrument (presumably focused for relaxed accommodation), various aberration measurement techniques and instruments have been utilised which may account for the broad inconsistencies between these studies. Given that myopia typically develops during childhood and adolescence, it is difficult to draw conclusions from these cross-sectional cohort studies of adult subjects with established refractive errors and it is therefore also valuable to examine the association between refractive error and HOAs in children and adolescents.

Fewer cross-sectional studies have examined HOAs in children (mostly under cycloplegia), and like studies of adults, there is disagreement regarding the relationship between HOAs and refractive error. Kirwan et al.[95] examined children aged four to 14 years and found that myopic children exhibited greater HOA RMS than hyperopes. He et al.[89] similarly found higher levels of HOA RMS in myopes than emmetropes in children aged 10 to 17 years, measured with a natural pupil and relaxed accommodation. Further supporting a role for HOA in myopia development, Zhang et al.[96] examined myopes aged between six and 16 years and observed that those with a higher rate of progression (greater than 0.50 D per year) exhibited significantly higher levels of HOA, third order and coma RMS than stable myopes. While several studies have found no difference in HOAs between refractive error groups in children,[80,97,98] Philip et al.[99] reported that low hyperopes and emmetropes exhibit increased HOAs compared to emmetropes and low myopes in a group of older adolescents aged 16 to 19 years.

Hyperopic adolescents exhibit more positive primary spherical aberration (Z_4^0)[99] and greater fourth order and spherical aberration RMS than myopic and emmetropic adolescents.[88] Additionally, and in agreement with the findings of adult studies, primary spherical aberration (Z_4^0) tends to become more negative with increasing myopia[100] or decreasing hyperopia;[101] however, not all studies agree.[80,98] Myopic and hyperopic adolescent eyes also exhibit more positive and negative levels of secondary spherical aberration (Z_6^0), respectively,[99] inversely associated with primary spherical aberration (Z_4^0). This inverse association, where negative secondary spherical aberration (Z_6^0) and positive primary spherical aberration (Z_4^0) exist, produces greater relative positive refractive power in the periphery of the pupil and vice versa, which suggests that myopic and hyperopic eyes experience more relative negative and positive refractive power in the periphery of the pupil, respectively (Figure 4). Some researchers have found that myopic eyes exhibit higher RMS values for vertical coma (Z_3^{-1}), horizontal coma (Z_3^1), and third order aberrations than emmetropic[89] and hyperopic[95] eyes; however, the majority of studies report minimal differences between refractive error groups.[80,98,99,101] Interestingly, Zhang et al.[96] reported that myopes with faster progression rates exhibited more negative primary vertical coma (Z_3^{-1}) than stable myopes.

Differences in off-axis HOAs have been reported between refractive error groups in adolescents (11 to 14 years).[88] Myopic eyes tend to display greater levels of HOA, third order and coma RMS than hyperopic eyes in the temporal visual field, while hyperopes exhibit higher amounts of fourth order and spherical aberration RMS than myopes. Philip et al.[88] also found that primary vertical coma (Z_3^{-1}) was more negative in myopic eyes than hyperopic eyes in the temporal field, while myopes displayed more positive primary horizontal coma (Z_3^1) than hyperopes in the inferior visual field. Like the findings for off-axis primary spherical aberration (Z_4^0) in young adults,[86,87] hyperopic eyes showed more positive values than emmetropic and myopic eyes at all observed eccentricities.[88]

The lack of consistency concerning on-axis HOA profiles between refractive error groups demonstrates the potential variability in the measurement of HOAs across individuals, different ethnicities and ages. Cross-sectional cohort comparison studies do not control for this individual variation and therefore longitudinal assessments of HOAs associated with changes in refractive error during childhood (repeated measures of the same children over time) may provide further insights into the relationship between HOAs and refractive error.

Longitudinal studies

Few studies have longitudinally examined HOAs and refraction (Table 2). Philip et al.[88,102] tracked refractive and HOA changes over approximately five years in Australian adolescents of mixed ethnicity. Emmetropic subjects who underwent a myopic shift of at least 0.50 D during the study, exhibited a reduction in third order and coma RMS,[102] while an increase was reported in subjects with stable refractions.[88] The emmetropes,[102] myopes and hyperopes[88] who underwent a myopic shift also showed a significant negative shift in primary spherical aberration (Z_4^0) and a reduction in fourth order and spherical aberration RMS, while the opposite was found in subjects with stable refractions.[88,102] Additionally, a moderate, statistically significant relationship ($r = 0.49$, $p < 0.001$) was observed between the changes in spherical equivalent refraction and primary spherical aberration (Z_4^0), after adjusting for age, gender and ethnicity, whereby a myopic shift was associated with a shift toward negative primary spherical aberration (Z_4^0).[102] Philip et al.[88] also reported small changes in off-axis primary horizontal coma (Z_3^1) in the nasal and temporal fields of myopes, emmetropes and hyperopes who underwent a myopic shift, becoming more negative and positive, respectively. This corresponded with increases in third order, coma and HOA RMS in both horizontal peripheral locations in these subjects.

Lau et al.[61] reported higher spherical aberration and HOA RMS values in Hong Kong children who underwent slower axial eye growth, after controlling for factors known to affect axial elongation such as age, gender, and baseline refractive error. Reduced axial elongation was also

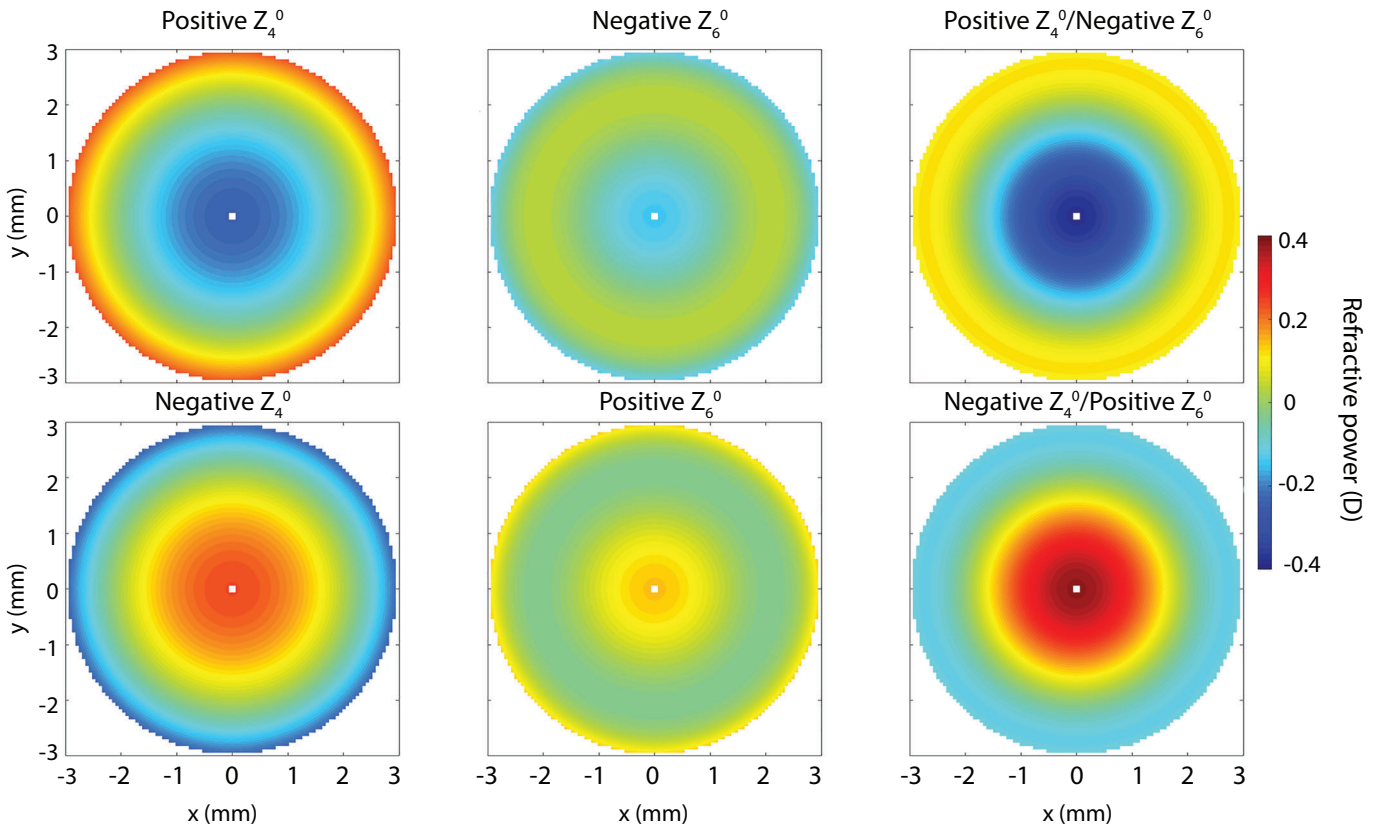

Figure 4. Refractive power maps generated for a 6 mm pupil demonstrating the oppositely signed combinations of ±0.08 µm primary spherical aberration (Z_4^0) and ± 0.02 µm secondary spherical aberration (Z_6^0). Note that the combination of positive primary spherical aberration (Z_4^0) and negative secondary spherical aberration (Z_6^0) results in more relative positive refractive power toward the pupil margin, whereas the opposite occurs for the counter-scenario.

associated with less positive oblique trefoil (Z_3^3), more positive primary trefoil (Z_3^{-3}) and more positive spherical aberration (Z_4^0), with each 0.1 µm increment of each term associated with ~0.13, 0.11 and 0.11 mm difference in axial eye growth per year, respectively.[61] Interestingly, given the partial compensatory effect of anterior corneal HOAs by internal HOAs,[68] Hiraoka et al.[103] found that myopia progression and axial elongation correlate independently with many corneal HOAs, and more strongly than ocular HOAs in Japanese children. Corneal HOAs exhibited strong positive and negative correlations with refractive error shift and change in axial length, respectively, indicating that increased corneal HOAs (baseline measurement or averaged across the study) were associated with reduced myopia progression and axial elongation. The strongest correlations for individual corneal HOA terms were observed for primary vertical coma (Z_3^{-1}), horizontal coma (Z_3^1) and spherical aberration (Z_4^0). Primary vertical coma (Z_3^{-1}) and spherical aberration (Z_4^0) exhibited a positive and negative correlation with the change in refractive error and axial length, respectively, while the opposite trends were observed for corneal primary horizontal coma (Z_3^1). Both ocular coma terms followed the same correlations as the corneal coma terms, but the positive correlation between ocular primary spherical aberration (Z_4^0) and refractive change was not significant.

Greater levels of HOAs and reduced retinal image quality in myopic eyes is not a universal finding. McLellan et al.[104] showed that HOAs measured in myopic adults (mean age 41 years) consistently degraded the modulation transfer function less than randomly generated HOA profiles, which suggests that HOA terms are likely to be interdependent and interact to minimise the overall effect on image quality in myopic eyes. In young adults (19 to 28 years), Collins et al.[18] reported greater dispersion of the point spread function, and a decreased modulation transfer function and Visual Strehl ratio in progressing myopes compared with emmetropes, at both far and near distances. Conversely, a cross-sectional study of children (nine to 10 years) and adolescents (15 to 16 years) found minimal differences in the Visual Strehl ratio between myopes, hyperopes and emmetropes; however, subject numbers varied considerably between the refractive groups.[98] In a cohort of emmetropic adolescents (16 to 19 years), Philip et al.[102] showed that the Visual Strehl ratio reduced significantly during the five-year study period, and this reduction was larger in subjects who became myopic; however, there was no difference in the Visual Strehl ratio between refractive groups at the initial visit. The inconsistent findings of these studies suggest that any differences in retinal image quality observed between refractive error groups may be related to individual variability or methodological differences

Authors	Year	N	Initial age (years)	Duration (years)	Measurement technique	Accommodation control	PD (mm)	↑ MP	↓ MP	↑ AE	↓ AE
Philip et al.[102]	2014	176 E	11.24–13.77	5	Hartman-Shack	1% Cyclopentolate; 1% Tropicamide	5	↓ initial 3rd order; ↓ initial coma; ↓ Z_4^0 (+ve); ↑ 3rd order; ↓ 4th order; ↑ coma; ↓ SA	↑ initial 3rd order ↑ initial coma ↑ Z_3^{-1} (–ve) ↑ Z_4^0 (+ve) ↑ 4th order ↑ SA	NR	NR
Hiraoka et al.[103]	2017	64 M	6–12	2	Hartman-Shack (ocular); Placido disc (corneal)	1% Cyclopentolate (3 drops)	6	↓ corneal HOA; ↓ corneal and ocular Z_3^{-1}; ↑ corneal and ocular Z_3^1; ↓ corneal Z_4^0	↑ corneal HOA; ↑ corneal and ocular Z_3^{-1}; ↓ corneal and ocular Z_3^1; ↑ corneal Z_4^0	↓ corneal HOA; ↓ corneal and ocular Z_3^{-1}; ↑ corneal and ocular Z_3^1; ↓ corneal and ocular Z_4^0	↑ corneal HOA ↑ corneal and ocular Z_3^{-1} ↓ corneal and ocular Z_3^1 ↑ corneal and ocular Z_4^0
Lau et al.[61]	2018	113 M; 24 H	6.1–12.6	2	Hartman-Shack	1% Cyclopentolate; 1% Tropicamide	6	NR	NR	↓ HOA; ↓ SA; ↓ Z_3^{-3} (+ve); ↓ Z_4^0 (+ve); ↓ Z_3^3 (–ve)	↑ HOA; ↑ SA; ↑ Z_3^{-3} (+ve); ↑ Z_4^0 (+ve); ↑ Z_3^{-3} (–ve)
Philip et al.[88]	2018	91 M; 166 E; 361 H	11.09–13.9	5	Hartman-Shack	1% Cyclopentolate; 1% Tropicamide	5	↑ 3rd order (E); ↑ coma (E); ↓ 4th order (M, E, H); ↓ SA (M, E, H)	↑ 4th order (E, H); ↑ SA (E, H)	NR	NR

Coma: coma RMS, E: emmetropia, H: hyperopia, HOA: higher order aberrations RMS, M: myopia, NR: not reported, PD: pupil diameter used for analysis, SA: spherical aberration RMS, Z_4^0: primary spherical aberration, Z_3^{-1}: primary vertical coma, Z_3^1: primary horizontal coma, +ve: positive, –ve: negative, ↑: increase, ↓: decrease.

Table 2. Summary of longitudinal studies examining temporal associations between on-axis higher order aberrations, myopia progression (MP) and axial elongation (AE)

rather than a cause of refractive error development, therefore further longitudinal studies are required.

Cross-sectional cohort and longitudinal studies have demonstrated that HOAs such as coma (Z_3^{-1} and Z_3^1), vertical trefoil (Z_3^{-3}) and primary spherical aberration (Z_4^0) show relatively consistent trends between refractive error groups, and temporal variations of these terms are associated with changes in refraction and axial length, respectively. This indicates that the composition of the HOA profile (the combination or interaction of the terms) may play a more significant role in the modulation of eye growth and refractive error development rather than the magnitude of individual Zernike term co-efficients. These HOAs may provide image cues to the retina to enable the eye to rapidly and accurately respond to different visual stimuli. Wilson et al.[105] reported that only even, not odd, radial order HOA terms (such as fourth and sixth order), provide odd-error cues within the retinal image which may enable the correct identification of the sign of defocus.

Additionally, the accommodative response of the eye appears to be driven by the detection of optical vergence to guide direction and magnitude;[106] therefore, it is likely that the retina can detect relative optical vergence variations across the pupil. For example, in an eye with no HOAs, light rays from the centre and the periphery of the pupil would focus perfectly at the same retinal location; however, in the same eye with the addition of positive or negative primary spherical aberration (Z_4^0), the peripheral light rays would be relatively convergent or divergent to the central light ray, respectively. Horizontal and vertical meridional retinal shape are non-identical[107] and therefore, asymmetric terms such as coma or trefoil may also produce relatively convergent or divergent light rays through different pupil positions which may be detectable by the retina.

HOAs and abnormal visual development: anisometropia and amblyopia

Non-amblyopic anisometropia

Given that the fellow eyes of an individual typically display a high degree of interocular symmetry for both spherical and astigmatic refractive error (isometropia),[108] non-amblyopic anisometropia is a unique ocular condition in which the two eyes experience

a similar environment but develop markedly different refractive errors in the absence of ocular pathology or an amblyogenic factor, typically due to asymmetric axial eye growth.[109] Interestingly, the majority of HOAs are highly correlated between the eyes of both isometropes[16,70,89,110,111] and anisometropes.[110,112,113] Tian et al.[112] found that the more myopic eye of non-amblyopic myopic anisometropes exhibited more positive primary spherical aberration (Z_4^0) than the fellow, less myopic eye, and suggested that this may simply be a consequence of the eye being more myopic, rather than an underlying cause of excessive eye growth. Osuagwu et al.[111] examined off-axis HOAs and conversely found that the less myopic eye of non-amblyopic myopic anisometropes exhibited more positive primary spherical aberration (Z_4^0) on average across the visual field; however, there was negligible interocular difference in the rate of change with increasing eccentricity. Primary vertical coma (Z_3^{-1}) was found to increase more rapidly from the superior to inferior visual field in the more myopic eye; however, the rate of change for primary horizontal coma (Z_3^1) across the horizontal meridian exhibited no significant interocular difference.[111] These cross-sectional findings do not provide clear and consistent evidence of a solitary role for on- or off-axis HOAs in the development of non-amblyopic anisometropia and longitudinal studies are required to elucidate potential underlying mechanisms.

Amblyopia

Unilateral amblyopia results from a significant interocular difference in image quality or visual experience during early life, typically hyperopic anisometropia,[114] strabismus or form deprivation.[115] In children, significant differences in HOAs have generally not been observed between the amblyopic and the non-amblyopic fellow eye in monocular amblyopes, whether the cause of their amblyopia is strabismic[95] or refractive.[116] In 'idiopathic' amblyopia (reduced visual acuity with no amblyogenic factor), while there was no interocular difference in the means of individual terms, interocular differences were observed in the composition of the HOA profile and the interaction between individual terms.[117] Vincent et al.[118] reported no difference in total ocular HOA RMS between the fellow eyes of adult refractive amblyopes; however, the amblyopic eye of strabismic amblyopes, which were typically more hyperopic, exhibited a greater amount of trefoil (Z_3^3) than the fellow non-amblyopic eyes. A weak correlation was observed between the interocular difference in primary spherical aberration (Z_4^0) and the magnitudes of anisometropia and amblyopia, where the more hyperopic, or more amblyopic eye, had more positive primary spherical aberration (Z_4^0). The latter finding supports the typical trend of primary spherical aberration (Z_4^0) to be less positive (or more negative) with increasing levels of myopia. However, these cross-sectional contralateral studies do not provide convincing evidence that HOAs underpin the development of refractive error, anisometropia or amblyopia and suggest that additional factors are involved.

HOAs during near work and accommodation

Near work has long been considered an environmental risk factor for myopia development;[119,120] however, this association remains contested.[121,122] Changes in the magnitude of HOAs have been reported to occur during near work and accommodation, which provides a potential mechanism for the reported link between myopia development and near work.

Buehren et al.[123] demonstrated that a two-hour reading task increased HOA RMS in both emmetropes and myopes. Myopes exhibited greater HOA RMS at both distance and near, and a larger increase in HOA RMS from distance to near fixation. Correspondingly, the increase in HOA RMS associated with the near task resulted in a reduction in retinal image quality, with myopic eyes exhibiting poorer retinal image quality at distance and near than emmetropes, and undergoing a greater reduction at near than emmetropes.[18] Given that near work typically involves accommodation, downgaze and convergence, it is of interest to understand the changes in HOAs that occur independently with each aspect of near work.

For a fixed pupil diameter, HOA RMS consistently increases with greater accommodation demands,[124,125] although some have found this occurs only with demands above 3 D.[126–129] The major consistent change in HOAs that occurs during accommodation is a decrease in primary spherical aberration (Z_4^0), becoming less positive or more negative.[124–126,129–132] Secondary spherical aberration (Z_6^0) also undergoes a relatively small change,[124,132] but is less consistent with respect to the direction of change. Consistent with HOA differences between myopes and emmetropes, myopes exhibit less positive, or more negative, fourth order aberrations than emmetropes, and show larger fourth order aberration changes than emmetropes during accommodation.[131]

In a study of off-axis HOAs during accommodation, a significant interaction was reported between accommodation and eccentricity for all third and fourth order aberrations except primary trefoil (Z_3^{-3}), secondary astigmatism (Z_4^{-2}) and primary spherical aberration (Z_4^0).[84] This suggests that accommodation produces a change in the variation of these HOAs across the visual field; however, Mathur et al.[84] reported these off-axis variations were of minimal magnitude except for primary horizontal coma (Z_3^1) and spherical aberration (Z_4^0) which became more positive and negative with accommodation, respectively, averaged across the visual field.

The on-axis HOA profile also varies during downgaze, with most of the change arising from a negative shift in primary trefoil (Z_3^{-3}) and positive shifts in secondary spherical aberration (Z_6^0) and primary (Z_3^{-1}) and secondary vertical coma (Z_5^{-1}), although significant changes also occur in secondary astigmatism (Z_4^{-2} and Z_4^2), tetrafoil (Z_4^4) and pentafoil (Z_5^{-5}).[132] Ghosh et al.[132] also showed that accommodation during downgaze produced a greater negative shift in primary spherical aberration (Z_4^0) and primary vertical coma (Z_3^{-1}), and a greater positive shift in secondary spherical aberration (Z_6^0) than during accommodation alone. Given these findings, and that anterior corneal HOAs[133] and elevation[134] remain stable during accommodation in primary gaze, the changes in terms such as primary vertical coma (Z_3^{-1}) and trefoil (Z_3^{-3}) during downgaze (and near work) are likely associated with lid-induced corneal deformation at the superior pupil margin,[123,135,136] while the variations in primary (Z_4^0) and secondary (Z_6^0) spherical aberration are likely the result of accommodation.

Subsequent studies have confirmed that typical accommodation demands (2–3 D) produce poorer retinal image quality than a 0 D accommodation demand for a fixed pupil

diameter[124] and Buehren et al.[137] also reported similar results during accommodation for a natural pupil. These findings indicate that with normal levels of accommodation during near work, even with natural accommodation-induced pupil miosis, HOAs increase and retinal image quality is reduced. Long periods of exposure to reduced retinal image quality as a result of increased HOAs or altered HOA profile during prolonged near work may therefore provide a stimulus within the retinal image to which the eye responds by increasing its axial growth.

The combination of different HOA terms can cause different effects on the quality of the retinal image. Thibos et al.[138] demonstrated that the combination of hyperopic defocus and negative primary spherical aberration (Z_4^0) produces a retinal image of poorer quality than if positive primary spherical aberration (Z_4^0) was present with hyperopic defocus. Given that myopes have been shown to exhibit higher accommodative lags[139,140] (producing hyperopic defocus), and primary spherical aberration (Z_4^0) typically becomes negative with accommodation, this combination of optical changes may result in reduced retinal image quality and provide a stimulus for ocular growth. Buehren et al.[141] also modelled different combinations of the terms that most consistently vary with near work; positive vertical trefoil (Z_3^{-3}), negative primary vertical coma (Z_3^{-1}) and negative primary spherical aberration (Z_4^0). The sphero-cylindrical correction that minimised the wavefront error and maximised retinal image quality produced by the typical combination of these terms was a low hyperopic, against-the-rule astigmatic correction. This indicates that the change in the wavefront generated during near work may mimic hyperopic defocus and provide a stimulus to the retina that promotes myopic eye growth (Figure 5).

HOAs and myopia control interventions

The use of optical and pharmacological interventions in clinical practice to prevent or slow the progression of myopia have become more widespread in recent years;[142] however, the underlying mechanisms of these treatments are not fully understood. Given that most myopia control treatments alter the quality of the retinal image, changes in the profile or magnitude of HOAs associated with these interventions may influence axial eye growth and myopia progression.

Anti-muscarinic agents

Arguably the myopia intervention that has shown the greatest efficacy in animals[143] and humans[144,145] is the non-selective anti-muscarinic pharmacological agent, atropine. Atropine reduces myopia progression in a dose-dependent manner,[144–146] although, questions remain about its efficacy in slowing axial elongation, particularly for lower concentrations.[146,147] Given the cycloplegic effect of atropine in humans,[148] its mechanism of myopia control was originally thought to be related to changes in the accommodative system.[149] However, animal studies suggest that anti-muscarinic agents influence growth via an alternative, non-accommodative mechanism.[143,149] While yet to be confirmed in humans, evidence from the chick suggests that atropine binds to receptors within the retina (possibly a combination of muscarinic and non-muscarinic)[149] and triggers a signalling cascade to the sclera via the retinal pigment epithelium and choroid, mediated by nitric oxide.[150] However, the cycloplegic and mydriatic effects of atropine, which change the pupil diameter and the crystalline lens shape and thickness, alter the ocular HOA profile and may provide an optical signal which influences eye growth.

The twice-daily instillation of 1% atropine eye drops for one week in hyperopic Japanese children (three to 12 years) produced a small but significant increase of 0.044, 0.032 and 0.023 µm in ocular HOA, coma-like and spherical-like RMS, respectively, with no demonstrable change in corneal HOAs.[151] Both primary horizontal coma (Z_3^1) and spherical aberration (Z_4^0) approximately doubled following the use of atropine, becoming more positive; however, given that the HOAs were analysed over the same fixed pupil size (6 mm) before and after atropine, the authors suggested that these changes were likely the result of the 1.18 D hyperopic shift.[151]

Although Hiraoka et al.[151] did not report on the changes in pupil size due to 1% atropine, post-hoc analysis indicated that if pupil size increased from 4 to 6 mm, HOA RMS would have increased by ~0.28 µm. Chia et al.[152] reported a change in photopic pupil size with 0.01%, 0.1% and 0.5% atropine from a baseline of ~4.7 mm to 5.8, 7.4 and 7.9 mm, respectively. Based on the polynomial regression reported by Salmon and van de Pol,[153] HOA RMS would have increased by ~0.14, 0.43 and 0.54 µm due to the pupil dilation associated with 0.01%, 0.1% and 0.5% atropine, respectively. Therefore, the change in HOA RMS resulting from pupil mydriasis is significantly greater than the change in HOAs resulting from the cycloplegic hyperopic shift. This suggests that if the effect of atropine on eye growth is mediated via a mechanism involving HOAs, it may be the result of the increased pupil size rather than the changes in HOAs associated with the hyperopic shift from cycloplegia.

The effect of other concentrations of atropine on HOAs have not been examined, although similar findings have been demonstrated following the instillation of other topical anti-muscarinic agents. In similarly aged myopic children, an increase in HOA and spherical-like RMS of 0.025 and 0.014 µm for a 6 mm pupil, respectively, was observed following the instillation of 1% cyclopentolate eye drops.[154] Additionally, a positive shift in ocular primary spherical aberration (Z_4^0) occurred coincidentally with a 0.50 D hyperopic shift, but these changes were of smaller magnitude compared to atropine and there was no change observed in coma-like RMS or primary horizontal coma (Z_3^1).[154] Interestingly, 0.5% tropicamide eye drops produced a small increase of 0.017 µm in total coma but negligible changes in HOA and spherical aberration RMS;[155] however, given the post-instillation interval prior to measurement was only five minutes in this study, the full manifestation of optical changes may not have been observed since maximal cycloplegia due to tropicamide occurs approximately 20 minutes post-instillation.[148] One per cent cyclopentolate and 0.5% tropicamide have been shown to have some[156] and negligible[157] effect in slowing myopia progression, respectively. The magnitude of the changes in HOAs with cyclopentolate and tropicamide are smaller than with atropine; therefore, this may contribute to the differences observed in their myopia control efficacy. Like atropine, the mydriasis from these pharmacological agents are likely to influence HOAs more significantly than the hyperopic shift associated with cycloplegia. Longitudinal studies are required to examine a potential link between the changes in HOAs from anti-muscarinic agents and myopia control.

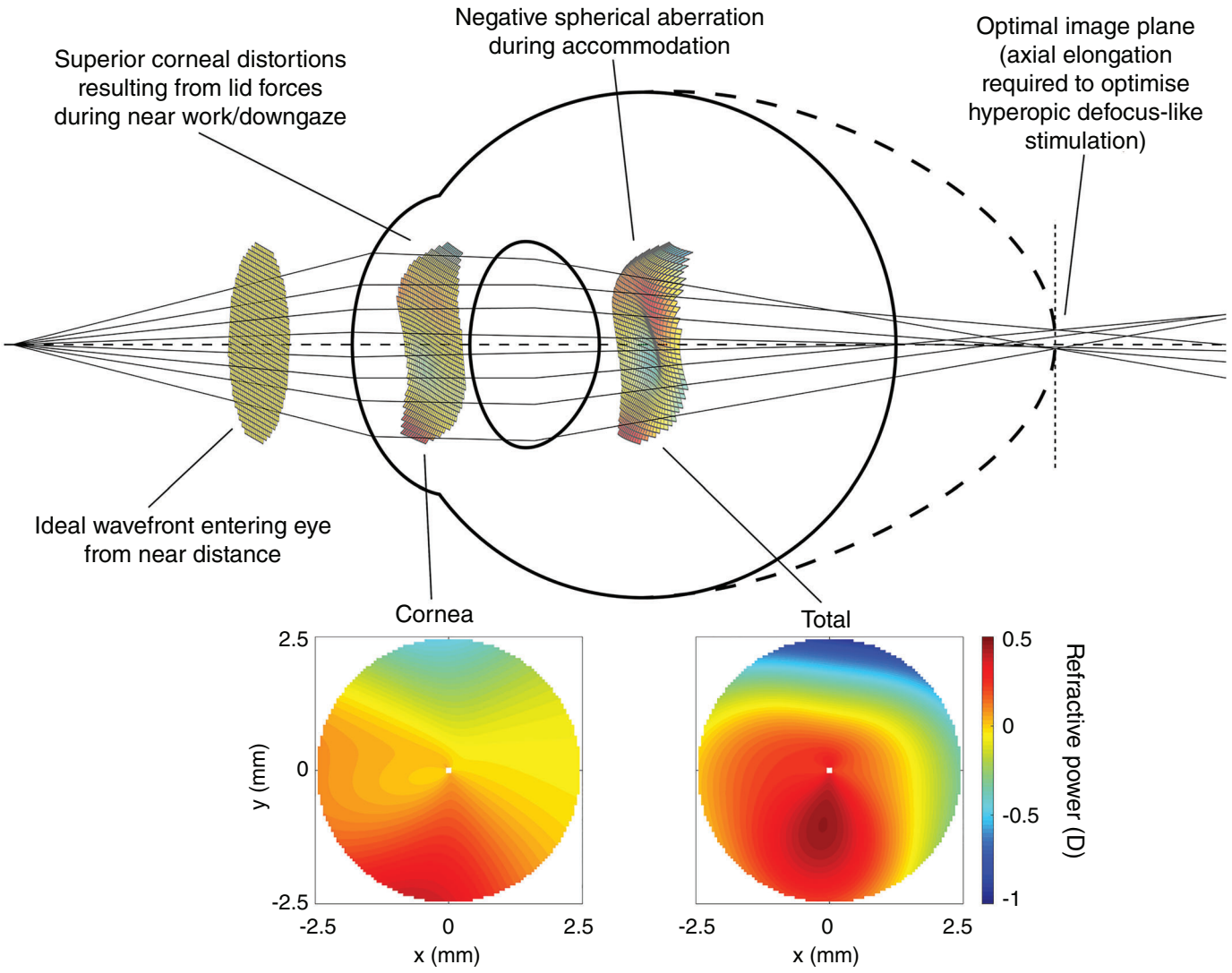

Figure 5. Schematic of a potential mechanism between near work and myopia development involving higher order aberrations (HOAs). The increase in positive trefoil (Z_3^{-3}) and negative primary vertical coma (Z_3^{-1}) from lid-induced superior corneal distortion during downgaze, and increase in accommodation-induced negative primary spherical aberration (Z_4^0) from the change in the crystalline lens results in rays from the edge of the entrance pupil exhibiting negative vergence relative to paraxial pupil rays. These rays produce a plane of best focus (optimal retinal image) posterior to the retina, emulating hyperopic defocus which may encourage axial eye growth. Note the increase in negative refractive power, particularly in the superior third of the pupil in the included corneal and total ocular refractive power maps (generated from third and fourth order HOAs for a 5 mm pupil). Figure and data adapted from Buehren et al.[123,135,141]

Spectacle lenses: bifocal and progressive addition lenses

Several optical interventions, including spectacles and contact lenses, have been developed and studied for their potential ability to slow the progression of myopia. Of the spectacle lens designs, the most promising have been progressive addition and bifocal spectacle lenses.[145] In comparison to single-vision designs, progressive addition lenses reduced myopia progression over three years by approximately 14 per cent,[158] or 25 per cent in those with near esophoria and a lag of accommodation at near.[159] Bifocal lenses, with and without base-in prism in the near segment, have demonstrated a greater level of myopia control over three years, with a reduction in myopia progression of approximately 40 per cent and 50 per cent, respectively.[160]

Near addition lenses were originally thought to act by reducing the near accommodation demand.[158–161] Since the near addition zones induce localised superior relative peripheral retinal myopic defocus,[162,163] and the relative superior peripheral refractive shift was found to be associated with a reduction in the rate of central myopic refractive progression of a one-year period in progressive addition lens

wearers, this may be a possible alternative mechanism by which these lenses slow myopia progression.[163] Progressive addition and bifocal spectacle lenses will vary the optics of the eye as a result of a change in accommodation response from the near addition[161,164] as well as the variable optics in the periphery of the lenses.

It is currently unknown what changes occur to the HOA profile when looking through the different segments of a bifocal lens; however, the intermediate and near zones of a progressive lens produce an increase in HOA RMS of 0.119 and 0.071 µm, respectively, relative to the distance area (for a 5 mm pupil).[165] Predominantly, vertical coma (Z_3^{-1}) and trefoil (Z_3^{-3}) exhibit changes, particularly in the lens periphery.[166,167] While the optics vary substantially across a progressive addition lens, it is unknown what effect this may have on the HOAs of the eye or how this may affect eye growth and refractive error development, since pupil size and accommodation during lens wear will also vary and may influence retinal image quality.

Orthokeratology

Some contact lens designs have shown significantly greater myopia control efficacy than spectacle lenses. Overnight wear of rigid reverse-geometry lens designs, or orthokeratology, produces central corneal flattening and mid-peripheral corneal steepening. Numerous studies[168–170] have demonstrated a significant and repeatable slowing of axial elongation in children by approximately 45 per cent on average with orthokeratology.[145]

Orthokeratology produces a significant increase in on-axis HOAs, even after one night of wear.[171] Following seven nights of treatment, the increase in corneal HOAs ranges from 0.199 µm over a 5 mm pupil,[172] to 0.71 µm over a 6 mm pupil.[173] Additionally, the increase in ocular HOAs has been reported to be 0.175 µm over a 5 mm pupil[172] to 0.63 µm over a 6.5 mm pupil,[174] with the changes in ocular and corneal HOAs typically stabilising after 30 nights of lens wear.[174] The predominant changes in HOAs are positive shifts in corneal[172,173] and ocular[171–174] primary spherical aberration (Z_4^0), and corneal[173] and ocular[171,173,174] primary horizontal coma (Z_3^1). In addition, changes in corneal primary vertical coma (Z_3^{-1}) have been reported.[175,176] The change in primary spherical aberration (Z_4^0) is thought to be the result of mid-peripheral corneal steepening,[173] and comatic changes are likely the result of lens, and therefore treatment zone, decentration.[173,177] While both the corneal and ocular HOAs increase, the corneal changes are substantially greater[172,173] which suggests some internal optical adaptation in response to the corneal modifications over time, perhaps due to an altered accommodative response.[178]

Significant changes in off-axis HOAs also occur as a result of orthokeratology treatment. On average, orthokeratology produces a significant increase in the magnitude and peripheral rate of change of HOA RMS across the visual field.[179] Typically, minimal variation in primary spherical aberration (Z_4^0) is observed across the visual field; however, Mathur et al.[179] demonstrated a significant positive shift on average following orthokeratology, with one subject exhibiting a quadratic variation (more positive at the centre of the visual field) and another subject showing an overall positive shift along the horizontal meridian. Most notably, vertical coma increased from superior to inferior eccentricities and horizontal coma increased from nasal to temporal prior to treatment, which reversed post-orthokeratology.[179]

Hiraoka et al.[60] reported that the change in corneal coma-like aberrations following one year of orthokeratology in Japanese children exhibited a moderate negative linear correlation with axial elongation ($r = -0.46$, $p = 0.0003$), whereby less axial eye growth was associated with a larger change in coma-like aberrations. Conversely, Santodomingo-Rubido et al.[175] found no significant correlation between corneal HOA changes and axial elongation after three and 24 months of orthokeratology in European children. Chen et al.[180] found that a larger pupil size during orthokeratology treatment in Chinese children was associated with slower axial eye growth than a smaller pupil, and suggested that this is due to a greater relative peripheral myopic shift. This change in peripheral refraction was confirmed with modelling by Faria-Ribeiro et al.,[181] who also demonstrated that on- and off-axis HOAs, particularly primary horizontal coma (Z_3^1) and primary spherical aberration (Z_4^0), also increase with greater pupil size as a result of corneal topographical changes during orthokeratology. This finding may indicate that HOAs influence the myopia control effect of orthokeratology; however, further longitudinal studies that examine the changes in on- and off-axis corneal and total ocular HOAs, pupil size and their association with eye growth before and during orthokeratology are required to provide further insights into a potential role for HOAs in the myopia control effect of orthokeratology.

Soft contact lenses: multifocal and dual-focus

Soft contact lenses with modified refractive profiles have also shown significant efficacy in reducing myopia progression and axial eye growth. On average, multifocal and dual-focus lenses reduce myopia progression by approximately 30–50 per cent; however, there is significant inter-study variation as a result of lens design, study duration, and participant characteristics.[182] These lenses can be broadly categorised as multifocal or dual-focus lenses, according to how the optical profile of the lens varies across the optic zone. A multifocal or aspheric lens design provides a central zone of distance power with a progressive increase in positive power toward the edge of the optic zone. A dual-focus lens similarly has a central distance zone, surrounded by multiple concentric alternating zones of relative positive power and the central distance refraction. Given that single-vision spherical rigid[183] and soft contact lenses[184] have minimal effect on myopia progression, the modified optics must contribute to the myopia control effect of multifocal and dual-focus lenses.

The measured effect of different soft contact lens designs on HOAs are similar; however, there are some notable differences (Figure 6). Distance-centre multifocal contact lenses[185,186] produce significant positive shifts in primary spherical aberration (Z_4^0) ranging from 0.125 µm with a low (+1.50 D) to 0.245 µm with a high add (+2.50 D) for a 5 mm pupil.[185] In addition, Fedtke et al.[186] demonstrated that primary horizontal coma (Z_3^1) increases with multifocal contact lenses due to lens decentration. On-eye modelling of distance-centre dual-focus lenses through a schematic eye[185] showed that these lenses also shift primary spherical aberration (Z_4^0) more positively when measured across a 3 mm pupil; however, primary spherical aberration (Z_4^0) became negative when analysed over a 4 mm pupil and more so over a 5 mm pupil. This suggests that the concentric, alternating power profile of the

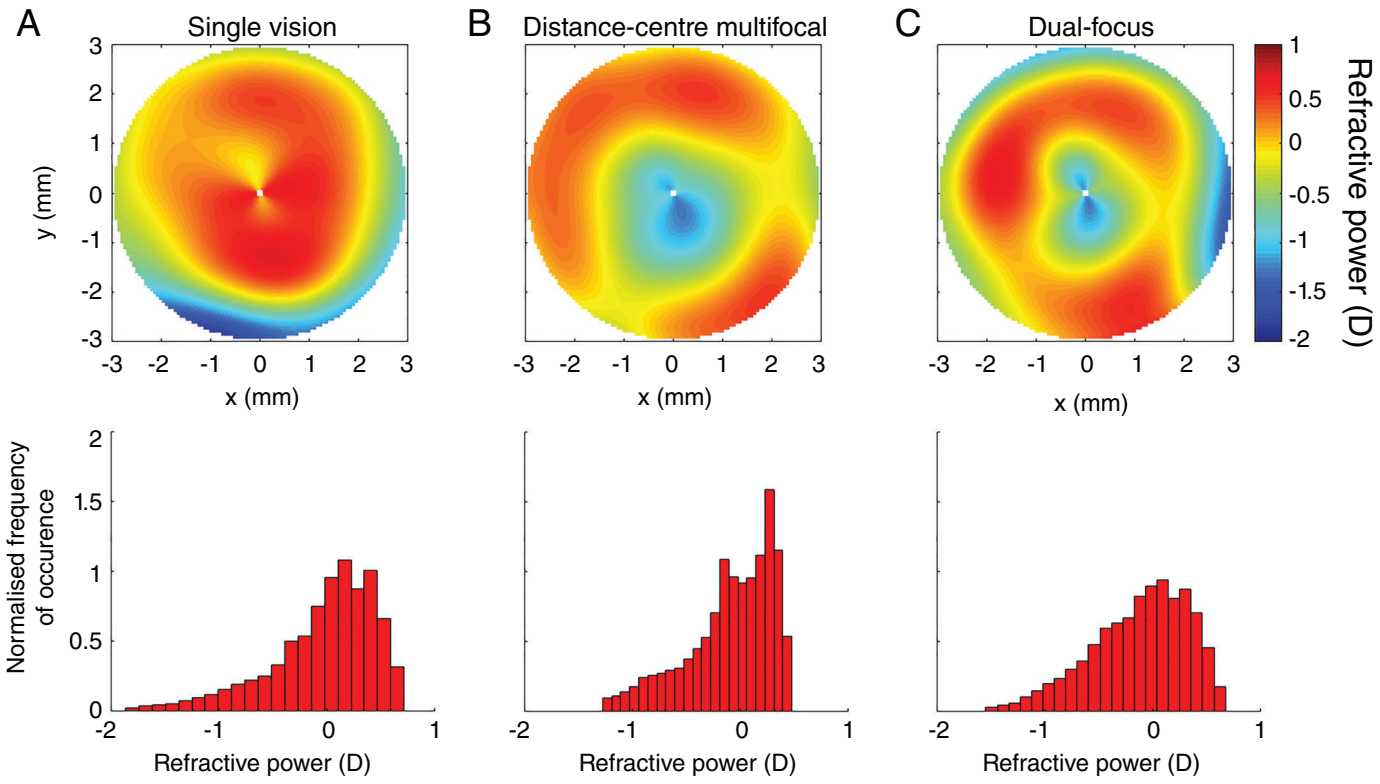

Figure 6. Refractive power maps and associated histograms generated from the difference in ocular higher order aberrations (HOAs) (third to eighth order), measured using a commercial Hartmann-Shack wavefront sensor (COAS-HD, Wavefront Sciences) during soft contact lens wear compared to a bare eye condition in a moderately myopic young adult with normal vision for A: single-vision, B: distance-centre multifocal, and C: dual-focus soft contact lenses over a 6 mm pupil. Each lens had the same distance zone refractive power (−4.00 D), with a +2.00 D addition power in the distance-centre multifocal and dual-focus lens. Note that although the overall refractive power distribution is similar between the three lenses, the location of the refractive powers within the pupil plane varies between the three lenses, with an increase in positive refractive power in the mid-periphery and periphery of the dual-focus and distance-centre multifocal contact lenses compared to the single-vision lens, consistent with the differences in primary spherical aberration (Z_4^0) between these lenses.

lenses causes changes in HOAs that are markedly pupil-dependent. Multifocal contact lenses have been shown to affect the accommodation response;[187,188] however, the change in HOAs during accommodation with multifocal contact lens wear is yet to be examined. Future studies examining the change in HOAs during accommodation while wearing dual-focus and multifocal contact lenses may provide valuable insights into accommodative function during lens wear and potential mechanisms for myopia control.

A multifocal soft lens design by Sankaridurg et al.,[189] which incorporated +2.00 D at 4.5 mm from the optical centre (9 mm optic zone diameter), resulted in a reduction in myopia progression and axial elongation of approximately 34 per cent over one year of wear in Chinese children. Fujikado et al.[190] reported on the myopia control effect of a multifocal soft contact lens which included +0.50 D at 4 mm from the lens centre with a unique 0.5 mm nasal decentration of the optic zone. The decentration was designed to better align with, and produce more symmetrical optics across, the pupil, and produced a reduction in axial elongation of 47 per cent over 12 months in Japanese children but did not demonstrate a significant effect on refractive myopia progression. Another novel soft contact lens design incorporated positive spherical aberration (+0.175 µm for a 5 mm pupil, an amount purported by the authors to negate the accommodation-induced negative shift of spherical aberration) and resulted in a 65 per cent and 54 per cent reduction in axial elongation and myopia progression in American children after six months, respectively; however, the efficacy reduced by 12 months to 39 per cent and 20 per cent, respectively.[191] A crossover study in New Zealand children examining the effect of a dual-focus lens design with +2.00 D zones reported a reduction in myopia progression and axial elongation of 36 per cent and 50 per cent, respectively, over 10 months.[192] A recent two-year randomised, controlled trial in Chinese children[193] examined four novel contact lens designs, two of which incorporated peripheral positive refractive shifts of +1.50 and +2.50 D at 3 mm from the lens centre (similar to the commercial distance-centre multifocal), and two which manipulated the HOAs to improve retinal image quality at

and anterior to the retina, but diminished image quality for planes posterior to the retina. These lenses reduced myopia progression and axial elongation by ~30 per cent and 22 per cent, respectively, with negligible differences between the lens designs.[193]

Based on the difference in refractive power between the centre and periphery of the lenses, and calculations described by Carkeet et al.,[80] the lens designs by Fujikado et al.[190] and Sankaridurg et al.[189] would have produced approximately +0.055 µm of primary spherical aberration (Z_4^0) over a 5 mm pupil, while the lens designs recently reported by Sankaridurg et al.[193] would have produced approximately +0.102 µm over a 5 mm pupil. The Anstice and Phillips[192] lens would have produced a greater level of positive spherical aberration (approximately +0.213 µm over a 4.78 mm pupil) and showed a greater reduction in myopia progression and axial elongation. This, together with the reports that commercially available soft multifocal and dual-focus lenses also produce positive spherical aberration, support a role for spherical aberration in the myopia control effect of these lenses, in what may be a magnitude-dependent manner.

Consideration of pupil size

Although HOAs may influence refractive error development and the treatment effect of myopia control interventions via several potential mechanisms, an important consideration is the effect of pupil size. Most studies typically report HOAs over a fixed pupil size of 5 mm or greater; however, this may not be a realistic pupil size for children across a range of visual tasks and environments, and accommodation demands.[194] Pupil size is dynamic and influenced by several factors, including age,[81,82] ambient illumination,[81,194] and accommodation.[137,194] Exposure to photopic illumination conditions, such as bright outdoor lighting, is likely to reduce the pupil diameter to under 3–4 mm and may result in HOAs of negligible magnitude (diffraction-limited pupil size, or Marechal criterion). It is possible that the reduced HOAs in bright outdoor lighting may explain the reduced axial elongation in non-myopic and myopic children[195] as a result of the improved retinal image quality. Further research is required to examine pupil size dynamics and HOAs under varying levels and combinations of illumination and accommodation, and how these factors may temporally interact to influence eye growth and refractive development.

Conclusion

Several plausible theories based on retinal image quality and vergence cues suggest that HOAs may play a role in the development and control of refractive error and eye growth. However, animal studies suggest that changes in the HOA profile may simply be a consequence of experimentally induced refractive error rather than a cause. Likewise, variations in the HOA profile between myopic, hyperopic and emmetropic eyes in both children and adults have not produced clear, consistent, and reliable evidence to substantiate these theories. Characteristic temporal variations and changes during near work and accommodation provide some evidence of a role for certain HOAs, such as primary spherical aberration (Z_4^0) coma (Z_3^{-1} and Z_3^1) and trefoil (Z_3^{-3} and Z_3^3); however, longitudinal studies examining the changes in HOAs during infancy, childhood and adolescence, and their association with refractive error and ocular structural development are required to comprehensively investigate these theories. Additionally, further longitudinal studies of the changes in HOAs before and after the introduction of various pharmacological and optical interventions for the control of myopia progression are necessary to establish a clearer link between the optical changes associated with these treatments and their demonstrated efficacy.

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