

INVITED REVIEW

Myopic anisometropia: ocular characteristics and aetiological considerations

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Anisometropia represents a unique example of ocular development, where the two eyes of an individual, with an identical genetic background and seemingly subject to identical environmental influences, can grow asymmetrically to produce significantly different refractive errors. This review provides an overview of the research examining myopic anisometropia, the ocular characteristics underlying the condition and the potential aetiological factors involved. Various mechanical factors are discussed, including corneal structure, intraocular pressure and forces generated during near work that may contribute to development of anisomyopia. Potential visually guided mechanisms of unequal ocular growth are also explored, including the influence of astigmatism, accommodation, higher-order aberrations and the choroidal response to altered visual experience. The association between binocular vision, ocular dominance and asymmetric refraction is also considered, along with a review of the genetic contribution to the aetiology of myopic anisometropia. Despite a significant amount of research into the biomechanical, structural and optical characteristics of anisometropic eyes, there is still no unifying theory, which adequately explains how two eyes within the same visual system grow to different endpoints.

Key words: anisometropia, myopia, ocular biometrics, ocular growth, refractive error

Previous studies of both animals and humans have shown that refractive error is largely determined by axial length and that ocular growth is influenced by visual experience.¹ While there is evidence to suggest a genetic influence in the development of refractive errors (in particular myopia),^{2,3} it is now generally accepted that environmental factors, such as near work^{4–6} and outdoor activity⁷ also play significant roles; however, there is currently no single theory that adequately explains the physiological mechanisms underlying the development of myopia. Commonly proposed hypotheses of potential mechanisms leading to myopia development include those where mechanical or optical factors promote excessive axial ocular growth.

Myopic anisometropia or anisomyopia typically defined as a between-eye difference in myopic spherical equivalent refractive errors of 1.00 D or more (usually due to an interocular asymmetry in axial lengths)⁸ is a unique refractive condition, in which the fellow eyes of an individual have grown to two distinctly different end points. The investigation of anisometropia in myopia research (that is, comparing the more

myopic eye to the fellow relatively less myopic eye within the same individual) allows for potentially novel insights into the mechanisms underlying refractive error development, as it allows for greater control of potentially confounding variables such as age and gender, minimisation of inter-subject variations in genetic and environmental factors and thus provides an increased sensitivity in detecting a between-subject (eye) difference in a variable of interest. The aim of this review is to summarise the literature regarding myopic anisometropia (primarily non-amblyopic anisometropia), with a specific focus on the optical (for example accommodation and higher-order aberrations) and mechanical characteristics (for example, corneal structure, intraocular pressure and forces generated during near work) of anisomyopia, which may provide further insight into the genesis of myopic refractive errors.

CHANGES IN ANISOMETROPIA THROUGHOUT LIFE

Numerous studies have examined the prevalence and magnitude of anisometropia at

various stages throughout life. Figure 1 (based on the data from a large clinical population⁹) illustrates the typical changes observed from early childhood to older age. A decrease in the prevalence of anisometropia occurs during infancy and an increase throughout childhood and in older age groups. The change in the magnitude of anisometropia follows a similar trend, with an interocular difference of 1.00 D or more (or an asymmetry in axial length greater than 0.3 mm) being outside the typical range of anisometropia observed across all ages (0.00 to 0.75 D). The hypotheses related to the underlying mechanisms governing such age-related changes in anisometropia are discussed in the following section.

Infancy and amblyopic anisometropia

The subject of amblyopic anisometropia is outside the scope of this paper (for review see Barrett and colleagues¹⁰); however, in this sub-group of amblyopic anisometropes the change in refraction of hyperopic, astigmatic and strabismic anisometropes does

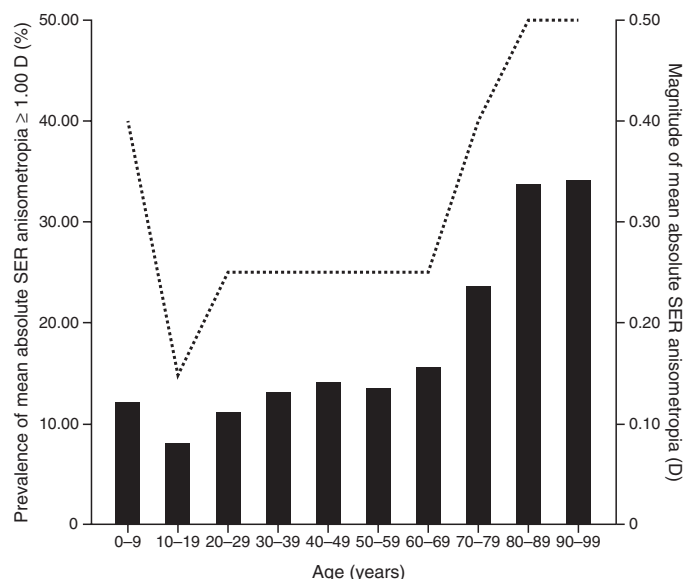


Figure 1. The prevalence and magnitude of anisometropia throughout life (based on data from a large clinical study of more than 85,000 patients, including myopes, hyperopes, amblyopes and cases of ocular pathology⁹). The black bars represent the prevalence of mean absolute spherical equivalent refraction anisometropia of 1.00 D or more (corresponding to the left y-axis). The dotted line represents the magnitude of mean absolute spherical equivalent refraction anisometropia, for all patients including isometropes and anisometropes (corresponding to the right y-axis). The prevalence and magnitude of anisometropia vary significantly over time.

provide some insight regarding the development of asymmetric refractive errors.

Abrahamsson and colleagues¹¹ followed 310 astigmatic one-year-olds (1.00 D or more in one eye) over a three-year period and observed that large amounts of anisometropia can diminish during infancy. Anisometropia persisted in 46 per cent of the anisometropic infants throughout the study period, and approximately 25 per cent of these children developed amblyopia. In another study, Abrahamsson and Sjöstrand¹² retrospectively examined the change in refraction of 20 children who had marked anisometropia of 3.00 D or more at one year of age. Thirty per cent of these children experienced an increase in the magnitude of their anisometropia (mean 1.4 D) and developed amblyopia between the ages of three to 10 years. Anisometropia decreased in the remaining 70 per cent of children over time. Half of these children had a significant decrease in anisometropia (mean 3.00 D) and did not develop amblyopia; however, the other half of this cohort experienced only a mild decrease in anisometropia (mean 1.2 D) but all of these children developed amblyopia.

A number of studies have also observed that the change in refraction over time varies between the amblyopic and non-amblyopic eyes of strabismic^{13,14} and non-strabismic¹⁵ children, with the non-amblyopic eye typically undergoing a significantly greater myopic shift. Caputo and colleagues¹⁶ retrospectively reviewed the change in cycloplegic refractions of 46 young myopic anisometropes, more than half of whom had an eye movement disorder. The authors observed that the less myopic eye at the initial examination became more myopic over time, whereas the more myopic eye (often with amblyopia or strabismus) had a relatively stable refraction during development.

In summary, in early childhood, anisometropia typically decreases during emmetropisation (the reduction in neonatal refractive error toward emmetropia through co-ordinated ocular growth) with the development of binocular co-ordination. When anisometropia persists beyond three years of age, it typically results in amblyopia. The refractive error of amblyopic eyes (associated with hyperopic anisometropia, strabismus or dysfunctional binocular vision)

remains relatively stable over time, whereas fellow non-amblyopic eyes tend to undergo a myopic shift during youth. This suggests that clear vision and possibly accommodation (which is impaired in amblyopia^{17,18}) are required for successful emmetropisation and potentially also for the development of myopia. Dysfunctional or compromised binocular vision may also be related to the development of asymmetric myopic refractive errors.

Non-amblyopic anisometropia in childhood

Several longitudinal studies have examined the development of anisometropia during childhood and typically report an increase in the magnitude of interocular difference in refraction with age, which is proportional to the increase in myopia (Figure 2). It has been suggested that divergent refractive errors between fellow eyes during childhood associated with development and progression of myopia are the result of a failure of internal (between eye) homeostatic mechanisms regulating symmetrical ocular growth.²⁴ Deliberate unilateral optical interventions in young children,²⁵⁻²⁸ which result in asymmetric ocular growth (discussed in detail later) suggest that a local vision-dependent mechanism may also play a role in the development of anisometropia in youth.

The Ojai longitudinal study²⁹ followed the refractive development of children from age six to 17 years. Of 359 children with at least 22 refractive time points (over an 11 to 12 year period), 2.5 per cent developed myopic anisometropia (1.00 D or more spherical equivalent refraction). In this first study examining the development of non-amblyopic myopic anisometropia during childhood, Hirsch stated that '... any theory for the development of myopia must explain how two eyes in an individual attain different refractive states, since both eyes accommodate and converge similarly, receive the same hormonal influences, perform the same tasks and have many other similarities'.

Parssinen²⁰ followed the change in refraction of 238 myopic children aged nine to 11 years over a three-year period and found that anisometropia remained stable in 67 per cent, increased in 27 per cent and decreased in six per cent of subjects. As myopia increased over time (mean spherical equivalent refraction changed from -1.43 to -3.06 D), the magnitude of spherical equivalent anisometropia increased from

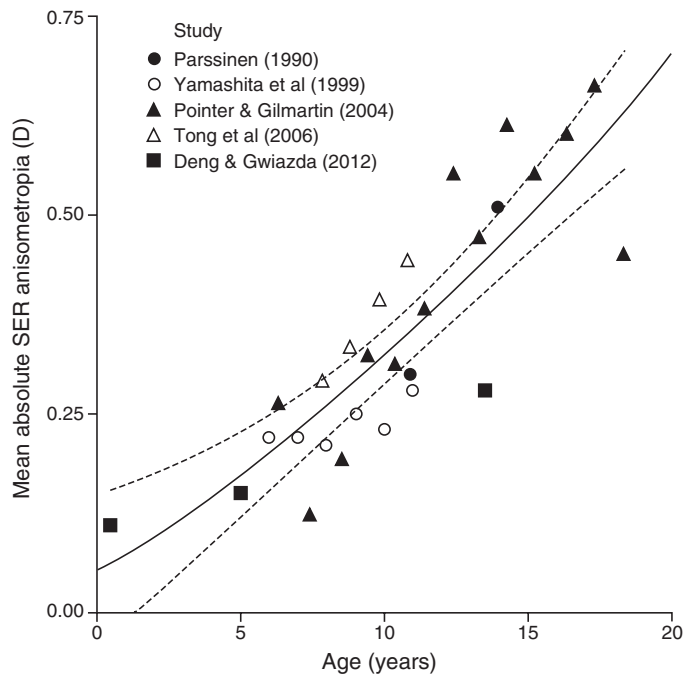


Figure 2. Combined data from longitudinal studies of non-amblyopic anisometropia throughout childhood and adolescence.^{19–23} A small but significant increase in the magnitude of mean absolute spherical equivalent refraction anisometropia is observed with increasing age, which is associated with the progression of myopic and astigmatic refractive errors. Solid line represents the line of best fit and dotted lines 95 per cent confidence intervals.

0.30 to 0.51 D. The initial refractive error, magnitude or axes of astigmatism and type of spectacle correction (single vision or bifocal) were not related to the change in anisometropia; however, the development of anisometropia correlated with the increase in myopia. The authors suggested that the greater the disruption in emmetropisation, due to either genetic or environmental factors, the greater the potential for an asymmetry in ocular length to develop.

In a cohort of predominantly emmetropic Japanese schoolchildren (initial mean spherical equivalent refraction +0.91 D), Yamashita, Watanabe and Ohba²³ also observed that spherical anisometropia remained relatively stable over a five-year period (mean approximately 0.25 D) from age six to 11 years. Over the study period, anisometropia remained stable in 84 per cent of children, while in 16 per cent the magnitude increased or decreased with age. The interocular difference in the magnitude of astigmatism was also stable over time (mean approximately 0.32 D);

however, there was a significant positive correlation between the magnitude of spherical and astigmatic anisometropia. The interocular difference in astigmatism could be a factor contributing to the development of spherical anisometropia or may be a consequence of asymmetric ocular growth.

In a three-year longitudinal study of almost 2,000 children in Singapore aged seven to nine years, Tong and colleagues²² found the mean spherical equivalent anisometropia increased slightly over time from 0.29 D at baseline to 0.44 D at study completion. Less than four per cent of children had anisometropia of 1.00 D or more at baseline. Of these children with 1.00 D or more of anisometropia, 5.1 per cent had an increase in anisometropia of at least 0.50 D, whereas 3.4 per cent had a decrease of at least 0.50 D. The change in anisometropia correlated with the change in inter-eye axial length. Compared with isometropic children, each eye of the anisometropic children had a higher rate of myopia progression but the change in anisometropia over time was similar between the two cohorts.

Pointer and Gilmartin²¹ retrospectively examined the longitudinal change in refraction of a slightly older population aged six to 19 years. They compared the rate of refractive change in 21 unilateral myopic anisometropes (one eye myopic, fellow eye emmetropic) to an age-matched control group of bilateral myopes. The rate of progression in the myopic eye of anisometropes was not significantly different from the rate of progression in bilateral myopes, the opposite trend from that reported by Tong and colleagues.²²

Recently, Deng and Gwiazda¹⁹ examined the change in anisometropia during a longitudinal study of children from the age of six months to 12 to 15 years. The magnitude of anisometropia increased over time and was associated with an increase in both myopic and hyperopic refractive errors. This suggests that mechanisms other than excessive ocular growth during childhood may promote the development of anisometropia (for example changes in binocular vision or ocular dominance).

The magnitude of anisometropia in children with active accommodation could vary depending upon the method used to assess refractive error. However, there is evidence to suggest that the use of cycloplegia during the determination of refractive error has minimal influence upon the magnitude and prevalence (less than one per cent difference in prevalence between cycloplegic and non-cycloplegic techniques) of anisometropia in both children³⁰ and adults³¹ of varying refractive errors.

In summary, the prevalence and magnitude of anisometropia typically increase steadily throughout childhood to young adulthood in association with age (Figure 2) and an increase in myopic or astigmatic refractive error. Changes in anisometropia during childhood correlate with asymmetric changes in axial length between the fellow eyes. The evidence regarding the rate of myopic progression in anisometropic compared to isometropic eyes is conflicting.

Myopic anisometropia in adulthood

While anisometropia decreases during the early years of life (presumably through emmetropisation and binocular vision development) and increases during childhood and adolescence (associated with myopia development), throughout middle age (approximately 30 to 50 years) the prevalence and magnitude of anisometropia

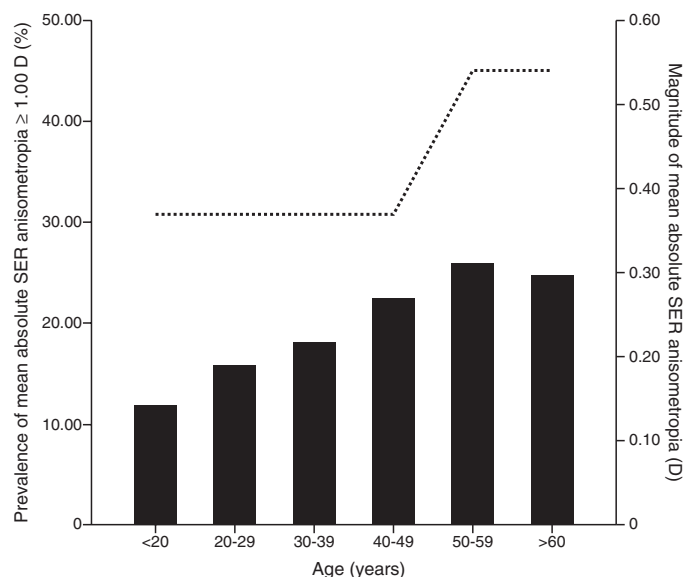


Figure 3. The prevalence and magnitude of anisometropia throughout life in myopia (based on data from a clinical study of refractive surgery candidates³¹). The black bars represent the prevalence of mean absolute spherical equivalent refraction anisometropia of 1.00 D or more (corresponding to the left y-axis). The dotted line represents the magnitude of mean absolute spherical equivalent refraction anisometropia, for myopic patients only including both isometropes (corresponding to the right y-axis).

remains relatively stable (Figures 1 and 3). This may be related to the stability of distance refraction during this period of adult life; however, later in life (beyond 60 years), there is a marked increase in the prevalence of anisometropic refractive errors.^{31–35}

It has been suggested that the increase in anisometropia in older adults may be a result of asymmetric cataract development or unilateral cataract extraction. Studies restricted to phakic patients still demonstrate an increase with age and a higher proportion of anisometropia in patients with bilateral compared to unilateral cataract³² and anisometropia is found to be significantly associated with age even after controlling for the presence of cataract.³⁶

Figure 3 illustrates the age-related changes in magnitude and prevalence of anisometropia for a large cohort of myopic subjects (refractive surgery candidates), excluding cases of pathology, such as unilateral cataract (based on the data of Linke and colleagues³¹). While this study has fewer younger (less than 20 years) and older (more than 60 years) subjects compared to the analysis of Qin and colleagues⁹ (Figure 1), the data display an increase in

the prevalence of anisometropia into old age in healthy eyes without pathology.

Weale³⁴ collated data from several studies examining the association between the prevalence of anisometropia and age and observed an approximate increase in prevalence of one per cent for every seven years of life. He suggested that an asymmetry in cataract development could not explain the significant increase in anisometropia and suggested that neuro-senescence, or a breakdown in binocular vision may play a role in the genesis of divergent refraction in the later years. A recent study has shown that the prevalence of disorders of binocular vision does increase significantly in older age groups.³⁷

In summary, the prevalence and magnitude of anisometropia vary throughout life. Studies of large clinical populations over a wide range of age groups and refractive errors have shown that while anisometropia is associated with spherical ametropia and astigmatism, it is also independently associated with age. A rapid decrease in anisometropia is observed during the early years of life, followed by an increase from childhood to adulthood. Anisometropia is typically stable in adulthood but increases signifi-

cantly in prevalence in older age. The increase observed later in life may be related to a regression of neural control of binocular vision. The increase in the prevalence and magnitude of anisometropia during the period of life typically associated with the onset and development of myopia is of particular interest, as understanding the mechanism underlying the development of anisometropia may provide insight into the development of myopia.

GENETICS AND ANISOMYOPIA

While numerous studies have investigated the influence of genetics on the development of myopia (for example, familial studies,^{38,39} twin studies,^{2,3} identification of genetic loci in high myopia⁴⁰), relatively few studies have examined the heritability of anisometropic refractive errors. In an early genealogical study, Goldschmidt⁴¹ investigated the immediate families of 36 teenagers with high myopia (greater than 6.00 D in one eye), nine of whom had moderate to severe unilateral myopia (average 8.00 D, range four to 14 D). None of the siblings of the anisometropic probands displayed significant asymmetric refractive errors. Also, the refractive status of parents varied considerably; with 55 per cent showing emmetropia or low hyperopia, 22 per cent with isometropic myopia, 11 per cent with myopic anisometropia and 11 per cent with antimetropia. Based on these findings, Goldschmidt⁴¹ concluded that unilateral high myopia does not 'conform to a simple, monomeric mode of inheritance' and speculated that environmental factors may also influence the symmetry of refraction between the fellow eyes.

Several other studies have examined the pedigree of myopic anisometropes, with conflicting findings. Ohguro and colleagues⁴² observed an autosomal-dominant inheritance pattern in a young male with 20 D of anisomyopia. More recently, Feng, Candy and Yang⁴³ reported an autosomal-recessive inheritance pattern in a Chinese family with myopic anisometropia of approximately 5.00 D. In a study of 48 anisometropic children, Weiss⁴⁴ reported that three female patients had a strong family history of anisomyopia and suggested an x-linked recessive inheritance pattern existed in cases of unilateral high axial myopia.

Several case reports of young monozygotic and dizygotic twins also suggest that genetics

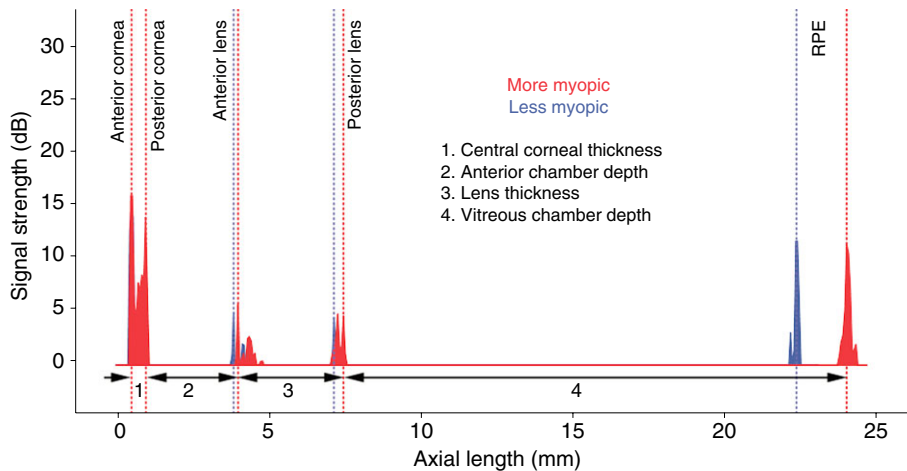


Figure 4. Optical low coherence reflectometry A-scan output for the more myopic (red, axial length 24.70 mm, refraction $-2.75/-1.75 \times 5$) and the less myopic (blue, axial length 23.11 mm, refraction $+1/-0.25 \times 5$) eyes of a typical non-amblyopic anisometrope. Biometric studies of anisometropic eyes have shown a high degree of symmetry between the two eyes for measures of anterior segment structures. In this particular example, central corneal thickness (1) (more 501 μm , less 501 μm), anterior chamber depth (2) (more 3.12 mm, less 2.98 mm) and lens thickness (3) (more 3.53 mm, less 3.47 mm). The biometric basis of axial anisomyopia is the interocular difference in the vitreous chamber depth (4) (more 17.55 mm, less 16.15 mm). RPE: retinal pigment epithelium.

may play a role in the aetiology of moderate to severe myopic anisometropia (approximately 8.00 to 10.00 D). Mirror-image (Sibling 1 refraction: R-L $\propto$ Sibling 2 refraction: L-R) or directly symmetric (Sibling 1 refraction: R-L $\propto$ Sibling 2 refraction: R-L) severe anisometropia has been observed in both twins^{45–47} and non-twin siblings.^{48,49} Such high levels of anisometropia are typically due to abnormal ocular development in the affected eye, such as optic nerve hypoplasia,⁴⁵ macular hypoplasia⁴⁷ or coloboma⁴⁸ or are associated with significant pathology such as chorioretinal atrophy.⁵⁰

Conversely, Angi and colleagues⁵¹ observed two cases of discordant anisometropia in young monozygotic twins (that is, anisometropia in one twin only). Asymmetries in refractive astigmatism were also observed in each of the affected (anisometropic) twins with a higher degree of astigmatism in the more myopic eye. The authors hypothesised that asymmetric visual deprivation due to uncorrected astigmatism during the preschool years directly influences development of anisomyopia. In a pair of older monozygotic twins (62 years old), Dirani and colleagues⁵² also observed significant discordant anisometropia (8.00 D of anisomyopia in one twin only). Given the

identical genetic makeup and the absence of any ocular pathology or significant astigmatism, the refractive asymmetry between the twins might be a result of environmental factors, such as trauma during embryonic development, injury during birth or incomplete genetic penetrance.⁵³

While conflicting evidence exists from familial studies regarding the inheritance of myopic anisometropia (which potentially suggests a multifactorial mode of inheritance), moderate to severe anisometropia present from a young age appears to be a result of genetic rather than environmental influences. Such cases of anisometropia are typically associated with a unilateral structural abnormality causing excessive axial elongation; however, in the absence of ocular pathology, it is likely that anisomyopia is a result of a combination of genetic and environmental factors, such as abnormal (asymmetric) visual experience.

No studies have specifically examined the role of genetics in the development of lower levels of myopic anisometropia, which are more commonly encountered; however, recent advances in genetic testing, which have enabled the identification of numerous genetic loci associated with myopic refractive errors^{54–57} could provide new

insights into the genetic contributions to anisometropic refractive errors.

OCULAR CHARACTERISTICS OF ANISOMETROPIA

In this section, we discuss the anatomical differences between the fellow eyes of anisometropes and speculate how such differences may come about or potentially influence the development and progression of anisomyopia. A number of studies have examined the various structural elements of anisometropic eyes (Table S1). Briefly, the primary biometric basis of anisometropia is the between-eye difference in axial length, in particular the vitreous chamber depth (Figure 4).

There appears to be minimal contribution from the anterior segment, including corneal thickness, anterior chamber depth or crystalline lens thickness (except in lenticular anisomyopia associated with cataract⁶⁶), suggesting that anisometropia is primarily an interocular asymmetry in the magnitude or rate of posterior ocular growth. Numerous studies have reported on the ocular characteristics in anisometropic amblyopia with the asymmetry in refractive errors also being primarily axial in nature¹³ (but may also involve interocular differences in the cornea^{67–69} or crystalline lens structure⁷⁰) and has been associated with alterations in optic nerve head morphology.^{71,72} Some debate still exists as to whether higher-order aberrations play a role in the genesis of amblyopic anisometropia.^{73–77}

MECHANICAL CONSIDERATIONS IN ANISOMYPIA

If mechanical factors contribute to anisometropic ocular growth, then differences may be apparent in the biomechanical properties between the fellow eyes, such as corneal thickness, corneal hysteresis or intraocular pressure (IOP). This section summarises the literature on the between-eye symmetry of biomechanical factors in anisometropia and discusses potential mechanically driven pathways of asymmetric axial elongation.

Cornea

An early study examining the between-eye symmetry of corneal thickness with an electronic digital pachometer revealed that both epithelial and stromal corneal

thicknesses are similar between the two eyes of hyperopic and myopic anisometropes (mean absolute anisometropia 3.33 ± 3.15 D; 1 to 2 μm interocular corneal thickness differences).⁷⁸ This finding has been confirmed using more recent technology (optical coherence tomography, OCT) in severe levels of anisomyopia (approximately 10 D, with less than 3.0 μm interocular difference in central corneal thickness).⁷⁹

While corneal thickness appears highly symmetrical between the fellow eyes of anisometropes, Xu and colleagues⁷⁹ observed a small but statistically significant reduction in corneal hysteresis (1.00 mmHg) in the more myopic eye of severe anisometropes (mean anisometropia greater than 10 D), suggesting a slight change in the cornea's mechanical properties. Hysteresis is also reduced in conditions associated with corneal thinning such as advanced keratoconus or following corneal laser refractive surgery.⁸⁰ Shen and colleagues⁸¹ also observed significantly lower levels of corneal hysteresis in high myopes (spherical equivalent refraction greater than -9.00 D) compared to a control group of emmetropes and low myopes with similar corneal thickness and suggested that the structure of corneal collagen may be altered with higher levels of myopia, similar to the changes in scleral composition and biomechanics observed in high myopia.^{82,83} Conversely, in lower levels of myopic anisometropia (around 2.00 D) corneal biomechanics appear to be unaltered between the fellow eyes.⁶² These studies suggest that changes in corneal structure or biomechanics appear to be limited to high levels of myopic anisometropia.

Intraocular pressure

Another potential mechanical factor in myopia development is IOP. The role of IOP in the development of myopia has been studied extensively in both animals and humans; however, the findings have been equivocal. As myopia is primarily axial in nature, early theories proposed that raised IOP was responsible for excessive inflation or elongation of the globe. Van Alphen⁸⁴ demonstrated that increasing IOP in both enucleated cat and human eyes resulted in significant axial elongation of the globe without radial expansion. The author concluded that the tone of the ciliary muscle mediates the tension within the choroid and subsequently the sclera, which in turn influences expansion of the globe and leads to an increase in axial length.

As the measurement of IOP may be influenced by variables such as age, blood pressure, corneal thickness⁸⁵ and diurnal variation,⁸⁶ numerous studies have compared the more and less myopic eyes of anisometropes to control for individual variations, which may confound results in comparative cohort studies investigating the association between IOP and different refractive errors (for example, emmetropes compared with age-matched myopes) (Table S2).

If a relationship does exist between IOP and axial elongation, one might expect that IOP would be higher in the more myopic eye of anisometropes, at least during the development or progression of myopia; however, cross-sectional studies using both contact and non-contact applanation techniques have shown no significant differences in IOP between the fellow eyes of low to moderate level anisometropes (approximately 2.00 to 5.00 D).^{62,87,89-91} These studies suggest that axial elongation due to a simple IOP-induced expansion of the globe is unlikely to be involved in the development of axial anisomyopia. However, studies examining the symmetry of IOP in moderate to severe anisometropes (on average approximately 5.00 to 10.00 D anisomyopia)^{61,88} observed a slightly higher IOP (one to two mmHg) in the more myopic eye, which approached⁷⁹ or reached^{61,88} statistical significance. An isolated case report of unilateral chronic angle closure in a young female described a marked myopic shift in the affected eye (8.00 D change in spherical equivalent refraction over 11 years); however, the asymmetric change in refraction was primarily due to altered corneal curvature (5.45 D interocular difference in mean corneal power) and not axial elongation (0.4 mm interocular difference).⁹²

It may also be possible that anisometropia could develop through an IOP-dependent mechanism in the presence of symmetrical IOP, if between-eye differences exist in scleral biomechanics. Lee and Edwards⁹⁰ calculated that the stress exerted upon the sclera was significantly higher in the more myopic eyes of anisometropes compared to the fellow eyes. The authors⁹⁰ proposed that an interocular difference in scleral thickness due to different rates of collagen synthesis might result in asymmetric axial elongation and the development of anisomyopia despite symmetrical IOP.

While small, clinically insignificant differences in IOP have been detected

between the fellow eyes of severe myopic anisometropes (around one to two mmHg), in general, cross-sectional studies of anisomyopes do not support an IOP-related mechanism of asymmetric axial expansion of the globe. The cross-sectional nature of the above studies leaves open the possibility that either short-term (for example, diurnal variations or IOP spikes⁹³) or longer-term fluctuations in IOP may vary in anisometropic eyes. Although no studies have specifically reported on the change in IOP over time during the development of anisometropia, longitudinal studies of development of myopia in children have failed to find an association between IOP and axial growth.^{94,95}

Mechanical effects of near work

Since several epidemiological studies^{4,96-98} have reported an association between near work and myopia, it has been suggested that mechanical forces generated during near work such as those produced during convergence or ciliary muscle contraction could promote axial elongation. When near work is performed the eyes typically converge and accommodate to maintain clear, single binocular vision of near targets. Here, we consider potential mechanical pathways associated with convergence and accommodation in asymmetric myopia development.

Convergence

Forces exerted by the extraocular muscles during convergence are thought to have the potential to lead to changes in axial length.⁹⁹ Bayramlar, Cekiç and Hepson¹⁰⁰ concluded that transient axial elongation associated with near work is a result of convergence rather than accommodation after observing significant vitreous chamber elongation measured with ultrasonic biometry in young subjects following near fixation with and without cycloplegia. However, Read and colleagues¹⁰¹ reported that axial length measured with partial coherence interferometry appears largely unchanged in adults both during and following a period of sustained convergence.

Recently, Ghosh and colleagues¹⁰² examined the influence of gaze direction (nine different directions were examined) upon axial length during distance fixation and also found no significant change in axial length with nasal gaze (that is, convergence); however, a significant increase in axial length (relative to primary gaze) was

observed during inferior and infero-nasal gaze directions. Importantly, axial elongation was only evident when the eye was turned to maintain fixation, rather than a head turn, suggesting that the changes in eye length were due to extraocular muscle forces. Interocular differences in the size or insertion points of the extraocular muscles, in particular those associated with convergence and downward gaze (that is, the superior oblique and inferior rectus) or asymmetric convergence in downward gaze (one eye converging more than the fellow eye) as a result of an abnormal head turn could result in different forces transmitted between fellow eyes and an asymmetry in transient axial length changes during near work.

It has also been suggested that anisometropia may be related to facial structure, specifically the position of the orbits. Lateral displacement of one orbit would induce an asymmetric convergence demand between the two eyes, potentially causing greater mechanical stress on the eye further from the vertical midline. Martinez¹⁰³ noted that anisometropes tended to have asymmetric naso-pupillary distances; however, the interocular difference did not correlate with the magnitude or sign of the between-eye difference in refractive error. If convergent muscle forces do play a role in the development of anisomyopia, one might expect that in cases of unilateral esotropia, the squinting eye would typically be myopic relative to the fixating eye; however, studies of strabismic children have found the opposite to be true (the fixing eye becomes more myopic relative to the squinting eye over time).^{13–15}

Accommodation

Ciliary muscle contraction is associated with small but significant increases in the eye's axial length. Various studies have documented transient changes in axial length using highly precise non-contact instruments during^{104–106} or following¹⁰⁷ periods of accommodation; however, the magnitude of axial elongation between myopic and emmetropic cohorts varies between studies.

In two separate studies of anisomyopes, no significant difference was observed between the two eyes with respect to transient changes in axial length following a 10-minute binocular reading task (2.50 D accommodative demand) or during an accommodative task at 2.50 and 5.00 D

stimuli during monocular fixation.¹⁰⁸ While the more myopic eye displayed a slightly greater change in axial length during accommodation compared to the less myopic eyes for both the 2.50 D (three μm greater) and 5.00 D stimuli (four μm greater), these interocular differences did not reach statistical significance. Over time or for larger accommodative demands, it may be possible that an asymmetric accommodative response could lead to transient axial length elongation of different magnitudes between the two eyes, potentially leading to axial anisometropia.

If ciliary body forces or choroidal tension generated during accommodation cause transient axial length changes following near work and are related to longer-term changes in ocular growth, then ciliary body (or ciliary muscle) thickness might be larger in myopes compared to emmetropes or larger in the more myopic eye of anisomyopes relative to the fellow eye. This finding has been reported in children (emmetropes compared to myopes)¹⁰⁹ and in cases of unilateral high myopia (mean anisometropia 8.00 D);¹¹⁰ however, in a recent study of anisometropes (1.00 D or more of spherical anisometropia), ciliary muscle size was largely symmetrical between the two eyes (although slightly thinner in the more myopic eye).¹¹¹

Factors other than ciliary body size may influence the amount of force transmitted to the posterior eye during accommodation, such as the structural and biomechanical properties of the choroid and sclera. Significantly thinner choroids have been observed in myopic children compared to emmetropes¹¹² and in the more myopic eyes of anisomyopic adults,⁶⁴ which could promote unequal axial elongation (or at least result in asymmetric biomechanical stress at the posterior globe) in the presence of symmetrical ciliary body structure and function. On the other hand, it has been suggested that a thicker ciliary muscle may restrict equatorial ocular growth (producing greater axial expansion) or result in poor contractility leading to a reduced accommodative response, both of which could initiate axial elongation and the development of myopia.¹¹³

In a retrospective case series examining long-term complications of unilateral traumatic hyphaema, Lin and Lue¹¹⁴ observed significant anisometropia (1.00 D or more) in 44 per cent of their patients. On average, the unaffected eye was 1.23 ± 2.13 D more

myopic than the injured eye for all trauma patients and 2.76 ± 2.47 D for the subset of 'traumatic' anisometropes. A strong correlation was observed between the extent of anterior chamber angle recession (that is, zero to 360 degrees) and the between-eye asymmetry in refraction ($r = 0.60$, $p < 0.01$) and axial length ($r = -0.57$, $p < 0.01$). Following trauma, the majority of patients also displayed an asymmetry in accommodation. Given that IOP was not significantly different between the two eyes, the authors suggested that 'traumatic cycloplegia' halted myopic progression in the injured eye compared to the fellow eye, similar to the effect of atropine¹¹⁵ or pirenzepine.¹¹⁶ This study adds some weight to the theory that the ciliary body (or accommodation) is involved in asymmetric axial elongation; however, whether this is an optical or mechanical mechanism (or a combination of the two) remains unclear.

OPTICAL FACTORS IN ANISOMYOPIA

Numerous studies with animal models have shown that unilateral manipulation of visual input such as hyperopic defocus (via a spectacle lens) or form deprivation (via lid suture or diffuser) results in compensatory ocular growth (choroidal thinning and axial elongation to adjust the position of the retina) to achieve emmetropia in the experimentally treated eye.^{1,117,118} This results in the development of anisometropia (or unilateral myopia). If anisomyopic ocular growth in humans is influenced by an interocular difference in visual experience, then asymmetries in optical properties (for example, corneal or total ocular higher-order aberrations) may be evident between the two eyes of anisometropes.

Asymmetric visual experience and ocular growth

Deprivation of form vision during infancy results in the most severe form of amblyopia. Retinal image degradation due to ptosis,¹¹⁹ corneal scarring,¹²⁰ congenital cataract¹²¹ or vitreous haemorrhage¹²² typically leads to excessive axial elongation (form deprivation myopia) and dense amblyopia. The magnitude of myopia and thus anisometropia is related to the degree and age at the onset of image degradation.

Similarly, studies have shown that deliberate unilateral manipulation of the retinal image in humans can alter axial elongation

between the two eyes. Cheung, Cho and Fan²⁶ observed asymmetric ocular growth in an 11-year-old myopic anisometrope undergoing unilateral orthokeratological treatment in the more myopic eye. Over a two-year treatment period, the less myopic eye grew 0.34 mm (an increase in myopia of approximately 1.00 D) compared to the treated more myopic eye, which grew only 0.13 mm, suggesting that the corneal reshaping slowed myopic progression in the treated eye. Similarly, in a contralateral design clinical trial of 26 children wearing an orthokeratology lens in one eye and a conventional rigid gas-permeable lens in the fellow eye, Swarbrick and colleagues²⁸ observed a significant interocular difference in both ocular growth and refraction after one year; the eye wearing the conventional rigid gas-permeable lens was on average 0.09 ± 0.17 mm longer and 0.57 ± 0.66 D more myopic than the fellow eye wearing the orthokeratology lens.

Phillips²⁷ followed 13 11-year-old myopes fitted with monovision spectacles (2.00 D or more) over a period of 30 months. Using dynamic retinoscopy, the author observed that all children accommodated to read using the distance-corrected dominant eye rather than the near-corrected eye. As a result, the near-corrected eye received myopic defocus for all levels of accommodation. Myopic progression was significantly slower in the near-corrected eye compared to the fellow distance-corrected eye. All subjects developed anisometropia due to the interocular symmetry in vitreous chamber growth (interocular difference of 0.13 mm per year). When these subjects returned to conventional distance spectacle wear, the anisometropia reduced to baseline levels within 18 months.

In a larger study, Anstice and Phillips²⁵ examined the change in refraction and axial length in 40 young non-anisometric myopes (11 to 14 years old) over a period of 20 months, while wearing a different design of soft contact lens in each eye. A single vision lens was worn in one eye and a multifocal lens (simultaneous vision—distance centre) was worn in the fellow eye. The mean increase in myopic progression (spherical equivalent and axial length) over 10 months was significantly reduced in the eyes wearing the multifocal lens (-0.44 ± 0.33 D and 0.11 ± 0.09 mm) compared to the single vision lens (-0.69 ± 0.38 D and 0.22 ± 0.10 mm). The reduction in myopia progression associated with multifocal lens wear

was attributed to the constant peripheral myopic defocus induced during all levels of accommodation.

Recently, Read, Collins and Sander¹²³ examined the short-term change in axial length and choroidal thickness in young adults following one hour of imposed monocular defocus. Using an optical biometer, significant changes in axial length were observed, which corresponded to the direction of the induced defocus. Lens-induced hyperopic defocus (-3.00 D) and form deprivation (diffuser) both resulted in choroidal thinning and axial elongation, while lens-induced myopic defocus ($+3.00$ D) resulted in a thickening of the choroid and a decrease in axial length (only in the eye with the imposed defocus). This study suggests that the adult human visual system is capable of detecting the direction of defocus and adjusting the position of the retina to minimise the imposed blur by altering the thickness of the choroid. Previous studies with young animals have shown similar short-term changes in choroidal thickness occurring within minutes in response to defocus that precedes longer-term changes in ocular growth.

These studies demonstrate that deliberate manipulation of the focal properties of the retinal image in young subjects has the potential to influence ocular growth and lead to changes in the refractive state of the eye. It follows that interocular differences in retinal focus may underlie anisomyopic ocular growth.

A recent case report of non-amblyopic progressive adult antimetropia¹²⁴ (anisometropia in which one eye is myopic and the fellow eye is hyperopic) also adds weight to the above evidence for a local mechanism of ocular growth regulation in humans with relatively independent control in each eye. In this particular case, the increase in antimetropia was due to a combination of unilateral axial elongation in one eye and the gradual manifestation of latent hyperopia in the fellow eye.

Sorsby, Leary and Richards⁸ reported on the ocular characteristics of six antimetropic children (aged seven to 16 years). All of the children exhibited low hyperopia in one eye (1.00 to 2.00 D) and a moderate degree of myopia in the fellow eye (mean absolute anisometropia 4.93 ± 1.33 D). The origin of the antimetropia varied substantially; three cases of axial length asymmetry (mean 2.44 ± 0.13 mm), two due to an interocular differ-

ence in crystalline lens power (mean 4.25 ± 0.48 D) and one as a result of an asymmetry in corneal power (1.7 D). Using more sophisticated techniques (ultrasonography and corneal topography), Kuo, Shen and Shen⁶¹ examined a larger cohort of older antimetropes of similar magnitude (19 to 30 years old, mean spherical equivalent refraction antimetropia 5.28 D) and found no significant differences between the two eyes for anterior eye biometrics (corneal thickness and anterior chamber depth) but a significant difference in axial lengths (mean 2.00 mm, 95 per cent CI 1.7 to 2.5 mm) and concluded that the biometric basis of antimetropia is the interocular asymmetry in axial length.

Antimetropic ocular growth in the absence of amblyopia or pathology is an intriguing refractive anomaly, perhaps even more so than anisomyopia, as the two eyes within the one visual system have not only developed markedly different refractive errors but in opposite directions from emmetropia. While the existing literature regarding antimetropia is limited (potentially due to its low prevalence, up to 0.1 per cent^{125,126}), future research into antimetropic ocular growth may provide valuable insights into retinal image-mediated asymmetric ocular growth and the development of myopia.

Pupil size

When considering the optical properties or image quality of the eye, an important factor to take into account is pupil size. Asymmetry in pupil size (anisocoria) or an interocular difference in the quality and size of the fundus reflex is often used as a screening technique for interocular differences in refractive errors or ocular misalignment in children;¹²⁷ however, in a cohort of anisomyopic subjects,¹⁰⁸ pupil dimensions were measured using digital photography and customised software and were found to be highly symmetrical between the more and less myopic eyes. Although the difference in pupil diameter between the more and less myopic eyes approached significance (more 3.53 mm and less 3.48 mm, $p = 0.09$) there was no correlation between the degree of physiological anisocoria and anisometropia.

Corneal power

It is generally accepted that in an individual with no eyelid abnormalities, the two eyes display some degree of corneal symmetry

(direct or mirror symmetry) with respect to the axes of astigmatism.^{128,129} A high degree of symmetry exists between two eyes for corneal power in both isometric¹³⁰ and anisometric eyes measured with keratometry (that is, the central cornea)^{58–60,63} (Table S3). Although there is significant variability in corneal power in emmetropia and myopia,¹³¹ several studies have shown greater corneal power^{132–134} and a less prolate corneal shape¹³⁵ in myopes compared to emmetropes.

Using videokeratoscopy, Vincent and colleagues⁶² observed small interocular differences between the flat and steep corneal meridians of two the eyes in a cohort of anisomyopes. The more myopic eyes exhibited more prolate corneas, in contrast to previous studies, which have shown that corneas tend to become less prolate with increasing levels of myopia.^{136,137} The mean refractive corneal power (average of the steep and flat corneal meridians) was also significantly greater (steeper) in the more myopic eyes, which is in contrast with previous biometric studies of anisometric subjects^{8,58,61} and may be due to the more accurate method used to assess the corneal shape.

Gwiazda and colleagues¹³⁸ followed a cohort of children from the age of one year and observed that infantile against-the-rule astigmatism was associated with increased myopia and astigmatism during childhood (school age) and hypothesised that uncorrected astigmatic errors during the emmetropisation period may play a role in the development of myopia.

Buehren and colleagues¹³⁹ also postulated that altered mid-peripheral corneal shape and optics due to lid pressure during reading might be a trigger for refractive error development. Temporary corneal distortions (changes in corneal astigmatism or higher-order aberrations) resulting in hyperopic defocus or retinal image degradation may lead to compensatory axial elongation. A similar mechanism could be proposed in the development of myopic anisometropia. A greater amount of peripheral corneal flattening in one eye could result in peripheral hyperopic defocus, triggering asymmetric axial elongation.

Vincent and colleagues¹⁴⁰ investigated the change in corneal optics following a short reading task in young non-amblyopic anisomyopes. The more myopic eye displayed a small but significantly greater increase in against-the-rule astigmatism

compared to the less myopic eye over a 6.0 mm analysis diameter. This finding lends some support to the notion of an astigmatic image-mediated mechanism associated with the development of anisomyopia.

It could also be argued that altered corneal shape may be a result of vision-dependent ocular growth rather than a cause of development of myopia. Kee and Deng¹⁴¹ reported significant changes in corneal astigmatism following various visual manipulations in young chicks, including form deprivation, hyperopic and myopic defocus. Small corneal differences observed between the eyes of anisometric subjects may be attributed to axial elongation (rather than causing it) and subsequent alterations in scleral structure, which could impact upon the cornea at the limbus.

Together, these studies suggest that alterations in corneal optics could potentially play a role in the development of myopia and anisometropia. Given the association between the progression of astigmatism and anisometropia during childhood and the observation of higher levels of astigmatism in the more myopic eye of anisometric twins, the relationship between astigmatism, retinal image quality and asymmetric ocular growth requires further research.

Accommodation

The accuracy of the accommodative response and optical effects of accommodation in various refractive error groups has been investigated in detail.¹⁴² Typically a greater lag of accommodation (under accommodation during near work) has been reported in myopes compared to emmetropes.^{143–146} It has been suggested that hyperopic defocus associated with a lag of accommodation may provide a cue to ocular growth and the development of myopia.

Numerous studies have explored the plausibility of aniso-accommodation in isometric individuals. Koh and Charman¹⁴⁷ reported that during binocular viewing, when the eyes are presented with stimuli of unequal accommodative demand, the eye which requires the least accommodative effort to maintain clear focus of the target will control the accommodative response in both eyes. Marran and Schor¹⁴⁸ also observed that when presented with unequal accommodative targets, subjects demonstrated aniso-accommodation to approximately one quarter of the interocular difference in demands. At a stimulus difference of approximately 3.00 D, there appeared to

be a suppression mechanism involved in eliminating the image from the eye with the higher accommodation demand. Conversely, Troilo, Totonelly and Harb¹⁴⁹ suggested that the binocular accommodative response in marmosets reared with imposed anisometric defocus was an average of the two different demands rather than an aniso-accommodative mechanism or a response driven by the lower of the two demands.

Thus, interocular differences in the accommodative demand (or response) could provide a stimulus to asymmetric ocular growth. Charman¹⁵⁰ postulated that the simple act of reading across a page induces an unequal accommodative demand between the eyes (when not viewing directly along the midline), which increases as the working distance to the text is decreased (or interpupillary distance increases). If the eyes remain relatively centred and stationary over the reading task, the defocus experienced in one eye will also be experienced in the fellow eye in the opposite direction of gaze and each eye would receive the same amount of blur (averaged over time). When a head tilt or turn is adopted or any position in which the reading material is not centred in front of the eyes, the accommodative demand for each eye will again change. At a working distance of 10 cm, when reading on an A4 page, the interocular difference in accommodative demand at the end of a line of text may reach up to 2.00 D.¹⁵⁰ Therefore, viewing reading material at a short working distance (with a head tilt) may lead to hyperopic defocus in one eye, assuming a consensual accommodative response to the lower of the two demands.

In a qualitative study, Childress, Childress and Conklin¹⁵¹ examined refractive error types in a range of occupations and considered the potential influence of specific work-related visual tasks (with respect to the vertical midline) upon the development of anisometropia. The authors questioned participants regarding their typical visual demands, in particular the position of reading material and work instruments. In general, those who reported a habitual reading posture centred on the vertical midline displayed symmetrical refractive errors (both spherical and astigmatic), while individuals who placed reading material to one side (due to office environment or job requirements) were more often anisometric with the eye closer to the visual task usually the more myopic eye.

In a similar study, Harris¹⁵² investigated the association between the specific visual demands of different musicians in a symphony orchestra (that is, the effect of instrument type on head tilt or turn and seat position relative to the conductor and sheet music) and their refractive errors. A number of musicians exhibited myopic and astigmatic anisometropia. Typically, the eye positioned closer to the visual task at near displayed greater spherical myopia and less astigmatism compared to the fellow eye. The findings from these studies suggest a potential role for asymmetric viewing during near work in the development of anisomyopia; however, the underlying mechanism (for example, unequal accommodative demands, eyelid forces or asymmetric convergence) remains unknown.

A limited number of studies have directly examined the accommodative response in myopic anisometropes (Table S4). In an early study, Hosaka, Matsudo and Chuang¹⁵³ measured the monocular amplitude of accommodation in a large cohort of anisometropes (interocular differences of 1.00 D or more and including some amblyopes) and a control group of isometropes. Ninety-seven per cent of isometropes had an interocular difference in amplitude of accommodation of less than 2.00 D, compared to 69 per cent in the anisometropic cohort. Of the anisometropic subjects with an interocular difference in accommodation greater than 0.50 D, the amplitude of accommodation was reduced in the more myopic eye 70 per cent of the time; however, there was no significant correlation between the interocular difference in accommodative amplitude and the magnitude of anisometropia. Seventeen subjects (mean age 21 ± 7 years) exhibited an interocular difference in accommodative response between 2.00 and 3.00 D but again, there was no clear evidence of a refractive error-accommodation interaction (that is, the more myopic eye showed a greater lag in only 50 per cent of these cases).

Xu and colleagues¹⁵⁴ used an infrared optometer to measure the interocular symmetry of the accommodative response in 20 anisometropes with 2.50 to 7.00 D of spherical anisometropia at a range of accommodative demands. The more myopic eyes exhibited a larger accommodative lag compared to the less myopic eyes for accommodative demands of 2.00, 3.00 and 4.00 D; however, these differences did not reach statistical significance.

Recently, Lin and colleagues⁶⁵ investigated the magnitude of near work-induced transient myopia (NITM, a slight myopic shift in refractive error following near work) in the more and less myopic eyes of young anisomyopes (approximately 2.00 D anisometropia) during binocular viewing. On average, the more myopic eyes displayed a slightly greater level of transient myopia and a longer decay period to baseline refraction, which reached statistical significance. A moderate correlation was also observed between the interocular difference in NITM and the magnitude of anisometropia ($r = 0.31$, $p < 0.05$). The authors suggested that interocular differences in ciliary body thickness¹¹⁰ may be related to the observed differences in NITM between the fellow eyes; however, for this relatively low level of anisomyopia, ciliary body biometrics are similar between the more and less myopic eyes.¹¹¹

To our knowledge, these are the only studies to directly examine the interocular symmetry of accommodation in anisomyopia. This may be due to previous research, which has shown a symmetric accommodative response between the eyes of normal subjects during both monocular¹⁵⁵ and binocular¹⁵⁶ viewing. It has been suggested that the dominant eye (traditionally the preferred eye for distant sighting) may exhibit different accommodative responses to the fellow non-dominant eye. In amblyopia, the non-dominant (amblyopic) eye shows impaired accommodation;^{76,157,158} however, few studies have examined the role of ocular dominance and accommodation in non-amblyopic subjects. Given the potential association between accommodation and development of myopia, the characteristics of accommodation between the dominant and non-dominant eyes are of interest with respect to refractive error development.

Higher-order aberrations

Higher-order aberrations are optical imperfections of the eye (excluding defocus and astigmatism) that degrade retinal image quality and may influence ocular growth. Although the unaccommodated eyes of myopes and emmetropes exhibit similar levels of aberrations,^{159,160} during or following near work, myopes tend to have higher levels of aberrations in comparison to their emmetropic counterparts.^{161–163} Recent studies suggest this may be due to differences in the cornea or palpebral aperture morphology.^{162,164} Several studies have com-

pared the higher-order aberration profiles between the two eyes of anisometropes, with conflicting results (Table S5).

Corneal higher-order aberrations

In non-anisometropic populations, there is a high degree of symmetry between the two eyes for measures of corneal aberrations.^{169,170} Plech and colleagues⁷⁴ also observed that corneal higher-order aberrations were similar between fellow eyes in cases of unilateral amblyopia, including isometropic and anisometropic refractive errors. In a population of non-amblyopic anisomyopes, Vincent and colleagues⁶² found a high degree of interocular symmetry for corneal higher-order aberrations, which increased as the corneal analysis diameter increased. This suggests that the optical quality of the cornea is similar for the two eyes of myopic anisometropes, which does not support a model of development of myopia driven by corneal aberrations; however, these measurements were not taken during or following near work, which has been shown to alter corneal optics due to eyelid pressure. Using the same non-amblyopic anisomyopes, a further study¹⁴⁰ was conducted to examine the symmetry of the change in corneal optics following a short-duration reading task. The changes in corneal higher-order aberrations following reading were not significantly different between the two eyes; however, the more myopic eyes exhibited a significantly greater increase in corneal against-the-rule astigmatism, which resulted in a greater reduction in image quality over a 6.00 mm pupil diameter.

Total ocular higher-order aberrations

A high degree of interocular symmetry also exists for the total higher-order aberrations of the eye after correcting for enantiomorphism (between eye mirror symmetry) in various isometropic populations during distance^{171–175} and near fixation.¹⁷⁶ Studies of chicks^{177,178} have reported a significant increase in higher-order aberrations following monocular form deprivation and the development of myopia, and recently Colletta, Marcos and Troilo¹⁷⁹ observed that experimentally form-deprived eyes of marmosets had significantly higher levels of the asymmetric aberration trefoil compared to the fellow control eye. These animal models suggest that interocular

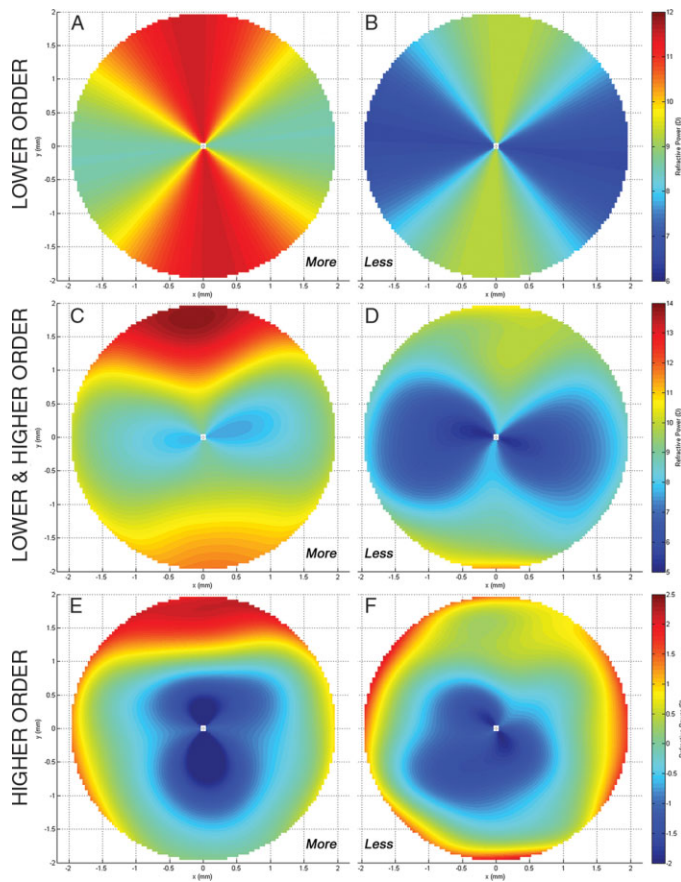


Figure 5. Mirror symmetry of astigmatism and comparison of higher-order aberrations in a typical anisometropic subject (R: $-4.25/-1.75 \times 15$ and L: $-2.75/-1.75 \times 170$). The above refractive power maps (4 mm pupil) are generated from the total ocular wavefront for Zernike terms up to the eighth radial order: 4–6 (lower order terms, A and B), 4–45 (lower and higher-order terms, C and D) and 7–45 (higher-order terms only, E and F). Cross-sectional studies of anisomyopes typically report similar levels of aberrations between the two eyes or slightly higher levels in the less myopic eye.

asymmetries in higher-order aberrations may be a result of asymmetric visual experience and/or ocular growth, rather than a cause.

In a cohort of human anisomyopes (approximately 3.40 D anisometropia), Kwan, Yip and Yap¹⁶⁵ also observed significant interocular symmetry in higher-order aberrations; however, they also noted significantly higher levels of third-order and total higher-order aberrations in the less myopic eye compared to the more myopic eye. Conversely, more recent studies examining lower levels of anisomyopia (around 1.75 D anisometropia) have found a high degree of interocular symmetry (and no significant interocular differences) in individual higher-order aberrations, third-order,

fourth-order and fifth-order aberrations or total higher-order aberrations^{62,166} (Table S5, Figure 5). Retrospective clinical studies of total higher-order aberrations in anisometropia also report a high degree of symmetry between the two eyes for almost all individual wavefront coefficients¹⁶⁷ or a higher degree of interocular symmetry in anisometropes compared to isometropes.¹⁶⁸

In summary, these studies (which generally measured aberrations during distance fixation) do not support the hypothesis that increased aberrations (and hence reduced retinal image quality) in the unaccommodated eye play a role in the development of myopic anisometropia; however, this does not rule out the possibility that higher-order aberrations play a role in

the development of myopia or anisometropia during or following near work, or that the sign of the aberrations (for example, relative peripheral hyperopia) may play a role. Additionally, no longitudinal studies have currently been published examining the symmetry of higher-order aberrations in children during the development of myopia.

THE POSTERIOR EYE IN ANISOMYopia

Structural alterations of the posterior eye, such as staphyloma and optic disc abnormalities are often associated with high myopia and excessive axial elongation.¹⁸⁰ With recent advances in posterior eye imaging (OCT), more subtle changes in retinal and choroidal thickness have also been observed over a range of myopic refractive errors (typically a thinning of the retina and choroid with increasing levels of myopia).^{181–183}

Retina

While several studies have examined the interocular symmetry of retinal thickness in amblyopic anisometropia, few studies have examined retinal biometrics in myopic anisometropia. For lower levels of myopic anisometropia (1.50 to 3.00 D), there appear to be no obvious structural differences between the two eyes with respect to retinal thickness at the macula¹⁸⁴ or in paramacular regions⁶⁴ or the retinal nerve fibre layer thickness surrounding the optic nerve.¹⁸⁵ Additionally, a recent study examining retinal characteristics in severe myopic anisometropia (approximately 10.00 D) found no significant differences between the two eyes for measures of foveal retinal thickness, but some retinal thinning was observed in the inferior and nasal paramacular regions in the order of 10 to 20 μm .¹⁸⁶

Logan and colleagues⁵⁸ calculated the posterior retinal contour in Asian and Caucasian low myopic anisometropes of about 2.00 D (using peripheral refraction coupled with corneal curvature and axial length data) and observed an ethnic influence upon interocular differences in the shape of the posterior eye. Caucasians exhibited between-eye differences in axial length that were greater nasally compared to temporally in the posterior retinal contour, while in anisometropes of Taiwanese-Chinese descent, the interocular difference in axial length was similar between corresponding nasal and temporal locations.

Choroid

Until recently, choroidal thickness had not been measured directly in anisometropic eyes. Early studies estimated the interocular symmetry of choroidal blood flow in anisomyopes by measuring the ocular pulse amplitude and the pulsatile ocular blood flow. Shih and colleagues⁸⁹ observed that when anisometropia exceeded 3.00 D, there was a significant interocular difference in the ocular pulse amplitude (0.27 mmHg). Similarly, Lam and colleagues⁹¹ found that in anisometropic subjects (greater than 2.00 D) both ocular pulse amplitude and pulsatile ocular blood flow were significantly lower in the more myopic eye of axial anisometropes and the interocular differences in ocular pulse amplitude and pulsatile ocular blood flow were both significantly correlated with the interocular difference in axial length. These studies suggest that reduced choroidal blood flow is associated with increasing myopia.

Vincent and colleagues⁶⁴ directly measured choroidal thickness in adult anisomyopes using OCT and observed significant interocular differences proportional to the degree of axial anisometropia. These differences (thinner choroid in the more myopic eye) were more apparent in Asian anisometropes compared to Caucasians. This finding was consistent with the previous posterior retinal findings of Logan and colleagues,⁵⁸ as Asians displayed relatively symmetrical interocular differences in choroidal thickness at corresponding nasal and temporal locations, while in Caucasians choroidal thinning was limited to a region nasal to the fovea of the more myopic eye. Together, these studies suggest that some of the structural changes in the eye associated with anisomyopia differ between Asian and Caucasian subjects.

Since previous animal studies have shown an active choroidal mechanism to emmetropise (by adjusting the position of the retina) to imposed defocus^{118,187} and evidence for a similar mechanism has been reported in humans,¹²³ it is possible that the choroid plays a role in the development of anisomyopia. As the above study⁶⁴ was cross-sectional it is unclear if the thinning of the choroid in the more myopic eye was a cause or consequence of development of myopia; however, modelling suggested that the interocular differences observed were not accounted for by a simple passive stretching of the globe. This supports the theory that the between-eye differences in choroidal

thickness may be a result of an active ocular mechanism, similar to the response observed in monocular manipulation of refractive error in animal models.

OCULAR DOMINANCE

Several studies have investigated the association between ocular sighting dominance (the preference for the visual input from one eye when viewing binocularly) and anisometropia (Table S6). In a cohort of adult Asian myopes Cheng and colleagues¹⁸⁸ observed that when the degree of anisometropia exceeded 1.75 D, the dominant eye was always the more myopic eye and hypothesised that an aniso-accommodative response (due to unequal accommodative demands during reading) may be responsible for the dominant eye being more myopic. **Similarly, a study examining predominantly Asian myopic anisometropes found that when the magnitude of anisometropia exceeded 1.75 D, the more myopic eye was almost always the dominant sighting eye (90 per cent of cases) and when anisometropia exceeded 2.25 D the more myopic eye was always the dominant eye.⁶² This finding is in agreement with studies of young amblyopic strabismics, in which the fixating (dominant) eye typically undergoes a greater myopic shift during childhood compared to the fellow amblyopic eye.^{13–15}**

Conversely, in a study of Asian children, Chia and colleagues¹⁸⁹ found no such association. The authors reported that when anisometropia was greater than 1.50 D, the dominant eye was more myopic in only 56 per cent of subjects. A large retrospective study of over 10,000 patients screened for refractive surgery in Western Europe³¹ (presumably a predominantly Caucasian/European cohort) also recently found that in myopic anisometropia the dominant eye is typically the eye with the lower refractive error. While these studies all employed similar techniques to determine ocular dominance (variations of the hole-in-the-card test¹⁹¹), differences in subject ethnicity and age may account for some of the discrepancies observed in the findings between the studies.

In summary, cross-sectional studies of adult myopes (of predominantly Asian ethnicity) have found that beyond a threshold level of anisometropia (1.75 to 2.25 D), the more myopic eye is typically the dominant sighting eye; however, studies of Asian children or European adults have observed that

the non-dominant eye is typically the more myopic eye or the eye with a greater level of astigmatism.

Retinal image quality and ocular dominance

In anisometropic amblyopia, the dominant sighting eye is typically the eye with better visual acuity, although there may be exceptions in some cases with intermittent strabismus.¹⁹² If visual acuity influences ocular dominance in myopic anisometropia, one might expect to see a significant difference in acuity between the two eyes of anisometropes or a greater difference in acuity between eyes with increasing levels of myopic anisometropia. In non-amblyopic myopic anisometropes, no significant difference in visual acuity was observed between the two eyes for either high (more than 1.75 D) or low levels of anisometropia (up to 1.75 D).⁶² Furthermore, total higher-order monochromatic aberrations (which alter the retinal image) were compared between the dominant and non-dominant eyes to examine if subtle optical differences between the eyes might somehow influence ocular dominance. The dominant and non-dominant eyes displayed similar root mean square error values for measurements of higher-order aberrations taken during distance fixation. This does not point to an obvious underlying optical reason (that is, reduced retinal image quality) for the more myopic eye typically being the dominant eye for higher levels of anisometropia.

Some studies have reported that the non-dominant eye has a significantly higher level of astigmatism compared to the dominant eye, which increases with greater levels of anisometropia.^{31,189,193} While this suggests that image quality may play a role in the development of ocular dominance or anisometropia, the cross-sectional nature of these studies prevents any firm conclusions regarding the causal nature of this association. One longitudinal study¹⁹⁰ examined the rate of development of myopia between dominant and non-dominant eyes of young Asian myopes and concluded that sighting dominance has no influence upon refractive error development; however, this study included only isometropic children (mean anisometropia, 0.22 D; range zero to 1.00 D at initial examination) and excluded moderate myopes, astigmatic myopes and children whose parents had myopia greater than -3.00 D, significantly reducing the likelihood

of including participants who may have developed anisometropia.

Accommodation, binocularity and ocular dominance

Studies measuring ocular changes of both eyes simultaneously during near tasks with binocular viewing may provide insight into characteristics that influence ocular dominance. Yang and Hwang¹⁹⁴ compared the interocular equality of the accommodative response in children with intermittent exotropia, without amblyopia or anisometropia. During monocular viewing, the dominant and non-dominant eyes of intermittent exotropes both showed a small lag of accommodation; however, during binocular fixation, a significant number of subjects displayed a greater lag of accommodation in the non-dominant eye compared to the fellow dominant eye. This finding suggests a potential mechanism for the non-dominant eye becoming more myopic (due to hyperopic defocus) compared to the dominant eye, in cases of atypical ocular alignment.

There is conflicting evidence regarding the association between the magnitude of myopic anisometropia and ocular dominance and its role, if any, in asymmetric refractive development. The fact that the more myopic eye is typically the dominant eye in some cohorts with higher levels of myopic anisometropia^{62,188} seems counter-intuitive. In amblyopic eyes, the dominant eye is the eye with better visual acuity, which has experienced normal emmetropisation and has a lower degree of ametropia. Conversely, in non-amblyopic myopic anisometropia, initial reports suggested that the dominant eye tends to be the eye with the greater refractive error and further from emmetropia^{62,188} but more recent findings from a much larger population³¹ suggest that the eye with the greater refractive error is typically the non-dominant eye, a trend which is amplified with increasing magnitude of anisometropia.

One explanation may be that ocular dominance is genetically predetermined.¹⁹⁵ The eye which is then favoured for near work (as genetically determined) may be exposed to greater amounts of optical blur or mechanical stress resulting in greater axial elongation and myopia in the dominant eye causing anisometropia to develop. If this were the case, we might expect to see a greater lag of accommodation in the dominant eyes of anisometropes. An alternative

explanation may be that ocular dominance is influenced by the development of anisometropia (particularly in Asian ethnicities). Beyond a certain degree of anisometropia, the more myopic eye may be favoured for near work during binocular vision due to the reduced ocular accommodative demand relative to the fellow eye, and thus it may dominate during binocular viewing. This could explain why there is a significant shift to the more myopic eye as the dominant sighting eye when anisometropia exceeds 1.75 D in adult Asian myopes but not children.

Studies examining ocular dominance and anisometropia have been cross-sectional and have employed a simple forced-choice method of determining sighting preference (the hole-in-the-card test¹⁹¹). A longitudinal study into the ocular changes of dominant and non-dominant eyes during the development of anisometropia (using more sophisticated techniques to quantify ocular dominance¹⁹⁶) may provide further insight into the potential causal nature of this association. Characteristics of the dominant eye during binocular near work may help explain the underlying mechanism, if ocular dominance influences the development of myopic anisometropia. Apart from one study of myopic children,¹⁸⁹ the majority of adult subjects examined in other cohorts were presumably established anisometropes (that is, not developing anisometropia). As such, we cannot rule out that visual acuity (or the quality of vision) during development of anisometropia plays a role in determining sighting dominance.

CONCLUSION AND FUTURE RESEARCH DIRECTIONS

A high degree of symmetry exists between the two eyes of myopic anisometropes for a range of biomechanical, biometric and optical parameters. A single specific optical or mechanical factor has not been identified that is consistently associated with asymmetric axial elongation, but it is possible that there are many individual or combined stimuli that lead to a difference in ocular growth between two eyes. The findings from the studies discussed in this review suggest many areas of potential interest that require further research.

There appears to be a strong association between ocular dominance and myopic anisometropia in Asian adults. A longitudinal study into the ocular changes of dominant

and non-dominant eyes during the development of anisomyopia may provide further insight into the potential causal nature of this association. Characteristics of the dominant eye during binocular near work may also help to explain the underlying mechanism, if ocular dominance influences the development of myopic anisometropia.

An interocular asymmetry in choroidal thickness has been observed that is proportional to the magnitude of anisomyopia. Previous animal studies have shown an active choroidal mechanism to emmetropise to imposed defocus^{118,187} and evidence for a similar mechanism in humans has recently been reported.¹²³ Given that the between-eye differences in choroidal thickness cannot be explained by a simple passive stretch model, interocular differences in myopiagenic stimuli may be driving asymmetric development of myopia. Therefore, a longitudinal study examining factors such as the interocular symmetry of ocular biometry, optical quality (including corneal and total ocular astigmatism and higher-order aberrations) and changes in the choroid during childhood-adolescent development of myopia may provide important information regarding the development of asymmetric refractive errors.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article at the publisher's website:

- Table S1. Summary of biometric studies of myopic anisometropia
- Table S2. Summary of cross sectional studies of IOP in anisometropic cohorts
- Table S3. Summary of cross-sectional studies of corneal power (or radius of curvature) in anisometropia
- Table S4. Summary of studies of accommodation in myopic anisometropia
- Table S5. Summary of studies of higher-order aberrations in anisometropia
- Table S6. Summary of studies of ocular sighting dominance and refractive error