CLINICAL APPLICATIONS OF SHORT-TERM CHOROIDAL THICKNESS MODULATION IN MYOPIA MANAGEMENT

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THESIS ABSTRACT

A growing body of evidence shows the choroid to be a key component in the visual regulation of eye growth. Responsive to various optical and pharmaceutical stimuli, the choroid is a highly dynamic structure capable of rapid thickening and thinning. However, the significance of the fast-acting bidirectional choroidal response with respect to long-term ocular growth remains obscure. To explore the prospect of using choroidal thickness as a predictor for myopia progression, this thesis investigated transient changes in human choroidal thickness following modifications to the visual environment relevant to global myopia management strategies.

Over recent years, the uncertain role of choroidal imaging in myopia management has led to its inconsistent use in clinical practice worldwide. Further, promising prescribing trends showed myopia control spectacles to be the most frequently prescribed intervention. With such lenses often employing defocusing peripheral optics, regional alterations in the choroidal spatial distribution were quantified using appropriate instrumentation following short-term exposure to patterns of spectacle lens-induced myopic defocus. The results indicated localised expansion and recovery following 45 minutes of hemifield blur in myopic and emmetropic eyes. Significant differences between the nasal and temporal choroidal alterations suggest non-uniform sensitivities to defocus across the choroid. Additionally, the impact of immediate and longstanding myopia control spectacle wear was explored, evidencing separate yet associated mechanisms mediating short- and long-term choroidal thickness changes provoked by peripheral retinal myopic blur.

This thesis provides important insights into existing worldwide uses of choroidal thickness modulation in myopia management, clinical considerations when using choroidal imaging to quantify small changes, and characteristics of local choroidal responses to retinal defocus. This thesis demonstrates that immediate choroidal thickness changes may be predictive of long-term regional changes, uncovering research directions to further understand the choroid’s role in ocular growth and to identify specific choroidal regions that matter the most for myopia control.

Keywords: Myopia management, choroid, choroidal thickness, myopic defocus, optical myopia interventions

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I dedicate this thesis to my parents, Jane and Shakir. They have offered endless wisdom and treasured words of advice throughout the ups and downs of this journey. I will forever be grateful for the sacrifices they have made for me and my siblings to accomplish our goals. Thank you for everything, Mum and Dad.

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LIST OF ABBREVIATIONS

AC/A	Accommodative-Convergence to Accommodation Ratio
ANOVA	Analysis of Variance
ART	Automatic Real Time
BCVA	Best Corrected Visual Acuity
COR	Coefficient of Repeatability
CSI	Chorioscleral Interface
CVA	Choroidal Vascular Area
CVD	Choroidal Vascular Density
CVI	Choroidal Vascularity Index
DIMS	Defocus Incorporated Multiple Segments
DISC	Defocus Incorporated Soft Contact Lenses
DOT	Diffusion Optics Technology
DRI-OCT	Deep Range Imaging Optical Coherence Tomography
EDI	Enhanced Depth Imaging
HAL	Highly Aspherical Lenslets
HD-OCT	High-Definition Optical Coherence Tomography
ICC	Intraclass Correlation Coefficient
ILM	Internal Limiting Membrane
IMI	International Myopia Institute
IOP	Intraocular Pressure
LCD	Liquid-Crystal Display
LED	Light Emitting Diode
LOA	Limits of Agreement
LogMAR	Logarithm for the Minimum Angle of Resolution
LT	Long-Term
MM	Myopia Management
MSE	Mean Spherical Equivalent
OCT	Optical Coherence Tomography
OLCR	Optical Low Coherence Reflectometry
Ortho-K	Orthokeratology

PALS	Progressive Addition Lens Spectacles
PCI	Partial Coherence Interferometry
pIOL	Phakic Intraocular Lens
RAF Rule	Royal Air Force Rule
RCL	Rigid Contact Lens
RPE	Retinal Pigment Epithelium
SAL	Slightly Aspherical Lenslets
SD	Standard Deviation
SD-OCT	Spectral-Domain Optical Coherence Tomography
SFCT	Subfoveal Choroidal Thickness
SLD	Super Luminescent Diode
SS-OCT	Swept-Source Optical Coherence Tomography
ST	Short-Term
TV	Television
UVR	Ultraviolet Radiation
WDT	Water Drinking Test
WVL	Wavelength Variable Laser

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Chapter 1. Introduction

1.1 THE IMPACTS OF MYOPIA

Myopia, or shortsightedness, forms a fundamental part of current ophthalmological research. Despite the refractive error being easily corrected with conventional spectacles or contact lenses, the widespread increase in the prevalence of myopia is now recognised as a major public health concern[1]. Epidemiological studies show that myopia has reached epidemic levels in countries within East and South-East Asia, with around 80% or more children and teenagers being shortsighted in areas such as Korea[2, 3], Taiwan[4], Singapore[5] and Shanghai, China[6]. Further research shows the upsurge in myopia prevalence is not limited to Asian populations; numbers within the United States[7, 8], United Kingdom[9, 10] and Australia[11] are rising, and are now thought to be between 25-50% among young adults. Even countries with a lower prevalence of myopia today are expected to be seriously affected in the future, with nearly half of the entire world's population predicted to be myopic by the year 2050[12]. This increase will also see the level of high myopia (≤-5.00D) rise close to 1 billion individuals globally[12].

The upsurge in myopia, particularly high myopia, carries significant clinical and economic consequences on both an individual and global level. Uncorrected refractive error has become the leading global cause of vision impairment and the second leading worldwide cause of blindness after cataract[12, 13]. With the increasing number of myopes comes the concomitant increase in sight threatening complications placed on these individuals. Although high myopia carries the greatest risk, low levels of myopia also carry a significant risk of ocular pathology[14], the most common being myopic maculopathy; through pathological changes such as progressive stretching of blood vessels, geographic atrophy, choroidal neovascularisation, and posterior staphyloma, this irreversible and often bilateral macular disease can have devastating effects on a person's eyesight[14]. Myopia is also a significant risk factor for developing retinal detachments[15], cataracts[16, 17], and glaucomatous optic neuropathies[18-20]. To put into perspective, the risks of a myope developing glaucoma and cataracts is comparable with the risk of a stroke when smoking >20 cigarettes daily[14].

Additionally, such impacts are a detriment to the economy; lost productivity due to visual impairment caused by uncorrectable myopic maculopathy and uncorrected myopia was estimated at $244 billion in 2015[21], and the global cost of uncorrected distance refractive error was estimated at $202 billion per annum[22, 23]. The NHS and healthcare providers elsewhere are faced with the repercussions of increasing numbers of myopic patients[14, 24].

The physical and psychological impacts must also be considered, whereby cosmetic, practical, and financial implications of myopia can negatively impact a person's quality of life[24-27]. These factors were found to particularly resonate with high myopes, where unsightly, thick spectacles or the high cost of more cosmetically appealing alternatives worsens their myopic burden[24]. Research suggests the negative impact of myopia of 10.00D or greater on an individual's quality of life is comparable with that of keratoconus[24], and around 25% of high myopes are likely to suffer with anxiety and depression disorders[28].

The significant adverse effects of myopia seen increasingly over recent years has heightened the need for further understanding of myopia aetiology and urgent development of effective control methods. Advances in both animal and human studies have enabled rapid adoption of myopia intervention treatments in routine clinical practice[29, 30] and directed ongoing research to determine optimum methods. However, there are many aspects of myopia which remain obscure. The risk factors associated with the onset and subsequent progression of human myopia can be essentially divided into two categories: a person's genetics and their surrounding visual environment. Numerous researchers have provided evidence for both genetic and environmental contributions to axial elongation which collectively show no isolated root cause. Evidence of familial correlations in the inheritance of myopia for both high and mild to moderate juvenile onset types is plentiful, and it is well established that children born with one or two myopic parents are more likely to become myopic than children born to non-myopic parents[31-35]. Twin studies provide further indication of a genetic link, where monozygotic (identical) twins resemble each other more than dizygotic (fraternal) twins[34, 36-38].

Although considerable research shows some level of genetic predisposition to myopia, it is the general consensus that genetics alone cannot account for the recent sharp rise in the prevalence of myopia. The upsurge of myopes across multiple populations shows that external factors must be involved, for the gene pool has not changed as dramatically as the human environment in recent years. Research suggests the key environmental factors behind the increasing prevalence of myopia are excessive near work[39-43] and minimal time outdoors[43-47]. There is still uncertainty in determining the specific mechanisms involved due to the difficulty in isolating the causal factors from one another. For example, research shows that individuals with a higher IQ are more likely to be myopic[35, 48, 49], but the near visual demands associated with education may be the contributory factor behind this association. However, it can be argued that intensive near work is concurrent with less time outdoors, as these tasks tend to be conducted inside. Furthermore, the division between the influence of environment and the influence of genetics is not well-defined due to possible

and probable complex interplay of the two, indicating the extent of myopia's multifactorial nature.

Despite the extensive research conducted over several years, numerous questions about myopia remain. In particular, the mechanisms behind myopia-inducing ocular growth, and the optimum approach to combat this. The dramatically increasing prevalence and associated significant consequences of myopia indicate the vital need for efficacious treatments. Although several approaches are being increasingly prescribed across the world[29, 30], it is unknown why certain myopes respond well to a particular control method whereas others do not.

Discussed in the following sections of this chapter, research investigating transient and structural changes of ocular components subsequent to altered visual states has shed light on how the refractive status of an eye can be manipulated. Exploration of the visual regulation of eye growth has not only revealed conditions that are myopigenic, but also demonstrated how vision itself may be used to control myopia progression.

1.2 VISUAL REGULATION OF EYE GROWTH

Emmetropisation is the active matching of the optical power of the cornea and crystalline lens to the eye's axial length, which minimises the residual refractive error[50-52]. Normally, human neonates have a hyperopic refractive error, approximately +2.00D, which reduces from 6 to 12 months of age[53-56]. As the child grows, the refractive error gradually reduces further to result in a lower hyperopic refractive error by the time the child reaches 5 to 7 years of age[57]. As emmetropisation occurs, the optical components balance in order to create an image on the fovea, creating a clear, sharp percept[58-60]. Myopia is the result of an imbalance between these optical components, where the refractive power of the cornea and lens does not offset the axial length growth[61-63]. This results in light converging to focus the image anterior to the retina, impairing a person's ability to see clearly in the distance. With axial growth occurring during childhood, myopia generally occurs in school-age children and adolescents, typically emerging between the ages of 7-14 years with possible further progression up to the age of 30[64-66], sometimes termed juvenile-onset or school myopia.

The understanding of emmetropisation and the visual regulation of eye growth has been considerably enhanced through experimental animal and human research. Animal experiments exploring the effects of visual form deprivation on a developing eye show ocular axial growth to be an active process, responding directly to the image quality presented to the retina. In rhesus monkeys, having complete form deprivation through eyelid suturing consistently resulted in axial myopia[67-69]. The same response has been found in other species, such as chicks[70-72], marmosets[73-75] and mice[76-78]. These findings reflect those also

found in form deprived humans through neonatal eyelid ptosis and hemangioma[79-82]. Upon removal of the obscuring function, the induced myopic defocus is perceived by the animal and the formerly deprived eye responds by rapidly reducing the rate of axial elongation, subsequently decreasing the level of myopia[83-87].

More clinically relevant evidence for visual regulation of eye growth comes from the axial response to lens-induced defocus. The homeostatic control of eye growth means the eye will grow to maintain a sharp image on the retina, which can be manipulated using positive and negative lenses[88-93]. If the eye elongates slower than the focal length, hyperopic defocus occurs as the focal plane sits behind the retina, which can be induced by using a negative lens[87, 88]. Conversely, producing myopic defocus on the retina is achieved using a positive lens. To reclaim a sharp retinal image, the eye must elongate in response to a hyperopic defocus or shorten in response to a myopic defocus in order for the retina to coincide with the image plane.

Rather than a general response to retinal image quality, vision-induced refractive error development has been found to be mediated by local retinal mechanisms, first seen in chicks. When chicks were exposed to hemi-retinal form deprivation using field diffusers, the axial elongation and concomitant myopia developed in a selective manner within the treated hemifields[94, 95]. This regionally selective response has also been seen in mammals such as infant monkeys, where localised myopia occurred in the area of the visual field that was degraded[96]. The same peripheral deprivation was found to have effect when the monkey's foveae were ablated[97, 98], indicating that foveal vision is not fundamental to axial growth or emmetropisation. These findings have been attributed to the differences in the distribution of retinal neurons across the peripheral retina and the central retina. Although the fovea contains the greatest density of neurons, it is a relatively small area in comparison to the entire retinal surrounding, thus having fewer neurons overall[87]; this indicates the effect of central retinal image degradation on refractive error development is relatively modest by comparison to that of the periphery. Lens-induced peripheral defocus produced similar results in monkeys, where monkeys both with and without a functioning fovea developed foveal myopia when exposed to peripheral hyperopic defocus[96, 97]. Therefore, similar to form-deprivation, the retinal periphery can detect and respond to defocus without the involvement of foveal signals.

The ocular response to experimentally induced refractive error has been attributed to changes within various ocular structures, resulting primarily in alterations in vitreous chamber depth[99]. So far, research suggests that the anterior segment does not play a direct role in the visual regulation of eye growth[100-102], whereas structures within the posterior

segment have been implicated in axial length fluctuations. For example, within the retina, lens-induced image defocus has been found to cause significant changes in gene expression associated with structural changes in eye growth[103-108]. This includes evidence for bidirectional signalling pathways, whereby gene expression in response to hyperopic defocus differed to that in response to myopic defocus[103]. Furthermore, long-term scleral changes in experimental myopia include thinning of the fibrous connective tissue[75, 109-111] and restructuring of the extracellular matrix[109, 112, 113] across various species, with such changes being similar to those associated with human high myopia[114].

The choroid also appears to play an important role in facilitating the compensatory ocular response to retinal image defocus. First discovered in chicks, lens-induced defocus was found to cause large changes in choroidal thickness, thinning with hyperopic defocus and thickening with myopic defocus[115, 116]. This bidirectional response has since been observed in other species such as macaque monkeys[117], marmosets[118], guinea pigs[119] and humans[120, 121]. It has been hypothesised that this choroidal response acts as a mechanism to maintain focus on the retina until the long-term, slower-paced scleral remodelling offsets the anterior optics through the altered globe size, eventuating in the development of myopia or hyperopia, respectively[122].

Interestingly, the compensatory choroidal and axial response to myopic or hyperopic defocus can be detected within a matter of minutes following exposure to defocus and recovers rapidly following removal of the defocusing stimuli[115, 116, 120, 123-128]. This phenomenon is discussed further in Section 1.4.2. At present, it is yet to be established whether there is any significant relationship between this fast-acting compensatory nature of the choroid and longer-term development of refractive error.

1.3 THE CHOROID

1.3.1 The roles of the choroid

When exploring the influence of the choroid in determining overall eye size, it is important to consider the histological components and functions involved. The choroid is the highly vascular, pigmented layer of tissue positioned between the retina and sclera, with its dense network of blood vessels thermoregulating and nourishing the outer retinal layers. It consists of four layers (Figure 1.1) and forms part of the uveal tract together with the iris and ciliary body. The outermost layer of the choroid, also known as Haller's layer, is composed of large diameter blood vessels and adjoins the chorioscleral interface (CSI). Vessel calibre reduces in Sattler's layer, leading to the choriocapillaris. Sandwiched between the choriocapillaris and the retinal pigment epithelium (RPE) sits Bruch's membrane, which acts as a molecular sieve by regulating the exchange of oxygen, metabolic waste and other biomolecules

between the retina and general circulation. Choroidal circulation is thought to be responsible for around 85% of ocular blood flow[129], thus having a vital role in maintaining proper functioning and overall ocular health.

However, the choroid appears to do considerably more in addition to its vascular functions[130, 131], principally the homeostatic control of eye growth through its ability to shift the retina towards the plane of focus. Human[132] and various animal[133-136] choroids contain large lacunae which can significantly change their volume, which in turn expands the choroid and moves the retina forwards. It is possible that the choroid's dense vascularisation also contributes to its changeable thickness, where increased choroidal blood flow and associated enlarged blood vessel diameter results in choroidal thickening. For example, in chicks, form deprivation-induced myopia has been found to decrease choroidal blood flow and induce choroidal thinning[137]. Non-vascular smooth muscle cells contained within the choroid may contribute to this effect[116]. These cells are concentrated posteriorly and subfoveally, and at the arrival sites of blood vessels into the choroid. Contraction and expansion of this muscle may play a part in changes to blood vessel diameters[116, 130].

In their comprehensive review of the numerous choroidal functions, Nickla et al. (2010) considered the extensive evidence implicating the choroidal state in regulating the production and secretion of specific growth-altering molecules presented to the sclera[130], which regulate the long-term scleral remodelling seen in ocular growth[111, 116, 138]. For example, retinoic acid (RA) and its synthesising enzyme, retinaldehyde dehydrogenase 2, are synthesised primarily by unidentified cells in the choroid and cause changes in scleral proteoglycan synthesis[139, 140]. These molecules are affected by an experimentally altered refractive state; elevated in experimentally induced ocular elongation[140-143] and suppressed in reduced ocular growth[140]. Nickla et al. also argued that the choroid must play a role in the alteration of ocular growth as retinal neurons respond in opposite directions to positive

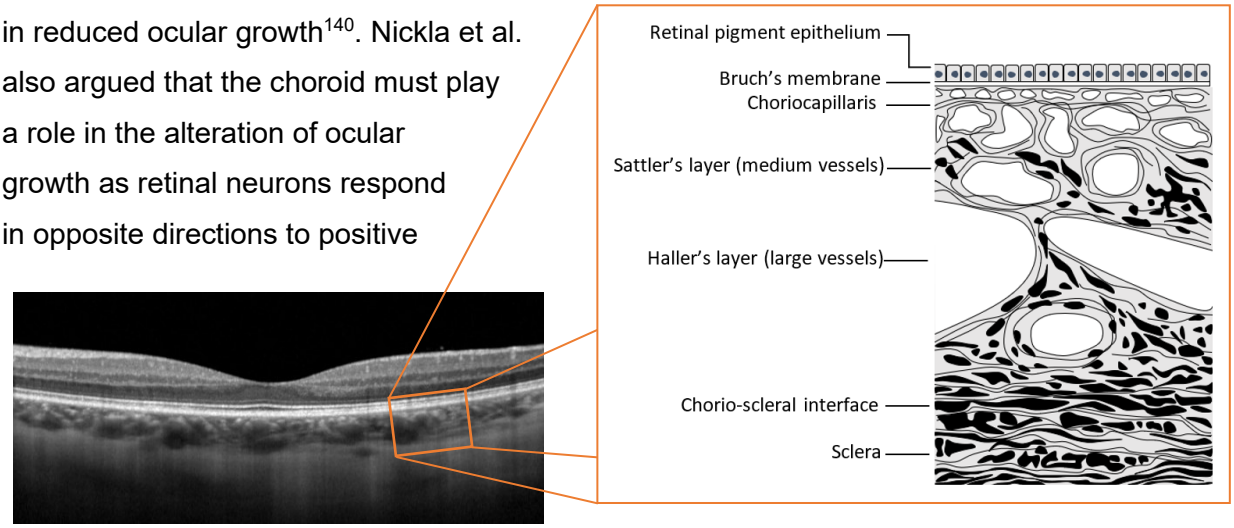


Figure 1.1: Schematic diagram showing the location and cross-section of the human choroid. Cross-section re-sketched from Nickla et al. (2010)[130]

and negative lens-induced defocus[104, 139, 140], yet the sclera is not innervated. Therefore, they concluded that the signal cascade would either have to begin in or pass through the choroid. In this case, theoretically, thickening of the choroid may impede the growth signal cascade, resulting in slower scleral growth and reduced eye elongation. Thinning of the choroid may facilitate transmission of these signals to the sclera, producing the opposite effect[144, 145].

The choroid has been an element of ophthalmological research for many years, yet some features and functions of the choroid remain partly obscure. For instance, intrinsic choroidal neurons were first identified over 150 years ago[146], yet their true functions are still largely unknown[147]. It is thought these neurons may innervate the non-vascular smooth muscle contained within the choroid and regulate choroidal blood flow[130], but this is yet to be established. Additionally, the non-vascular smooth muscle is thought to be involved in the regulation of moving fluid into and out of the choroid[116, 130], expanding and contracting the choroid accordingly. However, this is largely theorised and hasn't been confidently determined thus far.

Notwithstanding, there is consensus that the choroid is multifunctional[131] and is involved in regulating and facilitating eye growth through changing its thickness. The extent of this involvement is less obvious, with the underlying mechanisms requiring further exploration.

1.3.2 Choroidal imaging and analysis

1.3.2a Choroidal imaging techniques

In order to obtain accurate choroidal measurements, cross-sectional images with sufficient resolution are required. Formerly, contact methods such as ocular ultrasonography were used to assess the biometrics of the posterior eye in vivo. Nowadays, conventional ocular ultrasounds are not recommended for such measurements due to the insufficient axial resolution (approximately 150μm) and associated difficulty in delineating the CSI[148]. This has been superseded by more advanced imaging systems, primarily optical coherence tomography (OCT). OCT offers non-contact cross-sectional images[149] and more recent advances in spectral domain OCT (SD-OCT) provides three-dimensional, high-speed imaging

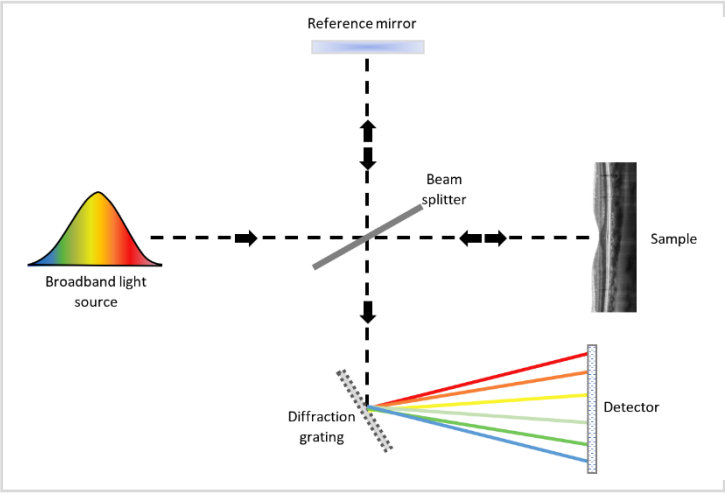


Figure 1.2: Schematic diagram representing the components of SD-OCT with the retina as a sample.

with highly detailed visualisation of the layers within the retina[150]. In SD-OCT, light from a continuous broadband source (super luminescent diode, SLD) illuminates the sample (the eye). An interferogram is produced through combining backscattered light from the sample with that from a reference mirror (Figure 1.2). The higher the frequency from the interference signals, the further the depth of origin. A diffraction grating spreads the differing frequencies and the information is identified using a spectrometer and charged coupled device camera (detector). A mathematical operation (a Fourier transformation) of the interferogram converts the measurements of light into physical delays. Group delay indicates the depth of the objects within the image; superficial objects show a smaller group delay, which results in a lower frequency of the interferogram and imaged at the top of the display. The opposite is true for deeper objects, which are imaged at the bottom of the display. Conventional SD-OCT imaging (where the inner sections of the retina are shown facing upwards) enables clear visualisation of the intraretinal layers, however incident light is scattered as it hits the pigmented cells of the RPE, attenuating as it penetrates the deeper ocular structures[151]. This consequently reduces the image quality of the underlying choroid - particularly the outer choroidal border - creating difficulty in measuring choroidal thickness and assessing small changes. Although standard SD-OCT may provide choroidal images of sufficient visibility to measure thinner choroids (<240μm)[152], image enhancement is often required to permit clear imaging and examination of the posterior choroidal border. This can be achieved through various techniques, namely enhanced depth imaging (EDI) combined with the averaging of multiple B-scans. EDI, first described by Spaide et al., involves deliberately focusing the instrument at a shorter distance from the eye to obtain an inverted image, improving the clarity of the deeper posterior ocular layers[153]. This method has been found to be successful in providing measurable images of the choroid[154]. B-scan (two-dimensional scan) averaging aims to optimise the signal-to-noise ratio[155] to reduce signal-degrading speckle[156],

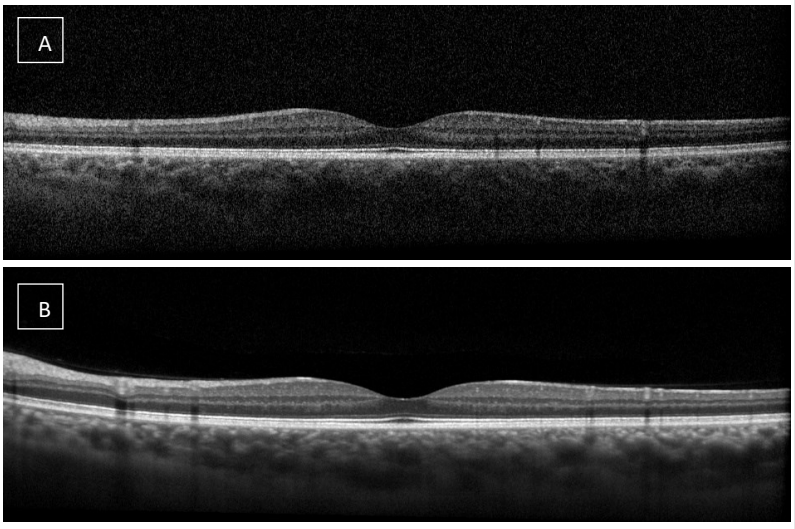


Figure 1.3: SD-OCT images taken on the same individual demonstrating the difference between 2 averaged B-scans (A) and 50 averaged B-scans (B).

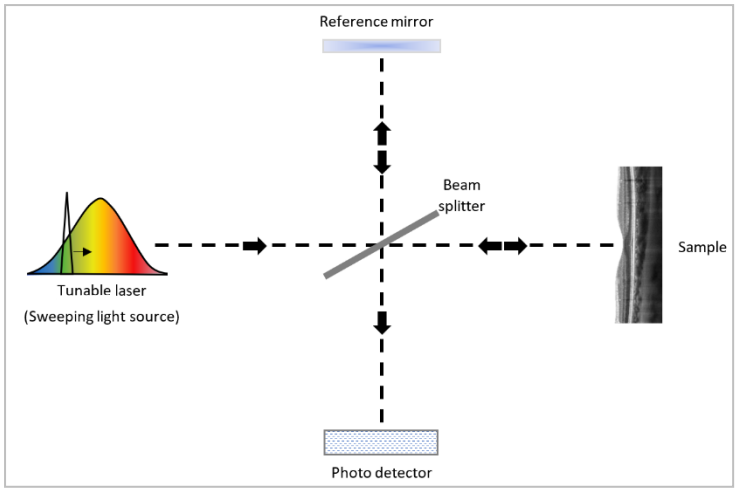


Figure 1.4: Schematic diagram representing the components of SS-OCT with the retina as a sample.

enabling clearer visualisation of the posterior eye (Figure 1.3). It is possible to take 100 B-scans at a time, however averaging a minimum of 30 B-scans is sufficient to accurately estimate choroidal thickness across a 60° area[157].

Alternative to EDI, image enhancement can be achieved by utilising longer wavelengths of light. This is due to the lower scattering of light deeper into the infrared spectrum, which allows deeper penetration into the posterior ocular tissues than conventional imaging[158, 159]. Longer wavelengths tend to be employed by swept-source OCT (SS-OCT), which works differently to SD-OCT (Figure 1.4). A tunable swept laser is used as the light source, emitting a single wavelength at any instant in time. This sweeps across a broadband light as a function of time. In SS-OCT, the interferogram is detected by a single detector, where a digital output is produced as the wavelength is swept. SS-OCT devices generally have faster scanning speeds and use wavelengths greater than 1000nm, allowing deeper penetration into the ocular structures and reduced signal delay without the need for EDI. Although longer wavelengths enable greater visualisation of the choroid and sclera, they are more readily absorbed by the vitreous body, limiting the imaging of the eye[160] including the more superficial retinal layers. Further, SS-OCT tends to provide a lower axial resolution than SD-OCT[161]; the bandwidth of the light source is directly proportional to axial resolution, so the limited bandwidth caused by absorption by the vitreous body consequently restricts this.

Optical low coherence reflectometry (OLCR) and partial coherence interferometry (PCI) are two alternative non-contact methods of assessing ocular tissue thickness. Both techniques produce a one-dimensional A-scan with a resolution of approximately 10-12μm[162, 163]. Although these instruments are primarily used to measure axial length, retinal and choroidal biometric measurements are possible by analysing the A-scan peaks[126, 162, 164, 165]. Therefore, OLCR and PCI allow simultaneous biometric measurements of the anterior ocular structures and axial length with retinal and choroidal thickness (Figure 1.5). However, this is isolated to a single retinal location, and it is hard to identify where exactly on the retina the scan is

located. Modern SD-OCT is therefore advantageous when measuring retinal or choroidal thickness, as it can image at a range of locations across the posterior eye, with a higher resolution of approximately 3-7μm[166]. Furthermore, despite choroidal thickness measurements taken using OLCR comparing closely with those taken using OCT[162], OLCR measurements tend to have lower repeatability than those with OCT[125].

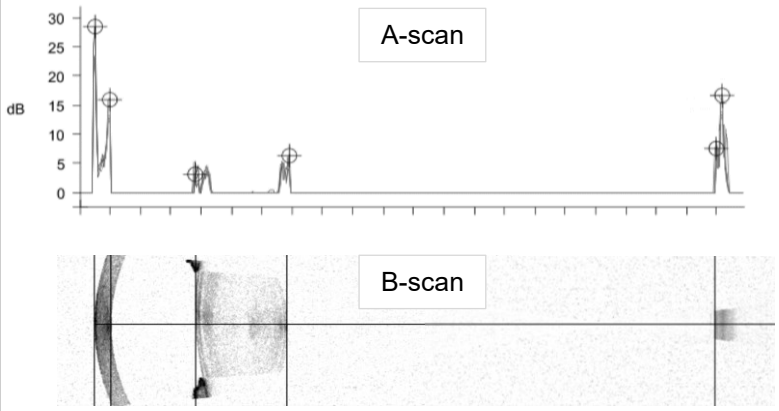


Figure 1.5: Example of a whole eye A-scan captured using OLCR (Lenstar Optical Biometer, Haag-Streit, Köniz, Switzerland) compared to a corresponding whole eye B-scan (captured using the IOLMaster700, Carl Zeiss Meditec AG, Jena, Germany). Choroidal thickness can be measured by the distances between the posterior peaks of the A-scan.

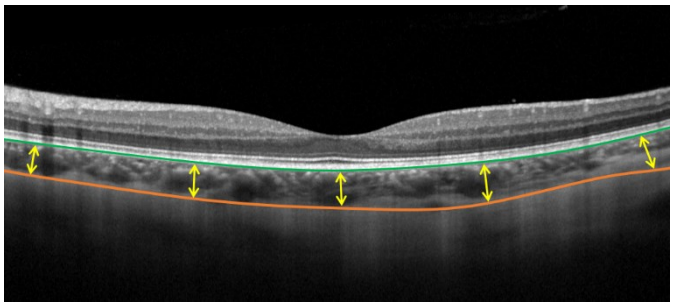


Figure 1.6: Example of enhanced-depth imaging optical coherence tomography (EDI-OCT) line scan with 50 averaged B-scans. Anterior (green line) and posterior (orange line) boundaries of the choroid have been manually marked to demonstrate achievable visibility of the choroidal layers.

1.3.2b Choroidal image analysis

Once imaged with OCT, choroidal thickness can be measured through segmentation of the anterior and posterior choroidal limits. The thickness is determined as the distance between the outer limit of Bruch's membrane/RPE (seen as a hyperreflective line) and the inner border of the CSI (Figure 1.6). A variety of approaches have been used to do so, including both manual and automated segmentation. Many studies examining choroidal thickness with OCT have utilised a manual approach[120, 124, 127, 167-170], where an observer selects a series of points along the anterior and posterior choroidal borders and manually marks the foveal centre. The thickness is then measured as the distance between the anterior and posterior points. In addition to being time consuming, these techniques are potentially open to bias due to their subjective nature, so typically two or more independent masked observers are employed to ensure reliability in ophthalmic research. Automated segmentation provides a more objective measure of choroidal thickness, and various algorithms to detect the choroidal boundaries have been developed

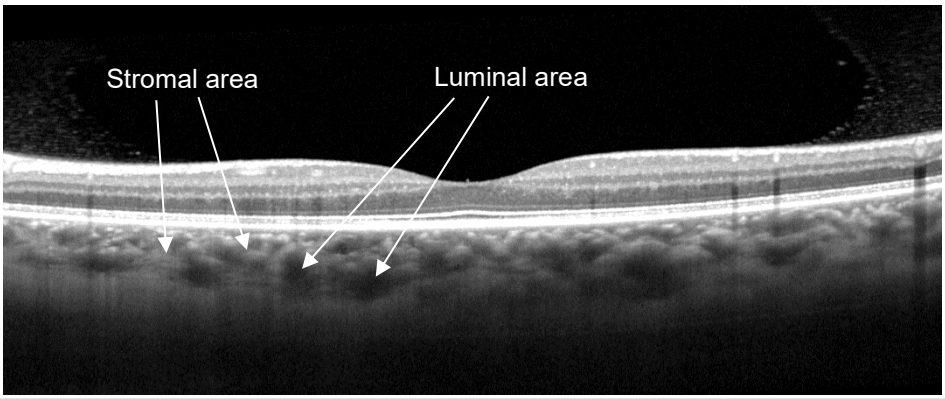


Figure 1.7:

Non-binarized EDI-OCT image with labelled stromal (hyperreflective) and luminal (hyporeflective) choroidal areas.

with varying degrees of success[171-176]. Relative to the anterior choroidal boundary, detecting the posterior boundary presents the most challenging task due to its non-uniformity and, in some cases, low contrast, which is particularly prevalent in eyes with thicker choroids[171]. Despite this, some automated approaches have shown promising consistency, fast processing speeds and high correlation with manual segmentation[171, 172, 174].

Choroidal binarization offers further valuable analysis of choroidal OCT images[177]. Rather than choroidal thickness overall, choroidal binarization enables assessment of structural changes within the choroid's subcomponents by discriminating the blood vessel walls and stromal connective tissue[177]. Proposed by Sonoda et al., 2014, converting greyscale choroidal images into black and white binaries forms a repeatable and reproducible method to quantitatively measure the vascular luminal and interstitial stromal areas (Figure 1.7)[178]. In doing so, detailed within-tissue alterations associated with pathological changes, axial elongation, and refractive error progression can be identified. Rather than using manual techniques, automated strategies to binarization have since been developed[179-181]. These advances have seen the model of the choroidal vascularity index (CVI) be introduced; the CVI is the ratio (presented as a percentage) between the choroidal vascular area to the total choroidal area[182]. Binarization has also been applied to en face SS-OCT choroidal images[177], where the choroidal vascular area or density (CVA or CVD = VA/total choroidal area)[183-185] and choroidal vascular volume (CVV = CVA x choroidal thickness)[184] measures are used to replace the CVI.

1.3.3 Transient fluctuations in choroidal thickness

It appears that the choroid is not just sensitive to retinal image quality and defocus; despite some inconsistencies, extensive research demonstrates the choroid is sensitive to many environmental factors and further supports the evidence for its fast-acting, dynamic nature. A summary of different physiological and pharmacological influences is shown in Table 1.1.

1.3.3a Diurnal variations

Several research studies have documented significant diurnal variations in human axial length[186-188]. Over a 24-hour period, one study found axial lengths of emmetropic eyes to peak in the early afternoon (around 1pm) and trough at night (around 10.30pm), with the mean amplitude of change in axial length to be 46μm[186]. Similarly, when assessed at 3-hour intervals between 9am to 9pm over two consecutive days, maximum axial length was found at around midday, and the minimum at around 9pm. During this time, the average change in axial length was around 32μm[187]. This effect worked in antiphase with choroidal thickness; the diurnal rhythms involved a corresponding shift in choroidal thickness, with the maximum choroidal thickness seen at night and the minimum during the day. Additionally, it appears the extent of these diurnal shifts are independent of refractive error[187]. Other research studies have reported similar significant diurnal fluctuations (amplitude of approximately 25μm) in choroidal thickness in adults[189, 190] and children[191] over 24 hours, peaking in the early hours (between 2.00am and 4.00am) and troughing at approximately midday. There is little contradiction to the research presenting diurnal rhythms in choroidal thickness. Therefore, if being assessed over separate days in a particular individual, choroidal thickness needs to be measured at a similar time of day to obtain comparable data.

Further, it is possible that diurnal fluctuations in intraocular pressure (IOP) are associated with these changes. Daily rhythms in IOP have a positive association with axial length and negative association with choroidal thickness[186, 187], where IOP is highest during the day and lowest at night-time. However, it is unclear whether axial length and choroidal thickness undergo passive expansion and contraction due to these IOP fluctuations.

1.3.3b Alcohol

Possibly due to its effect of vasodilation[192], alcohol intake has been found to significantly increase choroidal thickness. When compared to drinking the same volume of water, 1.0mg/kg of ethanol (14.0% red wine taken orally over 10 minutes) was found to increase choroidal thickness by 25μm at 1 hour after consumption when measured at 30-minute intervals. This thickening returned to baseline after 2 hours[193].

1.3.3c Caffeine

Several experiments have found caffeine to cause temporary choroidal thinning in human adults[194-198]. Additional to being a central nervous system stimulant, caffeine increases blood pressure, slows heart rate, and decreases cerebral blood flow. This caffeine-induced reduction in blood flow has been identified within the human optic nerve head, retina, and choroid[199]. A significant difference in choroidal thickness occurs at approximately 30 minutes after consumption of a cup of coffee (75mg caffeine/200ml)[195] and 1 hour after consumption

of an energy drink (80mg caffeine/250ml)[198]. These changes occur in the subfoveal choroid, with identifiable thinning of the luminal area, stromal area, and total choroidal area following image binarization. Interestingly, the peripapillary choroid appears to be unaffected. Caffeine-induced choroidal thinning returns to baseline between 4 to 6 hours after consumption[196, 198]. Despite one study finding no significant impact of oral caffeine on choroidal thickness[200], most studies investigating choroidal thickness specify that participants were asked to avoid caffeine due to the likely confounding effects.

1.3.3d Water

When studying aqueous outflow in glaucoma patients, the subfoveal choroid was found to thicken following the intake of 1 litre of water within a 15-minute time period (termed 'water drinking test', or 'WDT')[201]. The impacts of WDT on choroidal thickness has also been studied in healthy subjects with normal eyes. Using binarization of choroidal images, water intake was found to significantly increase choroidal thickness at 30 minutes after the WDT and return to baseline by 120 minutes. It was determined that the changes in subfoveal choroidal thickness were due to changes in the choroidal vascular space, where dilation of the choroidal vessels was observed[202]. Another study found a similar level of choroidal thickening at 30 minutes following the WDT, however the recovery appeared to occur much sooner, at 45 minutes[203]. In addition, there appears to be no statistically significant difference between the WDT induced choroidal thickness changes in emmetropic and highly myopic eyes, indicating no influence of refractive error or baseline choroidal thickness[204].

1.3.3e Ophthalmic drugs

Various topical pharmacological agents have been shown to induce rapid changes in choroidal thickness. This includes nonspecific muscarinic antagonists commonly used in clinical practice to induce mydriasis and cycloplegia, such as tropicamide 1%, cyclopentolate 1%, and phenylephrine 2.5% (Table 1.1). Tropicamide 1% has been found to induce significant choroidal thinning at 45-50 minutes post-instillation[205, 206]. Similarly, choroidal thinning has been observed at 30 minutes following instillation of phenylephrine 2.5%[207]. However, research investigating the impact of such ophthalmic drugs is inconsistent; some researchers reported no significant change in choroidal thickness following instillation of either mydriatic[208-210]. Conflicting evidence is also present amongst studies of choroidal thickness following instillation of cyclopentolate 1%; at 40 to 50 minutes post-instillation, some researchers found significant choroidal thinning[206], some found significant thickening[208], and others found no significant change[211].

Pilocarpine 2%, a nonspecific muscarinic agonist used to induce miosis and accommodation, appears to increase choroidal thickness; an approximately 22μm increase

in subfoveal choroidal thickness was observed 30 minutes after instillation[211]. Curiously, despite axial length and choroidal thickness changes typically working in antiphase, this study unexpectedly identified an increase in axial length (approximately 30μm) at the same timepoint. The authors concluded this was most likely due to lens changes associated with pharmacologically induced accommodation, which is supported in other literature[212].

Like cyclopentolate, tropicamide, and phenylephrine, atropine and homatropine are nonspecific muscarinic antagonists, therefore causing mydriasis and cycloplegia. Topical atropine is being increasingly used for controlling myopia progression across the world[29, 30], with efficacious low-dose formulations being desired to minimise the associated adverse effects. Unlike choroidal thinning associated with tropicamide 1%[205, 206] and phenylephrine 2.5% instillation[207], both atropine 0.01% and homatropine 2% have separately been found to cause significant choroidal thickening within 1 hour[209, 213]. Interestingly, long-term use of 0.01% atropine use may cause the opposite effect, further discussed in Section 1.4.4.

The findings of studies exploring the impacts of ophthalmic drugs on choroidal thickness provide some indication of receptor types present within the human choroid. The underlying mechanisms remain obscure due to the conflicting evidence between studies, particularly when results differ between pharmacological agents of the same mode of action.

1.3.3f Nicotine

Characterised by retinal atrophy, drusen, and choroidal neovascularisation, the greatest risk factor of developing age-related macular degeneration (AMD) is cigarette smoking[214, 215]. This is due to nicotine being the main constituent of cigarette smoke; present within the retina and choroid[216], nicotine acetylcholine receptors are activated by nicotine. Therefore, it can be argued that acute changes of choroidal thickness are likely following activation of these receptors. Following the consumption of nicotine through smoking tobacco cigarettes, electronic cigarettes, and chewing nicotine gum, differing acute effects on choroidal thickness have been reported. In habitual smokers, no significant difference in choroidal thickness was identified at 5 or 30 minutes after smoking tobacco and electronic cigarettes[217]. Conversely, in non-smokers, a significant increase in choroidal thickness was identified 1 hour after chewing nicotine gum[218]. Whether a sample of established smokers impacts the results is unknown; it is possible non-smokers may exhibit a different response following the consumption of nicotine.

1.3.3g Physical exercise

Physical exercise has also been suggested to alter choroidal thickness. Due to the choroid’s

Variable	Author	Exposure method	OCT imaging timepoints	Choroidal thickness change
Alcohol	Kang et al., 2016[193]	14% red wine (1.0mg/kg of ethanol)	Baseline to 30-minute intervals up to 2 hours	+25µm at 1 hour Returned to baseline at 2 hours
Caffeine	Koçak et al., 2022[195]	Cup of coffee (75mg caffeine/200ml)	Baseline to 30 minutes, 1, 2 and 4 hours	-25µm at 30 minutes -33µm at 4 hours
	Vural et al., 2014[194]	Cup of coffee (57mg caffeine/100ml)	Baseline to 5 and 30 minutes, 1, 2, 3, 4, 6, and 24 hours	-31µm at 5 minutes Returned to baseline at 6 hours
	Altinkaynak et al., 2016[196]	200mg caffeine capsule	Baseline to 30 minutes, 1, 2, 3, 4 and 6 hours	-10µm at 30 minutes -31µm at 4 hours Returned to baseline at 6 hours
	Arej et al., 2021[198]	250ml can of energy drink (80mg caffeine)	Baseline to 5 and 30 minutes, 1, 2, and 4 hours	-14µm at 1 hour -5µm at 2 hours Returned to baseline at 4 hours
Water	Nagasato et al., 2019[202]	1 litre of water consumed within 5 minutes	Baseline to 15, 30, 45 minutes, and 2 hours	+5µm at 30 minutes Returned to baseline at 2 hours
	Mansouri et al., 2013[203]			+3µm at 30 minutes Returned to baseline at 45 minutes
	Germano et al., 2016[204]		Baseline to 10 and 45 minutes	+8µm at 10 minutes +9µm at 45 minutes
Nicotine	Makri et al., 2020[217]	Tobacco and electronic cigarette smoking (habitual smokers)	Baseline to 5 and 30 minutes	No significant difference
	Cinar et al., 2019[218]	4mg nicotine gum (non-smokers)	Baseline to 1 hour	-50µm at 1 hour
Ophthalmic drugs	Sander et al., 2019[213]	Atropine 0.01% (topical instillation)	Baseline to 30 minutes and 1 hour	+6µm at 1 hour
	Yuvaci et al., 2015[206]	Cyclopentolate 1% (topical instillation)	Baseline to 50 minutes	-20µm at 50 minutes
	Bahar et al., 2021[211]		Baseline to 45 minutes	No significant difference
	Öner et al., 2016[208]		Baseline to 40 minutes	+22µm at 40 minutes
	Sander et al., 2014[209]	Homatropine 2% (topical instillation)	Baseline to 30 minutes and 1 hour	+7µm at 30 minutes +14µm at 1 hour
	Yuvaci et al., 2015[206]	Tropicamide 1% (topical instillation)	Baseline to 50 minutes	-27µm at 50 minutes
	Öner et al., 2016[208]		Baseline to 40 minutes	No significant difference
	Kara et al., 2014[205]		Baseline to 45 minutes	-22µm at 45 minutes
	Yuvaci et al., 2015[206]	Phenylephrine 2.5% (topical instillation)	Baseline to 50 minutes	-26µm at 50 minutes
	Kara et al., 2014[205]		Baseline to 45 minutes	-17 at 45 minutes
	Casado et al., 2019[207]		Baseline to 30 minutes	-10µm at 30 minutes
	Sander et al., 2014[209]		Baseline to 30 minutes and 1 hour	No significant difference
	Bahar et al., 2021[211]	Pilocarpine 2% (topical instillation)	Baseline to 30 minutes	+22µm at 30 minutes
Exercise	Sayin et al., 2015[221]	10 minutes of low-impact, moderate-intensity exercise	Baseline to 5 and 15 minutes	+27µm at 5 minutes Returned to baseline at 15 minutes
	Insa-Sanchez et al., 2021[222]	10 minutes of going up and down stairs at a moderate pace	Baseline to 3 and 10 minutes	+10µm at 3 minutes Returned to baseline at 10 minutes
	Kinoshita et al., 2016[223]	Two-step exercise (amount dependent on participant age, weight, and sex)	Baseline to immediately after exercise and 10 minutes	No significant difference
	Hong et al., 2014[224]	15 minutes on a treadmill	Baseline to immediately after exercise	No significant difference
	Li et al., 2021[220]	20 minutes of stationary cycling	Baseline to immediately after exercise and 30 minute rest	-13µm immediately after exercise -7µm at 30 minutes
Pregnancy	Yildirim et al., 2022[228]	Healthy pregnancies in third trimester	OCT imaging in pregnant vs non-pregnant women	No significant difference
	Su et al., 2020[229]			No significant difference
	Azuma et al., 2021[230]	Healthy pregnancies in first trimester		No significant difference
	Dadaci et al., 2015[231]	Healthy pregnancies	OCT imaging in first trimester and third trimester	-16µm at third trimester
	Shalaby et al., 2021[232]	Pregnant diabetic women in first and second trimester	OCT imaging in pregestational pregnant women vs non-diabetic pregnant women	+65µm in pregestational pregnant women
	Evcimen et al., 2019[233]	Preeclamptic pregnant women in second or third trimester	OCT imaging in preeclamptic women vs healthy pregnant women	+60µm in preeclamptic women

Table 1.1: Comparison of methods and findings of studies exploring transient fluctuations in choroidal thickness associated with different environmental variables. Cells shaded in green indicate a statistically significant increase in choroidal thickness, and cells shaded in red indicate a statistically significant decrease in choroidal thickness.

densely vascular nature, it seems fitting that cardiovascular changes associated with vigorous exercise would impact the choroid in some way. Marathon running appears to induce thinning of the choroid[219], whereas research contributions exploring shorter episodes of exercise (<20 minutes) have provided contradictory results; some research indicates the choroid thins post-exercise[220], some indicates it thickens[221, 222] and others have found no significant change[223, 224].

1.3.3h Pregnancy

Like all systems within the body, the great extent of hormonal and metabolic changes associated with pregnancy[225] has been found to affect the eyes. This includes refractive changes and worsening of pre-existing ocular pathologies[226, 227]. In healthy pregnancies from the first to the third trimester, some research has shown choroidal thickness to be unaffected[228-230]. However, one study identified significant choroidal thinning in females from their first to third trimester[231]. In complicated pregnancies, the opposite has been identified; a significant increase in choroidal thickness was associated with diabetic pregnant women compared to non-diabetic pregnant women at the same stages of pregnancy[232]. Similarly, preeclampsia presented similar levels of choroidal thickening[233].

1.3.3i Conclusion

Together, this collection of research studies provides evidence of physiological and environmentally influenced intermittent choroidal thickening and thinning, albeit with various conflicting reports. Although inconsistencies exist, these factors are worth considering in the design of research studies and participant inclusion criteria to avoid confounding influences.

1.4 THE CHOROID AND HUMAN MYOPIA

Although animal models provide valuable insight into myopia aetiology and intervention, there are limitations when translating these findings to human myopia and the expected efficacy of control methods. Developmental stages of animals are difficult to compare to those in humans[234] and experimental incident myopia occurs much earlier in an animal's visual development than juvenile-onset myopia occurs in humans[234]. For example, animal models correlate with form deprivation myopia in human neonates[79-82], however the ongoing rapid increase in the prevalence of myopia is amongst school-aged children and adolescents[2-8, 11, 12]. When it comes to choroidal involvement, there are significant differences in the histological components of the choroid between animals and humans, including non-human primates[130]. Even amongst different species of animal, choroidal responses to lens-induced defocus can vary substantially, such as the dramatically larger

degree of choroidal thickening and thinning seen in chicks[115, 116] compared to non-human primates[118, 128, 130].

It could therefore be argued that animal models may overestimate the extent to which visual blur influences common human myopia, including choroidal involvement. The current understanding of the human choroidal response to retinal blur and refractive error development is considered here.

1.4.1 Human choroidal thickness and refractive error

Based on histologic study, the choroid was thought to be approximately 200μm thick in human neonates, gradually thinning to around 80μm by 90 years of age[235]. Since the aforementioned advances in non-invasive choroidal imaging techniques[150, 153, 162], the human choroid has been found to be much thicker than originally thought. In children with little to no refractive error, the mean subfoveal choroidal thickness has been found to be over 300μm thick between the ages of 4 to 12 years[167] (Table 1.2). There is significant choroidal thickening between the 4 to 6 and 7 to 9 age groups, which appears to plateau at 10 to 12 years of age. Similar mean subfoveal choroidal thickness measurements and negative correlations between age and choroidal thickness have been obtained by several researchers[236-238]. Subsequently, throughout adolescence and adulthood, cross-sectional studies have reported significant choroidal thinning of approximately 15 to 20μm per decade[238-240].

Human choroidal thickness has also been found to vary with retinal location. Across the central 5mm area surrounding the fovea, there are significant differences in choroidal thickness within foveal, parafoveal and perifoveal choroidal regions[167] (Table 1.3). Generally, the choroid is thicker closer to the fovea, thinning slightly in parafoveal regions, and thinner still in the perifovea. The thickest areas are slightly superior to the foveal centre. Significant nasal-temporal asymmetry in choroidal thickness has been consistently observed in children and adults: the nasal choroid – typically considered as the underlying area between the fovea and optic nerve[131] – has been reported to be up to 100μm thinner than the temporal region[167, 236, 240-244].

Age (years)	Subfoveal Choroidal Thickness (μm)
4 to 6	312 ± 62
7 to 9	337 ± 65
10 to 12	341 ± 61

Table 1.2: Mean subfoveal choroidal thickness in children found by Read et al., (2013)[167]. Data are presented as mean ± standard deviation.

There have been several conflicting reports about the association between choroidal thickness and gender; some studies identified no impact of gender[167, 238, 245-247], some

	Mean Choroidal Thickness (μm)			
	Foveal (0.5mm from foveal centre)	Parafoveal (1.5mm from foveal centre)	Perifoveal (2.5mm from foveal centre)	**Mean of All Regions**
Temporal	333 ± 64	331 ± 63	318 ± 61	**327 ± 63**
Superior-temporal	334 ± 64	336 ± 60	328 ± 55	**333 ± 60**
Superior	332 ± 64	335 ± 61	331 ± 59	**333 ± 61**
Superior-nasal	329 ± 65	313 ± 65	279 ± 61	**307 ± 67**
Nasal	323 ± 65	285 ± 63	215 ± 56	**274 ± 76**
Inferior-nasal	325 ± 65	303 ± 64	268 ± 59	**299 ± 67**
Inferior	328 ± 65	321 ± 63	312 ± 59	**320 ± 62**
Inferior-temporal	329 ± 65	323 ± 64	315 ± 63	**322 ± 64**
Mean of All Locations	**329 ± 64**	**318 ± 60**	**296 ± 51**	

Table 1.3: Mean choroidal thickness averaged across each choroidal region. Table adapted from Read et al. (2013)[167]. Data are presented as mean ± standard deviation.

identified girls to have thicker choroids[241, 248], and others identified adult males as having thicker choroids[248, 249]. Similarly, there is no clear relationship between ethnicity and choroidal thickness[250, 251]. However, there appears to be a much stronger association between choroidal thickness and axial length. Similar to age, research has shown a negative correlation between the two parameters, where individuals with longer axial lengths have thinner choroids[167, 252, 253]. In attempts to quantify this association, studies have reported choroidal thinning of 20 to 60μm per 1mm increase in axial length[242]. Myopic individuals tend to have thinner choroids than non-myopes, which is particularly evident in high myopia[252, 253]. A recent study identified the rate and extent of choroidal thinning to be associated with progression of refractive error, where children with rapidly progressing myopia (defined as increasing myopia of >1.00D over 2 years) also experienced significant choroidal thinning compared with children with stable myopia (<1.00D increase in myopia over 2 years)[254]. The thickness profile of the choroid by retinal location also appears to be impacted by refractive error; the nasal-temporal asymmetry in choroidal thickness is present in children with and without myopia, however the extent of asymmetry is exaggerated in the presence of myopia[255].

Interestingly, the choroidal components which thin may be different depending on the causal factor. The initial choroidal thickening in early childhood hasn't been studied in great detail, however the later thinning associated with increasing age tends to be due to a decrease in the stromal area of the choroid, whereas the thinning associated with longer axial lengths tends to be due to a decreasing luminal area of the choroidal vasculature[256]. Longer axial lengths showed no significant association with stromal thinning, indicating the restrictions in blood vessel area may be the main structural component of choroidal thinning seen in axial myopia. Although this suggests a different mechanism behind the choroidal thinning seen in myopia compared with that of age, it doesn't determine whether overall choroidal thinning is

purely a product of axial myopia, or also a contributory factor. Further research is warranted to determine whether choroidal thickness alone can act as a biomarker for axial elongation and associated refractive error.

1.4.2 Choroidal response to short-term defocus in humans

As previously mentioned, it is well established that the choroid thins in response to short-term hyperopic defocus, thickens with myopic defocus and recovers once the defocusing stimulus is removed[115, 118, 120, 121, 125-128]. Therefore, if a myope was to have consistent exposure to hyperopic defocus on the peripheral retina, it seems logical that the choroid would have an integral role in the corresponding long-term axial growth. Similarly, with the deliberate induction of myopic defocus, the opposite choroidal response could have an integral role in the success of various optical myopia interventions[257].

Due to the rising number of myopes worldwide and associated pathological consequences[258], the effect of myopic defocus on reducing axial elongation in humans is an area of key interest[131]. Over recent years, several researchers have investigated the immediate choroidal response to varying patterns of short-term spectacle and contact lens-induced myopic defocus across differing age groups (Table 1.4).

1.4.2a Full-field defocus

Monocular exposure to short-term spherical myopic defocus generally demonstrates a rapid increase in subfoveal choroidal thickness – and a concomitant decrease in axial length - with the opposite being true for hyperopic defocus[120, 121, 123, 125-127]. However, there are various inconsistencies between studies.

Read et al. (2010) found a significant increase in choroidal thickness after 30 minutes of full-field myopic defocus in young adults and a relative decrease in choroidal thickness at 30 minutes of hyperopic defocus[126]. Participant refractive error didn't appear to have an impact on the baseline or resultant choroidal thickness. When measured at closer time intervals, Chiang et al. (2015) found a similar but greater response[120]. The first significant change in choroidal thickness was recorded at 10 minutes across the sample, and the overall change at 60 minutes was significantly thicker than that recorded by Read et al. Interestingly, Chiang et al. found a significant difference in baseline choroidal thickness and resultant thickening between myopes and emmetropes. Unlike the participants recruited by Read et al., the myopic participants in this study had statistically significantly thinner choroids at baseline than emmetropes. Chiang et al. also identified a difference in the time taken for the maximum choroidal thickening or thinning from over the 60-minute period between refractive error groups, where myopes reached peak choroidal thickness change significantly faster

Authors (Year)	Number of Eyes Tested	Participant Age (years)	Participant Refractive Error	Instrumentation	Scanning Protocol	Choroidal Segmentation Method	Type of Lens	Field of Defocus	Power of Myopic Defocus	Duration of Defocus (minutes)	Target Viewed	Measurement intervals (minutes)	Baseline SFCT (mean ± S.D)	Time of First Significant CT Change (minutes)	Time of Maximum CT Change (minutes)	Maximum CT Change Recorded
Read et al. (2010)[126]	28	25 ± 3	14 emmetropes (+0.75 to -0.75D) 14 myopes (≥-1.25D) <1.50D astigmatism <1.00D anisometropia	Haag Streit Lenstar LS 900 optical biometer (OLCR)	Individual A-scan	Manual	Spherical spectacle lens	Full-field	3.00D	60	TV screen at 6 metres	30	Emmetropes: 269 ± 44µm Myopes: 259 ± 43µm	30	60	~+12µm
Chiang et al. (2015)[120]	12	22.91 ±5.90	6 emmetropes (+0.56 to -0.75D) 6 myopes (-2.00 to -4.94D) <1.00D astigmatism <1.00D anisometropia	Nidek RS-3000 RetinaScan Advance EDI SD-OCT	6mm macula line scan. 'Ultra Fine' B-scan averaging mode.	Manual	Spherical soft contact lens	Full-field	2.00D	60	TV screen at 6 metres	5	Emmetropes: 423 ± 62µm Myopes: 256 ± 42µm	Emmetropes: 10 Myopes: 10	Emmetropes: 40 Myopes: 25	Emmetropes: +19.92 ± 4.86µm Myopes: +15.16 ± 4.15µm
Wang et al. (2016)[124]	17	8-16	-0.50 to -6.00D <1.00D astigmatism <1.00D anisometropia	Heidelberg Spectralis EDI SD-OCT	3 horizontal and vertical 9mm macula line scans. 100 averaged B-scans.	Manual	Spherical spectacle lens	Full-field	3.00D	120	TV screen at 5-6 metres	60	241.40 ± 15.18µm	120	120	-0.36 ± 1.43µm
Breher et al., (2018)[261]	18	25 ± 3	-1.00 to -6.00D ≤1.00D astigmatism	Carl Zeiss Cirrus HD-OCT 5000	6x6 macular cube	Automated	Spherical soft contact lens Multifocal soft contact lens	Full-field Progressive centre-distance Progressive centre-near	2.50D	30	TV screen at 4.5 metres	30	220 ± 44.5µm	N/A	N/A	+2.0 ± 11.1µm +2.1 ± 11.1µm +1.6 ± 11.3µm
Chiang et al. (2018)[127]	37	57.74 ± 4.06	-3.00 to +3.00D	Nidek RS-3000 RetinaScan Advance EDI SD-OCT	9mm macula line scan. 'Ultra Fine' B-scan averaging mode.	Manual	Spherical spectacle lens	Full-field	2.00D	60	TV screen at 6 metres	20	226 ± 72µm	20	60	+10 ± 5µm
Sander et al., (2018)[373]	30	26.1 ± 5	15 emmetropic (+0.75 to -0.50D) 15 myopic (≥-0.75D)	Copernicus HR SD-OCT, 'chorioretinal' mode	6mm macular horizontal and vertical cross. 30 averaged B-scans	Manual	Spherical spectacle lens	Full-field	3.00D	60	Binocular distance viewing	30	Emmetropes: 327 ± 50µm Myopes: 286 ± 52µm	60	60	+12 ± 3µm
Hoseini-Yazdi et al. (2019)[262]	25	26 ± 5	+0.50 to -5.00D <1.00D astigmatism <1.00D anisometropia	Heidelberg Spectralis EDI SD-OCT	Vertical 5mm macular line scan. 100 averaged B-scans.	Semi-automated	Spherical spectacle lens Half-diameter spectacle lens Half-diameter spectacle lens	Full-field Superior hemifield Inferior hemifield	3.00D	60	LCD screen at ≥6 metres	60	Not published	60	60	+2 ± 8µm +5 ± 9µm +3 ± 7µm
Hoseini-Yazdi et al. (2020)[263]	18	28 ± 6	+0.75 to -7.00D 0.00 to -2.00D astigmatism <1.00D anisometropia	Heidelberg Spectralis EDI SD-OCT	Horizontal and vertical macular 30° cross-scan. 100 averaged B-scans.	Semi-automated	Spherical spectacle lens Cylindrical spectacle lens	Full-field Astigmatic (Axis 180) Astigmatic (Axis 90)	3.00D	60	Projector screen at 3 metres	20	Not published	20 60 60	60 60 60	+8 ± 5µm +5 ± 6µm -4 ± 5µm
Kubota et al. (2021)[264]	20	19-31	-2.02 to -4.13D <0.75D astigmatism	Heidelberg Spectralis EDI SD-OCT	Radial (30°) macular scan. 50 B-scans	Semi-automated	Fresnel lens with 11.5mm central clear aperture	Peripheral	3.50D	240	Projector screen at 4 metres	240	Not published	N/A	N/A	~-8 µm
Ostrin et al., (2024)[260]	15 16 15	Children: 6-<18 Young adults: 18-30 Adults: >30-45	-1.27 ± 1.23D (range -7.30 to +2.07D)	Heidelberg Spectralis EDI SD-OCT	Six macular line 30° radial scans 16 averaged B-scans	Semi-automated	Spherical spectacle lens	Full-field	3.00D	50	Projector screen at 2 metres	10	Children: 350 ± 51 Young adults: 360 ± 95 Adults: 353 ± 88	N/A	N/A	Not disclosed

Table 1.4: Comparison of methods and findings of human choroidal thickness response to myopic defocus across different studies. TV= television, LCD= liquid-crystal display. Cells shaded green show significant choroidal thickening, cells shaded red show significant choroidal thinning, and non-shaded cells indicate no significant difference.

than emmetropes (25 and 40 minutes for myopic defocus, 20 and 35 minutes for hyperopic defocus, respectively). Lastly, in response to myopic defocus, the overall choroidal thickness increase was greater in emmetropes than myopes, with both values being greater than that found by Read et al.

Chiang et al. (2015) recognised these differences and ruled out instrumentation and analysis repeatability as being the sole cause[120]. Although some research suggests ethnicity and choroidal thickness have no significant relationship[250, 259], Chiang et al. hypothesised this may be a contributary factor; their study consisted of solely East Asians, whereas there was a mixture of ethnicities in the sample employed by Read et al. (East Asians, white Europeans, and Indians)[126]. Furthermore, the power and method of inducing defocus differed between the two studies. Read et al. (2010) used a spectacle lens of +3.00D defocus and Chiang et al. used a soft contact lens of +2.00D defocus. This could suggest a non-linear choroidal response to the power of defocus, or potentially demonstrate different peripheral refraction profiles of a soft contact lens and a spectacle lens induce different degrees of choroidal thickening.

One factor not considered here is the effect of baseline choroidal thickness. The average baseline choroidal thickness of emmetropic participants was vastly thicker in the sample used by Chiang et al. (Chiang et al.: 423 ± 62μm, Read et al.: 269 ± 44μm), whereas that of the myopic participants was similar between the studies. This poses the question as to whether those individuals with thicker choroids will respond to myopic defocus more slowly and to a greater extent than those with thinner choroids. However, this is difficult to gauge between these two studies alone due to the difference in measurement intervals, power of defocus and type of defocusing lens used.

In addition to young adults, the effect of full-field myopic and hyperopic defocus on choroidal thickness has been researched in myopic children and adolescents. Wang et al. (2016) found a 2-hour defocus period induced significant thinning of the choroid with 3.00D of hyperopic defocus in schoolchildren[124]. However, no absolute thickening of the choroid was seen following the same period of 3.00D myopic defocus. Wang et al. determined this was accounted for by diurnal fluctuations, as myopic defocus elicited significantly less choroidal thinning than both the control and hyperopic defocus conditions, suggesting relative choroidal thickening. In this study, every participant had 1% cyclopentolate instilled for all test conditions, which may have had some contribution to the choroidal thinning seen[206].

In presbyopes (57.7 ± 4.1 years of age), Chiang et al. (2018) found an increase in choroidal thickness with myopic defocus and thinning with hyperopic defocus[127]. Significant changes in choroidal thickness were seen at 20 minutes in both defocus conditions. Although the results

are not as relevant to myopia development and progression as that investigated in younger generations, the findings demonstrate human choroidal sensitivity to retinal blur is still present and fast-acting in later life, even in eyes with reduced accommodative power.

However, not all studies employing short-term, full-field myopic blur have reported choroidal thickening. Using a +3.00D spectacle lens, Ostrin et al., (2024) measured choroidal thickness at 10-minute intervals over a 50-minute period which did not achieve any statistically significant difference from baseline[260]. This was consistent over three age groups: children (6 to <18 years), young adults (18 to 30 years), and adults (>30 to 45 years), all of which had no significant difference in baseline choroidal thickness. Like that reported by Read et al. (2010)[126], participant refractive error did not appear to have an impact on the findings. In young adults with low to moderate levels of myopia, Breher et al., (2018) also found there to also be no change in choroidal thickness change following 30 minutes of 2.50D myopic blur induced with a spherical soft contact lens[261].

Despite some discrepancies in the extent and speed of thinning or thickening between studies, there is evidence to suggest imposed blur may result in changes to choroidal thickness in the defocused eyes. This builds upon the theory of local visually guided mechanisms of human ocular growth, which has been enhanced further through experiments of regional monocular defocus.

1.4.2b Regional defocus

Investigations of regional myopic defocus and its impact on choroidal thickness have yielded compelling results; there is evidence to suggest the choroid responds in a regionally selective manner when presented with localised myopic retinal blur.

Hoseini-Yazdi et al. (2019) induced 3.00D of superior and inferior retinal myopic defocus separately by using half-diameter spectacle lenses, and found significant choroidal thickening was largely contained within the hemifield exposed to blur[262]. Furthermore, hemifield myopic defocus appeared to elicit greater choroidal thickening (in the defocused region) than full-field defocus. For example, the superior choroid thickened significantly more when exposed to superior hemifield defocus than it did to full-field defocus, despite the superior choroid being exposed to the same power of myopic defocus in each condition. This suggests that the differential effect has a greater impact on the choroid than a uniform effect.

In the separate superior and inferior hemifield defocus conditions, Hoseini-Yazdi et al. (2019) also found the increase in superior choroidal thickness was double that of the inferior choroid[262]. Even with full-field myopic defocus, the superior choroid thickened to a greater extent than the inferior choroid. Additionally, the choroidal thickening following inferior

hemifield defocus was contained within the inferior choroid, however choroidal thickening following superior hemifield defocus spread beyond the superior boundary into the inferior foveal choroid. Hoseini-Yazdi et al. concluded these findings suggest that following myopic defocus, the mechanisms of ocular growth are either more sensitive within the superior choroid or can expand to a greater extent when compared with the inferior choroid.

In addition, short-term astigmatic defocus has been found to alter choroidal thickness, with the orientation being a key factor in the type of choroidal response[263]. After 60 minutes of with-the-rule astigmatic defocus (cylindrical axis at 180), Hoseini-Yazdi et al. (2020) found a significant increase in the mean choroidal thickness averaged across the choroid[263]. Contrastingly, a decrease in mean choroidal thickness was found following against-the-rule astigmatic defocus (cylindrical axis at 90), suggesting the ocular compensatory mechanisms for defocus may be orientationally selective. In both conditions, the extent of choroidal change was similar across both the horizontal and vertical meridians. At present, this theory requires further exploration.

On the other hand, a study exploring the effect of peripheral myopic defocus found no significant change in choroidal thickness following 4 hours of exposure[264]. Kubota et al. (2021) used stick-on Fresnel lenses with a central clear aperture to induce 3.50D of myopic defocus purely on the retinal periphery. The thickness of the central 0.5mm choroidal region was compared before and after the defocus session, finding no significant difference, but the resultant choroidal thickness in the test condition was thicker than that in the control condition (where no myopic defocus was induced). In this study, the duration of the defocus period and interval between measurements were much longer compared with those discussed previously, making it difficult to truly decipher the choroid's response throughout this time.

1.4.2c Conclusion

It is evident that full-field and regional defocus can result in change to choroidal thickness of some extent, which can occur in as little as 10 minutes[120]. However, several obscurities remain. For example, some research suggests a significantly different response to an identical power and type of defocus depending on an individual's refractive error[120], however other research suggests refractive error plays no part[126]. It is unclear whether the difference in peripheral refraction profiles between soft contact lenses and spectacle lenses is a contributor to inconsistencies seen between studies[120]. Alternatively, a participant's rate of refractive error progression, differing sample age-ranges, differing experimental set-ups, and choice of choroidal segmentation software used across studies (Table 1.4) may be contributing factors.

Where a statistically significant alteration in choroidal thickness has been detected, the nature of the choroidal recovery immediately following removal of a defocusing condition hasn't been widely investigated in humans. Wang et al. (2016) found the relative choroidal thickening associated with myopic defocus and thinning with hyperopic defocus to significantly decay at 2 hours post-removal of defocus in children under cycloplegic conditions[124]. Other studies have shown choroidal thickness to have returned to baseline around 24 hours following removal of a defocusing lens[121, 125], however little is known about these changes within a shorter timeframe. Further, it is not known whether choroidal thickness will naturally regress back to baseline when the short-term defocus is sustained for longer periods, or whether the thickening or thinning is maintained until cessation of defocus. Understanding how the choroid recovers can provide further insight into the mechanisms behind the homeostatic control of eye growth; in particular, whether the recovery time of a myopic eye differs to that of a non-myopic eye and, as a result, whether the homeostatic properties of the choroid are impacted by refractive error.

Increasing choroidal thickness is believed to be a contributory factor to slowing ocular elongation[116] and full-field myopic defocus causes choroidal thickening[120, 126, 127], yet myopic defocus induced by deliberate full-field undercorrection has been largely unsuccessful in controlling axial growth in children[265-267]. The greater choroidal thickening seen in regional defocus compared with full-field defocus[262] may provide some explanation for why alternative interventions are more efficacious than undercorrection. Exploring the impacts of defocus patterns on choroidal thickness is an area which holds plenty of research promise in better understanding the underlying mechanisms of eye growth; in particular, whether varying degrees of sensitivity across the choroidal profile exist, and whether the initial choroidal response reflects the overall efficacy of an intervention in slowing long-term myopia progression.

1.4.3 Choroidal response to long-term defocus

Clinical trials using various patterns of retinal blur have investigated the long-term impacts of defocus on myopia progression in children. In humans, most myopic eyes have relative off-axis hyperopia[268], and conventional spectacle or contact lens on-axis myopia correction maintains peripheral hyperopic defocus (Figure 1.8). Additionally, some evidence suggests children who become myopic appear to have more hyperopic relative peripheral refractions 2 years before myopia onset than those that remain emmetropes[269, 270]. From this, it has been theorised that some degree of uncorrected myopic refractive error should slow axial elongation in children due to the constant exposure to retinal myopic defocus[271]. However, research suggests this has little impact on long-term eye growth[265] or may produce a greater

degree of myopia progression[266, 267, 272]. Following these findings, using undercorrection as a strategy for myopia control has decreased amongst eye care practitioners over recent years[29, 30], which is explored further in the following chapters of this thesis.

Techniques adopting deliberate peripheral myopic defocus appear to have more promising results. In addition to the efficacy of these interventions, several researchers have explored the associated changes in choroidal thickness with long-term use, and how these compare with axial elongation in time.

1.4.3a Bifocal and multifocal spectacles

Prescribing bifocal and progressive addition spectacle lenses (PALs) as a method of myopia control was originally intended to reduce the higher levels of accommodative lag and the associated foveal hyperopic defocus seen in myopic children[273, 274]. When compared with single vision lenses, bifocals and PALs have been largely unsuccessful in establishing clinically meaningful efficacy[61, 275-278]. One promising bifocal spectacle lens study was provided by Cheng et al. (2014), where executive bifocals with base-in prism at near were found to reduce myopia progression in children by at least 0.50D per year[279]. However, this study was conducted at a single site with only Chinese participants involved and there is little other research supporting bifocals as being such an efficacious control method. Alternatively, it is possible that the bifocal design was a contributory factor towards the promising results; an executive design will naturally cover a greater area of the retina compared to smaller segment sizes used in other studies, but this is yet to be determined.

Other spectacle lens approaches to control myopia employ altered peripheral optics with a clear central optical zone. Defocus Incorporated Multifocal Segments (DIMS) spectacle lenses achieve this by incorporating a circinate zone of multiple segments with 3.50D of

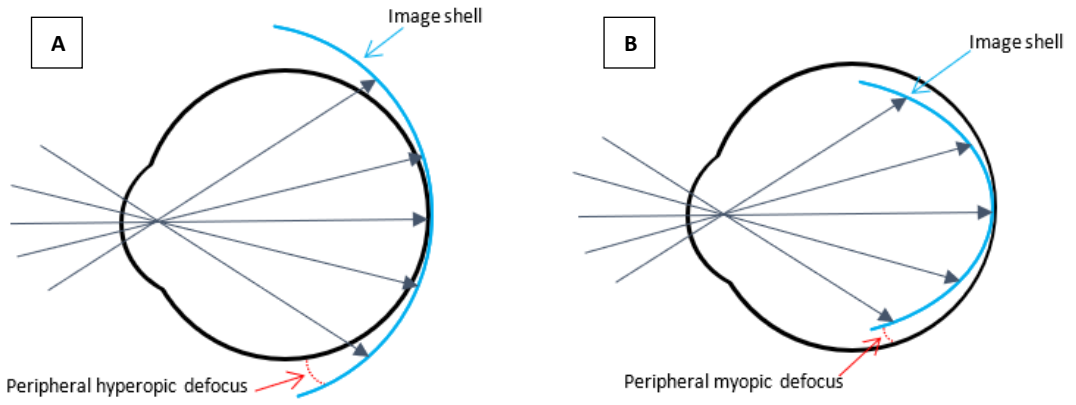


Figure 1.8: Schematic diagram showing A) peripheral hyperopic defocus with conventional on-axis myopic correction and B) desired effect of an optical intervention with altered peripheral optics to induce peripheral myopic defocus with maintained on-axis correction.

relative positive power[280]. This enables clear vision independent of the viewing distance whilst simultaneously maintaining constant peripheral myopic defocus. Recent clinical trials show promising results; after 2 years of wear, children wearing DIMS lenses showed over 50% slower myopia progression and 62% less axial elongation than those with single vision lenses[280]. Chun et al. (2021) examined the effect of these lenses on subfoveal choroidal thickness in myopic school-aged children in China and found subfoveal choroidal thickness to increase significantly after just 1 week of daily DIMS wear compared to children wearing single vision spectacles[281]. This choroidal thickening increased further over the initial 6 months. Following a secondary analysis of this data, the authors identified the mean change in choroidal thickness from baseline to 1 week to be +6.75 ± 1.52μm, which more than doubled by 12 months (+13.64 ± 2.62μm)[282]. Although these values may appear modest in isolation, measures from the control (single vision) group showed the opposite effect; significant choroidal thinning was observed in children wearing single vision spectacles at 1 week and 12 months (-3.17 ± 1.48μm and -9.46 ± 2.55μm, respectively). With daily DIMS spectacle lens use, the authors found the choroidal thickening to be sustained over a 24-month period. Interestingly, after controlling for the effect of participant age and gender, Chun et al., (2023) reported the level of choroidal thickening achieved at 3 months showed a significant negative association with the changes in axial length at 12 months of wear (R^2=0.126, p=<0.005)[282]. Therefore, this indicates the short-term choroidal thickening to be a predictor for the efficacy of DIMS lenses in controlling ocular growth and concomitant refractive error.

Also marketed for myopia management, spectacle lenses incorporating peripheral concentric rings of slightly aspherical lenslets (SAL) and highly aspherical lenslets (HAL) have provided promising reports of efficacy[283], with similar levels to that of DIMS spectacles. Throughout a 2-year, randomised clinical trial, choroidal thickness across the 3mm and 6mm nasal, temporal, inferior, and superior macular regions was assessed at 6-monthly intervals. Children wearing spectacles containing SAL (n=51) exhibited significant choroidal thickening at 6 months which decreased thereafter, whereas those wearing HAL spectacles (n=54) exhibited choroidal thickening throughout the first year, which subsequently decreased. Following this decrease, a lower degree of macular choroidal thinning was observed in children who wore either the SAL or HAL than single vision spectacles, with the HAL having the greatest impact, suggesting a dose-dependent effect. A greater negative correlation between axial length and choroidal thickness changes at 2 years was seen with HAL than SAL and single vision lenses (r=-0.53 p<0.001, r=-0.48 p<0.001, and r=-0.36 p=0.01, respectively), whereas no correlation between axial length change and baseline choroidal thickness was present. This study identified regional variations in their choroidal analysis;

the outer choroidal regions (6mm) showed less thinning than their inner counterparts. Additionally, the greatest choroidal thickening with the HAL group and least choroidal thinning with the SAL group occurred superiorly, reflecting that discovered by Hoseini-Yazdi et al., (2019), where the superior choroid appeared the most sensitive in the presence of short-term regional myopic defocus[262]. However, as recognised by the authors, the choroidal images were taken at inconsistent times of day, fluctuating over a period of 7 hours. Therefore, diurnal variations may have confounded the results[187, 189-191]. Further, choroidal images were taken 30 minutes post-instillation of 1% cyclopentolate eye drops, so, although consistent at every follow-up, this may have altered choroidal thickness[206, 208], and it is not known whether such cycloplegic agents impact choroidal thickness in a uniform manner.

1.4.3b Dual-focal and multifocal contact lenses

Unlike a spectacle lens, the refraction pattern of a contact lens remains fairly consistent during eye movements (providing good lens centration) so hypothetically should be able to provide sustained peripheral myopic defocus in all positions of gaze. Several randomised controlled trials of centre-distance dual-focus (concentric rings of relative positive power) and multifocal (gradient design of increasing peripheral relative positive power) soft contact lenses have shown a subsequent reduction in axial elongation and myopia progression following regular wear[284-294]. Some trials have suggested greater efficacy than others; using a centre-distance bifocal lens, Aller et al. 2016 found greater than 70% reduction in myopia progression and axial elongation compared to single vision contact lenses after a year of wear[288]. Using a custom-made bifocal lens comprised of alternating defocusing and correction zones, Lam et al. 2014 found 25% less myopia progression and 31% less axial elongation over 2 years than that seen in single vision contact lens wear[290]. In their comprehensive report of myopia interventions, Wildsoet et al. (2019) compared several of these clinical trials and found concentric ring (bifocal) designs showed better control of axial elongation than progressive (multifocal) designs (44.4% versus 31.6%)[295]. Questions remain about the optimum refraction profile of a soft contact lens to manage myopia, and it is likely a ‘one-size-fits-all’ approach isn’t suitable. Variations in efficacy could be due to different retinal curvature profiles or peripheral refraction between individuals. For example, although uncommon in myopes[296], individuals with a very prolate retinal profile would receive less induced peripheral myopic defocus than those with a more spherical retinal profile.

In regard to the choroid, when investigated in the short-term, both centre-distance and centre-near multifocal contact lenses (both with +2.50D addition) showed no significant effect on choroidal thickness after 30 minutes of monocular wear[261] (Table 1.4). From this, the authors concluded choroidal thickness may not be a contributor to the success of

multifocal contact lenses in slowing myopia. It is unclear whether different contact lens designs and/or addition powers may influence choroidal thickness to a greater extent than seen in this study. Alternatively, different choroidal mechanisms might be involved when exposed to the non-uniform defocus induced by dual-focus or multifocal soft contact lenses compared to single-vision spectacle and contact lenses.

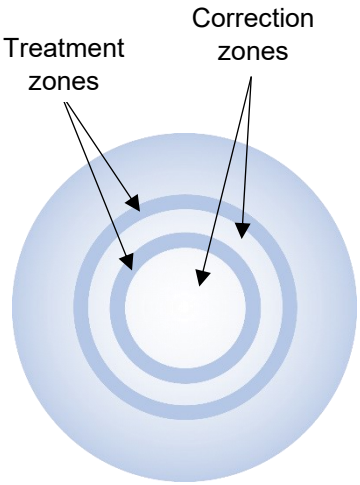


Figure 1.9: Schematic diagram of treatment and correction zones of the MiSight 1-day contact lens (CooperVision).

However, when observed over a longer duration of time, dual-focus contact lenses have been found to significantly impact choroidal thickness. Currently marketed for myopia control in various parts of the world, MiSight daily disposable contact lenses (CooperVision, Inc) are comprised of a large central correction zone surrounded by alternating concentric rings of 'treatment' (containing 2.00D relative plus power) and correction zones (Figure 1.9). This provides the wearer with clear vision at all distances whilst maintaining 2.00D peripheral retinal myopic defocus. Prieto-Garrido et al., (2022) discovered children who showed an increase in axial length of <0.22mm/year over 24 months of MiSight lens wear (n=16, mean axial length change 0.13mm over 24 months) to show a significantly thicker choroidal thickness across the temporal and nasal 1mm and 3mm macular area at 12 months of wear (6 days per week, 10 hours per day) compared to those whose axial lengths increased ≥0.22mm/year over 24 months of wear (n=25, mean axial length change 0.38mm over 24 months) or children wearing single vision contact lenses (n=33, mean axial length change of 0.45mm over 24 months)[297]. This effect was only identified over the first 12 months; at 24 months, there was no significant difference in choroidal thickness change between the children with faster axial progression and the children with slower axial progression. As recognised by the authors, the sample size of this study limits the interpretation of the results on a wider scale.

A randomised controlled trial of defocus incorporated soft contact (DISC) multifocal lenses - containing a central correction zone with alternating defocusing (2.50D relative plus power) and correction zones towards the periphery – has found these lenses to impact choroidal thickness with long-term wear[298]. In addition to effectively slowing axial and refractive progression in a sample of Chinese schoolchildren (n=17) compared to those wearing single vision contact lenses (n=15) over 12 months of wear (5 days per week, 8 hours a day), DISC multifocal lenses significantly thickened the vertical 6mm macular area at 6 and 12 months of wear. The refractive progression of these myopic children was significantly correlated with

the choroidal thickening observed at 12 months, suggesting the reported efficacy may be related to changes in the choroid. However, the participants involved in this randomised controlled trial were primarily female (81%), and the sample size itself was relatively modest[298]. The lack of ethnic diversity of the sample provides a further limitation.

1.4.3c Orthokeratology

Orthokeratology (ortho-k) lenses are specially designed reverse-geometry rigid contact lenses which temporarily eliminate central refractive error by reshaping the cornea during sleep[299, 300]. In addition to providing clear unaided vision during waking hours, ortho-k treatment has been found to have a protective effect against myopia; several studies show ortho-k slows axial elongation by around 30-60%[301-309]. It has been proposed that this protective effect is due to changes in refraction beyond the central 20° of the retina, where the central corneal flattening results in peripheral myopic defocus relative to peripheral hyperopia seen at baseline[270, 310].

Some research has found ortho-k treatment to completely halt ocular elongation and, albeit statistically insignificant, slightly reduce axial length[303]. This shortening of axial length was hypothesised to be due to compensatory thickening of the choroid in response to one year of ortho-k use[303]. Short-term ortho-k treatment has shown significant choroidal thickening across the macular region after just 3 weeks of nightly use, which was correlated with a decrease in axial length[311]. Li et al. (2017) found a significant increase in subfoveal choroidal thickness after 1 month of ortho-k lens wear, which showed no further increase at the following 6-month review[312].

Contrastingly, Gardner et al. (2015) found no significant change in choroidal thickness following 9 months of ortho-k treatment[313], however several experimental limitations accompanied this study. Only 9 participants were recruited and there were considerable intra-sample variations in choroidal thickness (with no compensating control group), which questions the ability of this experiment to detect small, yet significant, choroidal thickening.

Although reduced axial elongation secondary to ortho-k is well-established, variations in individual responses have been identified[303, 314]. Li et al. (2019) explored the possibility to use early detectable choroidal thickening induced by ortho-k lenses as a predictor for the long-term axial response[315]. Like previous research, significant choroidal thickening was identified in children at 1 month of nightly ortho-k treatment. The magnitude of this thickening was maintained over the following 12 months of ortho-k use, and axial elongation was significantly reduced. After a month of ortho-k cessation, subfoveal choroidal thickness reduced close to baseline. Li et al., found that baseline age and changes in subfoveal choroidal thickness, and biometric measurements at the 1-month visit explained 58% of the

variance in axial length change over 13 months (12 months with ortho-k treatment and the final month without, R^2=0.58, p=<0.001). Both baseline age and changes in subfoveal choroidal thickness at the 1-month visit were significantly associated with axial length changes at the 13-month visit, whereas no other biometric parameters (lens thickness, anterior corneal power, central corneal thickness and anterior chamber depth) showed a significant association with long-term axial growth. Therefore, it is possible that the short-term choroidal response may be a valuable precursor in determining an individual's likelihood to respond well to ortho-k as a method of myopia management.

Not all studies exploring the impact of orthokeratology on choroidal thickness have identified this predictive possibility; in a sample of 80 school-aged children, Xu et al., (2023) found a significant level of choroidal thickening present after 1-, 6-, 12-, 18-, and 24-months of ortho-k wear (n=40) compared to those not using any myopia intervention (n=40)[316]. The choroidal thickness changes measured at 24 months were only significantly associated with axial length changes at 24 months in the control group (r=-0.52, p<0.001); the study found no significant association between axial elongation and choroidal thickening at any timepoint with ortho-k wear. Although no correlation was identified, the authors did find there to be variable responses in thickness changes across the horizontal choroidal profile following the ortho-k induced peripheral defocus; a greater change in choroidal thickening and contour was observed in the temporal 3mm horizontal choroidal region than that of the nasal region, highlighting the need for further exploration of regional changes across the wider choroidal profile.

1.4.3d Conclusion

Overall, clinical trials of optical methods that induce a deliberate, spatially variable pattern of myopic defocus have generally produced promising results regarding myopia management, however the efficacy of a particular intervention varies between individuals[257, 295]. The reasons behind the inconsistencies are unclear. Understanding the choroidal response to frequent exposure to such patterns of defocus may provide useful insight into the effectiveness of various interventions on an individual level, particularly if negatively correlated with longitudinal axial growth.

1.4.4 Choroidal response to long-term use of pharmacological agents

As discussed in Section 1.3.3e, several pharmacological agents can stimulate rapid choroidal thickness changes. Two of these are atropine and the closely related, less potent, homatropine eye drops, which have been shown to thicken the choroid within an hour[209, 213]. Although not yet licensed for use in the UK, atropine eye drops are being used as a method of myopia control across various parts of the world[29, 30] due to various clinical trials and

reviews deeming it effective in reducing axial elongation and myopia progression in myopic children across different populations[317-320]. Given the adverse effects of non-selective antimuscarinic antagonists such as photophobia and blurred vision, efficacious intervention using low concentrations of atropine is desirable for long-term use. At present, there is no consensus for the underlying mechanisms mediating its effectiveness. With this, the impact of long-term use of atropine on the choroid has become of interest.

A double-blinded, randomised controlled trial of three low concentrations of atropine (0.05%, 0.025%, and 0.01%) identified a significant increase in subfoveal choroidal thickness from baseline to 2 years of nightly instillation (1 drop in both eyes) with 0.05% (n=81) and 0.025% (n=80) concentrations[321]. There was no significant change in choroidal thickness associated with 0.01% (n=86) atropine instillation. The extent of choroidal thickening was dose-dependent; significantly thicker choroids were observed in the eyes that received 0.05% than 0.025% atropine (+21.15 ± 32.99μm and +3.34 ± 25.30μm, respectively). This dose-dependent choroidal thickening had already been achieved by 4 months of use and was maintained throughout the following 20 months of the trial. The increase in choroidal thickness showed a significant association with slower progression of refractive error and axial elongation (both of which were slowest with the 0.05% concentration), indicating the early choroidal response may be a valuable tool in assessing the prognosis for the long-term treatment outcome.

The use of choroidal thickness changes as a guide for atropine dose titration has been supported by more research. Ye et al., (2020) also found a significant dose-dependent choroidal response between 1.0% and 0.01% atropine, where the higher dose resulted in choroidal thickening over the central 6mm area at just one week of daily use (+26 ± 14μm)[322]. This thickening was maintained up to 6 months and was negatively associated with axial elongation over this time. Conversely, significant choroidal thinning was observed at 6 months of the low-dose atropine (-5 ± 17μm), contradicting the thickening previously identified at 60 minutes post-instillation[213].

Additional to the pattern of concentration with the degree of choroidal thickening, combining atropine with a peripheral-defocusing optical intervention has shown to increase choroidal thickness to a greater extent than atropine alone. After 1 month of daily use, children who used 0.01% atropine with single vision correction (n=22) and children who used orthokeratology (n=24) showed a significant level of choroidal thickening (+5.41 ± 1.65μm and +17.46 ± 2.79μm, respectively), whereas the choroids of children who used 0.01% atropine with orthokeratology (n=21) showed the greatest extent of thickening (+20.19 ± 2.18μm)[323]. Similar to the aforementioned studies, this early significant change was

maintained for the remainder of the 12-month trial and was negatively associated with the change in axial length at the 12-month visit in all study groups, further indicating the possibility of a predictive effect.

1.4.5 Choroidal response to alternative visual stimuli

1.4.5a Light intensity and spectral composition

Further to lens-induced defocus, experiments exploring the effects of alternative visual stimuli have produced interesting results. There is consistent evidence that time outdoors provides a shielding effect against myopia onset and progression[44-47], which has been attributed to the significantly brighter light intensity seen outdoors (several thousand to 200,000 lux) than indoors (100 to 1000 lux)[324]. At present, the mechanisms behind this protection of time outdoors remain to be elucidated. No parameter has been identified as the sole cause, however pupil constriction[324, 325], vitamin D levels[326-329], and violet light exposure[330, 331] have all been investigated as possible contributors. The dominant theory is that bright light exposure stimulates the release of retinal dopamine, which slows ocular growth and reduces the risk of myopia onset and progression[332-335].

Animal studies have provided evidence for short-term and longitudinal changes in choroidal thickness following varying light levels. For example, in chicks, exposure to 2 hours of light (700 lux) at night abolished the normal diurnal choroidal thickening seen at nighttime[336]. Following daily 6-hour periods of bright lighting (15,000 lux), chick choroids showed sustained relative thickening over 5 days, whereas choroidal thinning was seen in chicks exposed to ‘normal’ light levels (500 lux)[337]. In dim light (55 lux), rhesus monkeys showed sustained choroidal thickening for around 300 days, however this did not significantly alter the eye’s refractive state[338]. Although animal studies suggest the choroid can actively respond to varying light levels, there is little evidence to determine whether a choroidal response plays a part in the reduced myopia progression associated with increased light exposure in humans. Only recently has this been investigated; Ulaganthan et al. (2019) explored the effects of daily light exposure on diurnal and longitudinal changes in choroidal thickness and axial length in young adults. Over a 6-month period, they found only axial length changes (diurnal rhythms and longitudinal axial growth) to be associated with daily bright light exposure[339], therefore suggesting no direct impact on choroidal thickness. Conversely, Lou and Ostrin (2023) found 2 hours of exposure to sunlit outdoor environments (6,000 to 50,000 lux) resulted in macular choroidal thinning, which returned to baseline at 1 hour post-exposure[340]. Given that choroidal thinning is associated with axial elongation and time outdoors seems to protect against this effect, this finding is arguably unexpected. It may be that the short-term, transient changes exhibited by the choroid operate according to

different mechanisms than those associated with long-term exposure, whether this be variables such as light intensity, retinal defocus, or pharmacological agents.

However, exposure to varying intensities of white light do not account for spectral differences. Animal experiments across several species including chicks[330, 341-345], guinea pigs[346, 347], tree shrews[348] and rhesus monkeys[349-351] show that refractive error development can be influenced by the spectral composition of light. Using chromatic cues from longitudinal chromatic aberration (where short wavelengths of light focus anterior to long wavelengths), the eye is able to decode the type of defocus and respond accordingly. As part of this compensatory response, experimental animal studies show the choroid to respond differently when exposed to light with different spectral compositions[344-346, 348]. In chicks, lens-induced compensatory changes in eye length showed no change in choroidal thickness with exposure to dim short-wavelength ambient light. On the other hand, dim long-wavelength ambient lighting elicited changes in choroidal thickness, although not to the extent seen in white light[345]. It is therefore possible that the differing compensatory ocular responses, including choroidal thickness, to the spectral composition of light are regulated by different retinal cone types[345].

Interestingly, the effects of narrow-band illumination on compensatory eye growth are inconsistent across different species. In tree shrews, monocular hyperopic defocus accompanied with long-wavelength ambient lighting still induced relative myopia in the defocused eye, but a binocular hyperopic shift was seen[348]. Contrastingly, long-wavelength lighting prevented significant compensation for myopic and hyperopic defocus in guinea pigs, whereas short-wavelength light did not[347]. In rhesus monkeys, lens-induced monocular hyperopic defocus did not elicit the usual myopic shift when accompanied with long-wavelength lighting, but rather a relative binocular hyperopic shift was exhibited. Conversely, monocular myopic defocus still produced the expected hyperopic shift in the presence of long-wavelength light[351]. Despite no effect on blur-induced hyperopia, this evidence suggests long-wavelength light may shield the development of blur-induced myopia.

As it stands, the reasons behind the inconsistent responses to narrow-band illumination between species are unclear, however there is some evidence suggesting the spectral composition of light does play some role in myopia progression in humans. Increased sunlight exposure includes an increased exposure to ultraviolet radiation wavelengths (UVR, 10-400nm). Just below the visible spectrum, violet light (360-400nm) has been found to upregulate the production of the myopia suppressive gene EGR1 in chicks[330], suggesting that minimal UVR exposure may be a contributary factor in increasing myopia prevalence. This has been supported in human studies, as it appears that violet light may have a

protective effect against human high myopia. When trialled in young adults over a 5-year period, non-violet light transmitting phakic intraocular lenses (pIOLs) showed double the amount of myopia progression compared to that found with violet light-transmitting pIOLs[331]. Naturally, there is difficulty in recommending UVR exposure as a myopia intervention method due to the potential harmful ocular impacts of UVR, particularly during childhood[352].

Furthermore, research exploring the impact of visible red light on myopia progression has yielded promising results. In the absence of alternative myopia intervention methods, research conducted in China has found bi-daily exposure to 3 minutes of low-intensity red light of approximately 650nm, 5 days per week, to successfully slow axial and refractive progression in myopic school-aged children (n=264) by 69.4% and 76.6%, respectively[353]. With these impressive reports of efficacy yet obscurity regarding the processes underlying the effect, the immediate and long-term impacts of red-light therapy for myopia management has since been investigated. In 25 children who were not using any form of myopia management, subfoveal choroidal thickness was measured at 5 and 60 minutes following a single 3-minute session of low-level red-light therapy, and no significant difference was identified from baseline[354]. Long-term red-light therapy accompanied with single vision spectacles appeared to cause significant macular choroidal thickening in Chinese children (n=60)[355]; over 1 year of use, the greatest level of choroidal thickening occurred at 1 month (+14.76μm), gradually decreasing close to baseline over the subsequent 5 months (+1.54μm) and thickening again by 12 months (+9.09μm). Significant choroidal thinning occurred in children wearing only single vision spectacles at all timepoints (n=60). This study also found evidence of the choroid's predictive ability; for those eyes exposed to the repeated low-level red-light, the choroidal thickening exhibited at 3 months was significantly associated with the amount of axial elongation and refractive progression recorded at 12 months. The choroidal changes associated with red light therapy may be a contributing factor to its myopia controlling effect, however the reasons behind the thickening itself are widely theorised at present. It may be due to alterations in choroidal vasculature[356], whereby the increased luminal aperture resulting from increased blood flow may cause direct choroidal thickening[116].

Questions remain about the safety of commercially available, low-level red-light emitting devices marketed for myopia management. One meta-analysis confirms frequent exposure these devices to be of very little risk[357], whereas another publication identifies such devices to be Class 1 laser products, putting children's eyes at risk of photochemical and thermal damage[358]. Additional to safety data, the effect of narrow-band illumination on human eye growth needs more investigation as research conducted in humans suggests both short-wavelength light[331] and long-wavelength light[354, 356] reduces ocular growth. It is possible that

a direct change in choroidal vasculature plays a part, however more research is required to determine this.

1.4.5b Altered contrast signals

The first high-grade myopia locus on chromosome X (MYP1) was identified over 30 years ago, with inherited mutations at this region being responsible for familial high myopia[359]. The genetic mutation involved in producing the myopia was found to be within the chromosomal regions encoding retinal cone photopigments, affecting either the long (L, red) or middle (M, green) wavelength photopigments and causing protan or deutan colour defects accordingly[360]. The mutation was later found to also cause extremely reduced light sensitivity, therefore maintaining a constant, abnormal high contrast in light sensitivity between cones with mutant photopigments and cones with normal photopigments[361]. From this, it has been hypothesised that the resultant abnormal contrast signals may encourage axial elongation and consequential myopia.

SightGlass VisionTM spectacles have since been manufactured as a myopia management option which adopt the contrast signals theory. The lenses are powered by Diffusion Optics TechnologyTM (DOT), where a central 5mm clear optic zone is surrounded by microscopic diffusers of approximately 0.14mm in diameter and 0.2mm in height[362]. Two designs of this peripheral contrast reducing lens – low density (0.37mm diffuser spacing) and high density (0.24mm diffuser spacing) - have been shown to significantly reduce axial and refractive progression in myopic children (n=256) in a 3-year randomised controlled trial[362]. These findings support the theory of high retinal contrast as a stimulant for ocular growth.

Currently, literature detailing the effect of reduced contrast signals on choroidal thickness is sparse. Given the hypothesis and manufacture of this approach to myopia management being only a recent development in the field, it is likely that research exploring the association will emerge in due course. Alternatively, the impact of contrast reducing and image degrading ocular pathology on choroidal thickness is worth considering. In the absence of other pre- or post-operative pathology, subfoveal choroidal thickness appears to be thinner in patients with clinically significant cataracts, and thicker post-recovery of uncomplicated phacoemulsification at 12 weeks[363]. This thickness change directly correlated with the nuclear lens density. Due to the invasive nature of cataract surgery, it is possible that these findings were not predominantly visually guided as inflammatory processes in the posterior segment may have an impact. On the other hand, one study identified subfoveal choroidal thickening following successful removal of cataracts to be maintained at 6 months in elderly patients, with no impact on retinal thickness[364]. When solely altering retinal contrast, the opposite outcome would be expected if the choroid is a direct contributor to the

myopia controlling effect; choroidal thickening would occur in the instance of reduced contrast signals.

It is clear that the impact of reduced contrast signals on choroidal thickness isn't well understood at present. Rather than a reduction in retinal image contrast, there is evidence to show contrast polarity impacts axial length (here used as a surrogate measure for choroidal thickness). Compared to standard contrast (dark letters on a light background), reading large text with inversed contrast (bright letters on a darker background) on a TV screen at 2 metres for 30 minutes induced significant axial shortening, suggesting this change in contrast thickened the choroid[365]. Therefore, there is already some evidence for using altered contrast as a visual stimulus for axial shortening. The effect of contrast polarity with reading on choroidal thickness is considered further in the next section.

Following deliberate reduced peripheral retinal contrast, it will be useful to establish the short and long-term choroidal changes in the eyes of myopic children, and how this compares with the choroid's bi-directional response seen with lens-induced defocus anterior or posterior to the retina.

1.4.5c Accommodative targets

The impact of ocular accommodation on choroidal thickness in the absence of pharmacologically induced cycloplegia (Section 1.3.3e) has been under scrutiny for many years. In 1998, Drexler et al., found the axial lengths of myopic and emmetropic young adults to significantly elongate during their maximum subjective accommodative amplitudes, measured using PCI[366]. With the choroid forming a continuous component of the uveal tract, the authors concluded that the accommodation-induced contraction of the ciliary muscle likely resulted in a forward and inward pulling of the choroid, concurrently decreasing the scleral circumference and elongating the posterior segment. More recently, using EDI-OCT, accommodation-induced choroidal thinning has also been achieved with a 6D stimulus (mean change -5 ± 7μm)[367]. The magnitude of choroidal thinning was dependent on region; the thinning was greatest in the temporal and inferotemporal parafoveal choroid. The authors suggested the regional differences may be associated with the distribution of non-vascular smooth muscle within the uvea, as it corresponds with the areas of greatest choroidal change.

In the latter study, choroidal thinning was not present with a smaller accommodative demand using a 3D stimulus, however a separate study identified significant axial elongation and choroidal thinning (-13 ± 14μm) following a 10 minute near task in downward gaze (25°) with a 2.5D accommodative stimulus[368]. In this case, the choroidal thinning accounted for 50% of the total axial length change. In contrast, participants who conducted the same task in

primary gaze showed significant axial elongation yet no significant change in choroidal thickness, providing evidence for the additional impact of scleral contraction or stretch associated with extraocular muscle force. Consequently, the recurring small episodes of axial expansion or choroidal thinning accompanying accommodation in downgaze could play an active role in the well recognised relationship between myopia onset and excessive near work[43]. Other research suggests the resultant choroidal thinning following accommodation is present even after longer durations; thirty minutes of a 4D accommodative task produced choroidal thinning of -9 ± 18μm in the myopic eyes of young adults, which had a weak association with a corresponding increase in axial length (+22 ± 34μm)[369].

Relative activity of retinal ON and OFF pathways appears to impact accommodation-induced choroidal thinning. Existing at the synaptic level between the retinal photoreceptors and bipolar cells, the ON pathway responds to light increments (such as inversed contrast tasks: bright letters on a dark background), and the OFF pathway responds to light decrements (such as standard contrast tasks: dark letters on a bright background). With reading materials generally consisting of dark letters on a bright background (therefore stimulating the OFF pathway), Hoseini-Yazdi et al., (2021) explored whether the contrast polarity of such stimuli impacts the extent of choroidal change seen with accommodative tasks[370]. Young adult participants performed 30-minute-long viewing tasks with relaxed and 5D accommodative demands, including reading bright text on a dark background (ON pathway overstimulation) and reading dark text on a bright background (OFF pathway stimulation). It was discovered that reading text with standard contrast caused significant additive choroidal thinning to the thinning induced by accommodation alone (-11 ± 1μm and -7 ± 1μm, respectively). Thus, a direct mechanism involving accommodation and OFF pathway signalling may be an underlying factor in the relationship between near work and myopia.

In their comprehensive white paper reviewing the role of accommodation in myopia development, the International Myopia Institute (IMI) recognised the essential need for further research to understand the factors behind accommodative mechanisms in myopia[371]. Additional to ensuring children have a correctly functioning accommodative system[371], the aforesaid findings of accommodative effort-dependent choroidal variations, biomechanical influences, and the further impact of the contrast polarity of an accommodative stimulus provide valuable insight into possible myopigenic reading behaviours.

1.4.5d Conclusion

Collectively, research shows it is not just visual blur which drives choroidal alterations. There is strong evidence that narrow-band illumination directly impacts choroidal thickness, and it is possible that the spectral composition of light could play a part in the protective effect of

time outdoors. Additionally, retinal image contrast and accommodative behaviours may each have a direct and additive contribution to incident myopia through choroidal mechanisms. Although these mechanisms remain obscure, this area of research presents a strong basis for experiments exploring the ocular response to coloured filters, lens-induced reduced contrast, and narrow-band illumination on both an immediate and long-term scale.

1.5 DISCUSSION

It is clear that the choroid is a key component in the visual regulation of eye growth. Rapid advancements in myopia research have been accompanied by the development of optical, pharmacological, and alternative myopia intervention methods over recent years, and several research studies have evidenced choroidal thickness changes associated with such approaches. However, regarding myopia management, it is evident that not enough is known about the clinical relevance of choroidal imaging from baseline and beyond. There is a growing body of evidence to suggest choroidal alterations at an early timepoint are associated with axial growth in the longer-term; despite some conflicting evidence, randomised controlled trials have found these predictive associations to be present with relative peripheral myopic defocusing spectacle lenses (such as DIMS spectacles)[282], orthokeratology contact lenses[315], atropine eye drops[321], and repeated low-level red-light therapy[355]. These compelling discoveries require further exploration, for using choroidal modulation as a predictive parameter of intervention efficacy has the potential to drastically refine the present approach to trialling myopia intervention methods within ophthalmic research and clinical practice. Current methods to validate the efficacy of a particular myopia control treatment are longitudinal, with a minimum of 3 years being the recommended length for appropriate assessment[372]. Naturally, such clinical trials become costly, time consuming, and delay the ability to compare and enhance treatment options. On an individual level, the inability to detect whether a patient will respond well to a particular intervention could result in a less effective method being used, with the time taken in determining suitability potentially limiting the opportunity to try an alternative, more effective method.

Experiments show the compensatory human choroidal response to retinal defocus to be detectable within a matter of minutes across different age groups[120, 126, 127, 262, 263, 373]. Given that optical interventions marketed for myopia management often incorporate deliberate regional myopic blur, establishing the choroidal response to such refraction profiles both in the short- and long-term may provide further insight into the mechanisms underlying their efficacy. Advances in OCT imaging procedures have made the visualisation of the posterior choroidal boundary to high resolution possible, and widefield imaging permits exploration of choroidal alterations expanding beyond the subfoveal region. Already, there is research to

suggest a rapid differential response throughout the vertical choroidal profile in the presence of regional blur[262], warranting the need for a greater understanding of differing sensitivity and regional selectivity throughout the wider choroidal regions. Identifying such variance in the early choroidal response to visual stimuli, such as non-uniform lens-induced defocus, may ascertain ways to provoke the greatest degree of choroidal thickening, potentially shaping the optimum optical design to control eventual axial elongation.

On commencement of a specific myopia intervention, further research is essential to investigate the association between immediate changes in choroidal thickness (detected within minutes or hours) with changes in choroidal thickness and axial length identified after long-term use (several months or years). As there is evidence for a negative correlation between choroidal thickening at 1 week with axial length growth at 24 months in response to commercially available spectacle lenses designed for myopia management[281], research is warranted to assess whether a significant change in choroidal thickness is present any sooner, and whether a significant association with long-term axial growth still exists over an extended timeframe. Alongside the knowledge of the choroidal regions likely to exhibit the most rapid level of change in response to such visual blur, the optimum, highly repeatable imaging and analysis measures to detect such fine changes must also be determined.

Together, extensive choroidal and axial data collected from longitudinal clinical trials with short-term experiments may have the capacity to develop prediction algorithms in the form of a rapid provocation test; for example, if a particular degree of choroidal thickness change is identified within a recognised choroidal region sensitive to a certain stimulus (such as a defocusing optical myopia management intervention) over a defined short period of time, it could be used as a predictor for the expected axial growth at 12 months of wear.

To further explore the prospect of using of choroidal thickness as a predictor for myopia progression, additional research is essential to deepen the understanding of the extent and nature of choroidal thickness changes in response to deliberate modifications to the visual environment.

1.6 OBJECTIVES

To build upon the limited knowledge of the clinical applications of choroidal imaging in myopia management identified in this chapter, this thesis aims to:

A. Explore how global activity and strategies to manage myopia have shifted alongside advancements in myopia research over recent years, involving the changing opinions regarding the importance of considering choroidal thickness in clinical practice.

B. Assess the choroidal imaging capabilities and repeatability of three OCT devices employing different technologies, with consideration of how the clinical significance translates into a real-world, patient-facing setting.
C. Investigate alterations in the spatial distribution of the human choroid beyond the subfoveal region following short-term exposure to myopic blur contained within the temporal and nasal hemifields, and whether this occurs in a regionally selective manner. This includes exploring whether an individual's age and ocular refractive status impacts the choroidal response to regional blur.
D. Assess the effect of indoor light levels on human choroidal thickness, addressing how this may influence appropriate measurement conditions and the design of future choroidal experimental work.
E. Measure and compare regional changes in human choroidal thickness in response to short-term and long-term wear of a commercially available spectacle lens designed to slow myopia progression, and, in turn, explore whether immediate choroidal alterations could act as a predictor for future axial growth.

Collectively, this series of research projects aims to lessen the ambiguity surrounding the existing and prospective clinical functions of choroidal thickness modulation in the successful management of progressing young myopic eyes.

Chapter 2. Global trends in myopia management in 2022

Part of Chapter 2 was published in Investigative Ophthalmology & Visual Science in 2023[374]. The author was responsible for coordinating with ambassadors of the International Myopia Institute and co-authors, conducting the data analysis, and drafting the paper.

2.1 GLOBAL TRENDS IN MYOPIA MANAGEMENT ATTITUDES AND STRATEGIES IN CLINICAL PRACTICE—2022 UPDATE

2.1.1 Introduction

At present, there is no standardised approach to the management of young premyopic[375] and myopic patients in clinical practice despite several position papers having been published[376, 377]; furthermore, access to the various myopia intervention methods differs with location[29]. Within this field of research, practitioner perception of myopia management (which includes myopia control as a subset) and worldwide prescribing trends are of interest. A survey published in 2020[378] explored the practice patterns of paediatric ophthalmologists across the world (n=794), finding treatment rates varied significantly with location (mean 57%, range 39 to 89%)[378]. Encouragingly, of those respondents who practice myopia treatment, 98% used at least one type of effective controlling treatment, independent of location. Ninety-five percent of respondents used a combination of intervention modalities simultaneously; however, combination rates differed significantly among regions. Surveys conducted in 2015 and 2019 demonstrated the increasing myopia prevalence to cause a high level of concern among eye care practitioners and a self-reported high level of engagement in myopia control[29, 30]. The reported level of concern and activity had increased over the four years between the two studies. Despite this, the vast majority of respondents across both surveys still prescribed single vision refractive correction to young myopes. Using the same methodology as that used in 2015 and 2019, this study provides an update of the attitudes and myopia management strategies in clinical practice worldwide, allowing trends to be determined.

2.1.2 Methods

2.1.2.a Data collection procedures

A self-administered, internet-based, cross-sectional survey in 13 languages (English, Spanish, Italian, Traditional and Simplified Chinese, Greek, Russian, Turkish, Danish, Vietnamese, Norwegian, Dutch, Hebrew, and Swedish) was distributed using software SurveyMonkey (Momentive Inc, Palo Alto, California, USA); the survey was distributed through various professional bodies (general, rather than specific to myopia) across the

world to reach eye care practitioners (optometrists, ophthalmologists, contact lens opticians, and others) globally. The survey was live between March and November 2022. Ethics approval was received from the Aston University Research Ethics committee, and informed consent was received from all respondents. Several questions matched the 2015 and 2019 versions[29, 30]; however, modifications and additions were made to the current survey, such as:

- Adding myopia management spectacles and combination therapy (more than two treatments simultaneously) to the list of possible myopia approaches
- Only asking a general question about the level of minimum amount of myopia that would need to be present to consider myopia management options
- Adding accessibility of treatments to the list of possible factors preventing them from prescribing myopia management options

A total of 15 questions relating to the self-reported clinical management behaviours of practitioners for progressing myopia and practitioner's current opinions on myopia-related clinical care were asked, including:

- Level of concern about the increasing frequency of childhood myopia in their clinical practice (rated as "Not at all" to "Extremely" on a 10-point scale)
- Perceived effectiveness, defined as the expected level of reduction in childhood myopia progression of a range of myopia management options (rated as a percent age from 0% to 100%)
- How active they would consider their clinical practice in the area of myopia management (rated as "Not at all" to "Fully" on a 10-point scale)
- Frequency of prescribing different myopia correction options for progressing/young myopes during a typical month
- Minimum age a patient would need to be for them to consider myopia management options (assuming average handling skills and child/parent motivation)
- Minimum amount of myopia that would need to be present to consider myopia management options (specified in half-dioptre steps)
- Minimum level of myopia progression (dioptres/year) that would prompt a practitioner to specifically adopt a myopia management approach (specified in quarter-dioptre steps)
- Frequency of adopting single vision undercorrection as a strategy to slow myopia progression (reported as "no," "sometimes," or "always")
- If they had only ever fitted single vision spectacles/contact lenses for myopic patients, what had prevented them (multiple options could be selected) from

prescribing alternative refractive correction methods; options consisted of the following:

- They don't believe that these are any more effective
- The outcome is not predictable
- Safety concerns
- Cost to the patient makes them uneconomical
- Additional chair time required
- Inadequate information/knowledge
- Low benefit/risk ratio
- Accessibility of treatment options
- Other

- Rank their criteria for starting myopia management in a young progressing myope (numbered 1 to 10); options consisted of the following:
  - Refractive error
  - Age
  - Myopic parent (one)
  - Myopic parents (two)
  - Axial length
  - Choroidal thickness
  - Choroidal thickness responsiveness to early treatment
  - Binocular vision status
  - AC/A ratio
  - Lifestyle
  - Patient pressure
  - Parent/guardian pressure
- How they select which myopia management strategy to use first on a young progressing myope; options consisted of the following:
  - Only have one treatment available to me
  - Only comfortable/trained to use one treatment
  - Age
  - Refractive error (non-cycloplegic)
  - Cycloplegic refraction
  - Axial length
  - Choroidal thickness
  - Binocular vision status
  - Patient preference
  - Parent/guardian preference

    - Other
- Triggers to adjust their myopia management strategy; options consisted of the following:
    - I don't
    - Progression of refractive error
    - Progression of axial length
    - Changes in choroidal thickness
    - A new treatment with a scientifically reported better efficacy
    - Poor compliance
    - Complications
    - Other
- How has managing myopia changed their patient loyalty, practice revenue and job satisfaction (each rated as "much less," "less," "no change," "more," and "much more")

There was an option to add further comments to each of the questions and the topic as a whole. Voluntary participation in the survey, following an explanation of the research, was anonymous; however, respondents were asked to provide basic demographic information about themselves (years of being qualified and everyday working environment).

2.1.2b Statistical analysis

The data was divided into the continents the eye care practitioner was based in. Where a sample from a country of ≥30 was received, the data was also analysed comparing countries within a continent[29, 30]. Statistical analyses were conducted with IBM SPSS (Statistics for Windows v28; IBM Corp., Armonk, NY, USA). Ordinal data are presented as medians and interquartile range and continuous data as means and standard deviation (SD). As the data were determined not to meet the normality assumption of parametric testing based on the Shapiro-Wilk test, the nonparametric Kruskal-Wallis test was used to compare responses between continents and regions. Statistical significance was set at $p<0.05$. For conciseness, only significant comparisons have been reported.

2.1.3 Results

A total of 3195 complete survey responses were received, with the distribution by continent being: Africa 74, Asia 1396, Australasia 101 (Australia, New Zealand, and neighbouring islands in the Pacific Ocean), Europe 931, North America 338, and South America 177. The remaining 178 respondents did not state their location. Country-specific responses could be extracted from the following:

- Africa: none
- Asia: China (n=1001), India (n=65), Israel (n=42), Philippines (n=58), Turkey (n=78), and Vietnam (n=101)
- Australasia: Australia (n=87)—hence, no within continent comparison was possible
- Europe: France (n=31), Italy (n=202), Norway (n=40), Russia (n=80), Spain (n=380), and United Kingdom (n=67)
- North America: Canada (n=107), Mexico (n=86), Puerto Rico (n=30), and United States of America (n=77)
- South America: Argentina (n=42), Brazil (n=36), Ecuador (n=40), and Peru (n=37)

The breakdown of respondents' professions is presented in Table 2.1. All study participants were registered eye care practitioners with a median number of years qualified of 11 to 20 years (with a normal distribution). The vast majority of respondents considered clinical practice to be their principal working environment (Table 2.2).

Profession	
Optometrists	68.4% (n=2185)
Ophthalmologists	23.0% (n=736)
Contact lens opticians	6.1% (n=194)
Other	2.4% (n=76)
Did not state	0.1% (n=4)

Table 2.1: Distribution of professions across study participants (n=3195).

Principal Working Environment	
Clinical practice	78.5% (n=2507)
Academia	7.6% (n=244)
Industry	5.2% (n=165)
Other	8.5% (n=272)
Did not state	0.2% (n=7)

Table 2.2: Distribution of principal working environments across study participants (n=3195).

2.1.3a Self-reported concern about the increasing frequency of childhood myopia

Practitioners' concern about the increasing frequency of childhood myopia in their practices differed between continents (Figure 2.1), being significantly higher in Asia (9.0 ± 1.5) than all other continents; Africa (8.1 ± 2.4; $p=0.001$), Australasia (7.7 ± 2.1; $p<0.001$), Europe (8.0 ± 2.0; $p<0.001$), North America (8.2 ± 1.9; $p<0.001$), and South America (8.0 ± 2.3; $p<0.001$).

The level of concern among practitioners in Australasia was significantly lower than in Africa ($p<0.001$), Asia ($p<0.001$), North America ($p=0.018$), and South America ($p=0.022$). There were no other significant differences between continents.

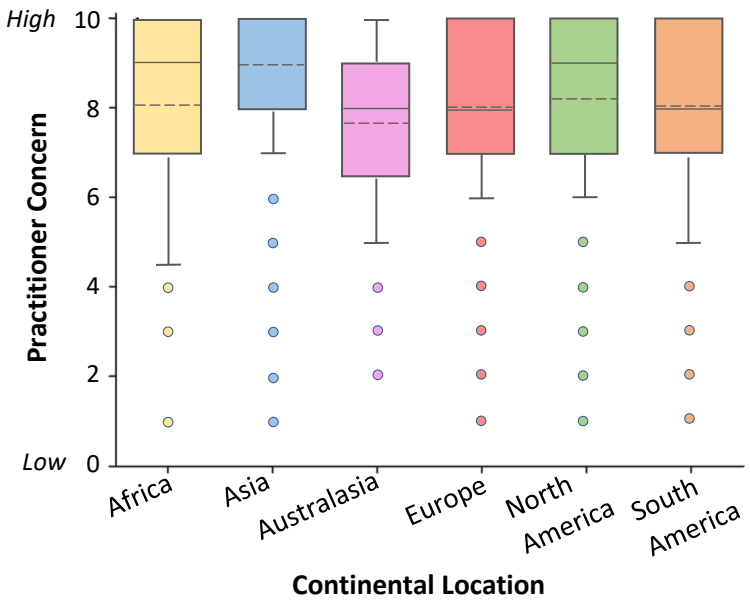


Figure 2.1: Level of concern (rated from 0 [low] to 10 [high]) regarding the perceived increasing frequency of paediatric myopia in their practice for practitioners located in different continents. N = 3017. Box = 1 SD; solid line = median; dashed line = mean; whiskers = 95% confidence interval.

In Asia, Turkey showed the lowest level of concern (7.6 ± 2.1, all $p<0.05$); followed by Israel (8.4 ± 2.1) and Vietnam (8.6 ± 1.9), which had a lower level of concern than China (9.1 ± 1.2; $p<0.05$) and India (9.2 ± 1.5; $p<0.05$), with Israel also having lower concern than the Philippines (9.1 ± 1.5; $p=0.036$). In Europe, Norway showed the lowest level of concern (5.9 ± 2.4; all $p<0.05$); Russia (8.7 ± 1.8) showed a higher level of concern than France (7.5 ± 2.4; $p=0.002$), Italy (8.1 ± 1.9; $p=0.004$), Norway (5.9 ± 2.4; $p<0.001$) and Spain (8.3 ± 1.6; $p=0.006$). In North America, Canada (7.8 ± 1.9) showed a significantly lower level of concern than the USA (8.5 ± 1.7; $p=0.007$) and Mexico (8.6 ± 1.6; $p=0.001$). There was no significant difference across countries within South America.

2.1.3b Practitioners' perceived effectiveness of management options for myopia

Overall, combination therapy was perceived by practitioners to be the most effective method of myopia management, followed by orthokeratology and pharmaceutical approaches. The least effective methods were perceived to be undercorrection and single vision spectacles, as well as single vision soft contact lenses and bifocal spectacles (Table 2.3). For undercorrection, the perceived effectiveness was highest in Africa (all $p<0.05$) and lowest in Australasia (all $p\leq0.001$), followed by Europe and North America (all $p<0.05$). A similar pattern was seen for single vision and bifocal lens spectacles, single vision contact lenses and rigid contact lenses (RCLs). For progressive addition lens spectacles (PALS), the pattern was again similar, but there was no difference between Australasia, Europe, and

Technique \ Continent		Africa	Asia	Australasia	Europe	North America	South America
Spectacles	Undercorrection	17.3 ± 24.2	11.2 ± 19.6	-0.1 ± 1.8	4.6 ± 13.1	6.1 ± 14.5	14.4 ± 22.5
	Single Vision	41.4 ± 35.5	19.8 ± 22.2	2.2 ± 7.1	8.6 ± 17.3	12.3 ± 23.7	22.9 ± 29.2
	Bifocals	40.3 ± 26.1	23.5 ± 20.4	21.8 ± 15.3	17.0 ± 18.0	20.3 ± 21.9	23.2 ± 25.1
	PALS	40.9 ± 26.8	29.7 ± 23.0	19.6 ± 13.6	19.1 ± 18.7	20.9 ± 22.2	27.0 ± 27.0
	Approved MM	59.8 ± 24.3	43.4 ± 23.9	50.0 ± 14.7	49.9 ± 21.1	46.0 ± 24.4	40.7 ± 29.4
Contact Lenses	RCLs	43.9 ± 33.4	30.0 ± 26.6	8.4 ± 18.0	17.4 ± 23.1	18.6 ± 26.7	24.5 ± 28.3
	Single Vision Soft	37.9 ± 34.1	21.1 ± 25.7	3.1 ± 8.4	11.3 ± 18.5	13.5 ± 24.5	24.6 ± 29.4
	Multifocal Soft	45.9 ± 27.2	34.6 ± 25.1	32.8 ± 14.7	26.7 ± 20.6	32.8 ± 21.9	26.6 ± 25.7
	Approved MM Soft	50.6 ± 27.0	43.1 ± 26.2	51.7 ± 14.9	51.1 ± 21.9	49.8 ± 23.6	43.1 ± 29.9
	Orthokeratology	57.4 ± 23.5	60.4 ± 22.9	55.6 ± 15.9	54.4 ± 24.0	49.7 ± 24.3	45.6 ± 29.9
Pharmaceutical		47.7 ± 22.7	51.7 ± 24.7	49.2 ± 15.8	51.4 ± 24.2	43.7 ± 23.6	47.0 ± 25.8
Combination therapy		59.9 ± 24.9	66.4 ± 25.9	61.0 ± 16.1	61.1 ± 24.9	53.9 ± 27.3	54.1 ± 30.9
Increased Time Outdoors		46.9 ± 26.9	56.6 ± 28.4	27.1 ± 21.5	39.8 ± 27.2	28.5 ± 24.9	45.3 ± 30.7

Table 2.3: Perceived effectiveness (defined as the expected level of reduction in childhood myopia progression in percent) of myopia management options by practitioners in different continents. PALs = progressive addition spectacle lenses, MM = myopia management, RCL = rigid contact lenses. Data are expressed as mean ± SD.

North America. Myopia management spectacles were deemed as most effective in Africa (all $p<0.01$), followed by Australasia and Europe (both $p<0.01$). Multifocal contact lenses were thought to be least effective by South American and European practitioners (all $p<0.05$) and most effective in Africa (all $p<0.01$). Myopia management spectacles were felt to be less effective in Asia and South America than on the other continents ($p<0.05$). Orthokeratology was deemed most effective in Asia (all $p<0.05$) and least effective in North and South America (all $p<0.05$). Pharmaceuticals were considered more effective in Asia, Europe, and Australasia than in North or South America (all $p<0.05$). However, combination therapy was felt to be most effective in Asia compared to all other continents (all $p<0.05$). Time spent outdoors was rated as less effective in Australasia and North America (all $p\leq0.001$), most so in Asia (all $p<0.05$) followed by Africa and South America (all $p<0.05$).

In Asia, compared to other regional countries ($p<0.05$): myopia management spectacles were believed to be less effective, and orthokeratology and outdoors more effective in China; undercorrection, single vision spectacles and contact lenses, and RCLs were considered less effective in Israel; bifocal and PALs spectacles, single vision contact lenses and time outdoors were felt to be more effective in the Philippines; single vision and myopia control spectacles, RCLs, multifocal and myopia management contact lenses, orthokeratology, pharmaceuticals, and combination therapies were rated less effective in Turkey; and bifocal and PALS, single vision contact lenses, and orthokeratology were considered more effective in Vietnam. In Europe, compared to other regional countries ($p<0.05$): PALS, RCLs, myopia management contact lenses and orthokeratology was felt to be less effective in France; myopia management spectacles and single vision and multifocal contact lenses were

considered more effective in Italy; undercorrection and RCLs were scored as less effective in Norway; single vision spectacles and contact lenses, bifocal and PALS, multifocal contact lenses, orthokeratology, pharmaceuticals, and combination therapies were considered more effective in Russia; orthokeratology, pharmaceuticals, and combination therapies were considered more effective in Spain; and undercorrection, RCLs, and time outdoors was felt to be less effective and myopia management spectacles, multifocal contact lenses, pharmaceuticals and combination therapies more effective in the United Kingdom. In North America, compared to other regional countries ($p<0.05$): Canada and the USA considered undercorrection, single vision spectacles and contact lenses, and time outdoors as less effective and combination therapy as more effective than Mexico or Puerto Rico; myopia management spectacles were considered more effective in Canada and Mexico; multifocal and myopia management contact lenses were felt to be less effective in Puerto Rico; and PALS and pharmaceuticals were rated as less effective and RCLs and single vision contact lenses more effective in Mexico. In South America, compared to other regional countries ($p<0.05$): undercorrection, single vision, bifocal, PALS and myopia management lens spectacles, RCLs, single vision and myopia management contact lenses were considered less effective in Argentina and Brazil, whereas multifocal contact lenses were considered more effective in Ecuador.

2.1.3c Practitioners' perceived level of clinical activity in myopia management

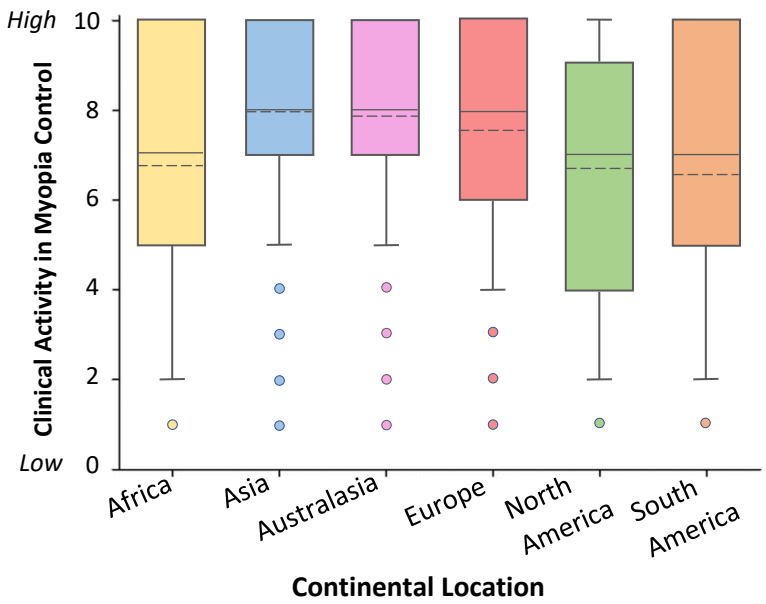


Figure 2.2: Perceived level of clinical activity in myopia management (rated from 0 [low] to 10 [high]) for practitioners located in different continents. N = 3017. Box = 1 SD; solid line = median; dashed line = mean; whiskers = 95% confidence interval.

South American practitioners rated themselves less active (p<0.05) in myopia management (6.6 ± 2.9) followed by North American (6.7 ± 2.9) and African (6.7 ± 2.8) compared to European (7.5 ± 2.4), Australasian (7.9 ± 1.2), and Asian (7.9 ± 2.2) practitioners (Figure 2.2). The most active rating was from Asian practitioners, which was also higher than those from Europe (p<0.001). In Asia, practitioners from Vietnam rated their activity as the lowest (4.7 ± 2.8, all P < 0.05) followed by Turkey (6.4 ± 2.6), which was lower than India (7.0 ± 3.0) and the Philippines (7.4 ± 2.4), with Chinese practitioners rating themselves the most active (8.5 ± 1.6, all p<0.001). In Europe, French practitioners rated their activity lowest (5.7 ± 2.5 vs. 7.4 to 7.9 in all other European counties, p<0.05). In North America, USA (7.4 ± 2.7) and (7.5 ± 2.5) Canadian practitioners rated themselves as more active (p<0.05) than those in Puerto Rico (5.1 ± 2.8) and Mexico (5.9 ± 2.9). There were no significant differences among countries within South America (p>0.05).

2.1.3d Frequency of prescribing different myopia management methods by practitioners

Single vision spectacles are still the most prescribed options for young progressing myopes, being highest in Africa (p<0.05) followed by South America (all p<0.05) and lowest in Australasia (all p<0.001; Table 2.4). Bifocal spectacles were prescribed least in Australasia (p<0.05) and were prescribed most in Africa (all p<0.001). PALS were prescribed least in Europe (all p<0.001 except for South America), with North America prescribing fewer than Africa or Asia (both p<0.05). Myopia management spectacles are prescribed least in South America (all p<0.05) except for Africa, with North America prescribing fewer than Europe (p<0.001), who prescribed fewer than Asia (p=0.020), and Australasia prescribing the most (all p<0.05). RCLs were prescribed least in Australasia (all p<0.05), followed by Europe and

Technique \ Continent		Africa	Asia	Australasia	Europe	North America	South America
Spectacles	Single Vision	53.7 ± 35.1	32.3 ± 29.3	16.4 ± 24.3	30.1 ± 28.1	32.8 ± 32.6	42.2 ± 33.8
	Bifocals	7.5 ± 11.6	3.2 ± 8.5	1.0 ± 3.8	1.3 ± 5.0	3.9 ± 9.2	3.1 ± 10.9
	PALS	8.7 ± 16.9	6.5 ± 12.8	7.0 ± 12.9	2.7 ± 8.0	4.9 ± 11.9	3.7 ± 10.5
	Approved MM	11.1 ± 20.0	16.8 ± 19.6	22.0 ± 21.7	15.0 ± 20.2	12.6 ± 19.5	6.6 ± 14.7
Contact Lenses	RCLs	0.9 ± 2.7	3.8 ± 9.7	0.2 ± 1.4	1.1 ± 5.4	2.1 ± 9.0	3.6 ± 10.4
	Single Vision Soft	7.0 ± 12.6	3.2 ± 9.8	3.5 ± 7.2	12.7 ± 15.2	10.3 ± 14.9	13.0 ± 18.3
	Multifocal Soft	3.4 ± 8.2	2.2 ± 7.3	4.7 ± 8.8	3.0 ± 7.9	5.7 ± 10.7	4.1 ± 11.0
	Approved MM Soft	1.7 ± 4.4	3.5 ± 10.3	18.2 ± 15.9	16.1 ± 18.9	9.3 ± 14.8	5.1 ± 12.9
	Orthokeratology	0.9 ± 3.1	14.6 ± 18.1	9.9 ± 16.5	11.5 ± 17.8	7.5 ± 16.2	4.6 ± 13.9
Pharmaceutical		3.1 ± 7.8	8.7 ± 15.3	13.1 ± 16.6	3.3 ± 9.9	8.4 ± 14.3	11.1 ± 21.4
Combination Therapy		1.8 ± 5.7	5.3 ± 9.4	4.1 ± 8.1	3.0 ± 8.2	2.6 ± 6.3	3.0 ± 7.8

Table 2.4: Frequency of prescribing myopia correction and control options (in percent) for progressing / young myopes by practitioners in different continents for progressing / young myopes. PALS = progressive addition lens spectacles, MM = myopia management, RCL = rigid contact lenses. Data are expressed as mean ± SD.

Africa, with North America prescribing fewer than Asia ($p<0.001$), which had the highest prescribing rate (all $p<0.001$). Single vision contact lenses were prescribed least in Asia and Australasia ($p<0.05$) followed by Africa (all $p<0.05$), with Europe and South America prescribing more than North America ($p<0.05$). Multifocal contact lenses were prescribed more in Australasia and North America than in Asia or Europe ($p<0.05$), with North American practitioners prescribing more multifocal contact lenses than African and South American practitioners ($p<0.05$). Australasia prescribed myopia management contact lenses the most, followed by Europe ($p=0.037$), with all other continents prescribing fewer (all $p<0.001$). Orthokeratology is prescribed most in Asia, followed by Europe, Australasia, North America, South America, and Africa (each significantly different $p<0.05$). Australasia prescribed the most pharmaceuticals (all $p<0.05$), followed by South America, which prescribed more than North America and Asia (both $p<0.05$), followed by Europe and Africa (both $p\leq0.001$). Asian practitioners are most likely to use combined therapies (all $p<0.05$), with Australasia prescribing more than Europe or Africa (both $p<0.05$). In Asia, compared to other regional countries ($p<0.05$): Vietnam prescribed more single vision spectacles and pharmaceuticals, while adopting other myopic management options less; Turkey prescribed more single vision contact lenses and myopia management spectacles while prescribing fewer bifocals spectacles, PALS, RCLs, and combination therapies; the Philippines prescribed more PALS and fewer RCL, orthokeratology, pharmaceuticals, and combination therapies; Israel prescribed more multifocal and myopia management contact lenses and fewer bifocal lens spectacles and combination therapies; China prescribed more myopia management spectacles, orthokeratology, and combination therapy and fewer single vision contact lenses; and India prescribed less orthokeratology. In Europe, compared to other regional countries ($p<0.05$): more myopia management spectacles and pharmaceuticals, and fewer single vision and myopia management contact lenses were prescribed in France; fewer myopia management contact lenses and combination therapies in Italy; more myopia management contact lenses and fewer single vision spectacles, myopia management spectacles, RCLs, and combination therapies in Norway; more bifocal spectacles, multifocal contact lenses, orthokeratology pharmaceuticals, and combination therapies, and fewer single vision and myopia management spectacles in Russia; fewer PALS and pharmaceuticals in Spain; and more single vision spectacles and fewer PALS, RCLs, single vision contact lenses, pharmaceuticals, and combination therapies in the UK. In North America, compared to other regional countries ($p<0.05$): more myopia management spectacles and fewer bifocal spectacles, PALS and myopia management contact lenses in Canada; more single vision spectacles, RCL, and fewer myopia management contact lenses, pharmaceuticals, and combination therapies in Mexico; more PALS and fewer myopia management spectacles, pharmaceuticals, and combination therapies in Puerto Rico; and more multifocal spectacles,

myopia management contact lenses, orthokeratology, pharmaceuticals, and combination therapy in the USA. In South America, compared to other regional countries ($p<0.05$): more pharmaceuticals and fewer PALS and RCLs in Argentina; more pharmaceuticals and fewer myopia management spectacles and multifocal contact lenses in Brazil; more orthokeratology in Ecuador; and more bifocal and PALS and fewer combination therapies in Peru.

2.1.3e Minimum age of prescribing myopia management options by practitioners

The minimum average ages of prescribing the various corrections for myopia are presented in Table 2.5. For single vision spectacles this was higher in Asia (all $p<0.05$ except Africa) and was lowest in Australasia, Europe, and North America (all $p<0.05$). For bifocal spectacles this was highest in Africa and lowest in Europe, followed by North America (all $p<0.05$). For prescribing PALS this was lowest in Australasia (all $p<0.01$) and highest in South America (all $p<0.05$) and Africa (all $p<0.001$). For myopia management spectacles this was lowest in Australasia (all $p<0.05$) and higher in Africa ($p<0.001$), Asia (all $p<0.001$), and South America (all $p<0.01$). For corneally aligned RCLs this was lower in Asia (all $p<0.001$ except Australasia). For single vision soft contact lenses, this was higher in Africa (all $p<0.05$) and South America (all $p\leq0.001$). For multifocal contact lenses this was highest in Africa (all $p<0.05$ except South America). For myopia control contact lenses this was highest in Africa (all $p<0.001$) and lowest in Europe (all $p<0.05$ except Australasia and North America). For orthokeratology this was lowest in Australasia (all $p<0.05$ except for North America), and highest in South America (all $p<0.01$) and Africa (all $p<0.001$). There was no difference in the minimum age for pharmaceuticals across continents. For combination therapies, the minimum age for prescribing myopia management options was highest in South America (all $p<0.01$) and Africa ($p<0.001$).

Technique \ Continent		Africa	Asia	Australasia	Europe	North America	South America
Spectacles	Single Vision	6.7 ± 3.4 (8)	6.9 ± 3.4 (3)	6.7 ± 4.2 (26)	6.0 ± 3.0 (18)	5.8 ± 2.5 (16)	6.2 ± 2.7 (12)
	Bifocals	9.0 ± 3.9 (34)	7.1 ± 2.9 (12)	5.2 ± 0.8 (53)	6.3 ± 2.3 (55)	6.4 ± 2.7 (37)	7.9 ± 3.6 (53)
	PALs	9.9 ± 4.0 (34)	7.6 ± 3.1 (12)	5.9 ± 1.5 (32)	7.2 ± 2.9 (50)	7.6 ± 3.4 (38)	8.7 ± 3.8 (42)
	Approved MM	7.7 ± 3.5 (14)	6.8 ± 2.6 (7)	5.2 ± 0.6 (6)	5.8 ± 1.5 (6)	6.1 ± 2.3 (8)	6.6 ± 2.6 (17)
Contact Lenses	RCLs	12.4 ± 3.3 (43)	8.3 ± 3.5 (14)	9.6 ± 3.4 (67)	9.8 ± 3.1 (53)	10.1 ± 3.5 (49)	11.0 ± 3.9 (33)
	Single Vision Soft	11.8 ± 4.6 (20)	9.3 ± 4.1 (10)	9.1 ± 3.4 (33)	9.0 ± 3.4 (21)	9.0 ± 3.3 (20)	10.3 ± 3.6 (18)
	Multifocal Soft	11.2 ± 4.5 (31)	8.4 ± 3.5 (14)	7.9 ± 2.0 (25)	8.6 ± 2.9 (44)	8.8 ± 3.0 (25)	9.8 ± 3.9 (41)
	Specific MM Soft	11.1 ± 4.6 (15)	8.3 ± 3.3 (9)	7.5 ± 1.7 (2)	7.5 ± 2.4 (7)	7.8 ± 2.8 (5)	9.2 ± 3.6 (16)
	Orthokeratology	12.3 ± 4.4 (27)	8.5 ± 2.7 (7)	7.5 ± 1.9 (23)	8.4 ± 2.7 (18)	8.6 ± 3.5 (24)	9.9 ± 3.8 (23)
Pharmaceutical		7.7 ± 3.6 (31)	6.6 ± 2.5 (7)	5.9 ± 1.2 (14)	6.2 ± 2.0 (47)	6.8 ± 3.1 (22)	6.8 ± 2.6 (21)
Combination Therapy		10.5 ± 4.4 (32)	7.9 ± 2.6 (10)	7.1 ± 1.8 (26)	7.6 ± 2.5 (44)	8.0 ± 3.3 (29)	8.8 ± 3.1 (31)

Table 2.5: Minimum patient age considered necessary by practitioners (from different continents) who prescribed these options for different myopia correction options. PALs = progressive addition spectacle lenses, MM = myopia management, RCL = rigid contact lenses. Data are expressed as mean ± SD years (% that would not prescribe this refractive modality).

In Asia, compared to other regional countries ($p<0.05$), the age of prescribing was: higher for myopia management spectacles in Vietnam; lower for RCLs, single vision, multifocal and myopia management contact lenses in China (compared to Vietnam, the Philippines, and Turkey). In Europe, compared to other regional countries ($p<0.05$), the age of prescribing was lower for single vision spectacles and RCLs in the UK than in Spain and Italy; lower for orthokeratology in the UK and Russia than in Spain and Italy; higher for bifocal, PALS, and myopia control spectacles, as well as pharmaceuticals, in Russia; higher for single vision, multifocal, and myopia management contact lenses, pharmaceuticals in France and combination therapies (except compared to Norway and Italy). In North America, compared to other regional countries ($p<0.05$), the age of prescribing was higher for single vision spectacles in Mexico compared to in the USA and Canada; lower for bifocal, PALS, and myopia control spectacles in Canada and the USA; higher for single vision contact lenses in Puerto Rico; lower for multifocal contact lenses in the USA; lower for myopia management contact lenses in Mexico (except compared to the USA) and higher for combination therapies in Mexico (except compared to Puerto Rico). In South America, compared to other regional countries ($p<0.05$), the age of prescribing was lower for single vision contact lenses in Peru than Argentina and higher for pharmaceuticals in Ecuador and Peru.

2.1.3f Minimum degree of myopia to begin myopia management

The minimum degree of myopia presenting in a child to warrant adoption of myopia management varied among continents (Figure 2.3), being lowest in Australasia (−0.64 ±

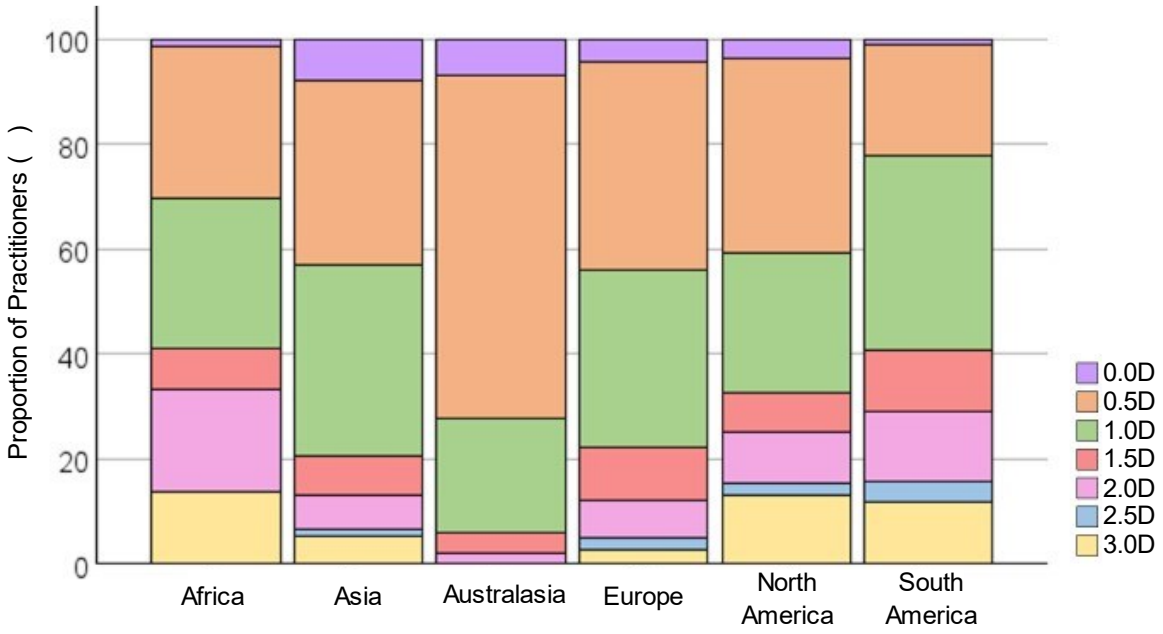


Figure 2.3: The minimum degree of myopia present in a child to warrant adoption of myopia management varied between continents. N = 3017.

0.37D, all p≤0.001), being similar in Asia (−0.97 ± 0.70D) and Europe (−0.97 ± 0.63D) and highest in North America (−1.21 ± 0.81D), Africa (−1.35 ± 0.86D), and South America (−1.37 ± 0.81D, all p<0.01). Within Asia, China reported the lowest level (−0.75 ± 0.46D) compared to regional countries (all −1.4 to −1.7D, p≤0.001). In Europe, Russia (−0.59 ± 0.24D) and Norway (−0.63 ± 0.43D) reported the lowest level (all p<0.01 except the UK −0.80 ± 0.43D), with France, Italy, and Spain between −1.0 and −1.1D. In North America, Canada (−0.87 ± 0.58D) and the USA (−0.90 ± 0.65D) were lower (p<0.001) than Mexico (−1.61 ± 1.00D) and Puerto Rico (−1.62 ± 0.96D). In South America, all countries reported a similar level (p>0.05).

2.1.3g Minimum level of myopia progression that necessitates myopia management

The median level of progression that warranted myopia management varied between continents, being −0.26 to −0.50D in Australasia and Europe and −0.51 to −0.75D in the other continents (all p≤0.001). It was lower in China than in the rest of Asia, lower in the USA compared to in the rest of North America, and higher in Spain than in the rest of Europe (all p<0.05).

2.1.3h Using undercorrection as a strategy to control myopia

Undercorrection is now rarely used as a myopia management strategy (never used 83.1%, sometimes used 14.4%). It is used less (1% sometimes) in Australasia (all p≤0.001) compared to in Africa (29.7% sometimes, 5.4% always; p<0.001) and South America (23.7% sometimes, 7.3% always; p<0.001) (Figure 2.4). In Asia it is used less in China and Israel than in other regional countries (all p<0.05). In Europe it is used less in the UK than in France (p=0.002), Italy (p<0.001), and Spain (p=0. 014). In North America it is used less in Canada, and in South America, it is used less in Brazil (all p<0.05).

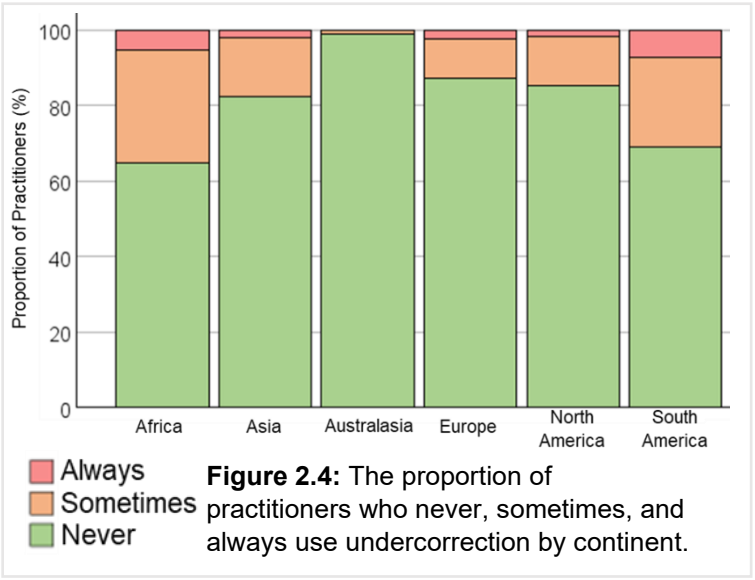


Figure 2.4: The proportion of practitioners who never, sometimes, and always use undercorrection by continent.

2.1.3i Reasons for not prescribing an alternative method to single vision correction

Reasons hindering prescribing of myopia management methods are presented in Figure 2.5. Less than 10% of practitioners thought myopia management options were not effective, ranging from no practitioners from Australasia to 9.2% in Asia (p<0.01). Around 10% of practitioners felt the outcomes were unpredictable, being higher in Africa (13.5%) and Asia (15.2%) than in the other continents (1.0 to 6.2%, p<0.05). Similarly, safety concerns were highest in Africa (23.0%) and Asia (22.2%) compared to other continents (1.0 to 7.3%, p≤0.001). Cost to the patient was of greater concern in Africa (43.2) , Asia (33.2) and Europe (25.7%), than Australasia (12.9%, p<0.01) and North America (16.6%, p≤0.001), with the concern being similar between South America (21.5%) and Europe. Additional chair time was only of concern in Asia (10.9%) compared to other continents (1.0 to 3.0%, p≤0.001). Inadequate information was of little concern in Australasia (2.0 , all p<0.05) and of highest concern in Africa (31.1%, all p<0.001) and South America (20.3%, all p<0.05). Concern about the risk-benefit ratio was low across continents (1.0% to 7.3%). Treatment availability was of significant concern in Africa (41.9%), Asia (24.1%), and South America (27.1%; all p<0.05), compared to Australasia (7.9%), Europe (10.5%), and North America (11.0%).

In Asia, compared to other regional countries (p<0.05), the reason for not prescribing myopia management treatments was lower for effectiveness or risk-benefit ratio concerns in the Philippines; higher for effectiveness, predictability, and chair time concerns but lower for availability issues in Turkey; higher for safety and lower for information availability concerns in China; and lower for availability issues in Israel. In Europe, compared to other regional countries (p<0.05), the reason for not prescribing myopia management treatments was higher for lack of information in France; lower for effectiveness and predictability concerns in

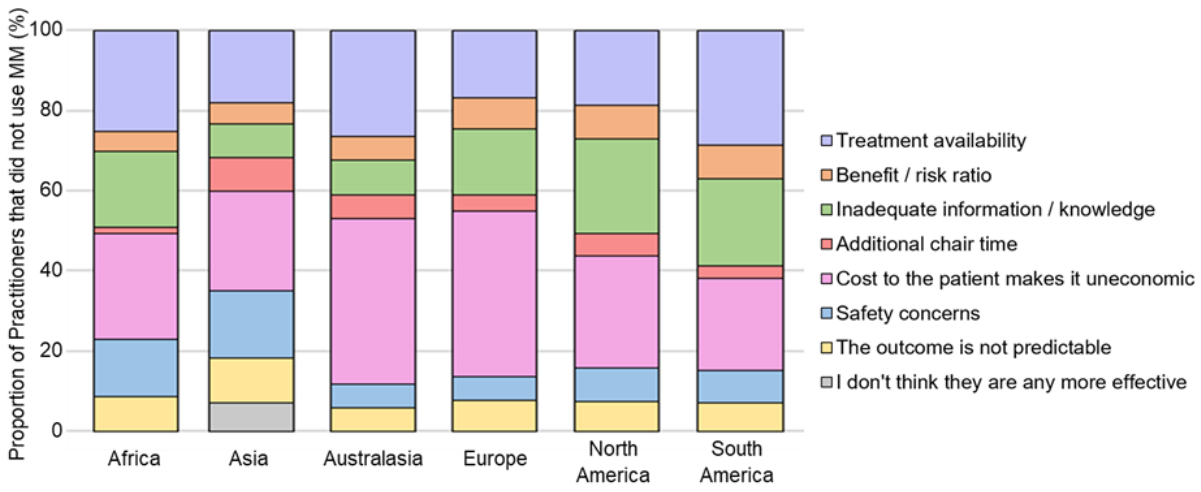


Figure 2.5: Factors cited by practitioners in different continents for not adopting myopia management approaches. N = 3017.

Italy; higher for treatment availability in Russia; and lower for cost issues in the UK. In North America, compared to other regional countries ($p<0.05$), the reason for not prescribing myopia management treatments was lower for availability issues in Canada; higher for information availability in Mexico; higher for predictability and safety concerns in Puerto Rico; and higher for chair time in the USA. In South America, the reason for not prescribing myopia management treatments was lower for cost and availability concerns in Brazil compared to other regional countries ($p<0.05$).

2.1.3j Ranked criteria for starting myopia management in a young progressing myope

Refractive error and patient age were the most highly ranked criteria for starting myopia management, followed by having myopic parents and axial length, then binocular vision status, accommodative-convergence to accommodation ratio (AC/A) and lifestyle, then choroidal thickness assessment and finally patient or parent/guardian pressure (Figure 2.6). Refractive error was more highly ranked (a lower number) in Australasia (all $p<0.05$) and lower ranked in Asia compared to other continents (all $p<0.05$). Age was more highly ranked in Australasia (all $p<0.05$); having one myopic parent was lower ranked in Asia ($p<0.05$) and having two myopic parents was ranked higher in South America than Asia or Africa ($p<0.005$). Axial length was ranked higher in Asia (all $p<0.05$). Choroidal thickness and its variability differed most in ranking between continents (all $p<0.05$ except between Africa and South America). Binocular vision was ranked similarly between continents. AC/A was more highly ranked in Africa followed by Europe and Australasia (all $p<0.05$). Lifestyle was higher ranked in Asia and lowest ranked in Africa (all $p<0.05$). Patient and parent/guardian pressure

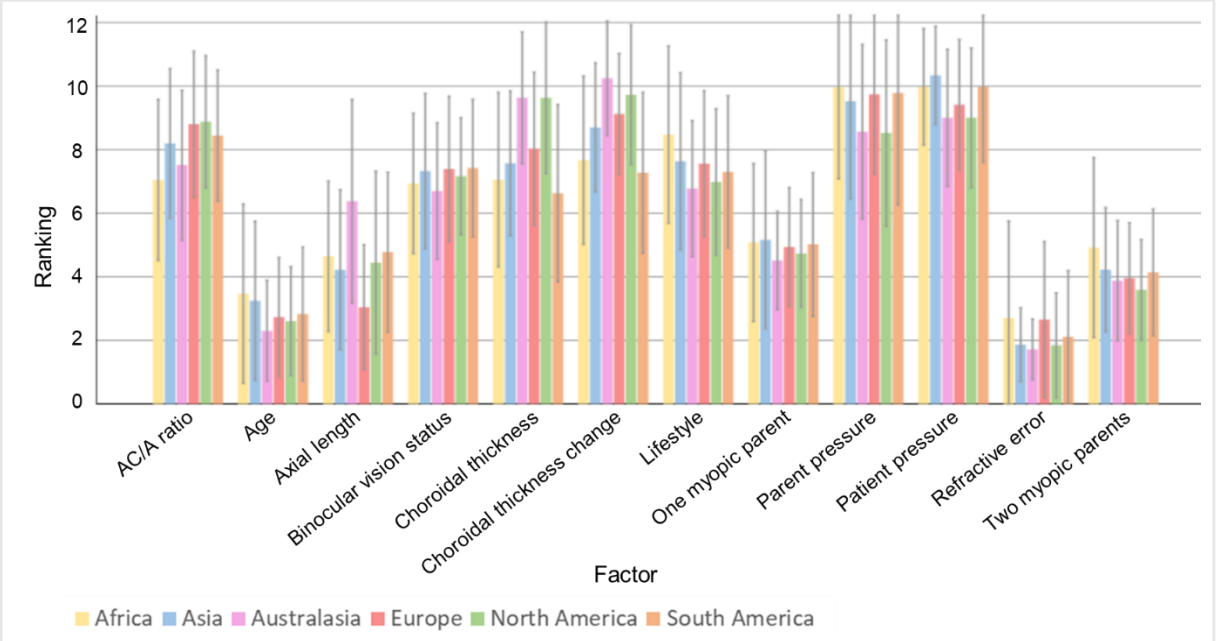


Figure 2.6: Ranked criteria for starting myopia management in young progressing myopes (where 1 = highest and 12 = lowest rank). N = 3017. Error bars represent ± 1 SD.

was more of a factor in Australasia and North America (all $p<0.05$) and less of a factor in South America (some $p<0.05$).

In Asia, compared to other regional countries ($p<0.05$), the ranking for myopia management starting criteria was higher for prescription, age, and one parent with myopia and lower for axial length and lifestyle in China; lower for patient pressure in India; lower for axial length and higher for two parents with myopia in Israel; lower for patient and parent/guardian pressure and higher for binocular vision and AC/A in the Philippines; lower for two parents with myopia in Turkey; and lower for one or two parents with myopia, patient and parent/guardian pressure and higher for choroidal thickness/change and binocular vision in Vietnam. In Europe, compared to other regional countries ($p<0.05$), the ranking for myopia management starting criteria was: lower for two parent with myopia and higher for axial length in France; higher for AC/A in Italy; lower for choroidal thickness/change and higher for patient and parent/guardian pressure in Norway; lower for age, one or two parents with myopia and AC/A, and higher for prescription and axial length in Russia; lower for one parent with myopia and choroidal thickness/change and higher for AC/A in Spain; and lower for choroidal thickness/change and higher for prescription, and patient and parent/guardian pressure in the UK. In North America, compared to other regional countries ($p<0.05$), the ranking for myopia management starting criteria was higher for prescription, two parents with myopia, lifestyle, and parent/guardian pressure in Canada; higher for choroidal thickness/change, binocular vision, and AC/A in Mexico; higher for choroidal thickness/change in Puerto Rico; and higher for prescription, lifestyle, and parent/guardian pressure in the USA. In South America, compared to other regional countries ($p<0.05$), the ranking for myopia management starting criteria was lower for two parents with myopia and parent/guardian pressure and higher for age and axial length in Brazil; and lower for prescription in Peru.

2.1.3k Factors considered when choosing which myopia management strategy to use first

The key factors for choosing the initial myopia management strategy in order were: patient age (75.5%), non-cycloplegic refraction (55.0%), cycloplegic refraction (52.4%), axial length (51.3%), parent/guardian preferences (48.4%), binocular vision (39.8%), patient preference (38.4%), only one treatment available (18.5%), only comfortable/trained in one treatment (15.8%) and choroidal thickness (9.8%). The responses are presented in Figure 2.7. Only one treatment available was more common in Asia (all $p<0.05$). Africa (21.6%), Asia (17.3%), and Europe (19.3%) were more likely (all $p<0.05$) to be only comfortable using one treatment than Australasia (4.0%), North America (6.5%), and South America (10.2%). Fewer practitioners in Asia (74.4%) and Africa (66.2%) used age as a factor than those in

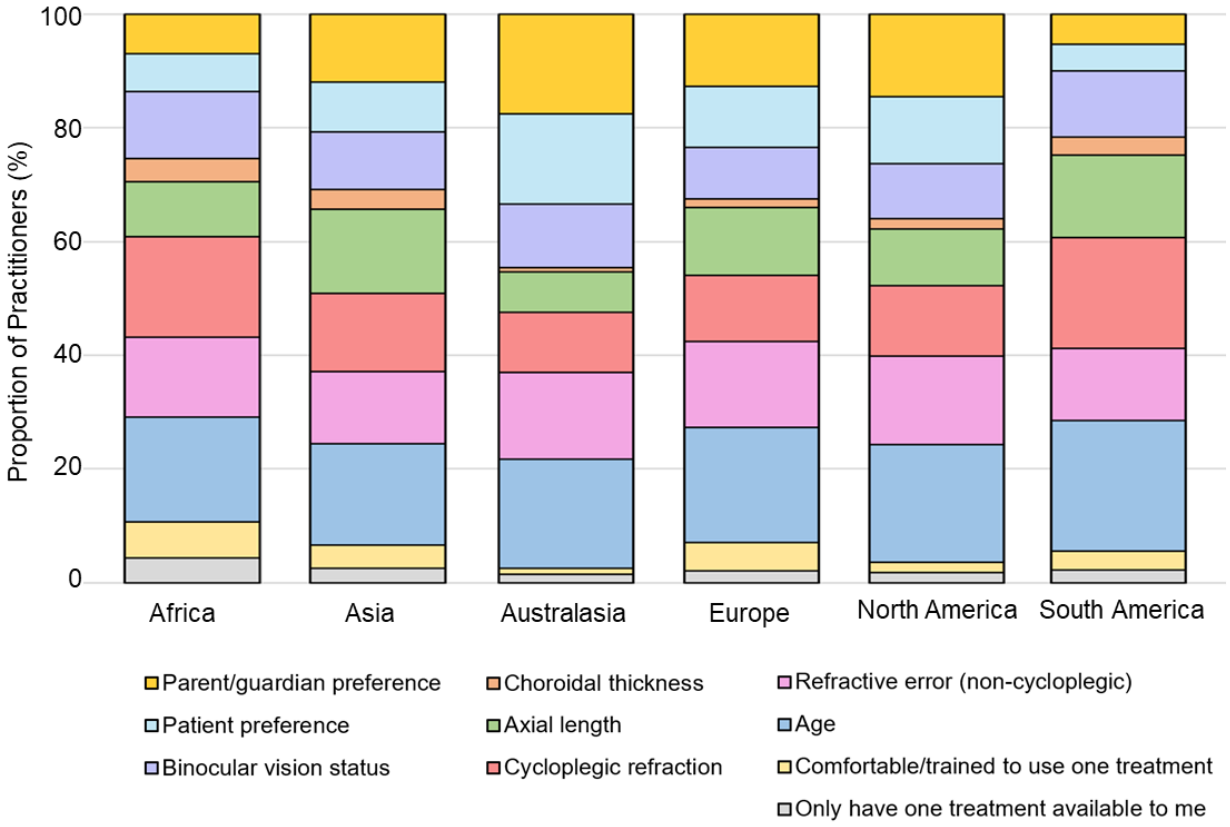


Figure 2.7: Factors considered when choosing which myopia management strategy to use first. N = 3017.

Europe (78.3%) or Australasia (85.2%). Practitioners in South America (40.7%) used noncycloplegic refraction less as a factor (all p<0.05 except for Africa at 50.0%) with Australia using this more (68.3%, p<0.05 versus Africa and Asia). Africa (63.5%), Asia (57.0%), and South America (62.7%) were more likely to use cycloplegic refraction as a factor (all p<0.05) than Australasia (46.5%), Europe (45.1%), and North America (45.9%). Axial length findings were used more in Asia (62.2%), followed by Europe (46.3%) and South America (46.9%) (both p<0.05). Choroidal thickness was used more in Asia (14.2%) and Africa (13.5%, all p < 0.05 except South America with 9.6%). Binocular vision use ranged from Australasia (49.5%) to Europe (35.3%, p<0.01). Patient and parent/guardian preference followed the same pattern and varied among all continents (p<0.05), being highest in Australasia (71.3%/78.2%, respectively) and lowest in South America (14.7%/17.0%).

2.1.3l Triggers to adjust myopia management strategy

On average, 4.0 of practitioners reported that they didn't adjust their myopia strategy, being lower in Australasia (0.0%) and Asia (2.1%, all p<0.05) than other continents (5.4 to 7.4%). Progression of refractive error was used by 84.4% of practitioners, being highest in Australasia (95.1%, all p<0.05) followed by Asia (87.5%, all p<0.05) compared to other

continents (77.0 to 81.7%). Progression of axial length was more important to practitioners in Asia (79.4%, all p≤0.001) than those in other continents (37.8 to 49.7). New treatments with better reported efficacy influenced more practitioners in Australasia (63.4%) and Europe (51.6%, all p<0.05) than other continents (34.5% to 42.6%). Poor compliance was least considered in South America (28.8%, all p≤0.001) and most important to Australasian (78.2%, all p<0.001) followed by Asian (63.4%) practitioners (p = 0.004). Compliance was a factor for more Australasian (60.4%, all p<0.001) followed by Asian (p=0.009) practitioners and fewer in South American (22.6%, all p≤0.001) and African practitioners (27.0 , all p<0.05).

2.1.3m Impact of myopia management on your practice

Embracing myopia management was felt to enhance patient loyalty (much more, 23.8%; more, 45.3%; and no change, 26.3%), increase practice revenue (much more, 10.6%; more, 8.5%; and no change, 39.3%), and increase job satisfaction (much more, 32.6%; more, 43.8%; and no change, 19.9%). Patient loyalty was felt to be lower in South America, followed by North America (all p<0.05), practice revenue to be lower in Europe and South America (p<0.05 with Asia and North America), and job satisfaction to be higher in Australasia and Europe (all p<0.05).

In Asia, resulting patient loyalty was felt to be higher in China and the Philippines (all p<0.01), additional practice revenue was felt to be lower in Turkey and Vietnam and higher in the Philippines, and resulting job satisfaction was higher in India and the Philippines (all p<0.05). In Europe, resulting patient loyalty was felt to be lower in France and Russia (all p<0.05), additional practice revenue was felt to be higher in the UK and resulting job satisfaction was generally higher in Italy, Spain, and the UK (all p<0.05). In North America, resulting patient loyalty and practice revenue were felt to be lower in Puerto Rico and Mexico than in Canada and the USA (all p<0.05).

2.1.4. Discussion

This report examines the self-reported attitudes and practices of eye care practitioners toward myopia management across the globe and forms the third contribution to a study beginning in 2015[30]. More than 3000 practitioners participated in this survey, nearly tripling the number of responses received in the previous report conducted in 2019[29]. For the first time, the number of responses from Africa was sufficient to be included in this continent-wide analysis, providing coverage across six continents. A similar proportion of respondents whose professions can legally prescribe vision correction and pharmaceuticals (depending on the region) were received: the vast majority of respondents were optometrists and

ophthalmologists across 2022, 2019, and 2015 surveys (91.4%, 92.1%, and 91.0%, respectively).

The self-reported level of concern about the increasing frequency of paediatric myopia was generally high across all six continents. Reflective of the high prevalence rate of paediatric myopia in Asia[379], practitioners in this part of the world once again showed the greatest level of concern compared with all other continents. The perceived level of clinical activity in myopia management was also highest in Asia; however, large differences were reported within the continent: practitioners in Vietnam reported just over half the activity level to that of practitioners in China. Similarly, significant countrywide differences in activity level were found in all continents besides South America. Despite this, all continents show an increase in the reported clinical activity level in myopia management compared with that reported in 2019[29].

Young children with levels of hyperopia lower than age-normal (or are even emmetropic) are considered to be at significant risk of becoming myopic[376, 380]. In 2019, practitioners considered a refractive error of approximately −1.50 D to be the minimum degree of myopia to begin management, which was argued to be an overly conservative approach[29]. Despite some regional differences, a shift toward a lower degree of myopia seems to have occurred since then, where, on average, practitioners felt a refractive error between −0.50 to −1.0 D still necessitates intervention. The latter might be attributed to significant advancements and developments in the field of myopia management together with an increased adoption of myopia management strategies by eye care practitioners worldwide. Considering the significant risk factors associated with mild-to-moderate levels of myopia[14, 381], it appears clinicians now adopt a more proactive response to incident myopia.

In the 2015[30] and 2019[29] surveys, orthokeratology was perceived to be the most efficacious intervention method. For the first time in this series of surveys, combination therapy was included as a control option, and practitioners from all six continents perceived this to be a more effective method of myopia management. Although clinical trials exploring specific approaches to combination therapy are relatively sparse, practitioner attitude reflects existing research showing a combination of pharmaceutical intervention (low-dose atropine) and orthokeratology to have an improved effect compared to orthokeratology alone (detailed in a comprehensive IMI white paper)[295, 382-384]. Although considered to be the most efficacious, combination therapy was one of the least prescribed myopia management techniques across all continents, ranging from 2% in Africa to 5% in Asia. The latter might be attributed to poor access to low dose atropine preparations and optometrists in many parts of the world not being licensed to prescribe atropine. In contrast, a recent article exploring

practice patterns of myopia management among paediatric ophthalmologists across the globe (n=794) reported nearly all respondents (95%) adopted a combination approach; however, this questionnaire offered behavioural advice to be included as a specific intervention technique[378].

Despite the self-reported increasing levels of clinical activity in the area of myopia management across the globe, single vision spectacles and soft contact lenses were still the most prescribed vision correction across all continents, averaging 43% overall. However, this is notably lower than what was reported in 2019[29] (52%) and 2015[30] (68%). Whether this lessening tendency to prescribe single vision correction to young myopes comes from an increase in practitioner's ability and resolve to practice myopia management, greater patient interest and uptake, or, most likely, a combination of the two; these results show an encouraging trend over the seven-year period.

Specific myopia management spectacles (a new category since 2019) were considered to be nearly equal in efficacy as specific myopia management soft contact lenses; however, respondents showed a greater frequency of prescribing myopia management spectacles than myopia management soft contact lenses to young myopes (overall 14.0% and 9.0%, respectively). The greater frequency of prescribing myopia management spectacles might be attributed to an increasing number of studies supporting the efficacy of this myopia intervention together with issues related to the fact that no additional practice equipment is needed for their prescription, and that spectacle lenses present no risk with regards to infection. The preference to prescribe myopia management spectacles was consistent across all continents besides Europe. Interestingly, the overall frequency of prescribing single vision spectacles to young myopes was over four times that of single vision soft contact lenses (34.6% and 8.3%, respectively), despite the use of contact lenses having been shown to improve how children and teenagers feel about their appearance and participation in activities[385]. A clear disparity between spectacle lenses and soft contact lenses was present among the six continents. Whether there is hesitancy to prescribe soft contact lenses to young myopes because of cost, safety concerns, patient/parent preference, or other reasons, the preference to prescribe spectacles over soft contact lenses appears to markedly reduce when prescribing those lens types marketed for myopia management; this may be due to compliance with contact lens wear during the day being better than with spectacles, and myopia management contact lenses being more established with long-term efficacy and safety data[294].

The minimum age (between 5 to 18 years) to prescribe myopia correction or control interventions varied depending on modality. Overall, practitioners were happy to prescribe

single vision spectacles and myopia management spectacles to children of similar ages, with the mean age of 6.4 years for both lens types separately. Interestingly, a significantly greater proportion of practitioners from Australia (26%), Europe (18%), and North America (16%) would not prescribe single vision spectacles to young myopes compared to prescribing approved myopia management spectacles (6%, 6%, and 8%, respectively). The opposite was true for Africa, Asia, and South America. In contrast, a greater proportion of practitioners from all six continents would not prescribe single vision soft contact lenses compared to myopia management soft contact lenses. However, the minimum age practitioners would fit young myopes with soft contact lenses (both single vision and those approved for myopia management) was greater than all spectacle lens types, averaging 9.8 years for single vision soft contact lenses and 8.6 years for soft contact lenses approved for myopia management. Country-wide comparisons showed no exception to this trend, where every region considered the minimum age necessary to prescribe soft contact lenses (single vision and myopia management) to be older than that for spectacle lenses (single vision and myopia management). The minimum age to prescribe orthokeratology was similar to that of soft contact lens types (on average 9.2 years). Hesitancy to prescribe contact lenses to young children often stems from safety concerns because of the necessary compliance required to minimise the risk of contact lens–related ocular adverse events. The risk of ocular complications has been found to be very low across different lens modalities, particularly daily disposables, and research has shown children and adolescents to be as safe as adults in contact lens wear[386-388]. Attitudes to soft contact lens modalities were not examined separately in the survey, so it may be useful to explore whether the minimum age to which practitioners fit soft contact lenses is consistent for daily disposable and reusable modalities. The average minimum age practitioners prescribe pharmaceuticals was similar to that of spectacle lenses; as expected, because of differing access across the globe, those who would not prescribe pharmaceutical intervention varied greatly among continents, with the highest percentage in Europe (47%) and lowest in Asia (7%), with the latter possibility related to differences among continents in practitioners' scope of practice and access. The frequency of prescribing pharmaceuticals for myopia management appears to have more than doubled in Asia since 2019 (previously 4.1%, now 8.7%), primarily within China, India, and Israel. Besides from Europe, practitioners from all other continents appear to be prescribing pharmaceutical intervention more often.

Research has shown single vision distance undercorrection to be ineffective at best or to increase, rather than decrease, the rate of myopia progression in children[265, 267, 389], yet some practitioners across the world still practice undercorrection as a method of "myopia management." The majority of respondents never use undercorrection as a control method

(83.1) ; however, more than one in 10 eye care practitioners at least “sometimes” use undercorrection across all continents besides Australasia. This was most evident in Africa (35.1%) and South America (31.1%). A recent publication exploring management attitudes and strategies to myopia management specifically in Africa found that a markedly higher percentage of African practitioners use undercorrection compared to this survey, where 52% of those surveyed at least sometimes used undercorrection in practice[390]; this may be due to their wider coverage of practitioners, which it is hoped can be encompassed in future surveys in this series. Fortunately, the overall percentage of practitioners who undercorrect young myopic patients at least some of the time has consistently declined over recent years; 27.3% in 2015[30], 20.4% in 2019[29], and 16.9% in 2022.

Compared to conventional correction, practitioners across all continents felt the higher cost to the patient to be the primary hindrance to prescribe myopia interventions. In Africa, concerns about cost were closely followed by limited availability to myopia treatments, with more than 40% of practitioners reporting this as a significant obstacle. Other research in Africa has found similar reasons for why practitioners may not prescribe myopia control interventions there, where cost to the patient and safety concerns were the two reasons most commonly reported[390]. Treatment availability also appears to be an issue for practitioners in Asia and South America, whereas practitioners in Australasia, Europe, and North America appear to be much less affected. This highlights the vital need for a collaborative effort across the eye care industry and clinical practice to increase accessibility, both financially and geographically.

In an additional question asked for the first time, respondents across all six continents ranked patient age and refractive error to be the two primary criteria for starting myopia management, followed by parental myopia, and patient axial length. The latter suggests a consistent approach to identifying a child’s risk of myopia progression independent of location, and extensive evidence supports these four criteria to be considered as significant risk factors[376, 391]. Interestingly, patient and parent/guardian pressure were the lowest ranked criteria for beginning myopia management across all continents besides Australasia. This could indicate a lack of information promoting the need for myopia management accessible to parents and patients/guardians or simply demonstrate the trust patients and parents/guardians have for practitioners to decide the correct management approach on their behalf.

Once a young patient starts using a myopia management method, the great majority of practitioners mostly used progression of refractive error as the key trigger to adjust their myopia management strategy, although other factors might also play a role (such as contact

lens discomfort). The latter finding was fairly consistent across all continents, averaging 84.3% overall. Using progression of axial length as a trigger was much more varied between continents, ranging from 39% in Africa to 79.4% in Asia, and the remainder between 45% to 50%. Considering patient axial length was ranked highly as a criterion to begin myopia management, it seems curious that few practitioners use progression of axial length as an indicator to adjust the management strategy in poor-responders. One potential explanation may be limited access to the instrumentation required to monitor axial length progression as a part of routine clinical practice. The practice of myopia management appears to positively impact clinicians and their practice, with the majority of practitioners reporting increased patient loyalty and enhanced job satisfaction. Practice revenue showed more mixed results, where similar percentages of practitioners reported either no change or an increase in revenue. The encouraging response promotes a strong foundation to pursue myopia management for the benefit of the eye care practice, the individual practitioner, and, of course, the patient.

Much like the previous two surveys in this study[29, 30], the exact response rate is not known, because maximum coverage was promoted by involving professional bodies whose members may not all be practicing eye care practitioners. It is unclear how representative the respondents are to the broader practitioner population in each region, with different eye care professions differing in their scope of practice. Access to equipment and treatment options are also dependent on regulatory approvals and health-care reimbursement. For example, the USA is one of few countries where optometrists can prescribe atropine, but only one soft lens is approved for myopia management, and myopia management spectacles are not yet available. The survey avoided being specific on myopia device brands and pharmaceutical concentrations, which would lead to a further layer of complexity. In conclusion, the third global survey of current trends in eye care practitioner myopia management attitudes and strategies in clinical practice has identified that, with growing evidence of the negative impact of even low levels of myopia on health economics, practitioner concern and perceived activity is increasing. This is translating into the uptake of appropriate, proven, myopia management techniques at lower levels of myopia; however, there is still plenty of scope for this to be accelerated, so proven myopia control treatments are applied to all children at high risk of developing myopia early enough in a child's ocular development to elicit an optimum effect. Adequate, evidence-based education of practitioners has improved, but further advocacy and collaboration with policy makers, health regulatory bodies, and industry is needed to enhance accessibility and affordability of treatment options to address the growing health burden of the myopia epidemic.

2.2 CHOROIDAL THICKNESS AND MYOPIA MANAGEMENT IN 2022

2.2.1 Introduction

Although myopic eyes tend to have thinner choroids than non-myopic eyes[252, 253], using choroidal thickness as a biomarker for future axial elongation has only recently been suggested as a possibility[281, 315]. From this, it may be that practitioners who are already measuring and monitoring choroidal thickness in their young myopic patients are based in regions that have reported a greater level of clinical activity in myopia management. Therefore, unlike the previous two surveys in this series[29, 30], the 2022 contribution questioned eye care practitioners about their consideration of the choroid when managing young myopic patients. This included how choroidal thickness ranked in their criteria for beginning myopia management, selecting which myopia management strategy to use first, and triggers an adjustment of their myopia management strategy. The following section presents the results of those questions.

2.2.2 Results

2.2.2a Ranking of choroidal thickness as a criterion for beginning myopia management

When ranking the twelve criteria for beginning myopia management in a child with progressive myopia (where 1 = highest rank and 12 = lowest rank, see Section 2.1.3j), overall, choroidal thickness was ranked 9th, being higher than choroidal thickness responsiveness to early treatment (10th), patient pressure (11th), and parent/guardian pressure (12th).

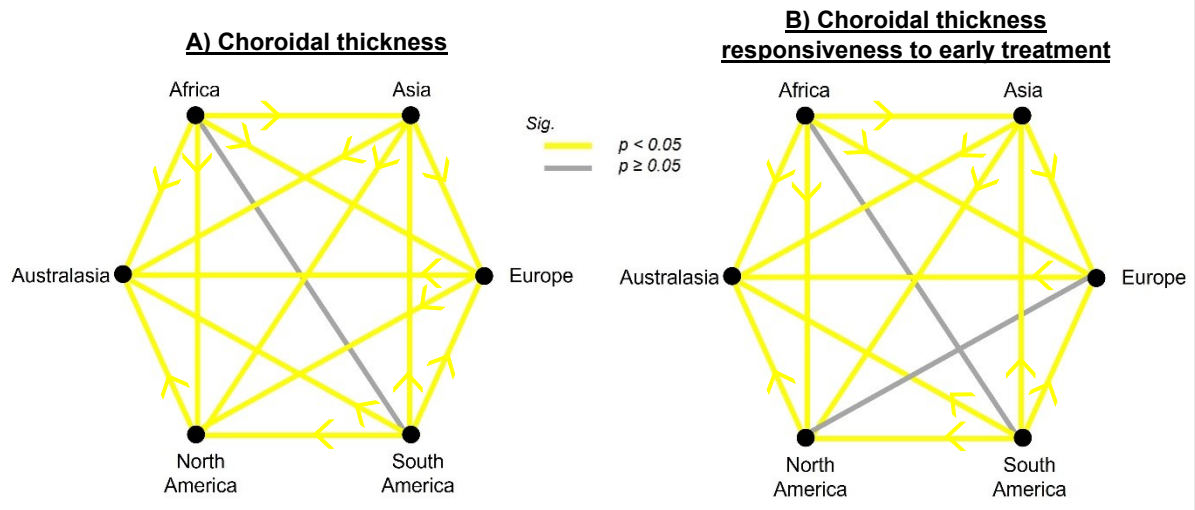


Figure 2.8: Significance plot showing differences between continents when ranking A) choroidal thickness and B) choroidal thickness responsiveness to early treatment as criteria for starting a method of myopia management, where 1 = the highest rank, and 12 = the lowest rank. Yellow lines represent significant differences ($p<0.05$), and grey lines represent insignificant differences ($p>0.05$). Direction of arrows indicate higher rank to lower rank.

Between continents, choroidal thickness was ranked highest by practitioners in South America (7.1 ± 2.5) and Africa (7.2 ± 2.6), followed by Asia (8.0 ± 2.4), Europe (8.1 ± 2.7) and North America (8.6 ± 2.4). Australasia ranked choroidal thickness lower than all other continents (9.8 ± 1.9). Statistical significance is presented in Figure 2.8A.

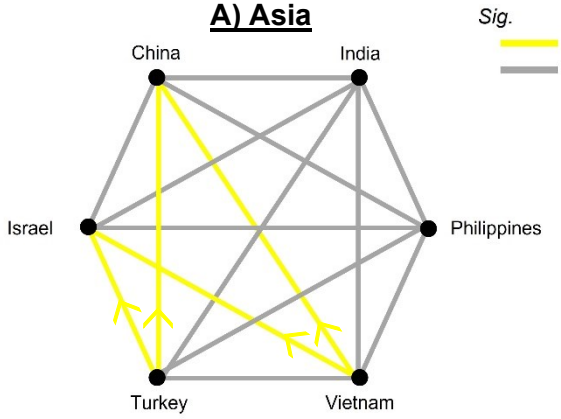
Similar to choroidal thickness alone, choroidal thickness responsiveness to early treatment was ranked highest by practitioners in Africa (7.4 ± 2.6) and South America (7.6 ± 2.4). This was followed by Asia (8.4 ± 2.4), Europe (8.7 ± 2.6), North America (8.9 ± 2.4), and ranked lowest in Australasia (10.1 ± 1.9). The statistical significance of these differences is presented in Figure 2.8B.

Within Asia, Vietnam and Turkey ranked choroidal thickness significantly higher than China and Israel (Figure 2.9A). Given the self-reported level of clinical activity in myopia management to be the lowest in Vietnam and Turkey within Asia (see Section 2.1.3c), it seems unusual for practitioners in these countries to view the less-traditional technique of measuring a young myope's choroidal thickness to start myopia management to be of a higher rank than other Asian countries. However, it is unclear whether these practitioners are actually measuring choroidal thickness when initiating myopia management, or simply perceive it to be of greater use than more clinically active regions. The same can be argued for choroidal thickness responsiveness to early treatment, where Vietnamese practitioners ranked this significantly higher than China, India and Israel (Figure 2.10A).

Russia and France ranked choroidal thickness and choroidal thickness responsiveness to early treatment significantly higher than other European countries besides Italy (Figure 2.9B and 2.10B). Interestingly, practitioners in France were the only country to report significantly lower activeness in practicing myopia management than all other countries in Europe, whereas Russia reported the highest (Section 2.1.3c). North America showed a similar trend to Asia, where the least active regions (Mexico and Puerto Rico) ranked both criteria significantly higher than the most active (Canada and The United States of America) (Figure 2.9C and 2.10C). South American practitioners generally ranked choroidal thickness and its responsiveness to early treatment higher overall, however, like the reported activity level (Section 2.1.3c), there were no significant differences within the continent (Figure 2.9D and 2.10D).

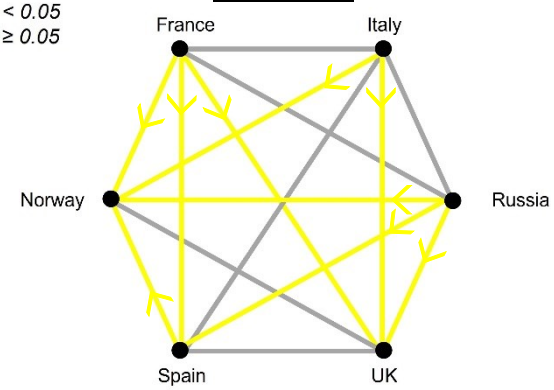
Choroidal thickness

A) Asia



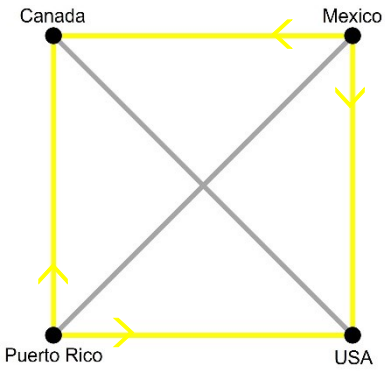
Asia	Mean	± SD
China	8.1	2.4
India	7.8	2.1
Israel	8.6	2.6
Philippines	7.7	2.1
Turkey	7.6	2.3
Vietnam	7.5	2.1

B) Europe



Europe	Mean	± SD
France	7.2	2.2
Italy	7.8	2.6
Norway	9.1	2.3
Russia	7.2	2.4
Spain	8.1	2.9
UK	8.6	2.5

C) North America



North America	Mean	± SD
Canada	9.4	2.2
Mexico	7.3	2.5
Puerto Rico	8.0	2.1
USA	9.4	2.2

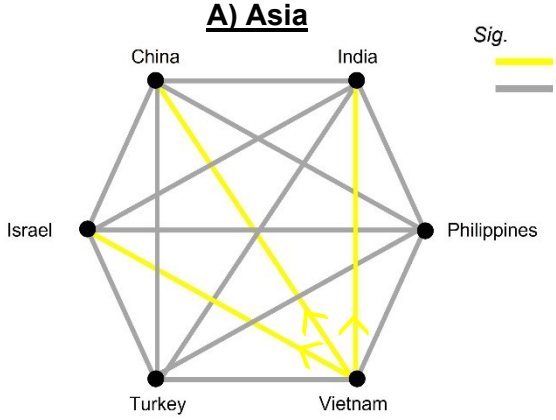
D) South America

South America	Mean	± SD
Argentina	6.8	3.1
Brazil	7.2	2.3
Ecuador	7.4	2.5
Peru	7.0	2.2

Figure 2.9: Significance plots showing differences between countries in A) Asia, B) Europe, C) North America, and D) South America when ranking **choroidal thickness** as a criterion for starting a method of myopia management, where 1 = the highest rank, and 12 = the lowest rank. Countries considered where n=≥30. Yellow lines represent significant differences (p<0.05) and grey lines represent insignificant differences (p>0.05). Direction of arrows indicate higher rank to lower rank.

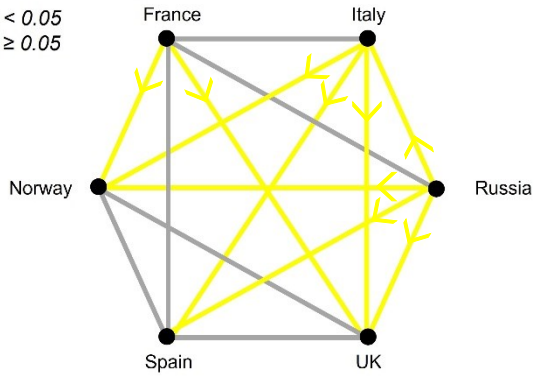
Choroidal thickness responsiveness to early treatment

A) Asia



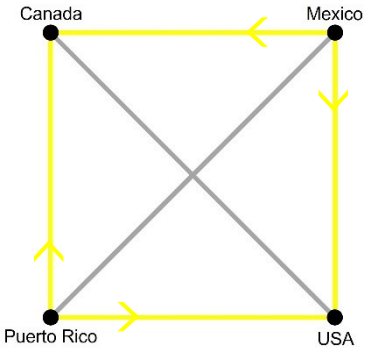
Asia	Mean	± SD
China	8.6	2.4
India	8.7	2.1
Israel	8.8	2.7
Philippines	8.1	2.3
Turkey	8.3	2.1
Vietnam	7.7	2.1

B) Europe



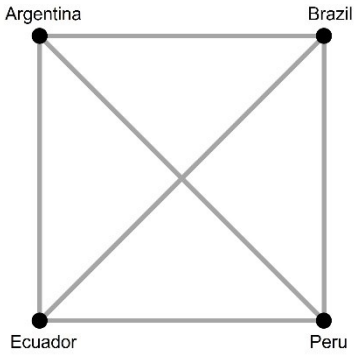
Europe	Mean	± SD
France	8.1	2.1
Italy	8.3	2.5
Norway	9.4	2.6
Russia	7.5	2.6
Spain	8.7	2.7
UK	9.4	2.6

C) North America



North America	Mean	± SD
Canada	9.6	2.2
Mexico	7.8	2.4
Puerto Rico	7.9	2.7
USA	9.8	2.2

D) South America



South America	Mean	± SD
Argentina	7.9	2.5
Brazil	7.4	2.3
Ecuador	8.0	2.4
Peru	7.3	2.6

Figure 2.10: Significance plots showing differences between countries in A) Asia, B) Europe, C) North America, and D) South America when ranking **choroidal thickness responsiveness to early treatment** as a criterion for starting a method of myopia management, where 1 = the highest rank, and 12 = the lowest rank. Countries presented where n=≥30. Yellow lines represent significant differences (p<0.05) and grey lines represent insignificant differences (p>0.05). Direction of arrows indicate higher rank to lower rank.

There doesn't appear to be a notable relationship between those areas with the significantly highest activity level in myopia management adopting measurement and/or monitoring of choroidal thickness in the early stages of managing young progressing myopes. With the influence of advocacy groups and member bodies across the world, eye care professionals and their patient bases are becoming increasingly aware of the need for myopia management. Despite this, it appears that eye care practitioners across the globe generally value choroidal thickness and its response to early treatment to be of greater importance when beginning myopia management than pressure from patients and parents/guardians.

2.2.2b Choroidal thickness as a factor considered when choosing which myopia management strategy to use first

In addition to beginning myopia management, respondents were asked to consider whether choroidal thickness influences the type of intervention method they would use first. Out of the ten proposed factors (Section 2.1.3k: patient age, non-cycloplegic refraction, cycloplegic refraction, axial length, parent/guardian preference, binocular vision status, patient preference, only one treatment available, only comfortable/trained in one treatment, and choroidal thickness), choroidal thickness was the least commonly used factor, at 9.8% of practitioners overall. This differed between continents: 14.2% of practitioners in Asia considered a patient's choroidal thickness when choosing a myopia management strategy, followed by 13.5% in Africa. 9.6% of practitioners in South America, 6.5% in North America, 5.5% in Europe, and 2.0% in Australasia. The statistical significance of these differences is presented in Figure 2.11.

When ranking criteria to begin myopia management, Vietnam and Turkey ranked choroidal thickness and its responsiveness to early treatment higher than the other surveyed Asian countries (Section 2.2.2a). When considering the factors used to choose which myopia management strategy to use first, the proportion of practitioners who consider choroidal thickness was significantly less in Vietnam and Turkey than all other Asian countries, besides Israel (Figure 2.12A). Oppositely, within Europe, the significantly greatest proportion of practitioners who consider

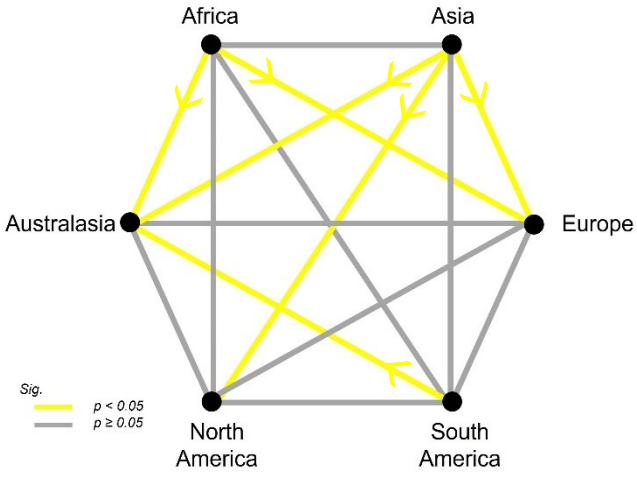
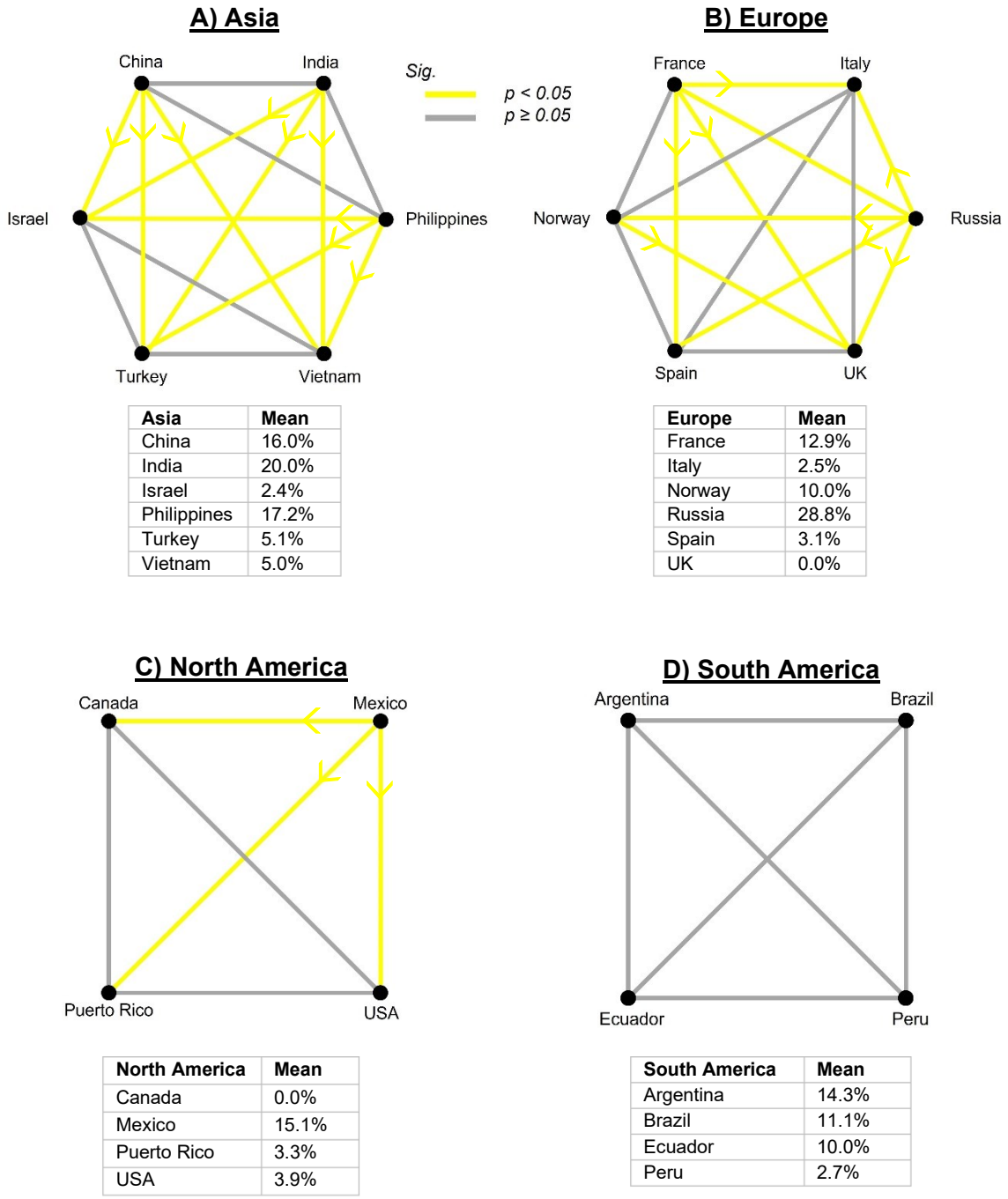


Figure 2.11: Significance plot showing differences between continents when considering **choroidal thickness as a factor when choosing which myopia management strategy to use first**. Yellow lines represent significant differences ($p<0.05$) and grey lines represent insignificant differences ($p>0.05$). Direction of arrows indicate higher percentage to lower percentage.



Asia	Mean
China	16.0%
India	20.0%
Israel	2.4%
Philippines	17.2%
Turkey	5.1%
Vietnam	5.0%

Europe	Mean
France	12.9%
Italy	2.5%
Norway	10.0%
Russia	28.8%
Spain	3.1%
UK	0.0%

North America	Mean
Canada	0.0%
Mexico	15.1%
Puerto Rico	3.3%
USA	3.9%

South America	Mean
Argentina	14.3%
Brazil	11.1%
Ecuador	10.0%
Peru	2.7%

Figure 2.12: Significance plots between countries in A) Asia, B) Europe, C) North America, and D) South America showing the proportion of practitioners who consider **choroidal thickness as a factor when choosing which myopia management strategy to use first**. Countries presented where n=≥30. Yellow lines represent significant differences (p<0.05) and grey lines represent insignificant differences (p>0.05). Direction of arrows indicate higher percentage to lower percentage.

choroidal thickness when choosing a management strategy was in Russia, at nearly 30% (Figure 2.12B). This is consistent with the previous consideration of choroidal thickness when ranking criteria to begin myopia management (Section 2.2.2a), being ranked highest in Russia across Europe. This was markedly different to the United Kingdom, where no practitioners considered choroidal thickness when choosing a management strategy.

Despite both Mexico and Puerto Rico ranking choroidal thickness and its responsiveness to early treatment significantly higher than Canada and the USA, only Mexico showed a significantly higher consideration of choroidal thickness in choosing a management strategy, at around 15% (Figure 2.12C). No significant differences were found within South America (Figure 2.12D)

It is clear that some regions show a notably higher consideration of the choroidal thickness of their young myopic patients than others, however the use of choroidal thickness appears to be inconsistent. Some class choroidal thickness as an indicator to start myopia management and a guide to choose which intervention to prescribe, whereas others value choroidal thickness for just one of these considerations. Further, practitioners in other regions don't appear use choroidal thickness at all when managing their young myopic patients.

2.2.2c Choroidal thickness as a trigger to adjust myopia management strategy

Respondents were asked to consider various factors that would trigger them to adjust their management of a young progressive myope, such as refractive error progression and axial length progression (see Section 2.1.3l). Changes in choroidal thickness was included as an option.

Of all the continents, practitioners in Asia reported a significantly greater tendency to use changes in choroidal thickness as a trigger to adjust their management strategy, at 20.0% overall. This was followed by Africa (14.9%), South America (12.4%), North America (7.1%), Europe (6.2%), and Australasia (1.0%). Statistical significance is presented in Figure 2.13.

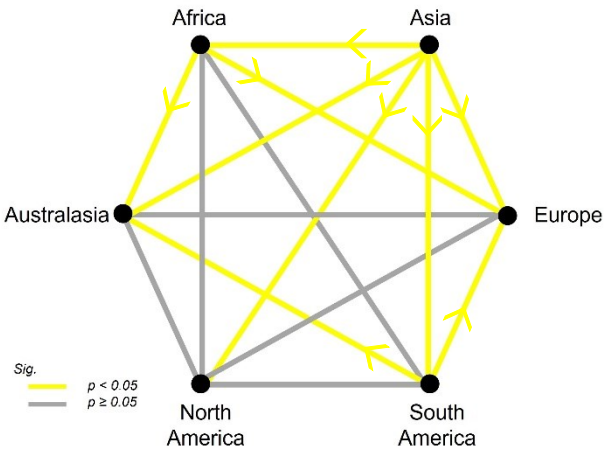
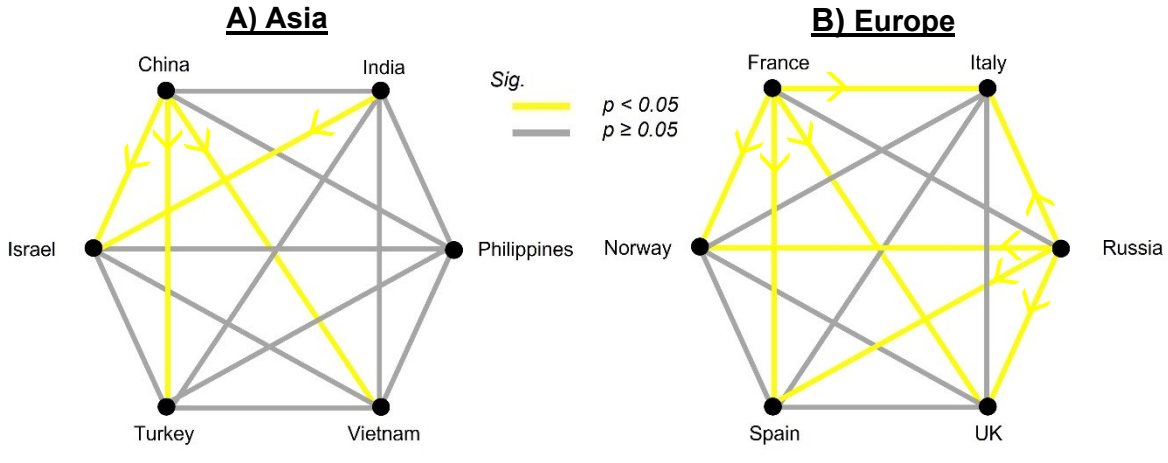


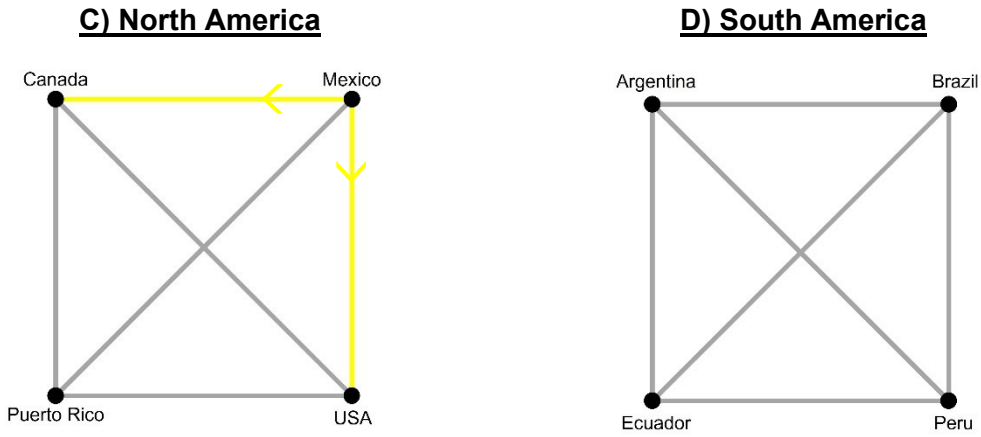
Figure 2.13: Significance plot showing differences between continents when considering **choroidal thickness as a trigger to adjust myopia management strategy**. Yellow lines represent significant differences (p<0.05) and grey lines represent insignificant differences (p>0.05). Direction of arrows indicate higher percentage to lower percentage.

Much like choroidal thickness as an indicator to choose a management strategy, China, India, and the Philippines had the greatest proportion of practitioners who considered choroidal thickness to be a trigger to adjust their management strategy in Asia. This was true for nearly a quarter of Chinese practitioners, being a significantly greater proportion of practitioners than that of Israel, Turkey, and Vietnam (Figure 2.14A).



Asia	Mean
China	23.8%
India	16.9%
Israel	0.0%
Philippines	13.8%
Turkey	11.5%
Vietnam	5.0%

Europe	Mean
France	22.6%
Italy	2.5%
Norway	2.5%
Russia	23.8%
Spain	4.7%
UK	1.5%



North America	Mean
Canada	1.9%
Mexico	15.1%
Puerto Rico	10.0%
USA	3.9%

South America	Mean
Argentina	9.5%
Brazil	8.3%
Ecuador	15%
Peru	5.4%

Figure 2.14: Significance plots between countries in A) Asia, B) Europe, C) North America, and D) South America showing the proportion of practitioners who consider **changes in choroidal thickness as a trigger to adjust their myopia management strategy**. Countries presented where n=≥30. Yellow lines represent significant differences (p<0.05) and grey lines represent insignificant differences (p>0.05). Direction of arrows indicate higher percentage to lower percentage.

France and Russia had the greatest proportion of practitioners who used choroidal thickness as a trigger to adjust their myopia management in Europe (Figure 2.14B). In North America, Mexico and Puerto Rico had the greatest proportion, and South America had no statistically significant differences (Figure 2.14C and Figure 2.14D, respectively).

These results largely follow the pattern of the previous question (Section 2.2.2b), where the same regions consider choroidal thickness to be more useful for choosing a management strategy and triggering a change of said strategy.

2.2.3 Discussion

The context in which choroidal thickness is valued when managing young myopic patients in practice appears to be inconsistent across regions. Some areas value choroidal thickness when beginning intervention but less so when choosing which strategy to use first, whereas those who value the latter tend to also have the greatest proportion of practitioners who consider choroidal thickness changes as a trigger to adjust their management strategy.

It remains uncertain whether the responses here are predominantly a consideration of prospectively using choroidal thickness or demonstrate regions where this is already being employed in clinical practice. Further, it is not clear in what context choroidal thickness alone may be used. For example, this may be because thinner choroids in young, non-myopic eyes may show a greater tendency to eventually become myopic[392]. Alternatively, the inverse relationship between decreasing choroidal thickness and increasing axial length may be used as a surrogate indicator of axial elongation in those regions where instrumentation to directly measure axial length isn't routinely used or accessible to practitioners.

Considering the overall results of the 2022 survey, choroidal thickness doesn't appear to be key measure used by practitioners when practicing myopia management. With the usefulness of choroidal thickness when managing young myopic patients not yet well established, it is expected that practitioners greatly value other objective measures such as refractive error progression, axial elongation, and binocular vision status. As choroidal research contributions progress over the coming years, it will be interesting to identify any changes in practitioner's attitudes towards measuring and monitoring choroidal thickness in clinical practice.

2.3 REFLECTIONS

The 2022 update of 'Global trends in myopia management attitudes and strategies in clinical practice' yielded an extensive amount of data. The results provided great insight into how eye care practitioners around the world are becoming increasingly proactive when managing their young myopic patients, whilst acknowledging areas which require further improvement.

In addition to the questions asked in 2015 and 2019, this survey included new questions and options for practitioners to consider, such as ranking criteria for beginning myopia management and triggers to adjust their strategy. As the awareness and availability of myopia management and evidence-based approaches increase, these additions provide a useful basis to identify how approaches will evolve between the year 2022 and the next instalment of this study.

This study successfully highlighted promising trends of myopia management across the globe, however the methodology and analyses could have been improved. With the increasing numbers of respondents, analysis by continent may not be the optimum approach for following versions. For example, in Asia, China yielded an overwhelming number of responses (n=1001) compared to Israel (n=42), so the data from Asia was heavily influenced by Chinese practitioners. Considering smaller regions, rather than the continent as a whole, could provide a more specific and insightful analysis of practitioner's attitudes and strategies toward myopia management. This is largely dependent on a growing number of responses in subsequent surveys.

Given the large number of respondents, additional questions, and the multiple options for various questions, a blanket approach to the statistical analyses provided an overwhelming amount of data. This arguably was not useful nor valuable to the outcomes and created some difficulty in sourcing the most important and perceptive results. Consequently, the analyses and write-up became a time-consuming process. Reflecting on the results of the first three surveys in this series has directed the analysis of the following instalment (Chapter 3) to improve efficiency and yield worthwhile results.

Furthermore, two of the questions included in this survey were open-ended, which caused difficulty in interpreting the responses. Given the internationalism of this study, the survey was available in thirteen different languages. With well over three thousand responses collected, translating each written response is a lengthy process with room for error for a sole researcher to interpret. Formatting these responses in a way which would allow statistical significance to be measured is also difficult to achieve accurately. These difficulties outweighed the benefit of including the results in the study, so the open-ended questions were disregarded from further analysis and were not included in the results.

Overall, this study provided an insightful and widespread advancement to the field of myopia research specific to clinical practice for practitioners and researchers alike. The visible patterns and changing techniques emphasised the relevance and rational to continue exploration of myopia management across the globe. The learnings from the limitations in

the study shaped the design and approach to the follow-up survey presented in the following chapter.

Chapter 3. Global trends in myopia management with time

3.1 GLOBAL TRENDS IN MYOPIA MANAGEMENT ATTITUDES AND STRATEGIES IN CLINICAL PRACTICE – A NINE YEAR REVIEW

3.1.1 Introduction

Extensive advancements in myopia research have led to significant changes in optical industry year by year, including updates of long-term efficacy data[294, 393] and the launch of newer management technologies[353, 394]. Additionally, non-profit organisations and membership bodies across the world are advocating for eye care practitioners to engage in myopia management, providing resources for practitioners and patients alike. With myopia research so dynamic at present, and no global consensus of standardised management methods, it is likely for practitioners' opinions and techniques of managing young myopic patients to adapt alongside the rapid developments in the field.

The first global survey of myopia management attitudes and strategies was conducted in 2015[30], followed by 2019[29]. The findings of Chapter 2 provided an overview of myopia management across the world in 2022. Each survey provided a valuable snapshot in time of the status of myopia management across the world. Since 2015, huge developments in identifying and controlling the myopia epidemic have occurred. Now cited well over 4000 times on Google Scholar (https://scholar.google.com), a systematic review and meta-analysis performed by Holden et al., was published in 2016, predicting 50 of the world's population to be myopic by the year 2050[12], leading to the World Health Organisation (WHO) to declare myopia as a public health issue. First formed in 2015, the International Myopia Institute (IMI) have since released three series of white papers and clinical summaries available in multiple languages, providing evidence-based recommendations in classifications and patient management[1]. In addition, rather than practitioners being limited to using conventional spectacles and contact lens options (such as traditional bifocals and progressive lenses), optical interventions specifically marketed for the purpose of myopia management have been manufactured, trialled, validated and made accessible across various parts of the world since 2015 (see Chapter 2). These landmark events in myopia management will naturally play a part in prescribing trends discussed in the previous chapter. Further analysis of how specific continent-wide responses have adapted with time will enable a deeper understanding of how advancements in ophthalmic research and industry are reflected in clinical practice.

Using the same methodology as that used in 2015[30], 2019[29], and 2022 (Chapter 2), this study forms the fourth instalment in the series, providing an update of the attitudes towards

myopia management strategies in clinical practice worldwide in 2024. Additionally, this study delves further into practitioner's reasoning behind the previously identified global and regional trends, and reviews specific changes in clinical opinions and care of young myopes over the nine-year period. Particular attention is paid to the use of choroidal thickness in myopia management, and how the changing perceptions of its clinical applications differ on a continent-wide and country-wide basis.

3.1.2 Methods

3.1.2a Data collection procedures

A self-administered, internet-based, cross-sectional survey was distributed in 18 languages (Simplified and Traditional Chinese, Danish, Dutch, English, French, Greek, Hebrew, Italian, Japanese, Norwegian, Polish, Portuguese, Russian, Spanish, Swedish, Turkish, and Vietnamese) using software SurveyMonkey (Momentive Inc, Palo Alto, California, USA). The survey was disseminated across the world through various professional bodies (not specific to myopia) to reach eye care practitioners globally (optometrists, ophthalmologists, contact lens opticians, and others). The survey was live between December 2023 and July 2024. Ethics approval was received from Aston University Research Ethics Committee, and informed consent was received from all respondents.

Several questions matched the previous versions; however, some important additions and modifications were made to the current survey based on IMI advisory board feedback and updated evidence, in the form of:

- Replacing the option of 'pharmaceuticals' with three concentrations of atropine (0.01 , 0.05 , and ≥0.5) in the list of possible management approaches
- Adding 'light therapy' (such as low-level red-light therapy) and 'alternating treatments' (using one intervention for a year to get the best effect, and then switching to a different intervention to try to get another first year effect) to the list of possible management options
- Separating 'specific myopia control soft contact lenses' into daily and reusable modalities within the list of possible management strategies
- Condensing the list of options to treatment modalities when asked the minimum age practitioners would prescribe different management approaches
- Adding 'myopia progression rate' and changing parent/patient 'pressure' to 'preference' to the list of options to be ranked for beginning myopia control treatment

- Adding ‘corneal topography’, ‘myopia progression rate’, and ‘risk factors’ to the list of possible options considered when selecting which myopia management strategy to use first
- Adding ‘eye growth faster than expected for age’ and ‘treatment comfort’ to the list of possible options when selecting triggers to adjust myopia management strategy

Fifteen questions relating to the self-reported clinical management behaviours of practitioners for progressing myopia and practitioner’s current opinions on myopia-related clinical care were asked (new questions refined by the IMI advisory board, indicated by an asterisk):

- Level of concern about the increasing frequency of childhood myopia in their clinical practice (rated as “Not at all” to “Extremely” on a 10-point scale)
- Perceived effectiveness, defined as the expected level of reduction in childhood myopia progression of a range of myopia correction and management options (rated as a percentage from 0% to 100%)
- How active they would consider their clinical practice in the area of myopia control (rated as “Not at all” to “Fully” on a 10-point scale)
- *Whether they have access to equipment to measure (yes or no):
    - Cycloplegic refractive error
    - Autorefraction
    - Corneal curvature
    - Axial length
- Frequency of prescribing different myopia correction options for progressing/young myopes during a typical month
- Minimum age a patient would need to be for them to consider myopia control options (assuming average handling skills and child/parent motivation)
- Minimum amount of myopia that would need to be present to consider myopia control options (specified in half-dioptre steps)
- Minimum level of myopia progression (dioptres/year) that would prompt a practitioner to specifically adopt a myopia control approach (specified in quarter-dioptre steps)
- Frequency of adopting single vision undercorrection as a strategy to slow myopia progression (reported as “never” “sometimes,” or “always”)
- If they had only ever fitted single vision spectacles/contact lenses for myopic patients, what had prevented them (multiple options could be selected) from prescribing alternative refractive correction methods; options consisted of the following:

    - They don't believe that these are any more effective
    - The outcome is not predictable
    - Safety concerns
    - Cost to the patient makes them uneconomical
    - Additional chair time required
    - Inadequate information/knowledge
    - Low benefit/risk ratio
    - Accessibility of treatment options
    - Other
- Rank their criteria for starting myopia control in a young progressing myope (numbered 1 to 13); options consisted of the following:
    - Refractive error
    - Age
    - Myopic parent (one)
    - Myopic parents (two)
    - Axial length
    - Myopia progression rate
    - Choroidal thickness
    - Choroidal thickness responsiveness to early treatment
    - Binocular vision status
    - AC/A ratio
    - Lifestyle
    - Patient preference
    - Parent/guardian preference
- How they select which myopia management strategy to use first on a young progressing myope; options consisted of the following:
    - Only have one treatment available to me
    - Only comfortable/trained to use one treatment
    - Age
    - Refractive error (non-cycloplegic)
    - Cycloplegic refraction
    - Myopia progression
    - Risk factors
    - Axial length
    - Choroidal thickness
    - Binocular vision status
    - Corneal topography

    - Patient preference
    - Parent/guardian preference
    - Other
- *How frequently they follow-up myopic children they are managing (specified in months)
- Triggers to adjust their myopia management strategy; options consisted of the following:
    - I don't
    - Progression of refractive error
    - Progression of axial length
    - Changes in choroidal thickness
    - Eye growth faster than expected for age
    - A new treatment with a scientifically reported better efficacy
    - Poor compliance
    - Treatment comfort
    - Complications
    - Other
- How has managing myopia changed their patient loyalty, practice revenue and job satisfaction (each rated as “much less”, “less”, “no change”, “more”, and “much more”)

Respondents had the option to add further comments to each of the questions as well as to the topic as a whole. Following an explanation of the research, participation was voluntary and anonymous; however, respondents were asked to provide basic demographic information about themselves (years of being qualified and principal working environment). For the questions consistent with those included in the previous surveys, the results of the current survey were then compared with the previous data collected in 2015, 2019, and 2022. For those questions first asked in 2022, data were only compared between the two years.

3.1.2b Statistical analysis

The data from all four surveys were divided into year group (2015, 2019, 2022, and 2024) and into the continents the eye care practitioner was based in. Statistical analyses were conducted with IBM SPSS (Statistics for Windows v28; IBM Corp., Armonk, NY, USA). Ordinal data are presented as medians and interquartile range, and continuous data as means and standard deviations. As the data were determined not to meet the normality assumption of parametric testing based on the Shapiro-Wilk test, the nonparametric Kruskal-

Wallis test was used to compare responses between continents and regions. Statistical significance was set at $p<0.05$. For conciseness, only significant comparisons are reported.

3.1.3 RESULTS

A total of 2,993 responses were received in 2024, with the distribution by continent being: Africa n=11; Asia n=746; Australasia (Australia, New Zealand, and neighbouring islands in the Pacific Ocean) n=94; Europe n=1,462; North America n=533; and South America n=147.

Survey	Continent							Total
	Africa	Asia	Australasia	Europe	North America	South America	Did not state	
2015	7*	291	119	339	133	82	None	971
2019	13*	207	79	717	147	173	None	1336
2022	74	1396	101	931	338	177	178	3195
2024	11*	746	94	1462	533	147	None	2993

Table 3.1: Total number of complete responses collected from each continent for each of the four global surveys. Figures marked with an asterisk were considered too low to be included in the analysis.

Survey	Continent					
	Africa	Asia	Australasia	Europe	North America	South America
2015	None	China (n=137) Hong Kong (n=61) India (n=37)	None	France (n=34) Italy (n=72) Netherlands (n=38) Portugal (n=48) Spain (n=34) UK/EIRE (n=52)	Canada (n=33) USA (n=100)	None
2019	None	China (n=37) Hong Kong (n=59) India (n=30)	None	Germany (n=68) Italy (n=102) Netherlands (n=40) Portugal (n=76) Russia (n=78) Spain (n=137) UK/EIRE (n=78)	Canada (n=37) USA (n=90)	None
2022	None	China (n=1001) India (n=65) Israel (n=42) Philippines (n=58) Turkey (n=78) Vietnam (n=101)	Australia (n=87)	France (n=31) Italy (n=202) Norway (n=40) Russia (n=80) Spain (n=380) UK/EIRE (n=67)	Canada (n=107) Mexico (n=86) Puerto Rico (n=30) USA (n=77)	Argentina (n=42) Brazil (n=36) Ecuador (n=40) Peru (n=37)
2024	None	China (n=232) India (n=39) Malaysia (n=65) Singapore (n=35) Taiwan (n=59) Turkey (n=107) Vietnam (n=143)	Australia (n=67)	Denmark (n=41) Italy (n=149) Norway (n=42) Portugal (n=67) Russia (n=666) Spain (n=325) Sweden (n=45) UK/EIRE (n=37)	Canada (n=143) Mexico (n=207) USA (n=101)	Brazil (n=49) Ecuador (n=32)

Table 3.2: Data presented for countries reporting ≥30 responses in surveys conducted from 2015 to 2024.

Survey	Profession				
	Optometrists	Ophthalmologists	Contact lens optician	Other	Did not state
2015	72.4% (n=698)	18.6% (n=180)	5.8% (n=56)	3.2% (n=31)	None
2019	72.5% (n=968)	19.6% (n=262)	6.7% (n=90)	1.2% (n=16)	None
2022	68.4% (n=2185)	23.0% (n=736)	6.1% (n=194)	2.4% (n=76)	0.1% (n=4)
2024	52.7% (n=1577)	41.1% (n=1230)	3.0% (n=90)	3.1% (n=92)	0.1% (n=4)

Table 3.3: Breakdown of respondents' professions for the surveys used from 2015 to 2024.

Survey	Principal working environment				
	Clinical practice	Academia	Industry	Other	Did not state
2015	84.4% (n=814)	11.3% (n=109)	1.6% (n=16)	2.7% (n=26)	None
2019	90.7% (n=1212)	5.1% (n=68)	2.1% (n=29)	2.1% (n=29)	None
2022	78.5% (n=2507)	7.6% (n=244)	5.2% (n=165)	8.5% (n=272)	0.2% (n=7)
2024	83.9% (n=2510)	5.8% (n=173)	3.1% (n=95)	6.3% (n=187)	0.9% (n=28)

Table 3.4: Breakdown of respondents' principal working environments for the surveys used from 2015 to 2024.

A comparison of the number of responses across the four surveys is presented in Table 3.1. Country-specific responses obtained from the four surveys are presented in Table 3.2.

Of the study participants in 2024, the majority were optometrists (52.7%, n=1577), followed by ophthalmologists (41.1%, n=1230), contact lens opticians (3.0%, n=90), and other types of eye care specialists (3.1%, n=92). The principal working environment for 83.9% (n=2510) of practitioners was clinical practice, 5.8% (n=173) worked in academia, 3.1% (n=95) worked within industry, and 6.3% (n=187) reported to work in other environments. Tables 3.3 and 3.4 show the breakdown for respondents' professions and principal working environments for surveys conducted from 2015 to 2024.

All study participants were registered eye care practitioners with a median number of years qualified of 11 to 20, with a normal distribution. This level of experience was consistent with the previous three surveys, where 11 to 20 years was the median number of years qualified also.

3.1.3a Self-reported concern about the increasing frequency of childhood myopia

Practitioners in Asia reported the greatest level of concern about the increasing frequency of childhood myopia; however, practitioners in South America showed similar levels of concern (8.6 ± 1.9 and 8.5 ± 1.9, respectively, $p=0.603$). Practitioners in Australasia reported a significantly lower level of concern than all other continents (7.7 ± 1.9, all $p<0.05$) with Europe and North America showing similar levels (8.1 ± 2.1 and 8.1 ± 2.0, respectively, $p=0.402$) (Figure 3.1).

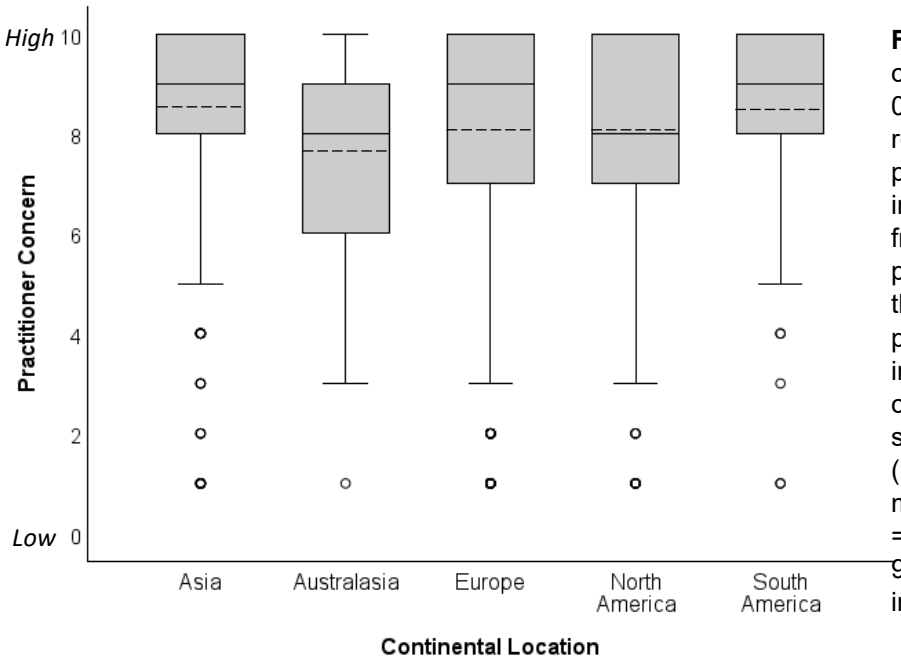


Figure 3.1: Level of concern (rated from 0 [low] to 10 [high]) regarding the perceived increasing frequency of paediatric myopia in their practice for practitioners located in different continents. Box = 1 standard deviation (SD); solid line = median; dashed line = mean; whiskers = 95% confidence interval.

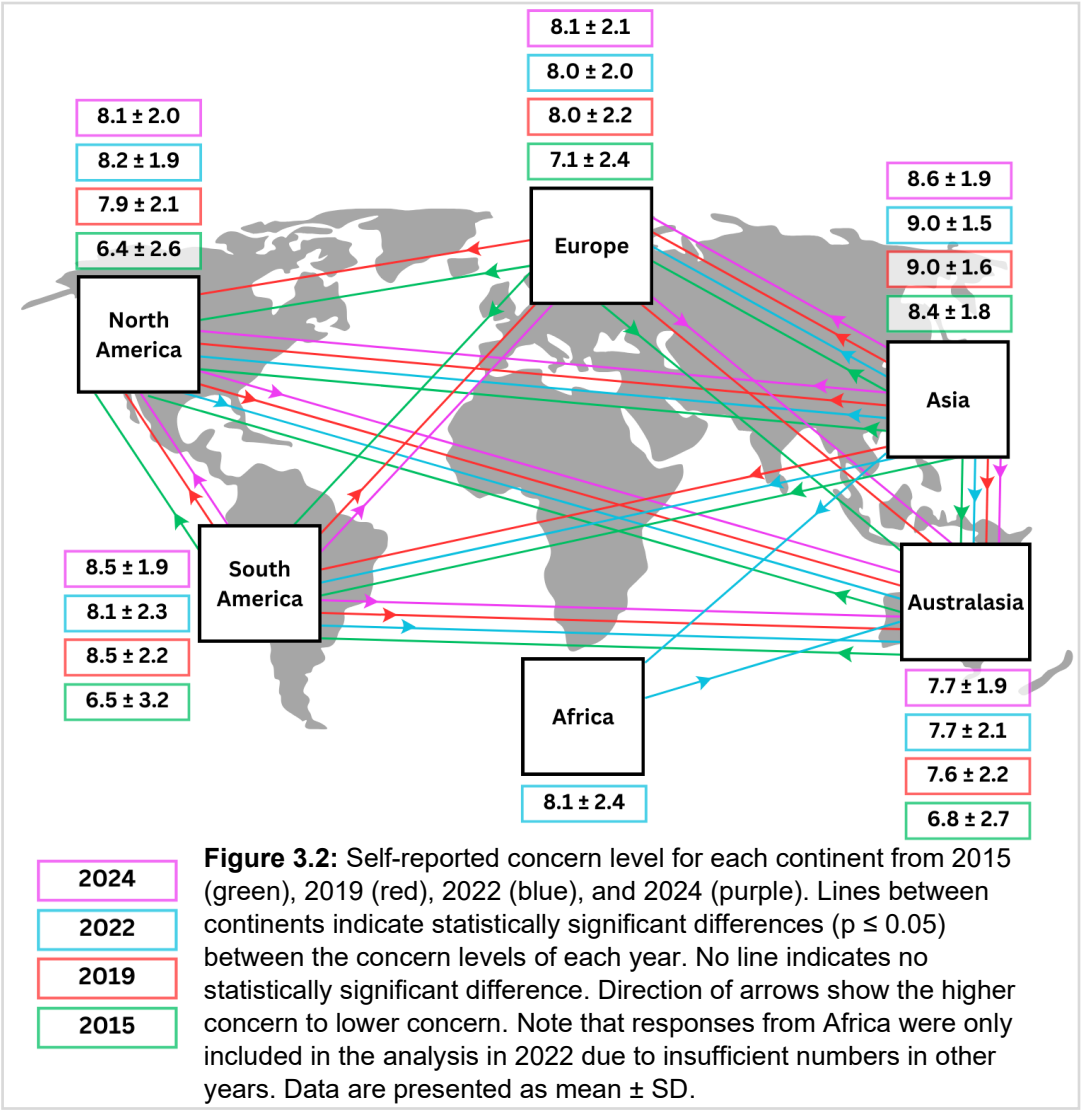


Figure 3.2: Self-reported concern level for each continent from 2015 (green), 2019 (red), 2022 (blue), and 2024 (purple). Lines between continents indicate statistically significant differences ($p \leq 0.05$) between the concern levels of each year. No line indicates no statistically significant difference. Direction of arrows show the higher concern to lower concern. Note that responses from Africa were only included in the analysis in 2022 due to insufficient numbers in other years. Data are presented as mean ± SD.

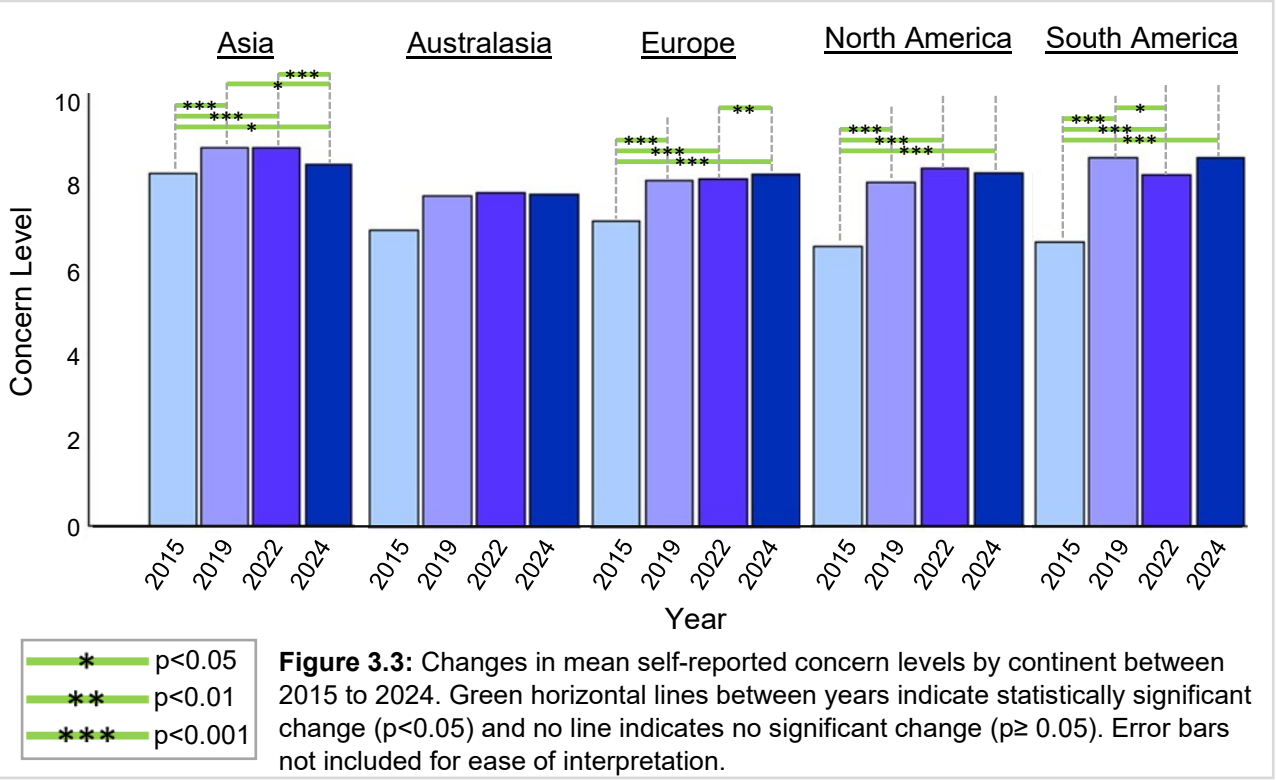


Figure 3.3: Changes in mean self-reported concern levels by continent between 2015 to 2024. Green horizontal lines between years indicate statistically significant change ($p<0.05$) and no line indicates no significant change ($p \geq 0.05$). Error bars not included for ease of interpretation.

This pattern of practitioner concern has been consistent over recent years; from 2015 to 2022, Asia had consistently showed a significantly greater level of concern about the increasing frequency of childhood myopia than all other continents analysed (all $p<0.05$, Figure 3.2). Conversely, practitioners in Australasia reported a statistically significant lower level of concern compared to all other continents since 2019 (all $p<0.05$), besides Europe in 2022 ($p=0.143$, Figure 3.2). All continents besides Australasia have shown a significant increase in the level of concern regarding the growing numbers of myopic children from 2015 to 2024, with the greatest shift in concern being in South America (Figure 3.3). Most recently, practitioners in all continents apart from Asia have reported consistent or increased concern from 2022 to 2024 (Figure 3.3), whereas practitioners in Asia have shown a significant reduction in concern level over this time despite having the greatest concern level overall.

3.1.3b Practitioners' perceived effectiveness of management options for myopia

Combination therapy was perceived to be the most effective management option overall (59.0 ± 27.9% expected level of reduction in childhood myopia progression), closely followed by orthokeratology (55.8 ± 25.2%), myopia control spectacles (52.3 ± 23.8%), and myopia control soft contact lenses (52.2 ± 24.0%) (all $p<0.001$). Undercorrection (7.1 ± 16.8%), single vision spectacles (16.7 ± 25.0%), single vision soft contact lenses (19.5 ± 26.2%), and light therapy (21.4 ± 25.4) were perceived to be the least effective options (all $p<0.001$). Continent-specific responses are presented in Table 3.5.

The worldwide changing perceptions of these correction and management techniques are presented in Figure 3.4. Of note, the perceived efficacy of orthokeratology as a myopia management method markedly increased by 12.6% ($p<0.001$) from 2015 to 2022, with little change from there onwards. The greatest change in perception was of soft contact lenses approved for myopia management, with the expected percentage expected level of reduction in childhood myopia progression more than doubling between 2015 and 2024 (24.4 ± 25.0% to 52.2 ± 24.0%, respectively, $p<0.001$). Although perceived to be the most effective management method in 2022 and 2024, the perceived efficacy of combination therapy by eye care practitioners has reduced by 9.7% since 2022 ($p<0.001$). Across the globe, the perceived effectiveness of single vision spectacles and single vision soft contact lenses in slowing myopia progression has increased significantly from 2015 to 2024, with the greatest increase seen in single vision soft contact lenses (10.0%, $p<0.001$).

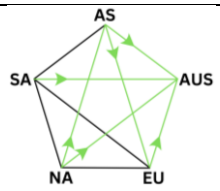
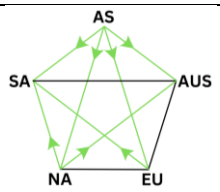
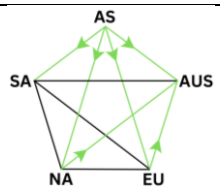
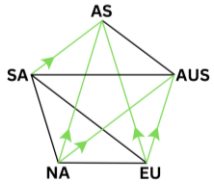
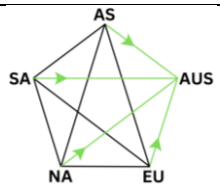
Technique \ Continent		Asia	Australasia	Europe	North America	South America	Significance Plot
Spectacles	Undercorrection	7.4 ± 15.7	0.1 ± 4.2	6.7 ± 16.6	9.4 ± 20.3	5.8 ± 13.8	
	Single Vision	18.1 ± 23.8	2.6 ± 8.0	15.4 ± 22.8	19.7 ± 30.7	21.8 ± 31.5	
	Bifocals	24.6 ± 21.4	13.8 ± 12.8	20.6 ± 21.8	22.6 ± 24.2	15.7 ± 20.0	
	Progressive Addition Lenses	27.6 ± 22.0	14.1 ± 10.9	23.9 ± 23.5	24.2 ± 25.8	21.4 ± 24.4	
	Approved MM	46.3 ± 21.7	47.5 ± 16.4	55.2 ± 23.6	53.5 ± 25.5	50.6 ± 27.9	
Contact Lenses	Rigid Contact Lenses	31.3 ± 28.2	10.4 ± 15.9	26.1 ± 28.5	22.5 ± 28.8	18.5 ± 26.9	
	Single Vision Soft	19.6 ± 24.7	3.6 ± 9.6	20.0 ± 25.2	20.7 ± 30.3	21.2 ± 30.8	
	Multifocal Soft	31.6 ± 23.2	30.0 ± 17.5	30.1 ± 24.5	31.7 ± 24.4	25.7 ± 29.0	
	Approved MM Soft	46.2 ± 22.5	50.5 ± 15.8	55.1 ± 23.7	52.8 ± 24.8	48.4 ± 28.7	

Table 3.5: Continued on next page.

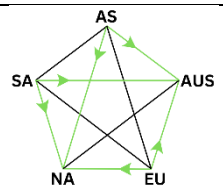
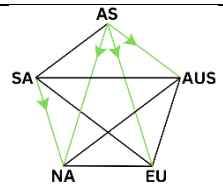
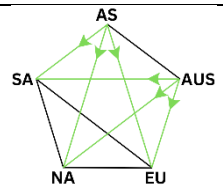
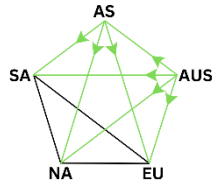
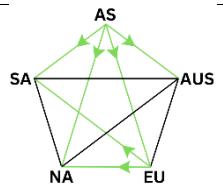
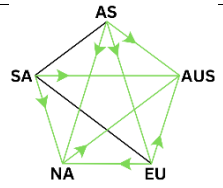
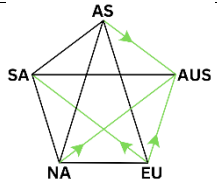
Technique \ Continent		Asia	Australasia	Europe	North America	South America	Significance Plot
Contact Lenses	Orthokeratology	56.2 ± 22.1	50.8 ± 16.4	59.1 ± 25.4	49.4 ± 26.7	45.6 ± 30.5	
Atropine	0.01%	41.4 ± 23.5	27.9 ± 21.7	41.7 ± 28.5	34.0 ± 25.9	42.6 ± 28.9	
	0.05%	48.0 ± 22.8	42.9 ± 18.5	41.7 ± 28.4	40.0 ± 24.8	46.0 ± 28.4	
	>0.05%	47.6 ± 28.2	49.5 ± 25.2	38.6 ± 29.8	38.0 ± 27.7	38.9 ± 31.4	
Light Therapy		31.6 ± 27.5	48.3 ± 28.0	16.7 ± 22.3	20.0 ± 25.8	19.4 ± 26.5	
Combination Therapy		64.2 ± 23.7	58.9 ± 19.9	60.0 ± 29.0	50.6 ± 28.8	50.6 ± 29.8	
Alternating Treatments		36.3 ± 29.1	27.7 ± 25.0	37.5 ± 31.5	37.2 ± 30.6	31.0 ± 32.6	
Increased Time Outdoors		48.1 ± 26.6	26.2 ± 19.5	41.9 ± 28.3	38.1 ± 30.4	47.5 ± 30.3	

Table 3.5: Perceived effectiveness (% reduction myopia progression) in 2024 of myopia management options across continents. Data are expressed as mean ± SD. Green lines in significance plots represent significant differences ($p<0.05$) and black lines represent no significant difference ($p\geq0.05$). Arrows direct higher percentage to lower percentage. MM = myopia management. AS = Asia, AUS = Australasia, EU = Europe, NA = North America, SA = South America. For each continent, the technique considered to be the least effective is shaded in orange and the most effective is shaded in green.

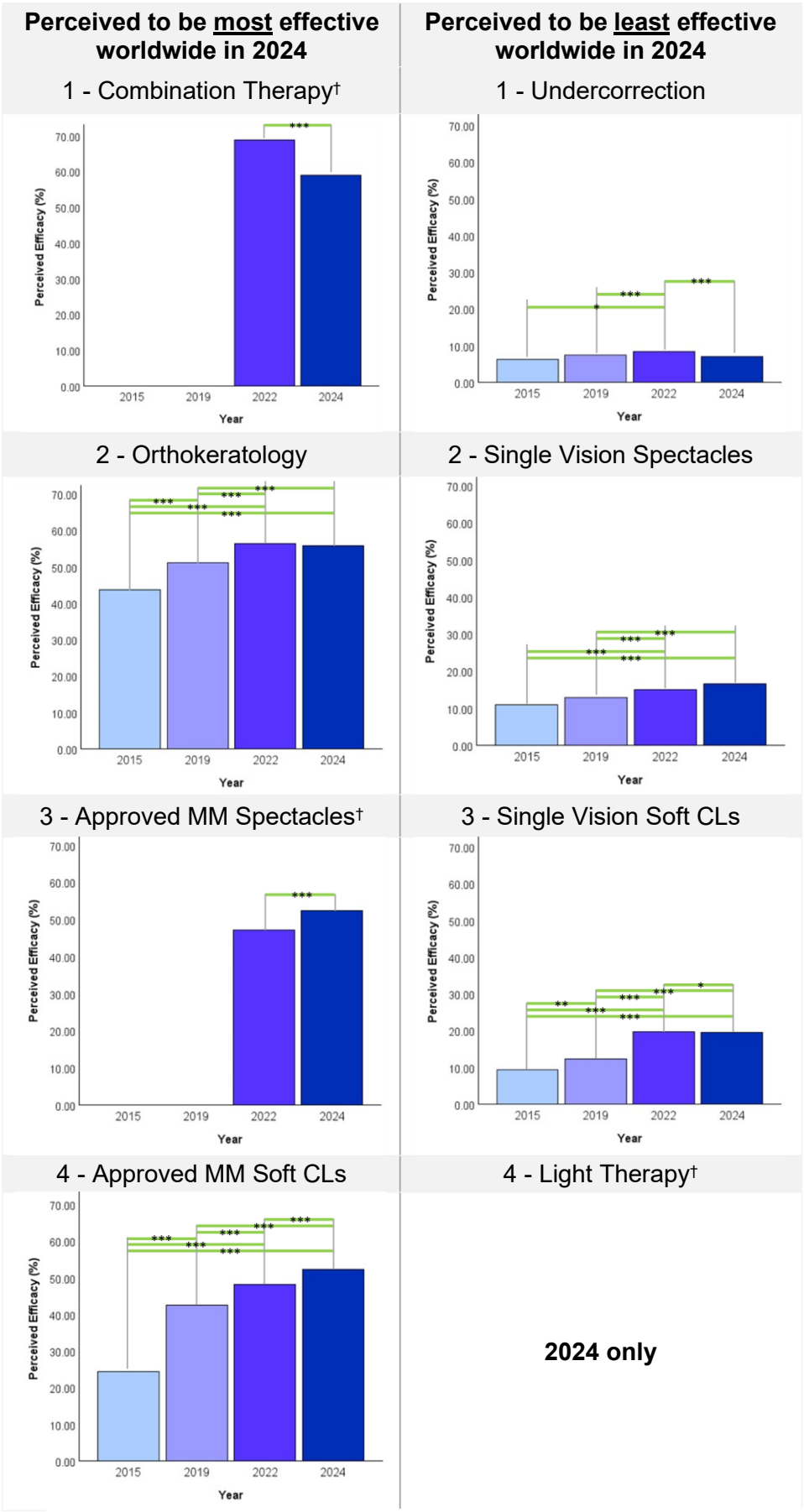


Figure 3.4: Worldwide changes of the four myopia management/correction options perceived to be the most and least efficacious techniques to slow myopia progression. Green horizontal lines between years indicate statistically significant change ($p<0.05$) and no line indicates no significant change ($p \geq 0.05$). Error bars not included for ease of interpretation. Options marked with † were not present in every survey since 2015.

3.1.3c Practitioners' perceived level of clinical activity in myopia management

In 2024, the most active ratings were from practitioners in Australasia (8.2 ± 2.0), Asia (7.9 ± 2.3), and South America (7.7 ± 2.6), with no significant difference between these three continents (all p>0.05, Figure 3.5). Europe and North America reported lower levels of clinical activity in myopia management (7.4 ± 2.4 and 7.1 ± 2.6, respectively, p=0.101).

Since 2015, practitioners in Asia have consistently perceived themselves to have a high level of clinical activity in myopia management, being significantly greater than all continents in 2015 and all continents besides Australasia in 2019 and 2022 (Figure 3.6). Conversely, the perceived level of clinical activity of practitioners in South America had notably increased in 2024 when compared to previous years; in 2022, practitioners in South America reported a significantly lower activity level than all other continents (all p<0.005, Figure 3.6), whereas responses of 2024 showed an activity level close to that of practitioners in Asia.

Every continent analysed since 2015 has shown an increasing level of clinical activity in myopia management from 2015 to 2024 (Figure 3.7). Practitioners in North America appear to have had the greatest increase over the 9-year period, from 4.7 ± 3.0 in 2015 to 7.1 ± 2.6 in 2024 (p<0.001) (Figure 3.7). Practitioners in Asia have shown the most consistent level of clinical activity over this time, with a small yet significant increase of 0.4 on the 10-point scale (p=0.001).

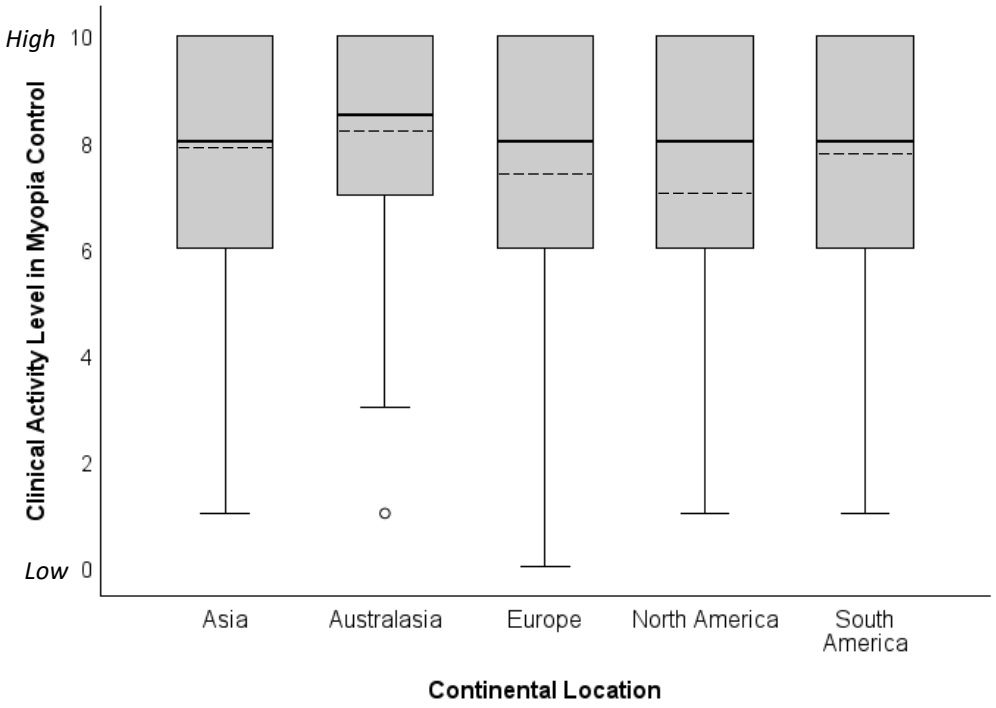


Figure 3.5: Perceived level of clinical activity in myopia control (rated from 0 [low] to 10 [high]) for practitioners located in different continents. Box = 1 SD; solid line = median; dashed line = mean; whiskers = 95% confidence interval.

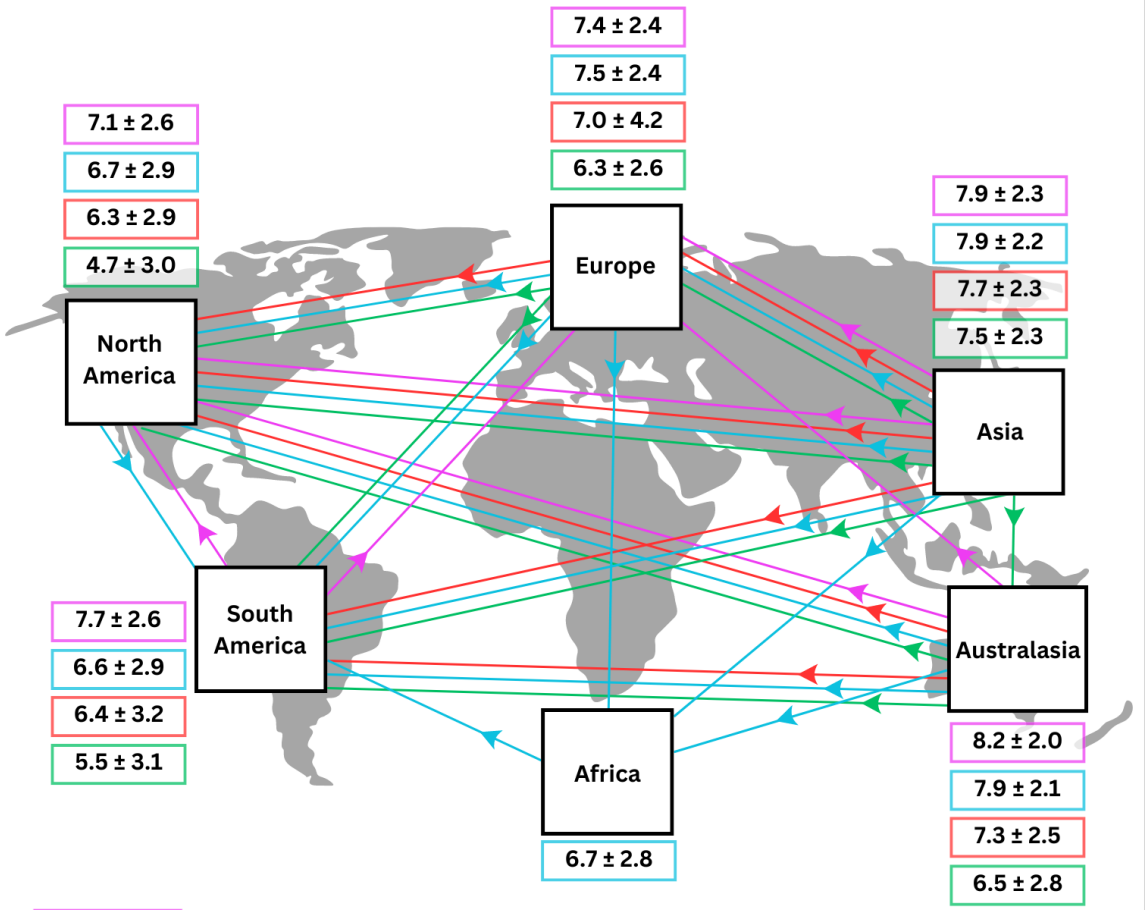


Figure 3.6: Self-reported activity level for each continent from 2015 (green), 2019 (red), 2022 (blue), and 2024 (purple). Lines between continents indicate statistically significant differences ($p \leq 0.05$) between the concern levels of each year. No line indicates no statistically significant difference. Note that responses from Africa were only included in the analysis in 2022 due to insufficient numbers in other years. Direction of arrows show the higher activity to lower activity. Data are presented as mean ± SD.

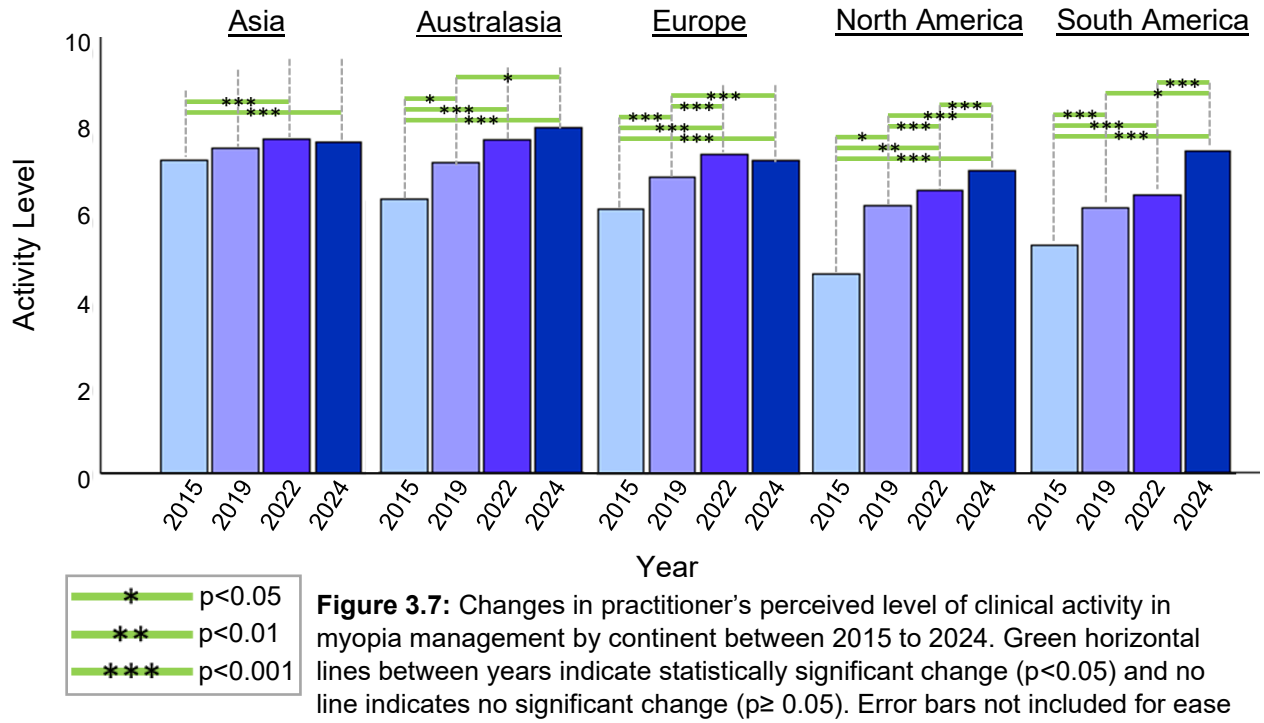


Figure 3.7: Changes in practitioner's perceived level of clinical activity in myopia management by continent between 2015 to 2024. Green horizontal lines between years indicate statistically significant change ($p<0.05$) and no line indicates no significant change ($p \geq 0.05$). Error bars not included for ease of interpretation.

3.1.3d Practitioners' access to instrumentation

Across the world in 2024, 69.3% of eye care practitioners reported having access to measure cycloplegic refractive error, 93.8% reported access to measure autorefraction, 86.3% reported access to measure corneal curvature, and 55.7% reported access to measure axial length (all p<0.001). The results and differences between continents are presented in Table 3.6.

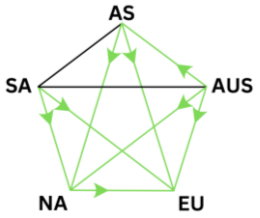
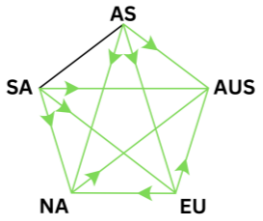
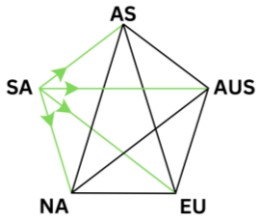
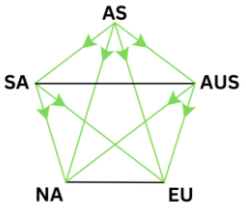
Measure \ Continent	Asia	Australasia	Europe	North America	South America	Significance Plot
Cycloplegic Refractive Error	85.7%	95.7%	56.4%	72.4%	85.0%	
Autorefraction	97.6%	78.7%	93.5%	90.8%	98.0%	
Corneal Curvature	87.3%	83.0%	84.5%	88.7%	95.2%	
Axial Length	81.6%	64.9%	45.6%	42.6%	67.3%	

Table 3.6: Percentage of practitioners with reported access to measure each of the listed ocular measurements in their clinical practice by continent. Green lines in significance plots represent significant differences (p<0.05) and black lines represent no significant difference (p≥0.05). Arrows direct higher percentage to lower percentage. AS = Asia, AUS = Australasia, EU = Europe, NA = North America, SA = South America.

3.1.3e Frequency of prescribing different myopia management methods by practitioners

Among all available prescribing options, single vision spectacles were the most frequently prescribed primary correction option for myopic children globally in 2024 (32.8 ± 30.7%, p<0.001), followed by myopia control spectacles (16.36 ± 21.4%, p<0.001). Consistent with the findings of Chapter 2, the tendency to prescribe single vision spectacles over any other option was not consistent between the continents; practitioners in Asia and South America prescribed single vision spectacles most often, whereas practitioners in Australasia

prescribed myopia control spectacles more frequently than they did single vision spectacles (Table 3.7).

Across the world, single vision soft contact lenses were prescribed more frequently than daily disposable and reusable soft contact lenses approved for myopia control (8.1 ± 12.4%, 7.8 ± 13.1%, and 3.3 ± 7.5%, respectively, all $p<0.05$); however, practitioners in Australasia and Europe deviated from this prescribing pattern (Table 3.7), opting to prescribe myopia control soft daily disposable contact lenses more frequently. Notably, practitioners in all continents prescribed daily disposable myopia control soft contact lenses more often than those of the reusable modality. Lower concentrations of atropine were more frequently prescribed than higher concentrations in 2024, with a frequency of 5.6 ± 13.3% for atropine 0.01%, 3.3 ± 9.6% for atropine 0.05%, and 0.9% ± 5.1% for atropine >0.05% (all $p<0.05$). This pattern was consistent across every continent (Table 3.7). A small percentage of practitioners across the world prescribed combination therapy, at 3.4 ± 8.7% averaged globally. However, this percentage significantly varied between continents; in particular, practitioners in Australasia prescribed combination therapy approximately double the worldwide average (Table 3.7). All results from 2024 are presented in Table 3.7.

When assessed globally over time, there was a significant reduction in the frequency of prescribing single vision spectacles as the primary correction option to young myopic patients across the world between 2015 and 2024 (-11.1%, $p<0.001$, Figure 3.8). However, a slight although statistically significant increase was found from 2022 to 2024 (+3.0%, $p=0.003$). No significant difference was identified in the frequency of prescribing spectacle lenses and soft contact lenses specifically indicated for myopia management between 2022 and 2024 (Figure 3.8). Despite this, a notable increased frequency in prescribing myopia management soft contact lenses between 2015 and 2024 was identified, from 1.9 ± 7.6% to 7.8 ± 13.1%, respectively ($p<0.001$). Other global changes with time of management options perceived to be the most effective or the most frequently prescribed are presented in Figure 3.8.

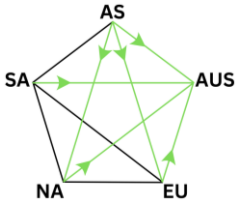
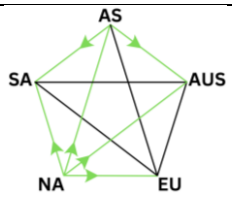
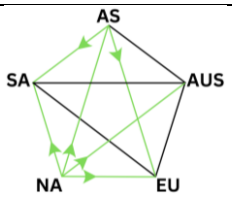
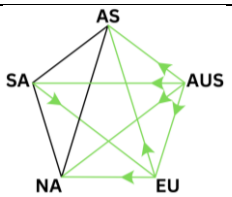
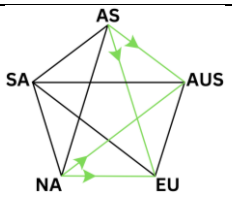
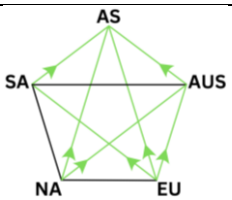
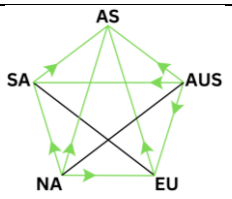
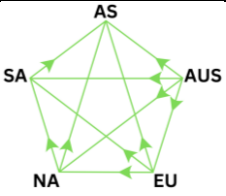
Technique \ Continent		Asia	Australasia	Europe	North America	South America	Significance Plot
Spectacles	Single Vision	39.0 ± 34.6	17.8 ± 24.3	30.1 ± 28.2	33.4 ± 29.6	37.0 ± 34.3	
	Bifocals	1.6 ± 5.3	0.6 ± 2.3	1.8 ± 6.9	3.9 ± 8.5	1.3 ± 4.2	
	Progressive Addition Lenses	3.6 ± 10.8	3.0 ± 11.9	2.2 ± 7.3	5.8 ± 11.5	3.0 ± 10.1	
	Approved MM	14.1 ± 20.3	22.9 ± 24.3	16.9 ± 20.0	16.5 ± 23.7	17.0 ± 26.3	
Contact Lenses	Rigid Contact Lenses	1.5 ± 2.7	0.5 ± 2.7	0.8 ± 3.2	1.6 ± 5.4	1.4 ± 4.5	
	Single Vision Soft	2.4 ± 7.0	5.0 ± 8.5	10.5 ± 13.5	10.1 ± 13.1	8.4 ± 11.9	
	Multifocal Soft	0.8 ± 2.7	3.4 ± 5.7	2.0 ± 5.6	3.4 ± 7.8	2.7 ± 7.6	
	Approved MM Soft Daily Disposable	2.1 ± 6.1	13.0 ± 10.5	10.7 ± 15.3	7.5 ± 11.7	4.6 ± 9.8	

Table 3.7: Continued on the following page.

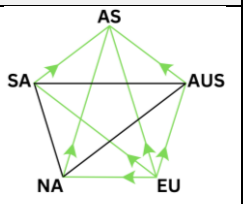
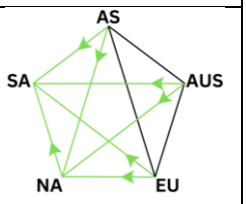
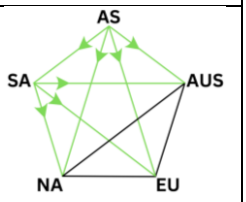
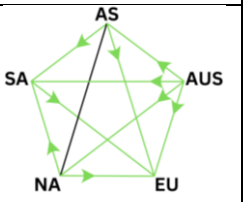
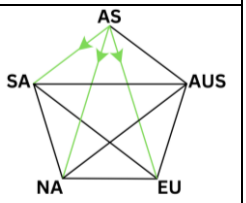
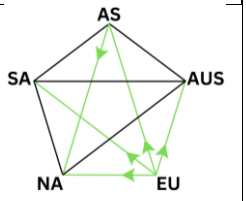
Technique \ Continent		Asia	Australasia	Europe	North America	South America	Significance Plot
Contact Lenses	Approved MM Soft Reusable	0.8 ± 3.7	3.2 ± 6.7	4.8 ± 8.2	2.8 ± 7.7	2.7 ± 9.8	
	Orthokeratology	6.6 ± 11.5	8.9 ± 12.3	10.4 ± 17.7	4.4 ± 10.5	2.7 ± 11.8	
Atropine	0.01%	13.5 ± 18.7	3.9 ± 8.6	2.1 ± 7.1	2.5 ± 7.7	12.6 ± 23.7	
	0.05%	6.1 ± 14.0	8.7 ± 11.3	1.2 ± 5.5	4.3 ± 9.5	3.1 ± 8.0	
	>0.05%	1.9 ± 8.5	1.1 ± 4.5	0.5 ± 3.4	0.4 ± 2.6	0.8 ± 4.2	
Light Therapy		1.7 ± 7.6	1.3 ± 6.3	2.6 ± 7.9	1.1 ± 6.6	1.3 ± 6.5	
Combination Therapy		4.5 ± 9.9	6.8 ± 8.7	3.4 ± 8.9	2.1 ± 6.3	1.5 ± 4.3	

Table 3.7: Frequency of prescribing myopia correction options (in percent) for progressing / young myopes by practitioners in different continents in 2024. MM = myopia management. Data are expressed as mean ± SD. Green lines in significance plots represent significant differences between continents ($p<0.05$) and black lines represent no significant difference ($p\geq0.05$). Arrows direct higher percentage to lower percentage. AS = Asia, AUS = Australasia, EU = Europe, NA = North America, SA = South America. For each continent, the option most frequently prescribed is shaded in green and the least frequently prescribed is shaded in orange.

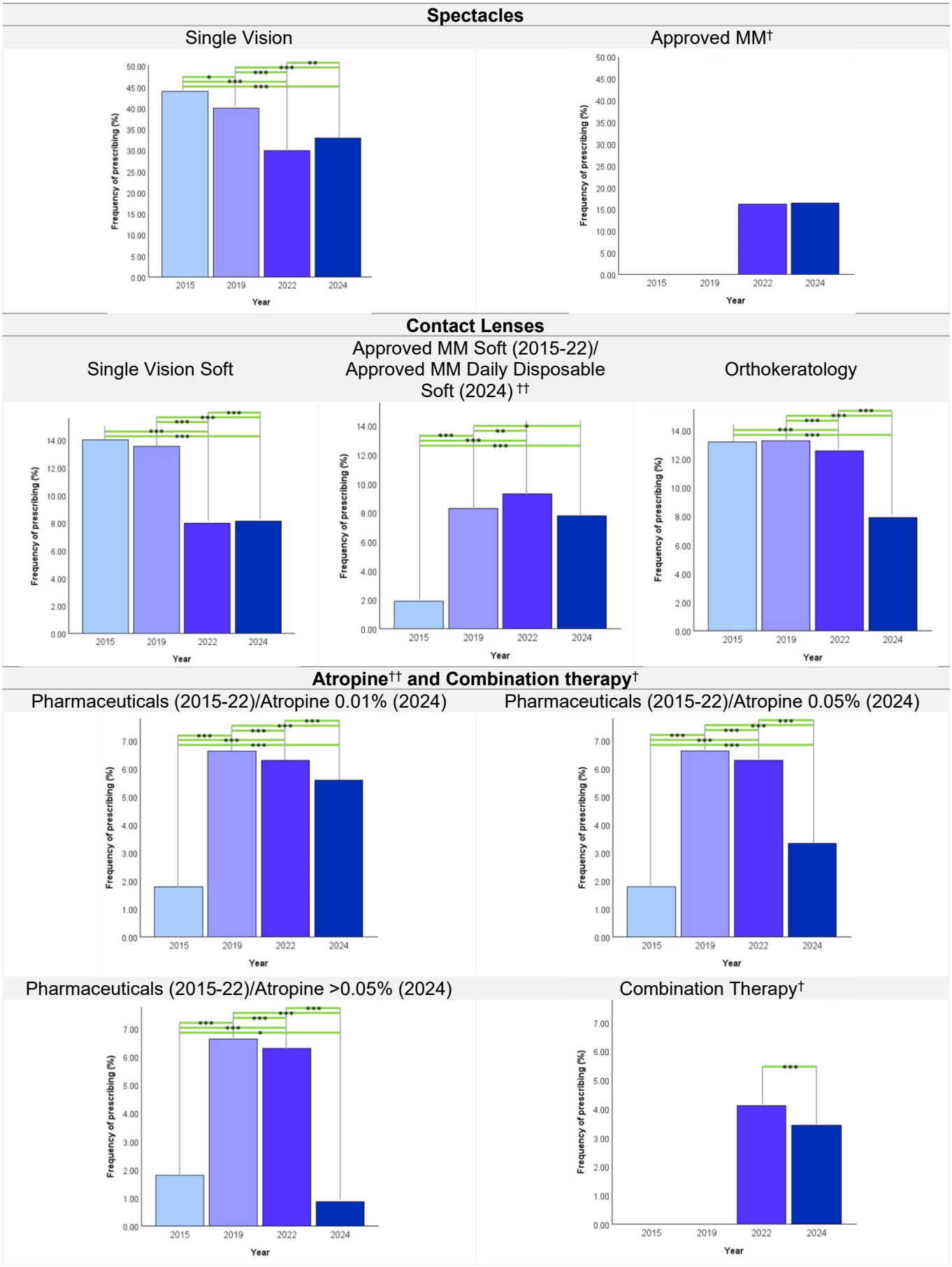


Figure 3.8: Changes in the worldwide averaged frequency of prescribing myopia correction options (%) for young myopes by practitioners from 2015 to 2024. MM = myopia management. Green horizontal lines indicate a significant difference ($p<0.05$) and no line indicates no significant difference ($p\geq0.05$). Error bars not included for ease of interpretation. Options marked with † were not present in every survey since 2015, and options marked with †† differed in wording in the 2024 survey (i.e. 'Pharmaceuticals' was listed in surveys from 2015 to 2022, whereas the different concentrations of atropine were listed in the 2024 survey, all presented above). Note that y-axis scales differ for spectacles, contact lenses, and atropine/combination therapy.

3.1.3f Minimum age of prescribing myopia management options by practitioners

Overall, the minimum patient age for prescribing the different myopia correction and management options was lowest for spectacles (5.3 ± 1.7 years, with 2.5% of all respondents choosing to not prescribe this option). This was followed by atropine (6.1 ± 2.3 years, 28.4% would not prescribe), light therapy (6.4 ± 2.9 years, 49.0% would not prescribe), daily disposable soft contact lenses (8.9 ± 3.6 years, 12.4% would not prescribe), and rigid contact lenses (10.0 ± 3.7 years, 26.5% would not prescribe). Of the six options provided, practitioners on average felt children needed to be oldest to receive reusable soft contact lenses, with a minimum age of 10.4 ± 3.6 years (12.4% would not prescribe). However, the minimum average ages considered necessary by practitioners to prescribe each option varied significantly between continents (Table 3.8). Similarly, there were significant changes in the averaged minimum ages globally since 2015 (Figure 3.9); in particular, practitioners were willing to prescribe pharmaceuticals such as atropine to myopic children of a younger age in 2024 than first reported in 2015 (6.1 ± 2.3 and 6.9 ± 2.7 years, respectively, $p<0.001$) (Figure 3.9B).

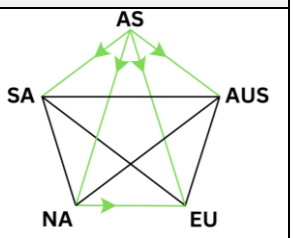
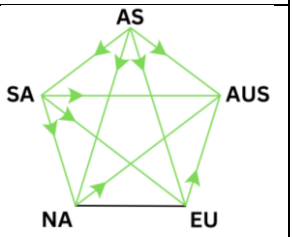
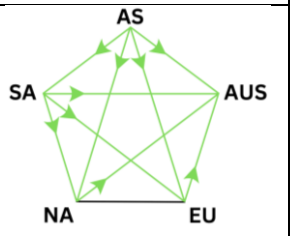
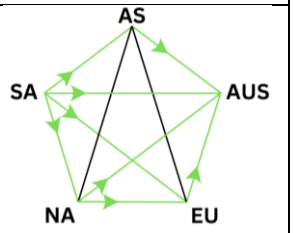
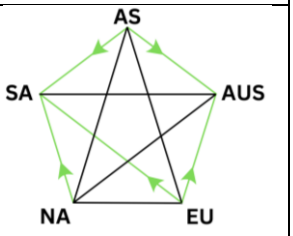
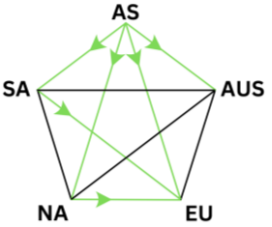
Technique \ Continent	Asia	Australasia	Europe	North America	South America	Significance Plot
Spectacles	5.8 ± 2.0 (6.0%)	5.3 ± 0.9 (0.0%)	5.1 ± 1.6 (1.1%)	5.4 ± 1.6 (2.3%)	5.6 ± 2.2 (1.4%)	
Daily Disposable Soft Contact Lenses	10.7 ± 3.6 (17.2%)	7.5 ± 2.1 (2.1%)	8.3 ± 3.0 (2.2%)	8.7 ± 3.4 (2.1%)	9.7 ± 3.4 (4.1%)	
Reusable Soft Contact Lenses	11.7 ± 3.7 (24.5%)	8.9 ± 3.0 (10.6%)	10.0 ± 3.5 (6.4%)	10.1 ± 3.8 (12.6%)	10.7 ± 3.5 (11.6%)	
Rigid Contact Lenses	10.0 ± 3.5 (23.3%)	8.6 ± 3.4 (24.5%)	9.7 ± 3.6 (27.3%)	10.6 ± 4.0 (27.6%)	11.6 ± 4.0 (31.3%)	
Atropine	6.2 ± 2.0 (11.5%)	5.5 ± 1.0 (13.8%)	6.0 ± 2.7 (39.9%)	6.3 ± 2.7 (25.9%)	5.7 ± 1.8 (18.4%)	
Light Therapy	7.2 ± 3.0 (46.4%)	6.1 ± 2.0 (70.2%)	5.8 ± 2.7 (45.5%)	6.9 ± 3.2 (57.8%)	6.3 ± 2.0 (52.4%)	

Table 3.8: Minimum patient age considered necessary by practitioners (from different continents) who prescribed these options for different myopia correction options. Data are expressed as mean ± SD years (% that would not prescribe this refractive modality). Green lines in significance plots represent significant differences ($p<0.05$) and black lines represent no significant difference ($p\geq0.05$). Arrows direct higher age to lower age. AS = Asia, AUS = Australasia, EU = Europe, NA = North America, SA = South America.

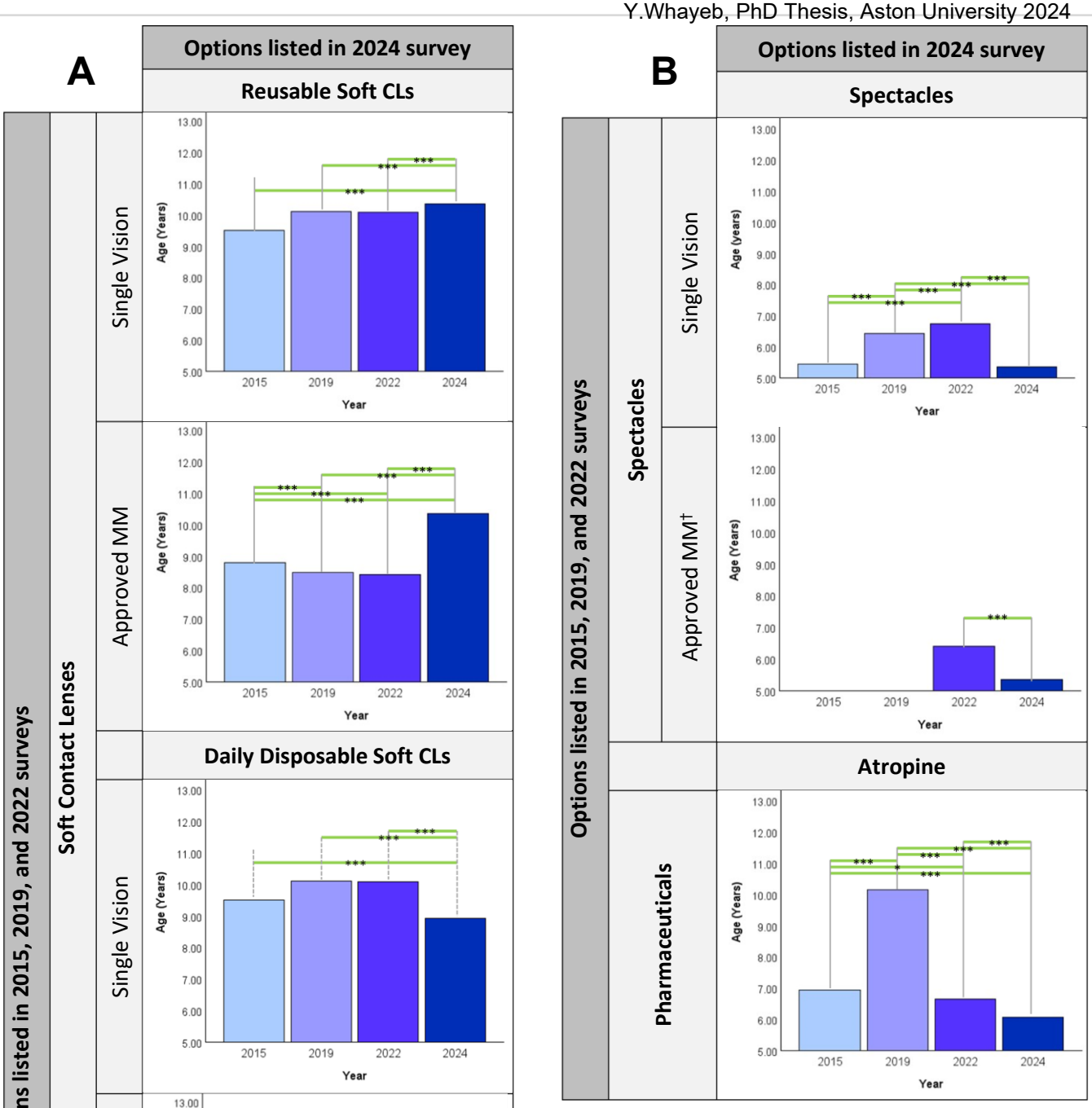


Figure 3.9: Minimum patient age (in years) considered necessary by practitioners who prescribed these options for different myopia correction options between 2015 to 2024, averaged globally.

Besides rigid contact lenses, the correction/management options listed in the 2024 survey (A: reusable soft contact lenses, daily disposable soft contact lenses, B: spectacles, and atropine) differed to the previous surveys, so here are compared with the specific spectacle, soft contact lens, and pharmaceutical options previously presented in the 2015, 2019, and 2022 surveys. MM = myopia management.

Horizontal green lines indicate statistically significant change ($p \geq 0.05$) and no line indicates no significant change. Error bars not included for ease of interpretation. Options marked with † were not present in every survey since 2015.

3.1.3g Minimum degree of myopia to begin myopia management

In 2024 alone, the minimum degree of myopia present in a child to warrant adoption of a myopia control approach was of no significant difference between all continents besides Australasia; practitioners in Australasia on average chose to introduce a myopia management approach to children with lower levels of myopia (Figure 3.10).

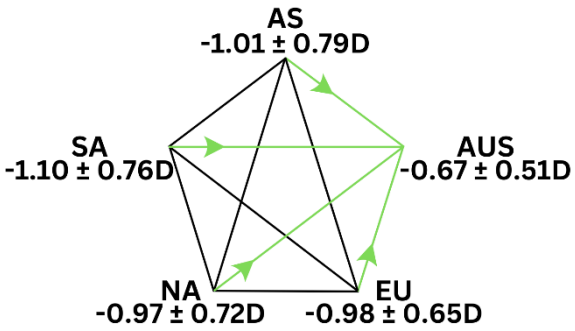


Figure 3.10: The minimum degree of myopia present in a child to warrant beginning myopia management, presented as a significance plot between continents. Data are expressed as mean ± SD. Green lines in significance plots represent significant differences ($p<0.05$) and black lines represent no significant difference ($p\geq0.05$). Arrows direct higher level of myopia to lower level. AS = Asia, AUS = Australasia, EU = Europe, NA = North America, SA = South

Since 2022, the global average had remained consistent, with a minimum degree of -1.01 ± 0.71D in 2022 and -0.98 ± 0.70D in 2024 ($p=0.052$). Significant differences in this time were only present in North America and South America, with significant lower levels of myopia seen to necessitate myopia management in 2024 in comparison to 2022 (Table 3.9).

Continent	2022	2024	P value
Asia	-0.97 ± 0.70	-1.01 ± 0.79	0.824
Australasia	-0.64 ± 0.34	-0.67 ± 0.51	0.645
Europe	-0.97 ± 0.63	-0.98 ± 0.65	0.906
North America	-1.21 ± 0.81	-0.97 ± 0.72	<0.001
South America	-1.37 ± 0.81	-1.10 ± 0.76	<0.001

Table 3.9: The minimum degree of myopia present in a child to warrant beginning myopia management by continent in 2022 and 2024. P-values represent significance in change with time from 2022 to 2024. Significant changes ($p<0.05$) are shaded in green). Data are expressed as mean ± SD.

3.1.3h Minimum level of myopia progression that necessitates myopia management

The median level of myopia progression that warranted myopia management in 2024 was the same in all continents (i.e., 0.51-0.75D/year) besides Australasia (i.e., 0.26-0.50D/year); the latter difference was statistically significant ($p<0.001$).

From 2015 to 2024, the median minimum level of myopia progression that practitioners reported warrants myopia management has significantly decreased in every continent (all $p<0.05$, Figure 3.11).

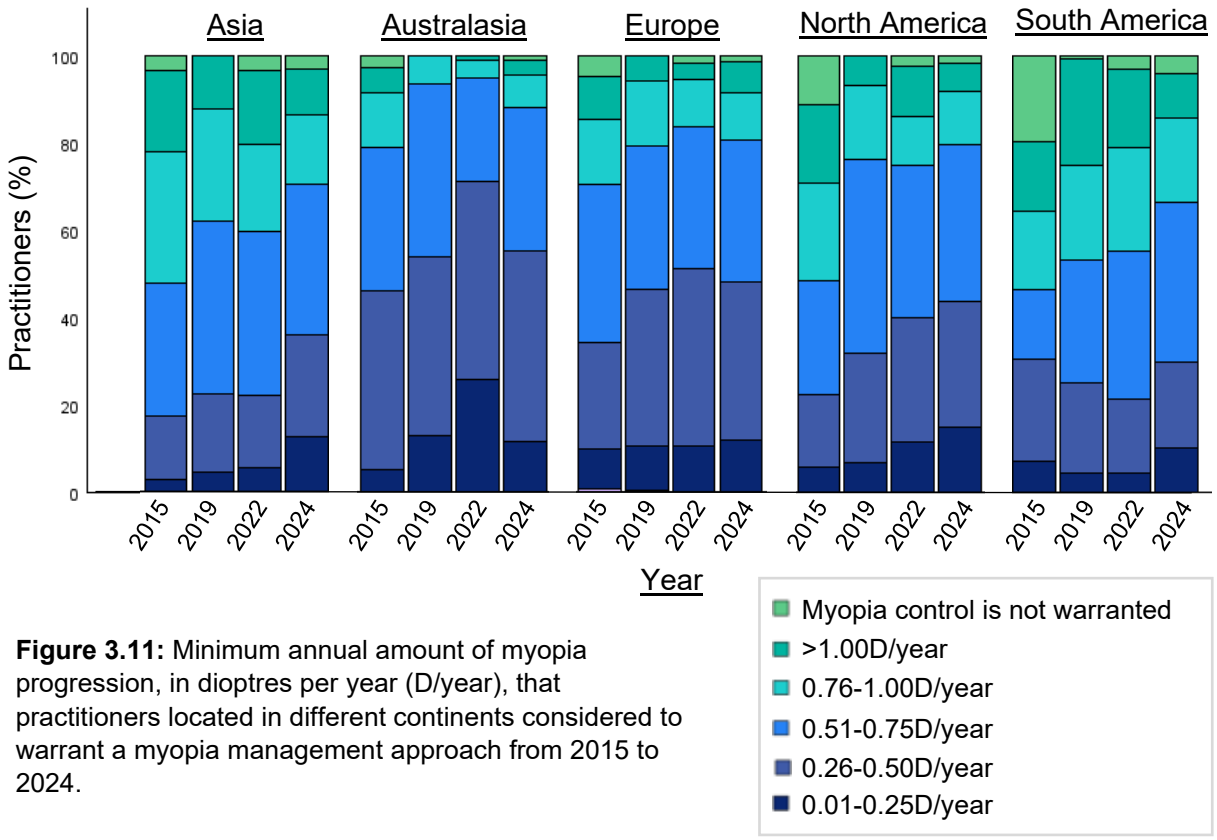


Figure 3.11: Minimum annual amount of myopia progression, in dioptres per year (D/year), that practitioners located in different continents considered to warrant a myopia management approach from 2015 to 2024.

3.1.3i Using undercorrection as a strategy to control myopia

Most practitioners did not use undercorrection as a strategy to manage myopia in 2024, with 82.8% responding the never undercorrect their young myopic patients. Worldwide, 2.1% of practitioners always use undercorrection as a method of myopia control, and 15.1% use it sometimes. The use of undercorrection varied significantly between continents; Australasia had the lowest proportion of practitioners who used undercorrection, and Asia had the highest (Table 3.10).

The use of undercorrection as a myopia management method has significantly declined since 2015 in all continents (all $p<0.05$) besides Asia, which has remained consistent over the nine-year period ($p=0.360$, Figure 3.12). Between 2022 and 2024, figures in Australasia and Europe did not change significantly (both $p>0.05$), whereas the use of undercorrection either always or sometimes significantly decreased in North America and South America (both $p<0.001$).

Continent / Frequency	Asia	Australasia	Europe	North America	South America	Significance Plot
Never	78.6	98.9	85.5	79.4	81.6	
Sometimes	18.6	1.1	12.6	19.1	15.0	
Always	2.8	0.0	1.9	1.5	3.4	

Table 3.10: Percentage of practitioners who never, sometimes, and always use undercorrection as a strategy to manage young myopic patients in 2024, presented by continental location. Green lines in significance plots represent significant differences ($p<0.05$) and black lines represent no significant difference ($p\geq0.05$). Arrows direct continents with a higher percentage of practitioners who use undercorrection as a myopia management method to continents with a lower percentage. AS = Asia, AUS = Australasia, EU = Europe, NA = North America, SA = South America.

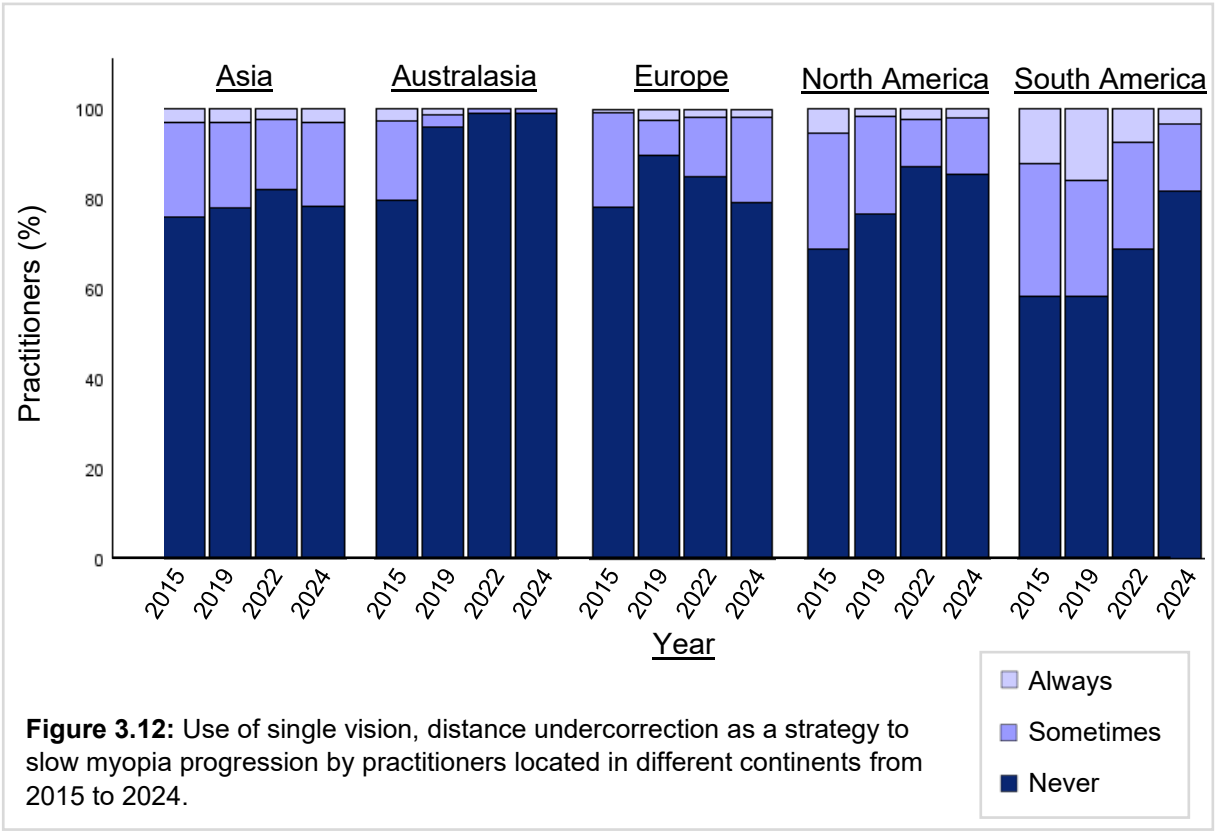


Figure 3.12: Use of single vision, distance undercorrection as a strategy to slow myopia progression by practitioners located in different continents from 2015 to 2024.

3.1.3j Reasons for not prescribing an alternative method to single vision correction

Over half of respondents in South America (60.5%) and Asia (55.8%) reported one or more reasons for prescribing single vision correction to young myopic patients instead of a myopia management option in 2024. This was followed by 49.3% of respondents in North America, 38.8% in Europe, and 26.6% in Australasia. Worldwide, 4.4% of practitioners thought myopia management options were not effective and 4.5% were concerned by unpredictable outcomes. The risk-benefit ratio, safety concerns, and additional chair time

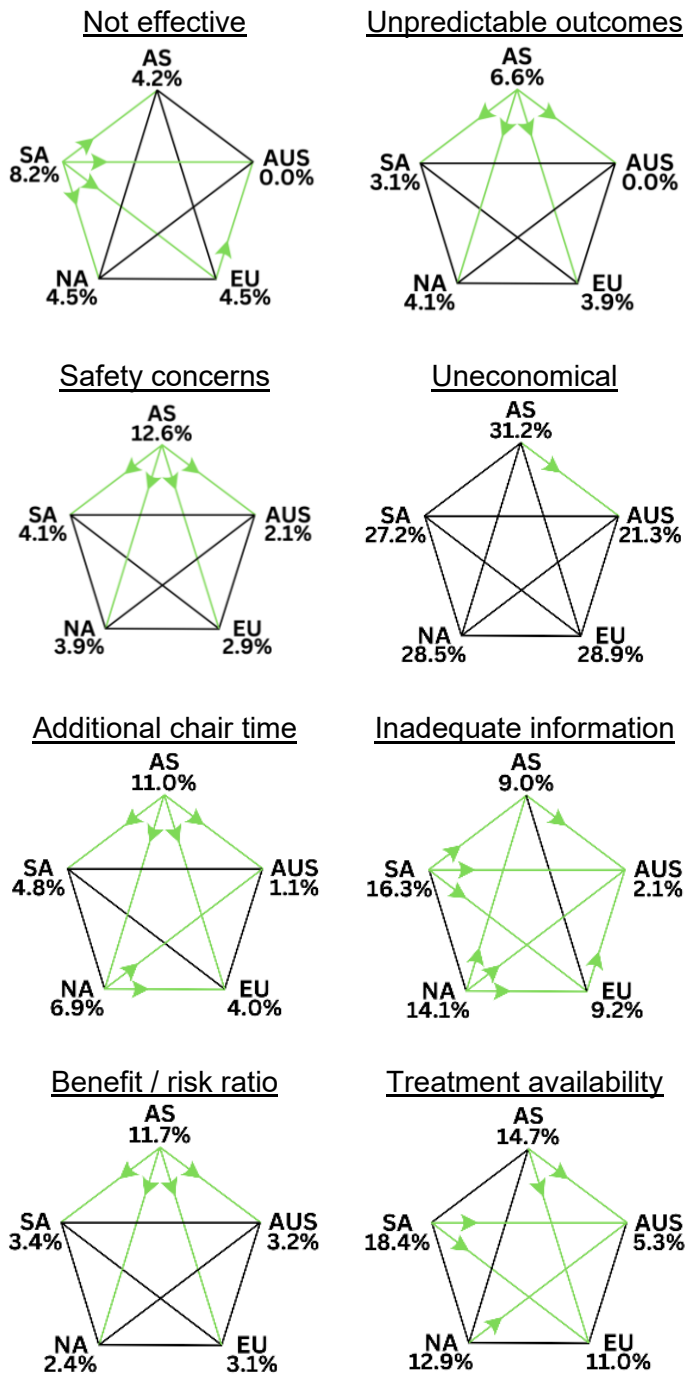


Figure 3.13: Significance plots of factors cited by practitioners in different continents for not adopting myopia control approaches in 2024 (percentage of practitioners). Green lines represent significant differences ($p<0.05$) and black lines represent no significant difference ($p\geq0.05$). Arrows direct a higher percentage of practitioners to a lower percentage. AS = Asia, AUS = Australasia, EU = Europe, NA = North America, SA = South America.

were of similar concern to practitioners, at 5.2%, 5.6%, and 6.2%, respectively. Inadequate information and treatment availability were of greater concern, with 10.2% and 12.5% of practitioners reporting these as reasons for not prescribing myopia management, respectively. Cost to the patient was of the greatest concern across the world, at 29.1%. Figure 3.13 presents the between-continent analysis of the reasons hindering practitioners from prescribing myopia intervention in 2024. Practitioners in Asia were significantly more concerned about safety, additional chair time, and the risk-benefit ratio than all other continents. Further, all continents showed similar concerns regarding the additional cost of myopia management to the patient; only practitioners in Australasia had statistically significantly less concern about this factor than practitioners in Asia (Figure 3.13).

From 2015 to 2022, the distribution of practitioners' reasons for not prescribing myopia management significantly differed across each continent (all $p<0.05$), and remained the same between 2022 and 2024 (all $p>0.05$) (Figure 3.14).

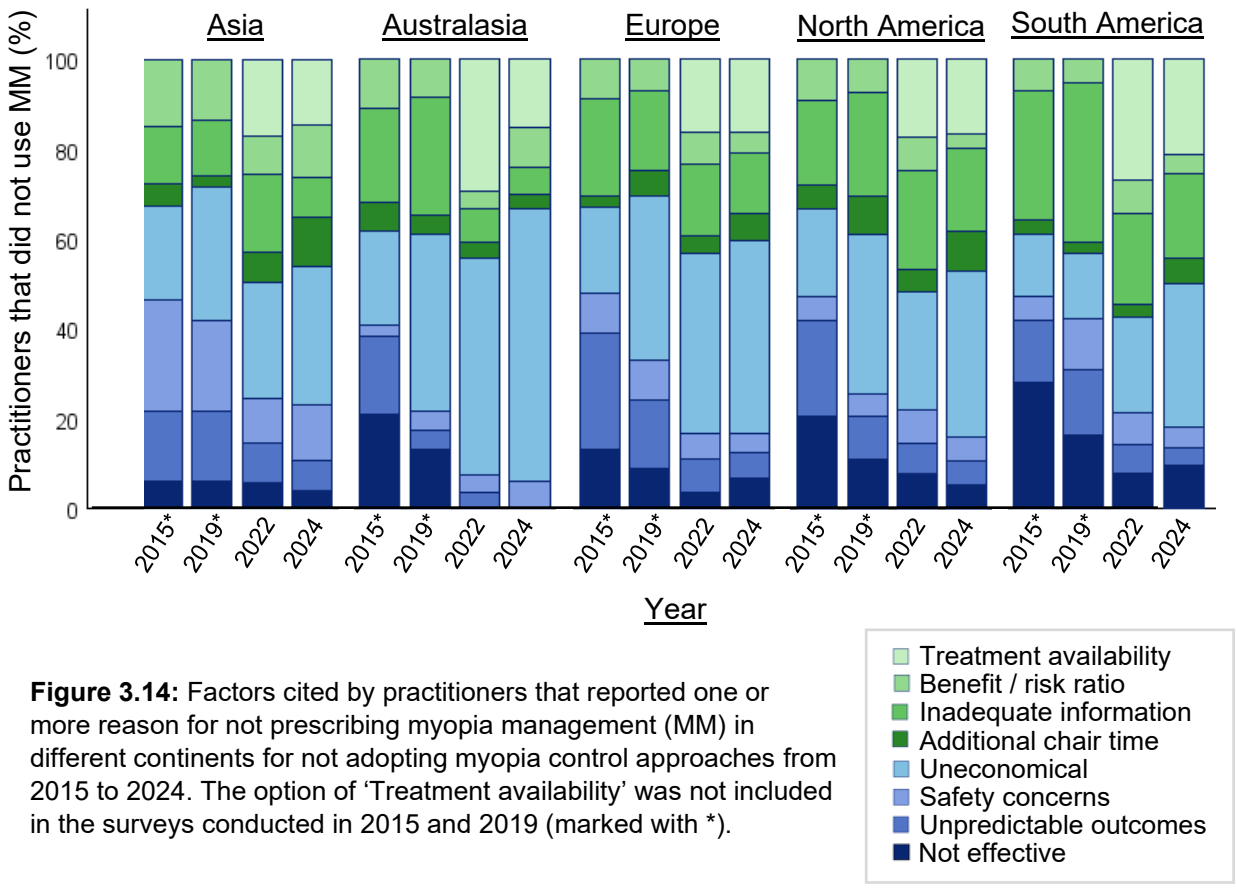


Figure 3.14: Factors cited by practitioners that reported one or more reason for not prescribing myopia management (MM) in different continents for not adopting myopia control approaches from 2015 to 2024. The option of 'Treatment availability' was not included in the surveys conducted in 2015 and 2019 (marked with *).

3.1.3k Ranked criteria for starting myopia management in a young progressing myope

In 2024, patient refractive error and age were the most highly ranked criteria for beginning myopia management across the world followed by (in order of importance): myopia progression, having two myopic parents, axial length, having one myopic parent, binocular vision status, lifestyle, choroidal thickness, choroidal thickness responsiveness to treatment, AC/A ratio, patient preference, and parent/guardian preference. Rankings by continent are presented in Figure 3.15, and differences between continents for factors ranked from highest (1) to lowest (13) are presented in Figure 3.16.

The rankings of the criteria for starting myopia management in a young progressing myope in 2024 were significantly different to the rankings in 2022 ($p<0.001$). Refractive error and patient age were ranked highest in both years. Similarly, practitioners ranked patient and parent preference lowest in both surveys. Converse to 2022, binocular vision status was ranked higher than lifestyle, and AC/A ratio was ranked lower than choroidal thickness (all $p<0.001$, Table 3.11).

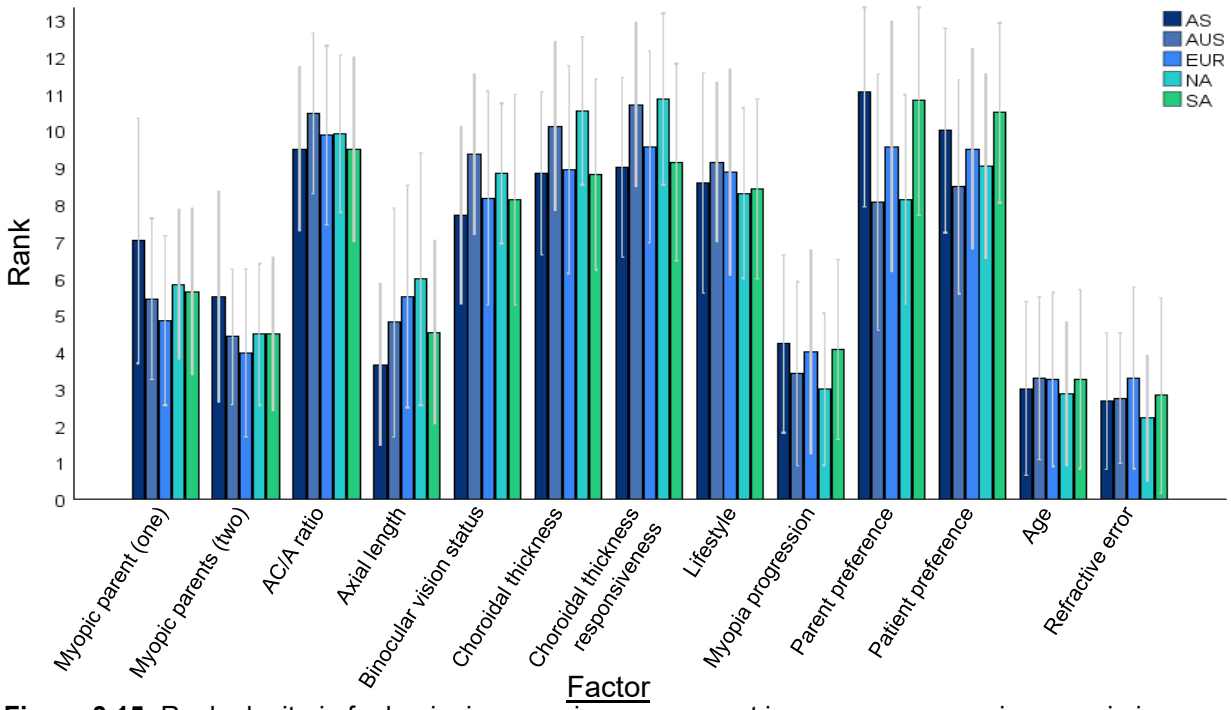


Figure 3.15: Ranked criteria for beginning myopia management in a young progressing myopia in 2024 (where 1 = highest and 13 = lowest rank). AC/A ratio = accommodative convergence / accommodation ratio. AS = Asia, AUS = Australasia, EU = Europe, NA = North America, SA = South America. Error bars represent ±1 SD.

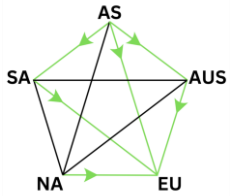
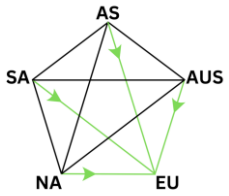
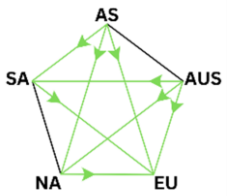
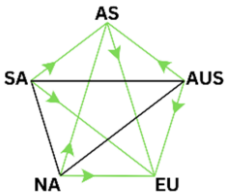
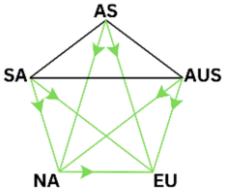
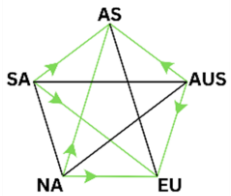
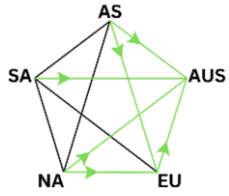
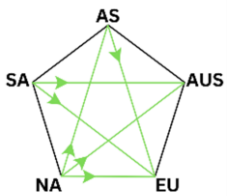
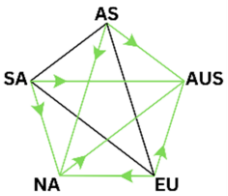
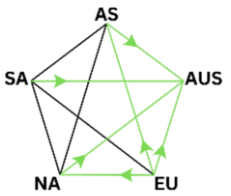
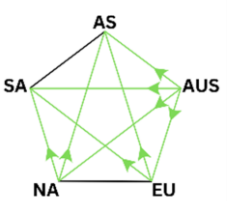
1) Refractive error	2) Patient age	3) Myopia progression	4) Myopic parents (two)	5) Axial length
				
6) Myopic parent (one)	7) Binocular vision status	8) Lifestyle	9) Choroidal thickness	10) Choroidal thickness responsiveness
				
11) AC/A ratio	12) Patient preference	13) Parent preference		
				

Figure 3.16: Significance plots of ranked criteria for beginning myopia management in 2024 (where 1 = highest and 13 = lowest rank). Green lines = $p<0.05$, black lines = $p\geq0.05$. Arrows direct a higher rank to a lower rank. AS = Asia, AUS = Australasia, EU = Europe, NA = North America, SA = South America.

	2022	2024
Highest rank	Refractive error	Refractive error
	Patient age	Patient age
		*Myopia progression**
	Myopic parents (two)	Myopic parents (two)
	Axial length	Axial length
	Myopic parent (one)	Myopic parent (one)
	Lifestyle	Binocular vision status
	Binocular vision status	Lifestyle
	AC/A ratio	Choroidal thickness
	Choroidal thickness	Choroidal thickness responsiveness
	Choroidal thickness responsiveness	AC/A ratio
	Patient preference	Patient preference
Lowest rank	Parent preference	Parent preference

Table 3.11: Ranked criteria, from highest at the top to lowest at the bottom, for beginning myopia management in a young progressing myopia in 2022 and 2024.

*Myopia progression was not included as a factor in 2022 survey

3.1.3l Factors considered when choosing which myopia management strategy to use first

The key factors considered when choosing which myopia management strategy to use first were (in order of preference): patient age (73.9%), myopia progression (71.8%), risk factors such as parental myopia (62.5%), cycloplegic refractive error (55.4%), axial length (53.9%), non-cycloplegic refractive error (50.3%), parent/guardian preference (43.7%), binocular vision status (35.2%), patient preference (33.4%), corneal topography (24.4%), only comfortable/trained to use one treatment (11.2%), choroidal thickness (8.8%), and lastly only have one treatment available (7.7%). Continent-wide responses are presented in Figure 3.17.

Compared to responses from 2022, the proportion of practitioners who consider patient age, cycloplegic refraction, axial length, and choroidal thickness when choosing which myopia management strategy to use first has remained unchanged (Table 3.12). A markedly lower proportion of practitioners across the world reported only have one treatment available to them (18.5% in 2022 and 7.7% in 2024). All other changes with time are shown in Table 3.12.

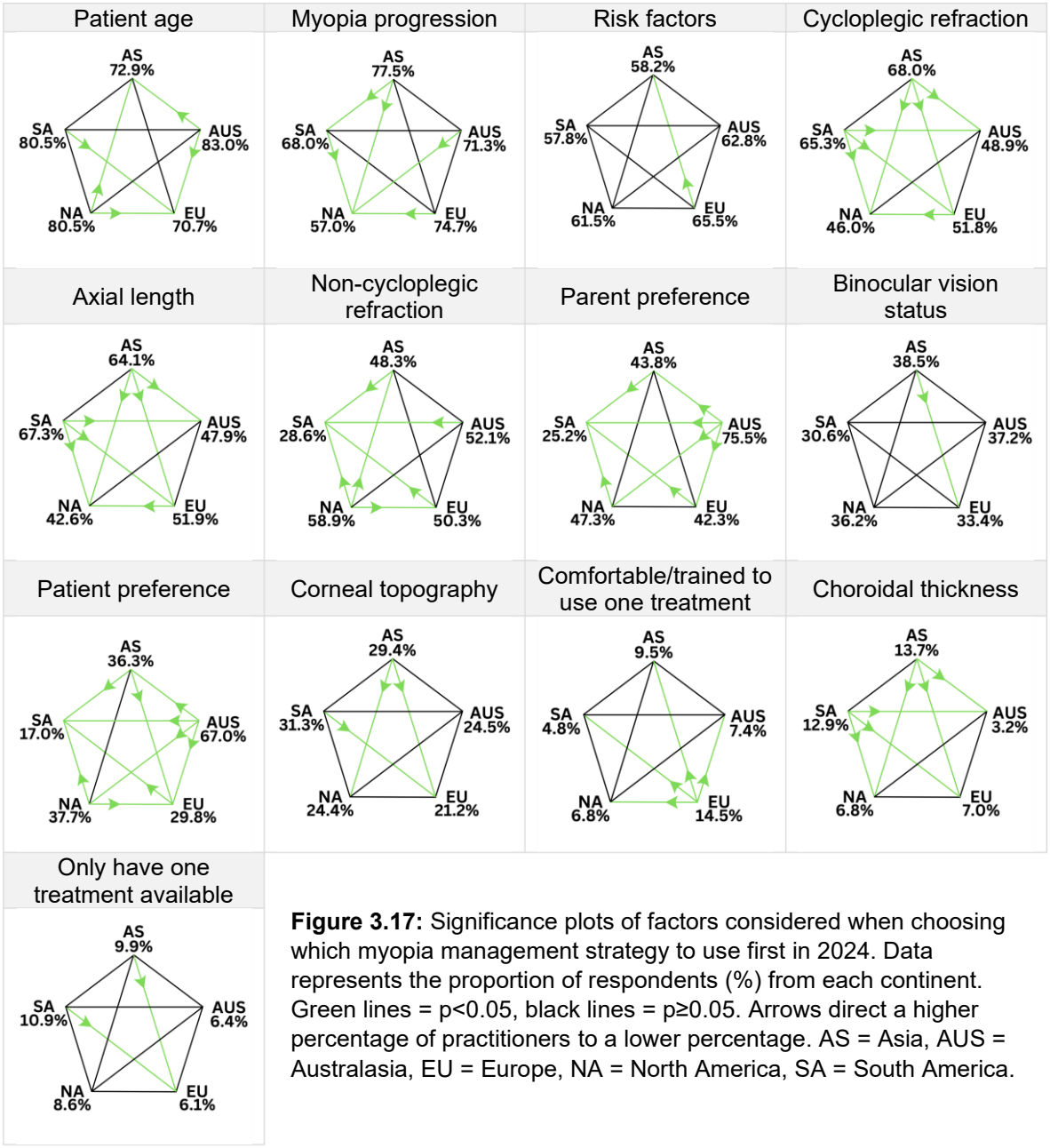


Figure 3.17: Significance plots of factors considered when choosing which myopia management strategy to use first in 2024. Data represents the proportion of respondents (%) from each continent. Green lines = $p<0.05$, black lines = $p\geq0.05$. Arrows direct a higher percentage of practitioners to a lower percentage. AS = Asia, AUS = Australasia, EU = Europe, NA = North America, SA = South America.

Factor	2022	2024	P-value
Patient age	75.5%	73.9%	0.054
Non-cycloplegic refraction	55.0%	50.3%	<0.001
Cycloplegic refraction	52.4%	55.4%	0.014
Axial length	51.3%	53.9%	0.118
Parent preference	48.4%	43.7%	<0.001
Binocular vision status	39.8%	35.2%	<0.001
Patient preference	38.4%	33.4%	<0.001
Only have one treatment available	18.5%	7.7%	<0.001
Comfortable/trained to use one treatment	15.8%	11.2%	<0.001
Choroidal thickness	9.8%	8.8%	0.124

Table 3.12: Factors considered by practitioners when choosing which myopia management strategy to use first in 2022 and 2024. P-values represent significance in changes with time from 2022 to 2024. Statistically significant changes are shaded in green ($p<0.05$). Data represents the proportion of respondents (%). The following factors were not included in the 2022 survey: myopia progression, risk factors, corneal topography.

3.1.3m Frequency of following up children undergoing myopia management

Over half of practitioners across the world followed-up their child patients undergoing myopia management every 6 months (55.0%), and nearly a third followed-up every 3 months (31.4%). A smaller percentage of practitioners conducted follow-ups every 1 month (4.3%), 12 months (3.7%), 0.5 months (2.2%), and 2 months (2.1%). A statistically significantly greater proportion of practitioners in Asia conduct follow-ups more frequently than practitioners from all other continents (all $p<0.005$), whereas practitioners in Europe follow-up their young myopic patients less frequently than all continents besides South America (Figure 3.18).

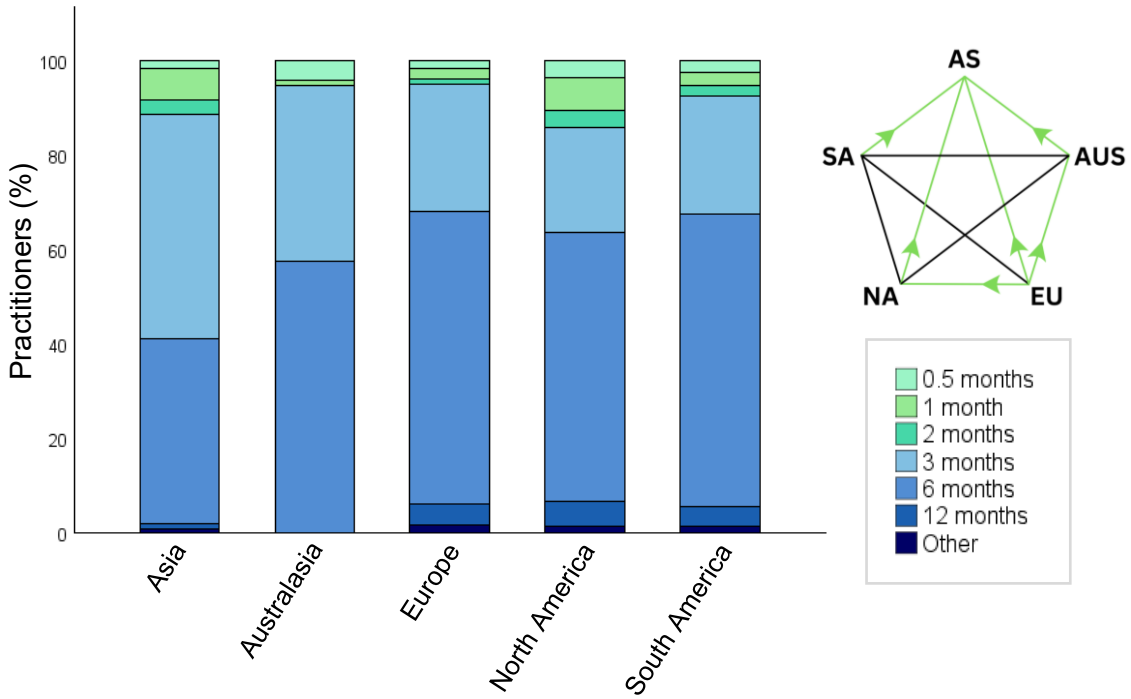


Figure 3.18: Frequency reported by practitioners (as a percentage) of following up children undergoing myopia management for different month periods.

Green lines of plot = $p<0.05$ and black lines = $p\geq0.05$. Arrows direct longer follow-up intervals to shorter follow-up intervals. AS = Asia, AUS = Australasia, EU = Europe, NA = North America, SA = South America.

3.1.3n Triggers to adjust myopia management strategy

Overall, 3.5% of practitioners did not adjust their myopia management strategy, whereas a greater percentage of practitioners used the following factors as a trigger to adjust their management approach in 2024 (in order of importance): progression of refractive error (80.3%), progression of axial length (50.9%), poor compliance (46.6%), faster eye growth than expected for age (45.3%), a new treatment with better reported efficacy (43.3%),

complications (38.7%), treatment comfort (38.6%), and changes in choroidal thickness (7.3%).

A greater proportion of practitioners in Asia and South America used axial length progression as a trigger to change management strategy than practitioners in Europe, North America, and South America. Further, a significantly greater proportion of practitioners in Australasia considered poor compliance, treatment comfort, and complications than practitioners in all other continents (Figure 3.19).

When compared with data from 2022, the proportion of practitioners around the world who did not adjust their myopia management strategy or changed strategy on access to

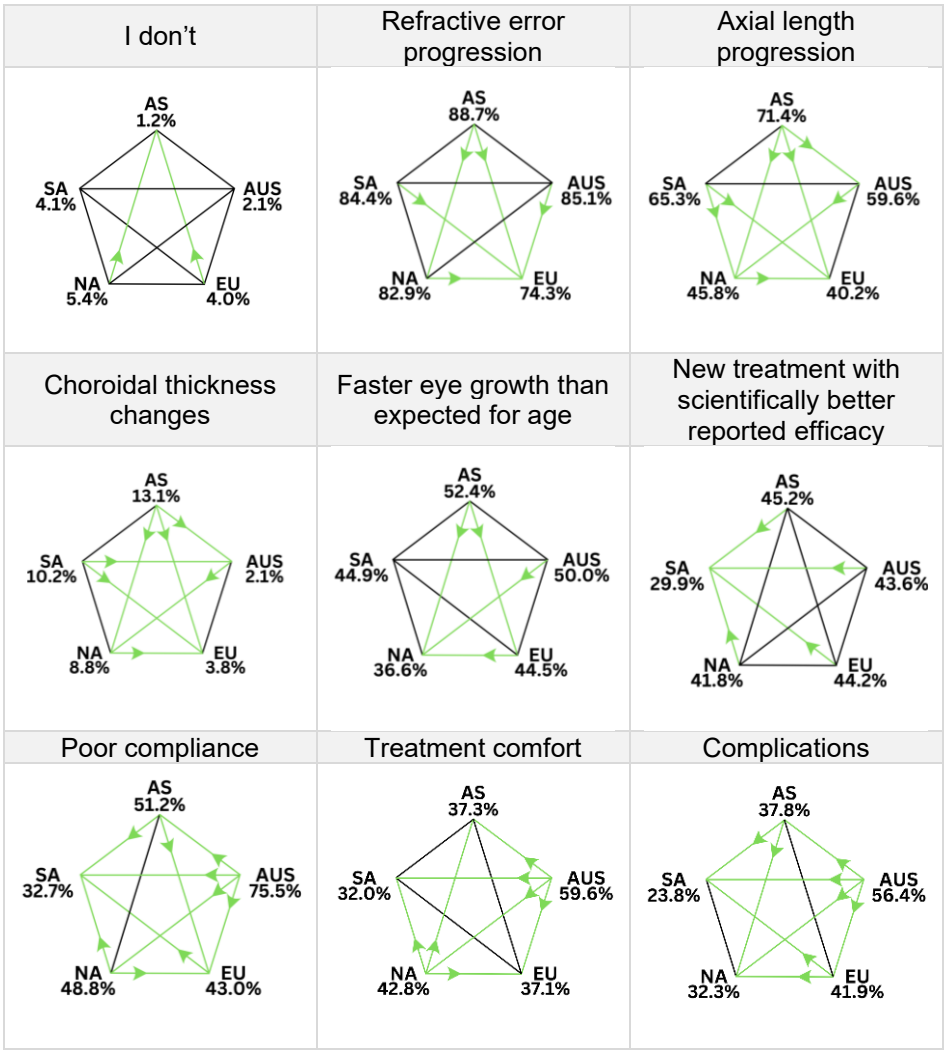


Figure 3.19: Significance plots of triggers to adjust myopia management strategy in 2024. Data represents the proportion of respondents (%) from each continent. Green lines = $p<0.05$, black lines = $p\geq0.05$. Arrows direct a higher percentage of practitioners to a lower percentage. AS = Asia, AUS = Australasia, EU = Europe, NA = North America, SA = South America.

Table 3.13: Proportion of practitioners (%) who used triggers to adjust myopia management strategy in 2022 and 2024. P-values represent significance in changes from 2022 to 2024. Statistically significant changes are shaded in green (p<0.05). The following factors were not included in the 2022 survey: faster eye growth than expected for age and treatment comfort.

Trigger	2022	2024	P-value
I don't	4.0%	3.5%	0.311
Refractive error progression	84.4%	80.3%	<0.001
Axial length progression	60.6%	50.9%	<0.001
Choroidal thickness changes	12.9%	7.3%	<0.001
New treatment with scientifically better reported efficacy	44.8%	43.3%	0.164
Poor compliance	55.02%	46.6%	<0.001
Complications	41.9%	38.7%	0.004

treatment with better reported efficacy remained unchanged in 2024 (Table 3.13). All other factors showed a statistically significant difference over the two-year period (Table 3.13).

3.1.3o Impact of myopia management on your practice

Practitioners overall felt practicing myopia management enhanced their patient loyalty (much more: 28.5%; more: 32.7%; and no change: 29.9%), increased practice revenue (much more: 15.0%; more: 34.5%; and no change: 40.9%), and improved job satisfaction (much more: 37.1%; more: 36.3%; and no change: 20.9%). There were some variations between continents, displayed in Table 3.14, which included practitioners in South America feeling the

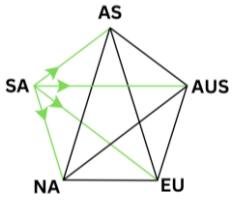
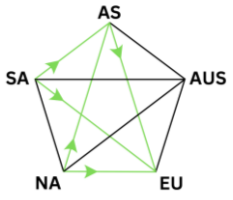
Factor	Impact	Asia	Australasia	Europe	North America	South America	Significance Plot
Patient loyalty	Much less	3.5	0.0	2.6	7.3	9.5	
	Less	6.3	2.1	2.1	0.4	1.4	
	No change	21.7	30.9	35.8	29.5	14.3	
	More	43.4	46.8	28.0	30.2	24.5	
	Much more	25.1	20.2	27.2	32.6	49.7	
Practice revenue	Much less	2.9	0.0	4.9	7.1	8.2	
	Less	5.0	1.1	1.8	0.8	0.7	
	No change	37.0	43.6	47.9	30.4	28.6	
	More	39.9	47.9	28.8	39.8	36.1	
	Much more	15.1	7.4	11.7	22.0	25.9	
Job satisfaction	Much less	1.3	0.0	2.0	5.4	2.7	
	Less	3.5	1.1	1.7	0.2	0.0	
	No change	19.2	17.0	22.6	20.6	16.3	
	More	48.9	54.3	32.1	28.9	27.9	
	Much more	27.1	27.7	38.5	44.8	52.4	

Table 3.14: Impact of myopia management on practitioners' practice in 2024, rated from 'much less' to 'much more' as a percentage of practitioners from each continent. Cells shaded in green highlight the response received from the greatest percentage of practitioners for each factor. Green lines of significance plots = p<0.05 and black lines = p≥0.05. Arrows direct practitioners who experienced more improvement overall to those who experienced lesser improvement of each factor. AS = Asia, AUS = Australasia, EU = Europe, NA = North America, SA = South America.

greatest improvement in job satisfaction and patient loyalty compared to practitioners from other continents.

The impact of myopia management on patient loyalty in 2024 reflected that recorded in 2022 as there was no significant difference in the distribution of practitioners' opinions between the two years ($p=0.199$). However, practitioners felt a significant enhancement in practice revenue and job satisfaction in 2024 compared to 2022 (both $p<0.05$).

3.1.4 Discussion

This study provides an update of the self-reported attitudes and approaches of eye care practitioners towards myopia management on young myopic patients across the world in 2024, forming the fourth contribution to a study beginning in 2015[30]. Further, this report examines how practitioner concern, activity, and strategies of myopia management have changed alongside the substantial advancements in myopia research and developments of novel intervention methods over the nine-year period.

Nearly 3000 practitioners responded to this survey in 2024, with such figure being close to that achieved in 2022. Unlike the survey conducted in the previous Chapter, responses from Africa were too low (n=11) to be included in the analysis; however, global changes from 2015, 2019, 2022, and 2024 were possible to assess in Asia, Australasia, Europe, North America, and South America. Respondents' scope of practice, such as those who can prescribe optical correction and pharmaceuticals (albeit differing by region), and level of experience were consistent across years; each survey yielded similar distributions of eye care professions (principally optometrists and ophthalmologists) and working environments (primarily clinical practice), with the same median number of years qualified.

The increasing frequency of paediatric myopia has sustained the previously recorded generally high levels of concern across the five continents analysed. As discussed in Chapter 2 Section 2.1.4, the high prevalence and progression rate of childhood myopia in Asia in comparison to the other continents[12, 379, 395, 396] is likely a contributing factor to practitioners in Asia consistently reporting the greatest concern level since 2015. However, the current study demonstrates that consistency throughout time is not uniform across the world. The most recent survey shows the concern level of practitioners in South America to have risen noticeably; originally reporting the second lowest concern level in 2015, practitioners in South America now report concern matching that of Asia. This was reflected in the reported clinical activity level of myopia management; in the previous Chapter, continent-wide analysis showed practitioners in South America to rate themselves the least active, yet practitioners in South America subsequently showed the greatest increase in perceived activity level between 2022 and 2024. Promisingly, although to varying degrees, it

appears that practitioners' engagement in myopia management has also grown over time in other parts of the world; the average perceived level of clinical activity in myopia management from each continent significantly increased from 2015 to 2022, remaining stable or increasing further in 2024.

For the first time, pharmaceutical approaches alone were not within the top three most effective options of myopia management as perceived by practitioners. Matching the results found in 2022, combination therapy and orthokeratology interventions were perceived to be the first and second most effective approaches (respectively); however, results from 2024 showed spectacle and soft contact lenses approved for myopia management were reported to be more efficacious than atropine preparations overall. This change may be attributed to an increasing awareness, regulatory approval, and accessibility of novel optical approaches to slow myopia progression together with their growing evidence base[397, 398]; this could explain the increased frequency of prescribing such interventions in this study; soft contact lenses approved for myopia management were prescribed significantly more frequently in 2024 than 2015 (from 2% to 8%), and the frequency of prescribing spectacles approved for myopia management remained at an encouraging level of 16% from 2022 onwards.

Across all four surveys, single vision spectacles have been the most frequently prescribed forms of primary optical correction to young myopic patients despite being rightly perceived as an ineffective myopia control option. Encouragingly, over the nine-year period, there has been a significant decrease in the frequency of prescribing single vision spectacles by 11%, indicating a greater number of practitioners are providing myopic children with alternative options. Although perceived to be the most effective option, combination therapy was one of the least prescribed methods, following the same pattern as that identified in the previous Chapter; this may be attributed to limited access to atropine or the ability to prescribe low dose atropine not falling within an optometrists' scope of practice in many parts of the world. This was emphasised when assessed on a regional basis in the current survey; practitioners in Australasia and Asia prescribed combination therapy the most often, and non-combined atropine 0.01% and 0.05% were prescribed most frequently by practitioners in Asia and Australasia, respectively. For those practitioners who can prescribe atropine for the purpose of myopia management, lower concentrations (≤0.05) were much more frequently prescribed than higher concentrations (>0.05%) in every continent, suggesting that avoiding the undesirable side effects associated with more potent preparations was of priority, although the long-term efficacy of low dose atropine use for slowing myopia progression is being questioned[399].

Detailed in an IMI white paper[376], monitoring a myopic child's axial length is the advisable method of observing myopia progression due to the pathological consequences of excessive ocular elongation[14, 400], stronger relation to visual impairment, and its immunity to accommodation artifacts[401]. The findings of Chapter 2 highlighted that a large proportion of practitioners were aware that the assessment of axial length is an important consideration for monitoring myopia progression; however, it was unclear whether this was routinely being measured. In addition, the accessibility of instrumentation to provide comprehensive myopia management, such as that used to measure cycloplegic autorefraction to objectively monitor of refractive progression, was unknown. Access to instrumentation to measure refraction and corneal curvature was generally high across all continents, ranging from 78.7 to 98% and from 83.0 to 95.2%, respectively. On the other hand, access to instrumentation/pharmaceuticals to measure cycloplegic refractive error and axial length was much more varied between continents (range 56.4 to 95.7% and 42.6 to 81.6%, respectively). In particular, practitioners in North America and Europe reported the least accessibility to both measures, whereas practitioners in Asia had high accessibility to both. As the market for myopia management intervention options expands further over time, it will be valuable to assess whether accessibility to the recommended instrumentation increases concurrently.

A patient's age was the most considered factor when choosing which myopia management strategy to use, which agrees with previous studies indicating that age the primary determinant of myopia progression[396, 402]. Previous surveys in this series identified a clear disparity between the minimum age (between 5 to 18 years) of prescribing spectacles versus soft contact lenses; in 2022, the minimum age practitioners were prepared to prescribe contact lenses (soft and orthokeratology) was over 3 years older than that of spectacles. The latest survey found that replacement frequency of soft contact lenses makes a significant difference; on average, practitioners were prepared to prescribe daily disposable soft contact lenses to children 1.5 years younger than that of reusable soft contact lenses, likely due to the practicality and lower risk of adverse ocular events seen with daily disposables[386, 387, 403]. However, the previously established age gap between in the prescription of spectacles and soft contact lenses remained, equalling 3.6 years for daily disposables and 5.1 years for reusable soft contact lenses. As both forms of myopia management were perceived to have similar efficacy, this is likely a contributing factor to the lower frequency of prescribing myopia management soft contact lenses than myopia management spectacles in every continent. This is despite the safety and efficacy of long-term myopia management soft contact lens wear in childhood being well established from longitudinal clinical trials[294, 404, 405].

Reports have suggested impressive efficacy of repeated low-level red-light therapy in reducing axial length and refractive progression in myopic children[353, 406, 407], yet over half of practitioners stated they would not prescribe light therapy as a myopia management intervention, at 55% worldwide. Researchers have questioned the safety of repeated exposure to such light sources, with one report determining two low-level red-light emitting devices marketed for myopia management to be Class 1 laser products, potentially putting the retina at risk of thermal and photochemical damage[358]. As the use of light therapies undergo further trials and more robust safety data emerges as a result, perhaps a growth in the use of light therapy for myopia management will be seen in the coming years.

The results of Chapter 2 identified an increase in proactivity of practitioners across the world in response to myopia onset, with a shift toward a lower minimum degree of myopia (between -0.50 to -1.0D) being considered to begin a myopia control intervention method than that seen in prior years (approximately -1.50D). Similarly, the minimum annual amount of myopia progression that practitioners feel necessitates myopia management has reduced since 2015, indicating a growing awareness of the detrimental impacts of seemingly small increases in a child's myopia[408]. These developments are arguably a work in progress; delaying treatment until a child's myopia progresses to approximately -1.0D may be too late to minimise the associated risks, particularly considering that age is the primary determinant of myopia progression[396, 402].

The declining proportion of practitioners who deliberately undercorrect their young myopic patients from 2015 to 2022 (and stable in 2024) also demonstrates increased practitioner knowledge of advisable management approaches. However, over 17% of respondents still either sometimes or always use undercorrection as a myopia management approach worldwide, despite ample reports of its ineffectiveness or exacerbation of myopia progression[265, 267, 389]. In particular, the results of the current survey show over 1 in 5 practitioners in Asia and North America adopt this method. As undercorrection was once thought to be an effective method of myopia management due to reducing a child's accommodative response[266], the results of the current study stress the importance of developments in research being readily accessible and communicated to those practitioners who may not be exposed to important updates in the field.

Practitioners felt the higher cost of myopia interventions relative to single vision correction in isolation was once again the primary prevention to prescribe such intervention techniques. Like that reported in Chapter 2, this was true for every continent, with no improvement over the last 2-year period. Correspondingly, treatment availability appears to still be an issue to some practitioners, mainly in Asia, South America, and North America. Unexpectedly, a

substantially greater proportion of practitioners in Asia reported safety concerns, additional chair time, unpredictable outcomes, and the benefit/risk ratio as reasons for not prescribing myopia management than practitioners from all other continents. Given that access to treatments and information regarding myopia management were less of a hindrance in Asia, plus the high self-reported clinical activity level in that part of the world, further research exploring the additional resources and support practitioners feel would enhance their management of young myopic patients may be of benefit to contextualise how these hindrances can be addressed.

Chapter 2 showed practitioners were aware of the four key risk factors of childhood myopia[376] (patient age, refractive error, parental myopia, and patient axial length), ranking these as the most important criteria for beginning myopia management. In the most recent survey, 'myopia progression' was a new factor for practitioners to consider. Interestingly, myopia progression was ranked below patient age overall, suggesting that practitioners may use a patient's age to gauge the risk of rapid myopia progression from the outset. Perhaps the understanding of the important risk factor of age prevents practitioners from monitoring myopia progression in the absence of intervention and encourages earlier action to be taken. Moreover, low levels of myopia progression can be difficult to assess due to variability in subjective refraction, and the time taken to establish true refractive and axial progression is of detriment to the child.

Reassuringly, few practitioners reported having only one myopia management treatment available to them; since 2022, the number of practitioners who could offer their patients only one management option has decreased by nearly 11%. Similarly, fewer practitioners are only comfortable or trained to use one management method, decreasing by nearly 5% from 2022. This shows that, despite treatment availability still being an issue in some parts of the world, there has been movement towards increased accessibility and training to prescribe management options in clinical practice.

For the first time in this series of surveys, practitioners were asked how frequently they generally follow-up patients undergoing myopia management to establish how this aligns with clinical guidance: The IMI Clinical Management Guidelines Report[376] suggests patients undergoing any myopia control method should be reviewed at least every 6 months to ensure safety and effectiveness of treatment. Positively, in every continent, few practitioners review their young myopic patients undergoing management at intervals longer than 6 months. Similarly, the majority of practitioners in every continent were receptive to the outcome of follow-up appointments, with over 80% on average adjusting their management approach if a patient's refractive error was still progressing. In the absence of a standardised

approach to manage myopic children across the world, these outcomes provide confidence in practitioners' clinical judgement in this field of paediatric eyecare.

Despite differences in prescribing patterns, methods of management, and levels of training and engagement, the practice of myopia management across the world continues to benefit the children undergoing treatment, eyecare practices and individual practitioners; engaging in myopia management has been felt by practitioners to positively enhance job satisfaction and practice revenue in every continent, even more so than that reported in 2022. Perhaps this is a result of an increasing uptake of myopia management as the new standard of care in young myopic patients.

This survey is subject to the same limitations as the previous versions; an accurate response count is unknown due to maximising exposure by involving professional bodies, whose members may not all be practicing eye care practitioners. Further, eye care professions may differ in their scope of practice within each region, questioning the representativeness to the wider practitioner population in each continent. Similarly, practitioners in parts of the world have limited access to certain treatment options and equipment. Comparisons between years does not involve an identical group of practitioners and the proportion of practitioners between countries differs slightly, but the trends observed and their interrelation gives confidence that the results are robust.

In conclusion, the fourth global survey and nine-year review of attitudes of eye care practitioners towards myopia management and prescribing patterns in clinical practice identified a substantial increase in perceived practitioner concern about the myopia epidemic. With this, a rise in self-reported clinical activity in myopia management has been seen across the world, with practitioners becoming increasingly aware of safe and effective intervention techniques and evidence-based practices to manage and monitor their young myopic patients. This is reflected by a growing proportion of practitioners prescribing efficacious intervention methods to children with lower degrees and slower rates of myopia progression, however consistent hindrances to the practice of myopia management need addressing. As also concluded in Chapter 2, this can only be addressed through a collaborative effort between eye care industry, health care regulatory bodies, and policy makers to increase affordability and accessibility of appropriate and effective management options[409]. Regardless of geographic location and financial status, inclusivity needs to be encouraged to aid individuals, healthcare systems, and economies burdened by the dramatically increasing prevalence of myopia across the world.

3.2 CHOROIDAL THICKNESS AND MYOPIA MANAGEMENT IN CLINICAL PRACTICE – A TWO YEAR REVIEW

3.2.1 Introduction

Chapter 2 Section 2.2 explored how choroidal thickness was viewed by eye care practitioners in the practice of myopia management in 2022. Across the world, various inconsistencies were present, with practitioners in some regions considering choroidal thickness of greater importance when managing myopic children than practitioners located elsewhere. However, no specific trend was discovered. Here, responses from the 2024 global survey are analysed and compared with responses from 2022 to identify any change in practitioners' attitudes towards measuring choroidal thickness when managing myopia in clinical practice.

In addition to comparing responses between continents, the data was also analysed to compare countries within a continent. Like Chapter 2, this was conducted where a sample from a country of ≥30 was received.

Country-specific responses could be extracted from the following:

- Africa: None
- Asia: China (n=232), India (n=39), Malaysia (n=65), Singapore (n=35), Taiwan (n=59), Turkey (n=107), Vietnam (n=143)
- Australasia: Australia (n=67)
- Europe: Denmark (n=41), Italy (n=149), Norway (n=42), Portugal (n=67), Russia (n=584), Spain (n=325), Sweden (n=45), United Kingdom (n=37)
- North America: Canada (n=143), Mexico (n=207), United States of America (n=101)
- South America: Brazil (n=49), Ecuador (n=32)

Country-specific changes with time could be assessed in countries where a sample of ≥30 was received in both 2022 and 2024, displayed in Table 3.15. Procedures of statistical analyses are detailed in Section 3.1.2b.

Survey	Continent			
	Asia	Europe	North America	South America
2022	China (n=1001) India (n=65) Turkey (n=78) Vietnam (n=101)	Italy (n=202) Norway (n=40) Russia (n=80) Spain (n=380) UK/EIRE (n=67)	Canada (n=107) Mexico (n=86) USA (n=77)	Brazil (n=36) Ecuador (n=40)
2024	China (n=232) India (n=39) Turkey (n=107) Vietnam (n=143)	Italy (n=149) Norway (n=42) Russia (n=666) Spain (n=325) UK/EIRE (n=37)	Canada (n=143) Mexico (n=207) USA (n=101)	Brazil (n=49) Ecuador (n=32)

Table 3.15: Countries where n=≥30 in both 2022 and 2024 permitting country-specific responses to be analysed with time. No within-continent comparison was possible from Africa and Australasia.

3.2.2 Results

3.2.2a Ranking of choroidal thickness as a criterion for beginning myopia management

When ranking criteria for beginning myopia management (where a lower number represents a higher rank), a patient's choroidal thickness and choroidal thickness responsiveness to early treatment were ranked similarly overall in 2022 and 2024; 9th and 10th respectively out of 12 criteria in 2022 (see Chapter 2 Section 2.2.2a), and 9th and 10th respectively out of 13 in 2024 (refer to Table 3.11). Despite little change overall, variations in the continent-wide responses from both surveys were present. In 2022, practitioners in South America ranked choroidal thickness and choroidal thickness responsiveness significantly higher when choosing a myopia management strategy than practitioners in all other continents besides Africa (Figure 3.20). However, in 2024, practitioners in South America, Europe, and Asia on average ranked both criteria at a similar level. Practitioners in North America and Australasia ranked choroidal thickness and choroidal thickness responsiveness the lowest in both 2022 and 2024, showing consistency over the two years (Figure 3.20).

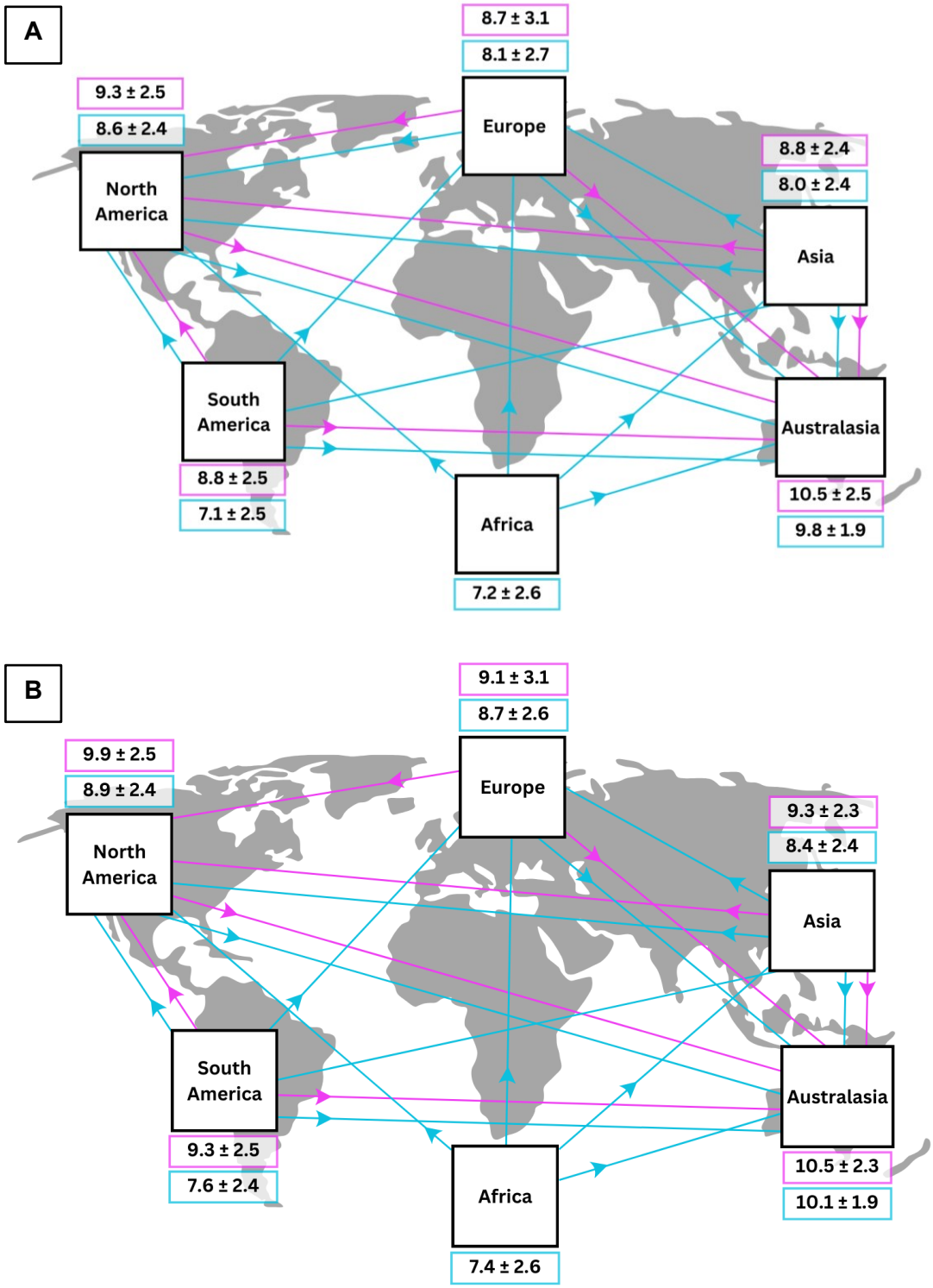
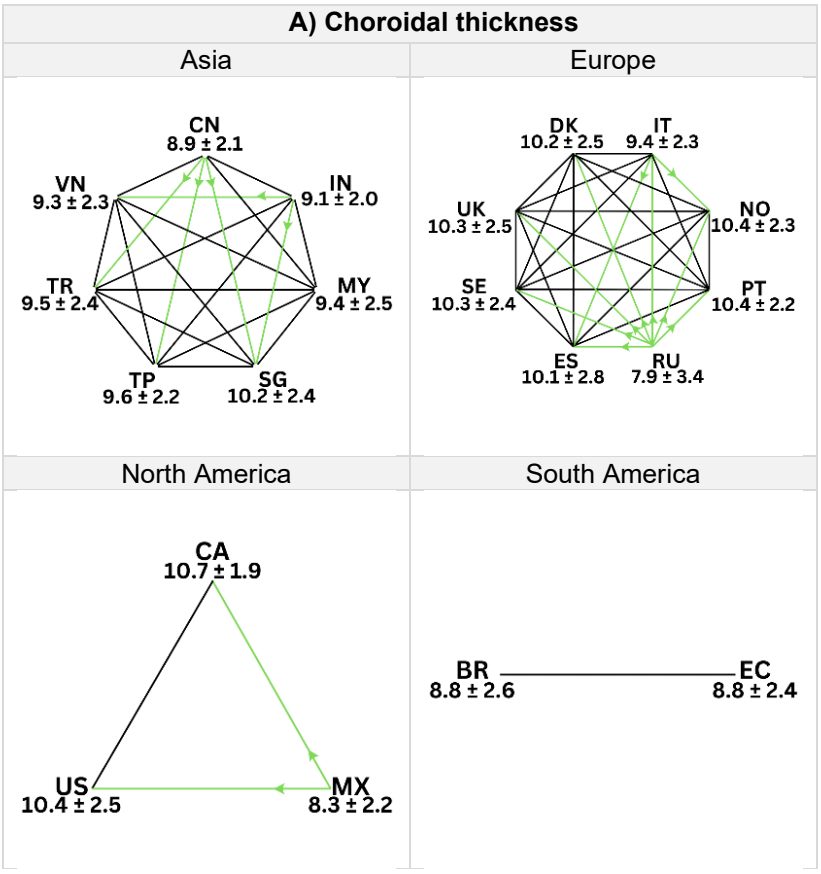


Figure 3.20: Ranking of **A) Choroidal thickness** and **B) Choroidal thickness responsiveness to early treatment** as criteria for beginning myopia control for each continent in 2022 (blue), and 2024 (purple). Lower numbers represent a higher rank. Criteria were ranked 1 to 12 in 2022, and 1 to 13 in 2024. Lines between continents indicate statistically significant differences ($p \leq 0.05$) between the rankings of each year. No line indicates no statistically significant difference. Direction of arrows show the higher rank to lower rank. Note that responses from Africa were only included in the analysis in 2022 due to insufficient numbers in 2024. Data are presented as mean ± SD.



Country-wide differences are presented in Figure 3.21. Interestingly, the within-continent differences (of those countries presented in Table 3.15) remained similar from 2022 to 2024 in all continents besides Asia. As shown in Chapter 2 Section 2.2.2a, choroidal thickness was ranked significantly higher by practitioners in Turkey, whereas responses from 2024 showed this to have dropped below the ranking from practitioners in China (Figure 3.21). Similarly, the ranking of choroidal thickness as a criterion for beginning myopia management was previously more highly ranked in Vietnam than China, but more recent results show practitioners in China ranked choroidal thickness at a

Figure 3.21: Significance plots of **A) Choroidal thickness** and **B) Choroidal thickness responsiveness to early treatment** ranked as a criterion for beginning myopia management in 2024, where 1 = highest and 13 = lowest rank. Green lines = $p<0.05$, black lines = $p\geq0.05$. Arrows direct a higher rank to a lower rank. Countries presented where $n\geq30$.

CN=China, IN=India, MY=Malaysia, SG=Singapore, TP=Taiwan, TR=Turkey, VN=Vietnam, DK=Denmark, IT=Italy, NO=Norway, PT=Portugal, RU=Russia, ES=Spain, SE=Sweden, UK=United Kingdom, CA=Canada, MX=Mexico, US=United States of America, BR=Brazil, EC=Ecuador.

comparable level. The ranking of choroidal thickness responsiveness to early treatment across Asia also varied over the two years. Previously, practitioners in Vietnam ranked this more highly than practitioners in China and India, however this rank has dropped to below that of India and close to that of China (Figure 3.21). Practitioners in China ranked choroidal thickness responsiveness higher than they previously did, with the average rank higher than that of Turkey, unlike that seen in 2022.

In Europe, there has been less variation with time; choroidal thickness has been consistently ranked lower by practitioners in Norway from 2022 to 2024, and higher in Russia. Ranking from practitioners in the United Kingdom has remained in a similar position amongst the other countries, and no significant differences have occurred between the United Kingdom and Spain in either year. Practitioners in Italy have ranked choroidal thickness significantly lower than the United Kingdom and Spain in both years. The ranking of choroidal thickness responsiveness to early treatment also showed consistency over the two years; practitioners in Russia ranked this factor significantly higher than Italy, Norway, Spain, and the United Kingdom in both years. Practitioners in Norway considered choroidal thickness responsiveness of less importance, ranking it lower than Italy and Spain in both 2022 and 2024.

In North America, practitioners in Mexico consistently ranked choroidal thickness and choroidal thickness responsiveness higher than the United States of America and Canada in 2022 and 2024. In South America, no significant differences in the ranking of both factors were observed between Brazil and Ecuador in either year.

In both 2022 and 2024, choroidal thickness and choroidal thickness responsiveness to early treatment were ranked more highly than patient preference and parent preference when starting myopia management in a young progressing myope. Further, in 2022, AC/A ratio was ranked ahead of both choroidal factors, but practitioners ranked this lower than choroidal thickness and choroidal thickness responsiveness in 2024.

3.2.2b Choroidal thickness as a factor considered when choosing which myopia management strategy to use first

Consistent with 2022, the percentage of practitioners who consider choroidal thickness as a factor when deciding which myopia management technique to use first was greatest in Asia and South America, and lowest in Australasia. The statistical significance of these differences are presented in Figure 3.22.

Within Asia, a dramatically greater proportion of practitioners in China and India considered choroidal thickness than the other countries assessed within the continent (Figure 3.23).

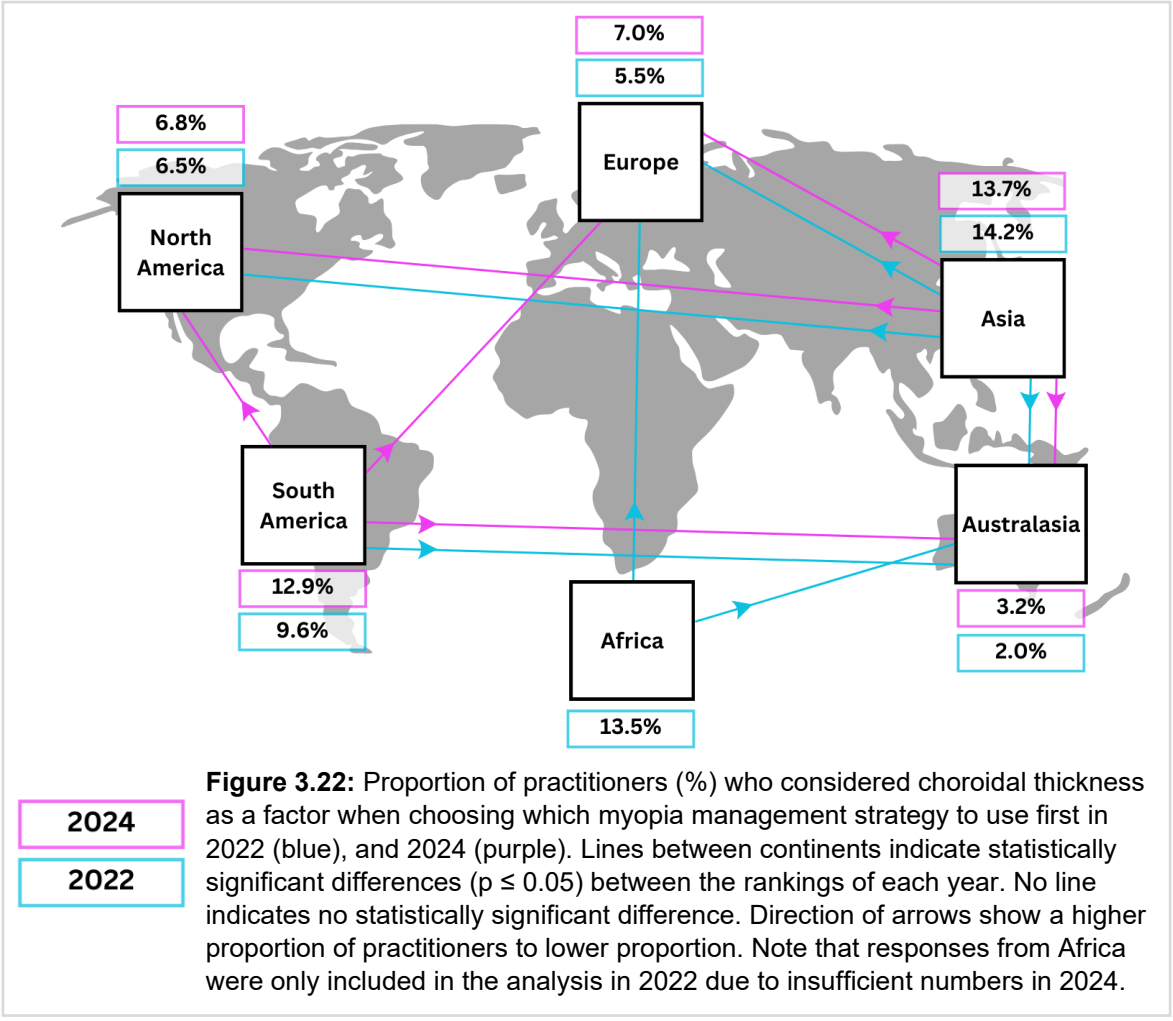


Figure 3.22: Proportion of practitioners (%) who considered choroidal thickness as a factor when choosing which myopia management strategy to use first in 2022 (blue), and 2024 (purple). Lines between continents indicate statistically significant differences ($p \leq 0.05$) between the rankings of each year. No line indicates no statistically significant difference. Direction of arrows show a higher proportion of practitioners to lower proportion. Note that responses from Africa were only included in the analysis in 2022 due to insufficient numbers in 2024.

Similarly, Russia contained the greatest proportion of practitioners who also use a patient's choroidal thickness when deciding which myopia management strategy to begin firstly, being significantly higher than all other regions in Europe besides the UK. A markedly larger percentage of practitioners in Mexico also considered choroidal thickness than other parts of North America, whereas no statistically significant country-wide difference was present within South America (Figure 3.23).

Continent	Country	2022	2024	P-value
Asia	China	16.0	30.2	<0.001
	India	20.0	20.5	0.944
	Turkey	5.1	5.6	0.929
	Vietnam	5.0	4.2	0.872
Europe	Italy	2.5	2.7	0.939
	Norway	10.0	0.0	0.074
	Russia	28.8	11.1	<0.001
	Spain	3.2	4.3	0.548
	UK	0.0	2.7	0.603
North America	Canada	0.0	3.5	0.268
	Mexico	15.1	11.6	0.266
	USA	3.9	2.0	0.608
South America	Brazil	11.1	8.2	0.649
	Ecuador	10.0	9.4	0.929

Table 3.16: Proportion of practitioners (%) who considered choroidal thickness as a factor when choosing which myopia management strategy to use first in 2022 and 2024. P-values represent significance in change with time from 2022 to 2024. Significant changes ($p<0.05$) are shaded in green.

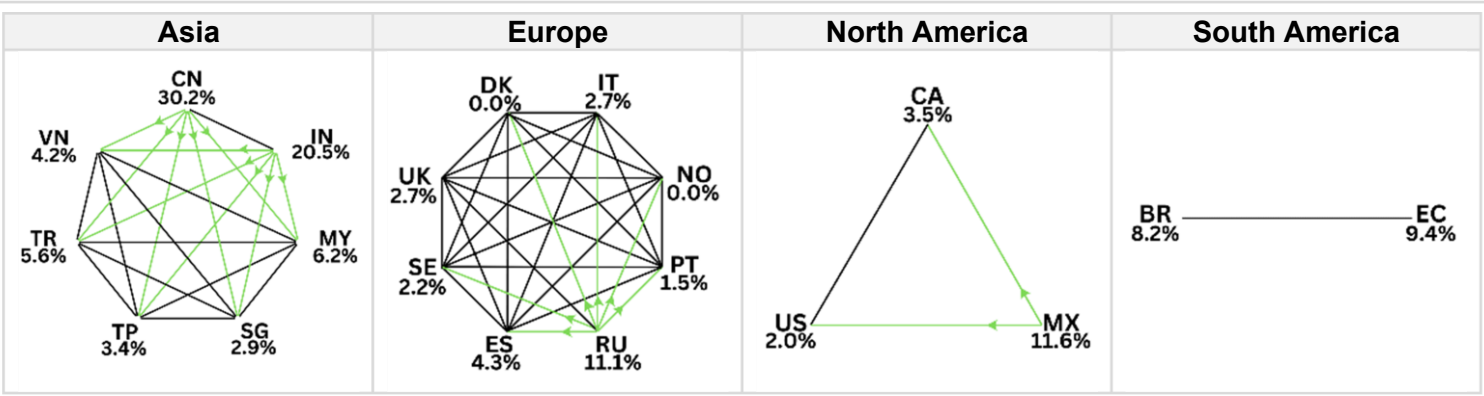


Figure 3.23: Significance plots of the proportion of practitioners (%) who consider choroidal thickness as a factor when choosing which myopia management strategy to use first in 2024. Green lines = $p<0.05$, black lines = $p\geq0.05$. Arrows direct a higher percentage of practitioners to a lower percentage.

CN=China, IN=India, MY=Malaysia, SG=Singapore, TP=Taiwan, TR=Turkey, VN=Vietnam, DK=Denmark, IT=Italy, NO=Norway, PT=Portugal, RU=Russia, ES=Spain, SE=Sweden, UK=United Kingdom, CA=Canada, MX=Mexico, US=United States of America, BR=Brazil, EC=Ecuador.

Between 2022 and 2024, a significant increase in the percentage of practitioners who use choroidal thickness as a factor to decide which myopia intervention method to begin firstly occurred in China, nearly doubling from 16.0% to 30.2% (Table 3.16). Conversely, in Russia, a significant decrease in this figure occurred over the two years, from 28.8% to 11.1%. No other significant changes with time occurred (Table 3.16).

3.2.2c Choroidal thickness as a trigger to adjust myopia management strategy

The proportion of practitioners who use choroidal thickness as a trigger to adjust their myopia management technique was greatest in Asia and South America in 2024, and lowest in Europe and Australasia (Figure 3.24). This aligned closely with that of 2022.

Within Asia, a significantly greater proportion of practitioners from China used choroidal thickness change as a prompt than all other participating regions in 2024 (Figure 3.25). This number from China was significantly greater than that of India, whereas results from 2022 had shown there to be a non-significant difference between the two countries previously. Country-wide comparisons within Europe and South America identified no significant differences, whereas practitioners in North America, a significantly greater proportion of practitioners in Mexico consider changes in choroidal thickness as a trigger than Canada and the USA (Figure 3.25).

With time, it appears there has been little change within the continents assessed; a significant change in the proportion of practitioners who use choroidal thickness change as a prompt to adapt myopia management strategy only occurred in Russia. However, this change was vast, reducing by 20.3% (Table 3.17). No other significant changes within regions were identified from 2022 to 2024 (Table 3.17).

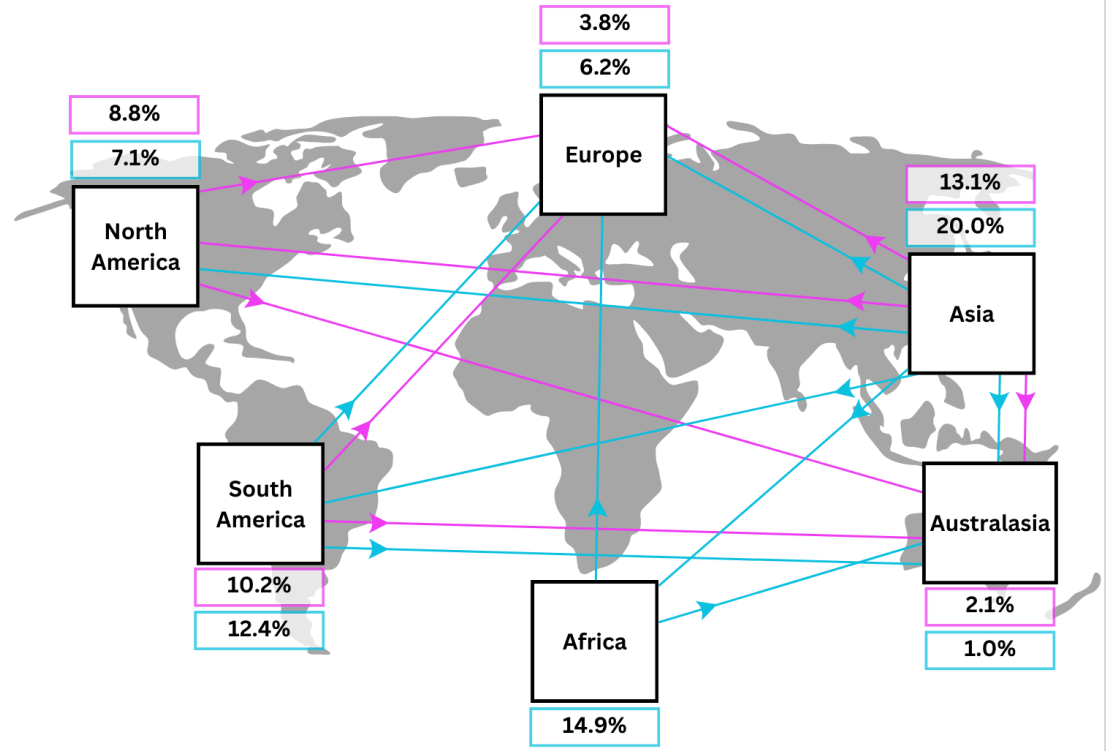


Figure 3.24: Proportion of practitioners (%) who used changes in choroidal thickness as a trigger to adjust myopia management strategy in 2022 (blue), and 2024 (purple). Lines between continents indicate statistically significant differences ($p \leq 0.05$) between the rankings of each year. No line indicates no statistically significant difference. Direction of arrows show a higher proportion of practitioners to lower proportion. Note that responses from Africa were only included in the analysis in 2022 due to insufficient numbers in 2024.

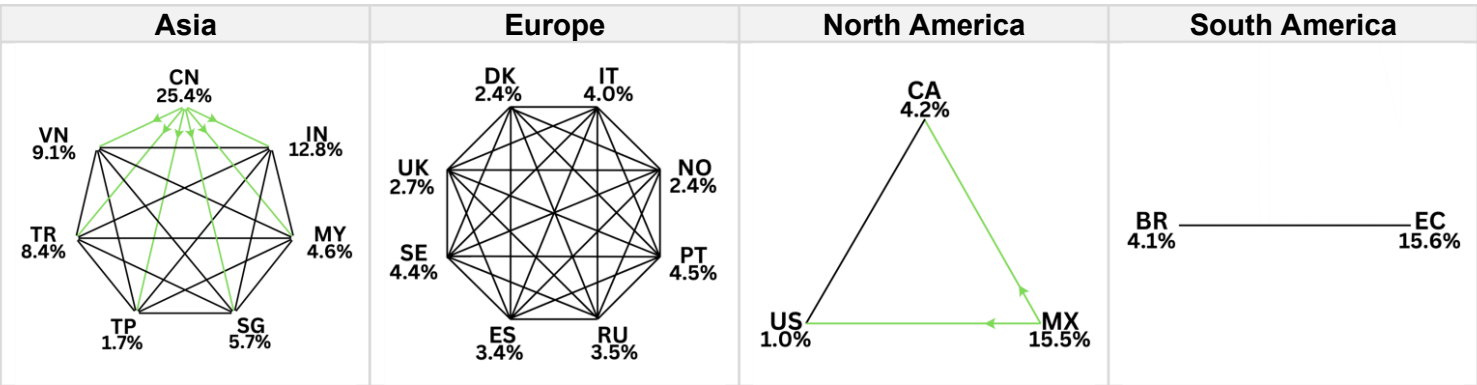


Figure 3.25: Significance plots of the proportion of practitioners (%) who used changes in choroidal thickness as a trigger to adjust myopia management strategy in 2024. Green lines = $p<0.05$, black lines = $p\geq0.05$. Arrows direct a higher percentage of practitioners to a lower percentage.

CN=China, IN=India, MY=Malaysia, SG=Singapore, TP=Taiwan, TR=Turkey, VN=Vietnam, DK=Denmark, IT=Italy, NO=Norway, PT=Portugal, RU=Russia, ES=Spain, SE=Sweden, UK=United Kingdom, CA=Canada, MX=Mexico, US=United States of America, BR=Brazil, EC=Ecuador.

3.2.3 Discussion

This study provided insight into the current and changing perceptions amongst eye care practitioners of using choroidal thickness as a clinical tool to aid the management of young myopic children. Practitioners from various parts of the world considered the choroid of greater use in their clinical practice than practitioners elsewhere. Now supported by another years' worth of data, some continent-wide variations in Chapter 2 have been reidentified. Of those countries able to be assessed over both years (where n≥30 in 2022 and 2024), country-wide variations have mostly remained unaffected with time.

Continent	Country	2022	2024	P-value
Asia	China	23.8	25.4	0.569
	India	16.9	12.8	0.611
	Turkey	11.5	8.4	0.598
	Vietnam	5.0	9.1	0.424
Europe	Italy	2.5	4.0	0.480
	Norway	2.5	2.4	0.979
	Russia	23.8	3.5	<0.001
	Spain	4.7	3.4	0.379
	UK	1.5	2.7	0.772
North America	Canada	1.9	4.2	0.500
	Mexico	15.1	15.5	0.921
	USA	3.9	1.0	0.477
South America	Brazil	8.3	4.1	0.523
	Ecuador	15.0	15.6	0.931

Table 3.17: Proportion of practitioners (%) who used choroidal thickness change as a trigger to adjust myopia management strategy in 2022 and 2024. P-values represent significance in change with time from 2022 to 2024. Significant changes (p<0.05) are shaded in green.

On deciding when to begin myopia management, data collected in 2022 and 2024 showed most practitioners saw choroidal thickness alone as more helpful in their decision making than using early changes in choroidal thickness. Given that the evidence supporting the use of short-term choroidal changes to guide clinical decision making is insufficient at present[131], it is not surprising that this was the case. Relative to other continents, those continents with higher proportions of practitioners who valued choroidal thickness generally also contained a higher proportion of practitioners who valued choroidal thickness responsiveness to early treatment. In Chapter 2, it was put forward that practitioners who often include choroidal thickness in their investigations when practicing myopia management may use choroidal imaging as a surrogate indicator of axial elongation (Chapter 2 Section 2.2.3), however the association between choroidal thickness and early choroidal thickness responsiveness indicates this may not be the case for the majority of respondents. Further, the 2024 update showed a significant proportion of practitioners had access to instrumentation to directly measure axial length (Section 3.1.3d), including those geographical locations where choroidal criteria were ranked relatively high; choroidal thickness and choroidal thickness responsiveness to early treatment were ranked the highest in South America, and a greater percentage of practitioners in South America had access to measure axial length compared to the other continents.

Despite practitioners typically classing other demographic and ocular features such as patient age, refractive error, and axial length as being the most important considerations for starting a myopia intervention, choroidal thickness and its responsiveness were consistently ranked higher than patient preference and parent preference in 2022 and 2024. Conflictingly, when choosing which myopia management strategy to use first, a markedly greater proportion of practitioners considered the parent's preference (43.7% in 2024, Section 3.1.3l) and patient's preference (33.4) than the patient's choroidal thickness (8.8%). Further, in all continents, the percentage of practitioners who used changes in choroidal thickness as a trigger to adjust management strategy was lower than the small percentage of practitioners who considered choroidal thickness when choosing which myopia management strategy to use first. Collectively these findings indicate that, of those practitioners who did consider a child's choroidal thickness when selecting a management strategy, choroidal thickness is not being used as a biomarker of long-term efficacy, but rather used to assess the potential of a child to benefit from a myopia control intervention. Once a child has begun a management approach, choroidal thickening or thinning observed at a later date is not commonly seen as an indicator of its effectiveness. Rather than being used as a predictive measure at this stage, it may be that measuring or observing a child's choroidal thickness is valued by some practitioners as an indicator of posterior ocular structural changes associated with axial myopia progression.

Although the results of this study indicate the choroid doesn't yet appear to play a key part in practitioners' practice of myopia management in comparison to other ocular parameters, the collective results suggest over 1 in 10 practitioners in Asia and South America consider a patients' choroidal thickness when deciding which myopia management technique to prescribe first. Country specific responses showed these figures to sit at 1 in 10 in Russia and Mexico, 1 in 5 in India, and nearly 1 in 3 in China. In China, this percentage of practitioners has nearly doubled since 2022, indicating a growing interest in the choroid specifically in the context of controlling myopia progression in clinical practice.

The representativeness of the sample is limited for the aforementioned reasons (Section 3.1.4), however the results from 2024 and emerging trends since 2022 demonstrate how the use of choroidal thickness in myopia management is not uniform across the globe. It is clear that practitioners in various parts of the world, such as Australasia, do not tend to analyse a myopic child's choroidal thickness in clinical practice, whereas greater proportions are doing so in other parts of the world, such as Asia and South America. More research is warranted to determine the instrumentation and methods practitioners use to measure choroidal thickness in their myopic paediatric patients and establish whether this impacts the geographical differences identified in this report. As more research exploring the use of the

choroid as a biomarker for axial growth emerges, it will be useful to examine how the proportions of practitioners who consider choroidal thickness important in the management of childhood myopia changes further with time.

3.3 CONCLUSIONS

The study of global trends in myopia management attitudes and strategies in clinical practice yielded valuable information not only for this research project, but the field of myopia research overall. It demonstrates that myopia management is a global practice, with eye care practitioners of different professions and working environments across the world becoming progressively more engaged over recent years.

The addition of the choroid as a factor for respondents to consider throughout the survey from 2022 provided the necessary starting point to understand whether baseline choroidal thickness, early choroidal thickness changes, or longer-term changes with intervention use are deemed clinically useful in the practice of myopia management as perceived by practitioners. Unsurprisingly, despite regional variations, Chapters 2 and 3 show that the relevance of choroidal thickness when managing young myopic patients is not established amongst eye care practitioners active in clinical practice, aligning with the conclusions of research experts[131].

With the growing uptake of effective, alternative optical correction options for myopic children, comes the increasing demand for additional advancements in the field to provide optimum control techniques. Paired with the need to further understand whether early choroidal changes can be incorporated into the practice of myopia management, specific takeaways from Chapters 2 and 3 direct parts of the later chapters of this thesis; as some practitioners (albeit low proportions relative to other ocular measures) are already routinely measuring the choroidal thicknesses of their young myopic patients to guide their management approach, choroidal imaging capabilities of OCT devices and the interpretation of repeatability when using early choroidal thickness change as a predictor of intervention efficacy in clinical practice is explored in the following chapter. In addition, with myopia management spectacle lenses being the most prescribed form of optical correction specifically marketed for myopia management worldwide, the short-term impact of spectacle lens-induced defocus on human choroidal thickness is explored in Chapters 5 and 7. This involves a myopia controlling spectacle lens design commercially available to practitioners in several parts of the world (Chapter 7). Furthermore, as the prescribing of optical interventions – in particular, spectacle lenses - falls within many eye care professions' scope of practice across the globe, the contribution of the choroidal research associated with

spectacle lens defocus in Chapters 5 and 7 aims to provide research outputs of widespread value.

Chapter 4. A comparison of choroidal imaging with 3 OCT devices using qualitative and quantitative parameters

4.1 INTRODUCTION

Although some choroidal functions are not yet fully understood, it is well known that the choroid is an integral structure to maintain the proper functioning of the eye[130] and is compromised in numerous ocular diseases. In ophthalmic clinical practice and research, thorough evaluation of the choroid can be crucial for exploration of the posterior ocular layers and to provide optimal patient care. Choroidal thickness measures can be highly useful for eye care practitioners when monitoring progression of posterior ocular pathologies such as myopic maculopathy, where key signs include progressive choroidal thinning and development of holes in Bruch's membrane. More recently, the choroid has become a topic of interest in childhood myopia onset and progression[131]. Therefore, accurate assessment of the of the overlying retina, outer limits of the retinal pigment epithelium (RPE), choroidal vasculature, and delineation of the chorioscleral interface (CSI) is imperative when assessing choroidal integrity and thickness.

Obtaining a clear image of the anterior and posterior choroidal borders can be challenging. The pigmented cells of the RPE and choroid, plus the choroid's highly vascularised non-uniform profile, causes scattering of incident light and consequential difficulty to capture high detail. OCT devices specifically designed for choroidal imaging would sacrifice retinal image quality, deeming the idea impractical for clinical use. Alternatively, various techniques can be used to maximise visualisation of the choroid whilst maintaining sufficient retinal image quality, as previously described in Chapter 1 Section 1.3.2. Employing longer wavelengths (1050nm) provides deeper penetration and improved image quality of the choroid compared to shorter wavelengths (800nm) due to the lower scattering of light further into the infrared spectrum[410, 411]. These longer wavelengths tend to be used in swept-source OCT (SS-OCT) devices, where tunable lasers and high scanning speeds provide deeper clarity of the choroidal components. Although this is a useful technique, many commercially available OCT instruments employ near-infrared wavelengths, which is typical of spectral domain OCT (SD-OCT). Conventional SD-OCT provides detailed visualisation of the intraretinal layers and measures of retinal thickness, however the shorter wavelengths limit penetration further past the retina. In these cases, enhanced depth imaging (EDI) can be used to enable visualisation deeper than the RPE, which is further detailed in Chapter 1 Section 1.3.2. This method is often provided by OCT manufacturers as a built-in feature in modern SD-OCT devices.

Significant technological advances over recent years have seen the development of OCT instruments with new and impressive capabilities of imaging the anterior and posterior segments. This study conducts a qualitative and quantitative comparison of choroidal images obtained by three OCT instruments: the Heidelberg Spectralis SD-OCT (Heidelberg Engineering, Heidelberg, Germany), Zeiss Cirrus 5000 HD-OCT (Carl Zeiss Meditec, Dublin, USA), and the Topcon Triton swept source DRI-OCT (Topcon, Japan).

4.2 METHODS

4.2.1 Instrumentation

4.2.1a Heidelberg Spectralis OCT

The Heidelberg Spectralis is a SD-OCT which is commonly used in clinical practice and research. The Spectralis simultaneously images the eye in two ways. Firstly, a beam of light captures a greyscale fundus image and tracks eye movements by mapping more than 1000 points. Using the position of these points, a second beam is positioned at the required location, unaffected by eye motion and blinking. This device uses light of 880nm in wavelength. The eye-tracking ability of this device enables the operator to avoid image distortion and artifacts through eye movements, obtaining accurate correlations between the retinal image and OCT scan. When tested, the eye-tracking software has been found to provide excellent repeatability in retinal nerve fibre thickness measurements taken by the Spectralis in both normal and glaucomatous eyes[412, 413]. Further, the accurate image mapping provides precise scanning of the same area over multiple visits[414] and an axial resolution of 3.9μm aids intricate analysis of the posterior ocular layers.

The Spectralis has a built-in EDI mode to enable optimal visualisation of the choroid. Additional to the EDI mode, the scanning pattern can be manipulated by the operator in several ways. B-scan averaging can be set between 2 to 100 B-scans with a maximum scan speed of 68,000 A-scans per second, depending on the image quality and scanning speed required. The orientation (horizontal, vertical, or radial), scan width (between 15 to 30°), and number of scanning locations can also be controlled, depending on whether a line or volume scan is required.

4.2.1b Zeiss Cirrus 5000 HD-OCT

Like the Heidelberg Spectralis, the Zeiss Cirrus HD-OCT (High-Definition OCT) uses spectral domain technology. This device can take between 27,000 to 68,000 A-scans per second and has an axial resolution of 5μm. The instrument uses light of 840nm wavelength,

and simultaneously provides a greyscale fundus image using a scanning laser ophthalmoscope.

The Cirrus provides various scan patterns, including en face visualisation. En face imaging is obtained through a dense raster scan to obtain an image cube of the posterior pole by construction of C-scans on the coronal plane. This reconstruction of B-scans permits the operator to view a volume scan presented in 3D, however visualisation of the posterior choroidal boundary is limited with en face OCT. Therefore, B-scan averaging combined with built-in EDI mode and fixation tracking is the optimal method when choroidal thickness measures are of interest with this device.

Similar to the Heidelberg Spectralis, the fixation tracking capabilities of this device enable repeatable measurements of optic disc and macular parameters[415]. However, when assessing the neuroretinal rim width in glaucomatous and non-glaucomatous eyes, the Zeiss Cirrus has been found to produce higher values when compared with the Spectralis[416], indicating caution to be applied when making comparisons between the two devices if the optic disc is of particular interest. Similarly, the Spectralis and Cirrus show significant differences when measuring retinal thickness[417]. However, neither device has the in-built capability to automatically segment the choroidal thickness, so little is known about the agreement of choroidal thickness measurements between the two devices.

4.2.1c Topcon Triton DRI-OCT

The Topcon Triton swept source DRI-OCT (Topcon, Japan) is the only swept-source device used in this study, with ‘DRI’ standing for ‘Deep Range Imaging’. A wavelength-variable laser (WVL) employs wavelength of 1050nm, maximising the visibility of the CSI without the operator having to reduce the working distance. Further, this instrument has the advantage of enhanced OCT imaging through media opacities compared to SD-OCT due to its longer wavelength, and provides simultaneous, true colour fundus images if required. The Triton has several different scanning patterns available, including line scans up to 12mm in length and macular and optic disc 3D visualisation.

Unlike SD-OCT, the participant is unable to see the light source due to the wavelength being in the invisible spectrum, likely improving participant compliance and visual comfort. SS-OCT provides a lower axial resolution (in this case, 8μm) but faster scanning speed than SD-OCT; the Triton is able to capture 100,000 A-scans per second, helping to reduce artifacts from involuntary eye movements.

The Triton has been found to produce reliable measurements of retinal thickness in healthy eyes and eyes with retinal diseases[418]. Following manual segmentation of 3D macular cube

scans, one study found the Triton to produce significantly lower values of choroidal thickness than the Heidelberg Spectralis, however both devices were able to clearly visualise the CSI[419].

4.2.2 Participants

Twenty participants (15 females, 5 males) aged 18 years and older (mean age 23.6 ± 5.9 years) were recruited from the staff and student population of Aston University (Birmingham, UK). All participants reported good general and ocular health, with no history of retinal and macular diseases or surgeries. Participants attended one visit to the Aston University School of Optometry building, where they had two OCT scans taken of each eye per each of the three OCT devices in a randomised sequence. Therefore, in total, two images of 40 eyes (80 images in total) were obtained per device. This sample size was confirmed to be sufficient for qualitative and quantitative analysis (further detailed in Section 4.2.5), calculated using G*Power 3.1 (University of Dusseldorf); with 80% statistical power, a medium effect size (0.3) and a p-value of <0.05 taken as significant, 79 images were required to show an effect with Chi-squared testing. For the same significance level, a sample size of 20 participants provided 80% power to detect an intrasession difference in subfoveal choroidal thickness of 8.5μm (close to the axial resolution of the OCT devices used in this study)[420].

All procedures adhered to the tenets of the Declaration of Helsinki and this study was approved by the Aston University Research Ethics Committee. All participants gave informed written consent (Appendix 1 and 2).

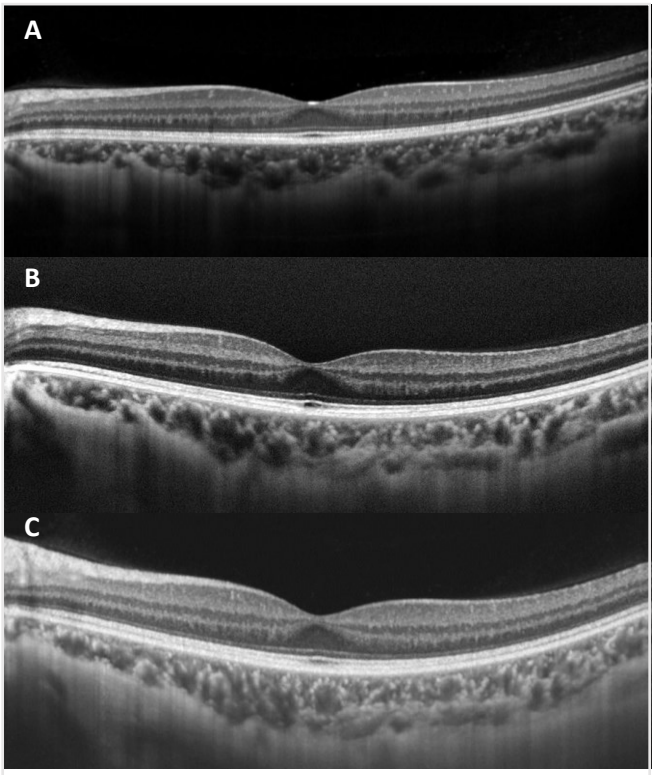


Figure 4.1: Three OCT images taken of the right eye of the same individual. Image A was taken using the Heidelberg Spectralis, image B with the Zeiss Cirrus, and image C with the Topcon Triton. Scanning protocols are described in Table 4.1.

4.2.3 Data collection procedures

All 80 images were captured by the same optometrist experienced in handling each instrument and the order of devices was randomised for each participant. Every image was captured under the same conditions; all three instruments were utilised under low illumination levels to increase undilated pupil size (between 5 to 15 lux, measured with using the CA810 Lux

Device	OCT technology	Scanning protocol	Scan angle	Fixation position	Scan length (mm)	Number of B-scans averaged	Light source and wavelength (nm)	Maximum A-scan velocity (A-scan/ second)	Axial resolution (µm)
Heidelberg Spectralis	SD-OCT	1 Line section EDI mode	0°	Macula	9.0	100	SLD, 880	68,000	3.9
Zeiss Cirrus 5000	SD-OCT	HD 1 Line 100x EDI mode	0°	Macula	9.0	100	SLD, 840	68,000	5.0
Topcon Triton	SS-OCT	Line(H)	0°	Macula	9.0	128	WVL, 1050	100,000	8.0

Table 4.1: Specifications of the Spectralis, Cirrus, and Triton OCT devices and scanning protocols employed in this study. SD-OCT = spectral domain OCT, SS-OCT = swept source OCT, WVL = wavelength variable laser, SLD= superluminescent diode.

Meter, Chauvin Arnoux, Asnières-sur-Seine, France). Participants were required to remove their spectacles and/or contact lenses prior to imaging. To avoid pathological interference with assessment of the choroid, central retinal and macular integrity was confirmed on immediate examination of the first OCT image taken of each eye. Participants were required to have all images captured within a 15-minute time window to avoid diurnal fluctuations in choroidal thickness. Device specifications and the scanning protocols used are summarised in Table 4.1 and an example of the images obtained are shown in Figure 4.1. Images were anonymised and exported, with each OCT instrument recorded using masked labels (Devices A, B, and C). Prior to analysis of the images, any identifiable markings on the exported B-scan were cropped out of the image by a separate individual external to the study to prevent investigators identifying which image came from which OCT device. The use of the OCT devices conformed with manufacturer recommendations for safe operation.

4.2.4 Image analysis

All images were imported into a software program compiled using MATLAB (The MathWorks, Inc., Natick, Massachusetts, United States)[171], developed for segmentation of the posterior ocular layers; this software is designed specifically to segment OCT images captured using the Heidelberg Spectralis, so wasn't used for choroidal segmentation described further on in this chapter. However, this software was used to enhance the images captured by the different OCT devices in this study; the contrast of OCT images from different devices can be manipulated using this software, improving discriminability of the retinal and choroidal layers, concurrently aiding subjective assessment of the ocular layer integrity. Two contrast enhancements were used in this study: 'Contrast-limited Adaptive Histogram Equalisation' (Figure 4.2b) and 'Girard' (Figure 4.2c). Rather than enhancing the

entire image as a whole, Contrast-limited Adaptive Histogram is a function which operates on small data regions termed ‘tiles’. The contrast of each tile is enhanced to match the histogram of the output region to the specified histogram. Originally designed for improved quality of optic nerve head assessment, the Girard algorithm was developed to reduce light attenuation and blood vessel shadowing[421]. This algorithm also proves useful when assessing choroidal vasculature and tissue boundaries.

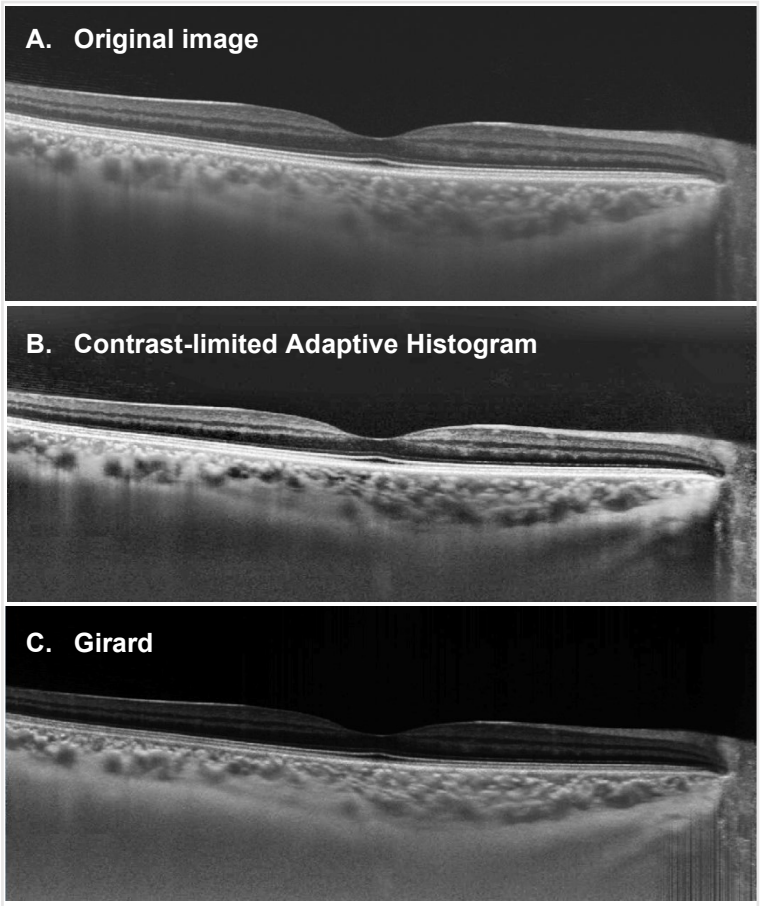


Figure 4.2: Example of enhancement of an original OCT image (A) using Contrast-limited Adaptive Histogram (B) and Girard (C) enhancement functions.

Two observers highly experienced in OCT

	Grade		
Image feature assessed	**+1**	**0**	**-1**
Distinguishability of the intraretinal layers	Intraretinal layers distinguishable without image enhancement	Intraretinal layers distinguishable with image enhancement	Intraretinal layers barely/not distinguishable with image enhancement
Discriminability of the RPE from the anterior choroid	RPE discriminable from the anterior choroid without image enhancement	RPE discriminable from the anterior choroid with image enhancement	RPE barely/not discriminable from the anterior choroid with image enhancement
Discriminability of choroidal vessel lumens in Sattler’s and Haller’s layers	Choroidal vessel lumens discriminable without image enhancement	Choroidal vessel lumens discriminable with image enhancement	Choroidal vessel lumens barely/not discriminable with image enhancement
Visibility of the subfoveal choroioscleral junction	Posterior subfoveal choroidal boundary visible without image enhancement	Posterior subfoveal choroidal boundary visible with image enhancement	Posterior subfoveal choroidal boundary barely/not visible with image enhancement

Table 4.2: Description of the image features and gradings of the four parameters assessed.

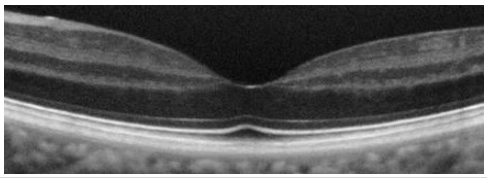
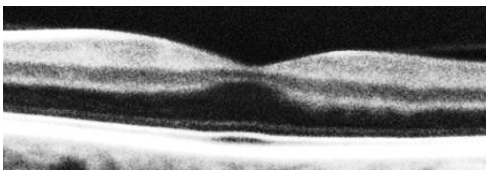
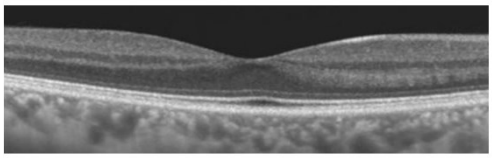
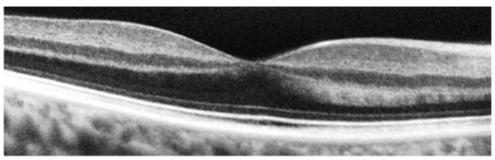
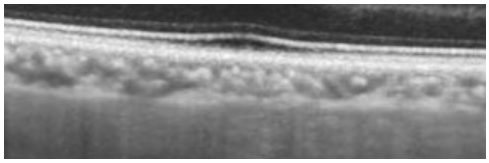
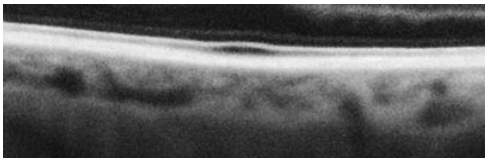
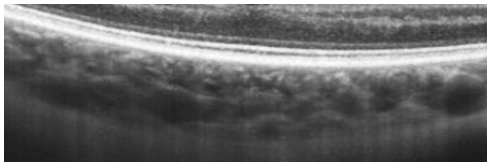
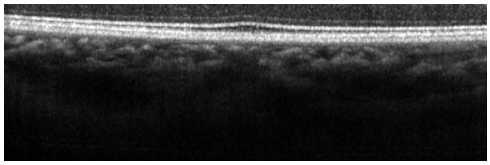
Feature assessed	Grade +1	Grade -1
Intraretinal layers		
Outer limit of RPE		
Choroidal vessel lumens		
Chorioscleral junction		

Table 4.3: Grading examples of the features assessed within each OCT image. Grade +1 indicates the feature is clearly visible without image enhancement, and grade -1 indicates the feature is not clearly visible with image enhancement.

interpretation conducted the qualitative analysis. The observers separately graded four image features of each OCT scan (distinguishability of the intraretinal layers, discriminability of the RPE from the anterior choroid, discriminability of choroidal vessel lumens in Sattler's and Haller's layers, and visibility of the subfoveal choroioscleral junction) using a grading scale of -1, 0, or +1, detailed in Table 4.2. This scoring system was based upon existing examples of ordinal scales used to qualitatively grade alternative features of OCT images, including OCT angiography, in published literature[422-424]. Examples of the graded features in the current study are presented in Table 4.3.

Distinguishability of the intraretinal layers was considered as 'barely/not distinguishable' (grade -1) where layers from the internal limiting membrane (ILM) to the RPE/Bruch's complex appeared soft and difficult to discriminate despite contrast enhancement. A highly discriminable RPE with no image enhancement (grade +1) was considered where the hyperreflective RPE showed a sharp outer limit from the anterior choroidal vasculature in the absence of hyperreflective bleaching. Choroidal blood vessel lumen grading was achieved by discriminating the luminal (hyporeflective) regions from the stromal (hyperreflective) regions within Sattler's and Haller's layers, with a grading of +1 indicating no contrast enhancement was required to do so. Due to vessel calibre changing in a progressive

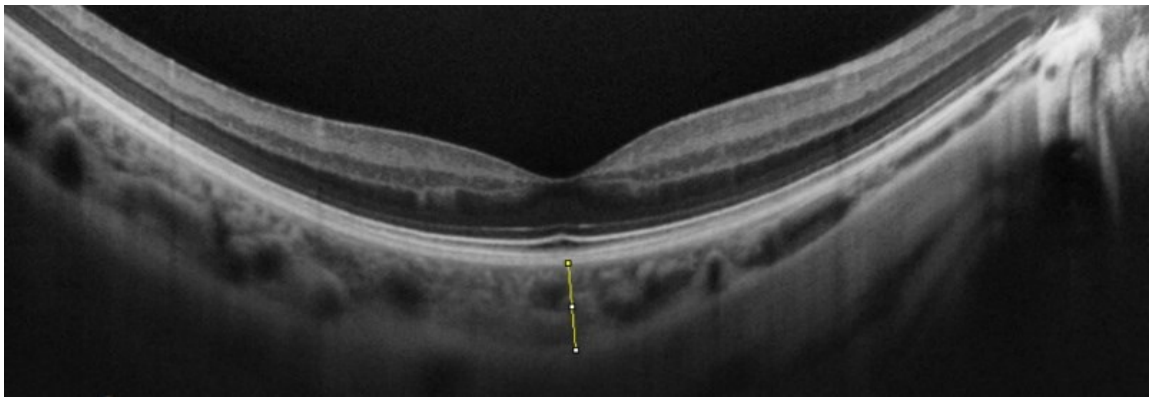


Figure 4.3: Example of manual line measurement of subfoveal choroidal boundaries using ImageJ software.

gradient through the choroid[425], vessel lumens within Sattler's and Haller's layers show no distinct anatomic boundary and so were analysed together. With the chorioscleral junction expected to be the most difficult feature to image clearly, visibility was assessed through the ability to manually mark the subfoveal outer choroidal boundary. Where this boundary was hardly or not visible with enhanced image contrast, a grade of -1 was given.

Quantitative measures were assessed by one observer using ImageJ software (LOCI, University of Wisconsin). With no image enhancement, the anterior and posterior subfoveal choroidal boundaries were manually marked, and the choroidal thickness was measured using a line tool (Figure 4.3). To ensure consistent measurements for each eye across the three devices, the pixel/μm scaling of the image outputs from each device was calibrated using ImageJ. The pixel aspect ratios were masked to the observer, labelled 'A', 'B', and 'C' to match the devices. The observer took 5 line measurements of the subfoveal choroidal thickness per image, and the mean value was calculated.

With line measurements relying heavily on accurate re-alignment of participant fixation and head position between each scan, alignment error was quantified for each device using a separate test: ten images were taken of the same individual's eye on each OCT device, and the variability between measuring each image once was compared to measuring one image 10 times.

4.2.5 Statistical analysis

All statistical analyses were performed using IBM SPSS (Statistics for Windows v28; IBM Corp., Armonk, NY, USA). P-values below 0.05 were considered statistically significant.

4.2.5a Statistical analysis of graded parameters

Both observers separately graded all four features of each image, and Cohen's kappa was run to determine whether there was agreement between the graders' judgements. Following

this, a consensus grading was performed, and a final score was given to each of the four parameters of every image. The scores of each parameter were then summed up per device and normalised to a minimum score of 0 and a maximum score of 100. The three devices were then ranked from highest (1st) to lowest (3rd) for each feature. Statistical differences between the normalised scores were calculated using Chi-square goodness of fit testing.

4.2.5b Statistical analysis of measured choroidal thickness

Intraobserver repeatability was evaluated by calculating the intraclass correlation coefficient (ICC) using a two-way mixed effect model (absolute agreement definition). For this, subfoveal choroidal thickness of 15 randomly selected images across the three OCT devices were re-measured by the same observer, separated by a minimum of 24 hours between the two measures. Next, the difference between the mean choroidal thickness of the two images per eye was calculated. The coefficient of repeatability (COR) was calculated for each device and Bland-Altman plots were used to further assess the repeatability and agreement of the devices. Due to the measurements from the right and left eye of a participant often being correlated[426], only data obtained from the right eye was used to determine the COR and produce Bland-Altman plots[427]. A repeated measures analysis of variance (ANOVA) was conducted to identify any statistically significant difference in the calculated differences between the three devices. Additional to the OCT device, the eye (right or left) was considered as a second within-subjects factor to permit inclusion of the data from both eyes[426].

To calculate the mean subfoveal choroidal thickness of each eye, all 10 measurements taken across the two images per eye (5 line measurements of each image), were averaged. A second two-way repeated measures ANOVA was used to identify any statistically significant differences in the mean choroidal thickness of each eye. Normality was confirmed using the Shapiro-Wilk test. For both ANOVA calculations, the Greenhouse-Geisser correction was applied where Mauchly's test of sphericity had been violated.

4.3 RESULTS

Inter-grader repeatability for each graded feature of the three devices is presented in Table 4.4, with the two graders showing moderate to very good strength of agreement for all features[428]. Table 4.5 shows the ranking of normalised scores for each device. The distinguishability of intraretinal layers was scored highly across all three OCT instruments, with the Heidelberg Spectralis ranking first. However, the difference in the scored ability to clearly distinguish the retinal layers showed no statistically significant difference between the three devices (p=0.290). The Topcon Triton was found to be superior to the Heidelberg

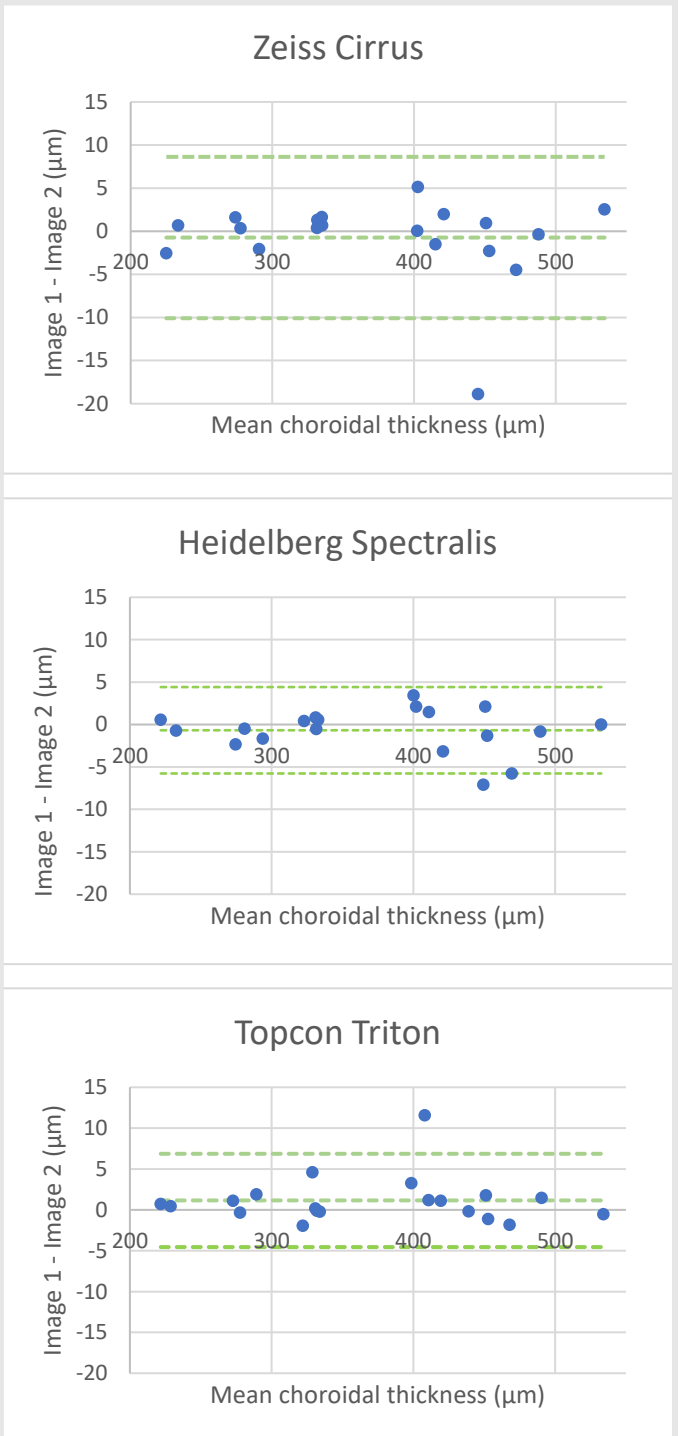


Figure 4.4: Bland-Altman plots of the **difference between the averaged choroidal thickness of images 1 and 2 per eye** for each device. For each plot, the upper and lower green dashed lines show the upper and lower 95% confidence interval limits, and the middle green dashed line shows the bias.

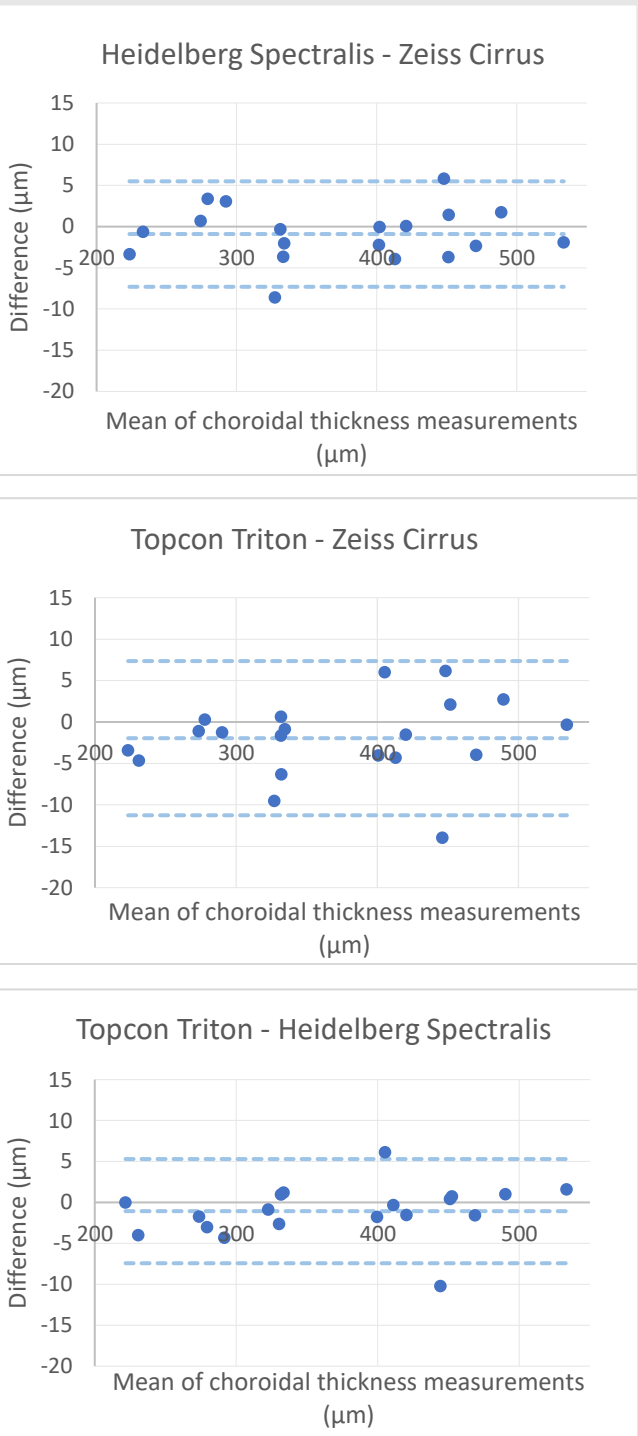


Figure 4.5: Bland-Altman plots of the **difference in the mean choroidal thickness of each eye between paired devices** (where the mean choroidal thickness for each eye was calculated by averaging the measurements of images 1 and 2 from each device separately). For each plot, the upper and lower blue dashed lines show the limits of agreement (95% confidence interval), and the middle blue dashed line shows the bias.

Spectralis and Zeiss Cirrus differed in the discriminability of the RPE from the anterior choroid (p=0.011), discriminability of choroidal vessel lumens in Sattler's and Haller's layers (p=0.004), and the visibility of the subfoveal choroioscleral junction (p=0.009). The normalised score of the Topcon Triton's ability to clearly distinguish the outer limit of the RPE was closely followed by the Heidelberg Spectralis, whereas the Zeiss Cirrus was notably lower (98, 96, and 63, respectively). There was a greater difference in the normalised scores between the Topcon Triton and the Heidelberg Spectralis in regard to the unenhanced clarity of the choroid itself (choroidal vessel lumens and outer subfoveal choroidal boundary). These features scored markedly lower in the images obtained with the Zeiss Cirrus than the Heidelberg Spectralis.

Repeated measures of subfoveal choroidal thickness showed an ICC of 0.98, indicating excellent intraobserver repeatability. Measurement error due to participant alignment and head position was negligible, with a difference in intra-device variability of ≤1μm between 10

	Zeiss Cirrus Kappa (p-value)	Heidelberg Spectralis Kappa (p-value)	Topcon Triton Kappa (p-value)
Intraretinal layers	0.843 (p<0.001)	0.530 (p<0.001)	0.562 (p<0.001)
Outer limit of RPE	0.541 (p<0.001)	0.534 (p<0.001)	0.654 (p<0.001)
Choroidal vessel lumens	0.640 (p<0.001)	0.552 (p<0.001)	0.532 (p<0.001)
Chorioscleral junction	0.547 (p<0.001)	0.847 (p<0.001)	0.582 (p<0.001)

Table 4.4: Inter-grader reliability presented as Cohen's kappa and p-values for graded parameters in respect to each OCT device. Kappa values in green indicate a very good strength of agreement (0.81-1.00), kappa values in blue indicate a good strength of agreement (0.61-0.80), and kappa values in orange indicate a moderate strength of agreement (0.41-0.60)[428].

	Ranking (scores)			p-value
	Zeiss Cirrus	Heidelberg Spectralis	Topcon Triton	
Intraretinal layers	3 (69)	1 (81)	2 (71)	0.290
Outer limit of RPE	3 (63)	2 (96)	1 (98)	**0.011**
Choroidal vessel lumens	3 (53)	2 (77)	1 (93)	**0.004**
Chorioscleral junction	3 (54)	2 (71)	1 (91)	**0.009**

Table 4.5: Ranking of normalised scores for the clarity of each image feature, where 1 represents the highest score, shaded in green. Normalised scores are presented in brackets. Statistical significance of differences between devices for each ranked parameter are presented as p-values. Bold p-values indicate statistical significance.

measures taken from one image and one measure taken from 10 images for each device (Zeiss Cirrus 0.82μm, Heidelberg Spectralis 0.17μm, and Topcon Triton 0.31μm). The Bland-Altman plots for individual devices showed random scatter, indicating no specific trend for each device (Figure 4.4). All three devices showed only a very small bias of ≤±1.15μm. The Zeiss Cirrus had the largest COR (±9.36μm) followed by the Topcon Triton (±5.71μm), and the Heidelberg Spectralis had the smallest (±5.09μm). Despite this, the differences in choroidal thickness measured between the two images (image 1 – image 2) per eye showed no statistically significant difference between devices ($F_{2, 32} = 1.73$, p=0.196).

Bland-Altman plots assessing the agreement between paired devices in the averaged choroidal thickness for each eye are presented in Figure 4.5. When compared with the Zeiss Cirrus, the Heidelberg Spectralis and Topcon Triton showed small biases of -0.90μm and -1.95μm, respectively. Between the Topcon Triton and Heidelberg Spectralis, a small bias of -1.07μm was found. The narrowest 95% confidence interval agreement limits were between the Heidelberg Spectralis and Topcon Triton (± 6.36μm). This was followed by the Heidelberg Spectralis and Zeiss Cirrus, with limits of agreement (LOA) found to be ±6.40μm. The Zeiss Cirrus and Topcon Triton showed the widest 95% LOA of ±9.31μm, indicating the images captured by these two devices had the greatest variability in measurements of subfoveal choroidal thickness. However, the mean subfoveal choroidal thickness measures showed no statistically significant difference between the three devices ($F_{1, 25} = 1.51$, p=0.237).

4.4 DISCUSSION

This study provided a qualitative and quantitative comparison of horizontal macular line scans obtained by three different OCT instruments: the Heidelberg Spectralis SD-OCT, the Zeiss Cirrus SD-OCT, and the Topcon Triton swept source DRI-OCT. In particular, this study focused on each device's ability to produce macular OCT scans of sufficient quality to assess retinal and choroidal structures, with further consideration of the repeatability of each device and agreement between devices when measuring subfoveal choroidal thickness.

The findings of this study can be interpreted differently depending on the intended use of a particular OCT device. In clinical practice, clear imaging of the posterior ocular layers has proved essential in diagnosing, classifying, and monitoring various maculopathies, including those highly associated with myopia[18]. Further, despite no clear understanding of the role of choroidal imaging when practising myopia management at present, choroidal thickness is an area of great interest in short- and long-term myopia-related research studies[131]. In both cases, it can be argued that the clarity and degree of accuracy required from an OCT device

will differ depending on the extent of precision a practitioner requires when measuring choroidal thickness. For example, when measuring changes in choroidal thickness, the level of change required to sufficiently aid diagnosis of polypoidal choroidal vasculopathy from typical age-related macular degeneration can be markedly larger than that required to detect short-term fluctuations in choroidal thickness[124, 262, 429]. In addition, using evidenced predictions of the magnitude of change in choroidal thickness expected over a particular length of time may also influence the requirements of an OCT device. For example, choroidal thickening associated with DIMS spectacle lens wear was significantly smaller at 1 week than at 12 months (as discussed in Chapter 1 Section 1.4.3a), despite both timepoints showing significant thickening from baseline[282]. As a result, an OCT device would require a higher degree of repeatability to establish significant choroidal thickening from baseline to 1 week and baseline to 12 months, whereas a less repeatable OCT device may be able to detect significant choroidal thickening from baseline to 12 months, but not that seen at 1 week. Furthermore, the relevance of graded distinguishability of the intraretinal layers, RPE, choroidal vasculature, and CSI is dependent on the area of interest to the observer. Therefore, when comparing each OCT instrument's repeatability, agreement, and order of ranking, what is deemed clinically significant is arguably dependent on the usage of the images to be obtained. In all cases, an OCT device which provides superior visualisation of the posterior ocular layers and high repeatability is unquestionably the ideal solution to ophthalmic practitioners and researchers alike.

Previous research assessing the repeatability and reproducibility of subfoveal choroidal thickness with different SD-OCT devices has supported interchangeable use of SD-OCT instruments[430]. Of the three OCT instruments assessed in the current study, the swept-source Topcon Triton DRI-OCT was identified to provide statistically significant better visualisation of three out of the four image features examined: discriminability of the RPE, the choroidal vessel lumens, and the CSI. The results indicate that the longer wavelengths employed by the SS-OCT device achieved the intended effect of minimal light attenuation through the RPE, which is reflected in other literature exploring the capabilities of choroidal imaging with SD-OCT and SS-OCT[431]. The better visualisation of the choroid achieved by the Topcon Triton may have been at the expense of the discriminability of the anterior intraretinal layers; using EDI, the Heidelberg Spectralis achieved a higher score for distinguishability of the intraretinal layers, suggesting the spectral-domain device may have provided a more balanced visualisation of the retinal and choroidal features. However, statistical significance between the ranking was not achieved. For the RPE and beyond, the Heidelberg Spectralis and Topcon Triton achieved markedly higher scores than the Zeiss Cirrus.

Improved discriminability of the RPE from the anterior choroid and clear visualisation of the CSI may be expected to provide more precise measures of subfoveal choroidal thickness when segmented manually. Therefore, although the Topcon Triton and Heidelberg Spectralis provided smaller repeatability coefficients, it was unexpected that there was no statistically significant difference in repeatability and agreement between the three devices. However, the significant difference between the ranked features of the Topcon Triton and Zeiss Cirrus may provide some explanation for why the LOA in subfoveal choroidal thickness measurements were widest between these two devices, at nearly ±10μm. This questions whether the lack of statistical significance reflects the clinical significance in this case. The clinical significance of this outcome should be a consideration if comparing choroidal thickness of a particular individual between the two devices. Perhaps less caution is required between the Heidelberg Spectralis and Topcon Triton, which showed the closest agreement (LOA ±6.36μm). These findings align with previous research supporting interchangeable use of three SD-OCT devices when manually measuring subfoveal choroidal thickness, which included the Heidelberg Spectralis and Zeiss Cirrus[430].

It appears that for all three devices, the level of repeatability was independent to choroidal thickness. Typically, thicker choroids prove more challenging to visualise due to difficulty for light to penetrate through the deeper ocular layers, yet each device appeared capable of maintaining similar levels of repeatability throughout the sample.

The subjective nature of both the qualitative and quantitative measures used in this study is an important limitation to consider. The assessment of inter-observer agreement showed mostly a moderate strength of agreement when subjectively grading the quality of each image feature. Although this was considered sufficient to subsequently conduct a consensus grading in this study, it demonstrates the variability of subjective measures and clinical interpretation, regardless of a practitioner's level of experience. Similar observations have been identified in subjective assessment of the optic disc, where considerable inter-observer variability has been found between expert eye care practitioners[432, 433]. Moreover, despite very good intraobserver repeatability of manual segmentation of the choroidal boundaries in this study, automated segmentation would have provided a more robust and efficient method of image analysis. This is a recognised difficulty amongst choroidal research studies, where intraobserver coefficients of repeatability of manual choroidal thickness measurements of healthy eyes have been reported to range from 7μm to 63μm[434, 435]. In the absence of commercially available automated segmentation algorithms, researchers often turn to custom-written software programmed to segment choroidal images captured by specific OCT instruments and scanning protocols. The lack of standardised automation remains a hurdle when minimising subjectivity of thickness measurements across differing OCT

instruments, particularly when exporting images of differing formats, resolutions, and dimensions.

In addition, the application of these findings in real-world setting is open for question; only participants with healthy eyes were recruited for this study, yet choroidal imaging and measurements of eyes with retinal and macular diseases may be of more interest to eye care practitioners in clinical practice. Some research has shown repeatability and reproducibility of different OCT devices to worsen with the presence of ocular pathology[418, 436], indicating the results of this study to be limited when applied to patient monitoring and management.

Further, participant ethnicity and eye colour on light absorption during OCT acquisition was not accounted for during this study. Despite modern OCT technologies capable of surpassing the highly pigmented RPE to image features of the choroid (see Chapter 1 Section 1.3.2a), the impact of ethnicity and eye colour on the qualitative and quantitative parameters assessed in this chapter would have been a useful consideration.

In conclusion, this study found the Zeiss Cirrus SD-OCT, Heidelberg Spectralis SD-OCT, and Topcon Triton DRI-OCT devices to capture choroidal scans of sufficient quality to produce repeatable measures of subfoveal choroidal thickness. Despite there being a statistically significant difference in the graded distinguishability of the RPE, choroidal vessel lumens, and CSI, no statistically significant difference in the measures of choroidal thickness was identified between devices. Clinical significance of the findings may vary depending on the intended use of OCT images captured over multiple devices; subject to the level of agreement required, accurate comparisons can be made between images taken on the same device, but not necessarily between devices. Caution should be applied if different instruments are being used to assess repeated measurements of choroidal thickness.

Chapter 5. Effect of short-term temporal and nasal myopic defocus on choroidal thickness

5.1 INTRODUCTION

As discussed in Chapter 1 Section 1.4.2, various research studies have shown human choroidal thickness to change in response to lens-induced retinal defocus, thinning with a negative lens and thickening with a positive lens (see Table 1.4 in Chapter 1 Section 1.4.2a). These changes appear to be rapid, with reports of change occurring within an hour[126, 127, 262]. A significant change in choroidal thickness has been found in as little as 10 minutes in response myopic defocus[120]. The majority of these research studies have explored full-field defocus, where defocus is induced using a full-aperture spherical spectacle or contact lens. Fewer studies have explored regional defocus, where only part of the retina is exposed to myopic or hyperopic blur. Some research has suggested that the choroid may respond in a regionally selective manner (see Chapter 1 Section 1.4.2a), where the area exposed to defocus shows the greatest thickness change; separate superior and inferior hemifield myopic defocus has been found to show choroidal thickening in that specific hemifield[262]. Optical interventions for myopia control often employ altered peripheral optics, where retinal myopic defocus is induced in the peripheral retina using a spectacle or contact lens[295]. With this, multiple studies have recorded choroidal thickening at one week[282] to several months of wear[281, 312, 313, 315]. However, clinical trials exploring the efficacy of defocusing myopia interventions and long-term choroidal thickness changes use child participants, yet most of the investigative work exploring thickness changes in the short-term use adult participants.

The immediate events following cessation of defocus is another uncertainty. Following short periods of full-field myopic defocus, resultant choroidal thickening has been found to return to baseline at 24 hours in adults following removal of the defocusing lens[121, 125], and significantly decline 2 hours post-removal of defocus in children under cycloplegic conditions[124]. However, little is known about these changes within a shorter timeframe, and whether this differs with patterns and degrees of defocus. Similarly, the impact of refractive error on the choroid's dynamic characteristics and short-lived thickness fluctuations is yet to be established. It may be that visual information is signalled differently in the retina of a myopic eye than emmetropic eye, leading to dissimilar transient choroidal modulation.

This research study aims to provide further insight into the aforementioned obscurities. In particular, how the choroid responds to the short-term onset and cessation of myopic defocus isolated to the nasal and temporal retinal areas, and whether the refractive status of

the eye influences the choroidal response. In addition, whether the eyes of children elicit the same response to that of young adults in the same defocused state.

5.2 METHODS

5.2.1 Participants

Participants were split into two age groups: children/adolescents (6 to 15 years of age), and young adults (18 to 25 years of age). Although research shows presbyopic eyes to elicit rapid choroidal compensation for lens-induced defocus[127], these age ranges were chosen to allow comparisons between eyes undergoing faster eye growth typically seen in childhood/adolescence[402, 437, 438], and eyes of young adults where axial growth and refractive error progression is expected to be more stable[439]. For each age group and defocus condition, a sample size of 10 was 80% powered to detect an intrasession difference in choroidal thickness of 5μm using repeated measures analysis of variance (ANOVA) with a 95% confidence level and p value of <0.05 taken as significant[440] (calculated using G*Power 3.1, University of Dusseldorf).

All participants had no history of ocular pathology, no systemic health problems, were non-smokers, and had no previous or existing use of myopia control treatments. This included orthokeratology, bifocal or multifocal spectacle/contact lenses, and atropine eye drops. Ocular health was screened using slit lamp biomicroscopy of the anterior and posterior segments, and fundus photography. Unaided, habitual, and best-corrected visual acuity (BCVA) was measured monocularly and binocularly in every participant. All participants were required to have a BCVA of +0.1 LogMAR (logarithm for the minimum angle of resolution) measured at both distance and near using 3-meter digital and 40cm printed logarithmic visual acuity charts. Oculomotor balance was examined using a cover test at 3 meters and at 30 centimetres, and stereoacuity was measured using the Titmus Fly stereotest at 40cm. Eligible participants showed no decompensating deviation on a cover test, and a minimum stereoacuity of 60'' arc.

Participants attended two or three visits to the Aston University Vision Sciences building, with each visit being a minimum of 48 hours apart. Due to diurnal fluctuations in choroidal thickness[187], each visit was arranged to be within ±1 hour of each other. Prior to each visit, all participants were instructed to avoid caffeine for a minimum of six hours, alcohol for a minimum of two hours, vigorous exercise for a minimum of 30 minutes, and near work for a minimum of 20 minutes to avoid confounding influences on choroidal thickness[193, 196, 220, 221, 369].

The study was approved by the Aston University Research Ethics Committee and adhered to the tenets of the Declaration of Helsinki. Informed consent (and assent from participants under 16 years of age) was obtained from all participants prior to any experimental procedures (Appendix 3, 4, and μ). Participants aged under 16 years were required to be accompanied by a parent or guardian (Appendix 6 and 7).

5.2.1a Young adult participants

In total, 21 young adults (6 male, 15 female) were recruited from the student population of Aston University, Birmingham, UK. The participants were predominantly of South Asian ethnicity (n=19), and included White European (n=1), African-Caribbean (n=1), and Middle Eastern (n=1) ethnicities. Participants were aged between 18 to 25 years (mean age 21.1 ± 1.5 years). Within this age group, participants were separated into two groups based on their refractive error: myopes (n=10) and emmetropes (n=11) (Table 5.1). Refractive error was measured both objectively (autorefraction) and subjectively. A +1.00DS blur test was used to ensure the subject's accommodation was relaxed during subjective refraction, followed by binocular balancing and binocular addition to elicit any residual or imbalanced accommodative demand. Due to the temporary thinning of the choroid following instillation of cyclopentolate hydrochloride or tropicamide[205, 206], cycloplegia was only considered in young adults if their autorefraction and subjective results were unexpectedly different (where autorefraction results were ≥0.50D more positive), however this wasn't required for any of the participants. Myopic participants were required to have a mean spherical equivalent (MSE) between -0.50D and -6.00D, and emmetropes a MSE between +0.50D and -0.25D. Only individuals with ≤0.75D astigmatism and ≤0.75D anisometropia were able to participate as determined by their subjective refraction result.

	Whole Sample (n=21)		**Myopes (n=10)**		**Emmetropes (n=11)**	
Age (years)	21.1 ± 1.50		20.8 ± 1.40		21.4 ± 1.71	
Eye	**Right eye**	**Left eye**	**Right eye**	**Left eye**	**Right eye**	**Left eye**
MSE (D)	-1.03 ± 1.49	-0.93 ± 1.38	-2.38 ± 1.12	-2.16 ± 1.12	0.08 ± 0.32	0.06 ± 0.28
Astigmatism (D)	-0.46 ± 0.25	-0.50 ± 0.23	-0.53 ± 0.22	-0.58 ± 0.17	-0.32 ± 0.24	-0.36 ± 0.18
Axial length (mm)	24.16 ± 0.95	24.06 ± 0.91	24.46 ± 0.77	24.35 ± 0.83	23.88 ± 1.04	23.79 ± 0.94

Table 5.1: The means ± standard deviations of age, mean spherical equivalent (MSE), level of astigmatism, and axial length for both eyes. Measures are presented as the whole sample and by refractive error groupings.

5.2.1b Child participants

Child and adolescent participants were recruited from the Aston University Ophthalmic Research and Primary Care clinics. Eleven children (5 male, 6 female) participated, with a mean age of 11.36 ± 2.11 years. The child participants were also of mixed ethnicities: South Asian (n=7), White European (n=3), and African-Caribbean (n=1). All child participants were myopic (Table 5.2) with the same eligibility criteria as the adult myopic participants (MSE between -0.50 and -6.00D, ≤0.75D astigmatism, ≤0.75D anisometropia, and monocular and binocular BCVA of +0.1 LogMAR). All child participants underwent cycloplegic autorefraction using 1% cyclopentolate hydrochloride eye drops, with the measurements taken when the participant's amplitude of accommodation was reduced to 2.00D or less, measured using a Royal Air Force (RAF) rule. To ensure cycloplegia had no impact on choroidal thickness, cycloplegic refractions were conducted at a separate study visit with a minimum of 48 hours before the defocus session.

	Child sample (n=11)	
Eye	**Right eye**	**Left eye**
MSE (D)	-2.10 ± 1.03	-2.07 ± 0.98
Astigmatism (D)	-0.43 ± 0.21	-0.50 ± 0.14
Axial length (mm)	24.28 ± 0.92	24.29 ± 0.96

Table 5.2: The means ± standard deviations of age, mean spherical equivalent (MSE), level of astigmatism, and axial length for both eyes of child participants.

5.2.2 Instrumentation

The instrumentation used during the screening process and thereafter are as detailed below.

5.2.2a Autorefraction

Autorefraction was measured with the Grand Seiko Autorefractor WAM-5500 (Grand Seiko Co. Ltd., Hiroshima, Japan). The WAM-5500 uses an open-field distance target under binocular viewing to produce an objective measure of refraction with relaxed accommodation. During the measurement, the subject looks through the open-field aperture at a Maltese cross target positioned 3 meters ahead in primary gaze, whilst an image of an infrared ring is reflected off the subject's retina. This ring target is brought into focus by a moving lens on a motorised track, immediately calculating the refractive error status. When studied, the instrument has been found to be largely successful in relaxing accommodation in myopic and emmetropic individuals[441]. The instrument provides repeatable, reliable measurements valid for both research and clinical practice in both adults and children[441, 442], with measurement increments as fine as 0.01D for power and 1° for cylinder axis. In this study, 5 autorefraction measurements are taken and averaged per eye, with mean spherical equivalent (MSE) calculated as sphere plus half the negative cylinder.

5.2.2b Keratometry

In addition to autorefraction, the Grand Seiko Autorefractor WAM-5500 (Grand Seiko Co. Ltd., Hiroshima, Japan) can calculate the central corneal radius. The instrument reflects an infrared ring off the corneal surface and, with image analysis, can use this reflection to calculate corneal curvature to 0.01mm increments. The autokeratometry readings measured with the instrument have been found to show close agreement with conventional keratometry[441], and arguably have the advantage of objectivity over manual devices.

5.2.2c Ocular biometry

During the baseline visit, participants had their axial length measured using the IOLMaster700 optical biometer (Carl Zeiss Meditec AG, Jena, Germany). This instrument was designed predominantly for intraocular lens biometry for cataract surgery; however, the non-invasive nature and fast measurement speed makes this device advantageous when measuring axial lengths in a wider context, particularly for child participants.

The IOLMaster 700 is based on the principal of swept source optical coherence tomography (SS-OCT), and can provide several measurements including corneal thickness, anterior chamber depth, lens thickness and axial length. By scanning through a series of wavelengths, SS-OCT improves the interference pattern and forms multiple A-scans, which are combined to produce a B-scan image.

Typically, 5 axial length measurements are taken and averaged. Through clinical evaluation, the IOLMaster700 has been shown to have highly repeatable and reproducible measures of axial length for both adult[443, 444] and child[445, 446] populations.

5.2.2d Optical coherence tomography

Enhanced depth choroidal imaging at baseline and thereafter was captured using the Heidelberg Spectralis SD-OCT (Heidelberg Engineering, Heidelberg, Germany). The qualitative assessment conducted in Chapter 4 of this thesis found the Topcon Triton DRI-OCT to provide visibility of the CSI slightly superior to the Heidelberg Spectralis, however the Heidelberg Spectralis was chosen due to aligning with previous research studies[124, 260, 262-264] and the Triton was not available within the research department on beginning this study. Further information about this instrument can be found in Chapter 4 Section 4.2.1a. A high-resolution (1536 x 496 pixels, axial resolution of 3.9µm per pixel) radial OCT scanning protocol was used in this experiment. This consisted of 6 radial spokes positioned 30° apart, with each spoke covering a 30° retinal area (Figure 5.1), permitting repeatable measurements of choroidal thickness with an intrasession repeatability coefficient of

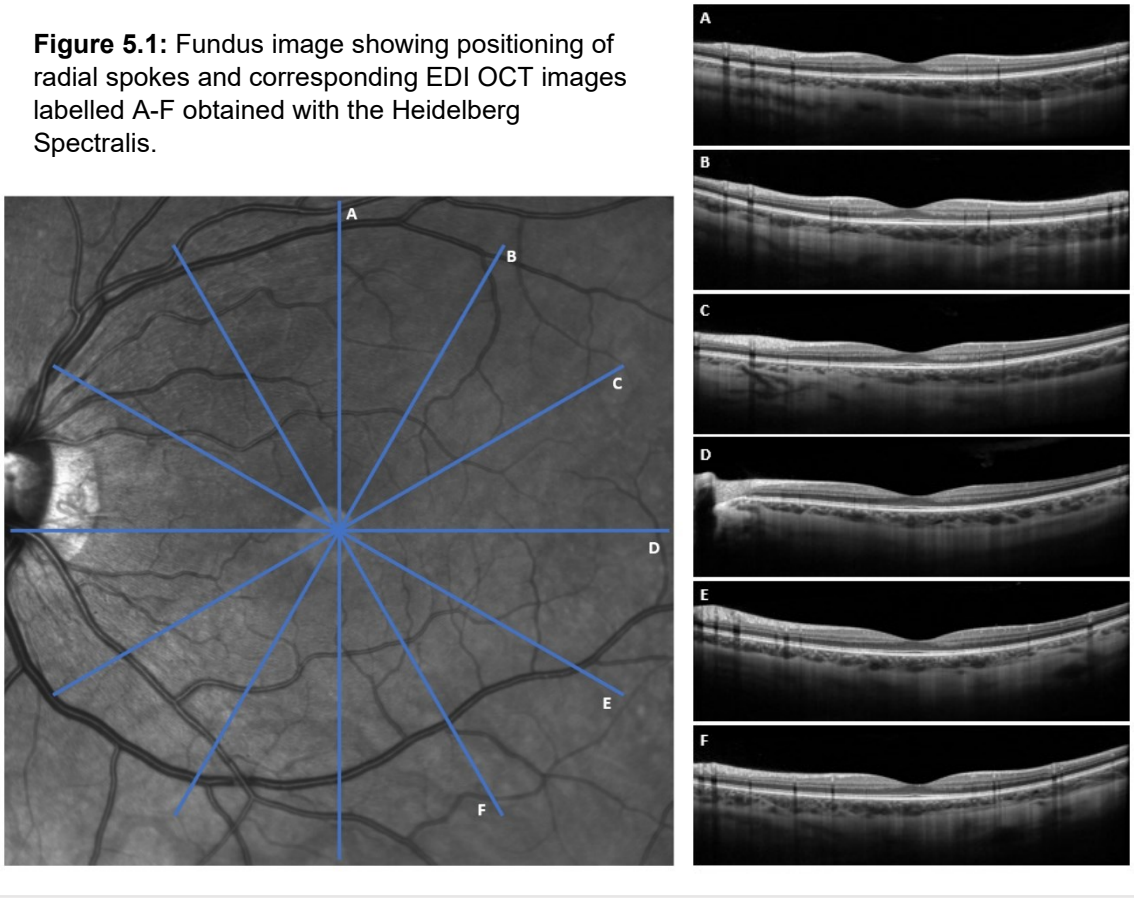


Figure 5.1: Fundus image showing positioning of radial spokes and corresponding EDI OCT images labelled A-F obtained with the Heidelberg Spectralis.

13µm[157, 434]. Each of the six images consisted of 50 averaged B-scans captured with software-based motion compensation (automatic real time, ART).

5.2.2e Fixation tracking

To ensure stable viewing throughout the study visit, participant fixation was tracked using the Tobii EyeX eye tracking device (Tobii Technology, Stockholm, Sweden) positioned within a metre from the subject below the primary position of gaze. The Tobii EyeX device uses the corneal reflection produced by an infrared illuminator to represent the pupil centre, which creates a real-time estimate of the position of gaze of both eyes relative to the monitor position. This device produces a visual marker on the monitor relative to the participant's fixation, so a loss of fixation causes the marker to disappear. The fixation marker appears as a translucent 'bubble' to minimise interference and distraction when viewing the TV display. Any fixation losses were actively timed to assess each subject's cooperation and the reliability of data collected.

5.2.3 Defocus conditions

Three different conditions were trialled in a random order: temporal myopic defocus, nasal myopic defocus, and a control condition (clear vision) (Figure 5.2). Regional myopic defocus was induced using a bespoke full-aperture executive bifocal trial lens; one half contained no

dioptric power and the other contained +3.00 dioptric power. Participants wore a trial frame containing their spectacle prescription using full-aperture trial lenses. The bifocal trial lens was placed in the trial frame vertically in front of one or both eyes, inducing 3.00D of relative plus power in the nasal or temporal hemifield. To ensure the participant was looking through the centre of each lens, the trial frames were adjusted to account for the participant's monocular pupillary distance and vertical heights relative to the trial frame and head position. The defocus conditions across both visits were randomly ordered so that one eye experienced nasal defocus, one experienced temporal defocus, and one eye experienced the control condition.

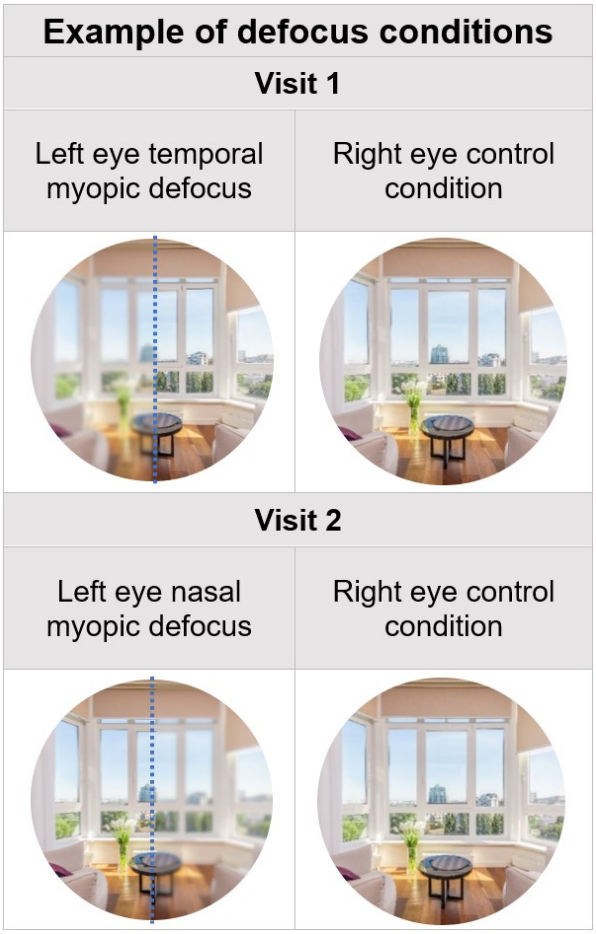


Figure 5.2: Example of hemifield defocus from a participant's perspective. The order of defocus conditions and eye used at each visit were randomised between participants.

5.2.4 Data collection procedures

Participants binocularly viewed a 24-inch LED-backlit monitor at 6 metres (subtending a 5.3° horizontal by 3.2° vertical visual angle) in low photopic lighting conditions (between 10 to 20 lux, measured using the CA810 Lux Meter, Chauvin Arnoux, Asnières-sur-Seine, France) to increase pupil diameters, enable rapid OCT measures, and minimise distraction by anything else in the room. Television brightness and contrast settings were consistent for every participant. To encourage maintained fixation and interest, participants were able to watch a programme or film of their choosing. The Tobii EyeX fixation tracker was calibrated and positioned below the participant's line of fixation to ensure unobstructed viewing of the monitor and accurate positioning of the fixation marker. When facing the monitor, participants sat perpendicular to the Spectralis OCT device (Figure 5.3). Participants sat on a swivel chair to ensure swift movements between facing the monitor and facing the OCT device.

An OCT scan was taken of both eyes to provide a choroidal image at baseline. Immediately after this, the randomly selected defocus conditions were introduced to each eye, beginning the defocus period. Participants were instructed to keep their head position as still possible. The total duration of the defocus period differed between the young adult (18-25 years) and

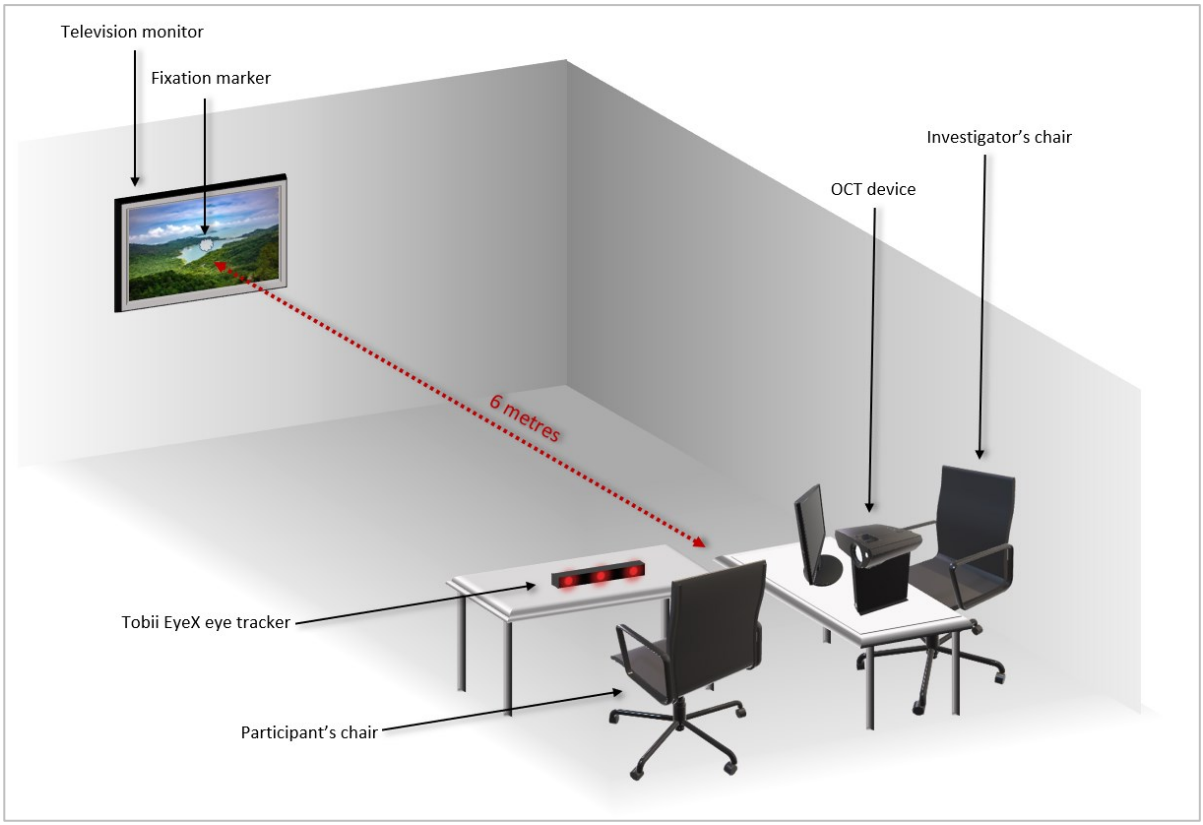


Figure 5.3: Schematic diagram of the room set-up used during the defocus and recovery periods.

child (6-17 years) participant groups: 45 minutes and 25 minutes, respectively (Figure 5.4). This was due to the expectation that prolonged fixation and head position would be more challenging for child participants, particularly in an unfamiliar visual environment. Given that changes in choroidal thickness have been found to occur in as little as 10 minutes with myopic defocus[120], 25 minutes was seen to be a realistic time period for a child to maintain interest in the viewing task whilst potentially eliciting a detectable choroidal response.

For young adults, OCT scans were taken of each eye at 2 intervals during the defocus period (25 minutes and 45 minutes), followed by a 'recovery period'; after 45 minutes of defocus, the defocusing lens was removed from the trial frame and participants continued to watch the television monitor for another 20 minutes, where a final OCT scan was taken (Figure 5.4). Children had OCT scans taken at 3 timepoints (5, 15 and 25 minutes), with no recovery period. At each timepoint, the trial frame was removed to provide clear OCT images, and immediately replaced.

Fixation was monitored for the entire duration of the defocus and, for adult participants, recovery periods. The investigator observed the presence and position of the fixation marker displayed on the television screen. If loss of fixation occurred, participants were verbally instructed by the investigator to keep looking at the monitor. Time looking away from the

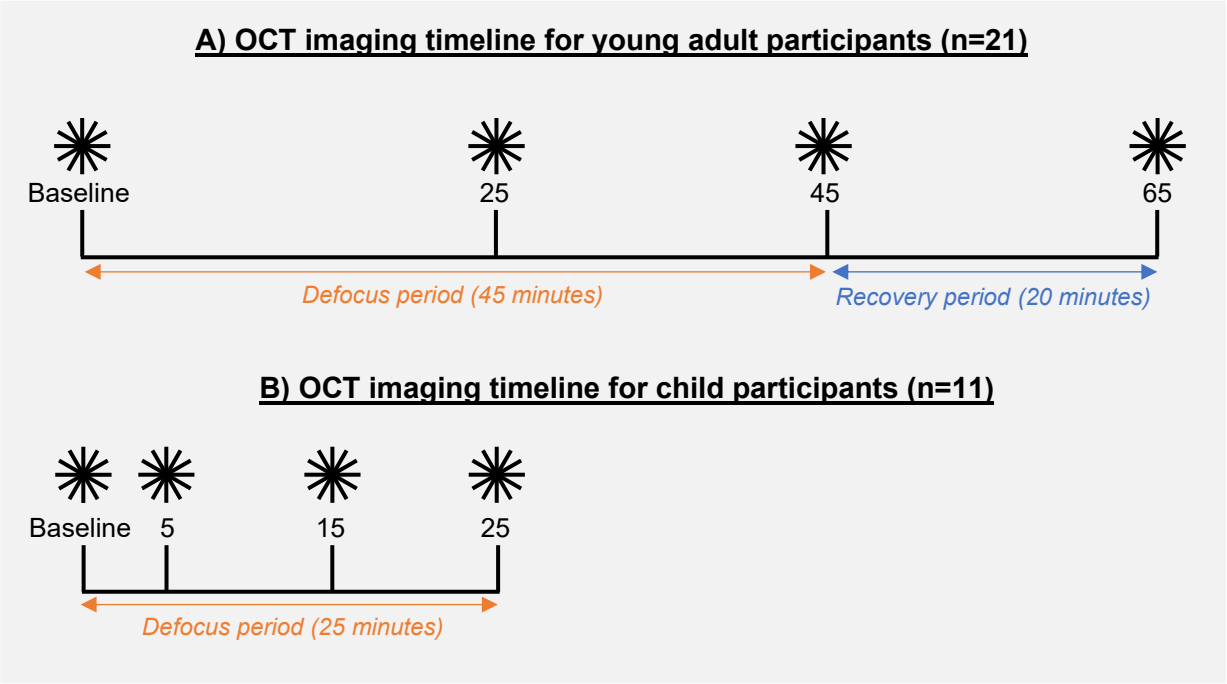


Figure 5.4: Timelines (in minutes) of radial OCT scans taken for the A) defocus and recovery periods for young adult participants and B) defocus period for child participants. OCT scans are depicted with the radial symbol: ✳.

screen was timed to provide a measure of each participant's fixation throughout the experiment.

5.2.5 Data analysis

5.2.5a Choroidal segmentation

To allow masked data analysis, the OCT B-scans were exported under anonymous ID numbers with no indication of which images related to which defocus condition. The 6 images captured per eye at each time interval were segmented using a software program developed and compiled using MATLAB (The MathWorks, Inc., Natick, Massachusetts, United States)[171]. This program employs semi-automated segmentation of the inner limiting membrane (ILM), retinal pigment epithelium (RPE), and the posterior choroidal boundary, where any automatic segmentation errors can be manually corrected by an investigator (Figure 5.5). All OCT images were segmented using the same software and, where applicable, manually corrected by the same investigator.

The investigator's repeatability was calculated to ensure any required manual adjustments were consistent across the sample. Ten randomly selected OCT images from 10 participants where manual adjustment was required were segmented on two occasions separated by a minimum of 24 hours, which included manually marking the foveal pit. The coefficients of repeatability of the mean choroidal thickness and selection of the foveal pit were calculated,

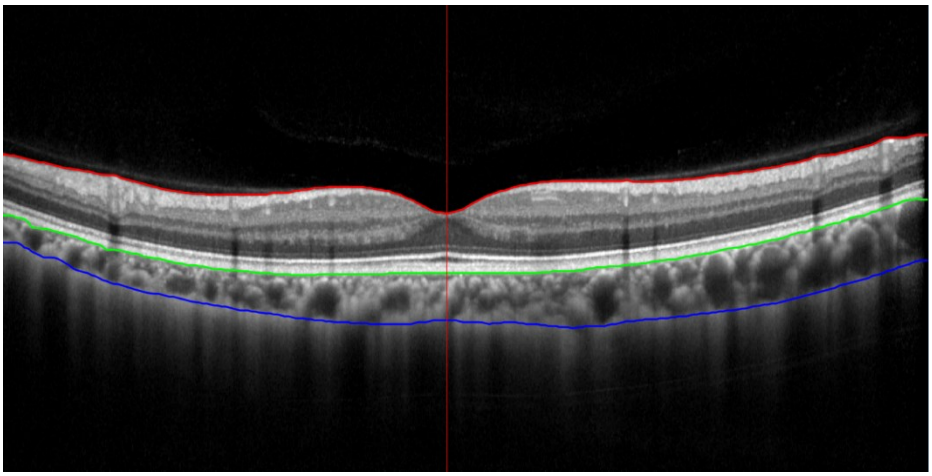


Figure 5.5: Example of an OCT image segmented using semi-automated software developed for MatLAB[171]. Red line marks the ILM, green line marks the RPE, and blue line marks the posterior choroidal boundary. Foveal pit has been marked manually.

giving a value of ±1.45µm and ±4.38 pixels, respectively. The scanning protocol employed in this study provides an axial resolution of 3.9µm and image output of 1536 x 496 pixels, indicating the calculated repeatability coefficients were sufficient for comparative analysis between images and participants.

5.2.5b Ocular scaling

With the varying refractive errors and biometric measurements across participants, choroidal images were adjusted for transverse magnification to account for the impact of ocular magnification at the posterior pole. The length of each 30° scan in millimetres was calculated using methods verified by other studies[435, 447].

Firstly, using a model of a three-surface schematic eye proposed by Bennett et al., (1988)[448], the participant's spectacle prescription, vertex distance, anterior chamber depth, lens thickness, corneal power, and axial length were used to calculate the eye's equivalent power. From this, the position of the eye's second nodal point was determined using the step-along method[449]. Using the distance from the second nodal point to the retina, the length of the retina in micrometres per angular degree from the nodal point was calculated[447], which, in turn, allowed the transverse scaling to be calculated specifically for the Spectralis scanning protocol and image output (1536 pixels x 3.9 µm/pixel) (Figure 5.7).

Following transverse scaling, a 6mm area of the choroid could be estimated for each participant, covering 3mm temporally and 3mm nasally from the foveal pit marker

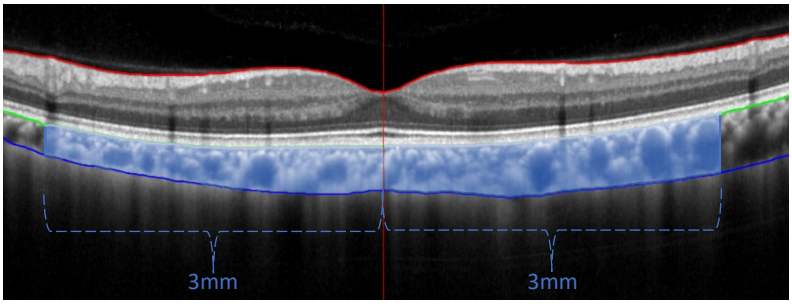


Figure 5.6: Segmented OCT image demonstrating the 6mm choroidal area analysed. The mean temporal and nasal choroidal thicknesses are calculated over a 3mm length either side of the foveal pit marker.

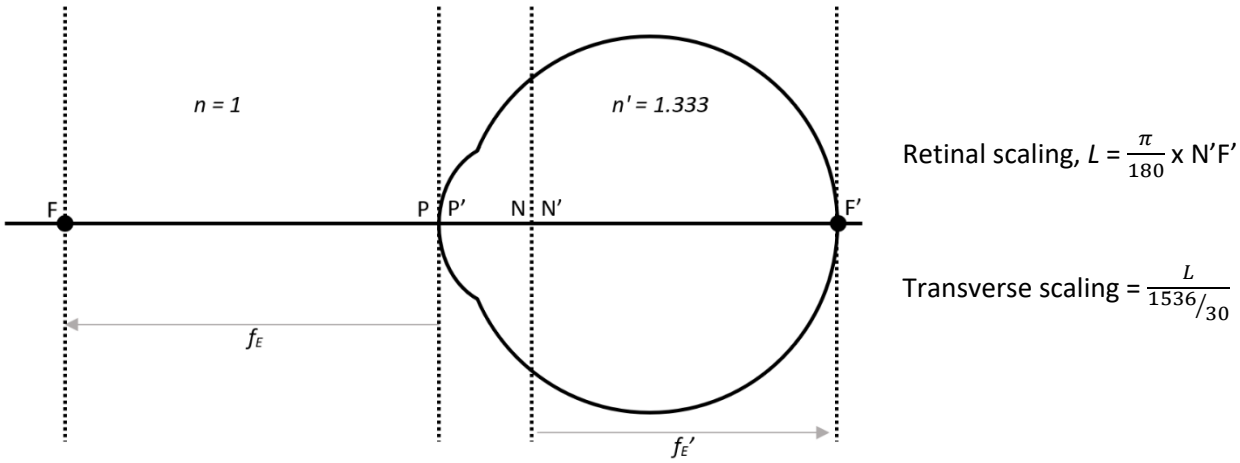


Figure 5.7: Schematic diagram of reduced eye used to calculate the distance between the second nodal point and the retina (N'F'). The distance is then used to calculate the retinal scaling and transverse scaling specific to the OCT images.

(Figure 5.6). The mean choroidal thickness of the temporal and nasal choroidal area was then calculated for statistical analysis.

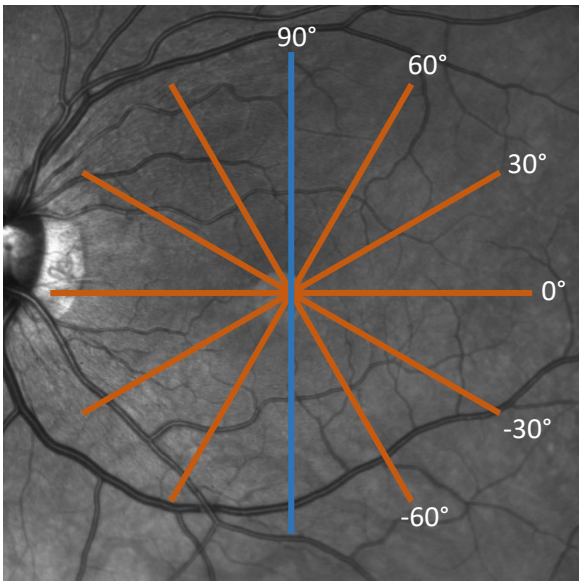


Figure 5.8: Fundus image with labelled angles of OCT line scans within the radial scanning protocol. The 90° line scan (blue line) was used to analyse superior and inferior choroidal thickness, and line scans from 60° to -60° (orange lines) were used to analyse nasal and temporal choroidal thickness. The analysis was completed on the grouped naso-temporal scans assuming independence between scans positioned from 60° to -60°.

5.2.5c Statistical analysis

All statistical analyses were performed using IBM SPSS (Statistics for Windows v28; IBM Corp., Armonk, NY, USA). The data for young adults and children were initially analysed separately and a p-value below 0.05 was considered statistically significant in all cases. The MSE, axial length, and mean baseline choroidal thickness measurements between the right and left eyes were assessed with paired t-tests. For each radial scan, the line scan positioned at 90° was analysed separately to scans positioned at 60° to -60° (Figure 5.8) to identify any statistically significant changes in choroidal thickness across the 3mm superior region, 3mm inferior region, and combined 6mm vertical region. All data was normally distributed as confirmed by the Shapiro-Wilk's W test. The Greenhouse-Geisser correction was applied where the sphericity assumption was violated, and Bonferroni-adjusted pairwise comparisons were conducted for statistically significant main effects and interactions.

Paired t-tests were used to assess the differences in MSE, axial length, and baseline choroidal thickness between the right and left eyes of participants. Data collected from young adult participants was analysed using the following methods: an unpaired t-test was conducted to compare the similarities in MSE, axial length, and baseline choroidal thickness between the eyes of myopic and emmetropic young adult participants. Levene's test for equality of variances was used to confirm there was homogeneity of variances. Changes in mean choroidal thickness within the 3mm temporal region, 3mm nasal region, and the entire 6mm region from baseline to each timepoint were calculated for each scan. As choroidal thickness was measured in the same participants at regular time intervals, a repeated measures ANOVA was conducted. Three within-subject factors were considered: defocus condition (temporal defocus, nasal defocus, and control condition), time (25 minutes and 45 minutes defocus, and 20 minutes recovery), and choroidal region (nasal choroid and temporal choroid). One between-subject factor of refractive error (myopic and emmetropic) was also included in the analysis.

Data collected from child participants was analysed using the following methods: to assess the statistical significance of the differences between defocus-mediated changes, the changes in choroidal thickness from baseline to each timepoint were calculated in the same way as that described for the young adult data, and a repeated measures ANOVA was conducted. Three within-subject factors of defocus condition (temporal defocus, nasal defocus, and control), time (5, 15, and 25 minutes of defocus) and choroidal region (nasal and temporal) were included.

For comparison between child and young adult data, an unpaired t-test was used to assess the measurements of MSE, axial lengths, and baseline choroidal thickness between the eyes of the child and myopic young adult participants. Homogeneity of variances was confirmed by Levene's test for equality of variances. An additional repeated measures ANOVA was run, which included the following within-subject factors: defocus condition (temporal defocus, nasal defocus, and control), time (25 minutes only) and choroidal region (nasal and temporal). As all child participants were myopic, data from myopic young adults were used in this analysis. One between-subject factor of age group (child and young adult) was also included.

5.3 RESULTS

5.3.1 Results for young adult age group

All young adult participants managed to maintain relatively stable fixation throughout the experimental session; 16 kept the fixation marker stable throughout both visits, and the

	Mean baseline choroidal thickness of young adult participants (µm)		
	Right eye	**Left eye**	**Mean of both eyes**
Whole sample (n=21)	344.53 ± 79.01	345.09 ± 73.15	344.81 ± 75.24
Myopes (n=10)	301.90 ± 77.10	311.45 ± 76.01	306.68 ± 74.67
Emmetropes (n=11)	383.28 ± 60.75	375.68 ± 57.80	379.48 ± 58.00

Table 5.3: Mean choroidal thickness of the 6mm region assessed at baseline. Data are presented as mean ± standard deviations for the whole sample and by refractive error groupings.

remaining 5 participants lost fixation intermittently at one or both visits for a range of 3 to 15 seconds in total (mean 6.8 ± 4.7 seconds). Paired t-tests found the MSE (p=0.120), axial length (p=0.425), and choroidal thickness (p=0.452) to not be statistically significantly different between the right and left eyes of the whole sample. Between the myopic and emmetropic participants, a statistically significant difference in MSE (p<0.001) and axial length (p=0.021) was identified (refer to Table 5.1), and mean baseline choroidal thickness (Table 5.3) was significantly thinner in the eyes of the myopic participants (p<0.001).

Choroidal thickness measurements from vertical scans positioned at 90° showed no statistically significant interaction between defocus condition, choroidal region (inferior and

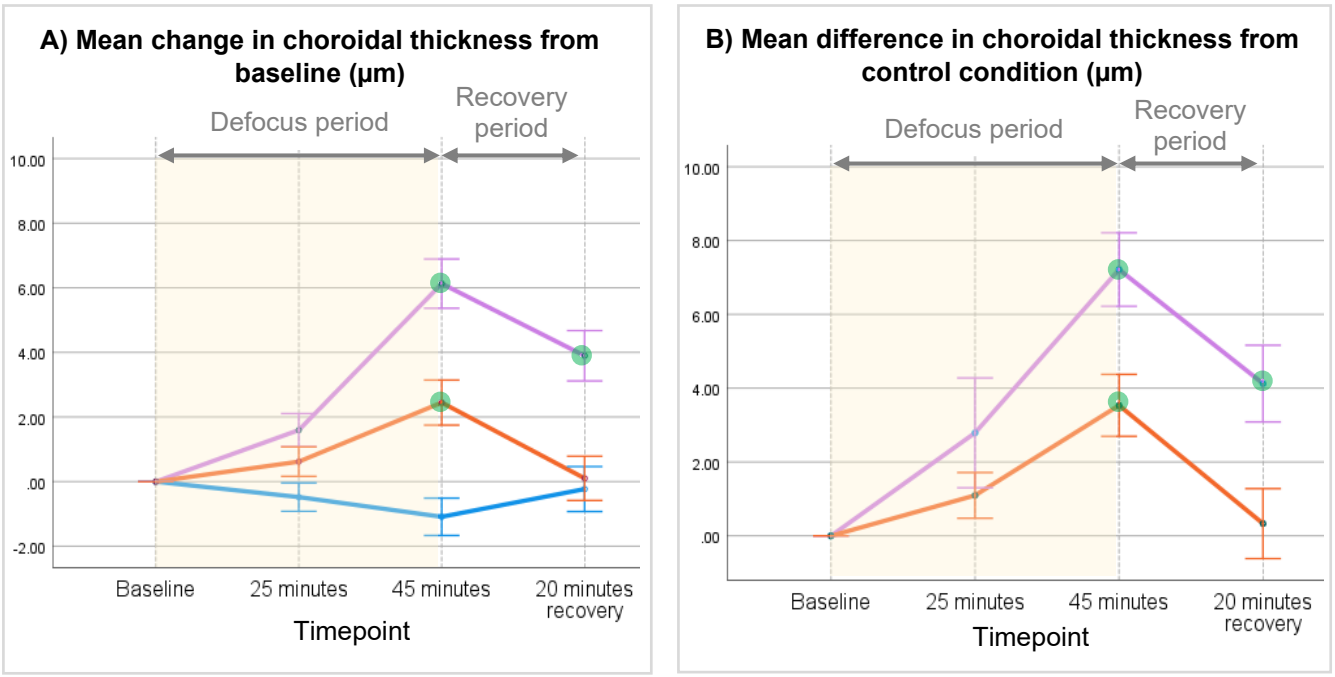


Figure 5.9: Means of A) changes in choroidal thickness from baseline, and B) differences in choroidal thickness from that measured during the control condition at each timepoint. **Purple line = nasal defocus, orange line = temporal defocus, and blue line = control condition**. Green markers indicate where a statistically significant difference in choroidal thickness was found in A) from baseline, and B) from control condition. Points with no green marker indicate no statistical significance (p≥0.05). Error bars represent the standard error of the mean.

superior), and time ($F_{5, 89}$ = 0.997, p=0.419). For changes in choroidal thickness measured at 60° to -60° (Figure 5.8), a statistically significant interaction was observed between the defocus condition and time ($F_{5, 500}$ = 12.522, p<0.001). The averaged choroidal thickness across the 6mm macular area showed no significant change from baseline to each timepoint in the control condition (all p>0.05), whereas significant choroidal thickening from baseline occurred at 45 minutes of defocus and 20 minutes of recovery in the nasal defocus condition (all p<0.05). Statistically significant choroidal thickening was also observed across the averaged 6mm region following 45 minutes of temporal defocus (Figure 5.9A). This was consistent when comparing the changes seen in nasal and temporal defocus to those measured during the control condition (Figure 5.9B). The specific averaged thickness changes are presented in Table 5.4. Further, the results indicate that the defocus-induced changes in choroidal thickness differed between the 3mm nasal and 3mm temporal regions; a statistically significant interaction between the defocus condition, time, and choroidal region (nasal and temporal) was observed ($F_{5, 523}$ = 6.687, p<0.001) (Table 5.4 and Figure 5.10). During the control session, the choroid showed statistically significant thinning from baseline within the temporal region at 45 minutes, whereas no change was seen within the nasal region at all timepoints. No significant change in choroidal thickness across the nasal and temporal regions at 25 minutes of nasal myopic defocus was found, however a statistically significant thickening was observed in both regions at 45 minutes of nasal defocus. At 45 minutes, this thickening was significantly greater within the 3mm nasal choroidal area compared to the temporal choroidal area (mean difference of 3.82 ± 1.09µm, p=0.002). At 20 minutes of recovery from nasal defocus, the significant thickening had

		Change in choroidal thickness from baseline (µm)								
		Control condition			**Nasal defocus**			**Temporal defocus**		
	Time interval	Nasal region	Temporal region	6mm mean	Nasal region	Temporal region	6mm mean	Nasal region	Temporal region	6mm mean
Defocus period	25 minutes	+0.09 ± 6.55	-1.04 ± 5.93	-0.48 ± 4.50	+1.64 ± 6.44	+1.55 ± 7.36	+1.60 ± 5.24	+0.70 ± 6.25	+0.53 ± 6.72	+0.62 ± 4.67
	45 minutes	+0.24 ± 8.43	-2.41 ± 6.40	-1.09 ± 5.93	+8.04 ± 9.76*	+4.22 ± 9.42*	+6.13 ± 7.81*	+0.62 ± 9.43	+4.28 ± 8.50*	+2.45 ± 7.15*
Recovery period	20 minutes recovery	-0.05 ± 9.40	-0.41 ± 8.58	-0.23 ± 7.14	+5.20 ± 9.08*	+2.59 ± 10.28	+3.90 ± 7.99*	+0.09 ± 10.70	+0.12 ± 8.12*	+0.10 ± 7.03*

Table 5.4: The mean change in choroidal thickness with time for all young adult participants from baseline for each defocus condition. + values indicate choroidal thickening, and – values indicate choroidal thinning. Statistically significant choroidal thickening is presented in green text and choroidal thinning in red text. Values shaded in grey indicate no statistically significant change from baseline. **Figures marked with * indicate a statistically significant difference in the change in choroidal thickness from the previous timepoint.** Data are expressed as mean ± SD.

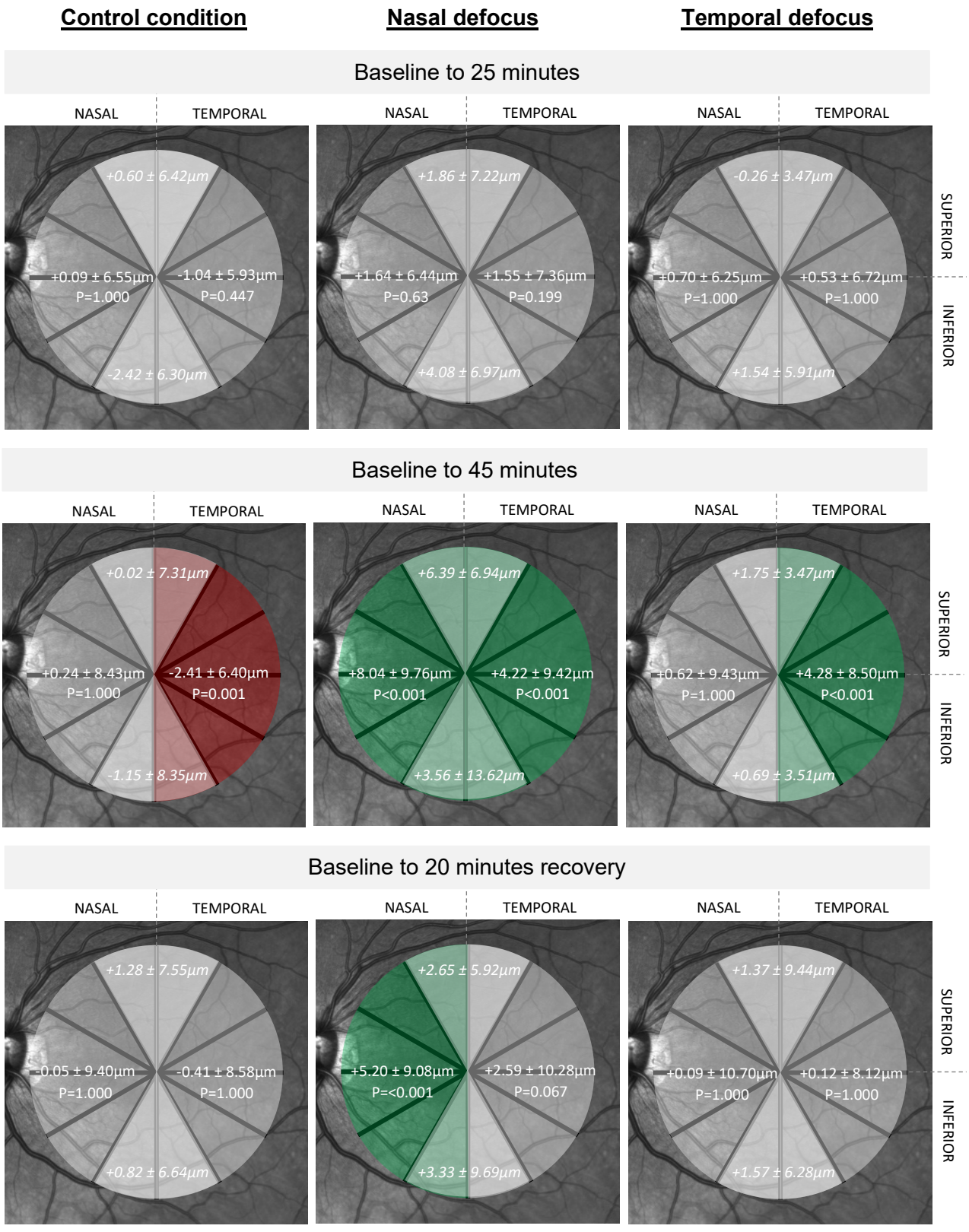


Figure 5.10: Thickness plots labelled with choroidal thickness changes from baseline across the 3mm inferior/superior (90°) and nasal/temporal (60° to -60°) 3mm regions. Green hemifields indicate significant choroidal thickening, red hemifields indicate significant choroidal thinning, and grey hemifields indicate no statistically significant difference from baseline. No statistically significant interaction was observed for inferior/superior choroidal thickness change from baseline (p=>0.05). Data are expressed as mean ± SD. P-values are presented for nasal and temporal thickness changes.

been maintained in the nasal region, however there was no statistically significant difference in thickening from baseline between the nasal and temporal regions (mean difference 2.61 ± 1.08μm, p=0.051).

At 45 minutes of temporal myopic defocus, a statistically significant choroidal thickening from baseline was found in just the temporal region, being significantly thicker than the nasal region at that timepoint (mean difference 3.67 ± 1.06μm, p=0.002). No statistically significant difference in choroidal thickness from baseline was observed at 25 minutes of temporal defocus and after 20 minutes of recovery (Figure 5.10). The timepoints in which statistical significance was achieved with nasal and temporal defocus were consistent when compared with the choroidal thickness measurements taken during the control condition. When comparing changes from baseline to changes from the control condition, a statistically significant difference was observed at 25 minutes of nasal defocus within the temporal region (p<0.001) (Table 5.5). Statistically significant differences from the control condition were otherwise consistent with that of changes from baseline.

When disregarding the factor of time, the defocus condition and choroidal region also showed a statistically significant interaction ($F_{2, 208} = 5.40$, p=0.005). The change in choroidal thickness from baseline averaged across the 6mm choroidal area was significantly greater with nasal myopic defocus than the control condition at 25 minutes (mean difference of 2.07 ± 0.68μm, p=0.009) and 20 minutes of recovery (mean difference 4.13 ± 1.04μm, p<0.001). Temporal defocus showed no statistically significant difference against the other two conditions at these two timepoints. However, a statistically significant difference between

		Change in choroidal thickness relative to control condition (μm)					
		Nasal defocus			**Temporal defocus**		
	Time interval	Nasal region	Temporal region	6mm mean	Nasal region	Temporal region	6mm mean
Defocus period	25 minutes	+1.55 ± 8.91	+2.59 ± 9.90	+2.07 ± 15.24	+0.62 ± 8.43	+1.58 ± 8.81	+1.09 ± 6.34
	45 minutes	+7.80 ± 13.57	+6.63 ± 11.17	+7.22 ± 10.20	+0.38 ± 11.68	+6.69 ± 10.85	+3.54 ± 8.61
Recovery period	20 minutes recovery	+5.25 ± 13.70	+3.00 ± 12.63	+4.13 ± 10.65	+0.14 ± 13.83	+0.53 ± 12.47	+0.33 ± 9.71

Table 5.5: The mean difference in choroidal thickness with time for all young adult participants from the control condition. + values indicate choroidal thickening, and – values indicate choroidal thinning. Green text represents statistically significant choroidal thickening, and values shaded in grey indicate no statistically significant difference. Data are expressed as mean ± SD.

control and nasal defocus (7.22 ± 1.00μm, p<0.001), control and temporal defocus (3.54 ± 0.84μm, p<0.001), and nasal and temporal defocus (3.68 ± 0.94μm, p<0.001) was identified. The 3mm nasal region showed no statistically significant difference between defocus conditions at 25 minutes (all p>0.05), whereas a significant difference between the control condition and nasal defocus was observed at 45 minutes (mean difference 7.80 ± 1.14μm, p<0.001). This difference was also present at 20 minutes of recovery (mean difference 5.25 ± 1.34, p>0.001). Contrastingly, the temporal defocus condition yielded no significant difference in nasal choroidal thickness from the control condition at any timepoint (all p>0.05). The 3mm temporal choroidal region showed a significant difference between the control condition and nasal defocus at 25 minutes (mean difference 2.59 ± 0.97μm, p=0.025), but no significant difference from the temporal defocus condition (both p>0.05). The changes in choroidal thickness from baseline to 45 minutes in the temporal 3mm choroidal region were statistically significantly greater with nasal and temporal defocus than the control condition (mean differences of 6.63 ± 1.09μm and 6.69 ± 1.06μm, respectively, both p<0.001), however showed no significant difference solely between nasal and temporal defocus (mean difference of 0.06 ± 1.15μm, p=1.000). At 20 minutes of recovery, the temporal choroidal region showed a statistically significantly greater choroidal thickness change with nasal defocus than the control condition (mean difference 3.00 ± 1.23μm, p=0.049), but no significant difference with temporal defocus (both p>0.05).

No statistically significant interaction between time and choroidal region was found ($F_{3, 285}$ = 1.184, p=0.315). Further, there was no statistically significant interaction between defocus condition, choroidal region, time, refractive error ($F_{5, 516}$ = 0.795, p=0.554), indicating myopic eyes and emmetropic eyes showed no differing response to the experimental conditions.

5.3.2 Results for child age group

Relative to the 25-minute viewing period, fixation was generally good for all child participants. Four out of 11 children were able to keep the fixation marker on the screen for the entire duration of both 25-minute sessions. Four children lost fixation during one session, ranging between a total of 3 and 10 seconds (mean 6.0 ± 2.9 seconds). The remaining children lost fixation at both sessions between a total of 3 to 25 seconds (mean 11.5 ± 9.5 seconds).

Refer to Table 5.2 for mean MSE and axial lengths of the children's right and left eyes. Mean baseline choroidal thickness was 293.28 ± 78.88μm and 290.74 ± 77.88μm in the right and left eyes, respectively. The MSE (p=0.389), axial length (p=0.402) and baseline choroidal thickness (p=0.449) were not statistically significantly different between the right and left

eyes of the child participants. Between the right and left eyes of the children and young adults, an unpaired t-test revealed there to be no statistically significant difference between the MSE, axial length, and baseline choroidal thicknesses (all p>0.05).

The Shapiro-Wilk's W test revealed the measurements of choroidal thickness change in the child participants to not be normally distributed in the temporal retina with nasal defocus and nasal retina with temporal defocus both at the 15-minute timepoint (p=0.015 and p=0.025, respectively). These data were still included in the ANOVA as simulation studies have shown deviations from normality to not greatly affect the false positive rate[450-452]. All other data adhered to the assumption.

In the child participants alone, the nasal and temporal choroidal thickness did not change significantly from baseline to each timepoint (5, 15, and 25 minutes) in any viewing condition (nasal defocus, temporal defocus, and control) (Table 5.6); there was no statistically significant three-way interaction between these factors ($F_{5, 239}$ = 0.795, p=0.552). Further, no statistically significant two-way interactions between defocus condition and choroidal region ($F_{2, 96}$= 1.783, p=0.174), defocus condition and time ($F_{5, 241}$= 1.788, p=0.117), or time and choroidal region ($F_{2, 109}$= 1.829, p=0.161) were observed. The same was true for the inferior and superior choroidal regions, where no significant three-way or two-way interactions occurred (all p>0.05).

When assessing nasal and temporal choroidal thickness changes from baseline to 25 minutes in the myopic young adult and child participants, no statistically significant interaction between defocus condition, choroidal region, time, and age was identified ($F_{4, 196}$

	Change in choroidal thickness from baseline (µm)								
	Control condition			**Nasal defocus**			**Temporal defocus**		
Time interval	Nasal region	Temporal region	6mm mean	Nasal region	Temporal region	6mm mean	Nasal region	Temporal region	6mm mean
5 minutes	+1.38 ± 7.41	-0.38 ± 6.17	+0.50 ± 5.54	-1.02 ± 4.92	-0.31 ± 5.54	-0.66 ± 4.01	+1.99 ± 4.61	+2.63 ± 5.81	+2.31 ± 4.45
15 minutes	+0.53 ± 7.23	-1.79 ± 7.67	-0.63 ± 6.10	+0.28 ± 4.85	-0.31 ± 7.65	-0.01 ± 4.40	+0.88 ± 5.72	-0.80 ± 6.59	+0.04 ± 4.94
25 minutes	+1.67 ± 7.68	-0.03 ± 9.24	+0.82 ± 7.25	+1.03 ± 6.20	+1.57 ± 9.51	+1.30 ± 6.85	+1.50 ± 5.65	+0.57 ± 6.27	+1.04 ± 5.19

Table 5.6: The mean change in choroidal thickness with time for all child participants from baseline for each defocus condition. + values indicate choroidal thickening, and – values indicate choroidal thinning. Note that values were not statistically significant. Data are expressed as mean ± SD.

= 0.200, p=0.819). This was also the case for inferior and superior choroidal regions ($F_{2, 34}$ = 0.420, p=0.166). No significant two-way interactions were identified between the two age groups in any choroidal region (all p>0.05).

Additionally, changes in choroidal thickness with hemifield defocus showed no significant three-way or two-way interactions when analysed relative to the control condition; this was assessed in the vertical and horizontal choroidal regions in child participants alone, and between the adult and child participants (all p>0.05).

5.4 DISCUSSION

This experiment showed 3.00D of short-term myopic defocus confined to each vertical hemifield to elicit detectable, regionally selective choroidal thickening within the corresponding 3mm horizontal regions in young adults, irrespective of their refractive error. The choroidal compensation of temporal and nasal myopic blur appears to be fast acting, with statistically significant choroidal thickening achieved at 45 minutes in both conditions. In a shorter timeframe of 25 minutes, the choroidal thickness of myopic children did not significantly change from baseline and did not respond differently to myopic adult eyes at the 25-minute timepoint.

Despite the presence of choroidal thickening in response to myopic defocus reflecting that of other studies[120, 124, 126, 127, 262], experiments employing full-field myopic defocus have found statistically significant choroidal thickening markedly sooner than 45 minutes. For example, significant choroidal thickening from baseline with full-field myopic defocus has been identified within 10 minutes in myopic and emmetropic young adults[120] and 20 minutes in presbyopes[127]. Although the recruitment criteria, defocus conditions, experimental set-ups, and procedures of analysis differ between studies (summarised in Chapter 1 Section 1.4.2, Table 1.4) the shorter timeframe required for choroidal thickening to reach statistical significance with full-field blur suggests the choroid's compensatory mechanisms may be slower with regional blur. However, inconsistencies between research studies and the limited understanding of local choroidal mechanisms make this difficult to establish at this stage.

Though controlled trials of efficacious optical myopia interventions[397] and animal experiments with foveal ablation[97, 98] indicate foveal defocus is not required to impede ocular axial growth, the extent in which the fovea impacts short-term defocus mediated changes in choroidal thickness is unclear. The executive bifocal lens design employed in this study would have induced 3.00D myopic defocus split vertically through the macular area when presented in either hemifield. This reflects the regional choroidal thickening seen across the vertical 5mm central choroidal area at 60 minutes with 3.00D of superior and inferior

hemifield myopic defocus, where defocus was split horizontally through the macula[262]. Conversely, when only the retinal periphery of young adults was exposed to 3.50D relative plus power, no statistically significant change in choroidal thickness across the central 0.5mm after 4 hours of defocus was found[264]. With these considerations, it is possible that the speed of choroidal thickening may be influenced by the centrality of the blur, where foveal involvement induces a more rapid choroidal response. On reflection, it would have been useful to include 3.00D full-field myopic blur as a defocus condition in this experiment to compare the extent of change to that seen with hemifield blur. With the knowledge that foveal visual signals do not dominate refractive development, further research is needed to establish how foveal blur impacts the rate of transient alterations in choroidal thickness.

Interestingly, in young adult participants, choroidal thickening produced by 3.00D of nasal relative plus power spread beyond the nasal boundary, where significant choroidal thickening was also detected within the temporal choroid. Conversely, with 3.00D of temporal myopic defocus, significant choroidal thickening was only identified within the temporal choroid, seeming to leave the nasal choroidal region unaffected. In both defocus conditions, the extent of choroidal thickening from baseline was similar within the temporal 3mm region (+4.22 ± 9.42μm with nasal defocus and +4.28 ± 8.50μm with temporal defocus). Additionally, the nasal choroid appeared to show a greater degree of thickening with nasal myopic defocus than that of the temporal choroid when exposed to temporal myopic defocus at 45 minutes (+8.04 ± 9.76μm and +4.28 ± 8.50μm, respectively). The distribution of retinal photoreceptor density may be a contributing factor to this outcome; at corresponding eccentricities, retinal cone density is 40-45% greater nasally than temporally, and rod density is greatest within the nasal and superior retina[453]. Ganglion cell density also differs across the retinal profile, where the nasal peripheral retina contains a 300% higher ganglion cell density than that of the temporal retina at equivalent eccentricities[454]. Therefore, differing levels of retinal sensitivity due to retinal photoreceptor and ganglion cell topography may be of impact within localised changes beyond the retina itself. This theory was also recognised by Hoseini-Yazdi et al., (2019), who hypothesised the greater extent of choroidal thickening seen with superior hemifield myopic defocus may be due to the superior-inferior asymmetry in retinal photoreceptor and ganglion cell density[262].

The variation of thickness across the choroidal profile is a further consideration. The human choroid is typically thinner nasally than temporally in children and adults with a range of refractive errors[242, 455] which may influence the rate of choroidal expansion; with the ocular growth signal cascade theorised to begin in or pass through the choroid[130], thinner choroidal areas may accelerate this cascade, resulting in faster rate of local choroidal expansion. The changes in temporal choroidal thickness could eventually reach the same degree of that

seen nasally, but a longer experimental period would be required to further investigate this. It could be argued that, when averaged, the thinner choroids of the myopic adult participants than their emmetropic counterparts showed baseline choroidal thickness to not be a causative factor of the differing regional responses due to refractive error having no impact on the results. However, the findings of the current study are limited in supporting or opposing the influence of choroidal thickness on regional defocus-induced alterations, as the degree of nasal-temporal asymmetry in baseline choroidal thickness was not considered. Therefore, it may be that regional selectivity and sensitivity differs relative to choroidal thickness topographic variations. More research is required to explore this in detail.

Unexpectedly, a significant level of choroidal thinning was identified within the temporal choroidal region at 45 minutes during the control condition. The control condition was anticipated to show no significant change in choroidal thickness at any timepoint due to avoidance of known confounders before and during the experimental session, and the unlikely impacts of diurnal fluctuations over 65 minutes. However, limitations of the study design may be responsible. Firstly, the participants did not undergo a timed washout period during the experimental viewing period; although the adult participants may have been unaffected, extending the fixation demand by adding an adaptation period may have impacted the child participants' level of concentration throughout the defocus period, so it was not included in either age group to permit comparison of results. Therefore, to avoid the impacts of prolonged accommodation on choroidal thickness[366, 367], participants did not do any near work for 20 minutes prior to beginning the experiment, however this 20-minute period was not conducted whilst watching the television monitor under low photopic lighting and wearing the trial frame. Further, participants were required to remove the trial frame before each OCT scan, consequently leaving their refractive error uncorrected and inducing uniform retinal defocus intermittently throughout the experiment. The time taken to capture the OCT images interrupted the fixation and duration of the hemifield defocus also; it took approximately 1 minute to capture the radial choroidal images of both eyes at each timepoint, as determined by the times referenced on the study records. Although allowing the participant to choose a film to watch during each session is likely to encourage fixation compliance, this also exposes the participants to different visual stimuli; previous research has indicated light flicker[456], intensity[457, 458], and spectral composition[459] may impact human choroidal thickness and blood flow. Perhaps even emotional reactions to the storyline were of relevance, leading to fluctuations in heart rate, blood pressure, and blood flow. However, the potential significance of this is unknown. Collectively, these disruptions to and differences in the experimental environments may have stimulated choroidal thinning in the

control condition and partly decayed the choroidal response to hemifield defocus. Ultimately, the results of this study are not able to establish the causative factors.

The distribution of refractive error throughout the study sample forms another limitation. Although the findings of the current study suggest the regional alterations in choroidal thickness were consistent between myopic and emmetropic young adults, the refractive and biometric differences between the refractive groups were comparatively modest. Within the myopic group, only individuals with low to moderate levels of myopia participated, and the difference in axial lengths between the two refractive groups was relatively small (a mean axial length of 0.57 ± 0.19mm greater in the myopic participants). It may be that the homeostatic control of eye growth differs with high levels of myopia, whether this be a driving force of ocular growth or simply a product of axial elongation. A larger sample size with a greater range of refractive and biometric measures may provide more insight into defocus-induced choroidal compensation between ametropic groups. Similarly, the sample of young adults consisted of primarily female participants (71%) and South Asian ethnicities (91%). A sample containing a balanced number of males to females and greater diversity of ethnic backgrounds will enable any influence of these factors to be ruled out.

Additional to localised alterations in nasal and temporal choroidal thickness, this research study found evidence of the choroid's ability to rapidly recover from lens-induced blur. The significant temporal choroidal thickening seen at 45 minutes of nasal and temporal defocus returned to baseline after 20 minutes following cessation of defocus. Furthermore, the extent of choroidal thickening within the nasal choroidal region following 45 minutes of nasal defocus was significantly less at 20 minutes of recovery. Considering significant choroidal thickening from baseline was found at 45 minutes of defocus, yet significant thinning was achieved from this point to 20 minutes of recovery, defocus-stimulated choroidal thickening seemed to diminish faster than its onset. Whether this is reflected in choroidal thickening associated with long-term wear of optical myopia interventions[282, 297, 315] would be an interesting avenue to explore. With some research indicating early choroidal thickness changes may be predictive of long-term axial elongation with myopia management[282, 297, 315], further understanding of the choroid's behaviour shortly following termination of such interventions may provide insight into the likelihood of a rebound effect.

The lack of significant change in choroidal thickness at 25 minutes of defocus in emmetropic and myopic young adults was reflected in myopic child participants, and this was found to be consistent from baseline throughout the shorter time intervals. Similarly, the results indicate the choroids of myopic children and young adults to respond in the same way to 25 minutes of hemifield defocus, with no significant difference in choroidal thickness change from

baseline identified between the two age groups at this time point. The factor of age having no impact on choroidal thickness change has been identified in another study, where choroidal thickness changes, albeit insignificant, in children aged 6 to 17 years were no different to that of adults at 50 minutes of full-field myopic blur[260]. Therefore, from the results of the current study, perhaps the same significant regional observations and recovery at 45 and 65 minutes in adult participants may also occur in the eyes of children with low to moderate myopia. It may be challenging to test this theory in children due to the necessary compliance for an extended period, however the fixation capabilities demonstrated by the child participants in this study exceeded expectations.

In conclusion, this study provides evidence of localised choroidal expansion within the nasal and temporal regions when these areas are exposed to short-term myopic retinal defocus in myopic and emmetropic young adults. Albeit sparse at present, these findings support the existing evidence of local choroidal mechanisms underlying the ocular response to retinal defocus. The results and limitations of the current study provide rationale for further research to build upon these findings. With the lack of adaptation period and concurrent change in room brightness, the potential impact of the experimental set-up on the choroidal thickness considered to be a baseline measurement must be determined. This is explored in the following chapter (Chapter 6). In Chapter 7, dose-dependent and location-dependent characteristics of defocus are explored; differing eccentricities and powers of relative plus power seen amongst commercially available optical myopia interventions may demonstrate differences in the choroidal response relative to their refraction profiles and provide valuable insight into the mechanisms behind their efficacy.

Chapter 6. Effect of indoor light levels on choroidal thickness in myopic and emmetropic young adults

6.1 INTRODUCTION

When exploring short-term changes in choroidal thickness, causative factors of transient choroidal fluctuations are often accounted for in experimental designs. For example, when investigating choroidal thickness over separate days, diurnal variations are well recognised[186, 187]. Furthermore, despite some conflicting evidence, caffeine[194-197], alcohol[193], certain pharmacological agents[209, 210], nicotine[218], and exercise[220, 221] are often acknowledged as confounding factors and avoided prior to an experimental session (see Chapter 1 Section 1.3.3). Additional to avoiding known confounders, studies exploring the impact of temporary retinal defocus on human choroidal thickness typically favour experimental conditions under low photopic lighting (Table 6.1). A large pupil size in the absence of topical mydriatics is beneficial in maximising deliberate retinal blur and facilitating clear choroidal imaging during such research studies, however there is little research to rule out the use of low light levels as a confounder. It is well recognised that light influences human eye growth, whereby time spent in brighter light levels is encouraged to minimise the onset and progression of myopia[44-47], but it is not known whether the choroid plays a significant role in this interaction. Further, in human myopia research, light exposure is often grouped into two categories: 'indoor' and 'outdoor'[44-46], yet light intensity can vary significantly in both conditions. As such, when exploring such short-term fluctuations, some researchers include a 'washout' or 'stabilisation' of around 10 to 20 minutes to allow participants' eyes to adapt to indoor experimental viewing conditions and relax accommodation (Table 6.1).

Authors (Year)	Defocus condition	Light level	Washout period
Read et al., 2010[126]	+3.00D full-field	~10 lux	20 minutes
Chiang et al., 2015[120]	+2.00D full-field	~10 lux	20 minutes
Chiang et al., 2018[127]	+2.00D full-field	~10 lux	20 minutes
Hoseini-Yazdi et al., 2019[262]	+3.00D hemifield	~20 lux	15 minutes
Hoseini-Yazdi et al., 2020[263]	+3.00D astigmatic	~10 lux	20 minutes
Kubota et al., 2021[264]	+3.50D peripheral	30 to 50 lux	10 minutes

Table 6.1: Comparison of myopic defocus, light levels, and washout protocols used in different studies designed to assess short-term defocus-induced choroidal thickness changes. Further information about these studies is detailed in Chapter 1 Section 1.4.2.

In Chapter 5, study visits were designed to provide accurate data in a reasonable timeframe to encourage compliance and comfort of the participants. Chapter 5 investigated choroidal thickness changes with 45 minutes of defocus an additional 20 minutes on cessation of defocus, meaning participants were required to hold their fixation and head position to the best of their ability for 65 minutes. To avoid the impact of prolonged accommodation on choroidal thickness[367], participants were instructed not to conduct any near tasks for 20 minutes prior to the defocus session and a 6-metre target was used during the experiment. As such, data were collected in the absence of a washout period. Despite the avoidance of the aforementioned fast-acting confounders, the change in indoor light levels during this study remained a possible confounder; the room lighting was dimmed from approximately 200 lux to levels between 10 and 20 lux on induction of the defocusing lens, without an adaptation period.

Some research indicates light exposure may impact choroidal thickness over a short period of time; in young adults, Read et al., (2018) found daily light therapy delivered by light-emitting glasses (506 lux) led to a small increase in macular choroidal thickness when used for 30 minutes each morning over a 7-day period[457]. However, these glasses emitted blue-green light (peak wavelength of 500nm), producing difficulty in identifying whether this change was due to the light intensity or spectral composition. Further, Chakraborty et al., (2022) discovered that, compared to darkness, 30 minutes of exposure to 500 and 1000 lux of illumination resulted in significant subfoveal choroidal thickening in emmetropic and myopic young adults[458]. The extent of choroidal thickening was not significantly different between both light conditions and refractive error groups. Otherwise, the short-term effects of changes in indoor ambient lighting on human choroidal thickness are yet to be established.

This study aims to determine whether the change from moderate to low-light levels seen in the research design of Chapter 5 significantly impacted the subsequent choroidal thickness measurements and, sequentially, address whether this change in light necessitated a washout period in the absence of another change in visual environment. More broadly, this study provides additional exploration of the choroid's dynamic nature by investigating the short-term response to differing indoor light levels and whether this should be acknowledged in future experimental designs.

6.2 METHODS

6.2.1 Participants

Ten myopic (MSE -1.82 ± 1.17D, mean axial length 24.49 ± 0.71mm) and 10 emmetropic (MSE +0.21 ± 0.33D, mean axial length 23.51 ± 1.01mm) young adults aged 18 to 25 years

(mean age 21.1 ± 1.1 years, 6 males and 14 females) were recruited from the student population of Aston University, Birmingham, UK. The eligibility criteria and required sample size matched that of Chapter 5 Section 5.2.1: a sample size of 10 per refractive error group was 80% powered to detect an intrasession difference in choroidal thickness of 5μm using repeated measures ANOVA with a 95% confidence level and p value of <0.05 taken as significant[440] (calculated using G*Power 3.1, University of Dusseldorf). The grouping of refractive error was also the same: emmetropes had a MSE of +0.50D to -0.25D, myopes had a MSE of -0.50D to -6.00D, and all participants had ≤0.75D astigmatism. All participants were non-smokers, reported good general health, and had no previous use of myopia management interventions.

Participants attended two visits to the Aston University School of Optometry department. Both visits were arranged to be a minimum of 48 hours apart and at the same time of day (within ±1 hour). Participants were instructed to avoid caffeine for a minimum of six hours, alcohol for a minimum of two hours, vigorous exercise for a minimum of 30 minutes, and near work for a minimum of 20 minutes to prevent confounding influences on choroidal thickness[193, 196, 220, 221, 367]. The study was approved by the Aston University Research Ethics Committee and adhered to the tenets of the Declaration of Helsinki. Informed consent was obtained from all participants prior to any experimental procedures (Appendix 8 and 9).

6.2.2 Data collection procedures

The instrumentation used was consistent with that of Chapter 5: autorefraction and keratometry were measured using the Grand Seiko Autorefractor WAM-5500 (Grand Seiko Co. Ltd., Hiroshima, Japan). The IOLMaster700 (Carl Zeiss Meditec AG, Jena, Germany) was used to measure anterior chamber depth, lens thickness, and axial length. For a detailed description of these instruments, see Chapter 5 Section 5.2.2. Choroidal imaging was obtained using the Heidelberg Spectralis SD-OCT (Heidelberg Engineering, Heidelberg, Germany), employing the same scanning protocol as used in Chapter 5 (6 radial spokes, 30° apart, each spoke covering a 30° retinal area). All choroidal images were captured using enhanced depth imaging (EDI) to maximise visualisation of the posterior choroidal boundary. Further information about the Spectralis SD-OCT can been found in Chapter 4 Section 4.2.1a.

The room set up was identical to that of Chapter 5 Section 5.2.4, however two indoor lighting conditions were used over the two visits. At one visit, room lights were dimmed to low photopic levels between 10 to 20 lux, matching that of Chapter 5. The other visit was considered as the control condition, where the room lighting was not dimmed, providing moderate light levels of approximately 200 lux (termed ‘full’ in this study). The light levels

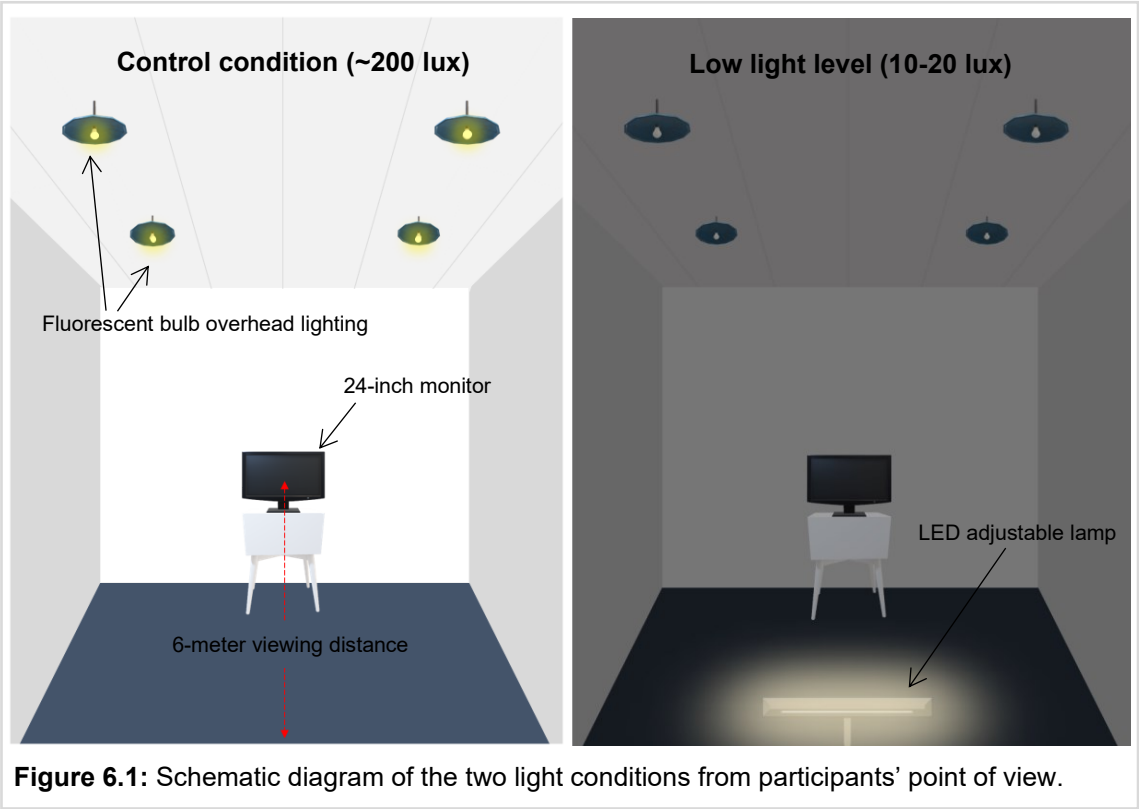


Figure 6.1: Schematic diagram of the two light conditions from participants' point of view.

were recorded using a digital light meter (CA810 Lux Meter, Chauvin Arnoux, Asnières-sur-Seine, France), measured at the same position as the participant's head. Full room lighting (the control condition) was provided by overhead fluorescent lightbulbs and low room lighting was provided by a dimmable LED lamp positioned at 1 meter in front of the participant without obstructing the view of the monitor (Figure 6.1). The order of light condition used over the two visits was randomised between participants.

Baseline OCT scans were captured from one eye in full room illumination. The eye chosen for each participant was randomised across the sample. Then, wearing their refractive correction with no imposed defocus, participants were asked to binocularly watch a programme of their choosing on a 24-inch LED-backlit television monitor positioned at 6 meters. Participants were instructed to fixate on the monitor at all times and keep their head as still as possible. As the viewing period began, the indoor light levels were either immediately reduced to 10-20 lux or maintained at ~200 lux (the control condition). The display brightness and contrast of the monitor screen was consistent across all visits. After 20 minutes, participants were asked to stop fixating and another radial EDI-OCT scan was captured of the same eye under the same lighting condition as the fixation period.

6.2.3 Image analysis

The OCT images were exported and masked using anonymous ID numbers with no indication of which imaged related to which lighting condition. The anterior and posterior choroidal boundaries in each of the 6 images per visit per participant were segmented using

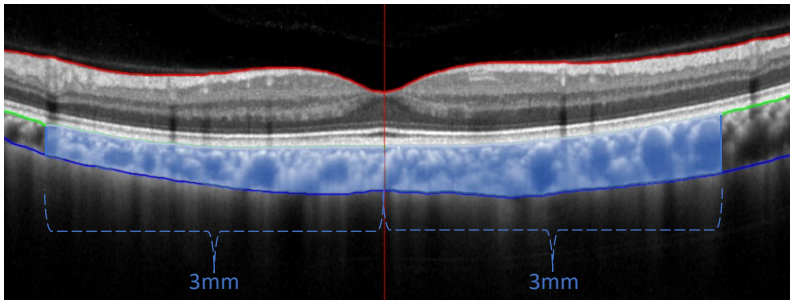


Figure 6.2: Segmented OCT image demonstrating the 6mm choroidal area analysed. The mean temporal and nasal choroidal thicknesses are calculated over a 3mm length either side of the foveal pit marker.

the same semi-automated MATLAB software program and same investigator as that in Chapter 5 Section 5.2.5a (The MathWorks, Inc., Natick, Massachusetts, United States)[171]. All choroidal images were adjusted for transverse magnification using the ocular scaling method described in Chapter 5 Section 5.2.5b. Choroidal thickness across the 6mm transverse area of the choroid was then obtained for each participant, covering 3mm nasally and temporally or 3mm inferiorly and superiorly (depending on the scan orientation) from the foveal pit (Figure 6.2). The mean choroidal thickness of the 3mm macular choroidal areas of each side from the foveal pit and overall 6mm choroidal region was calculated.

6.2.4 Statistical analysis

All statistical analyses were performed using IBM SPSS (Statistics for Windows v28; IBM Corp., Armonk, NY, USA). All 6 line scans from 90° to -60° were included in the analysis. The methods of statistical analysis were identical to that used in Chapter 5 Section 5.2.5c: to analyse superior and inferior choroidal thickness separately to nasal and temporal choroidal thickness, line scans positioned at 90° were analysed separately to those positioned at 60° to -60°. The analysis was completed on the grouped naso-temporal scans assuming independence between scans positioned from 60° to -60°. All data were normally distributed as confirmed by the Shapiro-Wilk's W test ($p>0.05$). A repeated measures ANOVA was conducted using three within-subject factors of light level (200 lux or 10-20 lux), time (baseline and 20 minutes), and choroidal region (nasal choroid and temporal choroid, or inferior choroid and superior choroid). One between-subject factor of refractive error (myopic and emmetropic) was also included. The Greenhouse-Geisser correction was applied where the sphericity assumption was violated.

6.3 RESULTS

The mean changes in choroidal thickness from baseline for each choroidal region are presented in Table 6.2 and Figure 6.3. For the whole sample, the temporal, superior, and nasal choroid appeared to slightly thin (<-2μm) in the control condition compared to low light, whereas the nasal choroid showed a very slight thickening (<+1μm). These differences did not achieve statistical significance and fell within the repeatability of the instrument; there was no statistically significant interaction between light level, time, and choroidal region (F_2,

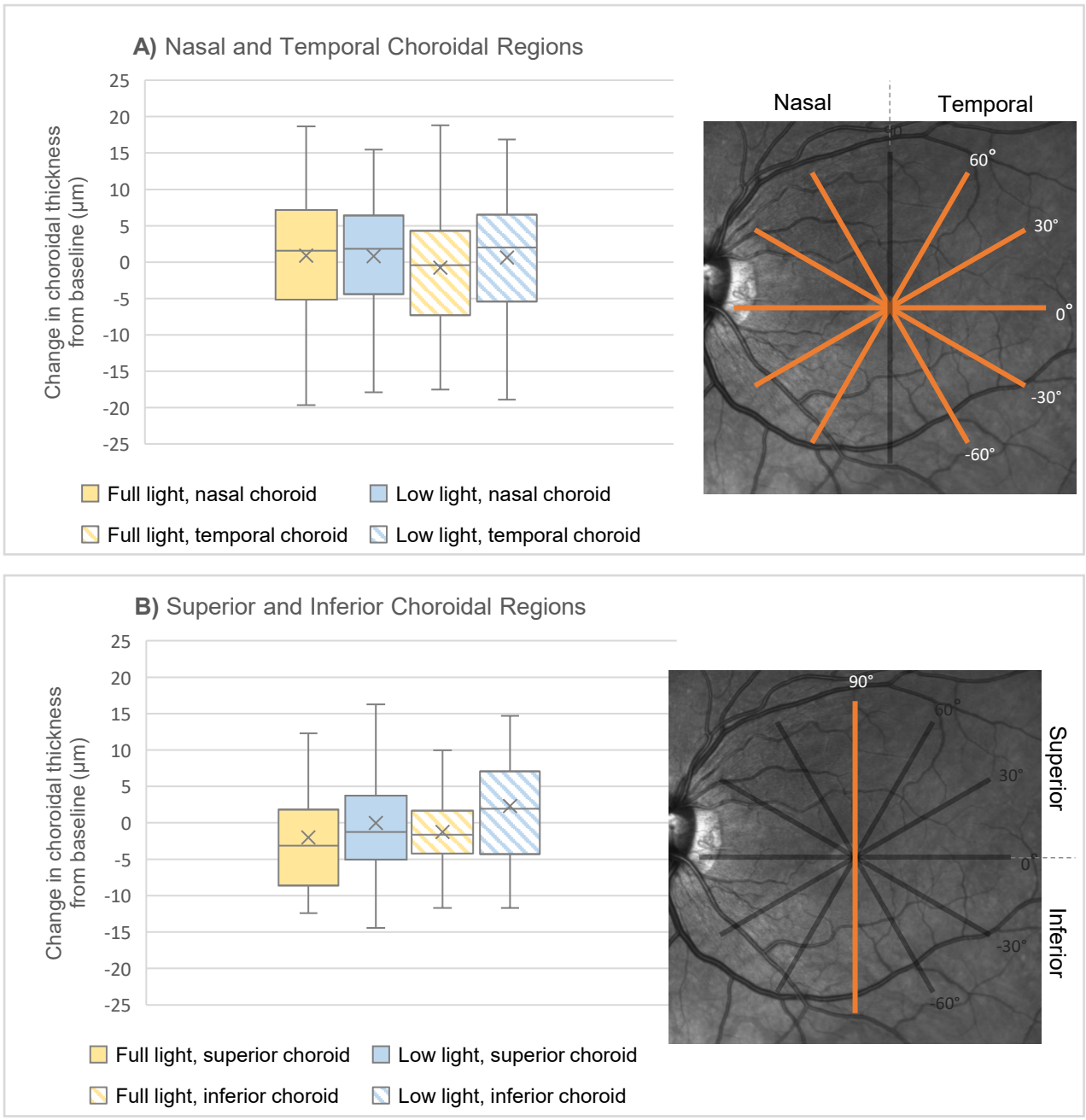


Figure 6.3: The change in choroidal thickness averaged across the 3mm A) nasal and temporal choroidal regions, and B) superior and inferior choroidal regions in both lighting conditions ('full' and 'low' light). Positive and negative values denote thickening and thinning of the choroid respectively. Fundus photos with orange radial spokes indicate the position of line scans averaged for the choroidal regions shown in the corresponding box and whisker plots. X = mean, solid line = median, whiskers = range.

$_{98}$ =0.401, p=0.528). When including the factor of refractive error, no difference within or between the myopic and emmetropic participant groups was found; there was no statistically significant interaction between light level, time, choroidal region, and refractive error ($F_{3, 98}$ =0.155, p=0.694). Further, there was no statistically significant interaction between light level and time alone ($F_{1, 84}$ = 0.392, p=0.533), indicating that choroidal thickness did not change

	Change in choroidal thickness from baseline (µm)					
	Whole Sample (n=20)		Emmetropes (n=10)		Myopes (n=10)	
3mm choroidal region	Full light	Low light	Full light	Low light	Full light	Low light
Nasal	+0.87 ± 8.05	+0.80 ± 7.95	+0.41 ± 9.45	-0.30 ± 8.91	+1.32 ± 6.43	+1.89 ± 6.78
Temporal	-0.75 ± 8.31	+0.64 ± 7.87	-0.39 ± 8.94	-0.76 ± 8.41	-1.12 ± 7.69	+2.04 ± 7.10
Superior	-1.99 ± 7.41	-0.03 ± 7.07	-0.96 ± 8.21	+0.43 ± 8.93	-3.02 ± 6.80	+3.17 ± 5.02
Inferior	-1.25 ± 5.30	+2.30 ± 7.31	-1.29 ± 6.30	-3.26 ± 5.24	+1.22 ± 7.90	+2.19 ± 9.00

Table 6.2: Mean changes in choroidal thickness from baseline across the nasal, temporal, superior, and inferior choroidal regions spanning 3mm from the foveal pit. Positive and negative values denote thickening and thinning of the choroid respectively. Data are presented as mean ± SD for the whole sample and for each refractive error group.

significantly in either viewing condition from baseline to 20 minutes. This appeared consistent across the choroid; choroidal region also showed no statistically significant interaction with light level ($F_{1, 98} = 1.720$, $p=0.193$), or time ($F_{1, 98} = 3.789$, $p=0.054$). There were no statistically significant interactions found between any remaining factors (all $p>0.05$).

6.4 DISCUSSION

The results of this study indicate the onset of low photopic light levels (10 to 20 lux) from moderate light levels (~200 lux) did not significantly change choroidal thickness over the 6mm radial macular area in healthy young adults. The results showed no significant thickening or thinning of the choroid following 20 minutes of exposure to either condition, irrespective of the participants' refractive error.

This study has various limitations. Firstly, the two light conditions were set using different light sources; the control condition (full room lighting, ~200 lux) used fluorescent light bulbs and the low light condition (10 to 20 lux) used a light emitting diode (LED) lamp. Fluorescent light bulbs use electricity to excite mercury vapor, emitting UV light and converting it into visible light. This process causes the light source to be susceptible to flickering. Research has shown short durations of flickering light, albeit at close working distances and high frequency, causes temporary dilation of retinal blood vessels in humans[460, 461]. The impact on the choroid is less apparent; some research indicates human choroidal blood flow to be unaffected by light flicker[462], whereas other research has found the opposite[456]. Alternatively, low light levels were achieved with a LED bulb, which converts electricity into light using a semiconductor and are less prone to flicker. No light flicker or fluctuation in intensity was

acknowledged during the experimental sessions in either condition, however the stability of the light sources was not actively monitored throughout the study.

Similarly, although visually similar in colour to the naked eye, the spectral power distribution of the fluorescent and white LED light sources differs greatly[463] (Figure 6.4). In particular, the emission of blue light is substantially greater from a LED light-source (peak of emission of 450 to 470nm) and appears visibly white due to its yellow phosphor (peak of emission around 580nm)[464]. With the spectral composition of light thought to impact choroidal thickness, even in the short-term[459], this notable difference is a potential confounder. Therefore, it is difficult to consider the sole difference between the two light conditions to be light intensity alone.

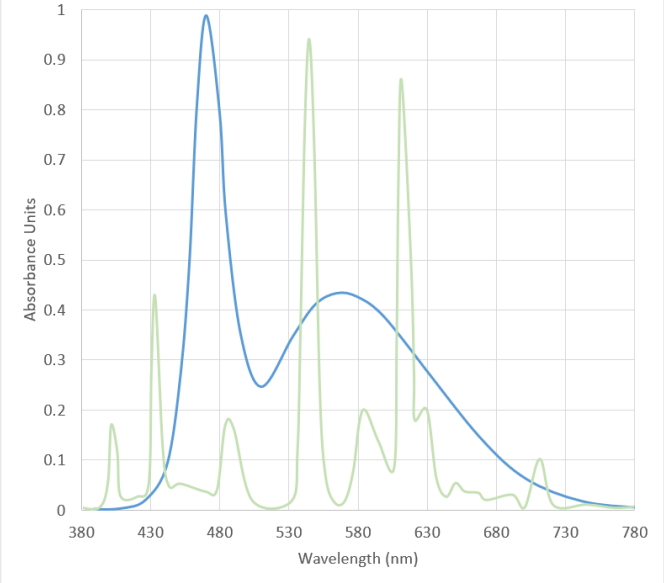


Figure 6.4: Comparison of the power spectrum of white light emitted from a LED (blue line) and fluorescent (green line) light source. Figure adapted from Tosini et al., 2016[463].

Additionally, the light sources also vary in the production of heat; fluorescent light bulbs produce substantially more heat than LED sources. With increased exposure to heat causing vasodilation, it is plausible that warmer temperatures may increase the luminal aperture of the choroidal vasculature, concurrently increasing choroidal thickness. Conversely, there is little research investigating the impact of external heat on choroidal thickness. In 10 healthy young adults with low to moderate myopia, application of a heated eye compress for 10 minutes resulted in no significant change in choroidal thickness besides the outer (6mm) nasal area[465]. A literature search revealed no study further supporting or opposing this. With the fluorescent bulbs positioned at a greater distance from the participant than the LED bulb, it could be argued that the effect of different levels of heat emission between the two light sources would be negligible. Nevertheless, room temperature was not measured during study visits and could have fluctuated significantly between each session, even if not directly associated with the light bulbs themselves. However, at present, there is no clear evidence to show the choroid to be affected by ambient temperature, and the study room was ventilated which may negate variations in temperature from lighting.

Allowing the participant to choose a television programme to watch during the experiment holds both advantages and disadvantages. Providing the participant with a target they find interesting encourages compliance when fixating for the whole study session. Furthermore, providing an entertaining experimental session likely minimises participant drop-out between multiple visits. Conversely, despite the display settings of the LED-backlit monitor being consistent across all visits, different television programmes contain scenes with varying visual stimuli. This may include scenes of different brightness, spectral composition, and flicker. When viewed at 6 metres, the 24-inch monitor provided a proportionally small target with the intention to minimise eye movements. This may have also lessened the impact of inconsistent visual stimuli, as the impacts of light flicker, wavelength, and light intensity tend to be examined at closer distances from the eye[457, 458, 462]. Perhaps a more confident comparison in choroidal thickness changes could have been made if the participants were to have been exposed to the same visual target. Similarly, as the final OCT scan of either visit was captured under different light levels, the effect of the concomitant difference in pupil size during scan acquisition is a further consideration. Although there is no consistent evidence to suggest pupil dilation and constriction causes detectable choroidal thickening or thinning (see Chapter 1 Section 1.3.3e), it is possible that the difference in pupil diameters between the light conditions may have been a confounding factor.

The findings of this study suggest the absence of a washout period seen in the experimental design of Chapter 5 is unlikely to have caused misinterpretation of the results. As previously described in Chapter 5, the introduction of lens-induced regional myopic defocus and dimming of the room lights from approximately 200 lux to 10-20 lux occurred simultaneously, with no washout period. The recruitment criteria (including age range and refractive error), study set up, and avoidance of known confounders of both studies were identical. Further, both studies required participants to conduct no near work for 20 minutes prior to beginning the experiment, and the same 6-meter target was used to prevent any impact of accommodation during the experimental session. Fundamentally, the low light condition used in this study simulated a 20-minute adaptation period of the experimental design of Chapter 5. As this study found there to be no difference in choroidal thickness from baseline to 20 minutes of exposure within each light condition, it suggests the baseline scan taken prior to inducing myopic defocus in Chapter 5 would not be of any statistically significant difference to that taken after a 20-minute washout period in low light conditions.

However, this comparison is limited. Although participants were strictly instructed to conduct no near tasks in the 20 minutes prior to the experiment, their compliance with this was not directly monitored in either this study or that of Chapter 5. Including a washout period within an experimental timeframe permits investigators to ensure participants abide by their

instructions. In addition, only adult participants were recruited, making it difficult to extrapolate the findings to that of child participants. Despite the identical adult recruitment criteria, different participants were used in either study so the repeated measures cannot be directly matched between the two. The mean age of participants was similar between this study and that of Chapter 5 (21.1 ± 1.1 years and 21.1 ± 1.5 years, respectively), as was the number of males to females (70.0% female and 71.4% female, respectively) and distribution of ethnic backgrounds (85.0% and 85.7% South Asian, 5% and 4.8% White European, 10% and 4.8% Middle Eastern, respectively). Conversely, the grouped refractive errors differed in MSE; in Chapter 5, myopic and emmetropic participants had a MSE of -2.27 ± 1.09D and +0.07 ± 0.29D, respectively. Myopic and emmetropic participants in the current study had a MSE of -1.82 ± 1.17D and +0.21 ± 0.33D, respectively. Although the results of this study and Chapter 5 suggest the outcome was not impacted by refractive error, the difference in MSE between the myopic groups was clinically significant, at 0.45D, weakening the refractive error matching.

With some research identifying significant changes in choroidal thickness following altered light levels[340, 457-459], the involvement of global (cortical) mechanisms also deserves consideration. Although reports are inconsistent at present, the effect of light levels on choroidal thickness could be mediated by local and global processes, with contrast gain mechanisms playing an important role. With contrast gain control modulating the response of neurons (in the visual system) based on the contrast of the visual input, objects remain distinguishable and detailed across a wide range of environments, including both indoor and outdoor light conditions. Therefore, in this context, absolute light levels are far less relevant than contrast. The impact of contrast on ocular growth already forms an area of interest in myopia research, with a contrast-altering spectacle lens design providing promising reports of reduced myopia progression (see Chapter 1 Section 1.4.5b). Further research is warranted to explore whether such altered visual input affects the way the visual cortex interprets and responds to this information, possibly leading to changes in neural activity patterns and slowing myopia progression. Alternatively, should local mechanisms alone mediate short-term choroidal thickness fluctuations and long-term ocular growth in response to differing visual stimuli, this wouldn't be a relevant factor.

In conclusion, unlike that seen following 20 minutes of lens-induced defocus[120, 127] this study revealed choroidal thickness to not significantly change over a 20-minute period following a reduction in light illumination to match that of Chapter 5. Additionally, no significant difference in choroidal thickness was identified between the low light condition and control condition in both myopes and emmetropes. These findings indicate the results of Chapter 5 were not impacted by the lack of an adaptation period in the experiment. However, the

inclusion of a washout period would provide a more robust experimental design. When considering the limitations of this study, further research is needed to investigate how the human choroid responds to fluctuating light levels indoors and the potential impact this could have in future experimental work.

Chapter 7. Comparison of immediate and long-term effects of Defocus Incorporated Multiple Segments (DIMS) spectacle lenses on choroidal thickness

7.1 INTRODUCTION

Across various parts of the globe, several spectacle lens designs marketed to slow myopia progression have become available for practitioners to prescribe to their young myopic patients. To eye care practitioners and patients alike, myopia control spectacles are an appealing method of myopia intervention due to offering both refractive correction and non-invasive myopia management in one. As identified by the global surveys presented in Chapters 2 and 3, this appeal is reflected in the growing uptake of myopia control spectacles over recent years, and the preference for practitioners to prescribe spectacles to myopic children of a younger age than that of contact lenses and pharmaceuticals.

Developed by Hoya® in partnership with The Hong Kong Polytechnic University, MiyoSmart® spectacle lenses are designed to slow childhood myopia progression using Defocus Incorporated Multiple Segments (DIMS) technology. Earlier described in Chapter 1 Section 1.4.3a, DIMS lenses adopt the theory of slowing axial elongation through inducing deliberate peripheral myopic defocus. Over 6 years' worth of data indicates these lenses to be efficacious in slowing childhood refractive and axial progression compared to single vision spectacles across Asian populations[393, 466]. Clinical trials conducted in European

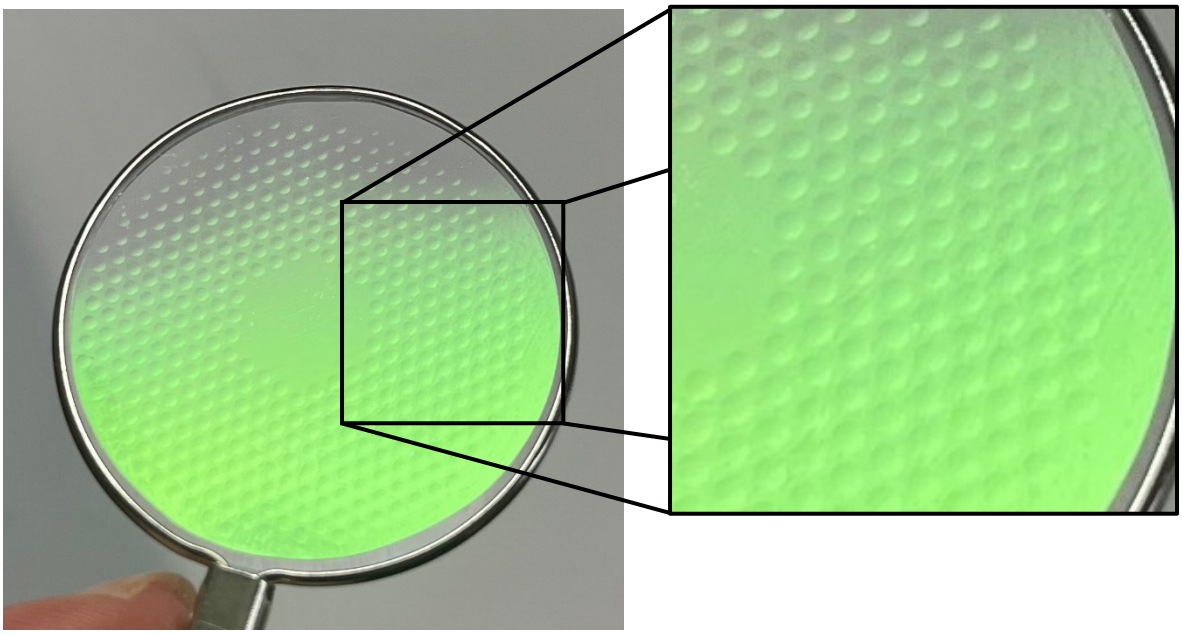


Figure 7.1: Photograph of a trial lens containing DIMS technology. The full honeycomb matrix and central clear aperture is visible in the image on the left. The image on the right shows a magnified view of the individual defocusing segments.

populations also show promising results[467]. The strong evidence-base along with the capacity to accommodate a large prescription range (plano to -10.00D, maximum cylinder -4.00D, maximum prism 3∆D) have seen DIMS spectacle lenses become commercially available in several parts of the world for young myopic children to use as their primary refractive correction, including the United Kingdom. DIMS lenses contain a 'honeycomb' treatment zone of multiple segments (pictured in Figure 7.1), approximately 33mm in diameter. Within this zone, each segment is 1mm in diameter and contains +3.50D relative plus power. The central 9.4mm contains no defocusing segments to provide the wearer with clear vision in primary gaze.

Significant choroidal thickening associated with DIMS lens use has been identified in as little as 1 week of full-time wear; a 2-year randomised controlled trial found a mean increase in subfoveal choroidal thickness of 6.75 ± 1.52µm from baseline to 1 week of DIMS wear in a cohort of 79 Chinese schoolchildren[282]. This change was significantly greater than those children wearing single vision spectacles (-3.17 ± 1.48µm, n=81). The thickening increased over the first 6 months of wear and was sustained for the remaining 18 months of the trial[282]. Interestingly, the researchers found the level of choroidal thickening exhibited at 3 months of DIMS wear to be predictive of axial length change after 24 months (as discussed in Chapter 1 Section 1.4.3a).

Given that previous studies have suggested that choroidal thickening seen at 1 or more months following commencement of optical myopia interventions may be predictive of long-term axial growth[282, 297, 315], the same could be hypothesised about changes in choroidal thickness in an earlier timeframe. Previous studies have identified 2.00D to 3.00D of myopic defocus covering the entire visual field to induce statistically significant subfoveal choroidal thickening in adults within 20 minutes[120, 127], but research exploring short-term choroidal changes following the same degree of defocus in the absence of foveal involvement is sparse. As discussed in Chapter 1 Section 1.2, animal models and human clinical trials have shown foveal vision not to be fundamental in visually guided ocular growth, which is supported by choroidal thickening seen with deliberate long-term peripheral myopic blur[281-283, 297, 298, 311, 312, 315]. Therefore, theoretically, short-term choroidal thickening may be identifiable when myopic defocus is isolated to the peripheral retina, such as when wearing a DIMS lens.

This study explores choroidal thickness changes following both short-term and long-term DIMS wear. It aims to identify whether, like full-field myopic defocus[120, 127, 263], peripheral myopic defocus induces detectable choroidal thickness changes within a short time period; 45 minutes in young myopic adults and 25 minutes in myopic children. To explore any

predictive properties, short-term data collected from child participants is compared with that of full-time DIMS wear over 12 months in children closely matched in age, refractive error, and axial length.

7.2 METHODS

7.2.1 Participants

The data used in the current study was collected from two separate study designs. This was to provide choroidal thickness data from long-term and short-term DIMS wear. Therefore, recruitment methods and eligibility criteria varied between the two studies.

Longitudinal data used in this study were collected at Aston University as part of a multi-site, national observational clinical study of DIMS spectacle lenses in children aged between 6 to 15 years. Children were recruited using social media adverts, posters, and by contacting local optometry practices to refer children who may be suitable to participate. Separately, short-term data were collected from children (aged 6 to 15 years) and young adults (aged 18 to 25 years) who were recruited primarily through the Primary Care clinics, Myopia clinic, and staff and student population of Aston University. The eligibility criteria of the two studies differed primarily in refractive status requirements, however the remaining visual, ocular health, and general health requirements were the same (Table 7.1). This included no existing or prior use of myopia management interventions (orthokeratology, bifocal or

	Short-term DIMS wear participants		**Long-term DIMS wear participants**
	Young adults	**Children**	**Children**
Age (years)	18 to 25	6 to 15	
Refractive error (MSE, D)	-0.50 to -6.00		-1.00 to -8.00
Astigmatism (DC)	≤0.75		≤1.50
Anisometropia (D)	≤0.75		≤1.50
BCVA (LogMAR)	+0.1 or better		
Binocular vision status	No amblyopia or strabismus Stereopsis of 60'' or better (measured with Titmus Fly Stereotest)		
Previous ocular history	No prior use of myopia management interventions No ocular disease/previous ocular surgery		
General health	Non-smokers Free of systemic abnormalities	Free of systemic abnormalities	

Table 7.1: Eligibility criteria for the short- and long-term DIMS wear research studies.

	Short-term DIMS wear participants		Long-term DIMS wear participants
	Young adults (n=10)	Children (n=10)	Children (n=10)
Age at enrolment (mean ± SD)	21.1 ± 1.20 years	11.40 ± 2.22 years	10.97 ± 2.16 years
Sex	5 males 5 females	4 males 6 females	7 males 3 females
Ethnicities	9 South Asian 1 White European	7 South Asian 2 White European 1 African-Caribbean	6 South Asian 4 White European

Table 7.2: Mean age, sex, and breakdown of ethnicities for participants enrolled into short- and long-term DIMS wear study groups.

multifocal spectacles/contact lenses, and atropine eye drops), and no systemic or ocular abnormalities which might affect visual functions or refractive development.

At the Aston University site, 62 participants were enrolled onto the DIMS longitudinal clinical trial. The current study uses data collected from 10 of those children deliberately chosen to be paired with 10 children who participated in the short-term experiment. Additionally, 10 young adults also participated in the short-term DIMS wear experiment, none of which were paired with the child participants. Therefore, data from 30 participants were collected in total for this study: 10 young adults and 20 children (10 for short-term data collection and 10 for long-term). For each group, a sample size of 10 was 80% powered to detect an intrasession difference in choroidal thickness of 5μm using repeated measures analysis of variance (ANOVA) with a 95% confidence level and p value of <0.05 taken as significant[440] (calculated using G*Power 3.1, University of Dusseldorf, Germany). With the same statistical power and significance level, this sample size was sufficient to assess the degree of association between the variables of choroidal thickness change (across a 6mm horizontal and vertical region), myopia progression, and axial elongation over a 12-month period using Pearsons's correlations, with a large effect size (where Pearson r correlation varies more than ±0.5 for each factor[468]) as determined by previously published literature[298]. Details of age, ethnicity, and sex for each group are presented in Table 7.2.

Both studies were approved by the Aston University Research Ethics Committee and adhered to the tenets of the Declaration of Helsinki. Informed consent (and assent from participants under 16 years of age) was obtained from all participants or parents/guardians before any experimental procedures (Appendix 3, 4, and 5). Participants aged under 16 years were required to be accompanied by a parent or guardian at all times (Appendix 6 and 7).

7.2.2 Ocular screening and baseline measures

Participants from both studies attended the Aston University Vision Sciences department for ocular screening and data collection. Prior to enrolment, all participants underwent a comprehensive eye examination to assess their visual acuity, oculomotor balance status, stereoacuity, ocular health, and refractive error assessed using the same protocol and instrumentation outlined in Chapter 5 Sections 5.2.1 and 5.2.2. Further described in Chapter 5 Section 5.2.2, the Grand Seiko Autorefractor WAM-5500 (Grand Seiko Co. Ltd., Hiroshima, Japan) and Carl Zeiss IOLMaster700 (Carl Zeiss Meditec AG, Jena, Germany) were used to measure autorefraction and ocular biometry for all participants.

To minimise the impact of accommodation, all child participants had autorefraction and ocular biometry conducted under cycloplegic conditions (where their amplitude of accommodation was confirmed as having been reduced to 2.00D or less measured using a RAF rule) using 1% cyclopentolate hydrochloride eye drops. Adult participants did not undergo cycloplegia; instead, binocular refraction and a +1.00DS blur test were used to ensure relaxed accommodation, further confirmed with open-field autorefraction using the WAM-5500[441]. With the temporary choroidal thinning associated with cycloplegic agents[205, 206], children undergoing short-term assessment of choroidal thickness had this conducted a minimum of 48 hours prior to choroidal imaging and DIMS wear. Children enrolled into the longitudinal DIMS clinical trial had OCT scans of their right eyes captured before the instillation of cyclopentolate hydrochloride at each visit. Baseline measures are presented in Table 7.3.

Children participating in the longitudinal clinical trial were seen at 6 months (±2 weeks) and 12 months (±2 weeks) following their baseline visit. The outline of each visit protocol is presented in Figure 7.2. Children and adults enrolled into the short-term experiment were seen for their following visit within 8 weeks after their baseline visit.

	Short-term DIMS wear participants				**Long-term DIMS wear participants**
	Young adults (n=10)		**Children (n=10)**		**Children (n=10)**
Eye	**Right Eye**	**Left Eye**	**Right Eye**	**Left eye**	**Right eye only**
MSE (D)	-2.51 ± 1.26	-2.39 ± 1.23	-2.05 ± 1.07	-2.01 ± 1.02	-2.13 ± 0.66
Astigmatism (DC)	0.47 ± 0.23	0.58 ± 0.18	0.44 ± 0.21	0.54 ± 0.10	0.87 ± 0.35
Axial Length (mm)	24.68 ± 0.67	24.59 ± 0.72	24.25 ± 0.97	24.25 ± 1.00	24.31 ± 0.79

Table 7.3: Means ± standard deviations of mean spherical equivalent (MSE), level of astigmatism, and axial lengths for all participants. Measurements are presented for the right and left eyes of the short-term DIMS wear participants. Right eye measurements are presented for long-term DIMS wear participants as choroidal thickness was only measured in the right eyes of these participants.

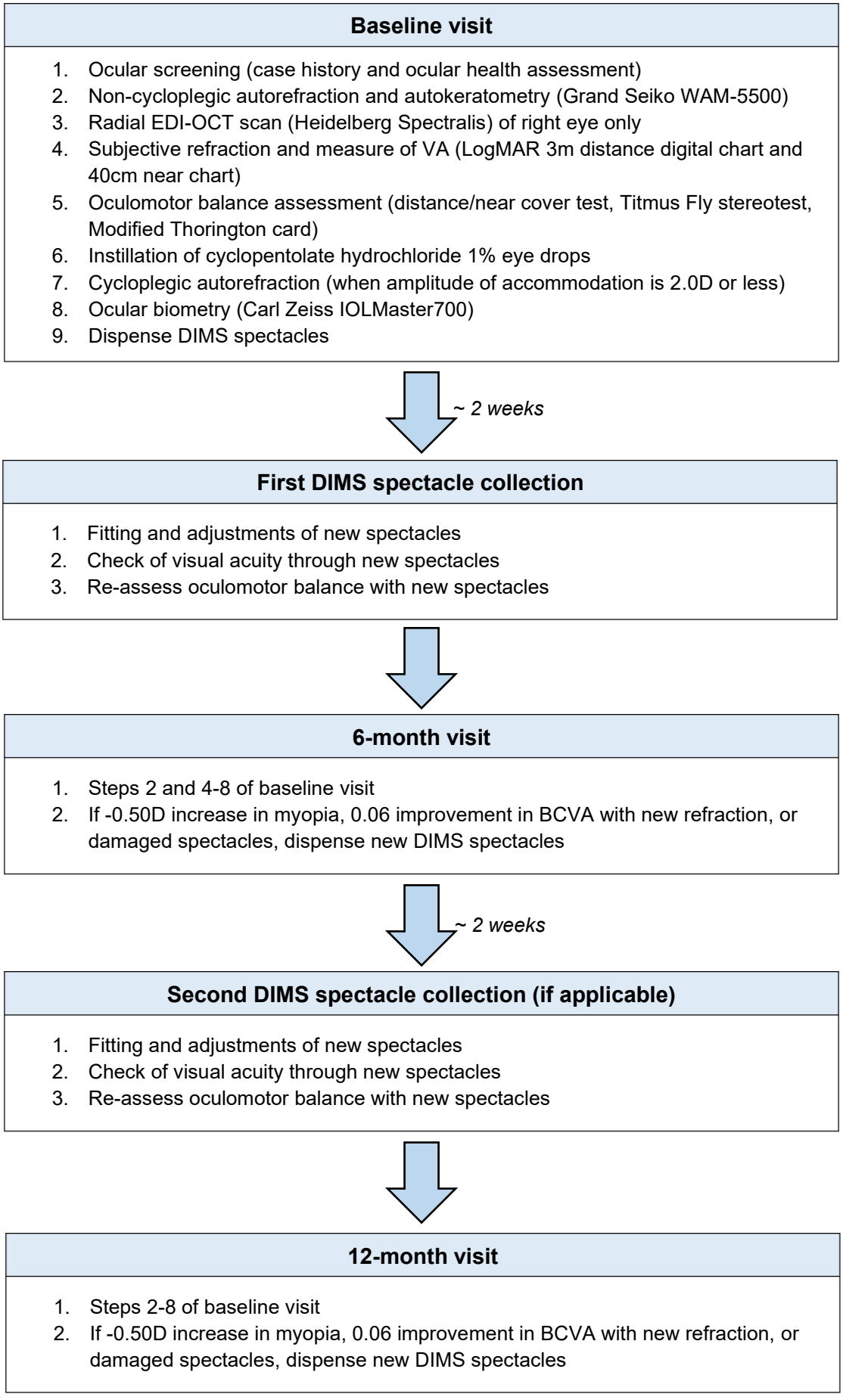


Figure 7.2: Summary of study visit protocols for longitudinal Hoya MiyoSmart clinical trial.

7.2.3 Choroidal imaging procedures with duration of DIMS wear

7.2.3a Long-term DIMS wear

Participants originally consented to a 12-month clinical trial and later had the option to continue for an additional 24 months. Of the 10 children whose data was used in the current study, 2 withdrew from the clinical trial extension. Therefore, although the DIMS clinical trial extended beyond 12 months, only data collected over the first 12 months are examined here.

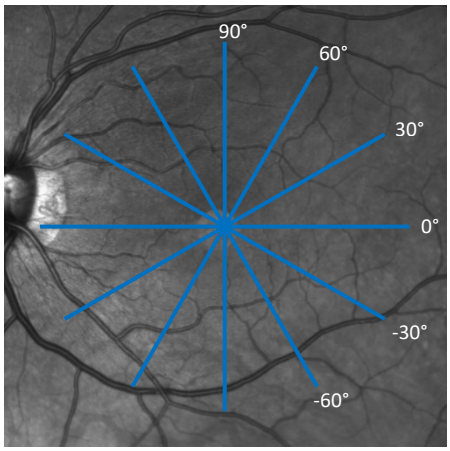


Figure 7.3: Fundus image showing the location of the 6 line scans captured with a radial EDI-OCT scanning protocol (6 radial line scans, 30° in length, positioned 30° apart) using the Heidelberg Spectralis SD-OCT. The analysis was completed on the grouped naso-temporal scans assuming independence between scans positioned from 60° to -60°.

As outlined in Figure 7.2, children received a pair of DIMS spectacles approximately 2 weeks after their baseline appointment. To confirm the correct positioning of the DIMS central clear zone relative to each child's pupil centres, the spectacles were adjusted by a dispensing optician and visual acuity was re-measured to ensure there was no unusual reduction in BCVA to that recorded at baseline. Children were instructed to wear the DIMS spectacles full-time and return for their follow-ups at 6 monthly intervals unless instructed otherwise by their usual optometrist. They were also advised to return sooner to the department if any damage was to occur to their spectacles, including noticeable scratches on the lenses. Parent and child questionnaires were used at each study visit to determine the wear time and tolerability of the spectacles, therefore gauging the child's compliance.

Additional to measuring axial elongation and refractive error progression, participants had a radial EDI-OCT scan using the Heidelberg Spectralis SD-OCT. To account for diurnal fluctuations in choroidal thickness[187], all visits were conducted at the same time of day ± 1 hour. The EDI-OCT scanning protocol was identical to that previously described in Chapter 5

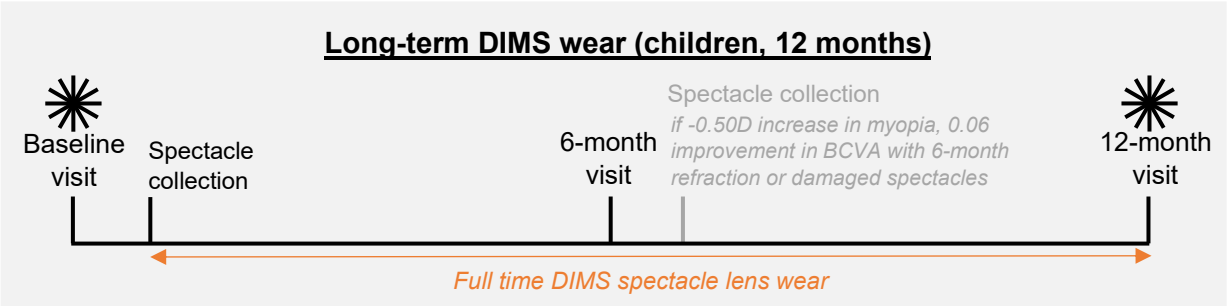


Figure 7.4: Timeline of radial OCT scans taken for the first 12 months of the DIMS longitudinal clinical trial. OCT scans are depicted with the radial symbol: ✳.

Section 5.2.2d and Chapter 6 Section 6.2.2 (Figure 7.3). The OCT scan was captured of each child's right eye at baseline and approximately 12 months of full-time DIMS wear (Figure 7.4).

7.2.3b Short-term DIMS wear

To explore the short-term choroidal impact of DIMS lenses, the same experimental design to that detailed in Chapter 5 was used. This is summarised in Figure 7.5. To avoid transient fluctuations in choroidal thickness, participants were instructed to avoid caffeine for 6 hours[194-197], alcohol for 2 hours[193], vigorous exercise for 30 minutes[220, 221], and near work for 20 minutes[367] prior to the experimental session. All OCT scans were captured using the same scanning protocol to that described in the previous section. To allow comparable

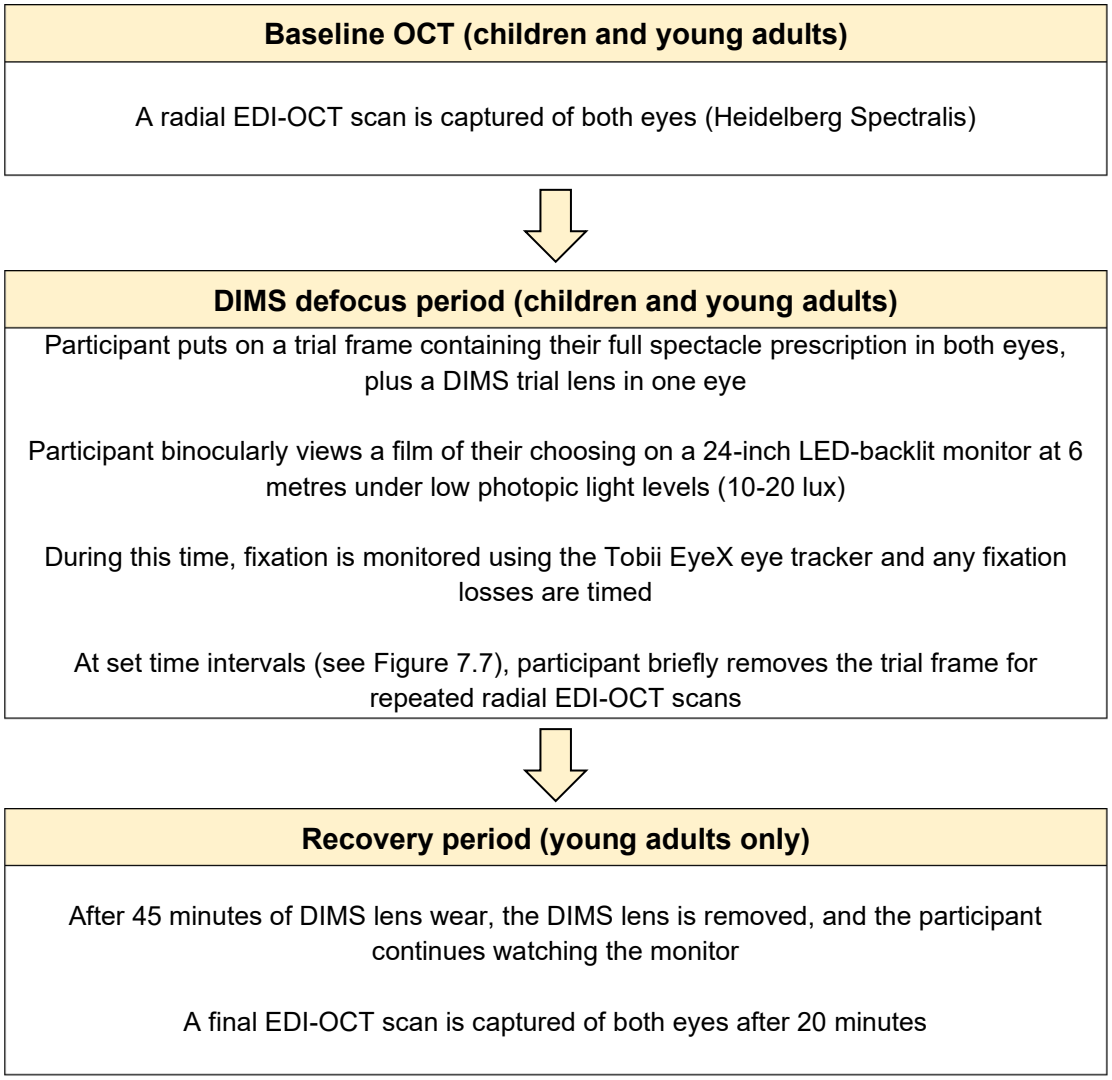


Figure 7.5: Outline of experimental procedure used to explore short-term DIMS wear on choroidal thickness. Further details of instrumentation, room set-up, and instructions given to the patient can be found in Chapter 5 Section 5.2.

Figure 7.6: Example of viewing condition from a participant's perspective where the left eye is exposed to a DIMS trial lens (spectacle prescription with +3.50 peripheral defocus) and the right eye is used as a control (spectacle prescription with no DIMS lens).

results with those of Chapter 5, no adaptation period was included.

For both the child and young adult participants, a DIMS trial lens was presented to one eye and the other eye used as a control (full spectacle prescription only) (Figure 7.6). The eye chosen to wear the DIMS lens was randomised between participants using computer random number generation.

The total duration of the experiment differed between the young adult and child participants. Consistent with Chapter 5, child participants experienced a shorter viewing session due to the likely difficulty to comply with fixation and minimal head movements over a prolonged period. Child participants viewed the monitor for a total of 25 minutes (refer to Chapter 5 Section 5.2.4), with 4 OCT scans taken over this time (baseline, 5, 15, and 25 minutes). Young adult participants viewed the monitor for a total of 65 minutes: 45 minutes wearing the DIMS lens (the DIMS defocus period), and 20 minutes following its removal (the recovery period). OCT scans were captured at

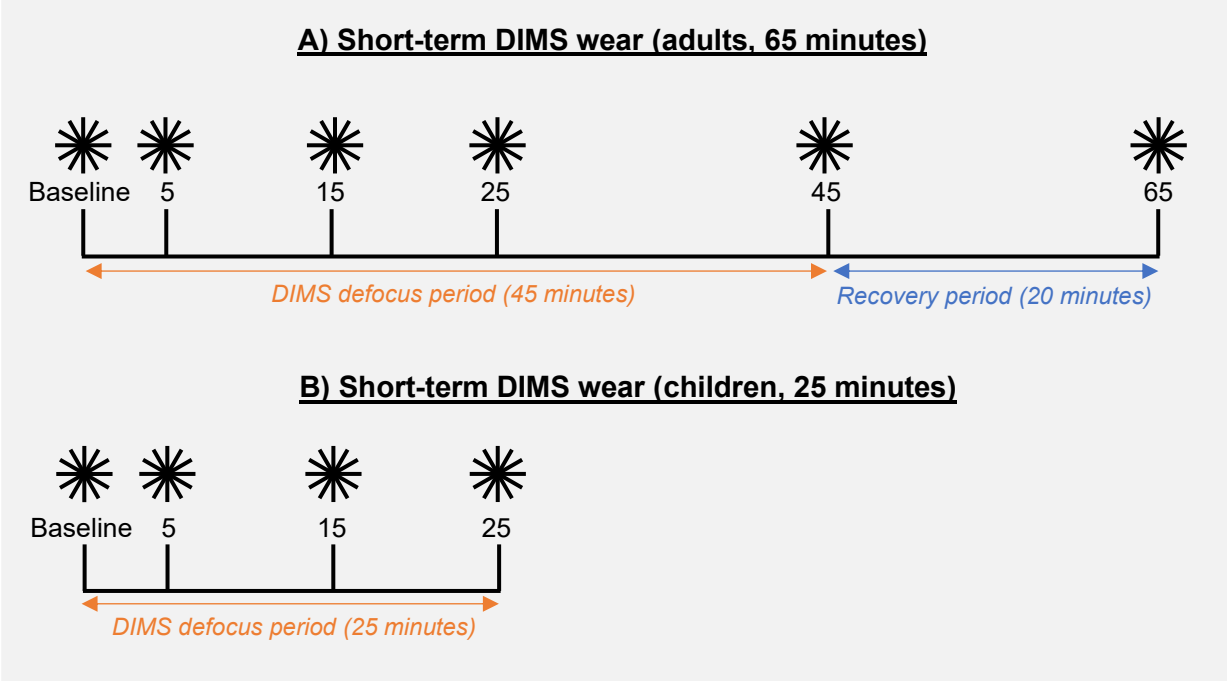


Figure 7.7: Timelines (in minutes) of radial OCT scans taken for the A) DIMS defocus and recovery periods for young adult participants and B) DIMS defocus period for child participants. OCT scans are depicted with the radial symbol: ✳.

baseline, 5, 15, 25, 45 minutes (DIMS defocus period) and on completion of the 20-minute recovery period (Figure 7.7).

7.2.4 Image analysis

The OCT B-scans were exported anonymously. The foveal pit was marked and the RPE and CSI were segmented using the same masked investigator and semi-automated procedures as those described in Chapter 5 Section 5.2.5a. The software outputs were scaled to account for transverse magnification (Chapter 5 Section 5.2.5b), providing an estimate of a 6mm length of each of the 6 line scans taken per radial EDI-OCT.

Within each of the 6 line scans (0° to -60°), the 6mm choroidal region (centred at the foveal pit) was split into 4 equal sections, each spanning 1.5mm in width (Figure 7.8A). In doing so, this provided a measure of choroidal thickness over the 1.5mm foveal/parafoveal and perifoveal superior, temporal, inferior, and nasal choroidal regions (Figure 7.8B).

Therefore, the choroidal thickness could be measured based on two variables: the choroidal region (superior, temporal, inferior, and nasal) and choroidal eccentricity (considered here as parafoveal and perifoveal).

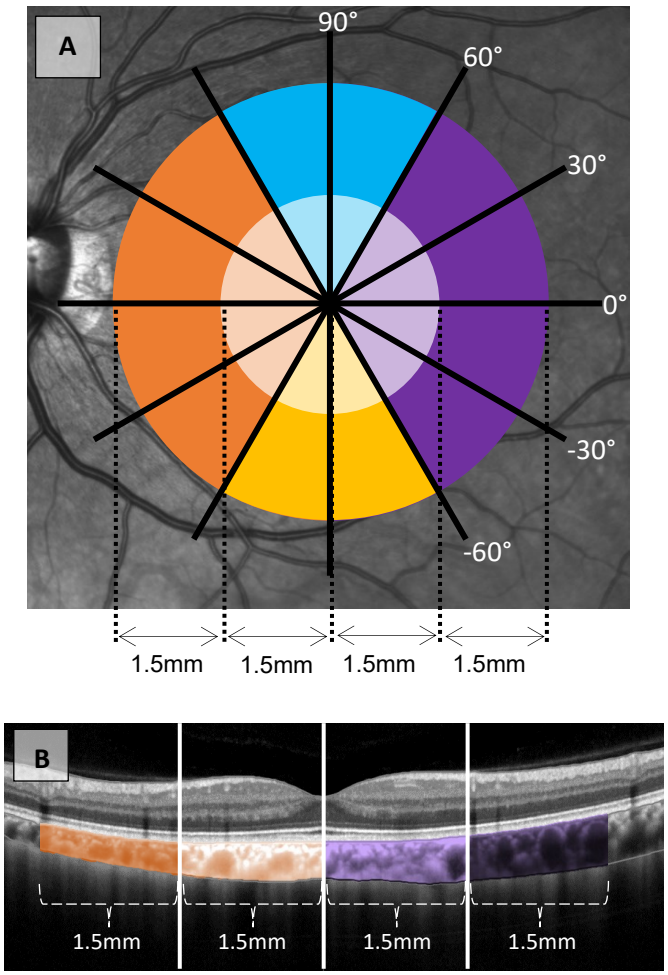


Figure 7.8: A) Fundus image showing the position of radial OCT line scans and their corresponding 1.5mm regions, where blue = superior region, purple = temporal region, yellow = inferior region, and orange = nasal region. Within each region, the lighter colour represents the 1.5mm foveal/parafoveal region, and the darker colour represents the 1.5mm perifoveal region). **B) Example of a B-scan showing the segmented 1.5mm choroidal regions.** This scan represents the line scan positioned at 0° in image A.

7.2.5 Pairing of child participants

As mentioned in Section 7.2.1, the 10 children participating in short-term DIMS wear (ST group) were matched with 10 of the children participating in the long-term DIMS clinical trial

(LT group). As well as being closest in age at the baseline appointments, the children chosen from the long-term DIMS clinical trial were of the closest refractive error (as determined by cycloplegic MSE) and axial length. The differences between the pairings are presented in Table 7.4 and statistical significance is calculated in Section 7.2.6b.

These parameters were chosen for several reasons. Firstly, it is established that myopia development and progression is heavily influenced by a child's age, where younger children exhibit faster eye growth and concurrent myopia progression than older children[402, 437, 469]. Whether a child's age impacts the speed of choroidal compensation to lens-induced retinal defocus isn't known. However, minimising the difference in the children's ages within the matched pairs may help lessen the potential impact this could have, particularly for those whose choroidal thickness is measured over a 12-month period.

Similarly, although there is no clear evidence to show that the level of refractive error and axial length impacts an individual's choroidal response to retinal blur[126, 260], choroidal thickness itself is significantly associated with myopia and axial length; individuals with higher degrees of myopia or longer axial lengths typically have thinner choroids[238, 253, 435]. Therefore, by limiting the difference in the refractive status and ocular biometrics within the matched pairs, it minimises the possibility of such measures confounding the choroidal thickness measures taken over differing durations of DIMS wear.

Pair	Difference (ST group – LT group)		
	Age (years)	MSE (D)	Axial length (mm)
1	0.88	0.31	1.68
2	-0.58	-0.25	-0.38
3	0.16	0.37	-0.16
4	0.49	1.00	1.74
5	0.89	0.25	-0.94
6	0.86	-0.20	-1.20
7	0.46	-0.69	1.74
8	0.41	0.42	-1.76
9	0.16	-0.32	-0.25
10	0.41	-0.44	0.57
Mean	**0.41**	**0.05**	**0.10**
±SD	**0.44**	**0.51**	**1.28**

Table 7.4: Differences in age, MSE, and axial length within the 10 matched pairs of child participants, where one child participated in the long-term DIMS clinical trial (LT group) and the other child participated in the short-term DIMS experiment (ST group). The differences in MSE and axial length were calculated from the right eye of the LT group and the eye exposed to the DIMS lens in the ST group. Statistical significance of differences is explored in Section 7.2.6b.

Pair	Ethnicity		Sex	
	ST group	LT group	ST group	LT group
1	South Asian	South Asian	Female	Male
2	South Asian	South Asian	Male	Male
3	South Asian	White European	Female	Male
4	South Asian	South Asian	Male	Female
5	African-Caribbean	South Asian	Male	Male
6	South Asian	White European	Male	Female
7	White European	White European	Male	Male
8	South Asian	South Asian	Female	Male
9	South Asian	South Asian	Female	Female
10	White European	White European	Male	Male

Table 7.5: Ethnicities and sex of each child in each pair. Cells shaded in green indicate a match in ethnicity or sex within the pair. ST = short-term DIMS wear group, LT = long-term DIMS wear group.

Although there is no clear association between choroidal thickness and sex[167, 238], nor choroidal thickness and ethnicity[250], there is evidence of a significant association between myopia progression and sex[470, 471] and myopia progression and ethnicity[43, 470]; young girls may experience more rapid myopia progression than boys[470, 471], and children of East and South Asian ethnicities often exhibit faster myopia progression than White European children[472]. Therefore, matching of these characteristics was preferable, but the cohort of children recruited for either study was not large enough to provide matches in ethnic background or sex for every pair: three out of the 10 pairs matched only in ethnicity, 1 pair matched only in sex, 2 pairs did not match in either ethnicity or sex, and 4 pairs matched in both ethnicity and sex (Table 7.5). Statistical analysis of the differences between the matched pairs is discussed in the following section.

7.2.6 Statistical analysis

All statistical analyses were performed using IBM SPSS (Statistics for Windows v28; IBM Corp., Armonk, NY, USA). The Shapiro-Wilk's W test was used to confirm normal distribution. The Greenhouse-Geisser correction was applied where the sphericity assumption was violated and a p-value below 0.05 was considered statistically significant in all cases.

7.2.6a Analysis of short-term data

The similarities in MSE, axial length, and baseline choroidal thickness between the right and left eyes of all the short-term DIMS wear participants were assessed using paired t-tests. Unpaired t-tests were used to compare the similarities in these measures between the young

adults and child participants, and Levene's test for equality of variances was conducted to confirm there was homogeneity of variances.

Changes in mean choroidal thickness within the parafoveal and perifoveal regions from baseline to each timepoint were calculated for each scan. Using the young adult data in isolation, a repeated measures ANOVA was conducted, considering 4 within-subject factors: viewing condition (DIMS and control), choroidal region (superior, temporal, inferior, and nasal), choroidal eccentricity (parafoveal and perifoveal), and time (5-, 15-, 25-, and 45-minutes, 20 minutes recovery).

Then including the child data, a second repeated measures ANOVA was conducted with 4 within-subjects factors: viewing condition (DIMS and control), choroidal region (superior, temporal, inferior, and nasal), choroidal eccentricity (parafoveal and perifoveal), and time (5-, 15-, and 25-minutes). One between-subject factor of age (young adult and child) was included.

7.2.6b Analysis of long-term data

Paired t-tests were used to assess the similarities in age, MSE, axial length, and baseline choroidal thickness of the 10 matched child pairs (Section 7.2.5). In the LT group, the significance of the changes in MSE and axial length from baseline to 12 months was assessed using paired t-tests.

To determine whether a statistically significant change in choroidal thickness occurred over a 12-month period of DIMS wear, a repeated measures ANOVA was conducted. Three within subjects factors were included: choroidal region (superior, temporal, inferior, and nasal), choroidal eccentricity (parafoveal and perifoveal), and time (baseline and endpoint). The degree of association between the variables of axial length, MSE, and choroidal thickness was assessed using Pearson correlations.

The change in choroidal thickness with DIMS wear from baseline to each subsequent timepoint was calculated for the LT group (baseline to 12 months) and the ST group (baseline to 5 minutes, baseline to 15 minutes, and baseline to 25 minutes). For each choroidal region and degree of eccentricity, paired t-tests were used to assess the differences between the choroidal thickness changes seen at 12 months with that seen at 5, 15, and 25 minutes according to the matched child pairs.

The linear regression model with sequential Bonferroni correction was used to investigate the association of short-term regional choroidal thickness changes measured at 25 minutes with those seen at 12 months of DIMS wear. This was conducted for the short-term measures taken with both the control condition and DIMS trial lens. Subsequent linear

regression models and Bonferroni adjustments were used to explore if short-term choroidal thickness changes could predict the change in axial length and MSE at 12 months. In all cases, normality of the residuals was assessed by visual inspection of normal probability plots.

7.3 RESULTS

7.3.1 Results of short-term DIMS wear

7.3.1a Young adult participants

Eight of the 10 young adult participants were able to maintain fixation throughout the entire experimental viewing period. Two participants lost fixation for a total of 3 seconds and 5 seconds, indicating steady fixation relative to the duration of the experiment. The MSE (p=0.186), axial length (p=0.083), and baseline choroidal thickness (p=0.852), were not statistically significantly different between the participants' right and left eyes.

		Young adult participants									
		Mean change in choroidal thickness from baseline to each timepoint (µm)									
Choroidal region	**Choroidal eccentricity**	**5 minutes**		**15 minutes**		**25 minutes**		**45 minutes**		**20 minutes recovery**	
		Control	DIMS	Control	DIMS	Control	DIMS	Control	DIMS	Control	DIMS
Nasal	**Parafoveal**	-2.18 ± 13.09	+2.27 ± 8.07	+0.26 ± 8.08	+0.31 ± 8.23	+0.04 ± 6.20	+4.37 ± 9.22	+0.87 ± 7.86	+2.09 ± 13.84	+2.02 ± 9.43	+1.79 ± 14.08
	Perifoveal	-0.72 ± 12.47	+2.64 ± 10.12	+1.37 ± 11.12	+0.04 ± 10.43	+0.93 ± 10.93	+4.56 ± 13.17	+3.62 ± 12.44	+4.01 ± 15.72	+3.35 ± 11.67	+0.99 ± 16.33
Temporal	**Parafoveal**	-1.51 ± 12.48	+0.38 ± 7.86	+1.26 ± 10.60	-0.53 ± 11.70	-2.31 ± 7.38	+3.69 ± 7.90	-0.85 ± 8.86	+3.71 ± 10.49	-1.51 ± 8.31	+2.94 ± 8.14
	Perifoveal	-2.85 ± 10.71	+0.16 ± 7.47	-2.11 ± 8.85	-1.23 ± 10.55	-2.67 ± 6.90	+2.38 ± 11.28	-3.89 ± 11.17	+2.44 ± 8.09	-0.21 ± 12.36	+1.87 ± 9.49
Inferior	**Parafoveal**	-1.91 ± 9.05	-0.71 ± 9.25	-5.24 ± 10.33	-1.50 ± 10.09	-2.82 ± 8.13	+2.19 ± 9.54	-2.38 ± 8.58	+5.04 ± 9.49	-3.25 ± 7.57	+3.24 ± 9.99
	Perifoveal	-0.82 ± 10.42	-0.24 ± 9.00	-2.21 ± 8.82	-0.99 ± 10.48	-1.56 ± 8.59	+2.24 ± 12.08	+0.79 ± 10.41	+5.45 ± 13.00	+0.18 ± 10.41	+4.09 ± 10.94
Superior	**Parafoveal**	-2.36 ± 9.72	+1.62 ± 9.13	-6.05 ± 11.06	-1.53 ± 7.49	-0.42 ± 7.52	+3.18 ± 11.19	-0.75 ± 8.99	+0.76 ± 7.57	+2.09 ± 9.59	+2.98 ± 9.54
	Perifoveal	+2.99 ± 10.83	+3.47 ± 8.13	+1.26 ± 8.77	+2.30 ± 8.80	+4.12 ± 8.83	+2.98 ± 8.55	+4.12 ± 9.36	+1.84 ± 8.97	+4.15 ± 8.77	+5.50 ± 12.48
Mean of all regions		**-1.17 ± 11.14**	**+1.20 ± 8.66**	**-1.43 ± 10.02**	**-0.39 ± 9.74**	**-0.59 ± 8.35**	**+3.20 ± 10.39**	**+0.19 ± 10.01**	**+3.17 ± 11.18**	**+0.85 ± 9.97**	**+2.92 ± 11.56**

Table 7.6: Mean change in choroidal thickness from baseline to each timepoint for each choroidal region, eccentricity, and viewing condition for **young adult participants**. Positive values (increases from baseline) are shaded in green and negative values (decreases from baseline) are shaded in red. Note that colours do not represent statistical significance of these changes. Data are presented as mean ± SD.

Over the averaged 6mm macular region, the choroid appeared to remain close to baseline at all timepoints under the control condition (range -1.43 ± 11.14μm to +0.85 ± 9.97μm) (Table 7.6). A greater difference in choroidal thickness from baseline was seen in the eyes exposed to the DIMS lens, with all values being more positive than those of the control condition (range -0.39 ± 9.74μm to +3.20 ± 10.39μm). However, repeated measures ANOVA revealed these differences to not be statistically significant; no statistically significant interaction was observed between the viewing condition, choroidal region, choroidal eccentricity, and timepoint ($F_{15, 435} = 0.789$, p=0.690).

There were no statistically significant interactions between viewing condition, choroidal region, and timepoint ($F_{15, 435} = 1.681$, p=0.052), or viewing condition, choroidal eccentricity, and timepoint ($F_{5, 145} = 0.324$, p=0.898), collectively indicating no particular area of the choroid responded differently. The remaining analyses revealed no other statistically significant interactions (all p>0.05).

Similarly, there was no significant interaction between the factors of time, viewing condition, choroidal region, and choroidal eccentricity with DIMS wear when analysed relative to the control condition ($F_{8, 219} = 0.789$, p=0.606). All other group differences were not significant (all p>0.05).

7.3.1b Child participants

Six of the 10 children were able to maintain steady fixation throughout the 25-minute viewing period, and the remaining 4 children lost fixation between 3 and 10 seconds (mean 6.8 ± 3.0 seconds). The paired t-tests showed the MSE (p=0.390), axial lengths (p=0.451) and baseline choroidal thickness (p=0.445) to have no statistically significant difference between the right and left eyes of the ST child participants. Compared with that of the young adult participants, the MSE (p=0.122) and axial lengths (p=0.185) were not statistically significantly different in the child participants. The Shapiro-Wilk's W test revealed baseline choroidal thickness of the complete sample (young adults and children) to not be normally distributed (p=0.039), however an unpaired t-test was still conducted due to being considered a robust form of analysis of group differences where equal sample sizes and equal variances are present[473]. From this, the difference in baseline choroidal thickness between the young adults and children was also found to be nonsignificant (p=0.193).

The choroids of the child participants did not statistically significantly change from baseline to each timepoint (5, 15, and 25 minutes) at any choroidal region or eccentricity in either the DIMS or control condition; no significant interaction between these four within-subjects

		Child participants					
		Mean change in choroidal thickness from baseline to each timepoint (µm)					
Choroidal region	**Choroidal eccentricity**	**5 minutes**		**15 minutes**		**25 minutes**	
		Control	DIMS	Control	DIMS	Control	DIMS
Nasal	**Parafoveal**	+0.60 ± 8.52	+4.38 ± 10.92	+2.70 ± 9.05	+4.16 ± 17.56	+3.09 ± 10.38	+0.84 ± 11.88
	Perifoveal	+0.66 ± 9.82	+4.21 ± 14.28	-2.48 ± 13.65	+1.38 ± 14.55	-1.73 ± 10.41	-0.25 ± 13.59
Temporal	**Parafoveal**	-1.18 ± 6.91	+1.49 ± 7.25	-2.16 ± 9.65	+0.80 ± 4.72	+0.13 ± 7.83	-1.77 ± 6.88
	Perifoveal	-1.57 ± 6.92	-0.94 ± 8.92	-2.28 ± 8.14	-2.94 ± 9.47	-2.10 ± 10.69	-2.54 ± 8.71
Inferior	**Parafoveal**	+1.75 ± 6.19	+3.12 ± 10.15	+0.37 ± 9.19	+2.41 ± 8.79	+2.19 ± 9.45	+0.18 ± 7.70
	Perifoveal	-0.52 ± 6.73	+3.06 ±13.26	+0.53 ± 13.33	+2.20 ± 11.42	+1.00 ± 9.78	+0.05 ± 9.60
Superior	**Parafoveal**	+1.80 ± 5.67	+1.58 ± 6.70	-1.29 ± 6.44	+3.76 ± 7.17	+0.89 ± 8.48	+0.03 ± 6.04
	Perifoveal	+2.26 ± 6.07	-0.20 ± 7.80	+0.93 ± 8.66	+1.15 ± 9.10	-0.02 ± 10.70	-0.21 ± 5.42
Mean of all regions		**+0.50 ± 7.68**	**+2.09 ± 10.28**	**-0.42 ± 10.05**	**+1.62 ±13.10**	**+0.34 ± 9.76**	**-0.46 ± 9.05**

Table 7.7: Mean change in choroidal thickness from baseline to each timepoint for each choroidal region, eccentricity, and viewing condition for **child participants**. Positive values (increases from baseline) are shaded in green and negative values (decreases from baseline) are shaded in red. Note that colours do not represent statistical significance of these changes. Data are presented as mean ± SD.

factors was observed ($F_{3,129}$= 0.537, p=0.633) (Table 7.7). Similarly, when considered relative to the control condition, there was no statistically significant interaction between time, choroidal region, and choroidal eccentricity with DIMS wear ($F_{9, 261}$= 1.044, p=0.405). At the 25-minute timepoint, when including the between-subjects factor of age, there was no statistically significant interaction observed between the two age groups ($F_{3, 151}$= 0.157, p= 0.903), indicating the child and adult eyes did not respond differently to the same experimental conditions in this timeframe.

7.3.2 Results of long-term DIMS wear

7.3.2a 12-month results

At 12 months of DIMS wear, MSE had decreased by -0.18 ± 0.47D, however this was not statistically significantly different from baseline (p=0.246). Axial length had increased by an average of +0.18 ± 0.16mm (p=0.028) and choroidal thickness has significantly increased from baseline (all p<0.05, see Table 7.8). This choroidal thickening appeared to be greatest in the nasal perifoveal region (+22.63 ± 22.83µm, p<0.001) and lowest in the temporal perifoveal region (+12.68 ± 22.05µm, p=0.004), but there was no statistically significant

Choroidal region	Choroidal eccentricity	Mean change at 12 months (µm)	± SD	P-value
Nasal	**Parafoveal**	+20.85	21.11	<0.001
	Perifoveal	+22.63	22.83	<0.001
Temporal	**Parafoveal**	+19.02	21.75	<0.001
	Perifoveal	+12.68	22.05	0.004
Inferior	**Parafoveal**	+13.24	17.86	<0.001
	Perifoveal	+17.64	21.96	<0.001
Superior	**Parafoveal**	+14.96	19.87	<0.001
	Perifoveal	+18.11	25.32	<0.001

Table 7.8: Mean change in choroidal thickness from baseline to 12 months of DIMS wear within each choroidal region and eccentricity.

	Mean choroidal thickness (µm)					
	Baseline			12 months		
Choroidal region	**Parafoveal**	**Perifoveal**	**P-value**	**Parafoveal**	**Perifoveal**	**P-value**
Nasal	290.08 ± 80.91	261.61 ± 92.17	<0.001	310.92 ± 86.64	284.24 ± 93.51	<0.001
Temporal	296.22 ± 67.48	297.34 ± 66.41	0.837	315.34 ± 79.36	310.02 ± 77.02	0.370
Inferior	300.03 ± 70.09	293.97 ± 75.53	0.295	313.26 ± 74.82	311.61 ± 76.96	0.759
Superior	298.68 ± 71.57	291.02 ± 79.05	0.139	313.64 ± 77.65	309.14 ± 83.24	0.362
P-value	0.164	<0.001		0.774	<0.001	

Table 7.9: Mean choroidal thickness within the parafoveal and perifoveal regions at baseline and 12 months. Data are presented as mean ± standard deviation. P-values show statistical significance of differences between the nasal, temporal, inferior, and superior regions, and between the parafoveal and perifoveal regions. Cells shaded in green indicate statistical significance (p=<0.05).

interaction between time, region, and choroidal eccentricity ($F_{2, 62}$ = 3.01, p=0.053). Further, no significant two-way interaction was observed between time and eccentricity ($F_{1, 29}$ = 0.267. p=0.609), or time and choroidal region ($F_{2, 65}$ = 0.825, p=0.456).

The degree of choroidal eccentricity and choroidal region showed a significant two-way interaction ($F_{2, 65}$ = 12.4, p<0.001); at both baseline and 12 months, the nasal perifoveal region was significantly thinner than all other choroidal areas (all p<0.005), including the nasal parafovea (Table 7.9).

In this sample, there was a significant negative association between progression of axial length and MSE (Pearson's correlation coefficient, r=-0.768, p=0.009), however no statistically significant correlation between choroidal thickness change and axial elongation or MSE progression was identified (Table 7.10).

Table 7.10: The association between choroidal thickness change at 12 months of DIMS wear with axial length change and MSE progression, expressed as Pearson's correlation coefficients with bracketed p-values.

		Pearson's Correlation (p-value)	
Choroidal region	**Choroidal eccentricity**	**Axial length**	**MSE**
Nasal	**Parafoveal**	-0.508 (p=0.134)	0.547 (p=0.102)
	Perifoveal	-0.307 (p=0.388)	0.479 (p=0.162)
Temporal	**Parafoveal**	-0.180 (p=0.619)	0.510 (p=0.132)
	Perifoveal	-0.209 (p=0.561)	0.236 (p=0.512)
Inferior	**Parafoveal**	-0.105 (p=0.773)	0.340 (p=0.337)
	Perifoveal	-0.405 (p=0.245)	0.532 (p=0.113)
Superior	**Parafoveal**	-0.307 (p=0.388)	0.407 (p=0.243)
	Perifoveal	-0.381 (p=0.277)	0.470 (p=0.171)
Averaged 6mm choroidal area		-0.291 (p=0.415)	0.521 (p=0.123)

7.3.2b Matched child pairs

The MSE (p=0.309), axial length (p=0.803), and baseline choroidal thickness (p=0.486) of the eyes analysed were not statistically significantly different between the individuals within each matched pair. However, there was a significant difference in age (p=0.016). Paired t-tests showed choroidal thickness changes to be statistically significantly different between the matched child pairs; children in the LT DIMS wear group experienced significantly greater choroidal thickening than those in the ST DIMS wear group at all timepoints (Table 7.11).

Figures 7.9a and 7.9b show the scatterplots of the measured difference in choroidal thickness between baseline and 25 minutes of both the short-term viewing conditions (control and DIMS wear) against the change seen at 12 months of DIMS wear. Linear

		LT – ST change in choroidal thickness from baseline (mean ± SD)					
Choroidal Region	**Choroidal Eccentricity**	**Change at 12 months – change at 5 minutes (μm)**	**P-value**	**Change at 12 months – change at 15 minutes (μm)**	**P-value**	**Change at 12 months – change at 25 minutes (μm)**	**P-value**
Nasal	**Parafoveal**	17.97 ± 24.11	<0.001	18.20 ± 30.07	0.001	21.51 ± 24.80	<0.001
	Perifoveal	15.55 ± 29.24	0.003	15.24 ± 30.10	0.005	20.01 ± 28.06	<0.001
Temporal	**Parafoveal**	21.10 ± 28.06	<0.001	21.79 ± 24.72	<0.001	24.36 ± 28.13	<0.001
	Perifoveal	22.98 ± 29.62	<0.001	24.99 ± 24.92	<0.001	24.58 ± 29.18	<0.001
Inferior	**Parafoveal**	16.62 ± 24.51	<0.001	17.31 ± 20.87	<0.001	19.56 ± 24.15	<0.001
	Perifoveal	20.83 ± 24.97	<0.001	21.69 ± 23.15	<0.001	23.85 ± 21.89	<0.001
Superior	**Parafoveal**	19.38 ± 19.35	<0.001	17.20 ± 18.72	<0.001	20.93 ± 19.05	<0.001
	Perifoveal	24.07 ± 21.74	<0.001	22.72 ± 22.43	<0.001	24.08 ± 21.79	<0.001

Table 7.11: Mean difference between the change in choroidal thickness from baseline measured at 12 months in the LT DIMS wear group and each timepoint of the ST DIMS wear experiment. Measures are presented according to the choroidal region and eccentricity. P-values were determined using paired t-tests.

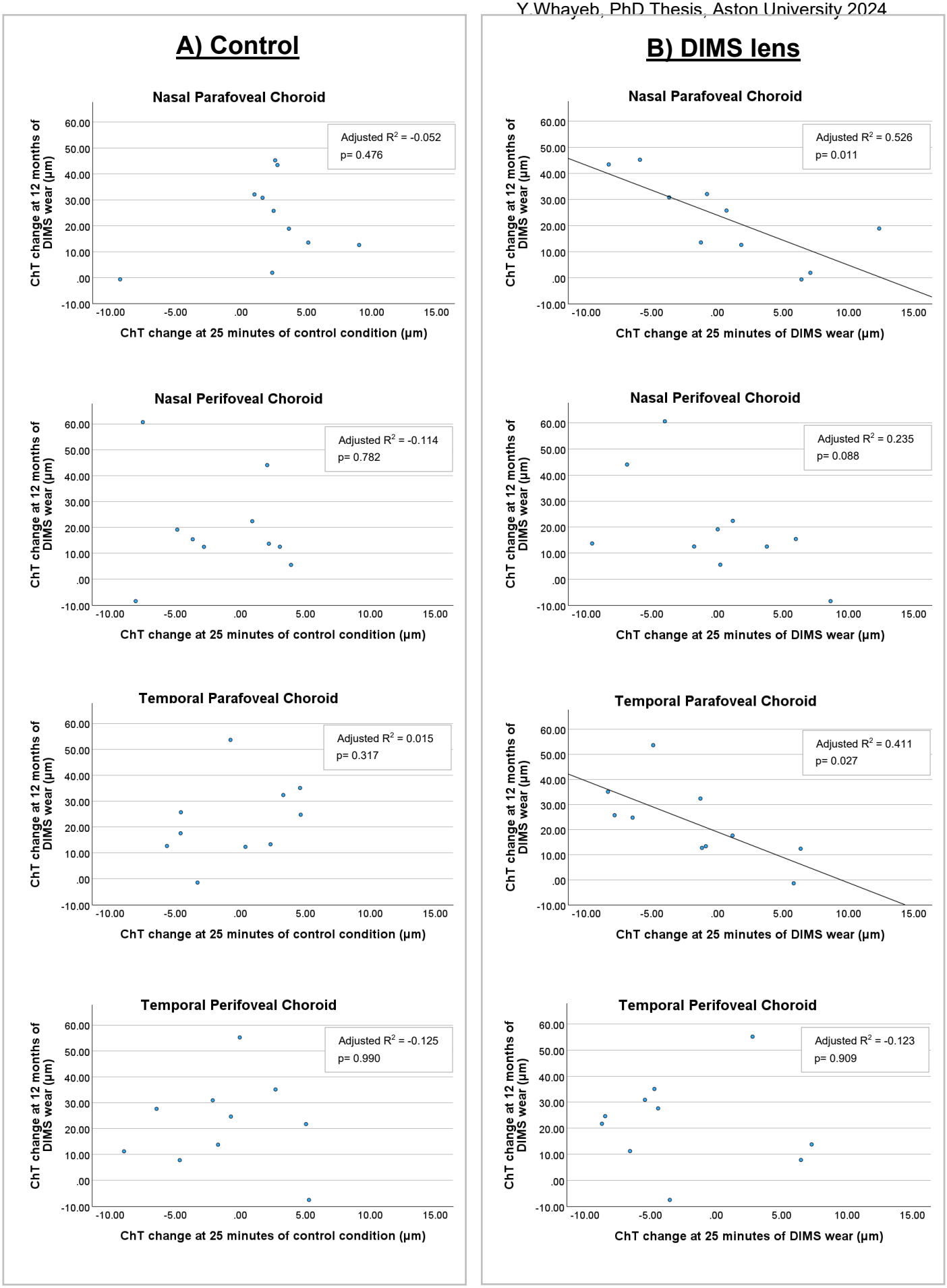


Figure 7.9a: Scatterplots of the regional choroidal thickness changes from baseline to 12 months of DIMS wear (y-axis) with baseline to 25 minutes of A) control condition and B) DIMS wear (x-axis) for each matched pair (n=10). Presence of a regression line indicates a statistically significant linear relationship.

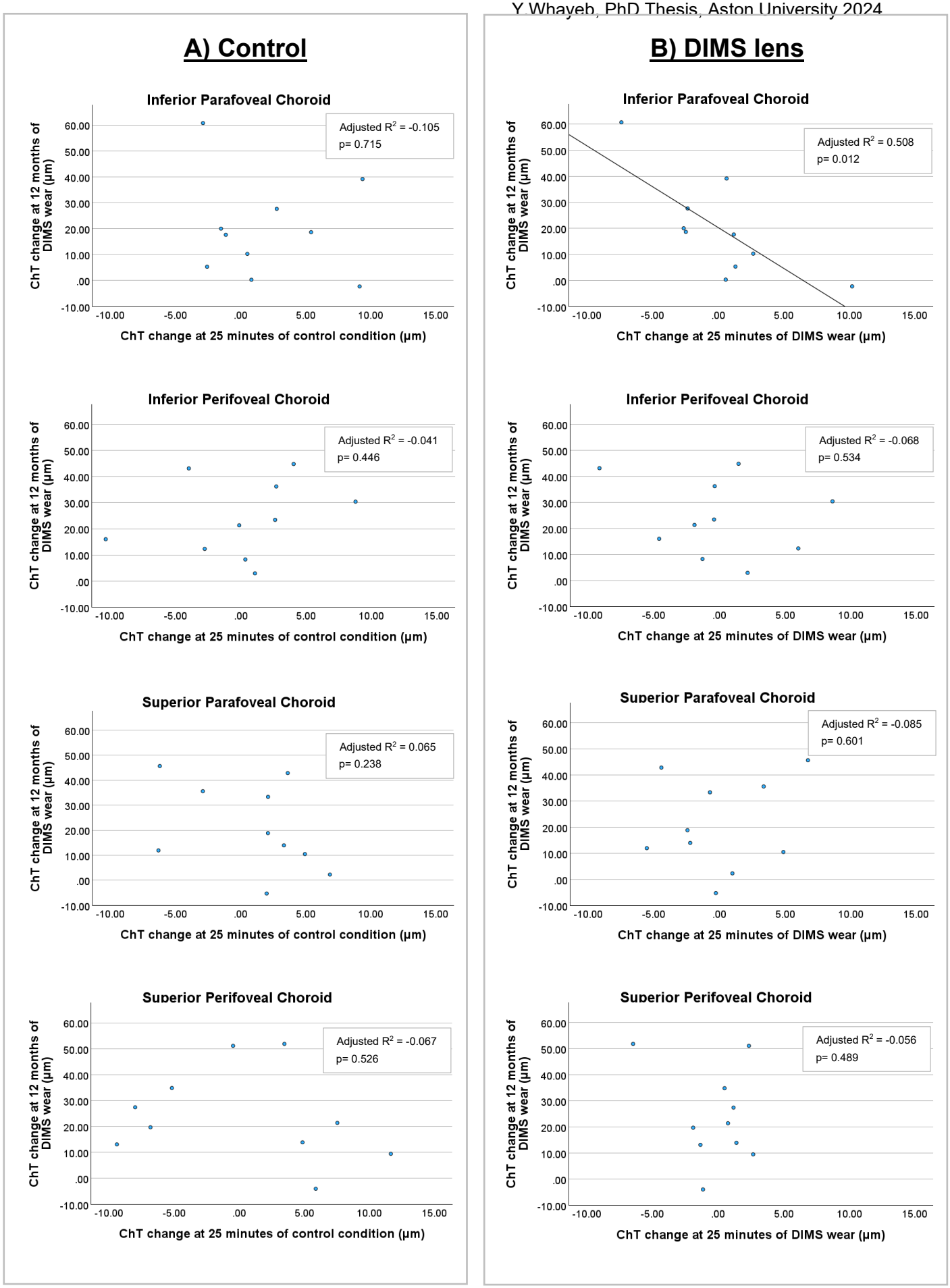


Figure 7.9b: Scatterplots of the regional choroidal thickness changes from baseline to 12 months of DIMS wear (y-axis) with baseline to 25 minutes of A) control condition and B) DIMS wear (x-axis) for each matched pair (n=10). Presence of a regression line indicates a statistically significant linear relationship.

regression models showed no statistically significant linear relationship between the choroidal thickness changes at 12 months and those measured at 25 minutes under the control condition in any choroidal region and eccentricity. Conversely, significant negative linear relationships between the differences in choroidal thickness at 12 months and 25 minutes of DIMS wear within the nasal ($F_{1, 8}$ = 10.983, p=0.011, adjusted R^2 of 0.526), temporal ($F_{1, 8}$ = 7.278, p=0.027, adjusted R^2 of 0.411), and inferior ($F_{1, 8}$ = 10.306, p=0.012, adjusted R^2 of 0.508) parafoveal regions were identified. However, the normality plot of the temporal parafoveal points showed the residuals to suffer from moderate positive kurtosis, indicating non-normality; due to the sample of pairs being of less than 15[474], it may be that the non-normal distribution makes the temporal parafoveal result more susceptible to Type I error.

On averaging the changes from baseline across the entire 6mm radial choroidal area, a statistically significant negative linear relationship was identified between 25 minutes and 12 months of DIMS wear ($F_{1, 8}$ = 8.94, p=0.018, adjusted R^2 of 0.467), whereas no significant linear relationship was present for that of the control condition ($F_{1, 8}$ = 0.079, p=0.786, adjusted R^2 of -0.114) (Figure 7.10). There were no significant linear relationships between the regional and overall choroidal thickness changes at 25 minutes in either viewing condition with the change in MSE or axial length from baseline to 12 months (all p>0.05).

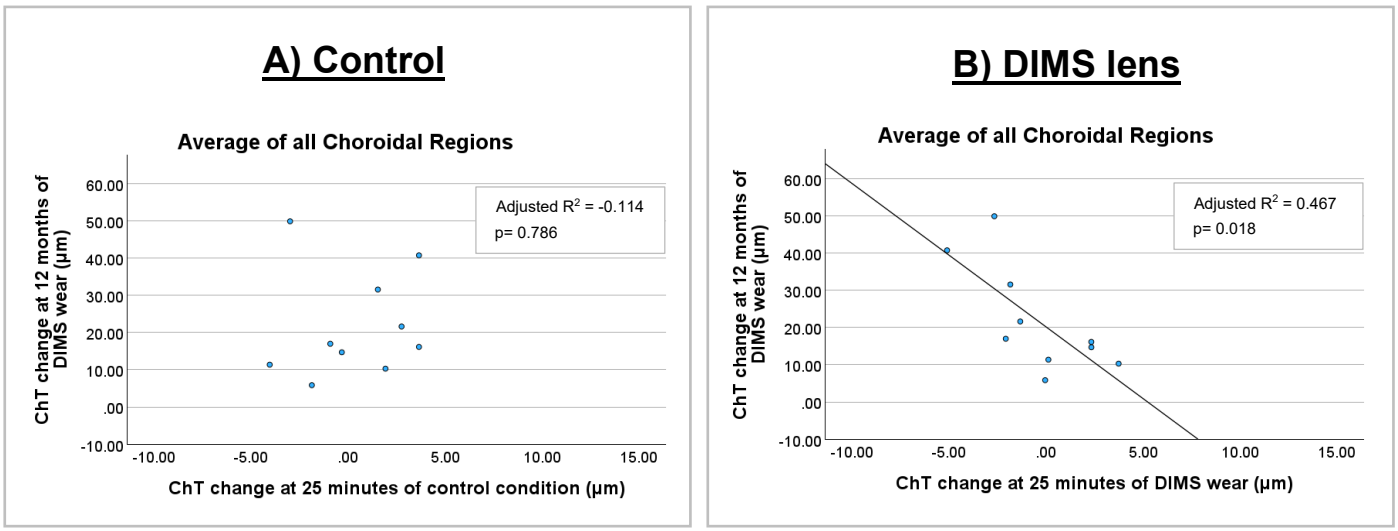


Figure 7.10: Scatterplots showing the choroidal thickness change over the 6mm radial area from baseline to 12 months of DIMS wear (y-axis) with baseline to 25 minutes of A) control condition and B) DIMS wear (x-axis) for each matched pair (n=10). Presence of a regression line indicates a statistically significant linear relationship.

7.4 DISCUSSION

This study measured and compared regional changes in choroidal thickness in response to short-term and long-term DIMS spectacle lens wear. In addition, this study assessed the association between changes in regional choroidal thickness, axial length, and myopia progression over a 12-month period in myopic children. This included exploration of using short-term choroidal fluctuations as biomarkers for long-term choroidal, axial, and refractive change.

In young adults, 45 minutes of DIMS lens wear did not cause a detectable change in choroidal thickness within the 3mm nasal, temporal, inferior, and superior macular choroidal regions. Twenty minutes following removal of the DIMS lens also revealed no significant change. This finding contrasts with that reported in Chapter 5 of this thesis; with the same sample size, participant eligibility criteria, experimental protocol, and choroidal segmentation method, a statistically significant level of choroidal thickening was observed in the nasal and temporal choroidal regions following hemifield myopic defocus. Further still, a higher dioptric level of myopic blur was imposed in the current study compared to that of Chapter 5 (3.50D and 3.00D, respectively) yet statistical significance was not achieved; this is despite existing literature evidencing a dose-dependent choroidal response where greater myopic defocus causes greater choroidal thickening[283].

Consistent with the findings of bifocal wear in Chapter 5, the choroids of child participants showed no significant difference in thickness at 25 minutes of DIMS wear. Correspondingly, there was no difference in thickness change from baseline between the child and young adult choroids at the 25-minute timepoint, further supporting existing evidence of the choroidal response to short-term blur being independent of age[260].

Consideration of the study setup and trial lens refraction profiles help to hypothesise why an executive bifocal lens design used in Chapter 5 elicited significant localised choroidal thickening at 45 minutes, yet a DIMS spectacle lens did not. Participants were required to watch a film on a small 24-inch television monitor at 6 metres, meaning the image subtended a 5.3° horizontal by 3.2° vertical visual angle. Its purpose was to promote steady fixation through the centre of the trial lens throughout the viewing period, preventing the participant from having to move their eyes to view different parts of the screen. The surrounding environment was in near darkness (between 10-20 lux), designed to maximise pupil size and prevent distractions in the room. This may have been disadvantageous when exploring the impact of myopic defocus in a DIMS spectacle lens; an executive bifocal lens positioned vertically in Chapter 5 was centred to blur the fixation target split midline, whereas a DIMS lens design leaves the central vision unaffected. Therefore, the defocusing stimulus may

have been isolated to the darker environment surrounding the television monitor, lessening the perception of the peripheral blur. Some studies of regional blur in adult eyes have adopted targets subtending a markedly greater visual angle (larger television and projector screens or closer working distances)[261, 263, 264]. To assess compliance, these studies either had the patient conduct an interactive task throughout the entire experiment[263], or did not monitor fixation[261, 264]. With child participants, it was considered essential for fixation to be monitored in the current study, but it could be argued that an interactive task may have been too challenging for some children to maintain for 25 minutes or distract their fixation further.

While not induced using a DIMS spectacle lens, there is evidence to suggest a longer duration of 3.50D relative plus power (using Fresnel lenses) isolated to the peripheral retina still does not impact choroidal thickness; measured before and after 4 hours of wear in adults, as Kubota et al., (2021) also found no significant change[264] (see Chapter 1 Section 1.4.2b). However, this was measured over the central 0.5mm subfoveal choroidal region with a larger central clear aperture than that of a DIMS lens (11.5mm to 9.4mm, respectively)[264]. At present, there doesn't appear to be any research challenging this, and it is unknown whether a significant change in choroidal thickness would be present over a wider choroidal area, such as that measured in this study, at multiple hours of wear.

In the eyes of the LT child participants, the nasal perifoveal area was significantly thinner than the remaining choroidal regions and eccentricities at both baseline and 12 months of DIMS spectacle lens wear, agreeing with previous research of choroidal topographic variations in myopic children[167]. Over the 12-month period, statistically significant choroidal thickening was identified across all regions and eccentricities of the choroid examined, with the nasal perifovea showing the greatest degree of change. However, the extent of thickening within the nasal perifovea was not significantly greater than that of the surrounding regions, suggesting baseline choroidal thickness may not impact the long-term change. Interestingly, a clinical trial exploring the impact of MiSight 1-Day contact lenses (see Chapter 1 Section 1.4.3b) identified no choroidal thickening within the nasal perifoveal area at 12 months of wear, only within the 1mm nasal and temporal regions, and the temporal 3mm region in children who responded to the intervention[297]. Additional research is required to explore how choroidal thickness prior to inducing blur is associated with that measured at a provoked point of significant thickness change, and whether this is impacted by the dose and spatial distribution of dioptric power. Further, the current study is unable to determine how the change compares to children wearing conventional spectacles. However, the finding of choroidal thickening aligns with previous reports of subfoveal choroidal thickening with long-term DIMS wear[282].

Although existing literature reporting a large treatment effect may indicate the sample size of the current study to be sufficient to measure the degree of association between choroidal thickness, MSE, and axial length at 12 months of optical intervention wear (see Section 7.2.6b) the previously reported correlations with DIMS spectacles specifically (albeit measured over 24 months) indicate a greater number of children may be required to do so in this study[282]. Therefore, it is possible that the small number of children assessed over the 12-month period (n=10) resulted in a study too insensitive to detect statistically significant correlations specific to DIMS spectacle lens wear. Despite the lack of significance, the Pearson's correlation coefficients showed a consistent trend: a negative association between choroidal thickness and axial length, and positive association between choroidal thickness and MSE, supporting published data from longitudinal clinical trials of other myopia intervention approaches[281, 282, 315]. When averaged over the four choroidal regions, Pearson's correlations of choroidal thickness and axial length or MSE appeared to be strongest (yet nonsignificant) in the nasal choroid; r=-0.408 and r=0.513, respectively (both $p>0.05$). With Chapter 5 reporting the greatest short-term choroidal thickening to occur nasally with regional blur, perhaps the nasal choroidal region is an area of interest. This topic is discussed further in the subsequent chapter.

Based on previous research[282], a significantly greater change in choroidal thickness with long-term than short-term DIMS wear was expected. Although the short-term choroidal thickness changes did not show a significant interaction between the within-subject factors, linear regression models suggest the measurements at 25 minutes of DIMS wear may have the potential to predict choroidal thickness changes at 12 months within the nasal, inferior, and, albeit questionable due to the non-normal distribution, temporal parafoveal regions. This was not the case for any region under the control condition. Unexpectedly, these regions showed a consistent negative association, where a greater increase in choroidal thickness at 25 minutes of DIMS wear may indicate a greater decrease at 12 months of wear. At present, there is insufficient knowledge of this association to theorise why this may be the case. Similar unanticipated findings of an inverse response have been identified with sunlight, where brief exposure to the outdoor environment has induced choroidal thinning which increased on recovery, yet the longer-term shielding effect of outdoor time is thought to prevent choroidal thinning[340]. Perhaps these paradoxical responses evidence the existence of separate mechanisms mediating the short-term choroidal thickness changes compared to changes in long-term ocular growth.

The investigation of early choroidal changes as a predictor for long-term change was subject to limitation by the aforementioned small sample size. Existing peer-reviewed publications of the predictive properties of the choroid for long-term axial elongation, myopia progression,

and choroidal thickness changes typically adopt markedly larger sample sizes[281, 282, 297, 315], providing increased precision and greater statistical power. Sourcing child participants who met the eligibility criteria and paired closely with those already enrolled onto the longitudinal DIMS clinical trial made recruitment for this study challenging, resulting in a small sample. Consequently, the impact of age and gender on ocular growth and myopia progression could not be controlled in the regression analyses. There was a statistically significant difference in age between the matched child pairs; children in the ST group were mostly older than the LT group (mean age difference 4.9 ± 5.3 months, range -7.0 to 10.7 months). Though the MSE, axial lengths, and choroidal thicknesses at baseline were not statistically different, a child's age is known to play a crucial role in the rate of eye growth and myopia progression due to younger children showing faster progression rates than older children[475, 476]. Further, on recruitment, the different refractive criteria for the LT and ST child groups yielded a clinically significant greater average level of astigmatism in the LT participants (refer to Table 7.3). On calculating baseline MSE for each group, this difference contributed to a greater degree of myopia by 0.20D in the LT group. However, the lack of statistical significance between the other biometric measures suggested the differing anterior optics of the matched pairs did not have a substantial effect on the degrees of axial myopia.

Even with matched pairs, the contrast between the protocols of the long-term clinical trial and short-term experiment of DIMS wear left differences in data collection procedures. For all participants, diurnal fluctuations in choroidal thickness and the impact of cycloplegic agents were accounted for in the study visit schedules. Ahead of the short-term defocus experimental sessions, the participants also avoided known confounding factors on choroidal thickness. However, this was not the case for children participating in the long-term DIMS clinical trial. Therefore, the choroids of these children were open to influence by factors such as caffeine, accommodation, and exercise (see Chapter 1 Section 1.3.3), possibly affecting the measurement outcomes. Furthermore, the compliance of children wearing DIMS spectacles full-time could not be objectively monitored; the attending parent was asked at each visit whether the child was wearing the spectacles full-time, however it cannot be known explicitly whether this was always the case. For example, the child may have been taking the spectacles off during school hours. In the absence of an in-built mechanism to monitor the wear time of a pair of spectacles, this is an unavoidable limitation of any longitudinal spectacle lens trial.

In conclusion, the findings of this study highlight the need for more research to establish the first detectable level of choroidal thickening with short-term DIMS wear and whether this differs across the choroidal profile. In addition, the findings of this study warrant further investigation of how short-term change corresponds to changes seen with long-term full-time

wear. A larger sample of paired myopic children more closely matched in age is important. Although time consuming, a longitudinal study design is another option, where the short- and long-term effects are explored in the same individuals. Notwithstanding, this study provides insight into the possibility of an association between short-term and long-term choroidal thickness with DIMS lens wear in myopic children which varies with choroidal region. The learnings of human choroidal behaviour from this study are discussed further in the following chapter.

Chapter 8. Discussion

8.1 SUMMARY

There is a growing body of research demonstrating the choroid to be a highly dynamic ocular component, responsive to various biological, optical, and pharmaceutical stimuli. Capable of rapid thickening and thinning within minutes, the significance of the bidirectional choroidal response with respect to long-term ocular growth forms an important part of current myopia research.

Although now considered a key structure involved, the specific role of the choroid in the regulation of eye growth remains obscure. Namely, its role in the growth-signalling cascade towards the sclera, and whether the associated short-term choroidal thickening or thinning impedes or facilitates long-term ocular growth. With this, understanding whether the early choroidal response to optical and pharmaceutical myopia interventions can act as a biomarker for long-term axial elongation has the potential to radically transform the management of childhood myopia in clinical practice. Therefore, the series of studies presented in this thesis were conducted to investigate the nature of changes in human choroidal thickness in response to deliberate modifications to the visual environment relevant to current global myopia management strategies.

The specific research objectives of this thesis outlined in Chapter 1 Section 1.6 were to:

A. *Explore how global activity and strategies to manage myopia have shifted alongside advancements in myopia research over recent years, involving the changing opinions regarding the importance of considering choroidal thickness in clinical practice.*
B. *Assess the choroidal imaging capabilities and repeatability of three OCT devices employing different technologies, with consideration of how the clinical significance translates into a real-world, patient-facing setting.*
C. *Investigate alterations in the spatial distribution of the human choroid beyond the subfoveal region following short-term exposure to myopic blur contained within the temporal and nasal hemifields, and whether this occurs in a regionally selective manner. This includes exploring whether an individual's age and ocular refractive status impacts the choroidal response to regional blur.*
D. *Assess the effect of indoor light levels on human choroidal thickness, addressing how this may influence appropriate measurement conditions and the design of future choroidal experimental work.*

E. *Measure and compare regional changes in human choroidal thickness in response to short-term and long-term wear of a commercially available spectacle lens designed to slow myopia progression, and, in turn, explore whether immediate choroidal alterations could act as a predictor for future axial growth.*

Addressing these research objectives, the findings from the experimental chapters of this thesis are summarised in the sections below.

8.1.1 Global myopia management strategies: measuring choroidal thickness and prescribing trends in clinical practice

(Research objective A: Summary of Chapters 2 and 3)

As identified in Chapters 2 and 3, choroidal thickness was generally considered to be less important than other ocular measurements eye care practitioners considered when assessing myopia progression and assisting their clinical decision making in recent years. These other ocular measures (such as refractive error, axial length, and binocular vision status) are arguably more established in the field of paediatric eye care and myopia management, so it was expected that fewer practitioners used choroidal thickness to guide their practice in comparison, particularly given the ambiguities regarding the choroid's association with enduring axial growth. Relative to biometric and refractive measures, the proportions of practitioners who measured choroidal thickness when managing their young myopic patients was highly inconsistent across the world, with little change from the years 2022 to 2024. The outcome of these surveys reflects that of existing literature; there is no clear consensus on the role of measuring choroidal thickness in the clinical practice of myopia management, and this uncertainty is apparent amongst many eye care practitioners when evaluated both between and within continents across the world.

Despite ambiguity surrounding the choroid's association with myopia intervention techniques, Chapter 3 established several promising trends in global myopia management attitudes and techniques of eye care practitioners from the years 2015 to 2024. The continent-wide increase in self-reported concern about the prevalence of myopia, rise in practitioner engagement and proactivity, and increased frequency of prescribing appropriate control methods demonstrate how the rapid advancements in myopia research have been translated into patient-facing environments over the nine-year period. Generally, the hindrances practitioners faced to begin myopia management were out of their control; the unaffordability of treatments compared to conventional correction was a consistent worldwide concern, and inaccessibility of effective treatments remained a problem in some geographic locations. With the solution to these issues primarily in the hands of policymakers, optical industry, and regulatory bodies, it suggests that practitioners would

otherwise be prescribing effective myopia interventions more regularly. The demand for knowledge about myopia is present amongst eye care practitioners of various professions and working environments, and practitioners seem receptive to research developments that aid optimisation of their management of young myopic patients on a global basis.

Worldwide, myopia management options such as orthokeratology and specifically designed myopia control spectacle and soft contact lenses were perceived by eye care practitioners to be the most effective optical forms of reducing myopia progression. Myopia control spectacle lenses were the most frequently prescribed form of myopia intervention to myopic children on average in 2022 and 2024. These lenses are often designed to minimise axial and refractive progression by inducing peripheral regions of myopic retinal defocus[283, 393, 466]. Therefore, later summarised in Section 8.1.3, investigating the impact of spectacle lens-induced regional defocus on human choroidal thickness provides a valuable and relevant contribution to the field of choroidal research, applicable to recent prescribing trends.

8.1.2 Choroidal imaging to quantify small changes in thickness: statistical versus clinical significance

(Research objective B: Summary of Chapter 4)

To measure choroidal thickness and quantify thickness changes with time, high-quality imaging methods and measurement protocols are vital. Even with modern OCT imaging technologies, visualising and delineating the chorioscleral interface can prove challenging, particularly in eyes with thicker choroids. Chapter 4 of this thesis assessed the choroidal imaging capabilities and repeatability of three commercially available OCT devices: the Heidelberg Spectralis SD-OCT, the Zeiss Cirrus SD-OCT, and the Topcon Triton swept source DRI-OCT. With the aid of enhanced depth imaging (Heidelberg Spectralis and Zeiss Cirrus spectral-domain technologies) and ‘Deep Range Imaging’ (Topcon Triton swept-source technology), each device was able to capture choroidal scans of sufficient quality to produce repeatable measures of subfoveal choroidal thickness. Additionally, the results suggested good agreement in measurements of choroidal thickness between the devices. However, lack of statistical significance did not indicate lack of clinical significance; the magnitude of spectacle lens-induced short-term choroidal thickness alterations previously reported in human research studies are extremely small in comparison to various pathological choroidal changes, including those associated with pathological high myopia[18]. With these minute transient choroidal thickness changes imperceptible to the individual, these devices could reliably quantify the difference in choroidal thickness between two images taken on the same device, but not necessarily be used interchangeably. Due to this, the studies presented in the following chapters used only the Heidelberg Spectralis SD-OCT

to capture all choroidal images, with the same scanning protocol and method of semi-automated choroidal segmentation[171].

8.1.3 Effect of regional myopic defocus on choroidal thickness: evidence of nasal-temporal asymmetry and paradoxical predictive properties

(Research objectives C, D, and E: Summary of Chapters 5, 6, and 7)

In Chapter 5, 45 minutes of 3.00D temporal and nasal myopic defocus was found to elicit statistically significant regional central and peripheral choroidal thickening in young adults. In myopes and emmetropes alike, regional thickening was identified within the corresponding 3mm nasal and temporal hemifields, with evidence of these alterations to rapidly recover at 20 minutes following cessation of defocus. Choroidal thickening of the nasal choroid when exposed to 45 minutes of 3.00D nasal myopic blur was of interest due to: (1) thickening to a greater degree than that of the temporal choroid when exposed to 45 minutes of temporal myopic defocus of equal plus power, (2) the thickening spreading beyond the nasal boundary to also significantly thicken the temporal choroid, whereas thickening was contained to the temporal choroid with temporal myopic defocus, and (3) the thickening of the temporal choroid seen with nasal myopic defocus was of a similar degree to that seen with temporal myopic defocus. Collectively, these characteristics suggest a non-uniform sensitivity to short-term, defocus-mediated changes in choroidal thickness across the wider choroidal profile. Alternatively, the nasal choroid may be capable of expanding to a greater magnitude than the temporal choroid.

Unlike the young adult participants in Chapter 5, child participants in the study (all of whom were myopic) underwent hemifield defocus for only 25 minutes, and the adult findings indicated significant thickness changes occurred after this timepoint; at 25 minutes of temporal or nasal myopic blur, no significant choroidal thickening was identified in the eyes of either age group. Additionally, no difference in choroidal thickness change from baseline to 25 minutes was identified between the eyes of myopic children or young adults. This suggests that there was no greater or lesser response seen in children, who are more likely to undergo rapid ocular growth than young adults. Furthermore, although the myopic young adult participants had statistically significantly thinner baseline choroidal thicknesses and longer axial lengths than their emmetropic counterparts, refractive error did not appear to impact the extent of regional choroidal alterations identified at 45 minutes and the recovery at 20 minutes post-defocus. This finding may potentially support the association of thinner choroids with longer axial lengths and higher myopia being a by-product of excessive ocular growth, rather than a causal factor.

Due to the nature of the lens design and set-up used in Chapter 5, it was vital for participants to maintain a stable head position and steady fixation for the entire duration of the experiment. Aiming to encourage cooperation from child participants in particular, a washout period was excluded to reduce the experiment length. Therefore, young adult participants also underwent a defocus session without a washout period to allow comparable data analysis between the two age groups. To investigate whether this may have confounded the results, Chapter 6 assessed the impact of the experimental set-up including the change in indoor light levels on human choroidal thickness. Using the same recruitment criteria and room set-up used in Chapter 5, the change in room brightness from approximately 200 to 10-20 lux did not cause a significant change in choroidal thickness over a 20-minute period. Like Chapter 5, there was no interaction with refractive error; no significant difference was identified between myopic and emmetropic young adults in either light condition. This simulated washout period indicated the results of Chapter 5 were unaffected by the lack of time for adaptation to the visual environment. However, like avoiding known confounding factors prior to measuring choroidal thickness, inclusion of a washout period where possible makes for a more robust experimental design. Besides aiding the interpretation of the results reported in Chapter 5, the findings of Chapter 6 led to further consideration of how environmental factors should be considered when assessing choroidal thickness within an indoor clinical environment; with research showing the choroid to be highly sensitive to various external stimuli, other features of indoor lighting such as greater fluctuations in room brightness, the heat emitted from a light source, and the differing spectral power distributions of light sources are worth exploring.

The final experimental Chapter of this thesis, Chapter 7, measured and compared regional changes in the choroidal thickness of myopic individuals in response to short- and long-term wear of the Hoya® MiyoSmart spectacle lenses. These CE marked spectacles work to slow childhood myopia and axial progression using Defocus Incorporated Multiple Segments (DIMS) technology (peripheral matrix of +3.50D lenslets with a central clear aperture), which are commercially available for eye care practitioners to prescribe to their patients in several parts of the world. Under the same experimental conditions as Chapters 5 and 6, 45 minutes of DIMS lens wear did not cause detectable regional alterations in choroidal thickness in young adults unlike that previously identified with nasal and temporal myopic blur in Chapter 5. Like that reported in Chapter 5, no significant change in choroidal thickness was identified after 25 minutes of DIMS wear in both myopic child and young adult participants. As a significant, regionally selective thickening response was evidenced following +3.00D nasal and temporal defocus in Chapter 5, it was hypothesised that evidence of peripheral regional choroidal thickening would also be present following exposure to the DIMS refraction profile.

However, compared to the defocusing lens used to induce nasal and temporal defocus in Chapter 5, the wearer's perception of peripheral myopic defocus through the DIMS lens may have been inhibited by the visual environment used during the experiment, consisting of a small central fixation target surrounded by near-darkness.

In a small sample of 10 child participants, significant choroidal thickening had occurred from baseline to 12 months of full-time DIMS spectacle lens wear, with no choroidal region showing a statistically significant greatest extent of change. Paired closely in refractive error, axial length, baseline choroidal thickness, and age, the choroidal thickness changes seen from baseline to 12 months in the 10 children were compared with that seen from baseline to 25 minutes of DIMS wear and clear vision (control condition) in 10 other child participants. Linear regression models suggested the measurements at 25 minutes of DIMS wear could hold predictive properties of 12-month choroidal thickness changes within the nasal, inferior, and temporal parafoveal choroidal regions, whereas this was not the case for any region under the control condition. Unexpectedly, these regions showed a consistent negative association, where a greater choroidal thickening/less choroidal thinning at 25 minutes of DIMS wear may indicate less choroidal thickening/more choroidal thinning at 12 months of wear. This paradoxical finding perhaps evidences the existence of separate mechanisms mediating the short-term fluctuations in choroidal thickness compared to long-term ocular growth. Given the numerous questions remaining about the choroid's complex nature, it is too premature to speculate how these mechanisms operate and whether an inverse process with time is at play. Regardless, this study provided clear rationale to further investigate how short-term changes in choroidal thickness correlate with long-term change when exposed to spectacle lens defocus, with direction of how to optimise methodology to potentially yield more conclusive results (see Section 8.3.3).

8.2 LIMITATIONS

The series of research studies presented in this thesis were subject to various limitations, several of which have been discussed within each chapter. A summary of the primary limitations of the data collection procedures and methods of analyses is provided below.

8.2.1 Global myopia management strategies: internet-based surveys

(Limitations of Chapters 2 and 3)

Using an online survey provided a practical, inexpensive, standardised, anonymous, and quick method of reaching thousands of eye care practitioners across the globe, with the extra advantage of being made accessible in several languages. However, in addition to aforementioned questions about representativeness and the exact response rate of actively

practicing respondents, internet-based surveys permit a respondent to be dishonest or exaggerate their answers. Misinterpretation of questions and response fatigue are further limitations to consider.

Like any voluntary survey, it can be argued that the voluntary nature of this project was likely to attract practitioners who were already heavily involved or interested in the topic, swaying the results to overstate the overall worldwide engagement in clinical myopia management. Alternatively, it may be that practitioners who were highly sceptical of the topic contributed, producing the opposite effect.

8.2.2 Choroidal imaging to quantify small changes in thickness: subjective grading and manual segmentation

(Limitations of Chapter 4)

As discussed in Chapter 4, the qualitative and quantitative comparison of choroidal imaging using 3 OCT devices was entirely subjective, and therefore susceptible to variability in clinical interpretation. The exclusion of diseased eyes also limits the application of these findings in a real-world setting.

Subjectivity of choroidal segmentation remains a limitation far beyond the research projects in this thesis; automated choroidal segmentation algorithms are not commercially available for eye care practitioners to utilise in their day-to-day practice, and custom-written software used in research typically requires an element of manual intervention from the user. Manual segmentation is a time-consuming process, therefore undesirable not only for research studies like Chapter 4, but also within fast-paced, patient-facing clinical environments. Thus, the methods used to quantify small changes in subfoveal choroidal thickness in Chapter 4 are arguably impractical for clinical practice. This remains an unavoidable limitation in the absence of widely accessible automated segmentation procedures.

Due to the time-consuming nature of manual choroidal segmentation, only one masked observer conducted the quantitative analysis. Ideally, two masked observers would have segmented every image, however this project did not have the scope to involve an additional trained observer.

8.2.3 Effect of regional myopic defocus on choroidal thickness: recruitment and confounding factors

(Limitations of Chapters 5, 6, and 7)

In Chapters 5, 6, and 7, larger sample sizes would have been preferrable. However, recruitment was challenging for several reasons. For participants involved in short-term data

collection, the inclusion criteria included limited age ranges (children 6 to 15 years; young adults 18 to 25 years), with strict limits of MSE (emmetropes +0.50 to -0.25D; myopes -0.50 to -6.00D), astigmatism (≤0.75D), and anisometropia (≤0.75D). Advertisements for the studies were displayed as posters around the Aston University School of Optometry building and included in staff newsletters, encouraging participation from individuals who are 'short-sighted' or 'do not need glasses'. Despite this, some responses were received from hyperopic young adults or the parents of hyperopic children. Similarly, several other responses were from prospective myopic participants, however their level of myopia, astigmatism, or anisometropia was too high. Moreover, it was difficult to source child participants who had no previous exposure to any form of myopia control, as many children who attended the university department were already using an optical or pharmaceutical myopia intervention. Difficulty recruiting children was most evident in Chapter 7, where the pairing of child participants added a further layer of complexity to the process. Sourcing children who met the eligibility criteria and paired closely (in baseline refractive error, age, axial length, and choroidal thickness) with those already enrolled onto the longitudinal DIMS clinical trial resulted in a small sample, particularly when also aiming to match the children's sexes and ethnicities. As discussed in Chapter 7, the small sample size likely limited the sensitivity of the statistical analysis.

The chosen criteria for MSE, astigmatism, and anisometropia enabled comparable results between the two eyes, minimal impact of astigmatism on MSE, and avoided complexities associated with high myopia. However, the criteria did not provide a true reflection of myopic refractive errors in a population of children and young adults, limiting translation of the findings to wider ranges of myopia and astigmatism.

As previously addressed, including an adaptation period may have provided a more robust experimental design in Chapters 5 and 7, and further consideration of the experiment set-up relative to the refraction profile of a lens may have been beneficial.

In Chapters 5, 6, and 7, the use of semi-automated choroidal segmentation software provided a superior method to measure choroidal thickness in comparison to the manual approach used in Chapter 4. Due to this software still requiring manual corrections on occasion, the lack of an additional masked observer is a limitation of these studies. This was not possible due to the extra funding it would have required; although the rate of segmentation was quicker when using semi-automated procedures, the time taken to segment the many hundreds of choroidal images captured during the three studies of Chapters 5, 6, and 7 was extensive.

8.3 FURTHER CONSIDERATIONS AND FUTURE RESEARCH

8.3.1 Monitoring the use and methods of choroidal imaging in global clinical myopia management

The uncertainty of the role of choroidal imaging in myopia management highlights the need for continuing efforts to evaluate its clinical value. Naturally, some answers to the numerous questions are likely to emerge over the coming years. With Chapters 2 and 3 of this thesis demonstrating that global trends in myopia management attitudes and strategies often reflect advances in myopia research, it is inherently important that these trends are repeatedly assessed over time. This includes monitoring changes in practitioners' perceptions, methods of examining, and utilisation of choroidal thickness measures, plus how this varies geographically.

In addition to continuing to monitor the changing clinical knowledge about the choroid in the context of myopia management, future evaluation of worldwide access to OCT imaging of the choroid and user-friendly choroidal segmentation methods is of interest. Hopefully, with advances in ocular imaging technologies and the likely incorporation of artificial intelligence in ocular image interpretation with time[477], fewer eye care researchers and practitioners will rely on manual methods of measuring choroidal thickness, and widespread access to commercially available automated segmentation algorithms will become the norm.

8.3.2 Exploring asymmetric nasal-temporal choroidal thickness alterations

At present, there is insufficient knowledge to understand why the nasal choroid of young adults thickened to a significantly greater extent than the temporal choroid when exposed to an equivalent degree and duration of short-term myopic defocus within the corresponding region (Chapter 5). As discussed in Chapter 5, the greater photoreceptor density in the nasal retina than the temporal retina at equivalent eccentricities may be a contributing factor[453], and retinal ganglion cell density is substantially higher nasally than temporally, by 300%[454]. Research suggests some specific types of retinal ganglion cells can detect signs of defocus[478] and respond more vigorously with increasing levels of blur[479, 480]. Similarly, it has been suggested that opposing alterations in human choroidal thickness following differing orientations of short-term astigmatic defocus could be attributed to orientation-selective retinal ganglion cells[263]. Therefore, it is plausible that the inner retinal neurons capable of detecting signs of defocus may initiate local signal cascades towards the choroid, driving the bidirectional choroidal thickness changes to occur in a non-uniform, regional manner. Further research is warranted to explore how the sensitivity to transient defocus-induced thickness changes across the choroidal profile correspond with retinal neuron topography. On addressing the limitations of the methodology described in Chapter 5, exploring the short-term effects of different spatial patterns of myopic and hyperopic defocus, longer

periods of defocus and recovery, and increasing degrees of blur on human choroidal thickness would make for an insightful contribution. Involving participants with high levels of myopia will advance the understanding of whether the retina of a myopic eye encodes visual information differently from the retina of an emmetropic eye.

8.3.3 Investigating the mechanisms underlying short-term and long-term choroidal thickness changes

It seems logical that the choroidal region exhibiting the greatest degree of transient thickening with optical myopic defocus is likely to also exhibit the greatest degree of thickening with sustained defocus. That region may be of particular interest when exploring the use of early choroidal thickening as a biomarker for long-term axial growth with a defocusing optical intervention. Therefore, given the results of Chapter 5, it would be expected that the choroid would show a greater level of thickening nasally than temporally when exposed to prolonged myopic defocus, or show less thinning over time. However, when assessed beyond the subfoveal region, longitudinal clinical trials of differing optical myopia management interventions have found a greater extent of relative choroidal thickening temporally than nasally in myopic children[297, 311, 316]. Additionally, compared to the surrounding regions, the nasal choroid thins to a significantly greater extent with increased axial length[481], and appears to be more susceptible to degeneration as myopia increases[131]. Furthermore, in Chapter 7, the indication of a negative linear relationship between short-term (baseline to 25 minutes) and long-term (baseline to 12 months) choroidal thickness changes suggests that there may be different mechanisms modulating choroidal thickness in action over time. Continued research to truly comprehend the relationship between direct and long-term choroidal thickness changes is essential. To the best of current knowledge, this thesis details the first attempt to compare immediate and longstanding localised choroidal thickness changes following exposure to a non-uniform spatial pattern of defocus. Exploring the unknown has led to an unanticipated question: when exposed to regional myopic defocus, do the choroidal areas eliciting a greater degree of choroidal thickening/less choroidal thinning in the short-term (within minutes) elicit less choroidal thickening/greater choroidal thinning in the long-term (over several weeks or months)? Following improved methodology to compare short and long-term regional choroidal alterations (discussed in Chapter 7 Section 7.4), closely monitoring the early effects of optical myopia interventions beyond 45 minutes would provide significant more insight into how the first detectable changes compare with those seen at 12 months. On commencing wear of a defocus-inducing optical myopia treatment, monitoring choroidal changes over several hours or days in real-world visual environments would be a worthwhile assessment. Whilst gaining insight into the mechanisms that underlie the choroid's dynamic nature, findings from this further

research would advance the understanding of the choroid's role in excessive ocular growth and concurrent myopia. This includes potentially using the early responses of an individual's choroid to aid the selection of an effective optical approach to slow their future myopia progression and give rise to the knowledge of which choroidal regions matter the most for myopia control.

8.4 CONCLUDING REMARKS

The choroid appears to be a key component in the visual regulation of eye growth, however current evidence is not sufficient to determine the applications of choroidal imaging in clinical myopia management. This thesis presented a detailed analysis of the worldwide approaches to slow the increasing prevalence of myopia, which identified that choroidal thickness is not yet a significant consideration in eye care practitioners' management of their young myopic patients. The challenges faced when measuring choroidal thickness warrant careful consideration of the imaging methods used, particularly when quantifying small changes with time. The finding of regional choroidal expansion to a non-uniform pattern of myopic defocus supports the limited existing evidence of local choroidal mechanisms underlying the ocular response to retinal blur in humans. It is possible that separate mechanisms mediate short-term fluctuations in choroidal thickness compared to long-term changes in response to defocusing optical interventions. The findings of this thesis uncover several potential directions for future research to further advance our understanding of the role of the choroid in eye growth regulation and myopia management.

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APPENDIX 1

Aston University
BIRMINGHAM UK

Comparing eye scans taken with different instruments

Participant Information Sheet

Invitation

We would like to invite you to take part in a research study, forming part of a PhD project for Yasmin Whayeb.

Before you decide if you would like to participate, take time to read the following information carefully and, if you wish, discuss it with others such as your family, friends or colleagues.

Please ask a member of the research team, whose contact details can be found at the end of this information sheet, if there is anything that is not clear or if you would like more information before you make your decision.

What is the purpose of the study?

Optical Coherence Tomography (OCT) is a non-invasive method of imaging the layers of your eye. Different OCT instruments are available for eye care practitioners and researchers to use in their work. The purpose of this study is to analyse the images obtained by different commercially available OCT devices and compare each instrument's ability to image the layers of your eye.

Why have I been invited?

You are being invited to take part in this study because you have responded to an advert and you work/study in Aston University's School of Optometry.

To be able to participate, you:

- are aged over 18 years old
- have no known retinal and/or macular disease (such as macular degeneration, macular hole, retinal and/or macular haemorrhage [bleeding], diabetic retinopathy, retinal vessel occlusion)
- have had no previous retinal or macular surgeries
- have no physical disability causing difficulty to lean forwards

Pictured here is one of the OCT instruments we will use during this study.

What will happen to me if I take part?

If you give consent to take part in the study, you will be asked to attend one visit to the Aston University's School of Optometry building. A scan will be taken of both eyes using four different OCT instruments. You

will be asked to remove your glasses and/or contact lenses for the scans. For each instrument, you will be asked to lean slightly forwards to place your chin and forehead on a rest and look at a target one eye at a time. The scan will begin, which lasts only a few seconds per eye. There will not be any bright flashes of light. The scans are not expected to cause you any discomfort and are will not harm your eyes in any way. You will be able to take breaks between scans if you want to. This visit is expected to take about 15 minutes in total and you will be able to put on your glasses/contact lenses immediately afterwards.

Please note, your participation in this study does not replace your routine eye examinations. You should still attend your eye examinations as normal to ensure you have a full eye health and vision assessment.

Do I have to take part?

No. It is up to you to decide whether or not you wish to take part.

If you do decide to participate, you will be asked to sign and date a consent form. You would still be free to withdraw at any time throughout the duration of the study without giving a reason. If you are a student at Aston University, not participating will not have any effect on your future learning.

You can halt your participation in the research at any time by telling the researcher. Any data collected up to that point will not be saved or used. Once the visit has ended, your data will be anonymised and it will not be possible to withdraw it. This is because the data will be saved under an anonymous ID number which is not traceable back to you, and your identity cannot be determined by looking at the scans.

Will my taking part in this study be kept confidential?

Yes. A code will be attached to all the data you provide to maintain anonymity.

Your personal data (name and contact details) will only be used if the researchers need to contact you to arrange study visits. Analysis of your data will be undertaken using coded data.

The data we collect will be stored in a secure document store (paper records) or electronically on a secure encrypted mobile device, password protected computer server or secure cloud storage device.

To ensure the quality of the research Aston may need to access your data to check that the data has been recorded accurately e.g. for the purposes of audit.

What happens if something is discovered during the study which requires further clinical investigation?

The investigations undertaken during this study are not intended to be diagnostic but occasionally we discover something unusual that we feel should be investigated. We call these incidental findings.

In the unlikely event of this happening, we will discuss with you how this should be addressed. We may advise you to arrange a sight test or refer you to a hospital eye service. If a referral is required, you may be asked to provide your GP address, home address, and date of birth to fulfil the hospital department's requirements. All investigators involved in this study are experienced optometrists, so will be able to manage the problem safely and

answer any questions you may have.

What are the possible benefits of taking part?

Although you may find participation in this research interesting, there may be no direct benefit to you as a result. However, we hope that the findings of this research will provide further insight into the most effective way to image the layers of your eye. The results may be helpful for researchers and eye care practitioners in the future.

What are the possible risks and burdens of taking part?

On each device, you will be required lean forwards to place your chin and forehead on a rest for a few seconds at a time. This may be slightly uncomfortable.

You will be asked to remove your glasses and/or contact lenses during the study visit. The time taken to complete the visit (approximately 15 minutes) may be a burden to you.

Please note, you are able to withdraw from the study at any point during your visit.

What will happen to the results of the study?

The results of this study may be published in scientific journals and/or presented at conferences. The results of this study will also be used in Yasmin Whayeb's PhD thesis, and will not be shared with the device manufacturers. If the results of the study are published, your identity will remain confidential.

A lay summary of the results of the study will be available for participants when the study has been completed and the researchers will ask if you would like to receive a copy.

Expenses and payments

There will be no expenses and payments.

Who is funding the research?

The study is being funded by Aston University. The device manufacturers are not providing any funding or instrumentation.

Who is organising this study and acting as data controller for the study?

Aston University is organising this study and acting as data controller for the study. Research data will be used only for the purposes of the study or related uses identified in this Information Sheet or Appendix A.

Who has reviewed the study?

This study was given a favorable ethical opinion by the Aston University Health and Life Sciences Research Ethics Committee.

What if I have a concern about my participation in the study?

If you have any concerns about your participation in this study, please speak to the research team and they will do their best to answer your questions. Contact details can be found at

the end of this information sheet.

If the research team are unable to address your concerns or you wish to make a complaint about how the study is being conducted you should contact the Aston University Research Integrity Office at research_governance@aston.ac.uk or telephone 0121 204 3000.

Research Team

Prof James Wolffsohn	j.s.w.wolffsohn@aston.ac.uk	01212044140
Prof Nicola Logan	n.s.logan@aston.ac.uk	01212044128
Yasmin Whayeb	[no. redacted]@aston.ac.uk	

Thank you for taking time to read this information sheet. If you have any questions regarding the study please don't hesitate to ask one of the research team.

Appendix A: Transparency statement

Aston University takes its obligations under data and privacy law seriously and complies with the Data Protection Act 2018 (“DPA”) and the General Data Protection Regulation (EU) 2016/679 as retained in UK law by the Data Protection, Privacy and Electronic Communications (Amendments etc) (EU Exit) Regulations 2019 (“the UK GDPR”).
Aston University is the sponsor for this study based in the United Kingdom. We will be using information from you in order to undertake this study. Aston University will process your personal data in order to register you as a participant and to manage your participation in the study. It will process your personal data on the grounds that it is necessary for the performance of a task carried out in the public interest (GDPR Article 6(1)(e). Aston University may process special categories of data about you which includes details about your health. Aston University will process this data on the grounds that it is necessary for statistical or research purposes (GDPR Article 9(2)(j)). Aston University will keep identifiable information about you for 6 years after the study has finished.
Your rights to access, change or move your information are limited, as we need to manage your information in specific ways in order for the research to be reliable and accurate. If you withdraw from the study, we will keep the information about you that we have already obtained. To safeguard your rights, we will use the minimum personally identifiable information possible.
You can find out more about how we use your information at https://www.aston.ac.uk/about/statutes-ordinances-regulations/publication-scheme/policies-regulations/data-protection or by contacting our Data Protection Officer at dp_officer@aston.ac.uk.
If you wish to raise a complaint on how we have handled your personal data, you can contact our Data Protection Officer who will investigate the matter. If you are not satisfied with our response or believe we are processing your personal data in a way that is not lawful you can complain to the Information Commissioner’s Office (ICO).

APPENDIX 2

Aston University
BIRMINGHAM UK

Comparing eye scans taken with different instruments

Consent Form

Name of Chief Investigator: Professor James Wolffsohn (j.s.w.wolffsohn@aston.ac.uk)

Name of Student Investigator: Yasmin Whayeb ([student no. redacted]@aston.ac.uk)

Please initial boxes

1.	I confirm that I have read and understand the Participant Information Sheet (HLS21104 Version3.0 13/07/2023) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.	
2.	I understand that my participation is voluntary and that I am free to withdraw at any time during the study, without giving any reason and without my legal rights being affected.	
3.	I agree to my personal data and data relating to me collected during the study being processed as described in the Participant Information Sheet.	
4.	I understand that the data collected in this study is anonymous and that I am not able to withdraw data after the study visit has ended.	
5.	I understand that I may be asked to provide further personal information (detailed in the Participant Information Sheet) if an incidental finding requires referral to a GP or hospital eye service.	
6.	I understand that I should continue going to my regular optometrist independently of my participation in this study to ensure I have an up-to-date spectacle prescription and full ocular health assessment.	
7.	I agree to my anonymised data being used by research teams for future research.	
8.	I agree to my personal data being processed for the purposes of inviting me to participate in future research projects. I understand that I may opt out of receiving these invitations at any time.	
9.	I agree to take part in this study.	

Name of participant	Date	Signature
Name of Person receiving consent.	Date	Signature

If you wish to receive a lay summary of the research project upon its completion, please provide an email address to which the summary can be sent.
Email address:

APPENDIX 3

Aston University
BIRMINGHAM UK

Effect of short-term regional myopic defocus on choroidal thickness in young adults.

Participant Information Sheet

Invitation

We would like to invite you to take part in a research study.

Before you decide if you would like to participate, take time to read the following information carefully and, if you wish, discuss it with others such as your family, friends or colleagues.

Please ask a member of the research team, whose contact details can be found at the end of this information sheet, if there is anything that is not clear or if you would like more information before you make your decision.

What is the purpose of the study?

The prevalence of myopia (or shortsightedness) is increasing across the world. Myopia increases the risk of developing sight-threatening eye diseases such as retinal detachment and glaucoma. Therefore, optical interventions, such as specialist spectacles and contact lenses, are now used in order to slow the progression of a person's level of myopia, particularly in children. These interventions adopt similar methods of producing blur in the peripheral parts of a person's vision, whilst keeping the central vision clear. Research shows that some individuals respond well to such interventions, whereas others do not. The reasons behind the differing responses aren't yet fully understood.

This research aims to provide further insight into the eye's temporary response to blur, in particular the choroid (a layer within the eye which is positioned directly behind the retina).

Why have I been chosen?

You are being invited to take part in this study because you:

- are aged 18-25 years old
- have good general and ocular health
- Are myopic (shortsighted) or don't need glasses
- Have no previous or current use of myopia control methods
- Can speak good English or are able to attend with an English-speaking translator

What will happen to me if I take part?

If you give consent to take part in the study, you will be asked to attend two separate visits to the Aston University Vision Sciences building. There may also be opportunity to attend additional visits which will take the same format as the second visit.

Before any examinations, the investigators will talk to you about the study. You will then need to sign the accompanying consent form if you are willing to participate. You will be asked to avoid consuming any alcohol 2 hours before your visit, and caffeine a minimum of 6 hours before your visit. You will also be asked to avoid doing any vigorous exercise a minimum of 30 minutes and any prolonged near work (e.g., reading or looking at a phone/tablet) for a minimum of 20 minutes prior to attending

At the first visit, your eyes will be imaged, without touching the eyes, so that the health of your eyes can be checked, and a scan of the layers of the back of your eyes will be taken. Your eye size and shape will be measured. Your vision will be checked by asking you to read letters on a letter chart, and your spectacle prescription will be measured. You will then have a lens which contains multiple different powers positioned in front of each eye and be asked to watch a television programme of your choosing. This lens will either be a spectacle lens or soft contact lens. You will only be asked to use soft contact lenses if you are an experienced soft contact lens wearer. During this time, you will have scans of your eyes taken at regular intervals. The lenses will then be removed, and you will be asked to watch the television screen again. The scans will again be taken at regular intervals during this time. If you were asked to wear a contact lenses, a small amount of dye will be put into your eyes and the front surface of your eyes will be checked. This visit will take approximately 90 minutes.

At the second visit, your vision will be remeasured, and a scan of the layers of the back of your eyes will be taken again. Different spectacle or soft contact lenses containing multple different powers will be positioned in front of each eye, and you will be asked to watch a television programme again. Similar to the first visit, the scan will be repeated at regular intervals during this time. The lenses will be removed, and you will watch the television screen, with the scans taken at regular intervals again. A small amount of dye will be put into your eyes if contact lenses were used again, and the front surface of your eyes will be checked. This visit will take approximately 75 minutes.

During these visits, if you agree, you may have drops put into your eyes to allow the investigator to take measurements of your eyes more easily. When put into your eyes, the drops may sting for a few moments. They take around 15 to 30 minutes to work and around 6 hours to wear off (in some cases up to 24 hours). The eye drops make your pupils larger which may make you more sensitive to light. The drops will make your vision slightly blurred, so you shouldn’t perform any activities such as driving and/or cycling until your vision is back to normal. This will be at least 6 hours after instillation. You will be advised before your visit whether eyedrops will be used, in which case you may need to make appropriate alternative arrangements to travel home.

Do I have to take part?

No. It is up to you to decide whether or not you wish to take part.

If you do decide to participate, you will be asked to sign and date a consent form. You would still be free to withdraw at any time throughout the duration of the study without giving a reason.

Will my taking part in this study be kept confidential?

Yes. A code will be attached to all the data you provide to maintain confidentiality.

Your personal data (name and contact details) will only be used if the researchers need to

contact you to arrange study visits. Analysis of your data will be undertaken using coded data.

If during the study you tell the research team something that causes serious concern in relation to your health and/or welfare, it may be required to breach your confidentiality.

The data we collect will be stored in a secure document store (paper records) or electronically on a secure encrypted mobile device, password protected computer server or secure cloud storage device.

What are the possible benefits of taking part?

Information from this study may provide further insight into the ocular mechanisms affected by optical myopia control methods. This could contribute to ongoing research in determining the efficacy of particular interventions in order to provide a more personalised approach to controlling myopia progression.

What are the possible risks and burdens of taking part?

Each visit will last up to 1.5 hours which can be tiring.

You may be asked to wear a soft contact lens in one or both of your eyes for the 45 minute period of watching television. Soft contact lens use is extremely common and carries minimal hazards, especially for the short wearing time required in this study. When the contact lens is first placed onto your eye, it can cause some eye watering and redness, which soon settles. Therefore, only experienced soft contact lens wearers will be asked to complete this task.

As part of the contact lens arm of the study, moisturised strips will be used to apply a standard dye (fluorescein 1.0%) to your tear film. This is a staining agent used to aid external examination of your eye. When applied to the eye, it may sting for a few moments. Due to its colouring (orange/yellow) it may cause the vision to take on a coloured appearance, but this will not last long. Sometimes, the eyelids and the skin around the eyes will be coloured by the stain, but this can be removed with cold water. Allergic reactions are incredibly rare, but if you feel short of breath or any swelling, please let the study team know immediately. This dye will be familiar to soft contact lens wearers as it forms a part of a standard contact lens check.

The eye drops (cyclopentolate/tropicamide 1.0%) you may be asked to take in the study are used to allow an accurate reading of your eyes prescription by suspending its focusing system. When applied to the eye, they may sting for a few moments. The drops take about 30 to 45 minutes to work and around 6 hours to wear off (in some cases up to 24 hours). The resultant large pupils will make you more sensitive to light, whilst distant and near objects may appear slightly blurred. Consequently, you shouldn't perform any activities such as driving and/ or cycling for at least 6 hours after the drops have been instilled. On a bright day, sunglasses may be advisable. It is very unlikely, but should you experience any unusual symptoms such as severe pain and/ or blood shot around the eye and cloudy vision during this period please contact James Wolffsohn (07833049245) immediately. If you are unable to do so, please attend casualty as you may be experiencing an adverse reaction to the drops.

Please note, you are able to withdraw from the study at any point.

What will happen to the results of the study?

The results of this study may be published in scientific journals and/or presented at conferences. If the results of the study are published, your identity will remain confidential.

A lay summary of the results of the study will be available for participants when the study has been completed and the researchers will ask if you would like to receive a copy.

Expenses and payments

You will receive £30 per visit to compensate you for your time.

Who is funding the research?

The study is being funded by Aston University.

Who is organising this study and acting as data controller for the study?

Aston University is organising this study and acting as data controller for the study. You can find out more about how we use your information in Appendix A.

Who has reviewed the study?

This study was given a favorable ethical opinion by the Aston University Health and Life Sciences Research Ethics Committee.

What if I have a concern about my participation in the study?

If you have any concerns about your participation in this study, please speak to the research team and they will do their best to answer your questions. Contact details can be found at the end of this information sheet.

If the research team are unable to address your concerns or you wish to make a complaint about how the study is being conducted you should contact the Aston University Research Integrity Office at research_governance@aston.ac.uk or telephone 0121 204 3000.

Research Team

Prof James Wolffsohn	j.s.w.wolffsohn@aston.ac.uk	01212044140
Prof Nicola Logan	n.s.logan@aston.ac.uk	01212044128
Yasmin Whayeb	[student no. redacted]@aston.ac.uk	

Thank you for taking time to read this information sheet. If you have any questions regarding the study please don't hesitate to ask one of the research team.

Appendix A: Transparency statement

Aston University takes its obligations under data and privacy law seriously and complies with the Data Protection Act 2018 ("DPA") and the General Data Protection Regulation (EU) 2016/679 as retained in UK law by the Data Protection, Privacy and Electronic Communications (Amendments etc) (EU Exit) Regulations 2019 ("the UK GDPR").

Aston University is the sponsor for this study based in the United Kingdom. We will be using information from you in order to undertake this study. Aston University will process your personal data in order to register you as a participant and to manage your participation in the study. It will process your personal data on the grounds that it is necessary for the performance of a task carried out in the public interest (GDPR Article 6(1)(e). Aston University may process special categories of data about you which includes details about your health. Aston University will process this data on the grounds that it is necessary for statistical or research purposes (GDPR Article 9(2)(j)). Aston University will keep identifiable information about you for 6 years after the study has finished.

Your rights to access, change or move your information are limited, as we need to manage your information in specific ways in order for the research to be reliable and accurate. If you withdraw from the study, we will keep the information about you that we have already obtained. To safeguard your rights, we will use the minimum personally identifiable information possible.

You can find out more about how we use your information at https://www.aston.ac.uk/about/statutes-ordinances-regulations/publication-scheme/policies-regulations/data-protection or by contacting our Data Protection Officer at dp_officer@aston.ac.uk.

If you wish to raise a complaint on how we have handled your personal data, you can contact our Data Protection Officer who will investigate the matter. If you are not satisfied with our response or believe we are processing your personal data in a way that is not lawful you can complain to the Information Commissioner's Office (ICO).

When you agree to take part in a research study, the information about you may be provided to researchers running other research studies in this organisation and in other organisations. These organisations may be universities, NHS organisations or companies involved in health and care research in this country or abroad.

This information will not identify you and will not be combined with other information in a way that could identify you. The information will only be used for the purpose of research, and cannot be used to contact you.

APPENDIX 4

Aston University
BIRMINGHAM UK

Effect of short-term regional myopic defocus on choroidal thickness in young adults.

Consent Form

Name of Chief Investigator: Professor James Wolffsohn (j.s.w.wolffsohn@aston.ac.uk)

Name of Student Investigator: Yasmin Whayeb ([student no. redacted]@aston.ac.uk)

Please initial boxes

1.	I confirm that I have read and understand the Participant Information Sheet (Version 3.0, 10th July 2022) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.	
2.	I understand that my participation is voluntary and that I am free to withdraw at any time during the study, without giving any reason and without my legal rights being affected.	
3.	I agree to my personal data and data relating to me collected during the study being processed as described in the Participant Information Sheet.	
4.	I understand that if during the study I tell the research team something that causes them to have concerns in relation to my health and/or welfare they may need to breach my confidentiality.	
5.	I understand that I will have to continue going to my regular optometrist independently of my participation in this study to ensure I have an up-to-date spectacle prescription and full ocular health assessment.	
6.	I agree to my anonymised data being used by research teams for future research.	
7.	I agree to my personal data being processed for the purposes of inviting me to participate in future research projects. I understand that I may opt out of receiving these invitations at any time.	
8.	I agree to take part in this study.	

Name of participant	Date	Signature
Name of Person receiving consent	Date	Signature

APPENDIX 5

Aston University
BIRMINGHAM UK

Effect of short-term regional myopic defocus on choroidal thickness

Child Information Sheet and Assent Form

What is this study about?

This study looks at how blurry vision affects your eyes. This study uses special spectacle lenses or soft contact lenses designed to make part of your vision blurry so we can see how the back of your eyes respond to them.

What will happen to me in this study?

You will need to attend the Aston Vision Sciences Research Clinics 3 times.

At the first visit, you will have an eye test like you have when you visit your optometrist. We also take some measurements of your eyes using some other instruments you may not have seen before. None of these instruments will touch your eyes. Some of them have a bright flash like a camera. We will also put some drops in your eyes which will make your pupils large and your vision a bit blurry for a few hours. This visit should take around 1 hour.

At the second and third visit, you will be asked to watch a TV programme of your choice for 30 minutes whilst wearing the special spectacle lenses or contact lenses. You will only be asked to wear contact lenses if you use them already. These lenses will make part of your vision blurry and keep part of your vision clear. You will also have some scans taken of your eyes. Afterwards, you will be asked to remove the spectacle lenses or contact lenses and your vision will go back to normal. These visits should take around 45 minutes.

Do I have to take part?

You do not have to take part if you don't want to, and you will not be in trouble if you say no. If you say yes now, it will be fine if you change your mind and say no later.

What are the good things about this study?

You will help us learn more about children's eyes and the results of this study may help other children who are shortsighted.

Can any not-so-good things happen in this study?

The eye drops used at the first visit can make your eyesight blurry for a few hours, but this is completely normal. Your pupils (the black part of the centre of your eye) may stay larger than normal for up to 24 hours, which might make bright lights feel uncomfortable.

The special glasses or contact lenses may feel a bit strange when you wear them, but your vision will be back to normal when the lenses are removed.

Aston University
BIRMINGHAM UK

Effect of short-term regional myopic defocus on choroidal thickness

Assent Form

Voluntary Participation:

1. I understand what this study is about. I have asked any questions that I had, and I am happy with the answers from the study investigator and my mum, dad or the person who looks after me.

2. I know that I can say no now, and I can also say no later if I don't want to be in the study anymore.

Please tick:

☐ Yes, I want to take part in the study

☐ No, I do not want to take part in the study

_____	_____	_____
Your name (participant)	Date	Your signature

_____	_____	_____
Name of person explaining assent	Date	Signature

_____	_____	_____
Name of study investigator	Date	Signature

☐ Or N/A if investigator is the person explaining assent

APPENDIX 6

Aston University
BIRMINGHAM UK

Effect of short-term regional myopic defocus on choroidal thickness

Parent/Guardian Information Sheet

We would like to invite your child to take part in a research study.

Before you and your child decide if they would like to participate, please take time to read the following information carefully and, if you wish, discuss it with others such as your family, friends or colleagues.

Please ask a member of the research team, whose contact details can be found at the end of this information sheet, if there is anything that is not clear or if you would like more information before you make your decision.

What is the purpose of the study?

The prevalence of myopia (or shortsightedness) is increasing across the world. Myopia increases the risk of developing sight-threatening eye diseases such as retinal detachment and glaucoma. Therefore, optical interventions, such as specialist spectacles and contact lenses, are now used in order to slow the progression of a person's level of myopia, particularly in children. These interventions adopt similar methods of producing blur in the peripheral parts of a person's vision, whilst keeping the central vision clear. Research shows that some eyes respond well to such interventions, whereas others do not. The reasons behind the differing responses aren't yet fully understood.

This research aims to provide further insight into the eye's temporary response to blur, in particular the choroid (a layer within the eye which is positioned directly behind the retina).

Why has my child been chosen?

Your child is being invited to take part in this study because they:

- Are aged 6 to 15 years old
- Have good general and ocular health
- Are myopic (shortsighted) or don't need glasses
- Have no previous or current use of myopia control methods (such as bifocals, orthokeratology or specialist myopia controlling glasses and/or contact lenses)
- Can speak good English or are able to attend with an English-speaking translator

What will happen to me if I take part?

If you give consent for your child to take part in the study, you will be asked to attend three separate visits to the Aston University Vision Sciences building. There may also be opportunity to attend additional visits which will take the same format as the second and third visit.

Before any examinations, the investigators will talk to you and your child about the study. You will then need to sign the accompanying consent and assent forms if you are willing to participate. Your child will be asked to avoid consuming caffeine a minimum of 6 hours before your visits and avoid doing any exercise a minimum of 30 minutes prior to attending.

First visit:

Your child's eyes will be imaged, without touching their eyes, so that the health of their eyes can be checked, and a scan of the layers of the back of their eyes will be taken. Your child's eye size and shape will be measured. Your child's vision will be checked by asking you to read letters on a letter chart, and their spectacle prescription will be measured.

If you and your child agree, they will have drops put into their eyes to allow the investigator to take measurements of their eyes more easily. These drops are the same as those used in routine optometrist appointments so your child may have had them before. The drops may sting for a few moments and take around 15 to 30 minutes to work and around 6 hours to wear off (in some cases up to 24 hours). The eye drops cause the pupils to dilate, which may make your child more sensitive to light. Their vision may also be slightly blurred, so they should perform any activities such as cycling until their vision feels back to normal. This will be at least 6 hours after instillation. This visit is expected to take around 1 hour.

Second and third visit:

Your child will be asked to watch a television programme of their choosing for 30 minutes whist wearing a lens which contains multiple different powers positioned in front of one or both eyes. This lens will either be a spectacle or soft contact lens. Your child will only be asked to wear soft contact lenses if they are an experienced soft contact lens wearer. During the 30 minutes, your child will have scans of the back of their eyes taken at regular intervals. The lenses will then be removed. These visits are expected to take around 45 minutes each.

Does my child have to take part?

No. It is up to you and your child to decide whether or not they will participate.

If you and your child do decide to participate, you will be asked to sign and date a consent form. Your child will also be asked to sign an assent form. You and your child would still be free to withdraw at any time throughout the duration of the study without giving a reason.

Will my taking part in this study be kept confidential?

Yes. A code will be attached to all the data you provide to maintain confidentiality.

All personal data (name and contact details) will only be used if the researchers need to contact you to arrange study visits. Analysis of your data will be undertaken using coded data.

If during the study you or your child tell the research team something that causes serious concern in relation to your child's health and/or welfare, it may be required to breach confidentiality.

The data we collect will be stored in a secure document store (paper records) or electronically on a secure encrypted mobile device, password protected computer server or secure cloud storage device.

What are the possible benefits of taking part?

Information from this study may provide further insight into the ocular mechanisms affected by optical myopia control methods. This could contribute to ongoing research in determining the efficacy of particular interventions in order to provide a more personalised approach to controlling myopia progression in children.

What are the possible risks and burdens of taking part?

Each visit will last up to 1 hour which can be tiring. You and your child will be able to take breaks where feasible.

Your child may be asked to wear a soft contact lens in one or both of their eyes for the 30 minute period of watching television. Soft contact lens use is extremely common and carries minimal hazards, especially for the short wearing time required in this study. When the contact lens is first placed onto the eye, it can cause some eye watering and redness, which soon settles. Therefore, **only experienced soft contact lens wearers will be asked to complete this task.**

As part of the contact lens arm of the study, moisturised strips will be used to apply a standard dye (fluorescein 1.0%) to your child's tear film. This is a staining agent used to aid external examination of the eye. When applied to the eye, it may sting for a few moments. Due to its colouring (orange/yellow) it may cause the vision to take on a coloured appearance, but this will not last long. Sometimes, the eyelids and the skin around the eyes will be coloured by the stain, but this can be removed with cold water. Allergic reactions are incredibly rare, but if your child feels short of breath or any swelling, please let the study team know immediately. This dye will be familiar to soft contact lens wearers as it forms a part of a standard contact lens check.

The eye drops (cyclopentolate/tropicamide 1.0%) your child may be asked to take in the study are used to allow an accurate reading of their eye's prescription by suspending its focusing system. When applied to the eye, they may sting for a few moments. The drops take about 30 to 45 minutes to work and around 6 hours to wear off (in some cases up to 24 hours). The resultant large pupils may make your child more sensitive to light, whilst distant and near objects may appear slightly blurred. Consequently, your child shouldn't perform any activities such as cycling for at least 6 hours after the drops have been instilled. On a bright day, sunglasses may be advisable. It is very unlikely, but should your child experience any unusual symptoms such as severe pain and/ or blood shot around the eye and cloudy vision during this period please contact James Wolffsohn (07833049245) immediately. If you are unable to do so, please attend casualty as your child may be experiencing an adverse reaction to the drops.

Please note, you and your child are able to withdraw from the study at any point.

What will happen to the results of the study?

The results of this study may be published in scientific journals and/or presented at conferences. If the results of the study are published, your identity will remain confidential.

A lay summary of the results of the study will be available for participants when the study has been completed and the researchers will ask if you would like to receive a copy.

Expenses and payments

You will receive £30 per visit to compensate you for your time.

Who is funding the research?

The study is being funded by Aston University.

Who is organising this study and acting as data controller for the study?

Aston University is organising this study and acting as data controller for the study. You can find out more about how we use your information in Appendix A.

Who has reviewed the study?

This study was given a favorable ethical opinion by the Aston University Health and Life Sciences Research Ethics Committee.

What if I have a concern about my child's participation in the study?

If you have any concerns about your child's participation in this study, please speak to the research team and they will do their best to answer your questions. Contact details can be found at the end of this information sheet.

If the research team are unable to address your concerns or you wish to make a complaint about how the study is being conducted you should contact the Aston University Research Integrity Office at research_governance@aston.ac.uk or telephone 0121 204 3000.

Research Team

Prof James Wolffsohn	j.s.w.wolffsohn@aston.ac.uk	01212044140
Prof Nicola Logan	n.s.logan@aston.ac.uk	01212044128
Yasmin Whayeb	[student no. redacted]@aston.ac.uk	

Thank you for taking time to read this information sheet. If you have any questions regarding the study please don't hesitate to ask one of the research team.

Appendix A: Transparency statement

Aston University takes its obligations under data and privacy law seriously and complies with the Data Protection Act 2018 (“DPA”) and the General Data Protection Regulation (EU) 2016/679 as retained in UK law by the Data Protection, Privacy and Electronic Communications (Amendments etc) (EU Exit) Regulations 2019 (“the UK GDPR”).

Aston University is the sponsor for this study based in the United Kingdom. We will be using information from you in order to undertake this study. Aston University will process your personal data in order to register you as a participant and to manage your participation in the study. It will process your personal data on the grounds that it is necessary for the performance of a task carried out in the public interest (GDPR Article 6(1)(e). Aston University may process special categories of data about you which includes details about your health. Aston University will process this data on the grounds that it is necessary for statistical or research purposes (GDPR Article 9(2)(j)). Aston University will keep identifiable information about you for 6 years after the study has finished.

Your rights to access, change or move your information are limited, as we need to manage your information in specific ways in order for the research to be reliable and accurate. If you withdraw from the study, we will keep the information about you that we have already obtained. To safeguard your rights, we will use the minimum personally identifiable information possible.

You can find out more about how we use your information at https://www.aston.ac.uk/about/statutes-ordinances-regulations/publication-scheme/policies-regulations/data-protection or by contacting our Data Protection Officer at dp_officer@aston.ac.uk.

If you wish to raise a complaint on how we have handled your personal data, you can contact our Data Protection Officer who will investigate the matter. If you are not satisfied with our response or believe we are processing your personal data in a way that is not lawful you can complain to the Information Commissioner’s Office (ICO).

When you agree to take part in a research study, the information about you may be provided to researchers running other research studies in this organisation and in other organisations. These organisations may be universities, NHS organisations or companies involved in health and care research in this country or abroad.

This information will not identify you and will not be combined with other information in a way that could identify you. The information will only be used for the purpose of research, and cannot be used to contact you.

APPENDIX 7

Aston University
BIRMINGHAM UK

Effect of short-term regional myopic defocus on choroidal thickness

Consent Form

Name of Chief Investigator: Professor James Wolffsohn (j.s.w.wolffsohn@aston.ac.uk)

Name of Student Investigator: Yasmin Whayeb ([student no. redacted]@aston.ac.uk)

Please initial boxes

1.	I confirm that I have read and understand the Parent/Guardian Information Sheet (Version 2.0, 1st September 2022) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.	
2.	I understand that my child's participation is voluntary and that they are free to withdraw at any time during the study, without giving any reason and without my and/or my child's legal rights being affected.	
3.	I agree to my child's personal data and data relating to my child collected during the study being processed as described in the Parent/Guardian Information Sheet.	
4.	I understand that if during the study I tell the research team something that causes them to have concerns in relation to my child's health and/or welfare they may need to breach my, and/or my child's, confidentiality.	
5.	I understand that my child will have to continue going to their regular optometrist independently of their participation in this study to ensure they have an up-to-date spectacle prescription and full ocular health assessment.	
6.	I agree to my child's anonymised data being used by research teams for future research.	
7.	I agree to my child's personal data being processed for the purposes of inviting them to participate in future research projects. I understand that I may opt out of receiving these invitations at any time.	
8.	I agree to my child taking part in this study.	

Name of parent/guardian	Date	Signature
Name of person receiving consent	Date	Signature

APPENDIX 8

Aston University
BIRMINGHAM UK

Effects of light on the choroid: an Optometry Elective Studies Project

Participant Information Sheet

Invitation

We would like to invite you to take part in a research study.

Before you decide if you would like to participate, take time to read the following information carefully and, if you wish, discuss it with others such as your family, friends or colleagues.

Please ask a member of the research team, whose contact details can be found at the end of this information sheet, if there is anything that is not clear or if you would like more information before you make your decision.

What is the purpose of the study?

The purpose of this study is to investigate how the choroid, a structure at the back of the eye varies in thickness when subjected to different lighting conditions and if the choroid varies between people who don't need glasses (emmetropic) and short-sighted (myopic) people. This will give insight into the development of the eye.

The study is being conducted by Aston University optometry students undertaking their Elective Studies (dissertation) module.

Why have I been chosen?

You are being invited to take part in this study because:

- You are between the ages of 18-25 years
- You are emmetropic (-0.25 DS to +0.50 DS) or myopic (-0.50DS to -6.00DS) - we will check this for you.
- You don't have any health conditions which affect your eyes.

What will happen to me if I take part?

First, we will use specialist equipment to determine the power of your eyes (an autorefractor). We will also measure the length of your eye using another instrument (the IOLMaster).
At the start of the study, measurements will be obtained of the thickness of your choroid using a scan of the back of the eye (using an OCT).
These instruments will be non-contact and will not cause any discomfort. You will then watch TV for 20 minutes in low lighting. After this your choroidal thickness will be measured again. You will then return approximately 48 hours later to repeat this study but in full room lighting. Each visit will take approximately one hour.

Do I have to take part?

No. It is up to you to decide whether or not you wish to take part.

If you do decide to participate, you will be asked to sign and date a consent form. You would still be free to withdraw from the study at any time without giving a reason.

Will my taking part in this study be kept confidential?

Yes. A code will be attached to all the data you provide to maintain confidentiality.

Your personal data (name and contact details) will only be used if the researchers need to contact you to arrange study visits or collect data by phone. Analysis of your data will be undertaken using coded data.

The data we collect will be stored in a secure document store (paper records) or electronically on a secure encrypted mobile device, password protected computer server or secure cloud storage device.

To ensure the quality of the research, Aston University may need to access your data to check that the data has been recorded accurately. If this is required, your personal data will be treated as confidential by the individuals accessing your data.

What are the possible benefits of taking part?

Although there will be no immediate personal gain, you will have the opportunity to learn more about your own eyes, which you may find interesting. Beyond this, you will get to experience being part of a research project. This study has the potential to contribute to knowledge and understanding of the eye and influence the ongoing research into the effects of light on the choroid.

What are the possible risks and burdens of taking part?

The main burden associated with this study is the time that it will take. We also will ask you to refrain from activities which may influence our measurements; these include caffeine consumption, partaking in vigorous exercise and smoking prior to the study visit. We also require that you don't take part in any near work 25 minutes before the visit. This study is very low risk as it is completely non-invasive. If a participant is identified to have an unusual OCT scan, then they may be advised to attend an eye test

What will happen to the results of the study?

The results of this study may be published in scientific journals and/or presented at conferences. If the results of the study are published, your identity will remain confidential.

A lay summary of the results of the study will be available for participants when the study has been completed and the researchers will ask if you would like to receive a copy.

The results of the study will also be used in Hafsah Bashir's, Sarah Kelly De Vasconcelos Campos', Sidhartha Sah's, Shnee Kadir's Elective Studies project report.

Expenses and payments

There is no payment for participation in this study.

Who is funding the research?

The study has not received external funding and is being conducted by optometry students at Aston University under the supervision of Aston University staff members.

Who is organising this study and acting as data controller for the study?

Aston University is organising this study and acting as data controller for the study. You can find out more about how we use your information in Appendix A.

Who has reviewed the study?

This study was given a favorable ethical opinion by the Aston University Research Ethics Committee.

What if I have a concern about my participation in the study?

If you have any concerns about your participation in this study, please speak to the research team and they will do their best to answer your questions. Contact details can be found at the end of this information sheet.

If the research team are unable to address your concerns or you wish to make a complaint about how the study is being conducted you should contact the Aston University Research Integrity Office at research_governance@aston.ac.uk or via the University switchboard on +44 (0)121 204 3000.

Research Team

Prof Nicola Logan (study lead and elective study supervisor):

Email: n.s.logan@aston.ac.uk

Yasmin Whayeb (PhD student)

Email: [student no.

redacted]@aston.ac.uk

Sarah Campos:

Email: [redacted]@aston.ac.uk

Hafsah Bashir:

Email: [student no. redacted]

@aston.ac.uk

Sidhartha Sah:

Email: [student no.

redacted]@aston.ac.uk

Shnee Kadir:

Email: [student no.

redacted]@aston.ac.uk

Thank you for taking time to read this information sheet. If you have any questions regarding the study please don't hesitate to ask one of the research team.

Appendix A: Transparency statement

Aston University takes its obligations under data and privacy law seriously and complies with the General Data Protection Regulation ("GDPR") and the Data Protection Act 2018 ("DPA").

Aston University is the sponsor for this study based in the United Kingdom. We will be using information from you in order to undertake this study. Aston University will process your personal data in order to register you as a participant and to manage your participation in the study. It will process your personal data on the grounds that it is necessary for the performance of a task carried out in the public interest (GDPR Article 6(1)(e). Aston University may process special categories of data about you which includes details about your health. Aston University will process this data on the grounds that it is necessary for statistical or research purposes (GDPR Article 9(2)(j)). . Aston University will keep identifiable information about you for 6 years after the study has finished.

Your rights to access, change or move your information are limited, as we need to manage your information in specific ways in order for the research to be reliable and accurate. If you withdraw from the study, we will keep the information about you that we have already obtained. To safeguard your rights, we will use the minimum personally identifiable information possible.

You can find out more about how we use your information at www.aston.ac.uk/dataprotection or by contacting our Data Protection Officer at dp_officer@aston.ac.uk.

If you wish to raise a complaint on how we have handled your personal data, you can contact our Data Protection Officer who will investigate the matter. If you are not satisfied with our response or believe we are processing your personal data in a way that is not lawful you can complain to the Information Commissioner's Office (ICO).

APPENDIX 9

Aston University
BIRMINGHAM UK

Effects of light on the choroid: an Optometry Elective Studies Project

Consent Form

Name of Chief Investigator: Professor Nicola Logan

Co-investigators: Hafsah Bashir, Sarah Kelly De Vasconcelos Campos, Sidhartha Sah, Shnee Kadir, Yasmin Whayeb

1.	I confirm that I have read and understand the Participant Information Sheet [REC ID: 1375-2023-005 v1.0 09/11/2023] for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.	
2.	I understand that my participation is voluntary and that I am free to withdraw at any time during the study, without giving a reason and without my legal rights being affected.	
3.	I understand that this study is anonymous and that I am not able to withdraw after completing the study.	
4.	I agree to my personal data and data relating to me collected during the study being processed as described in the Participant Information Sheet.	
5.	I agree to my anonymised data being used by research teams for future research.	
6.	I agree to my personal data being processed for the purposes of inviting me to participate in future research projects. I understand that I may opt out of receiving these invitations at any time.	
7.	I agree to take part in this study.	

Name of participant	Date	Signature
Name of Person receiving consent.	Date	Signature

If you wish to receive a lay summary of the research project upon its completion, please provide an email address to which the summary can be sent
Email address