INTERVENTIONS TO LIMIT THE PROGRESSION OF MYOPIA

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Doctor of Philosophy

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SUMMARY

Myopia is invariably a lifelong condition characterised by high prevalence, significant risk in terms of associated ocular pathology, due to its increased axial length, and a substantial economic and social burden. While myopia can be corrected with spectacles and standard contact lenses, neither protect the eye from continued growth nor increased progression.

At birth, the eye's refractive error can be significant. As the eye grows the magnitude of refractive error commonly reduces in a process termed 'emmetropisation'. Substantial evidence exists to suggest that emmetropisation is an active process which relies on a normal visual experience, the absence of which in early life typically results in a refractive error. Research from animal models has shown the peripheral retina also plays a role in the emmetropisation process. Modification of the peripheral focus has been found to influence myopia progression.

This thesis is stimulated by the findings of Anstice and Phillips (2011) who, using a Dual-Focus contact lens, which provided clear central vision and simultaneous peripheral myopic retinal defocus, showed a reduction in axial myopic progression in children.

This thesis aims to describe the efficacy of a parallel-group, double blind and randomised controlled trial of a dual focus contact lens to slow myopia progression in children. Biometric data were compared for 27 myopic child participants aged 8 to 12 years at baseline. Children who wore the test lens had 41% less progression of myopia as measured by cycloplegic refraction and 44.5% less axial elongation after 12 months of lens wear. Additionally, the effect of lag of accommodation, peripheral refractive error, pupil size and time spent outdoors were explored. This thesis demonstrates that peripheral retinal defocus plays a role in slowing the progression of myopia in children and that interventions to limit the progression of myopia may need to be tailored to individual characteristics.

Keywords: Dual focus, refractive error, peripheral retina, contact lenses, time spent outdoors

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This thesis is dedicated to my parents Ken and Marie who have provided endless love, support, belief and encouragement. Ever at hand, when needed, with advice, praise and a well-timed joke. To my wonderful husband, Wayne, a huge thanks for his generous patience, love, praise and vital IT support. Thank you for all having my back.

CONTENTS

LIST OF ABBREVIATIONS

ALSPAC	Avon Longitudinal Study of Parents and Children
ANOVA	Analysis of Variance
ATOM	Atropine for the Treatment Of childhood Myopia
cd/m^2	Candelas per Metre Squared
CI	Confidence Interval
CLEERE	Collaborative Longitudinal Evaluation of Ethnicity and Refractive Error
COMET	Correction of Myopia Evaluation Trial
cm	Centimetres
CREAM	Consortium for Refractive Error and Myopia
D	Dioptres
DISC	Defocus Incorporated Soft Contact
ETDRS	Early Treatment Diabetic Retinopathy Study
GEM	Genes in Myopia
GWAS	Genome-Wide Associated Study
LCD	Liquid Crystal Display
logMAR	Logarithm for the Minimum Angle of Resolution
m	Metres
mm	Millimetres
MSE	Mean Spherical Equivalent
n	Size of a set of numbers
NHANES	National Health and Nutritional Examination Survey
NICER	Northern Ireland Childhood Errors of Refraction study
Ortho-k	Orthokeratology
p	Probability
PALS	Progressive Addition Lenses
PCI	Partial Coherence Interferometry
r	Pearson correlation coefficient

REHS	Raine Eye Health Study
SAVES	Sydney Adolescent Vascular and Eye Study
SMS	Sydney Myopia Study
SNR	Sound to Noise Ratio
SVL	Single Vision Lenses
UK	United Kingdom
USA	United States of America
UV	Ultraviolet
UVAF	Ultraviolet Autofluorescence
%	Percentage
λ	Wavelength

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1. MYOPIA REVIEW

1.1 Myopia background

1.1.1 Myopia definition and refractive error

Myopia is a refractive condition of the eye where light rays entering through the pupil are brought to focus in front of the retina resulting in blurred distant objects (Atchison and Smith, 2000; Rabbetts, 2007).

In the diagram below the emmetropic eye has rays of light passing though the optical system and coming to focus on the retina. This would provide clear distance vision. In the myopic eye, however, the rays fall short and focus in front of the retina. Conversely, in the hyperopic eye, the focus falls behind the retina.

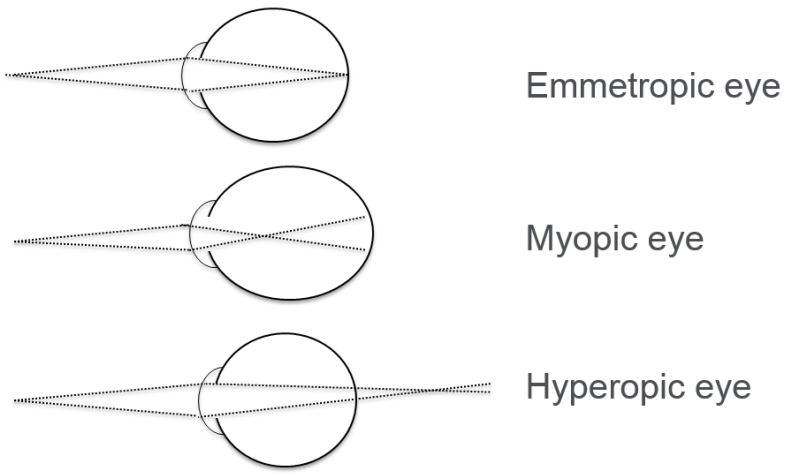


Figure 1.1 Diagram to show variation in focal planes in relation to the retina, for an emmetropic, a myopic and a hyperopic eye.

The focus of light rays, in myopia, fall short of the fovea due to a disparity between the optical power of the eye and the axial length. This foveocentric definition relates well to the mechanism of human vision, however, as will be explored in this thesis, it is now thought that the whole retina can influence eye growth and thus refractive development (Flitcroft, 2012).

1.1.2 Classification

There are a number of ways to classify myopia although they are all arbitrary and the majority have some level of overlap (Grosvenor, 1987). Myopia can be described in terms of being of a low (<-0.50 to -2.99 D), moderate (-3.00 to -5.99 D) or high (≤-6.00 D) dioptric level (Baird *et al*., 2010). Myopia could also be described as physiological (a mismatch between the eye's length and refracting power) versus pathological (high levels of myopia with associated degenerative changes), however, as will be discussed in section 1.1.4, all levels of myopia carry a risk of ocular pathology (Flitcroft, 2012).

One of the more widely used classifications was designed by Grosvenor (1987; Gilmartin, 2004) and uses four descriptions based on age of onset to classify the myopia:

1. Congenital myopia refers to myopia present at birth and persists through infant years to commencing school.

2. Youth-onset myopia occurs between 6 years and 20 years of age.

3. Early adult-onset myopia effects people between 20 and 40 years.

4. Late adult-onset myopia presents after the age of 40.

1.1.3 Myopia prevalence worldwide

Myopia prevalence is increasing worldwide and has reached highly significant levels particularly in East Asian countries, such as mainland China (Pan *et al.,* 2012; Smith, 2013; Lin *et al.,* 1999). A population based study in 2010 found myopia >0.5 D in 96.4% of the 23,616 South Korean 19 year old males examined (Jung *et al.,* 2012). In the United States, the National Health and Nutrition Examination Survey (NHANES) compared myopia prevalence from data obtained in 1971-72, with the 1999-2004 findings. For 12 to 54 year olds, there was a rise in myopia prevalence from 25% to 41.6%. The increase was present in both black and white individuals and across all levels of myopia (Vitale *et al.,* 2009).

Prevalence levels are also significant for children. Sizable differences have been found between countries, including regional variations between urban and rural areas. In urban China, myopia prevalence ranged from 5.7% in 5 year olds to 78.4% in 15 year olds, whereas in rural Southern China only 43% of 15 year olds were myopic (He *et al.,* 2004; He *et al.,* 2007). In urban Nepal, the prevalence of myopia ranged from 10.9% in 10 year old children to 27.3% in 15 year olds, however in rural Nepal, it was 1.2% in children aged 5 to 15 years (Sapkota *et al.,* 2008; Pokharel *et al.,* 2000).

The Sydney Myopia Study described a low prevalence of myopia of 1.4% for their cohort of 1724 children with a mean age of 6.7 years. When broken down by ethnicity the 1109 white children had 0.8% prevalence compared with 2.7% for the other ethnicities (Ojaimi *et al.,* 2005).

In the United Kingdom (UK) the Aston Eye Study assessed the ethnically diverse city of Birmingham and the Northern Ireland Childhood Errors of Refraction study (NICER), a sister study to the Aston Eye study, assessed white children of the same ages.

The white, South Asian and black 6 to 7 year olds were found to have a myopia prevalence of 5.7%, 10.8% and 11.4% respectively in Birmingham, compared with 2.8% of children in Northern Ireland. The white 12 to 13 year olds were both found to have higher, more comparable prevalence with 18.6% in Birmingham and 17.7% in Northern Ireland, however, the South Asian and black 12 to 13 year olds had 36.8% and 27.5% myopia prevalence respectively (Logan *et al*., 2011; O'Donoghue *et al.,* 2010). In a recent paper from the NICER study the proportion of myopes in the UK aged between 10 and 16 years, was reported to have more than doubled over the last 50 years (McCullough *et al.,* 2016). Table 1.1 shows myopia prevalence worldwide for children.

Authors	Race	Location	Age	Sample Size	Sample Size Myopes	Prevalence %
Li *et al.,* 2013	Chinese	China	5 – 9 years	2893	113	3.9
			10 – 15 years	2267	1526	67.3
Rezvan *et al.,* 2012	Iranian	Iran	6 - 17 years	1551	67	4.3
Casson *et al.,* 2012	Tai	Laos	6 - 11 years	2842	24	0.8
Gao *et al.,* 2012	Cambodian	Cambodia	12 - 14 years	5527	322	5.8
Pi *et al.,* 2012	Chinese	China	6 - 15 years	3079	422	13.7
Guggenheim *et al.,* 2012	White European (mother)	England	15 years	4759	821	17.3
Lam *et al.,* 2012	Chinese	Hong Kong	6-12 years	2651	1259	47.5
Logan *et al.,* 2011	White European, South Asian & Black African	England	6 - 7 years	327	31	9.4
			12 - 13 years	269	79	29.4
O'Donaghue *et al.,* 2010	White European	N. Ireland	6 - 7 years	392	11	2.8
			12 - 13 years	661	117	17.7
Rudnicka *et al.,* 2010	White European, South Asian & Black African	England	10 - 11 years	1179	140	11.9
Dirani *et al.,* 2010	Chinese	Singapore	0 - 6 years	2639	301	11.4
Yekta *et al.,* 2010	Iranian	Iran	7 - 15 years	1872	81	4.4
Hashim *et al.,* 2008	Malay	Malaysia	6 - 12 years	705	38	5.4
He *et al.,* 2007	Chinese	China	13 - 17 years	2229	945	42.4
Fotouhi *et al.,* 2007	Iranian	Iran	7 - 15 years	3490	119	3.4

Table 1.1 Studies of myopia prevalence in children. Myopia was defined in each study as ≤ -0.50 D.

1.1.4 Pathological and social impact of myopia

Myopia can often be regarded as a comparatively innocuous condition due to the simplicity with which the refractive error can be corrected with spectacles or contact lenses (Morgan *et al.,* 2012). High myopia, frequently described as greater than 6.00 D, can be referred to as 'pathological' myopia (Flitcroft, 2012). With higher myopia, where axial length is commonly longer, there is an increased likelihood of related pathology such as chorio-retinal abnormalities, cataract and glaucoma (Saw *et al.,* 2005). Flitcroft (2012) reviewed the calculated risk for ocular pathology for low levels of myopia and found comparable associations with systemic disorders. The risk level for developing glaucoma and cataract in eyes with low levels of myopia were akin to the risk of stroke for a person who smoked more than 20 cigarettes per day. When likened to population risk factors for cardiovascular disease, myopia carries a far greater risk for myopia maculopathy and retinal detachment. Myopes between -1.00 and -3.00 D have an increased risk of cataract and glaucoma indicating that there is no true safe level of myopia.

Beyond the costs to health are the financial costs of myopia. In the United States, NHANES survey estimated annual costs of between 3.9 and 7.2 billion dollars to correct distance vision impairment from refractive error (Vitale *et al.,* 2009). These figures may now be significantly higher due to the rise in prevalence of myopia since the data was obtained for the period 1999 to 2002.

The increase in myopia prevalence found internationally will, in turn, impact the associated risk of disease for the population (Flitcroft, 2012). In the absence of an innocuous level of myopia, it would be of significant benefit to work towards a future

of both less overall myopes and lower levels of myopia (Flitcroft, 2012; Morgan *et al.,* 2012).

1.1.5 Emmetropisation: animal models and humans

At birth, the refractive error in the eye can be significant (Cook and Glasscock, 1951; Goldschmidt, 1969). As the eye grows the refractive error commonly disappears and the process is termed 'emmetropisation' (Smith, 1998). This is demonstrated by comparison of refractive error data for infants, which follows a normal distribution pattern (Cook and Glasscock, 1951), with that of school children, adults and the elderly which have a much narrower, leptokurtic type distribution (Saunders *et al.,* 1995), indicating the process of emmetropisation.

Mutti *et al.,* (2005) evaluated the role of the ocular components of the human eye for 222 infant participants at 3 and 9 months of age. Sizeable emmetropisation occurred between the two measures with levels of ≥+3.00 D hyperopia falling from 24.8% to 5.4%. Axial growth was compensated for by the crystalline lens and cornea reducing in dioptric power (Mutti *et al.,* 2005).

Substantial evidence exists to suggest that emmetropisation is an active process which relies on a normal visual experience, otherwise a refractive error will occur (Wallman and Adams, 1987; Schaeffel *et al.,* 1988). A variety of animals have been studied for their refractive development (Wildsoet, 1997). Chicks are commonly used in research due to their rapid development and similar pattern of refractive error distribution to humans, with emmetropisation occurring over a 6 week period (Wallman *et al.,* 1981). In addition, chick eyes are independently functional, minimising binocular confounding effects (Wildsoet, 1997). When chicks are visually

form deprived they have been shown to develop axial elongation causing myopia, of which recovery can be demonstrated on termination of occlusion (Wallman and Adams, 1987) indicating the presence of active emmetropisation (Wildsoet, 1997). While the technique was effective in older chicks, slower and more incomplete recovery was found in comparison (Wallman *et al.,* 1987). While there are many differences between animals and humans, there have been similar findings of axial myopia development with human infant eyes, following persistent, dense, vitreous haemorrhages greater than 4 weeks duration (Mohney, 2002).

Localised form deprivation can result in a local axial eye growth in animals. When occlusion was placed to specifically deprive either just the nasal half or temporal half of the retina in chicks and monkeys, the resultant myopia was limited to that local area, the non-deprived area remaining almost emmetropic (Wallman *et al.,* 1987; Smith *et al.,* 2010).

In further animal studies, it has been possible to induce hyperopia and myopia by placing positive or negative lenses, respectively, in front of the eye. In a study with chicks Irving *et al.,* (1991) used goggles with hard lens inserts on newly hatched chicks. -10 D myopia was induced after 7 days and +10 D hyperopia after just 4 days. Similar effects have been found in other animals notably the tree shrew (Siegwart and Norton, 1993; Metlapally and McBrien, 2008), marmosets (Whatham and Judge, 2001; Benavente-Perez *et al.,* 2014) and monkeys (Hung *et al.,* 1995; Arumugam *et al.,* 2014). The effect is shown in Figure 1.2.

When the negative lens is placed in front of the eye, the focal point is behind the eye causing a hyperopic retinal defocus which will stimulate the axial elongation and

render the eye relatively myopic. Conversely, when a plus lens is placed in front of the eye, the focal point is in front of the retina. The resultant myopic retinal defocus will slow axial growth and cause relative hyperopia (Smith and Hung, 1999).

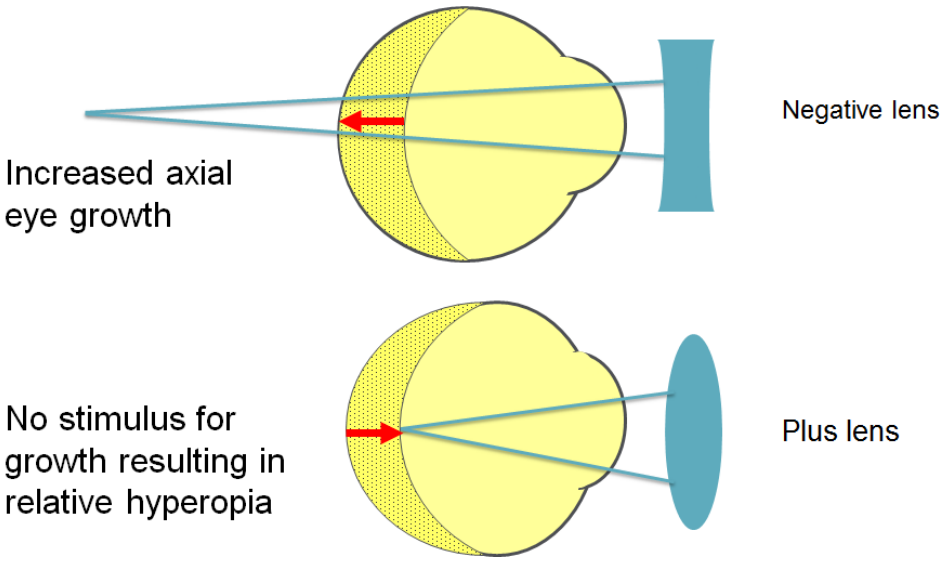


Figure 1.2 Diagram to show lens-induced defocus and the resultant effect on eye growth.

Animal models have also shown the importance of the peripheral retina in the role of eye growth. Peripheral retinal form deprivation in monkeys can disrupt the emmetropisation process (Smith *et al.,* 2005), however when the fovea and peri-fovea were ablated in primates, normal emmetropisation was unaffected. Additionally, some of the monkeys were given diffuser lenses to induce form deprivation, this process was unaffected by the damage to the central vision and caused the expected, resultant myopia (Smith *et al.,* 2007; Smith *et al.,* 2009).

1.1.6 Peripheral retina and myopia

In order to better understand the relationship between refractive error and eye growth, the off-axis peripheral refractive error has been measured extensively in relation to foveal refraction (Ferree *et al.,* 1931; Rempt *et al.,* 1971; Hoogerheide *et al.,* 1971; Millodot, 1981). Peripheral refraction has typically been measured along the horizontal and vertical meridians, at various eccentricities from fixation. The peripheral data can then be used to plot a refractive error pattern. Ferree *et al.,* (1931) identified 3 types of peripheral pattern, named A, B and C.

These were later termed I (type B), III (type C) and IV (type A), when two additional shapes, II and V, were added by Rempt *et al*., (1971). The term skiagram (skia meaning shadow) was used to describe the pattern, examples from Rempt *et al.,* (1971) are shown in Figure 1.3 to Figure 1.7.

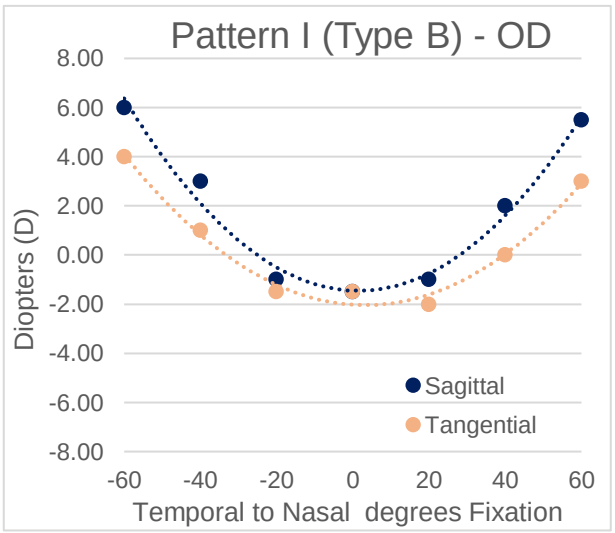


Figure 1.3 Pattern type I. Both sagittal and tangential foci become more hyperopic in the periphery (Ferree *et al.,* 1931; Rempt *et al.,* 1971).

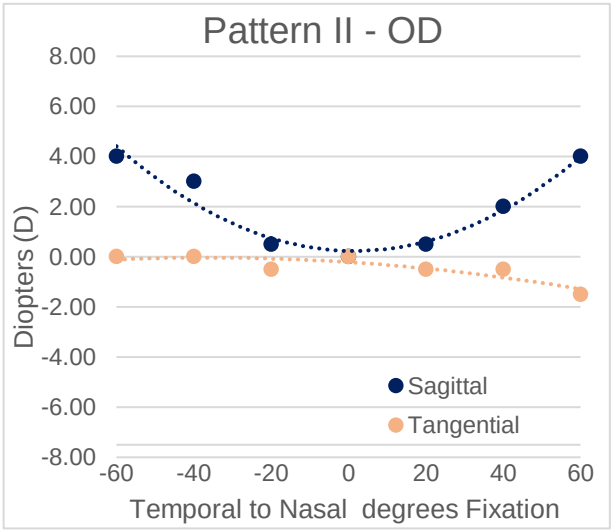


Figure 1.4 Pattern type II. The sagittal focus becomes more hyperopic in the periphery, whereas the tangential remains the same (Rempt *et al*., 1971).

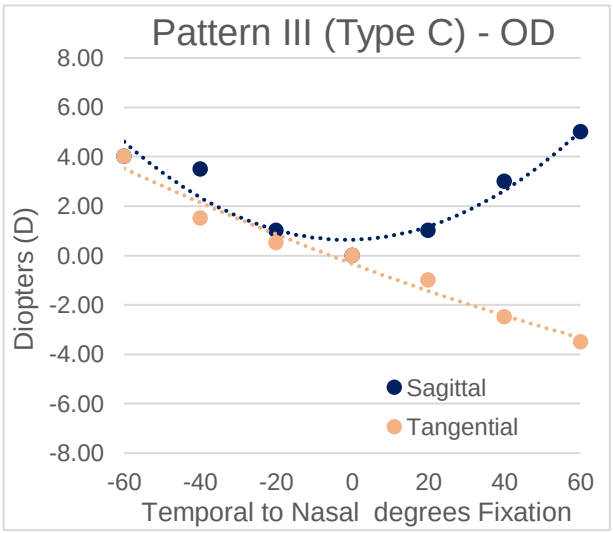


Figure 1.5 Pattern type III. There is asymmetry between the refraction in the temporal and nasal halves of the visual field (Ferree *et al*., 1931; Rempt *et al*., 1971).

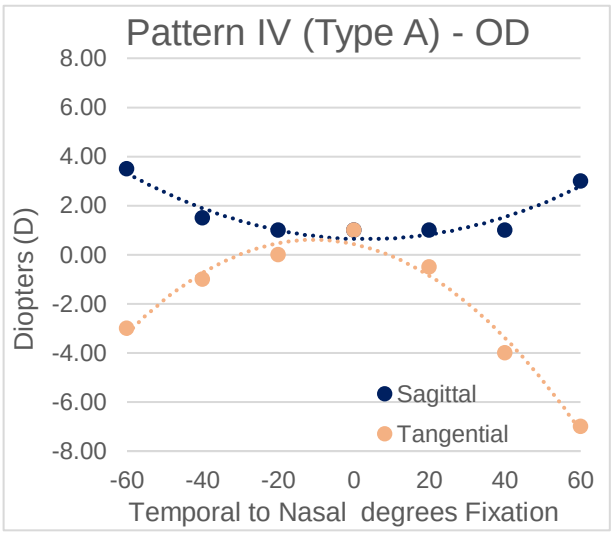


Figure 1.6 Pattern type IV. The sagittal focus becomes more hyperopic and the tangential focus more myopic in the periphery (Ferree *et al.,* 1931; Rempt *et al.,* 1971).

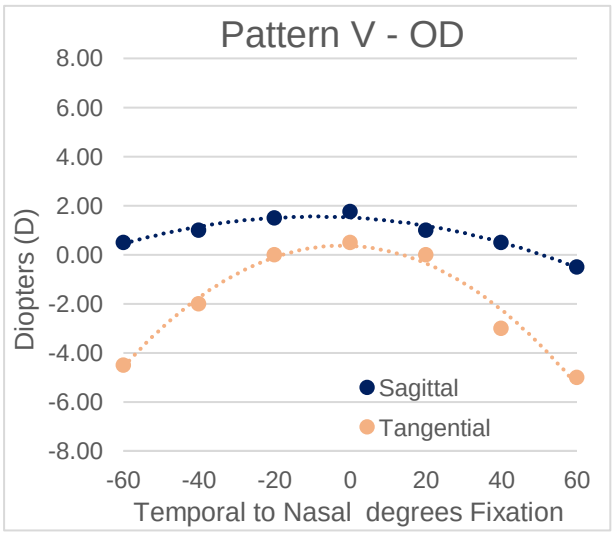


Figure 1.7 Pattern type V. The sagittal focus remains the same, whereas the tangential focus becomes more myopic (Rempt *et al.,* 1971).

In studies of eye shape comparing axial (cornea to retina), height and width dimensions Atchison *et al.,* (2004) were able to associate shape with refractive error.

Despite much individual variation between the 88 participants, aged 18 to 36 years, myopic eyes were larger in all dimensions with particular elongation of axial length (0.35 mm/D, 95% confidence interval (CI) 0.28–0.40 mm/D) when compared to height (0.19 mm/D, 95% CI, 0.09–0.29 mm/D). In a later study Atchison *et al.,* (2006) assessed peripheral refraction in both the horizontal and vertical visual fields. Myopia was found to have more effect on the periphery of the horizontal rather than the vertical field. The Orinda Longitudinal study of myopia, from 1995, measured central and 30 degrees nasal peripheral refractions. The 822 children aged between 5 and 14 years, additionally had axial, crystalline lens and corneal biometric data assessed. The emmetropes and, to a greater extent, the hyperopes showed relative peripheral myopia (-0.41 ±0.75 D and -1.09 ±1.02 D, respectively) suggesting oblate shaped posterior segments. The myopic participants were found to have relative peripheral hyperopia (+0.80 ±1.29 D) and therefore an accompanying relative prolate shape to their posterior segments. The myopic participants were also found to have steeper corneas, flatter crystalline lenses and deeper anterior/vitreous chambers (Mutti *et al.,* 2000).

Sng, Lin, Gazzard, Chang, Dirani, Chia *et al.,* (2011) measured peripheral refractive error on 250 Singaporean children aged between 3 and 15 years, centrally, at 15° and 30° both nasal and temporally. Children with high and moderate central levels (≥-3.00 D) of myopia displayed relative peripheral hyperopia at all eccentricities. The children with low central myopia (-0.50 to -2.99 D) interestingly did not show relative peripheral hyperopia at 15°, only at 30°. Emmetropes and hyperopes had relative peripheral myopia at all eccentricities.

Data supporting peripheral retinal hyperopia as a risk factor for myopia is equivocal. Hoogerheide *et al.,* (1971) studied 214 pilots, aged 18 to 20 years, and suggested that participants who were emmetropic or hyperopic were more likely to develop myopia if they had relative peripheral hyperopia. The predictive aspect of this paper and that of (Rempt *et al.,* 1971) has since been questioned by Rosen *et al.,* (2012), with the suggestion it was misinterpreted. The peripheral hyperopia presented may have been measured after the development of ametropia and therefore was not meant to be indicative as a precursor. The Collaborative Longitudinal Evaluation of Ethnicity and Refractive Error (CLEERE) study identified peripheral hyperopia in emmetropes who went on to develop myopia, up to 2 years before the refractive error emerged (Mutti *et al.,* 2007). Conflicting results have more recently been published, including a paper from the same study, indicating that baseline peripheral hyperopia is a poor predictor of future myopia (Mutti, Sinnott *et al.,* 2011; Sng, Lin, Gazzard, Chang, Dirani, Lim *et al.,* 2011).

Berntsen *et al.,* (2013) compared the effect of Progressive Addition Lenses (PALS) and single vision lenses (SVL) on peripheral defocus. The 84 myopic children, aged between 6 and 11 years, were randomly allocated either PALs or SVL spectacle lenses to wear for 12 months. At completion of the study, PALs had caused a relative myopic shift in peripheral defocus, on the nasal, temporal, and particularly, the superior retina due to the integrated plus addition. A slight asymmetry was found with more hyperopia on the temporal retina +0.63 (±0.76) D compared with the nasal, at +0.56 (±0.59) D. The SVLs caused a hyperopic shift in both horizontal and vertical meridians. Overall, the children with peripheral myopic defocus in the superior retina

experienced 0.24 D less myopia progression compared with those with hyperopic defocus in the superior retina.

1.2 Myopia risk factors

Myopia can be described as a multi-factorial condition with genetic, behavioural and environmental influences which may have implications for both myopia development and progression (Mutti *et al.,* 1996; Schaeffel *et al.,* 2003; Radhakrishnan, 2008). This section will explore possible risk factors and the notion of myopia prediction.

1.2.1 Ethnicity

Ethnicity may be considered a risk factor for myopia with children from some Asian populations (see section 1.1.3) having a higher risk of developing myopia than Western children (Pan *et al.,* 2012). Logan *et al.,* (2011) compared myopia prevalence in Birmingham, England between 655 South Asian, black African Caribbean and white European children aged 6 to 7 years and 12 to 13 years. Myopia levels in the older age group were higher for South Asian Children at 36.8% compared to just 18.6% for the white European participants.

In the United States of America (USA), the CLEERE study compared the biometric measurements of 4881 children with an average age of 8.8 (±2.3) years. The children were of African American, Asian, Hispanic, Native-American and white ethnicity. The spherical equivalent refractive error was most myopic in Asian children however their ocular components were described as mid-range when compared with the other children. The Native-American and Hispanic children had the longest eyes, white children the shortest (Twelker *et al.,* 2009).

There were similar findings in Australia. The Sydney Adolescent Vascular and Eye Study (SAVES) a follow-up to the Sydney Myopia Study (SMS) re-examined 2103 children from the original study. The younger cohorts were aged 12 years and the older, 17 years. East Asian children had a higher incidence (p<0.0001) of myopia in both the younger (48.5%) and older cohorts (35.8%) when compared with European children with 8.7% and 14.5% respectively (French, Morgan *et al.,* 2013).

A study in Hong Kong of 13 to 15 year old school children compared levels of myopia between 3 local schools (Chinese children) and 6 International schools (Chinese, white, Asian and mixed race children). Chinese children were found to have a higher prevalence of myopia in both schools compared with other ethnic groups. Chinese students had the highest prevalence at 85 to 88% in local schools and 82.8% in International schools. White children had the lowest prevalence at 40.5% (Lam *et al.,* 2004). Details for the inter-school variability for risk factors such as time spent outdoors and near work were not specified. However, Rose, Morgan, Smith *et al.,* (2008) compared the prevalence and risk factors for myopia in 124 children of Chinese ethnicity from the Sydney Myopia Study with 628 children, also of Chinese ethnicity, from the Singapore Cohort Study. Myopia prevalence was found to be substantially lower in Sydney, with only 3.3% having myopia compared with 29.1% in Singapore (p<0.001). In Sydney, 68% of children had one or more myopic parent compared with a fairly comparable 71% in Singapore. The children in Sydney spent on average 13.75 hours per week on outdoor activities a considerably higher duration than Singapore with just 3.05 hours per week.

1.2.2 Genetic influences

There are strong indications that myopia has a genetic element unexplained simply by a shared environment (Hammond *et al.,* 2001; Dirani *et al.,* 2006). The Genes in Myopia (GEM) study (Baird *et al.,* 2010) was established in 2004 in Australia and examined 1224 monozygotic and dizygotic twins, aged 18 to 88 years. A monozygotic twin had a 78% chance of developing myopia if their co-twin was myopic whereas that figure dropped to 47% for a dizygotic twin, 29.7% of the participants had myopia of -0.5 D or worse (Baird *et al.,* 2010).

The prevalence of myopia in children is commonly increased when one or both parents are myopic (Mutti and Zadnik, 1995; Saw *et al.,* 2002; Jones *et al.,* 2007). Studies discussing parental myopia as a risk factor commonly consider more than one element and therefore parental myopia will be revisited further in the next two sections.

Myopia can be found as a distinctive feature of certain disorders such as the heritable connective tissue disorders Marfan syndrome and Stickler syndrome (Wojciechowski, 2011). Myopia disease has been shown to be complex, with X-linked, autosomal recessive or autosomal dominant patterns of inheritance (Hammond *et al.,* 2001; Baird *et al.,* 2010; Edwards, 1998). In 1998 the first genetic locus for non-syndromic high myopia (MYP2) was mapped by Young *et al.,* (1998) and new loci for myopia continue to be identified. The Consortium for Refractive Error and Myopia (CREAM) collated data from a large genome-wide associated study (GWAS) to form a meta-analyses comparing European and Asian cohorts involving 45,758 participants. There were 16 new loci for refractive error in Europeans and 8, of which were shared with participants of Asian ancestry, were identified. The

CREAM group observed that the areas of cross-ethnicity commonality may provide evidence for shared genetic risk factors (Verhoeven *et al.,* 2013).

Early identification of those at risk of myopia could lead to earlier preventative intervention for susceptible individuals.

Myopia prevalence has increased worldwide in recent decades (Pan *et al.,* 2012) indicating that genetics is just one contributory factor to this condition (Wu and Edwards, 1999; Morgan and Rose 2005; Flitcroft, 2012).

1.2.3 Near work and education

Numerous studies have found a correlation between education level (Mutti *et al.,* 2002; Williams *et al.,* 1988), early schooling (Rose, Morgan, Smith *et al.,* 2008) and myopia. Weak associations have been made between myopia and levels of near work (Mutti *et al.,* 2002; Saw *et al.,* 2002; Morgan and Rose, 2005; Rose, Morgan, Smith *et al.,* 2008). Mutti *et al.,* (2002) explored the association between parental myopia, near work, school achievement and juvenile onset myopia exploring data from 366 children with an average age of 13.7 (±0.5) years. Parental myopia and, to a lesser extent, near work were both significantly associated with myopia. Children with myopic parents were found to carry out as much near work as children without myopic parents and therefore an inherited myopigenic lifestyle was not indicated. Saw *et al.,* (2002) assessed the relationship between near work and myopia in 1005 children aged 7 to 9 years in Singapore. The number of books read per week was found to be associated with both early onset myopia and higher levels of myopia. This was not found to be a conclusive link due to the eldest children being just 9 years old and all recorded myopia was early onset. Reading and myopia levels were both

measured at one point in time and therefore a cause-effect relationship could not be established. Using data from the SMS, Ip *et al.,* (2008) found that continuous reading for more than 30 minutes and reading distances of less than 30 cm increased the chances of a child having myopia. Conversely, the CLEERE study found that levels of near work had no significant effect on myopia progression (Jones-Jordan *et al.,* 2012).

Typically, when a person views a near target, they under-accommodate i.e. they use insufficient accommodation to bring an object into focus and this is termed a 'lag of accommodation (Gwiazda *et al.,* 2004). This results in hyperopic retinal blur. Associations have been made between the lag of accommodation during near work and the development and progression of myopia (Gwiazda *et al*., 1993; Gwiazda *et al*., 1995; Gwiazda *et al*., 1999). When compared with emmetropic children, myopic children accommodate less to a near target (McBrien and Millodot., 1986; Gwiazda *et al*., 1993) and show an insufficient accommodative response to blur (Gwiazda *et al.,* 1993). If myopia progression is related to hyperopic retinal blur at the fovea, then correcting this blur may reduce myopia progression. Interventions to reduce the lag of accommodation have shown to be statistically effective using both PALs and bifocals. In a study with Canadian-Chinese children (see section 1.3.4.1), executive bifocals with 3Δ base-in, in the near segment, further reduced the progression of myopia when compared to bifocals without prism and single vision lenses (Cheng *et al*., 2010). Unlike contact lenses, spectacle lenses require the child to view through the correct area of the lens. If the child views a near target using the distance portion of the lens, the positive lens treatment effect, from the near addition, would be reduced. Bifocals have a clear line, dividing the distance and near portions of the

lens, potentially providing a guide of the correct position for the child (Cheng *et al*., 2011). If a child routinely bends their head down to read, they will view through the distance portion in both PALs and bifocals, missing the treatment zone.

1.2.4 Time spent outdoors

Recent studies have demonstrated that light may play a protective role in refractive development (Jones *et al.,* 2007; Rose, Morgan, Ip *et al.,* 2008; Smith *et al.,* 2012; Wu *et al.,* 2013; Jones-Jordan *et al.,* 2012; He *et al*., 2015). Smith *et al.,* (2012) observed an 87% reduction in myopic anisometropia in monocular, form deprived infant monkeys who were exposed to an additional 6 hours per day of 25,000 lux illuminance in addition to normal laboratory illuminance (15-630 lux). The authors also reported that 75% of this group became more hyperopic in their treated eyes compared with fellow eyes. However, in a later study Smith, Hung, Arumugam *et al.,* (2013) assessed whether the protective effect of high light levels, found to prevent form deprivation myopia, would also be effective with lens-induced myopia. Using -3.00 D lenses to induce myopia monocularly in primates, under normal laboratory lighting, an additional 25,000 lux lighting was utilised 6 hours per day for some of the monkeys. Myopia was induced in all the monkeys regardless of light exposure thus indicating a difference in the mechanism between lens-induced and form deprivation myopia.

Ashby and Schaeffel (2010) found that chicks exposed to high illuminance of 15,000 lux for 5 hours per day had a significantly slower compensation to negative lenses when compared to those reared in normal laboratory illuminance of 500 lux. Conversely, 15,000 lux hastened compensation for positive lenses compared with

500 lux however, full compensation was achieved with both lens types. When the chicks were injected daily with Spiperone, a dopamine receptor antagonist, the protective effect was eliminated. Parenthetically, quartz-halogen lights were used in this study, which do not emit ultraviolet (UV) waves and thereby indicating that UV light is unlikely to be a factor in the protective quality of light in animal studies (Ashby *et al.,* 2009). McCarthy *et al.,* (2006) explored the protective effect of dopamine agonists on chickens kept in a 12 hour light, 12 hour dark cycle. When the translucent diffuser over one of the eyes was removed for 3 hours during the light period, there was protection from excessive eye growth. If the chicken was kept in the dark for those 3 hours, the protective effect was lost unless they injected dopamine agonists which restored the protective effect. Equally the introduction of dopamine antagonists injected prior to removal in the light period also blocked the protective effect of the light.

To explore the effect of time outdoors and parental myopia to predict juvenile onset myopia in children, Jones *et al.,* (2007) used data from the Californian Orinda Longitudinal Study of Myopia. Survey data was collected between 1989 and 2001 for 514 school–age children, of whom 111 became myopic. Less sports and outdoor activities combined with having myopic parents were found to be the best predictors of having myopia in the future. Less sports and outdoor activity increased the chances of developing myopia in children with two myopic parents more so than for children with either one or no myopic parents. In agreement those children without a myopic parent, who participated in the highest level of sports and outdoor activity, had the least likelihood of future myopia.

Similarly, Rose, Morgan, Ip *et al.,* (2008) assessed the correlation in Sydney, between outdoor activity and myopia prevalence for 1765 children of 6 years of age and 2367 children of 12 years of age. The group of children with the highest levels of outdoor activity had the lowest odds ratio for myopia, whereas no association was found between indoor sport and myopia.

Wu *et al.,* (2013) investigated whether outdoor activity during school break-time impacted myopic changes in 7 to 11 year old students from two schools in Taiwan. Children from the first school (n=333) were encouraged to spend their break-time outdoors for a total time of 80 minutes per day. The 238 children from the second school did not have any intervention to change behaviour. Initially, myopia prevalence was 47.8% in the outdoor intervention school compared with 49.2% in the control school. One year after implementing these changes there was less myopia onset and myopic shift in the outdoor intervention school with 8.4% and -0.25 D/year versus 17.7% and -0.38 D/year at the control school.

In contrast, Jones-Jordan *et al.,* (2012) investigated the association between the progression of myopia and time spent outdoors for the 835 myopic participants of the CLEERE study in the USA. Annually the parents of the 6 to 14 year old participants were asked, via questionnaire, to estimate how many hours their child spent in various categories of activities outside of school hours. They found no correlation between outdoor/sport activity and annual progression of myopia. Scheiman *et al.,* (2014) evaluated the relationship between time spent outdoors and myopia stabilisation by age 15 years for the participants of the Correction of Myopia Evaluation Trial (COMET). The 469 myopic 6 to 11 year old children were enrolled on the trial with each randomised to wear either single vision or progressive addition

spectacle lenses for a 5 year duration. No association was found between time spent outdoors and myopia stabilisation by age 15. These studies may indicate therefore that progression and stabilisation of existing myopia are not associated with time outdoors and that the protective effects may only benefit emmetropic children.

Data on time spent outdoors for the studies mentioned above was collected using questionnaires. The subjective responses rely on estimation and have the potential for memory bias (Alvarez and Wildsoet, 2013). In order to investigate any such inconsistencies, Alvarez and Wildsoet (2013) gave 27 young adults, in California, a light sensor to wear continuously for a 2 week period. The participants were additionally asked to complete a questionnaire on visual activity including an estimation of the amount of time spent indoors/outdoors. Subjective over-estimation caused poor agreement between light sensor data and questionnaire results.

To investigate effecting change in child outdoor behaviour Ngo *et al.,* (2014) evaluated an intervention to raise levels of outdoor hours in 285 children in Singapore aged between 6 and 12 years. Approximately half (n=147) of the participants were randomised to the intervention and educated in myopia, encouraged to partake in weekend outdoor activities and given incentives to encourage an increase in daily steps. The control group (n=138) were simply given resources to read that educated them on myopia. The children who took part in the intervention showed a statistically significant increase in outdoor time of 2.5 hours at 6 months (p=0.038) however by 9 months, when the trial concluded, the variance was not sustained (p=0.291).

In a similar study in Guangzhou, China, He *et al.,* (2015) assessed the efficacy of an additional 40 minutes of outdoor time each school day with encouragement to also

increase outdoor family time for 952 children with a mean age of 6.6 (±0.34) years. The control group (n=951) were advised to continue with their normal routine. There was a statistically significant (p=<0.001) reduction in the incident rate of myopia after 3 years in the test group (30.4%) compared with the control group (39.5%) and in the MSE (-1.42, -1.59 respectively, difference of 0.17 D [95% CI, 0.01 to 0.33 D]; p=0.04) however axial elongation was not significantly different (0.95 mm, 0.98 mm respectively, difference of -0.03 mm [95% CI, -0.07 to 0.003 mm]; p=0.07).

The exact mechanism to explain why time outdoors may lower the risk of and protect against myopia remains unclear (Pan *et al.,* 2012; Flitcroft, 2012; Smith *et al.,* 2012; Wu *et al.,* 2013). Rose, Morgan, Ip *et al.,* (2008) suggested that the increased intensity of light found outdoors may provide protection, due to the stimulation of an increase in the retinal transmitter dopamine, which inhibits eye growth. This theory is supported by animal studies (McCarthy *et al.,* 2006; Ashby *et al.,* 2009).

An alternative theory put forward by Flitcroft (2012) considers the outdoor environment and its effect on defocus on the retina. Flitcroft suggests that the greater distance experienced outdoors compared with indoors may cause a dioptric flattening, impacting how the eye responds to the resultant defocus. Associations have been made with myopia and Vitamin D receptor polymorphism (Mutti, Cooper *et al.,* 2011) additionally, there is some indication that myopes may have a lower average blood content of vitamin D than non-myopes (Mutti and Marks, 2011). Guggenheim *et al.,* (2014) analysed data for children participating in the Avon Longitudinal Study of Parents and Children (ALSPAC). They hypothesised that vitamin D mediated the protective effects of time outdoors against myopia. Vitamin D was found to be a biomarker for time spent outdoors although there was no

statistically significant data to suggest an association between the participant serum level and later myopia.

1.2.5 Myopia prediction

If there is an effective intervention for myopia control, then the ability to predict which children may be susceptible to myopia could enable earlier intervention. As previously discussed the Orinda Longitudinal Study of Myopia found that identifying children who took part in less sport and outdoor activities combined with having myopic parents were good predictors of future myopia development (Jones *et al.,* 2007). Refractive error measured when a child is young, however, has been shown to be a good predictor of later ametropia (Hirsch, 1964; Zadnik *et al.,* 1999). In a recent analysis, using data from the CLEERE study, Zadnik *et al.,* (2015) evaluated the ability of possible risk factors to predict myopia. The data for 4512 children of mixed ethnicity, aged between 6 and 11 years were all non-myopic when enrolled. Cycloplegic, spherical equivalent, refractive error was found to be the solitary best predictor of future myopia. Furthermore, they observed that if at age 6 years a child is measured at less than +0.75 D of hyperopia they are at increased risk of myopia.

1.2.6 Peripheral hyperopic defocus

As discussed in section 1.1.5, animal models have shown that while correcting a myopic refractive error with a negative lens in spectacles or a contact lens would allow light to focus on the fovea, there is simultaneously a hyperopic defocus produced in the periphery of the retina. This defocus is thought to stimulate the eye to grow longer and this peripheral hyperopic defocus could, therefore, be deemed a risk factor for myopia (Schaeffel *et al.,* 1988; Smith and Hung, 1999; Flitcroft, 2012;

Smith, Hung, Huang *et al.,* 2013). A similar effect has also been found in humans with high myopia. When correcting the on-axis myopia with single vision spectacles, a hyperopic defocus was found in the peripheral retina (Backhouse *et al*., 2012). In a 1 year longitudinal study, children with superior relative retinal myopic defocus experienced less myopia progression than those with superior relative retinal hyperopic defocus (Berntsen *et al*., 2013).

1.3 Therapeutic interventions to limit the progression of myopia

1.3.1 Introduction

A variety of interventions designed to slow or halt the progression of myopia have been considered and trialled in recent years. A variety of theories have been utilised including peripheral defocus manipulation and the reduction of near accommodative effort. The most notable therapeutic interventions will now be discussed.

1.3.2 Optical approaches to myopia intervention

As described in section 1.1.5, animal studies have demonstrated the retinal effect of plus and minus lenses. While a minus lens in spectacles or a contact lens form would give clear central vision, a simultaneous hyperopic defocus would be produced in the periphery of the retina (see Figure 1.8).

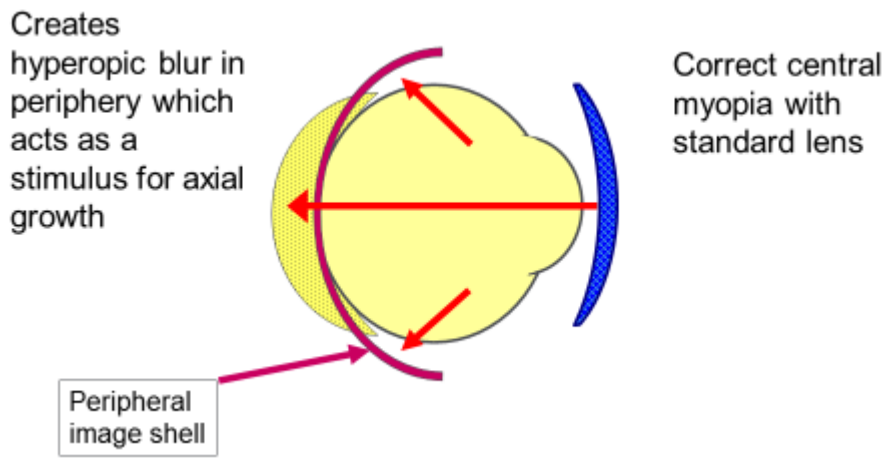


Figure 1.8 Effect of a traditional spectacle lens on peripheral hyperopic blur

When a relatively hyperopic lens is placed in front of the eye, the focal point is moved in front of the retina causing a myopic retinal defocus. This resultant myopic retinal defocus is believed to slow axial growth (see Figure 1.9) (Smith, 1998; Smith and Hung, 1999).

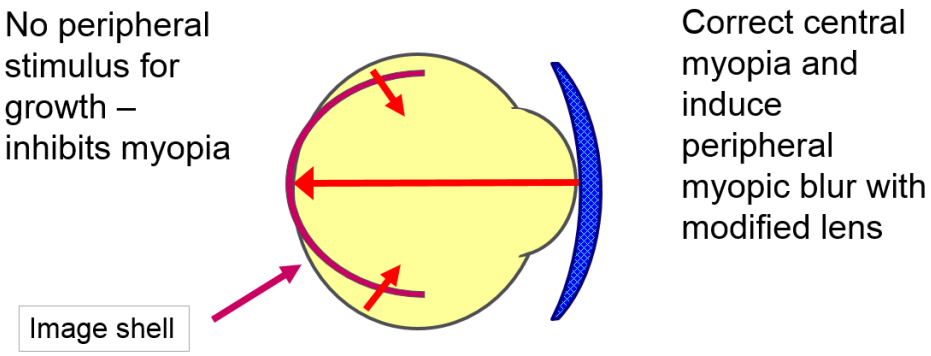


Figure 1.9 Effect of induced peripheral myopic blur

Theoretically, therefore, if human eyes respond in the same way, an under correction of myopia would slow or halt axial elongation.

1.3.3 Under correction

Several human studies have explored under correction as an intervention for myopia control in humans. Ong *et al.,* (1999) assessed 3 year data from 43 participants with myopia <-0.50 D, aged between 2.5 and 16.3 years. The 3 year myopia progression was cross-referenced with the spectacle wear pattern of the participant, which varied from full time wear, occasional use and no spectacles worn. The non-spectacle wearing group had a 3 year myopia progression approximately half that of the full time spectacle wearing group, however, when adjusted for age there was no statistically significant difference in progression between any of the wearing patterns of the participants.

Adler and Millodot (2006) evaluated the effect of wearing full correction of myopic refractive error and under correction of the myopia (by +0.50 D) in 48 myopic children aged 6 to 15 years over an 18 month duration. The under corrected participants showed a slight, although non-significant, increase in myopic progression of 0.17 D compared to the fully corrected children. Chung *et al.,* (2002) also considered the effect of full and under correction on myopia progression. The 94 myopic children, aged between 9 and 14 years, were allocated either full spectacle prescription or under correction by +0.75 D for a period of 2 years. The maximum distance visual acuity for the latter group was 6/12 Snellen acuity. At the end of the 2 year period, the under corrected group exhibited higher myopic progression of -1.00 D and

associated greater axial elongation when compared to the fully corrected group with -0.77 D myopia progression.

A possible consideration for the unexpected outcome of under correction, is the utilisation of induced myopia in animal studies compared with the more natural, if poorly understood, process in human beings. This variation in mechanism may account for any incongruity. Lighting studies in animals have shown entirely different outcomes when the myopia was lens-induced versus form deprived (Smith, Hung, Arumugam *et al.,* 2013), indicating that a change in mechanism may have a significant effect on a myopia progression intervention.

Myopic defocus was unexpectedly effective, however, in a 30 month monovision spectacle study aimed at lessening accommodative effort at near to effect a reduction in myopia progression. The 18 myopic children, aged 10 to 13 years, were given their full distance prescription (-1.00 to -3.00 D mean sphere equivalent (MSE)) in their dominant eye. The non-dominant eye was allocated either a plano lens or where necessary, a partial correction, to limit any resultant imbalance between the eyes from exceeding 2.00 D of induced anisometropia. The children were expected to use their non-dominant eye to read and therefore use less accommodation at near. Unexpectedly, all of the children adapted to read with their distance corrected eye, causing a resultant myopic defocus in the non-dominant eye. Monovision was not successful in reducing accommodative effort at near. However, myopia progression in the non-dominant eyes was significantly less by -0.36 D and 0.13 mm axial elongation per year, (Phillips, 2005).

1.3.4 Peripheral defocus theory

1.3.4.1 Spectacle Lenses

One theory related to myopia progression in children centres on the hypothesis that hyperopic retinal blur at the fovea caused by a high lag of accommodation during near work induces axial growth of the eye. This theory stems from findings that myopes have a reduced accommodative response compared to emmetropes and thus an insufficient accommodative response to blur (Gwiazda *et al.,* 1993). Research to evaluate the use of PAL and bifocal lenses to reduce myopia progression, by relieving accommodative effort at near, has been extensive (Goss, 1990; Fulk *et al.,* 2000; Edwards *et al.,* 2002; Gwiazda *et al.,* 2003; Leung and Brown, 1999; Hasebe *et al.,* 2008; Sankaridurg *et al.,* 2010; Berntsen *et al.,* 2012; COMET2, 2011; Cheng *et al.,* 2010).

Grosvenor *et al.,* (1987) in a randomised clinical trial, tested the effectiveness of single vision lenses on myopia progression, compared with children corrected with bifocal spectacles with +1.00 D and +2.00 D additions. 124 participants, aged between 6 and 15 years, completed the study and mean changes in refraction were not statistically significant with -0.34 D, -0.36 D and -0.34 D change in myopia progression per year respectively. When data for all 3 groups were combined, the younger participants with higher levels of myopia had the most rapid progression of myopia. Correspondingly the participants of greater age and lower levels of myopia progressed the least. Edwards *et al.,* (2002) alternatively, assessed the efficiency of PAL spectacles for 298 children in Hong Kong, aged between 7 and 10.5 years. The PAL spectacles incorporated +1.50 D addition and the control group wore single

vision spectacles. As with Grosvenor *et al.,* (1987), no statistically significant difference was found between the two groups.

Conversely, Leung and Brown (1999) compared single vision spectacles and PAL spectacles with +1.50 D and +2.00 D addition, with children in Hong Kong, aged 9 to 12 years. Mean myopic progression after 2 years was -1.23, -0.76 and -0.66 dioptres respectively, showing a reduction in progression that was most effective with a +2.00 D addition.

The Correction of Myopia Evaluation Trial (COMET) enrolled 469 children aged between 6 and 11 years and allocated them either PALs with +2.00 D addition, or single vision spectacles. After 3 years the increase in mean spherical equivalent was -1.28 (±0.06) D for the PAL group and -1.48 (±0.06) D for the single vision spectacle group. The difference in progression was 0.20 (±0.08) D and described as statistically significant (p=0.004), although not clinically meaningful (Gwiazda *et al.,* 2003; Gwiazda, 2009). The treatment effect was reported to have been mainly during the first year of the study. There was also a significant treatment effect in the children with higher baseline near accommodative lag (p=0.03) and lower baseline myopia (p=0.04). The children who progressed the most were those who wore single vision spectacles and had a lag of accommodation (>0.43 D for a 33 cm near target). The PAL spectacles were most effective for the children with accommodative lag and near esophoria (Gwiazda *et al.,* 2003; Gwiazda *et al.,* 2004), a finding supported in other similar studies (Goss, 1986; Fulk *et al.,* 2000; Hasebe *et al.,* 2008; COMET2, 2011). With a focus on this identified sub-group the COMET2, a follow up to the COMET study, assessed 118 myopic children with high accommodative lag and near esophoria. The children aged 8 to <12 years were allocated either single vision or

PAL spectacles with +2.00 D addition. A high accommodative response was initially deemed to be a lag of at least 0.50 D to a target at 33 cm, this was increased one year into recruitment to a lag of at least 1.00 D. There was a statistically significant mean change in spherical equivalent of -0.87 D in the PAL group compared with -1.15 D for the single vision spectacle wearers, treatment effect of 0.28 D over 3 years (COMET2, 2011).

While there is considerable evidence to suggest that children with a lag of accommodation and esophoria may benefit most from this type of therapeutic intervention, not all studies showed agreement. Berntsen *et al.,* (2012) measured the effect of PAL spectacles versus single vision spectacles in 85 children aged 6 to 11 years with high accommodative lag, for one year. The children were all then assigned single vision spectacles and followed for a further year. The PAL wearing group progressed -0.35 D and the single vision group by -0.52 D after the first year. At the end of the second year, there was no difference in the progression of myopia and accommodative lag was not found to be associated with progression.

Variations of traditional spectacles have also been considered to limit the progression of myopia. Cheng *et al.,* (2010) randomly allocated 3 different types of spectacles to 135 myopic Chinese-Canadian children, aged between 8 and 13 years. The spectacles were either single vision spectacles, +1.50 D executive bifocals or +1.50 D executive bifocals with 3Δ base-in, in the near segment. Myopic progression, after 24 months, was -1.55 D, -0.96 D and -0.70 D respectively. The two bifocal spectacle types had statistically significant treatment effects (p<0.001) of 0.59 D and 0.85 D respectively and associated less axial elongation when compared to the single vision spectacle group.

In another deviation from conventional optical correction Sankaridurg *et al.,* (2010) trialled three novel spectacle lenses, designed to reduce peripheral hyperopic defocus. Lens type I and II were rotationally symmetrical with clear central zones of 20 mm and 14 mm, respectively. Each lens had a progressively ramped treatment zone providing increasing positive power up to +1.00 D and +2.00 D relative peripheral power, respectively, at 25 mm. The type III lens was of an aspheric design. A clear central zone extended, from the centre, 10 mm inferiorly and in each direction horizontally. The lens was designed to reduce astigmatism in the horizontal meridian while providing 1.9 D of additional peripheral power, 25 mm from the axis. In the 12 month study, 210 Chinese children, aged 6 to 16 years old, were randomly allocated to one of four groups, receiving either one of the 3 novel lenses or a single vision spectacle lens. While there were no statistically significant findings between the four lens types, there was, however, a reduction in progression of myopia in children <12 years old, with a history of parental myopia, that had trialled the type III lens. The type III aspheric design lens had a clear centre and was designed to reduce astigmatism in the horizontal meridian while providing additional peripheral power (Sankaridurg *et al.,* 2010).

These studies have shown a large variation, with results varying from good effect to no significant effect. There are indications that treating children with relative plus power for close work may have greater effect on certain groups of children, such as those with large lags of accommodation and esophoria at near viewing distances. To effect wide-ranging clinical practice, treatment effects will likely need to be demonstrably substantial.

Spectacles of the nature discussed here require correct wear at all times if they are to work in the specific way they were designed. Children may not always use them to this high standard. Eyes also move independently of the spectacle lens, possibly further diminishing the treatment effect. Contact lenses may effectively solve these issues, keeping a more fixed position relative to the visual axis.

1.3.4.2 Contact lenses

Benavente-Perez *et al.,* (2014) studied the effect of placing monocular bifocal centre plano lenses with a peripheral power of either -5.00 D or +5.00 D, and a centre zone diameter of either 1.5 mm or 3 mm, in front of the eyes of marmosets. Following treatment, the marmosets exposed to the peripheral myopic lenses had more myopic refraction and longer axial lengths than the animals who wore the hyperopic peripheral lenses. This finding supports the theory that refractive state and eye growth can be altered by inducing differing degrees of peripheral retinal defocus, in animals.

Liu and Wildsoet (2011) assessed the effects of a 2-zone concentric lens with a central zone diameter of 3.5 mm on the refractive and ocular development of young chicks. A lens with a central power of -5.00 D and plano in the periphery induced -0.53 (±1.63) D, whereas, a lens with -5.00 D in the periphery induced -2.86 (±2.24) D of refractive change. For comparison purposes, myopia was induced in the control group using a -5.00 D single vision lens, which induced -5.84 (±0.50) D of myopia at the end of the treatment period. Following on from this study, Liu and Wildsoet (2012) then compared the effect of two further test lenses, again in a chick model. Centre zone diameters of 4.5 mm were used in this later study.

A -10.00 D lens with -5.00 D in the periphery induced -6.08 (±1.18) D of refractive change, whereas, a -5.00 D lens with -10.00 D in the periphery induced -9.17 (±1.07) D. The single vision -10.00 D control lens induced -9.61 (±1.25) D of myopia. Both test lenses in this study, which had relatively hyperopic peripheral lens powers resulted in less myopia progression.

Arumugam *et al.,* (2014), in a similar study, assessed the effect of a plano 2 mm centre zone diameter lens with alternating concentric zones of -3.00 D and plano, on the eyes of infant monkeys. The treatment effect was found to be dominated by the more anterior retinal image plane. This study further supports the theory that imposed, simultaneous, relatively myopic defocus may be an effective method for limiting myopia progression.

Many studies have indicated that children and young adults can proficiently wear contact lenses from 8 years of age (Sankaridurg *et al*., 2011; Walline *et al.,* 2004; Jones-Jordan *et al.,* 2010; Chalmers *et al.,* 2011) and experience an improved quality of life when compared with wearing spectacles (Rah *et al.,* 2010). Safety and hygiene in soft contact lens use in patients between 8 and 15 years of age has been associated with less risk of infiltrative events when compared with older adolescents and young adults (Chalmers *et al.,* 2011). Walline, Lorenz *et al*., (2013) reported that contact lens wearers who were first fitted at 12 years of age or less were found to be no more likely to report contact lens related adverse events than those fitted at 13 years of age or above.

Contact lenses are commonly used as an alternative to, or alongside spectacle lenses to correct refractive error. Recent research has suggested that spectacle lens

wear may increase myopia progression when compared to spherical contact lenses (Backhouse *et al.,* 2012; Kwok *et al.,* 2012). Backhouse *et al.,* (2012) investigated the effect on peripheral refraction between conventional spectacle lenses, conventional contact lenses and when no optical correction was worn. Using an open-field autorefractor, peripheral refraction measurements were taken using each of the 3 modes, with each of the 10 participants. The average peripheral refraction was relatively hyperopic when the participant was uncorrected, +0.90 (±0.14) D, and also when spectacles were worn, +1.01 (±0.13) D. The peripheral refraction was relatively myopic when contact lenses were worn, -1.83 (±0.61) D, theoretically removing the peripheral stimulus for axial growth.

Others studies have suggested the opposite standpoint (March-Tootle *et al.,* 2009; Fulk *et al.,* 2003), or have alternatively demonstrated no significant difference (Walline *et al.,* 2008) between spectacles and soft contact lenses, on myopia progression. Possible explanations for the lack of correspondence might be inter-participant variability, variation in lens powers (including peripheral optics) and differing lens materials. In a recent study by Wagner *et al.,* (2015), large differences were found between power profiles of single vision contact lenses, indicating that certain commercial lenses may cause increased hyperopic defocus and therefore potentially exacerbate myopia.

Historically contact lenses with more than one focus were intended for presbyopic use. In recent years, novel designs of contact lenses have been conceived for myopia. The dual focus soft lens described by Anstice and Phillips (2011) was designed specifically as an intervention to limit the progression of myopia. The lens has a central zone which corrects refractive error and concentric treatment zones

with +2 D addition to impose simultaneous peripheral myopic defocus for both distance and near viewing. The 40 children, aged 11 to 14 years wore the test lens in one eye with a single vision distance lens in the other. After 10 months lens assignment was swapped between the eyes for a further 10 months. In the first period, the dual focus test eyes increased in myopia by -0.44 (±0.33) D versus the control eyes, which progressed -0.69 (±0.38) D. Axial length changes were corresponding with an increase of 0.11 (±0.09) mm and 0.22 (±0.10) mm respectively. Similar figures were found in the second period. Myopia progression was reduced by 30% in 70% of the children who took part and by ≥50% in 50% of the children. These findings indicate that continuous myopic defocus with simultaneous clear images can act to slow the progression of myopia (Anstice and Phillips, 2011).

Sankaridurg, *et al.,* (2011) trialled a new contact lens also designed to reduce relative peripheral hyperopic blur. The test lens had a central clear zone with progressively more positive power reaching +1.00 D at 2 mm, and +2.00 D at the edge of the 9 mm treatment zone. In the 12 month study, 45 Chinese children aged 7 to 14 years were allocated the test lens and a further 40 wore single vision, spherocylindrical spectacles. The estimated myopic progression was -0.57 D with the test lens and -0.86 D for the spectacle wearers. There is a comparable difference in progression variance between these two studies despite the variation in control group correction of spectacle versus contact lenses.

Walline, Greiner *et al.,* (2013) explored the effect of a commercially available centre distance, multifocal lens (Proclear Multifocal ‘D’; CooperVision, Fairport, New York) with 40 myopic children aged between 8 and 11 years. When the 2 year data were compared with children from another study who wore single vision contact lenses the

difference in myopic progression was 50% less in the multifocal group (-1.03 ±0.06 D versus -0.51 ±0.06 D). There was also less axial length elongation by 29% for the multifocal group (0.41 ±0.03 D and 0.29 ±0.03 D).

Lam *et al.,* (2014) evaluated a custom-made 'Defocus Incorporated Soft Contact' (DISC) lens against single vision contact lenses. The 221 children aged between 8 and 13 years were randomly assigned to one of two groups and monitored for 2 years. The DISC lens was of concentric ring design and had an addition of +2.50 D, a slightly higher addition than the +2.00 D addition used in the Anstice and Phillips (2011) lens, alternating with the distance correction. At completion of the study, there was 25% less progression in the DISC group, with an associated reduction in axial elongation.

Although a common finding in BIFS/PALS research, these studies did not focus on myopic patients with esophoria at near distances. Aller and Wildsoet (2008) compared the effect of a single vision contact lens with a bifocal contact lens with one pair of 12 year old twins with near point esophoria. After one year the twin wearing the bifocal contact lens demonstrated no progression of myopia (+0.13 D) whereas the fellow twin, wearing the single vision lens, had progressed -1.19 D. This may indicate that, as found with BIFS/PALS, myopes with near esophoria may also benefit from the soft contact lens version of this therapeutic intervention.

1.3.4.3 Orthokeratology

The ability of orthokeratology (ortho-k) lenses to reduce myopia progression was an accidental find. Ortho-k contact lenses are worn overnight to reshape the cornea. The rigid gas permeable lenses flatten the central cornea, temporarily reducing or

eliminating refractive error (Smith, 2013; Phillips *et al.,* 2013). Furthermore, recent studies have shown an associated reduction in axial elongation over time (Cho *et al.,* 2005; Cho and Cheung, 2012; Hiraoka *et al.,* 2012; Santodomingo-Rubido *et al.,* 2012). It is thought that the steepening, relative to the central flattening, of the peripheral cornea caused by orthokeratology lenses (Phillips *et al.,* 2013) may, as with previous techniques, move the peripheral retinal image shell to myopic defocus (Kang and Swarbrick, 2011), causing less axial growth (Smith, 1998).

Cho and Cheung (2012) evaluated the effectiveness of orthokeratology lenses against single vision spectacles for 78 myopic participants, aged from 6 to 10 years. Axial elongation after 2 years was 0.36 (±0.24) mm for the ortho-k children and 0.63 (±0.26) mm in the spectacle wearing group. The participants who wore the ortho-k lenses were reported to have experienced an average slowing of axial elongation by 43%.

In a study of longer duration Hiraoka *et al.,* (2012) compared axial length change in 29 child participants wearing ortho-k and 30 wearing spectacles. At completion of the 5 year study, the increase in axial length was 0.99 (±0.47) mm for the ortho-k group and 1.41 (±0.68) mm for the spectacle wearers, and statistically significant (p=0.0236). Notably, when compared annually, axial length comparison was statistically significant for the first 3 years only (1st p=0.0002, 2nd p=0.0476 and 3rd p=0.0385), however, although of a diminishing level, axial elongation remained less in the ortho-k group for all 5 of the study years.

Ortho-k alters refractive error and corneal curvature, therefore axial length is a more reliable measure for comparison. Walline *et al.,* (2009) measured lens thickness and

both anterior and vitreous chamber depth. Associated changes in vitreous chamber depth were found when compared to axial changes.

Effective interventions to limit the progression of myopia ideally need to have a low risk of harm to the patient in addition to a lasting treatment effect on myopia level. Infection such as microbial keratitis may be of increased risk with overnight ortho-k wear (Watt and Swarbrick, 2005; Phillips *et al.,* 2013) although of similar risk level to that found with other overnight modalities (Bullimore *et al.,* 2013). Lee and Cho (2010) described the outcome for a young girl who commenced ortho-k at age 6 and after 38 months of lens wear changed to spectacles. The child experienced a rebound in the treatment effect when her eye elongation rate approximately doubled, an effect which slowed on ortho-k recommencement (Philips *et al.,* 2013).

1.3.5 Pharmaceutical agents

1.3.5.1 Atropine

Atropine, a non-selective muscarinic antagonist, has been shown to slow the progression of myopia (Shih *et al.,* 2001; Chua *et al.,* 2006; Tong *et al.,* 2009; Chia *et al.,* 2012). It is no longer thought to be related to the temporary paralysis of accommodation produced (Walline *et al.,* 2011; McBrien *et al.,* 1993). While the actual mechanism is unclear, this muscarinic antagonist may work through the M1 and M4 muscarinic receptor signalling pathways (McBrien *et al.,* 2011).

Shih *et al.,* (2001) randomly assigned 227 children aged 6 to 13 years into 3 groups. The children were given either 0.5% atropine with multi focal spectacles, multi focal spectacles or single vision spectacles. Of the 188 participants who completed the 18

month trial, the mean progression of myopia in the atropine with multi focal spectacles group was lowest at -0.42 (±0.07) D. A significantly lower figure (p<0.0001) than the other two groups, who progressed -1.19 (±0.07) D and -1.40 (±0.09) D respectively. A comparison of the multi focal group and the single vision group did not show statistical significance (p=0.44).

The 'Atropine for the Treatment of childhood Myopia' (ATOM) study reported similar findings when they evaluated the effect of 1% atropine. The 400 children aged between 6 and 12 years were treated with atropine eye drops in one eye and a placebo in the other. The study was designed in this manner to avoid blurred vision in both eyes at near distances, requiring additional, possibly confounding, optical correction. The 346 children completed the study and after 2 years the mean progression of myopia for the eyes treated with atropine drops was -0.28 (±0.92) D. Axial length remained essentially unchanged when compared with baseline difference -0.02 (±0.35) mm. The placebo treated eyes progressed -1.20 (-0.69) D and 0.38 (±0.38) mm in axial elongation (Chua *et al.,* 2006). Unwanted side effects from 'successful' uniocular treatment, however, can be anisometropia and aniseikonia. In addition to blurred near vision, the pupil dilation achieved with 1% atropine can cause glare and photophobia (Chua *et al.,* 2006).

A year after completion of the study and cessation of 1% atropine, the participants were re-assessed. The mean progression, after one year, in the atropine treated eyes was -1.14 (±0.80) D and the placebo group -0.38 (±0.39) D. When compared for the 3 year period, however, the atropine 1% eyes demonstrated less overall spherical equivalent myopia progression and axial elongation totalled just 0.29

(±0.37) mm compared with 0.52 (±0.45) mm in the placebo treated eyes (Tong *et al.,* 2009).

Following on from ATOM1, the ATOM2 study compared the efficacy of lower doses of atropine to reduce myopia progression and minimise the side effects found with cycloplegia and mydriasis. In phase 1 the 400 child participants were randomly assigned either 0.5%, 0.1% or 0.01% atropine, in a 2:2:1 ratio respectively. Myopia progression and axial length change, after 2 years, was found to be -0.30 (±0.60) D, -0.38 (±0.60) D and -0.49 (±0.63) D and +0.27 (±0.25) mm, +0.28 (±0.28) mm, and +0.41 (±0.32) mm correspondingly. When compared with the ATOM1 placebo group progression of -1.20 (±0.69) D, all 3 low concentration groups demonstrated a reduction in myopia progression. There were 16 dermatitis and allergic conjunctivitis adverse events noted for the 0.5% and 0.1% groups, no adverse events were recorded for the 0.01% group. In addition, the 0.01% dose had little effect on near visual acuity, pupil size or accommodation (Chia *et al.,* 2012).

A year after completion of phase 1 the participants, as with ATOM1, were re-assessed (phase 2) to monitor for any rebound of treatment effect. Myopic rebound was again present and was greatest (p<0.001) in the higher concentration of 0.5% with -0.87 (±0.52) D progression, compared with 0.1% (-0.68 ±0.45 D) and 0.01% eyes (-0.28 ±0.33 D). Axial length elongation was also greater in the 0.5% (0.35 ±0.20 mm) and 0.1% (0.33 ±0.18 mm) eyes, compared to the 0.01% eyes (0.19 ±0.13 mm, p<0.001). The 1% in the ATOM1 study had the largest rebound effect and resultant greatest progression of myopia, the 0.01% exhibited the least myopic rebound effect and most sustained effect of all the concentrations. Additionally, the 0.01% concentration had the least pupil dilation and accommodative loss when

trialled (Chia *et al.,* 2014). The children who had experienced myopia progression greater than 0.50 D during phase 2 were commenced on 0.01% atropine in phase 3. Phase 3 was of a further 2 year duration and all participants, including those who were not restarted on atropine treatment, were assessed every 6 months. The lower myopia progression previously experienced in phase 2 continued during phase 3. On completion of the 5 year study, atropine 0.01% had shown the greatest treatment effect at slowing the progression of myopia compared with the higher doses (Chia *et al*., 2016).

Figure 1.10 ATOM1 and ATOM2 change in spherical equivalent, comparing eyes that received 1.0%, 0.5%, 0.1% and 0.01% atropine or a placebo, during and one year after the completion of the study (Chia *et al.,* 2014). Reprinted from American Journal of Ophthalmology, Vol. 157, No. 2, Chia, A., Chua, W. H., Wen, L., Fong, A., Goon, Y. Y. and Tan, D., Atropine for the treatment of childhood myopia: Changes after stopping atropine 0.01%, 0.1% and 0.5%, Pages No.451-457, Copyright © 2014 by Elsevier INC.

A recent study by Cooper *et al.,* (2013) suggested that the highest concentration, to avoid clinically unacceptable side effects including dilation and loss of accommodation, was 0.02% atropine. Each of the 12 participants were allocated a bottle of eye drops for each eye, one bottle contained a placebo while the other contained a low dose of atropine. Atropine concentrations ranged from 0.025 to 0.5%. The authors defined criteria for comfort of ≥5 D of residual amplitude of accommodation and ≤3 mm between eye difference in pupil size. The concentrations greater than 0.025% were deemed by the authors to have caused a clinical loss of accommodation, and had a substantial effect on pupillary dilation, causing associated symptoms.

1.3.5.2 Pirenzepine

Pirenzepine, a relatively selective M1-antagonist, has been less widely explored. Tan *et al.,* (2005) evaluated the efficacy of 2% pirenzepine on 353 myopic 6 to 12 year old children. Each was assigned into one of three groups, either 2% pirenzepine gel twice daily, once daily or a placebo was given. Myopia progression after one year was 0.47 D, 0.70 D and 0.84 D respectively.

Siatkowski *et al.,* (2008) evaluated the efficacy of 2% pirenzepine gel. The 174 participants, aged between 8 and 12 years, were assigned either 2% pirenzepine gel or a placebo. After one year the pirenzepine group were found to have progressed by 0.26 D compared with the placebo group who became 0.53 D more myopic. At the 2 year point, the pirenzepine group had a mean increase of 0.58 D and 0.99 D for the placebo group. The 2 year results were taken from just 84 participants since the study was designed as a 1 year study and only a small number of the original

cohort agreed to continue for a second year. The majority of participants who returned were using the pirenzepine gel (n= 53, placebo = 31).

No further studies on the use of pirenzepine have been conducted and this may suggest that drug manufacturers have little interest in pursuing this intervention any further.

1.3.5.3 7-methylxanthine

7-methylxanthine, a caffeine metabolite, has recently been considered as an intervention for myopia. Following successful animal studies (Cui *et al.,* 2011) a 36 month pilot study was carried out in Denmark. The 68 myopic participants were allocated either an oral tablet of 7-methylxanthine or a placebo tablet, for the first 12 months, followed by a second 12 month period where all participants received the 7-methylxanthine tablets. Treatment was then stopped. At 24 months the group who had used the drug throughout the trial had myopia progression of 0.627 (±0.329) D whereas those who had used it only for the first 12 months progressed by 0.844 (±0.450) D. The 36 month assessment showed that myopia progression rate had only slowed during the time they were being treated with the drug. Notably, 7-methylxanthine is described as being free from side-effects although, it has not been tested in this capacity for any significant length of time (Trier *et al.,* 2008; Holden *et al.,* 2014). The drug is thought, from animal studies, to help regulate scleral expansion by altering the collagen fibrils.

1.3.6 Behavioural, combined interventions and patient identification

As discussed in section 1.2.4 there is now substantial evidence that time spent outdoors has a protective effect against myopia development (Jones *et al.,* 2007; Rose, Morgan, Ip *et al.,* 2008; Wu *et al.,* 2013; Jones-Jordan *et al.,* 2012; He *et al*., 2015). Other behavioural approaches have shown less promise such as vision training (Allen *et al.,* 2013) and the Bates Method which aimed to reduce habitual stress of the eyes using a series of techniques (Elliott, 2013). Near work (see section 1.2.3) was once a popular theory to explain increased levels of myopia, however only fairly weak associations have been made in recent years (Mutti *et al.,* 2002; Saw *et al.,* 2002; Morgan and Rose, 2005; Rose, Morgan, Smith *et al.,* 2008).

The studies in this section have shown myopic children would benefit from intervention as early as possible while myopia levels are still relatively low. Predicting which children are at risk of myopia, particularly high myopia, would be extremely valuable (see section 1.2.5).

Factors which increase the likelihood of myopia lay in family history, ethnicity, near work, time spent outdoors and from early (pre myopic) ocular changes in the eye such as increased axial length, peripheral refraction and central refraction at age 6 years. While individually many of the current techniques to limit progression of myopia have shown encouraging success, it is likely that a combination of current thinking or further evolution of theories will ultimately become commonplace treatments, and perhaps cures, for myopia.

1.4 Pupils

1.4.1 Pupil size and contact lenses

Pupil size can be important for certain myopia interventions such as dual or multi-focal contact lenses. The dual focus lens used in the Anstice and Phillips (2011) study contained a central correction zone, encircled with alternating treatment and correcting zones. The correction zones optical power matched that of the refractive error, while the treatment zones produced 2.00 D of myopic retinal defocus simultaneously. This coupling was intended to provide good visual acuity together with constant myopic defocus in both distance and near viewing. The zone parameters were selected based on Winn *et al.,* (1994) pupil data taking in to account age and varying light levels, however the participants of the study were aged 17 to 83 years and not children. The design aims were to make the central correction zone as large as possible thus encouraging accommodation and facilitating good visual acuity. This would still present some level of treatment zone area during near work. Additionally, the lens aimed to have equal areas of both treatment and control zones as the pupil enlarged (Anstice and Phillips, 2011).

1.4.2 Pupils, accommodation and the near pupil response

It is well documented that pupil size decreases during accommodation (Loewenfeld, 1999; Atchison and Smith, 2000; Zinn, 1972). To view a near object there are three key processes that take place: the eyes adduct to converge the visual axes and keep the image on the corresponding areas of the retina; accommodation occurs to focus the eye by changing the curvature of the crystalline lens; and the pupils constrict with the resulting miosis increasing depth of focus in a similar way to a pinhole camera

(Loewenfeld, 1999; Atchison and Smith, 2000; Rabbetts, 2007; Levin *et al.,* 2011; Zinn, 1972). These events are not tied together, rather they are thought to be simply associated and that any one of the three could be absent without effecting the other two (Levin *et al.,* 2011; Loewenfeld, 1999).

1.4.3 Pupil innervation

Pupil size is regulated by sympathetic and parasympathetic nerves, altered by the dilator and sphincter muscles in the iris working as antagonists. Constriction of the pupil occurs when the iris sphincter muscle, which is innervated by the Edinger-Westphal nucleus, contracts (Levin *et al.,* 2011; Loewenfeld, 1999). In addition to any accommodative changes, many other factors can effect pupil size including level of illumination, age, medication and pathology (Zinn, 1972; Loewenfeld, 1999).

1.4.4 Pupil size, age and illumination

Pupil diameter decreases with increasing age and also with higher levels of illumination (Winn *et al.,* 1994; Levin *et al.,* 2011; Loewenfeld, 1999; Birren *et al.,* 1950) causing much variability in size. Range of pupil diameter can approximate from a minimum of 2 mm up to a maximum of 8 mm (Atchison and Smith, 2000). In a study measuring child pupil diameter, MacLachlan and Howland (2002) photographed 1311 participants aged one month to 19 years old. The participants were placed under 300 lux ambient lighting for 5 minutes followed by 1 minute in mesopic lighting (15.9 ±0.5 lux) conditions after which time they were photographed from 1.5 m away using a flash powered isotropic photorefractor technique. The results for male participants were found to range from 5.77 (±1.00) mm at mean age 0.9 years to 7.53 (±0.90) mm at mean age 18.9 years. The pupils of the female

participants ranged from 5.55 (±1.12) mm at mean age 0.6 years to 7.45 (±0.67) mm at the peak mean age of 16.5 years after this age the numbers fell to 6.82 (±0.86) mm for the eldest group with a mean age of 18.8 years.

1.4.5 Mesopic pupil size at near

In a study of 39 participants aged 5 to 49 years (Schaeffel *et al.,* 1993) found little or no pupil constriction at near in child participants to either a 4 D or a 10 D target. Despite finding pupillary responses highly variable among participants, they also found a correlation (p=<0.01) with refractive error, showing that myopic participants with full refractive correction had weaker pupillary responses when compared with emmetropes and hyperopes. Wilhelm *et al.,* (1993) described a similar finding when measuring accommodation and near pupil response on 64 participants aged 5 to 55 years. The participants under 20 years of age exhibited smaller pupillary constriction than the older participants. The authors attributed this to age related changes to the crystalline lens and supranuclear control. In a more recent study Gislen *et al.,* (2008) compared children (9 to 10 years) with young adults (22 to 26 years) using accommodative stimulus of 4 D and 7 D at both 5 and 100 lux. They also found statistically significant (p>0.05) less pupil constriction in the 7 D stimulus at 5 lux, however, the rest of their data did not support this finding. The authors noted that the groups may differ further than they were able to explore due to limitations with instrumentation. They were unable to examine any patients with pupils smaller than 3 mm, and therefore some participants, mainly adults, were excluded. The 7 D at 100 lux and 4 D at both luminance levels gave variable data. This is a similar finding to Kasthurirangan and Glasser (2006) who assessed pupil response and dynamic accommodation using step stimuli of 1 D to 6 D in 66 participants aged 14 to 45 years.

They observed either no significant change with age (at 5 D), or a slight reduction (at 2 D) in near pupil constriction linearly with age. A binocular measurement system was used in all 3 of these studies with variation in target choice and accommodation control techniques.

Knowledge of pupil size can be important for certain myopia control interventions such as dual or multi-focal contact lenses that rely on having a pupil diameter large enough to allow access to the peripheral retina. Effective techniques to measure pupil size in children during their routine and regular state would be of most use.

1.5 Summary

It is evident that there are many unanswered questions regarding the aetiology of myopia and the mechanisms responsible for the control of eye growth. Myopia prevalence is increasing worldwide and has reached highly substantial figures particularly in East Asian countries (Pan *et al*., 2012; Smith, 2013; Lin *et al*., 1999). Myopia, particularly in higher levels, increases the possibility of a person developing an associated pathology in later life, such as chorio-retinal abnormalities, cataract and glaucoma (Saw *et al*., 2005). Risk factors for myopia development and progression are multi-factorial, influenced by genetics, behaviour and the environment (Mutti *et al*., 1996; Schaeffel *et al*., 2003; Radhakrishnan, 2008).

Given the high prevalence of myopia there is now an increased interest in exploring ways to slow or halt myopia progression. Ultimately, by better understanding the mechanism which drives myopia, it may be possible to prevent myopia from developing in the first instance.

There has been much research to suggest that myopia typically develops around 8 years of age (Walline *et al.,* 2007; Blum *et al.,* 1959; Goss, 1987) with the rate of growth slowing in early teenage years (Thorn *et al.,* 2005). Myopia that develops in this age group are commonly referred to as youth-onset, juvenile onset or school age myopias and are the focus of this thesis.

A range of interventions designed to prevent or slow the progression of myopia have been trialled in various research studies (Anstice and Phillips, 2011; Gwiazda *et al.,* 2003; COMET2, 2011; Sankaridurg *et al.,* 2010; Sankaridurg, *et al.,* 2011; Lam *et al.,* 2014; Cho and Cheung, 2012; Chia *et al.,* 2012; Trier *et al.,* 2008). Recent studies with animals have demonstrated a protective effect of light on myopia development (McCarthy *et al*., 2006; Ashby *et al*., 2009; Ashby and Schaeffel, 2010; Smith *et al*., 2012) using varying levels of laboratory or auxiliary lighting. Additionally, recent research with children indicated that those who spend the most time in outdoor activity have the least likelihood of developing myopia (Jones *et al*., 2007; Rose, Morgan, Ip *et al*., 2008; He *et al.,* 2015). Further research is required to explore whether artificial light could be adapted to protect against myopia progression in children. Optical interventions have been widely explored and include varying designs of soft contact lenses, rigid gas permeable contact lenses and spectacles (Anstice and Phillips, 2011; Sankaridurg *et al.,* 2011; Cho and Cheung, 2012; Hiroaka *et al*., 2012; Leung and Brown, 1999; Gwiazda *et al.,* 2003; Sankaridurg *et al.,* 2010). Many studies have shown a successful reduction in myopia progression and such techniques have been generally well received by children due to the ease of which they can be used. Pharmaceutical interventions have demonstrated a reduction in the progression of myopia (Chua *et al*., 2006; Chia *et al*., 2012; Trier *et al*., 2008). A

recent study indicated that, in low doses, atropine can be highly effective in slowing myopia progression with a very low risk of toxicity (Chia *et al*., 2012).

Associations have been made between lag of accommodation during near work and the development and progression of myopia (Gwiazda *et al*., 1993; Fulk *et al*., 2000; Cheng *et al*., 2011). Interventions to reduce the lag of accommodation have shown statistical effectiveness in reducing myopia progression (Gwiazda *et al*., 1993; Cheng *et al*., 2011). The original hypothesis to reduce near accommodative lag meant that the participant viewed, at near, through a progressive addition section of a lens (Gwiazda *et al.,* 2003; Gwiazda *et al*., 2004). The resultant defocus effect on the superior retina may give an insight into the mechanism by which this intervention effected change in myopia progression (Berntsen *et al*., 2013).

Many of the current interventions utilise peripheral defocus manipulation. Research models of myopia have revealed that eye growth may be manipulated by the environment (Smith and Hung, 1999). A minus lens in spectacles or a contact lens would give clear central vision while inducing a simultaneous hyperopic defocus, in the periphery of the retina. This peripheral hyperopic defocus is thought to stimulate the eye to elongate and increase levels of myopia (Schaeffel *et al*., 1988; Smith and Hung, 1999; Flitcroft, 2012; Smith, 2013; Berntsen *et al*., 2013).

Many studies have indicated that children and young adults can proficiently wear contact lenses from 8 years of age (Sankaridurg *et al*., 2011; Walline *et al.,* 2004; Jones-Jordan *et al.,* 2010; Chalmers *et al.,* 2011) and experience an improved quality of life when compared with wearing spectacles (Rah *et al.,* 2010).

Contact lenses with more than one focus were originally designed for presbyopic use. In recent years novel designs of contact lenses have been developed for myopia control. The dual focus soft lens described by Anstice and Phillips (2011) was designed specifically as a treatment to limit the progression of myopia. The lens has a central zone which corrects the refractive error and concentric treatment zones providing simultaneous peripheral myopic defocus for both distance and near viewing. The findings of this study indicate that continuous myopic defocus with simultaneous clear images can act to slow the progression of myopia in children (Anstice and Phillips, 2011).

The aims of this thesis are to determine the efficacy of a dual focus contact lens on myopia progression in a group of myopic UK children, to evaluate the role of accommodative lag and to assess the impact of time spent outdoors on myopia progression. In addition, to assess pupil size and peripheral refractive error change over an 18 month period for the same group of children. This thesis intends to provide further insight into aspects of myopia control.

2. PARTICIPANTS, INSTRUMENTATION AND METHODS

There are five experimental aspects considered in this thesis. The child participants took part in each of the five with a group of young adults included for comparison purposes in one experimental chapter (Chapter 6). Details of the participants, instrumentation and the methods used in this research will be described in this chapter.

2.1 Participants

Participants for the myopia intervention study were children aged between 8 and 12 years of age. There has been much research to suggest that myopia typically develops around 8 years of age (Walline *et al.,* 2007; Blum *et al.,* 1959; Goss, 1987) with the rate of growth slowing in early teenage years (Thorn *et al.,* 2005). Research also shows that this age group are proficient at wearing contact lenses (Anstice and Phillips, 2011; Walline *et al.*, 2004; Walline *et al.,* 2008; Jones-Jordan *et al.,* 2010).

The children were recruited over a 12 month period, joining the study at different points in time. Data are provided for the 27 children who completed the 18 month visit and the 25 participants who had reached the 24 month visit at the time of writing this thesis. Therefore, where possible, partial-cohort 24 month data are also included. The young adult participants (aged between 19 and 24 years) were recruited from the Aston University undergraduate Optometry population.

2.1.1 Child participants

Each participant was allocated a study number and was assigned to one of two age groups, either 8 to 10 years or 11 to 12 years. The children were then randomly

allocated to wear either a novel dual focus soft contact lens or a single vision soft contact lens. To ensure the contact lenses were the principal form of vision correction, the participants were advised of a wearing schedule of 10 to 15 hours per day, 6 to 7 days per week, for the 3 year duration of the study.

2.1.1.1 Recruitment of participants

Over 100 children were screened for suitability for inclusion; see Appendix 1 for full study inclusion/exclusion criteria. In summary, the children were required to be aged between 8 and 12 years, have -0.75 to -4.00 D of myopia, -0.75 D or less of astigmatism and 1.00 D or less of anisometropia. The best corrected vision was +0.1 logMAR or better in both eyes. The children needed to be in good health, with no eye conditions and possessing their own usable and functioning spectacles. There could be no previous myopia control treatment or contact lens wear prior to enrolment.

Aston University staff were informed of the recruitment in person, by newsletter and University social media. Optometry practices in the local area were contacted by telephone or mail and where possible visited in person to inform them of the study. Posters detailing the study were distributed (see Appendix 2) and a parent/guardian information summary was also supplied to any interested families (see Appendix 3). As recruitment progressed, there were recommendations from friends and families of children already enrolled. To increase recruitment figures further, a radio advert was used. This route was particularly successful, and over 50% of the children ultimately enrolled on the study were sourced following the ‘Birmingham Free Radio’

advert, which ran for 3 weeks. Recruitment route for the 28 children dispensed contact lenses is detailed in Table 2.1.

Recruitment route	Number of children enrolled
Aston University newsletter/social media	3
Aston University optometrist referral	6
Friends and family of enrolled children	5
Radio advertisement	14

Table 2.1 Breakdown of recruitment route for children enrolled (n=28).

A total of 105 children were screened for the study (see Table 2.2), 34 children completed a full baseline visit, of these, 29 children were enrolled and 28 were dispensed contact lenses at a later visit. One child was unable to put a contact lens in either eye and was therefore not enrolled onto the study. One child was lost to follow up, just prior to the 12 month visit. In addition, the participants had staggered dispense dates and therefore the number of participants varies between the 12 month and 24 month data.

Status		n=105
Enrolled	Dispensed	28
	Unable to complete insertion & removal	1
Failed to meet inclusion/exclusion criteria	Hyperopia	33
	Astigmatism	12
	High myopia	6
	Low myopia	5
	Eye condition	14
	Medication	1
	Medical condition	2
	Already wearing contact lenses	3

Table 2.2 Breakdown of screening outcome using inclusion and exclusion criteria, (n=105).

Children were trained in insertion and removal techniques for soft contact lenses. The children were dispensed their contact lenses, after having successfully inserted and removed their lenses 3 times in each eye. They were given a booklet to remind them of what they had learnt in note-form and pictures (see Appendix 4), and their parents were given written instructions with full details (see Appendix 5). The children and their parents were given a visit schedule (see Appendix 6) detailing the range of dates within which visits should be carried out.

2.1.1.2 Age and ethnicity

The participants were split into two age groups either 8 to 10 years or 11 to 12 years based on their age at enrolment. Ethnic differences were not directly investigated

however ethnic background of the children was recorded. The age and ethnic breakdown of the children enrolled was as follows in Table 2.3.

Age group	Ethnicity
8 to 10 years (n=17)	Asian British = 6 White = 11
11 to 12 years (n=11)	Asian British = 2 White = 6 Black British = 1 Multiple Ethnic Group = 2

Table 2.3 Breakdown of age group and ethnicity for children dispensed contact lenses (n=28).

The 2011 Census ethnicity classification system (Office for National Statistics, 2012) was utilised, with ethnicity categorised on the basis of self-identification by the parent or parents of the participant during baseline visit interview. Where ethnicity differed between the participant's two parents, they were categorised as 'multiple ethnic group'.

2.1.1.3 Informed consent

An assent form was given to the child participant and a consent form was given to the parents (Appendix 7 and 8). At the baseline appointment both the child and parent confirmed that the forms had been read, understood and signed. The forms were then signed by the investigator and copies were given to the child and parent for them to keep.

2.1.1.4 Questionnaire

Each participant and parent were given a questionnaire to complete at every scheduled visit. An example of each is shown in Appendix 9 and 10. The questions were intended to help assess for any problems the child or parent was facing and to explore lifestyle behaviours such as time spent completing homework or playing computer games.

2.1.1.5 Target sample size

Sample size for the study was based on a minimum treatment effect estimated at 0.25 D, per year, reduction in mean myopia progression, in the test group when compared to the control group. Sample size calculation for an independent samples t-test with a two-tailed α-level of 5%, a 90% power level and a standard deviation of 0.50 D, based on findings from comparable contact lens studies (Anstice and Phillips, 2011, Sankaridurg *et al*., 2011; Walline, Greiner *et al*., 2013; Lam *et al*., 2014) indicated that 168 children were required to complete the study. The expected attrition rate for the 3 year study was 14% per year based on similar contact lens studies (Cho and Cheung, 2012; Lam *et al*., 2014). A total sample size of approximately 265 participants across all sites, were required to achieve 168 participants completing the study (approximately 84 in each contact lens group) and to demonstrate statistical significance.

2.1.1.6 Participant number variation

The number of child participants included in the analyses varied for each experimental chapter. The children tired quickly in the initial few visits, whilst learning the research process and therefore, occasionally, not all data could be collected.

Where a comparison between two visits was made and data were not available for both, the participant was not included. One child was lost to follow-up before the 12 month visit and one child left the study prior to the 24 month visit due to the commencement of a medication that fell under the exclusion criteria (see Appendix 1).

2.1.2 Young adult participants

For the purposes of comparison, in Chapter 6, an additional group of 40 myopic, young adults, aged between 19 and 24 years, were recruited from the Aston University student population. The young adults were all myopic, wearing full optical correction and had a visual acuity of 0.0 logMAR or better. Written informed consent was obtained from each participant after they had received a verbal and written explanation (Appendix 11) of the investigational measurements that were to be taken.

2.1.2.1 Ethical considerations

For all investigations within this thesis, approval was obtained from Aston University Ethics Committee (Appendix 12) and all investigations were conducted in accordance with the tenets of the Declaration of Helsinki. All data were kept securely and confidentiality was upheld at all times. Participants were seen by a UK trained and registered optometrist at all visits.

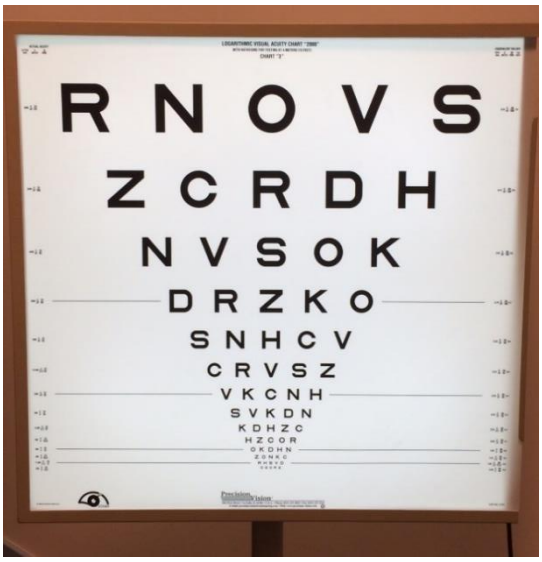
2.2 Instrumentation

2.2.1 Introduction

The experiments presented within this thesis investigated several parameters of the eye in children with myopia. A number of instruments were used. This chapter outlines the main details of the instruments and methods used in this thesis. Details of experimental design specific to a single experiment are described in that individual chapter.

2.2.2 Vision and visual acuity

Vision and visual acuity were measured monocularly for both distance and near. A backlit E.T.D.R.S. (Early Treatment Diabetic Retinopathy Study) 4 m chart (Precision Vision, Illinois, United States) was used to measure distance visual acuity and a hand held E.T.D.R.S. near point acuity chart (Precision Vision, Illinois, United States) at 40 cm was used for near acuity. Results were recorded using a logMAR (logarithm for the minimum angle of resolution) notation as used in comparable child studies (Logan *et al.,* 2011; O'Donoghue *et al*., 2010). The ETDRS chart was based on the 1982 modified Bailey-Lovie Chart and has many advantages over the Snellen chart such as uniformity in numbers per line and spacing between letters (Kaiser, 2009). The chart has a variable collection of optotypes that can be interchanged to minimise a patient learning effect. The distance chart was backlit and set to a luminance of 85 cd/m^2 (see Figure 2.1).



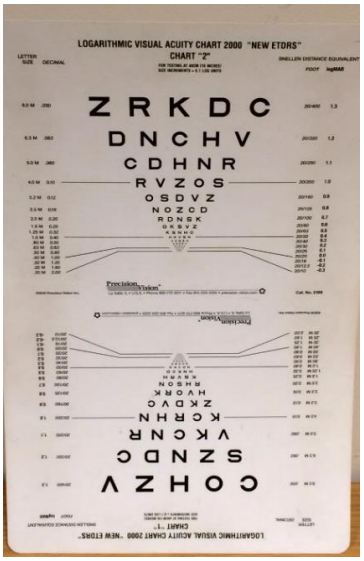


Figure 2.1 E.T.D.R.S 4 m and near vision charts.

Room illumination was measured in lux, a unit widely utilised in studies of pupil size and reaction (Schallenberg *et al.,* 2010; Bradley *et al.,* 2011; Gislen *et al.,* 2008; Kurz *et al.,* 2004). Photopic room conditions were 447 lux and mesopic 12.5 lux measured by Chauvin Arnoux CA810 Lux Meter (Chauvin Arnoux Group, Dewsbury, England), see Figure 2.2. The mesopic range is defined in terms of luminance, the Commission Internationale de L'Eclairage (CIE) Technical Report 191:2010 defines the range between 0.005cd/m^2 to 5 cd/m^2 (CIE, 2010). While not specified in academic sources, an illuminance of 12.5 lux would fall within the mesopic range, as even 100% reflectance would give less than 4 cd/m^2, the 447 lux used was anticipated to be a photopic condition as only viewing a material such as black paper would give less than 5 cd/m^2. (T. Goodman, Principal Research Scientist, National Physical Laboratory, Teddington, United Kingdom, personal communication, 25th August, 2016). Room lighting levels were monitored each study visit week.

Figure 2.2 Chauvin Arnoux CA810 Lux Meter

2.2.3 Shin-Nippon autorefraction

The Shin-Nippon NVision-K 5001 (Shin-Nippon, Japan), also known as the Grand Seiko WR-5100K autorefractor, is a binocular, open-view autorefractor. It shares a comparable technical specification to the older Shin-Nippon SRW-5000 (Davies *et al.,* 2003) which has been shown to produce highly repeatable results in both adults and children (Chat and Edwards, 2001; Mallen *et al.,* 2001).

A ring target of infrared light is projected onto the participant's retina and the resultant reflection is then employed, by a moving lens, to focus the instrument (Davies *et al.,* 2003; Cleary *et al.,* 2009). The NVision-K 5001 differs to the SRW-5000 with the addition of three infrared arcs of light which have a reduced radius of curvature compared to the measurement ring, allowing effective measurement of smaller pupil size ≥2.3 mm (Davies *et al.,* 2003). The information is digitally analysed in multiple

meridians to ultimately derive a sphere, cylinder and axis to form the refractive prescription data (Davies *et al.,* 2003; Cleary *et al.,* 2009; Tang *et al.,* 2014).

The NVision-K 5001 is reported to have a measuring range of ±22 D sphere and ±10 D cylinder in 0.12 D steps of power and cylindrical axis can be measured in increments of 1° (Davies *et al.,* 2003). The open-view design of this instrument reduces the effects of proximal accommodation and gives the investigator the flexibility to use a variety of real-world targets and variable viewing distances (Davies *et al.,* 2003; Tang *et al.,* 2014).

Figure 2.3 External view of Shin-Nippon NVision-K 5001

Davies *et al.,* (2003) clinically evaluated the Shin-Nippon NVision-K 5001 for repeatability and validity of refractive error compared with subjective refraction. Subjective refraction and autorefraction findings were compared for both eyes from 98 subjects aged 23.2 ±7.4 years. Autorefraction measurement was found to be similar to that found by subjective refraction (p>0.67) with a difference of 0.14 (±0.35) D. The autorefractor was tested over a large refractive error range (-8.25 to +7.25 D) and found to be both accurate and repeatable.

Cleary *et al.,* (2009) compared the accuracy of the Shin-Nippon NVision-K 5001 with a subjective refraction. Two eyes of 50 participants were autorefracted after completion of a subjective refraction. Agreement was then calculated using sphere, mean sphere equivalent and the cylindrical vectors ultimately showing good agreement. Cleary *et al.,* (2009) found a trend towards a smaller level of bias than Davies *et al.,* (2003) and concluded this may be due to the addition of a Badal lens used in their study. The authors also suggested that the Shin-Nippon NVision-K 5001 would be a useful tool for an objective measurement of accommodation due to the ability to detect small accommodative changes.

In the current study, MSE was used, where stated, to represent refractive error and calculated as sphere plus half the negative cylinder.

2.2.3.1 Lag of accommodation

Typically, when a person views a near target they under-accommodate i.e. they use insufficient accommodation to bring an object into focus and this is termed a 'lag of accommodation' (Gwiazda *et al.,* 2004). Associations have been made between

larger lags of accommodation at 3.00 D and the development and progression of myopia (Gwiazda *et al*., 1993; Gwiazda *et al*., 1995; Gwiazda *et al*., 1999).

The required accommodative response to a 33 cm target should be 3.00 D, the accommodative response was then compared with the 3.00 D stimulus. Where the exerted accommodative effort fell short of the accommodative demand, the difference was deemed the 'lag of accommodation'. This calculated figure was then compared amongst the participants in relation to their myopia progression and lens type.

With either the mean sphere equivalent of their spectacle refractive error in a trial frame or their allocated contact lenses, 10 measurements of the residual refractive error were taken while the child viewed a 4 m target and also while the child accommodated to a target at 33 cm, using a Shin-Nippon NVision-K 5001 autorefractor. The targets used were +0.4 logMAR optotype at near and +0.7 logMAR optotype at distance. Accommodative response can be effectively measured using the dominant eye (Flitcroft and Morley, 1997, Ibi, 1997) and therefore the child was asked to view the targets binocularly, however, the lag measurement was taken from their dominant eye.

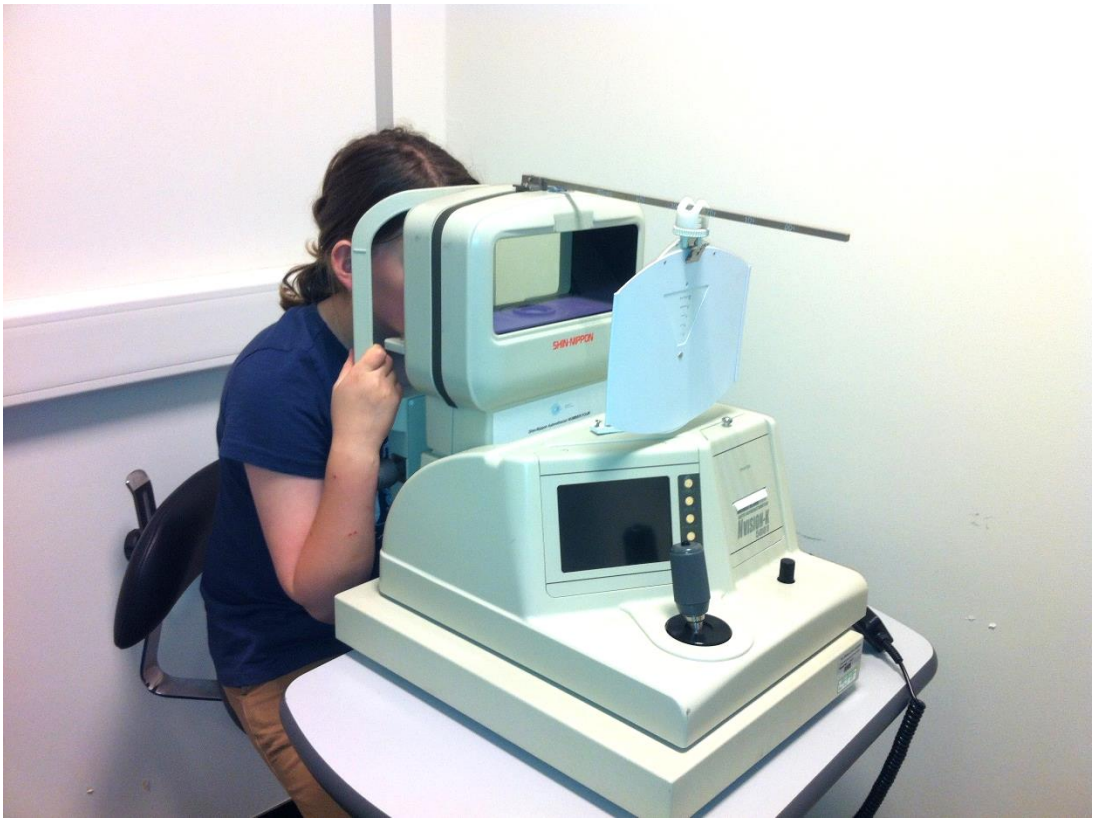


Figure 2.4 Child participant at Shin-Nippon NVision-K 5001 autorefractor.

2.2.3.2 Peripheral measurements

Peripheral refraction measurements were taken using a specially designed peripheral arm which was positioned over the Shin-Nippon autorefractor. The Shin-Nippon autorefractor has been widely used to assess peripheral refraction in children (Schmid, 2011; Mutti *et al.,* 2007; Lee and Cho, 2013; Kang and Swarbrick, 2011; Chen *et al.,* 2010) and has demonstrated good agreement with similar instruments used to obtain peripheral refraction measurements (Atchison, 2003). In the current study the participant fixated a Maltese cross through a +5 D Badal lens (see Figure

2.5 and Figure 2.6). Measurements were taken from the right eye centrally and horizontally at 10°, 20°, 30° to fixation, both nasally and temporally.

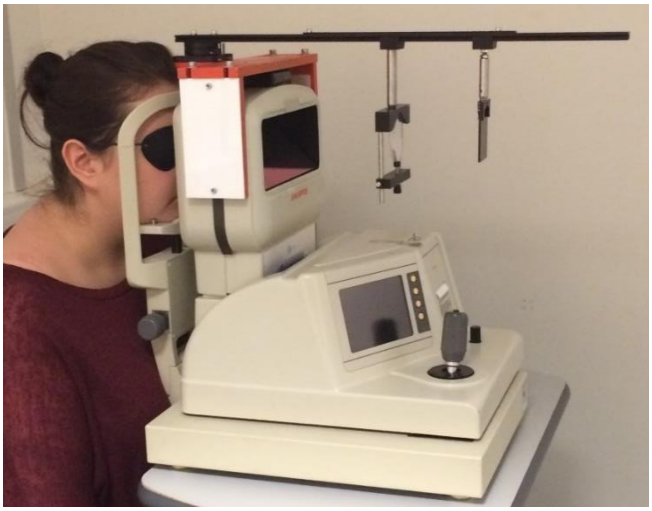


Figure 2.5 Shin-Nippon NVision-K 5001 with peripheral arm, Badal Lens and Maltese cross.

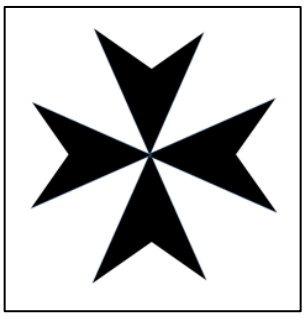


Figure 2.6 A Maltese cross example target

2.2.3.3 The +5.00 Badal lens

A Badal lens system, introduced in 1876 and named after the French Ophthalmologist Jules Badal was used for peripheral refraction data collection. The posterior focal plane of the plus lens in the system is placed coincident with the

anterior focal plane of the eye which results in a constant image size (Rabbetts, 2007). The +5.00 D lens was positioned 20 cm from the Maltese cross, to provide a fixation target while stimulating 0.00 D of accommodation (Atchison *et al.,* 1995; Clark *et al.,* 2015; Rabbetts, 2007).

2.2.3.4 Autorefraction methodology

The Shin-Nippon NVision-K 5001 was used to measure the participant's distant refractive error along with accommodative lag and off-axis measurements of refraction. Where distance and near measurements were to be compared, the targets used were +0.4 logMAR optotype at near, to encourage active accommodation and the slightly larger +0.7 logMAR optotype at distance, to be less likely to stimulate accommodation while providing an effective fixation target. All measurements are summarised in the following table.

Data measurement	Visual status	Distances	Target
DISTANCE REFRACTIVE ERROR			
Distance refractive error	Unaided vision	4 m	1 line higher than best visual acuity on distant EDTRS chart
Distance refractive error with cycloplegia	Unaided vision 25 minutes after Tropicamide and Proxymetacaine Hydrochloride	4 m	1 line higher than best visual acuity on distant EDTRS chart
LAG OF ACCOMMODATION			
Single vision spectacle (equivalent), dominant eye lag of accommodation	Mean sphere equivalent in trial frame	33 cm and 4 m	Distant: EDTRS +0.7 logMAR Near: EDTRS +0.4 logMAR
Contact lens dominant eye lag of accommodation	Contact lenses in situ	33 cm and 4 m	Distant: EDTRS +0.7 logMAR Near: EDTRS +0.4 logMAR
PERIPHERAL MEASUREMENTS			
Right eye horizontal peripheral measurements	Unaided vision	Central, 10°, 20°, 30° nasally and 10°, 20°, 30° temporally	Maltese cross 20 cm from +5 D Badal lens on a peripheral arm

Table 2.4 Summary of autorefraction measurements

2.2.3.5 Cycloplegia

Distant refractive error was measured by autorefractor every 6 months for each participant. Measurements of refractive error under cycloplegia were taken annually. Cycloplegia was instilled using the following regime, 1 drop of 0.5% Proxymetacaine Hydrochloride, followed after one minute by 1 drop of 1% Tropicamide. If the child had dark irides then a further drop of Tropicamide was instilled into each eye. After 25 minutes, when the Tropicamide was at maximum effectiveness (Eperjesi and

Jones, 2005), the autorefraction measurement was taken. Proxymetacaine Hydrochloride, a local anaesthetic, given prior to a cycloplegic drug can reduce the stress and discomfort the cycloplegic drug may cause (Leat *et al.,* 1999; Shah *et al.,* 1997). In addition, the local anaesthetic may increase the cycloplegic drug absorption (Viner, 2004). Tropicamide works more quickly and lasts less time than other muscarinic agents (Eperjesi and Jones, 2005) and was therefore seen as the least intrusive option for the participants on a longitudinal study. The child was asked to fixate the middle letter from a line above their best vision and 10 measurements were taken from each eye and averaged.

2.2.3.6 Ocular dominance

The 'hole in the card test' was used to determine ocular dominance. The child held a piece of card, with a hole in the centre, 3 cm by 3 cm, at a distance of approximately 30 cm. The investigator stood 6 m away and asked the child to view the investigator's nose through the hole. The investigator could then see which eye the child was using and this was documented as their dominant eye. Rosenbach in 1903, is thought to have first noted that the majority of individuals have a dominant eye (Kommerell *et al.,* 2003; Linke *et al.,* 2011). There are many techniques to assess for the preference (Walls, 1951; Coren and Kaplan, 1973; Porac and Coren, 1976; Kommerell *et al.,* 2003). The hole in the card test is one of the most widely used tests of dominance (Seijas *et al.,* 2007; Lopes-Ferreira *et al.,* 2013). It is a 'forced choice' test of sighting dominance which identifies the preferred eye for visual input and results in either a right eye or a left eye result (Porac and Coren, 1976; Cheng *et al.,* 2004; Seijas *et al.,* 2007; Linke *et al.,* 2011, Evans, 2001). The test was carried out twice to confirm

the result, had a finding differed, a 3rd attempt would have been performed to assign dominance.

2.2.4 Ocular biometry

2.2.4.1 IOLMaster

The IOLMaster 500 (Carl Zeiss Meditec AG, Jena, Germany) is a non-contact device which utilises partial coherence interferometry (PCI) to give biometric data for the eye (Santodomingo-Rubido *et al.,* 2002). The device was designed primarily for intra-ocular lens biometry in cataract surgery, however, it is also a useful tool in the study of myopia (Santodomingo-Rubido *et al.,* 2002). This model, the successor to the IOLMaster, has enhanced signal processing, thus allowing measurement of a greater number of eyes with severe cataract that were previously unquantifiable (Hirnschall, 2011).

Historically, prior to the use of PCI, an axial length measurement was gained through the use of ultrasound which required the patient to be given an anaesthetic. There was an increased possibility of corneal abrasion and over applanation (Lam *et al.,* 2001; Santodomingo-Rubido *et al.,* 2002; Kimura *et al.,* 2007). The lack of anaesthesia, any corneal contact and superior accuracy makes the IOLMaster a good choice of device for use with children (Hussin *et al.,* 2006; Kimura *et al.,* 2007).

To gain an axial length measurement the child was directed to place their forehead and chin on the rest and to fixate on the light within the device while 10 measurements were taken for each eye. A dual beam of infrared laser light (λ =780nm) is created after passing through a beam splitter and via two mirrors, one fixed and the other

moving at a constant speed. The beams enter the eye and reflect off the anterior cornea and retinal pigment epithelium, resulting in a total of 4 beams. The interference patterns of the reflected beams are detected by the photodetector and analysed by the machine to calculate an axial length (Drexler *et al.,* 1998; Santodomingo-Rubido *et al.,* 2002). A Gullstrand model eye is used as the basis for the calculations (Atchison *et al.,* 2004).

Ultra-sound analysis of axial length measures from the cornea to the internal limiting membrane whereas the IOL Master reaches to the retinal pigment epithelial layer. This difference has been adjusted for in the final measurement by the manufacturer (Lam *et al.,* 2001). As a safety precaution with the use of a laser, there is a maximum limit of 20 axial length measurements, per eye, per day permitted by the operating system (Lam *et al.,* 2001).

Figure 2.7 Operating principal of IOLMaster. Reproduced from British Journal of Ophthalmology, Santodomingo-Rubido, J., Mallen, E. A., Gilmartin, B. and Wolffsohn, J. S., Vol. 86, pages 458-462, Copyright © 2002 with permission from BMJ Publishing Group Limited.

The IOL Master has shown good repeatability and accuracy in measuring axial length in both adults and children (Santodomingo-Rubido *et al.,* 2002; Lam *et al.,* 2001; Kimura *et al.,* 2007; Hussin *et al.,* 2006; Carkeet *et al.,* 2004).

Kimura *et al.,* (2007), as part of a myopia control trial, assessed the IOL Master test-retest repeatability of axial length measurements on 95 children aged 7 to 13 years with a mean refractive error of -4.37 (±1.43) D. Axial length measurements were taken 3 times, the mean calculated and the process was then repeated 5 minutes later. Comparison of the distribution of differences showed a high repeatability of ±0.05 mm that was unaffected by age or refractive error (cycloplegic autorefraction).

Hussin *et al.,* (2006) compared the validity and repeatability of the IOL Master versus an A-scan ultrasound (Alcon) measurement of axial length in 20 children with a mean age of 11.4 years. Very close agreement was found between the two techniques and in contrast to Lam *et al.,* (2001) the IOL Master was found to measure slightly longer (0.017 mm) than ultrasound, however, the difference was not statistically significant. Similarly, Carkeet *et al.,* (2004) compared the repeatability of the IOL Master and ultrasound scan (US 800, Nidek) for axial length in 179 children with a mean age of 10.6 (±0.8) years participating in a longitudinal myopia development study. The IOL Master showed better repeatability with axial length measurements than the ultrasound biometry and in agreement with Hussin *et al.,* (2006) and co-workers the IOL Master measured a slightly longer axial length (0.14 mm). These findings tally well with Santodomingo-Rubido *et al.,* (2002) who assessed the validity and repeatability of the IOL Master compared with A-scan applanation ultrasonography (Storz Omega). The 52 participants were aged 18 to 40 and had refractive errors

ranging from +7.0 D to -9.50 D. Axial length difference between the two devices was not significant (p=0.47) at 0.02 mm.

These findings differ to Lam *et al.,* (2001), who evaluated the accuracy and repeatability of the IOL Master compared with ultrasound biometry (Humphrey Instrument Inc.) on 26 participants with a mean age of 19.3 (±0.55) years and a mean spherical equivalent of -2.28 (±2.67) D. Axial length measurements were found to be repeatable and accurate however a little shorter at -0.099 mm compared with the ultrasound technique.

2.2.4.2 Pupillometer

The NeurOptics pupillometer (NeurOptics Incorporated, Irvine, California) is a digital, infrared, portable, hand-held device powered by a rechargeable battery (Schallenberg *et al.,* 2010; Martínez-Ricarte *et al.,* 2013). The device uses a digital camera with autofocus and is designed to be used at 12 mm working distance so that the patient may wear spectacles. Natural change in the pupil size does not affect the ultimate result as the system takes a video recording of the eye and captures multiple pupil positions over a 2 to 3 second scanning period to produce an average to ±0.1 mm accuracy (Michel *et al.,* 2006; Schallenberg *et al.,* 2010). The participant's eye can be observed on the device's Liquid Crystal Display (LCD) screen which facilitates the investigator to manually centre the pupil image (Michel *et al.,* 2006; Schallenberg *et al.,* 2010). The pupilllometer's software then calculates the mean pupil diameter and standard deviation using the largest pupil diameter detected from each image, eliminating outlying readings (Schallenberg *et al.,* 2010).

Pupil measurements of children and young adults in both photopic and scotopic environments at distance and near were taken for comparison purposes. Using a NeurOptics pupillometer the diameter of the participant's pupils were recorded. Three measurements at distance (4 m) and near (40 cm) were taken from each eye in Photopic (447 lux) and mesopic (12.5 lux) conditions. This pupillometer has shown good pupil symmetry (Boev *et al.,* 2005) and inter-observer agreement and repeatability (Schallenberg *et al.,* 2010).

Figure 2.8 NeurOptics Pupillometer

Figure 2.9 NeurOptics Pupillometer in use

Using two examiners, Schallenberg *et al.,* (2010) compared the NeurOptics device with two other pupillometers (Colvard and Procyon) in 92 healthy adult eyes at both 0.04 and 0.4 lux following dark adaptation for 2 minutes. Pupil diameters were largest with the NeurOptics pupillometer under both light settings. From infrared photography laboratory data, the authors expected a mean pupil diameter of approximately 7 mm for this study age group ranging from 18 to 45 years (average age 25.7) in lighting conditions less than 1 lux. The NeurOptics pupillometer was in closest agreement to the laboratory findings with 6.99 (±0.67) mm at 0.04 lux and 6.73 (±0.72) mm at 0.4 lux. The NeurOptics pupillometer also had the best inter-observer agreement for both light conditions however despite the manufacturer technical specification describing a measurement range varying from 1 mm to 9 mm pupil size, the authors noted that the device occasionally failed to measure large pupils (>8 mm) and those with dark irides due to difficulty in finding the pupil edge (Schallenberg *et al.,* 2010).

Michel *et al.,* (2006) compared the NeurOptics pupillometer with the Procyon device in 42 eyes of patients of an older age group with a mean age of 71 (±7.6) years. While a smaller cohort was used in this study, the repeatability and agreement was found to be very similar for both devices. The authors note a key difference between the two devices in that the NeurOptics pupillometer is a monocular device whereas the Procyon is binocular. Binocular measurements may better simulate real life condition (Kurz *et al.,* 2004) however this device shows good accuracy, is more time efficient and may be more economical (Michel *et al.,* 2006).

2.2.5 Behavioural data collection

To quantify time spent outdoors, data are commonly obtained from use of a questionnaire (Guggenheim *et al.,* 2012; Alvarez and Wildsoet, 2013; Dirani *et al.,* 2009; Guo *et al.,* 2013; Jones *et al.,* 2007; Jones-Jordan *et al.,* 2012; Rose, Morgan, Ip *et al.,* 2008). At 1 week, 1 month, 6 month, 12 month and 18 month visits the children were asked to estimate the amount of time they spent outdoors. An approximate figure, in hours and minutes, for both a standard weekday and a standard weekend day were discussed and noted, with both the child and parent deciding duration.

2.2.6 Analysis

Raw data was entered into an Excel spreadsheet (Microsoft Corporation, Washington, USA). Conventional parametric statistics were used throughout the thesis. Shapiro-Wilk's test of normality was utilised to check for normal distribution and box charts aided identification of the outliers discussed within the research chapters. The 'box' in the box chart represented the interquartile range with the whiskers indicating the lowest and highest values which were ≤ 1.5 times the interquartile range. The median of the data was portrayed with a line across the box and outliers (with values between 1.5 and 3 times the interquartile range) were depicted with a small circle. Multifactorial Analysis of Variance (ANOVA) were performed to assess for evidence of a more complex relationship. To determine if there was homogeneity of variances in the ANOVA analysis, a Levene's test of equality of variances was performed. All statistical analysis was carried out using IBM SPSS Statistics version 21 (SPSS Inc., Chicago). The mean of measurements

was calculated and utilised throughout due to the small variability in data and for comparison purposes with similar research studies.

3. EFFICACY OF DUAL FOCUS LENSES TO SLOW MYOPIA PROGRESSION

3.1 Introduction

Animal studies have shown that when a relatively myopic lens is placed in front of the eye, the focal point is moved behind the retina and it is thought to encourage axial elongation as the eye grows to a new far point. Conversely, when a relatively hyperopic lens is placed in front of the eye, the focal point is moved in front of the retina causing a myopic retinal defocus. This resultant myopic retinal defocus is believed to slow axial growth (see Figure 1.9) (Smith, 1998; Smith and Hung, 1999).

Benavente-Perez *et al*., (2014) assessed the effect of monocular bifocal centre plano contact lenses with -5.00 D or +5.00 D in the periphery, in marmosets. Two centre zone diameters were used, 3 mm and 1.5 mm. At the completion of the treatment, the animals who had worn the peripheral myopic lenses had longer and more myopic eyes than the animals who wore the hyperopic peripheral lenses. This research supports the theory that refractive state and eye growth can be influenced in animals by an alternation of peripheral retinal defocus.

A similar effect has also been shown in chick eyes, Liu and Wildsoet (2011) assessed the effects of 2-zone concentric lenses on refractive development and ocular growth in young chicks. A -5.00 D 3.5 mm central zone diameter lens with plano in the periphery induced -0.53 (±1.63) D. A plano 3.5 mm central zone diameter lens with -5.00 D in the periphery induced -2.86 (±2.24) D. For comparison purposes myopia was induced in the control group using a -5.00 single vision lens which resulted in -5.84 (±0.50) D at the end of the treatment period. In a later study, Liu and Wildsoet (2012) compared the effect of two further test lenses on young chicks. The first,

a -10.00 D 4.5 mm central zone diameter lens with -5.00 D in the periphery induced -6.08 (±1.18) D, whereas the second, a -5.00 D 4.5 mm central zone diameter lens with -10.00 D in the periphery induced -9.17 (±1.07) D. The single vision -10.00 D control lens induced -9.61 (±1.25) D of myopia. In each example, the eye growth and resultant refractive error responded to the peripheral power of the lenses with the relatively hyperopic peripheral lens power resulting in less myopia progression.

This response to peripheral blur has also been shown in monkey eyes, Arumugam *et al*., (2014) assessed the effect of a plano 2 mm centre zone diameter lens with alternating -3.00 D and plano concentric zones, on infant monkeys. The more anterior retinal image plane dominated the treatment effect and also supported the theory that imposed, simultaneous, relatively myopic defocus may be an effective method to limit the progression of myopia.

In children, single vision spectacles and contact lenses, the main strategies currently utilised to correct myopic refractive error, effectively correct central retinal blur. These traditional corrections are thought in some cases to additionally cause hyperopic defocus in the periphery (Schaeffel *et al.,* 1988; Smith and Hung, 1999; Flitcroft, 2012; Smith, Hung, Huang *et al.,* 2013). Animal studies suggest that this hyperopic peripheral blur stimulates further elongation of the eye, even in the absence of central blur (Schaeffel *et al.,* 1988; Smith and Hung, 1999; Smith, Hung, Huang *et al.,* 2013).

A contact lens designed with zones offering both standard central correction while simultaneously imposing myopic defocus may provide an effective solution to create myopic defocus in the periphery (Anstice and Phillips, 2011). The dual focus soft

contact lens described by Anstice and Phillips (2011) was designed specifically as an intervention to limit the progression of myopia in children. Alternating concentric zones correct central refractive error while simultaneously imposing +2 D addition of peripheral myopic defocus for both distance and near viewing. The 40 child participants, aged 11 to 14 years wore the test lens in one eye with a single vision distance lens in the other. After 10 months lens assignment was swapped between the eyes for a further 10 months. In the first period, the dual focus test eyes increased in myopia by -0.44 (±0.33) D versus the control eyes, which progressed -0.69 (±0.38) D. Axial length changes were corresponding with an increase of 0.11 (±0.09) mm and 0.22 (±0.10) mm respectively. Similar figures were found in the second period (Anstice and Phillips, 2011). It is thought that the peripheral myopic defocus induced by a dual focus lens may, therefore, reduce the progression of myopia compared to traditional single vision lenses.

The aim of the current study is to evaluate the effectiveness of bilaterally worn, dual focus contact lenses on myopia progression in children, when compared to single vision contact lenses, worn by a control group.

3.2 Methods

In this longitudinal, multi-centre study, 28 children participated at the UK site at Aston University, to evaluate the effectiveness of a dual focus contact lens on myopia progression, versus a single vision contact lens. Data from the UK arm of the study are described and reported in this thesis. See section 2.1 for full details of participants. The children, aged, between 8 and 12 years at baseline, were recruited locally to the study site and assessed for up to 2 years, comparing refractive error

and axial length changes. The study is ongoing to continue to assess the effectiveness of the lenses over a prolonged period of time.

3.2.1 Inclusion and exclusion criteria

The full study criteria are detailed in Appendix 1. The main points of the study are described here. For entry into the study, the children were required to be aged between 8 and 12 years, have bilateral myopia of -0.75 to -4.00 D, -0.75 D or less of astigmatism and less than 1 D of anisometropia. The best corrected vision requirements were +0.1 logMAR or better in both eyes. The children needed to be in good health, with no eye conditions and possessing their own usable and functioning spectacles. There could be no previous myopia control treatment or contact lens wear. A consent form for the parent and an assent form for the child had to be read, understood and signed (see Appendix 7 and 8 for parent and child consent/assent forms). The children and their parents agreed to adhere to both the visit schedule and contact lens wearing schedules.

3.2.2 Wearing schedule

For uniformity the children agreed to wear the contact lenses for a minimum of 10 hours a day (maximum 15 hours), at least 6 days a week, for the duration of the study and to notify the study investigators if they deviated from this schedule. The children were advised that they should not sleep in, wear for more than one day or shower/swim in their contact lenses.

3.2.3 Visit schedule

Following completion of the appropriate consent a 'Baseline' visit was carried out. If the participant was found to be eligible, a 'Dispense' visit was arranged for 1 to 7 days after the baseline visit. A suitable lens power was chosen at that visit and the child was taught how to insert and remove lenses, lens hygiene and safe lens wear. The child, where necessary, attended more than one visit to learn to safely and effectively use contact lenses and only when they were competent could they take them home. They were then seen as follows:

Visits	Date Range
1 week (7 days)	±2 days from dispense
1 month (30 days)	±4 days from dispense
6 months (180 days)	±7 days from dispense
12 months (360 days)	±14 days from dispense
18 months (540 days)	±21 days from dispense
24 months (720 days)	±30 days from dispense

Table 3.1 Study visits date range

3.2.4 Randomisation and masking

Each participant was allocated a subject number prior to being randomised. An eligible participant, one that had all of the inclusion criteria and none of the exclusion criteria, was then sequentially randomised into either the test or control group. The child was allocated to one of two age groups, either into the 8 to 10 year group or the 11 to 12 year group. As used in myopia studies with spectacle lenses (Fulk *et al.,* 2000; Gwiazda *et al.,* 2003; COMET2, 2011), a random permuted block design was

used. Randomisation is achieved by creating blocks containing equal numbers of participant arrangements. In order to ensure masking was maintained the participants were identified using their allocated number and lenses were labelled as either A or B and therefore not identifying the test or control lens to the participants or investigators.

3.2.5 Contact lens material and specification

The test lens and the control lens are both CE Marked, soft, daily disposable contact lenses made from Omafilcon A. The test lens, named MiSight® was approved for distribution in Europe. The test and control lenses are available in one diameter, 14.2 mm and base curve 8.7 mm. Lenses are available from -0.75 D to -6.00 D in 0.25 D steps. All lenses received to the Aston site were signed in and their usage recorded throughout the study.

3.2.6 Reasons for discontinuation

Participants could be discontinued or withdrawn from the study if they had an adverse event, comfort or vision difficulties, any violation of protocol agreements or if they simply chose to leave the study. If ocular medication was required or lens wear was stopped for more than four weeks for medical reasons, then the participant may also have been discontinued from the study.

3.2.7 Baseline visit

At the first visit, after consent/assent forms were completed (see section 2.1.1.3), current spectacles were focimetered and information was collected about health, medication use, allergies, parent ethnicity and child birth weight.

As discussed more fully in Chapter 2, the following measurements were recorded during the baseline visit:

1. Vision and Visual Acuity
2. Non-cycloplegia autorefraction
3. Manifest Subjective refraction
4. Stereo Acuity
5. Ocular Dominance
6. Accommodative lag
7. Cycloplegia autorefraction
8. Cycloplegia axial length
9. Residual accommodation

In addition to these procedures, each participant was assessed for strabismus, using an occluder and cover-uncover test, and phoria, using an alternating cover test, at far (4 m) and near (40 cm), wearing their distance correction.

3.2.8 Dispense visit

A review of general and eye health, medication and problems or concerns commenced every dispense visit. A contact lens closest to the child's prescription was trialled. The fit of a contact lens is commonly evaluated at or after at least 5 minutes of wear (Brennan *et al.,* 1994, Kang *et al.,* 2013, Wolffsohn *et al.,* 2009) and

hydrogel lenses have been shown to be predictive of 8 hour wear time movement after 5 to 20 minutes wear (Boychev *et al.,* 2016). The contact lenses in the current study were assessed after they had settled for 10 minutes, vision was again recorded at distance and near and an over refraction was carried out.

Further lenses were trialled where necessary. When an appropriate lens was found, the child was taught to insert and remove the lenses independently. When successful, at this visit or a subsequent one, they were dispensed lenses to take away, given a calendar showing their visit schedule (see Appendix 6) and a '1 Week' visit was made. The children and parents were given advice sheets about contact lenses (see Appendix 4 and 5) as well as direction and support while they were learning. When they could competently insert and remove a lens 3 times in each eye, they were dispensed and each lens box identifier code was recorded.

3.2.9 Further patient visits

At each subsequent visit both the parent and child were asked about how they were adapting to contact lens wear and whether they had experienced any issues. Further questions explored whether lenses were being worn safely and not being slept in, or over worn. LogMAR visual acuity, while wearing contact lenses, was measured at both distance and near, with a distance over refraction also carried out. The child's eyes were examined with and without lenses and they were dispensed further lenses.

At the 6 and 18 month visits vision and visual acuity were recorded, a contact lens over refraction was carried out and a non-cycloplegic autorefraction measured. At 12 and 24 months many of the baseline measurements were repeated:

1. Vision and Visual Acuity
2. Non-cycloplegia autorefraction
3. Manifest Subjective refraction
4. Pupil Diameter
5. Accommodative lag
6. Cycloplegia autorefraction
7. Cycloplegia axial length
8. Residual accommodation

A contact lens insertion and removal review was repeated at all visits. Children could return at any time between scheduled visits if they felt their vision had changed or they had any concerns.

3.2.10 Study objectives

Axial length and refractive error have been shown to be correlated (see Figure 3.1). A change in axial length of the eye is generally regarded as the main structural difference between myopic and hyperopic eyes (Sorsby *et al.,* 1961; Sorsby and Leary, 1969; Gilmartin, 2004; Gwiazda, 2009; Leo and Young, 2011). Myopic eyes commonly demonstrate greater axial elongation and a relative prolate shape (Logan *et al.,* 2004) compared to emmetropic eyes, however myopic eyes can be short, just as hyperopic eyes can be long. To effectively monitor myopic changes over the study

duration, the two primary outcomes for this study were mean spherical refractive error and axial length.

Figure 3.1 Example of correlation between axial length and refractive error from a cross-sectional study of young adult university students (Gilmartin, 2004). [Myopia: Precedents for research in the twenty-first century, Gilmartin, B., Clinical and Experimental Ophthalmology, Vol. 32. Copyright © 2004].

3.2.11 Refractive error and axial length change

Refractive error was measured using a Shin-Nippon NVision-K 5001 autorefractor (see section 2.2.3) with an optotype target at 4 m, one line larger than best visual acuity and 10 measurements were taken and averaged. The MSE was calculated for final statistical analyses.

Non-cycloplegic measurements of refractive error were taken every 6 months. Refractive error under cycloplegic conditions was measured annually. At baseline

and at 12 month and 24 month visits the participant was given 1 drop of 0.5% Proxymetacaine Hydrochloride and after one minute 1 drop of 1% Tropicamide instilled into each eye. After 25 minutes, when the Tropicamide was at maximum effectiveness (Eperjesi and Jones, 2005), 10 autorefraction measurements were taken.

Axial length measurements were taken from each participant, using partial coherence interferometry, with an IOLMaster 500. Up to 15 measurements were taken from each eye with the 10 measurements with the highest sound to noise ratio (SNR) used, at baseline, 12 month and 24 month visits. Baseline data were averaged and compared with data from 12 and 24 months, for final statistical analyses.

3.2.12 Cycloplegia confirmation with residual accommodation assessment

Residual accommodation data were recorded to confirm the effectiveness of using 1% Tropicamide as a cycloplegic drug. With the mean sphere equivalent, of the spectacle refractive error, in a trial frame, 5 measurements were taken at 33 cm and 4 m distances, using a Shin-Nippon NVision-K 5001 autorefractor. The targets used were +0.4 logMAR at near and +0.7 logMAR at distance. The measurements were averaged and the MSE calculated from the mean at each distance for final statistical analyses.

3.3 Results

General baseline data for the 27 participants who completed the 18 month visit are detailed in Table 3.2. The participants were randomly allocated to the test and control lens groups. As can be seen in Table 3.2 both groups were of a similar size and age

range, however, the control lens group were almost 1.00 D more myopic than the test group at the baseline visit.

n= 27	Lens type	Sex	Ethnicity	Average Age at Baseline Visit (years)	8 to 10 Age Group	11 to 12 Age Group	Baseline Cyclo-plegic Refraction (D)	Baseline Axial Length (mm)
n= 14	Control	9 female 5 male	5 Asian British 9 White	10.4 (±1.48)	n=8	n=6	-2.68 (±0.65)	24.52
n= 13	Test	4 female 9 male	1 Black British 3 Asian British 7 White 2 Multiple Ethnic Group	10.5 (±1.56)	n=8	n=5	-1.69 (±0.66)	24.38

Table 3.2 Baseline data for participants

3.3.1 Refractive error and axial length change

Non-cycloplegic autorefraction data (see Table 3.3) gave a 6 monthly pattern showing a slowing of myopia in the test lens group after the initial 6 months.

The 12 month change in myopia progression for cycloplegic refraction MSE in the test lens group was -0.49 (±0.34) D, significantly (p=0.008) less than the control lens group, -0.83 (±0.27) D. The 12 month change in axial elongation was +0.17 (±0.15) mm in the test lens group, significantly (p=0.033) less than in the control lens group, +0.30 (±0.16) mm.

Percentage progression was also calculated. The 12 month findings were a 40.96% less progression in cycloplegic myopia progression with the test lens and 44.54% less axial elongation.

Non-Cycloplegic Autorefraction				
Visit Comparison	Lens Group	Progression (D)	Standard Deviation	Progression
6 months n=27				
Baseline to 6 months	Control	-0.25	±0.23	0.02 D or 6.47% more progression in test group
Baseline to 6 months	Test	-0.26	±0.28	
12 months n=27				
6 months to 12 months	Control	-0.47	±0.30	0.16 D or 33.99% less progression in test group
6 months to 12 months	Test	-0.31	±0.40	
18 months n=27				
12 months to 18 months	Control	-0.41	±0.52	0.20 D or 48.02% less progression in test group
12 months to 18 months	Test	-0.21	±0.38	
24 months n=25				
18 months to 24 months	Control	-0.02	±0.47	0.01 D or 57.74% less progression in test group
18 months to 24 months	Test	-0.01	±0.37	
Overall 24 months n=25				
Baseline to 24 months	Control	-1.07	±0.49	0.27 D or 25.59% less progression in test group
Baseline to 24 months	Test	-0.80	±0.59	

Table 3.3 Non-cycloplegic results at 6 monthly intervals and overall for 24 months between both lens wearing groups. Difference in progression shown by dioptre and percentage.

The partial cohort (n=25), 24 month total myopia progression in cycloplegic refraction MSE was -0.83 (±0.51) D in the test lens group and -1.18 (±0.49) D in the control lens group. The 2 year total axial elongation was +0.52 (±0.24) mm in the control lens group and +0.28 (±0.38) mm in the test lens group. Independent sample t-tests

were used to compare the MSE data. The 2 year percentage progression showed a 29.57% less progression in cycloplegic myopia progression with the test lens and 46.73% less axial elongation. The differences were not statistically significant (p=0.176, p=0.070, respectively). The annual axial elongation has been plotted for baseline, 12 month and 24 month visits demonstrating elongation in both groups with increasing divergence over time.

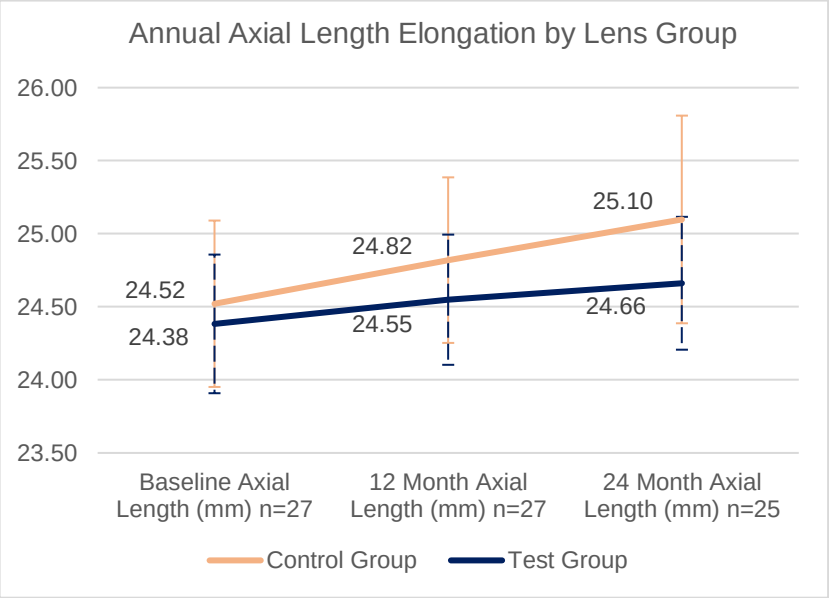


Figure 3.2 Line chart to show annual axial elongation over 24 months. Number of participants shown by visit.

There was no statistically significant treatment effect between baseline age groups, either 8 to 10 years or 11 to 12 years, for either 12 month cycloplegic refraction (p=0.875) or axial elongation (p=0.896).

With the exception of one child, all of the participants demonstrated myopic progression at the 12 month visit in both cycloplegic refractive error (control group ranged from -0.52 to -1.26 D, test group -0.20 to -1.15 D) and axial length progression (control group ranged from 0.06 mm to 0.68 mm, test group 0.04 mm to 0.42 mm). The refractive error for 'Child 17' exhibited a slight hyperopic shift of +0.10 D and axial length reduction of -0.19 mm, at the 12 month visit.

3.3.2 Depth of cycloplegia

Cycloplegia was achieved using 1 drop of 0.5% Proxymetacaine Hydrochloride and after one minute, 1 drop of 1% Tropicamide, instilled into each eye. After 25 minutes the participants viewed a 3.00 D stimulus target (33 cm) collectively demonstrating a mean refractive error of -0.33 (±0.62) D and to a 4 m distant target of -0.04 (±0.43) D. Mean residual accommodation was 0.29 (±0.69) D for all participants.

3.3.3 Cyclopleged versus non-cyclopleged autorefraction

A paired sample t-test was used to assess for differences between the cyclopleged and non-cyclopleged autorefraction data. The mean cyclopleged autorefraction for the participants was significantly (p=<0.0005) more positive by +0.19 (±0.18) D at the Baseline visit and by +0.17 (±0.22) D at the 12 month visit.

3.3.4 Multifactorial assessment of myopia progression and lens type.

Factorial ANOVAs were carried out to assess for any relationship between myopia progression (refractive and axial length change), the lens type (test or control) and one of the following additional factors:

1. Ethnicity: white or Asian British.

2. Age: 8 to 10 years or 11 to 12 years.

3. Sex: Male or Female

The factorial ANOVA results are summarised in Table 3.4 and Table 3.5.

Lens Type: Test or Control	+	Cycloplegic Autorefraction	+	Ethnicity	p = 0.118
				Age	p = 0.255
				Sex	p = 0.28

Table 3.4 Cycloplegic autorefraction myopia progression factorial ANOVA data for lens type with ethnicity, sex and age association

Lens Type: Test or Control	+	Axial Length	+	Ethnicity	p = 0.155
				Age	p = 0.634
				Sex	**p = 0.026**

Table 3.5 Axial length myopia progression factorial ANOVA data for lens type with ethnicity, sex and age association

The relationship from the factorial ANOVA was statistically significant only for lens group, 12 month axial length change from baseline (mm) and sex (p=0.026). The relationship and interaction effect are further presented in Figure 3.3 and Table 3.6.

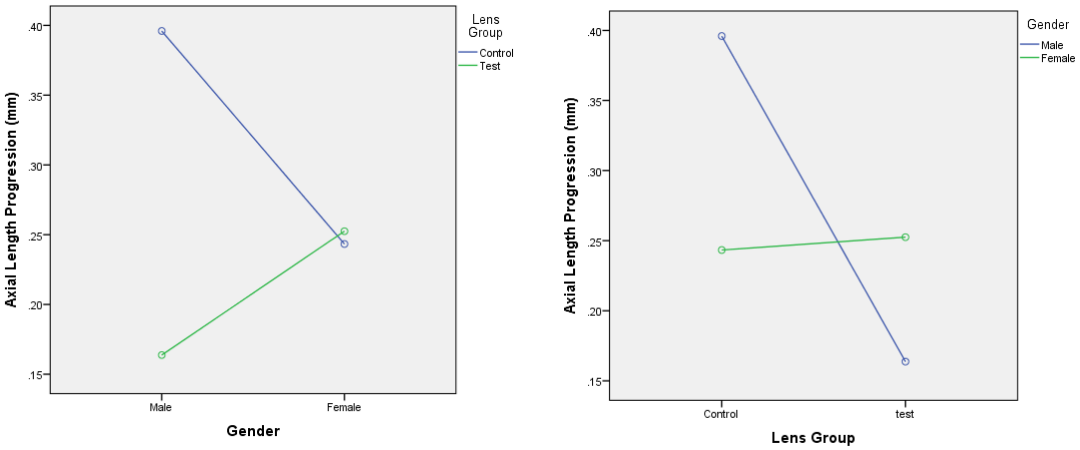


Figure 3.3 Factorial ANOVA of the interaction effect for the 12 month axial length change (mm) measurement with lens type and sex plotted using both sex and lens group.

A repeated factorial ANOVA analysis using average percentage change, rather than actual change, in axial length from baseline to 12 month visit revealed a comparable significance (p=0.025). Male participants who wore the test lens demonstrated the least progression in mean axial length change (+0.13 ±0.14 mm) and percentage change (0.51%) from baseline to 12 months.

Lens Group: Control or Test Lens	Sex: Male or Female	Axial Length Progression (standard deviation)	Percentage Change in Axial Length
Test	Male (n=9)	0.13 (±0.14) mm	0.51%
Control	Female (n=9)	0.24 (±0.12) mm	1.00%
Test	Female (n=4)	0.25 (±0.13) mm	1.06%
Control	Male (n=5)	0.40 (±0.19) mm	1.61%

Table 3.6 Axial length elongation by lens group and sex. Number of participants for each group shown in brackets.

3.4 Discussion

Refractive error and axial length change were compared between the two groups to measure the effectiveness of the dual focus lens to reduce myopia progression. The 12 month change in myopia progression for cycloplegic refraction MSE in the test lens group was statistically significantly (p=0.008) less than the control lens group. The 12 month mean change in axial elongation was also statistically significantly (p=0.033) less in the test lens group when compared with the control lens group. The reduction in myopia progression after 12 months in the test lens wearers indicates that the use of a dual focus contact lens had slowed the myopic shift in refractive error and resulted in less elongation of axial length.

The participants were measured using cycloplegic autorefraction annually and non-cycloplegic autorefraction measurements were additionally taken bi-annually. When cycloplegic and non-cycloplegic autorefraction data were compared the mean cycloplegic autorefraction for the participants was significantly (p=<0.0005) more positive by +0.19 (±0.18) D at the Baseline visit and by +0.17 (±0.22) D at the 12 month visit. The non-cycloplegic autorefraction data were compared with the baseline visit and the 6, 12 and 18 month visits. There was very little difference between the two groups in percentage change of myopia progression at 6 months (-0.25 ±0.23 D in the control group and -0.26 ±0.28 D progression in the test group), however between 6 to 12 months there was a total of 33.99% less progression in the test group, 48.02% less between 18 and 24 months and 57.74% at 18 to 24 months. This may suggest that any benefit of reduction in myopia progression from the use of a dual focus lens may take greater than 6 months to prove effective.

Despite the participants being allocated to test or control using a sequentially randomised method, the control group (see Table 3.2) had a greater mean baseline cycloplegic MSE (-2.68 ±0.65 D) when compared with the test group (-1.69 ±0.66 D) and therefore percentage progression was also calculated to allow more accurate comparison. At the 12 month visit, there was 40.96% less progression in cycloplegic autorefraction and 44.46% less axial elongation for the participants who wore the test lens. The 24 month findings, compared to baseline, for the current study were 29.57% less progression in cycloplegic myopic progression and 46.73% less axial elongation with the test lens. These findings are comparable to similar studies of novel contact lenses, to reduce peripheral hyperopic defocus. In the current study, the children were aged between 8 and 12 years with non-cyclopleged myopia between -0.78 to -3.95 D at the baseline appointment. Anstice and Phillips (2011) described 10 month findings of 38% less progression in cycloplegic refraction in their dual focus lens and 50% less axial elongation with the test lens. The 40 child participants were aged between 11 and 14 years with baseline non-cyclopleged myopia of -1.25 to -4.50 D. The children wore a dual focus contact lens, with alternating concentric rings of distance correction and +2.00 D addition, in one eye and a single vision distance contact lens in the other. After 10 months lens assignment was swapped between the eyes for a further 10 months. Lam *et al*., (2014) demonstrated 25% less myopia progression in their Defocus Incorporated Soft Contact (DISC) lens after 2 years and 28% less axial elongation. The 221 children aged between 8 and 13 years (baseline myopia between -1.00 and -5.00 D) were allocated to wear either the DISC lens with alternating concentric rings of distance correction and +2.50 D addition, or single vision contact lenses, for the duration of the 2 year study. Sankaridurg *et al*., (2011) in a 12 month study described adjusted

(for age, sex, parental myopia, baseline spherical equivalent values and compliance) figures of 34% reduction in myopia progression and a 33% reduction in axial elongation with their novel contact lens, when compared with single vision spectacles. The 85 children, aged between 7 and 14 years, had a baseline sphere range between -0.75 to -3.50 D and cylinder of ≤1.00 D. The novel lens had a central clear zone with progressively more positive power reaching +1.00 D at 2 mm, and +2.00 D at the edge of the 9 mm treatment zone.

Myopia intervention studies do not always remain effective into the second year of treatment (Gwiazda *et al.,* 1993; Charm and Cho, 2013). Neither group progressed to any great extent between visits 12 and 24 months according to cycloplegic autorefraction data (control -0.36 (±0.57) D and test group -0.34 (±0.29) D). This was even more apparent in the non-cycloplegic data from the 18 month to 24 month visits (control -0.02 (±0.47) D and test group -0.01 (±0.37) D, suggesting a plateauing of myopia levels for both groups. The continued slowing of axial elongation observed at each visit, however, is very encouraging (the test group demonstrated 0.13 mm less axial elongation in the first 12 months and 0.14 mm less elongation between the 12 month and partial cohort 24 month visit (see Figure 3.2).

There was an apparent hyperopic shift observed for Child 17 indicating a reduction in refractive error and axial length at the 12 month visit when compared with baseline data. Comparison of the non-cycloplegic autorefraction data otherwise shows a progression of myopia: baseline -1.63 D; 6 month -1.64 D; 12 month -1.53 D; 18 month -1.88 D and 24 month 1.83 D. In contrast axial length showed an ongoing reduction: baseline 24.55 mm; 12 month 24.37 mm and 24 month 24.37 mm. Animal studies may offer a possible explanation for this ‘improvement’. The choroid layer in

the retina has been shown to thicken in response to myopic defocus (Wallman *et al*., 1995; Wildsoet and Wallman, 1995). This child had worn the test lens and may, therefore, have theoretically experienced one year of central correction with simultaneous peripheral myopic defocus. This defocus may have increased the thickness of the choroid causing the axial length to have appeared shorter than when previously measured.

The factorial ANOVA analysis presented a relationship between axial length change, lens type and sex (p=0.026). Axial length change was lowest in male participants who wore the test lens (+0.13 ±0.14 mm) and highest in male participants who wore the control lens (+0.40 ±0.19 mm). See Table 3.6 for male and female data. Sex and myopia progression have been explored in several studies with either no association or an increase in myopia progression rate in females (COMET Group, 2013; Goss, 1990; Hyman *et al.,* 2005) which therefore provide no explanation for the finding in the current study. There are many behavioural aspects to gender that may have confounded these data. It was noted, although not objectively measured, that in the current study, many of the boys spent their free time either playing outdoor sports or staying indoors with computer games whereas the girls reported liking reading, television and family activities. It could be postulated that concentrated computer game play, coupled with an existing lag of accommodation may increase peripheral hyperopic defocus. The dual focus lenses may encourage more efficient accommodation and make concentrated work less myopigenic.

There was no statistically significant three-way interaction between myopia progression measured using cycloplegic autorefraction when compared with lens type and ethnicity; age or sex. There was also no significant interaction between

axial length change, lens type and ethnicity or age. Ethnic differences have been previously reported with African American children experiencing slower myopia progression (COMET Group, 2013) and Asian children undergoing faster progression and having the highest prevalence with higher levels of myopia at stabilisation (Mutti *et al.,* 2007; COMET Group, 2013; Saw *et al.,* 2005). Younger age at commencement has been previously associated with improved treatment effect of myopia interventions (Zhu *et al.,* 2014; Cho and Cheung, 2012) and therefore an improved slowing of myopia progression was expected in the younger test group. The small sample size along with confounding factors such as lifestyle and lens wear weekly duration may have masked any age related treatment benefit.

Cycloplegic refraction MSE was compared with non-cycloplegic MSE to assess the effectiveness of using 0.5% Proxymetacaine Hydrochloride and 1% Tropicamide to produce cycloplegia. Tropicamide works more quickly and lasts less time than other muscarinic agents (Eperjesi and Jones, 2005) and was therefore seen as the least intrusive option for the participants on a longitudinal study. Manny *et al*., (2001) described Tropicamide as an effective cycloplegic drug, when assessed in the COMET study, with a mean right eye residual accommodation, after 20 minutes, of +0.38 (±0.41) D. The mean residual accommodation in the present study after 25 minutes was +0.29 (±0.69) D on average for all participants (right eye) and therefore Tropicamide 1% was deemed an effective cycloplegic drug in the current study.

The original target sample size to complete the study was 168 total participants (84 in each group) across all sites based on a 0.25 D reduction in mean myopia progression, in the test group when compared to the control group. The 12 month treatment effect was greater than originally predicted at 0.34 D. A recalculation

reduced the sample size to 91 total participants required to complete the study in order to demonstrate statistical significance. This figure assumes a continued treatment effect in years 2 and 3. Additionally, this figure would need to be inflated to allow for an annual attrition rate, taking the total figure to 143 participants (across all four study sites), assuming the originally predicted 14% attrition rate. The UK site attrition rate was approximately 3% in the first year (1 participant) and 4% (1 participant) in the 2nd year. In their ortho-k study, Cho and Cheung (2012) reported that 78 of the 102 participants completed the 2 year study, giving an attrition rate of 24%. Lam *et al*., (2014) in a similar study to the current one, used soft contact lenses with peripheral defocus. Of the 221 child participants, 128 completed the study giving an attrition rate of 42%.

Factors which may have contributed to the low attrition rate in the current study may include patient/parent motivation, location of the study and the enjoyment of using contact lenses. Many of the participants responded to an advert describing the study and were therefore keen and interested in the study details from the beginning. The contact lenses were an exciting prospect for many of the children and they included them easily into their daily schedule. The Likert scale analysis from the questionnaires at one month showed that inserting and removing lenses were 'really easy' or 'kind of easy' for approximately 85% (23 out of 27 participants) and 100% (27 out of 27) of participants respectively. Similarly, 100% of the parents described their child's level of happiness at the 1 month visit with 'comfort, vision, handling and freedom from spectacles' as 'extremely happy' and 96% (26 out of 27) of parents described their own level of 'comfort' (ease) with their child wearing contact lenses as 'extremely comfortable'. The children did not report any difficulty wearing contact

lenses 6 or 7 days a week, for 10 to 15 hours per day and there were no adverse events related to contact lens wear. Aston University is centrally located in Birmingham and the participants were predominantly local to the area which regularly allowed for after school visits rather than missing any lessons. The families were all given an 'out of hours' phone number that they were encouraged to call with any concerns or questions. With hindsight it was felt this may have very much helped to catch any issues while they were small and manageable, keeping the children and the parent content with the study experience.

It was not possible to adjust the parameters to control for factors such as age or level of myopia due to the small sample size of 27 participants. It is a reasonable assumption that data may have altered had these adjustments been possible. The wear time of the lenses was not monitored beyond regular clarification of study protocol wear times between 10 to 15 hours a day, at least 6 days a week. Some participants wore their lenses 7 days a week, however, this was not formally documented and may have given an indication of the most beneficial lens wear time. Lam *et al.,* (2014) reported that myopia progression was inversely proportional to contact lens wear time with their DISC lens. The minimum duration of daily wear required to slow myopia progression was five hours per day and they suggested 7 to 8 hours might be optimal for treatment effect. Combined data at the conclusion of the multi-centre study will allow for further parameter adjustment.

3.4.1 Summary

The research described in the current study provides evidence that dual focus soft contact lenses are an effective intervention for myopia control in UK children,

reducing myopia progression by 40.96% and axial elongation by 44.54% in the first year of the study with effectiveness continued into the 2nd year of the study with a total of 29.57% less myopia progression and 46.73% less elongation.

4. LAG OF ACCOMMODATION AND MYOPIA PROGRESSION

4.1 Introduction

There is support from animal studies to show that eye growth can be controlled by altering the amount and sign of optical defocus (Wildsoet and Wallman, 1995; Smith and Hung, 1999). The eye grows longer in response to a negative lens imposing hyperopic blur on the retina thus rendering the eye myopic and reduces growth in response to a positive lens inducing myopic blur and making the eye hyperopic (Irving *et al*., 1991; Siegwart and Norton, 1993; Metlapally and McBrien, 2008; Whatham and Judge, 2001; Benavente-Perez *et al.,* 2014; Hung *et al.,* 1995; Arumugam *et al.,* 2014). The effect is shown in Figure 1.2.

Typically, when a person views a near target, they under-accommodate i.e. they use insufficient accommodation to bring an object into focus and this is termed a 'lag of accommodation' (Gwiazda *et al.,* 2004). This results in hyperopic retinal blur. Associations have been made between larger lags of accommodation during near work and the development and progression of myopia (Gwiazda *et al.,* 1993; Gwiazda *et al.,* 1995; Gwiazda *et al.,* 1999). When compared with emmetropic children, myopic children accommodate less to a near target (McBrien and Millodot., 1986; Gwiazda *et al*., 1993) and show an insufficient accommodative response to blur (Gwiazda *et al.,* 1993). If myopia progression is related to hyperopic retinal blur at the fovea, then correcting this blur may reduce myopia progression. Clinical trials in children using PAL spectacles to reduce the hyperopic blur at near resulting from a lag of accommodation have found only modest results (Gwiazda *et al.,* 2003; COMET2, 2011). However, this form of correction has been shown to be more

effective at slowing myopia progression for myopic children with a higher lag of accommodation and near esophoria (Gwiazda *et al.,* 2003; Gwiazda *et al.,* 2004).

A dual focus lens requires the wearer to have active accommodation during near viewing in order to keep the focal plane of the central lens power on or in front of the retina. The dual focus lens designed by Anstice and Phillips (2011) had concentric alternating zones of correction and treatment (the treatment zone having a power of +2.00 D relative to the correction zone) (see Figure 4.1). While viewing distant objects the focal plane of the correction zone would fall on the retina and the focal plane of the treatment zone would fall anterior to the retina (see Figure 4.2). Theoretically, when the participant accommodated to a near target the focal plane of the correction zone would remain on (or near) the retina and the focal plane of the treatment zone would, again, fall anterior to the retina (see Figure 4.3). Any focus anterior to the retina would produce myopic defocus, the desired outcome.

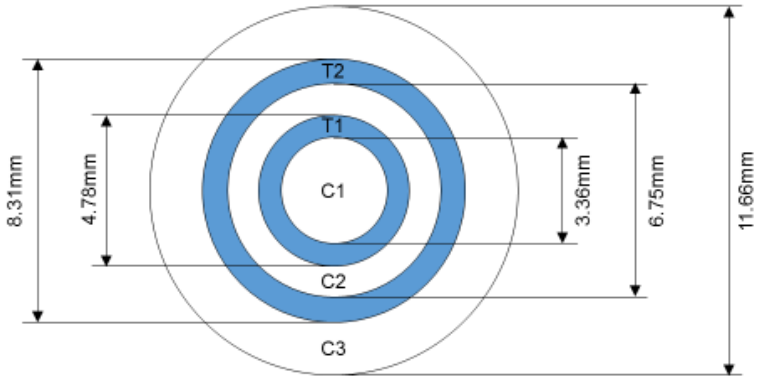


Figure 4.1 Dual focus contact lens showing correction and treatment zone diameters. Redrawn from Anstice and Phillips (2011).

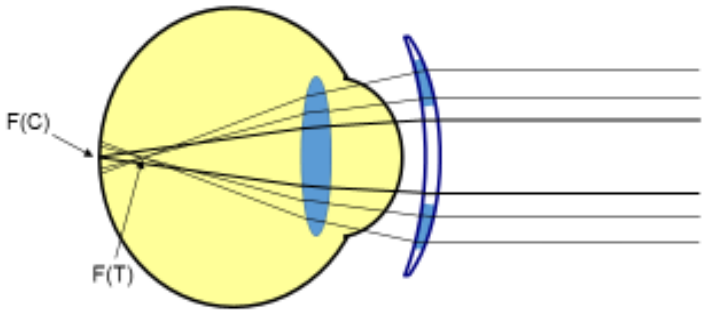


Figure 4.2 Redrawn from Anstice and Phillips (2011) showing focal plane position through correction F(C) and test F(T) zones for distance target.

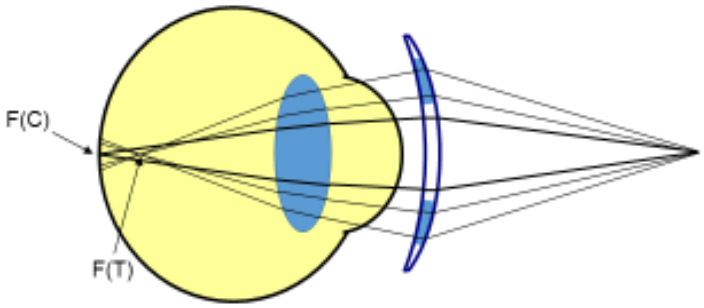


Figure 4.3 Redrawn from Anstice and Phillips (2011) showing focal plane position through correction F(C) and test F(T) zones for near target.

Dual focus contact lenses may also have the potential to reduce the accommodative lag for near work. This chapter aims to explore lag of accommodation in myopic children. The level of accommodative lag will be related to the efficacy of the dual focus lens (discussed in Chapter 3) to reduce myopia progression. Additionally, the impact on accommodative lag, when a near target is viewed through the dual focus lens will be explored.

4.2 Methods

See section 2.1 for full details of participants. A total of 27 children, aged between 8 and 12 years at enrolment, were assessed every 6 months over the next 18 months. The children had been randomly allocated to wear either a novel dual focus lens or a single vision lens, 10 to 15 hours per day, 6 to 7 days per week for 3 years (see section 3.2.2).

4.2.1 Lag of accommodation with spectacle MSE

The required accommodative response to a 33 cm target should be 3.00 D, the refraction (measured by autorefraction) when the participant fixates a target at this distance can then be examined for shortcomings when compared to the expected 3.00 D accommodative response. Where the exerted accommodative effort fell short of the accommodative demand the difference was deemed the 'lag of accommodation'. This calculated figure was then compared amongst the participants in relation to their myopia progression and lens type. A participant was deemed to have a 'low' lag of accommodation with less than 1.00 D lag and 'high' when the lag of accommodation was equal to or greater than 1.00 D.

With the mean sphere equivalent of their spectacle refractive error in a trial frame, 10 measurements of the residual refractive error were taken while the child viewed a 4 m target and also while the child accommodated to a target at 33 cm, using a Shin-Nippon NVision-K 5001 autorefractor. The targets used were +0.4 logMAR optotype at near and +0.7 logMAR optotype at distance. Accommodative response can be effectively measured using the dominant eye (Flitcroft and Morley, 1997) and for this reason, the measurements were taken only from the dominant eye and averaged.

The lag of accommodation was calculated as the difference between the mean of the response at each distance.

4.2.2 Lag of accommodation through study contact lenses

An accommodative lag measure was taken while the participant wore their contact lenses to assess whether they accommodated at near, rather than use the treatment zone and relaxed their accommodation. The participant was asked to view both a 33cm and a 4m target while 10 measurements were taken from the dominant eye at both distances using a Shin-Nippon NVision-K 5001 autorefractor. The targets used were letter optotypes +0.4 logMAR at near and +0.7 logMAR at distance. The measurements were averaged and the MSE used for final statistical analyses.

4.2.3 Factorial ANOVA of lens group, myopia progression and accommodative lag

Factorial ANOVAs were performed to assess for a relationship between lens group (i.e. test or control), myopia progression and accommodative lag. The accommodative response to a 3.00 D target was divided into two groups, less than 1.00 D lag or equal to/greater than 1.00 D accommodative lag. The one year myopia progression was assessed using cycloplegic autorefraction progression and then repeated with axial length change.

4.3 Results

4.3.1 Lag of accommodation with spectacle MSE

The mean lag of accommodation for all participants was -0.96 (±0.49) D. A lag of accommodation greater than 1.00 D (less than 2.00 D accommodative response to the 3.00 D target) was present in 55.56% of the children and therefore, 44.46% had a lag of accommodation less than 1.00 D. There was no statistically significant difference between lag of accommodation and sex (p=0.327) the male participants had a mean accommodative lag to a 3.00 D target of -1.18 (±0.49) D and the females -1.01 (±0.39) D.

When compared by lens group, the control group had a mean lag of accommodation of -1.08 (±0.53) and the test group -0.84 (±0.45) D. A lag greater than 1.00 D was present in 50% of the control lens group and 61.53% of the test lens group. To assess whether the test lens resulted in less myopia progression after 12 months of wear (and therefore greater treatment effect) for the participants with a greater lag of accommodation, a Pearson 2-tailed correlation test was performed. Lag of accommodation and refractive progression were positively moderately correlated although this was not statistically significant (r=+0.475, p=0.101). There was a moderate negative correlation when lag of accommodation was compared with axial length elongation, this was also not statistically significant (r=0.455, p=0.118). When a box chart was produced an outlier was clearly apparent (see Figure 4.4).

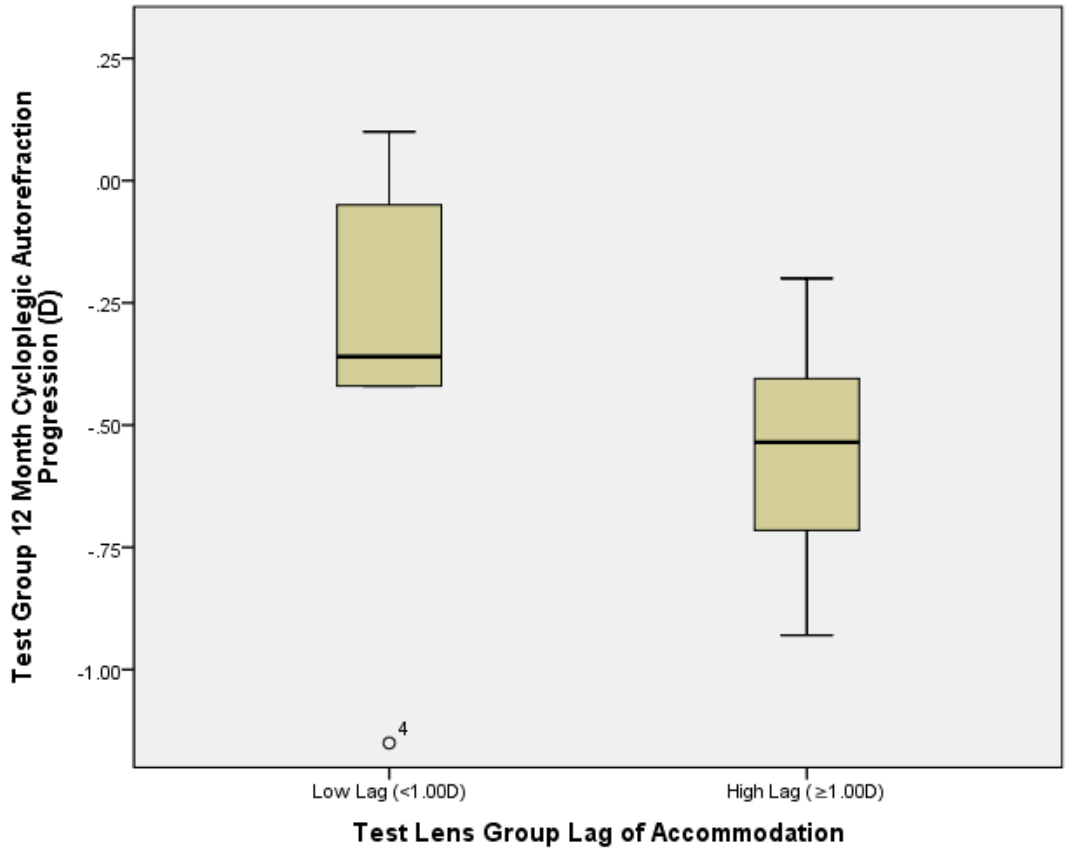


Figure 4.4 Box chart to show lag of accommodation in the test lens wearing group in relation to 12 month cycloplegic autorefraction progression of myopia.

The same participant was also an outlier in the axial elongation data and therefore the data was reanalysed without this participant. With the outlier data removed there was a strong positive correlation (r=+0.736) in the test group for 12 month cycloplegic autorefraction progression and lag of accommodation. The high lag group (≥1.00 D lag) averaged -0.56 (±0.23) D myopia progression, compared with the low lag group (<1.00 D) who averaged -0.18 (±0.25) D. This was a statistically significant correlation (p=0.006). (See Figure 4.5)

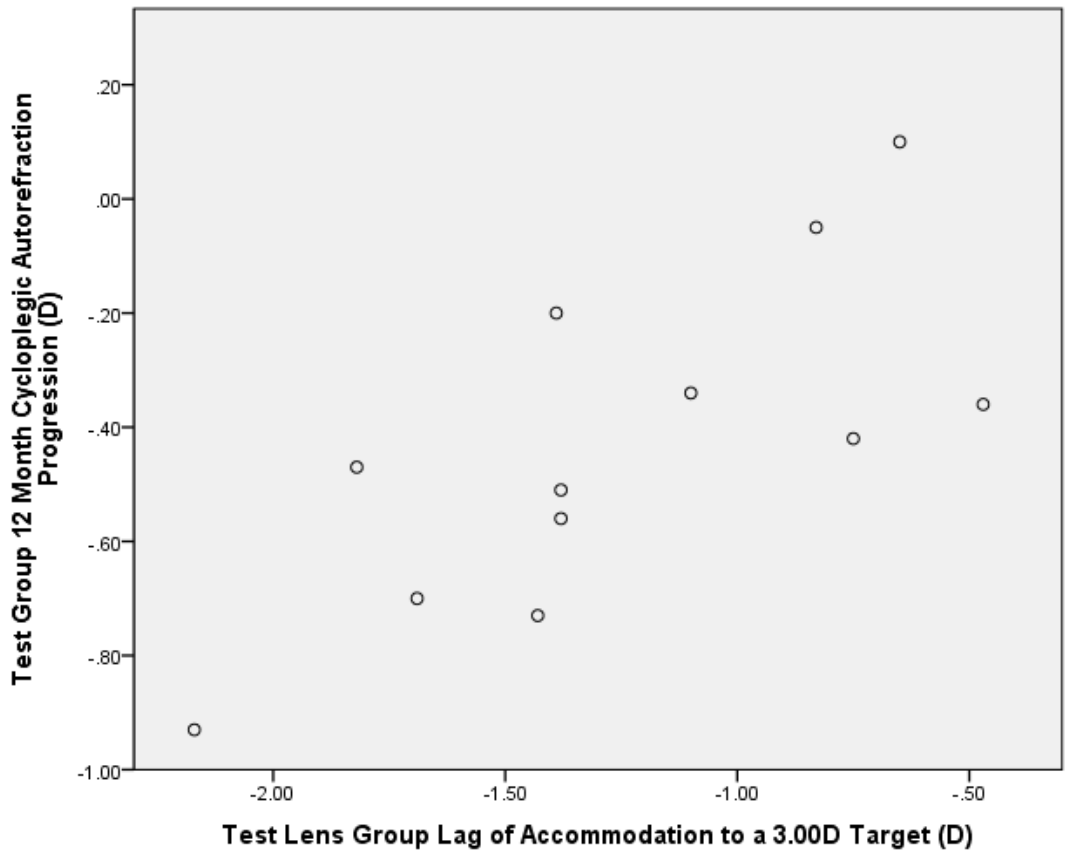


Figure 4.5 Correlation between the lag of accommodation to a 3.00 D target and 12 month cycloplegic autorefraction progression of myopia in the test lens wearing group.

There was a strong negative correlation (r=-0.665) in the test group for 12 month axial elongation and lag of accommodation. The high lag group averaged +0.21 (±0.07) mm elongation, compared with the low lag group who averaged +0.02 (±0.15) mm elongation. This was also a statistically significant correlation (p=0.018). (see Figure 4.6)

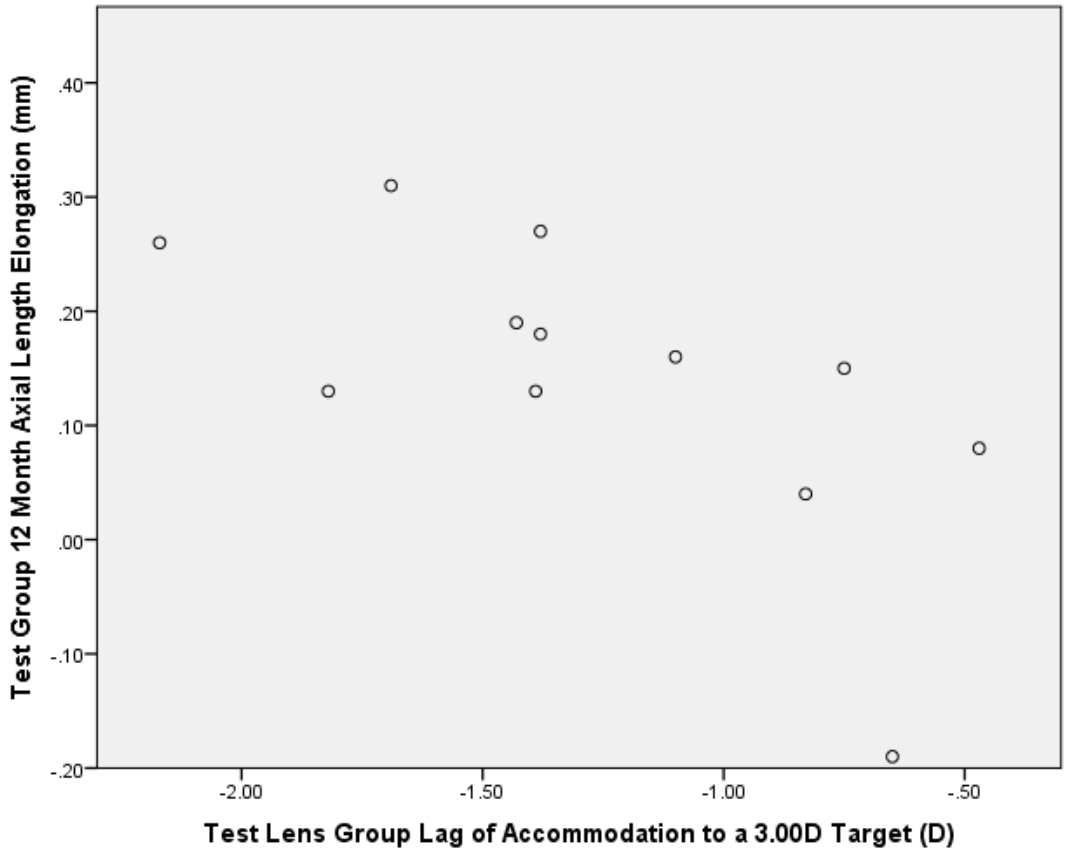


Figure 4.6 Correlation between the lag of accommodation to a 3.00 D target and 12 month progression of myopia using axial length elongation in the test lens wearing group.

There was no statistically significant correlation in the control lens group between lag of accommodation and 12 month myopia progression assessed using either cycloplegic autorefraction (r=-0.057, p=0.847) or axial length elongation (r=-0.146, p=0.619).

4.3.2 Lag of accommodation through study contact lenses

To determine the level of accommodation to a 3 D target when wearing the assigned lens type, non-cycloplegic autorefraction measurements were taken with the participants wearing their assigned contact lenses. The near lag of accommodation to a 3 D target was greater for control lens wearers (-0.73 ±0.59 D) than test lens wearers (-0.08 ±0.82 D). There was a statistically significant difference in mean lag of accommodation between the two groups (p=0.031).

The difference between distance (4m) and near (33cm) autorefraction measurements were additionally calculated and compared for each group. There was no statistically significant difference (p= 0.561) found between the control lens wearers (-1.97 ±0.56 D) and the test lens group (-1.84 ±0.58 D).

4.3.3 Factorial ANOVA of lens group, myopia progression and accommodative lag

Factorial ANOVAs were carried out to assess for a relationship between myopia progression (refractive and axial length change), the lens type and accommodative lag. Myopia progression after 12 months was assessed using both cycloplegic autorefraction progression and then repeated with axial length change. There was no statistically significant association between change in myopic refractive error (using cycloplegic autorefraction), lens type and level of accommodative lag (p=0.678) nor for myopic axial length change, lens type and accommodative lag (p=0.763).

4.4 Discussion

Associations have been made between the lag of accommodation during near work and the development and progression of myopia (Gwiazda *et al*., 1993; Gwiazda *et al*., 1995; Gwiazda *et al*., 1999). There are indications that correcting children with relative plus power for close work may have a greater effect on certain groups of children, such as those with large lags of accommodation and esophoria at near viewing distances (Gwiazda *et al.,* 2003; COMET2, 2011). Under-accommodation or 'lag of accommodation' refers to the status when a person uses insufficient accommodation to bring an object into focus (Gwiazda *et al.,* 2004). There is no clear definition of what level of this measurement is deemed 'high'. The original COMET study defined a high lag of accommodation as >0.43 D (Cheng *et al*., 2011), COMET2 study (2011) >1.00 D and Hasebe *et al.,* (2008) as >1.80 D. A high lag of accommodative response in the current study was an accommodative response ≥1.00 D, therefore, an accommodative response to a 3.00 D target of less than 2.00 D. Esophoria was not observed in the participants when assessed at baseline and was not assessed again during the study. Within the total cohort, with MSE worn, 55.56% of the children had a lag of accommodation greater than 1.00 D. The test lens group were assessed to see if they had demonstrated a greater treatment effect (less myopia progression) in the test participants with a higher lag of accommodation when compared to the test participants with a low lag of accommodation. A lag greater than 1.00 D was detected in 61.53% of the test lens group. Neither the 12 month cycloplegic autorefraction myopia progression nor axial length elongation were statistically correlated with lag of accommodation in the full test group (n=13). When an outlier was removed and the data reanalysed there was a strong statistically

significant (p=0.006) positive correlation between refractive error and axial length progression of myopia, however, the greater progression was present in the participants with the higher lag of accommodation. Correspondingly, there was a statistically significant (p=0.018) strong negative correlation for axial elongation and lag of accommodation with the greater elongation being present in the higher lag of accommodation group. These findings are in contrast to comparable studies of lag of accommodation in young myopes (Gwiazda *et al.,* 2003; COMET2, 2011).

Accommodation through the dual focus contact lens was also compared between the two lens groups. To measure accommodation through a dual focus contact lens required measurements to be taken through the central distance zone only. The central zone of the Anstice and Phillips (2011) dual focus lens was 3.36 mm (see Figure 4.1). The Shin-Nippon NVision-K 5001 requires a pupil size ≥2.3 mm (Davies *et al.,* 2003) and there was no apparent decentration noted in contact lens fitting assessment in the current study. Therefore, it could be asserted that the measurement for accommodative lag was likely taken through the central zone of the lens and not influenced by the concentric add zones. No difference was found between the distance and near comparison for both the control and test lens group when participants were wearing their respective contact lenses, which indicated that the test lens group accommodated appropriately for the near target rather than relying on the near addition power of the contact lens. The test lens group were found to accommodate more accurately to a 3.00 D target than the control group by approximately 0.65 D.

In a 30 month, monovision spectacle study aimed at lessening accommodative effort at near to effect a reduction in myopia progression, Phillips (2005) assessed 18

myopic children, aged 10 to 13 years. The participants were given their full distance prescription (-1.00 to -3.00 D MSE) in their dominant eye. The non-dominant eye was allocated either a plano lens or where necessary, a partial correction, to limit any resultant imbalance between the eyes from exceeding 2.00 D of induced anisometropia. It was assumed that the children would use their non-dominant eye to read and therefore use less accommodation at near. Unexpectedly, all of the children adapted to read with their distance corrected eye, causing a resultant myopic defocus in the non-dominant eye. Monovision was not successful in reducing accommodative effort at near, however, myopia progression in the non-dominant eye was significantly less by -0.36 D and 0.13 mm axial elongation per year, (Phillips, 2005). Correspondingly, Bradley *et al*., (2015) reported that young adult participants, aged between 21 and 28 years, focussed using the distance optics of a multifocal lens when viewing binocularly. Therefore, accommodation and hyperopic defocus were not effectively reduced in this group. In the present study however, the statistically significant (p=0.031) reduction in lag of accommodation in the test group (-0.08 ±0.82) D compared with the control group (-0.73 ±0.59 D) may indicate that the dual focus contact lens improved near accommodative lag and therefore may effectively reduce hyperopic defocus at the fovea (see Figure 4.3). Additionally, when the test group participants with a low lag of accommodation (see section 4.3.1) were further analysed, they were found to have an additionally reduced average lag of accommodation of -0.02 (±0.57) D, or -0.01 (±0.66) D excluding the outlier. This reduction was not statistically significant between the higher and lower lag groups who wore the test lens (p=0.971).

4.5 Summary

The present study has addressed the role of accommodative lag as a factor in myopia progression in children. The findings of this study do not support the hypothesis that there is a link between higher accommodative lag and myopia progression. However, there was a relationship detected between lower lag of accommodation and improved treatment effect of the dual focus lens.

How dual focus contact lenses impact on the accommodative status in children is of interest. The theoretical reduced retinal blur in children wearing the dual focus contact lenses may have improved the accommodation accuracy.

5. PERIPHERAL MEASUREMENTS AND MYOPIA

5.1 Introduction

Peripheral refractive error has long been considered as a factor related to the development and progression of myopia (Hoogerheide *et al.,* 1971). Studies have shown that the pattern of peripheral refraction varies with refractive type (Charman and Radhakrishnan, 2010).

The refractive error of the peripheral retina has been measured extensively in relation to foveal refraction (Ferree and Rand, 1931; Rempt *et al.*, 1971; Hoogerheide *et al.,* 1971; Millodot, 1981; Mutti *et al.,* 2000; Mutti, Sinnott *et al.,* 2011). Peripheral refraction can be assessed by actual refraction found at a peripheral location or described in relation to how it compares with central vision in primary gaze, either relatively myopic or hyperopic. Alternatively, peripheral data can be demonstrated diagrammatically with data points plotted to form a refractive error pattern. Ferree *et al.,* (1931) identified three types of peripheral pattern, named A, B and C. These were later termed I (type B), III (type C) and IV (type A), when two additional shapes, II and V, were added by Rempt *et al.,* (1971). The term skiagram was used to describe the pattern, examples are shown in section 1.1.6. When rays of light from an off-axis object pass through the crystalline lens the principal rays are refracted in two separate planes, the principal tangential ray and the sagittal ray which is perpendicular to it (Verkicharla *et al.,* 2012). The skiagram patterns were grouped depending on whether the tangential and sagittal foci became more myopic or hyperopic in relation to primary gaze. With the exception of type III there was

symmetry between the nasal and peripheral fields and the sagittal focus remained either relatively hyperopic or changed very little when compared with primary gaze.

Eyes with myopic refractive errors commonly demonstrate relative hyperopia in the periphery with a relatively prolate ocular shape whereas emmetropes and hyperopes have a more relative myopic peripheral refraction with an accompanying relative oblate shape (Hoogerheide *et al.,* 1971; Millodot, 1981; Mutti *et al.,* 2000; Seidemann *et al.,* 2002; Logan *et al.,* 2004; Mutti *et al.,* 2007; Davies and Mallen, 2009; Sankaridurg *et al.,* 2011). The majority of these studies are cross-sectional in nature thus making it difficult to determine if this type of peripheral defocus is a consequence of or a precursor to myopia development.

Relative peripheral hyperopia has been associated with myopia progression, however there is much debate as to whether it can be used as an effective predictor of myopia onset or progression. (Rosen *et al.,* 2012; Mutti, Sinnott *et al.,* 2011; Atchison *et al*., 2015). Hoogerheide *et al.,* (1971) studied pilots, aged 18 to 20 years, and demonstrated that participants who became myopic were more likely to have relative peripheral hyperopia. This paper suggested that the state of the peripheral refraction compared to central might be one way of predicting future myopia onset however this theory has been questioned by Rosen *et al.,* (2012), with concerns it was misinterpreted. Rosen *et al.,* (2012) suggested that the peripheral hyperopia presented may have been measured after the development of ametropia and therefore was not shown to be indicative as a precursor. Mutti *et al.,* (2007) evaluated refractive error, axial length and peripheral refraction in 605 children who became myopic. Assessing the findings the year before myopia onset, the year during and the year after onset, myopic eyes demonstrated similarities, tending towards longer

axial length with more negative refractive error and increased relative peripheral hyperopia present prior to, as well as after, onset. However peripheral refraction was only measured at one point, 30 degrees in the nasal visual field. Conflicting results have more recently been published, including a later paper from the same study with an increased sample size, 2043 non-myopic children were assessed and results indicated that baseline peripheral hyperopia was a poor predictor of future myopia development (Mutti, Sinnott *et al.,* 2011; Sng, Lin, Gazzard, Chang, Dirani, Lim *et al.,* 2011) or progression (Atchison *et al.,* 2015).

Atchison *et al.,* (2015) measured the horizontal visual field in over 1700 Chinese children at a baseline appointment when the participants were 7 years of age and again after 12 and 24 months. Additionally, over 1000 participants, aged 14 years at baseline appointment, were assessed with measurements repeated 12 months later. They concluded that relative peripheral hyperopia was a poor predictor of myopia development or progression and that the participants who developed myopia during the study did not have more relative peripheral hyperopia at the baseline appointment when compared to the children who did not develop myopia.

Despite these findings, many studies continue to demonstrate strong patterns of association between myopia and peripheral defocus. Sng, Lin, Gazzard, Chang, Dirani, Chia *et al.,* (2011) measured peripheral refractive error on 250 Singaporean children aged between 3 and 15 years, centrally and at 15° and 30° horizontally, both nasal and temporally. Children with high and moderate central levels (≤-3.00 D) of myopia displayed relative peripheral hyperopia at all eccentricities. The children with low central myopia (-0.50 D to -2.99 D) interestingly did not show relative peripheral

hyperopia at 15°, only at 30°. Emmetropes and hyperopes had relative peripheral myopia at all eccentricities.

Berntsen and Kramer (2013) compared the effect of Progressive Addition Lenses (PALS) and single vision lenses (SVL) on peripheral defocus. The 84 myopic children, aged between 6 and 11 years, were randomly allocated either PALs or SVL spectacles for 1 year. Unlike the current study, optical correction was worn during peripheral measurement and both the horizontal and vertical periphery were assessed. With the PALs in situ for the measurement, a relative myopic shift in peripheral defocus could be observed, on the nasal, temporal, and particularly, the superior retina due to the integrated plus addition. The SVLs caused a hyperopic shift in both horizontal and vertical meridians, although nearly half of the SVL wearers had superior myopic defocus. Overall, the children with peripheral myopic defocus in the superior retina experienced 0.24 D less myopia progression compared with those with hyperopic defocus in the superior retina.

This chapter aims to explore the natural variation in peripheral refraction longitudinally for myopic children randomly assigned to wear either a dual focus contact lens or a single vision contact lens.

5.2 Methods

See section 2.1 for full details of participants. A total of 27 myopic children aged, between 8 and 12 years at enrolment, had central refractive error and peripheral refraction assessed every 6 months for the period of 1 year and axial length measured annually. The children had been randomly allocated to wear either a novel dual focus lens or a single vision lens, 10 to 15 hours per day, 6 to 7 days per week

for 3 years (see section 3.2.2). Data collection commenced once the children had been wearing lenses for 6 months. No optical correction was worn while the central and peripheral refractive measures were taken.

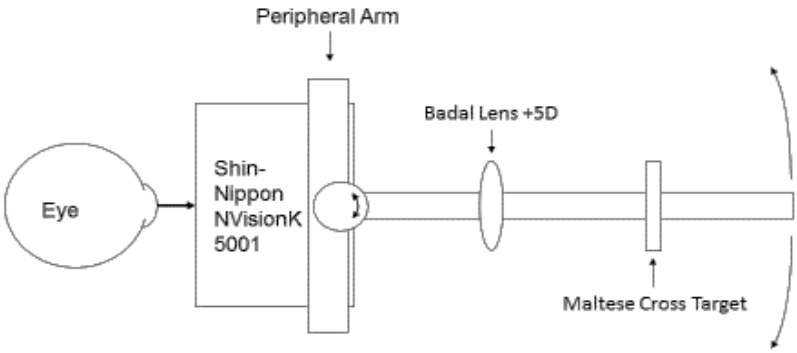


Figure 5.1 Shin-Nippon NVision-K 5001 with Badal lens and Maltese cross suspended on a rotational arm.

The participants were asked to sit at the Shin-Nippon NVisionK 5001, open-field autorefractor, resting their chin on the rest and their forehead against the support bar. Instructions were given to keep face forward throughout the measurements and fixate a Maltese cross (see Figure 5.1) through a +5 D Badal lens, which would be rotated in front of them. They were instructed to turn their eyes only and not their heads to view the eccentric targets. An eye turn technique is the most common method used for peripheral measurements with a Shin-Nippon autorefractor (Fedtke *et al*., 2009; Atchison, 2003; Atchison *et al.,* 2006; Mutti *et al.,* 2007; Calver *et al*., 2007) and while contact lenses can be displaced with a turned eye, affecting lens optical centre and therefore refractive measurements, the participants in the current study were measured without optical correction worn. Non-cycloplegic measurements were taken from the right eye, centrally and horizontally at 10°, 20°, 30° from fixation, both

nasally and temporally. Multiple peripheral locations were used to allow for variability in measurement, as they were taken towards the end of the appointment when the child was tired. Nasal and temporal measurements were each obtained to assess for asymmetry. Data were compared using both MSE and refraction additionally separated into sagittal (using power vectors M – J0 (Paune *et al.,* 2016)) and tangential (using power vectors M + J0 (Paune *et al.,* 2016)) foci to better define the expected increased astigmatism with greater peripheral field angle (Atchison *et al.*, 2006; Fedtke *et al.,* 2009).

5.3 Results

When data was assessed for normality, Child 12 was deemed an outlier for data which utilised the nasal peripheral retinal refraction. The control group, excluding this participant, showed a nasal retinal change in refraction ranging from -0.80 to +1.75 D at 6 months and from -0.67 to +2.30 D at 18 months, the nasal peripheral refraction change for Child 12 was +5.59 and +6.63 D respectively. Analysis with and without this participant has been stated where the participant was measured to be an outlier within a data set. Data are otherwise presented for this participant.

5.3.1 Mean data for both test and control groups

The mean data for all participants displayed overall relative hyperopia in both the nasal and temporal peripheral fields (see Appendix 13). A comparison of central and peripheral refraction data between participants between the 6 month and 18 month appointments can be seen in Figure 5.2 for the control group and Figure 5.3 for the

test group. Note length of error bars demonstrating the wide range of peripheral refraction data between participants.

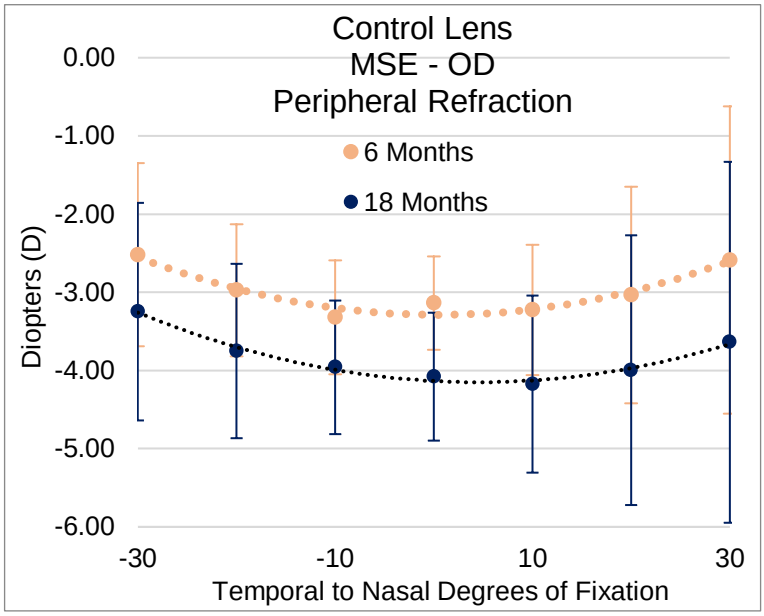


Figure 5.2 MSE central and peripheral refraction data comparing the 6 month and 18 month data for the control lens group.

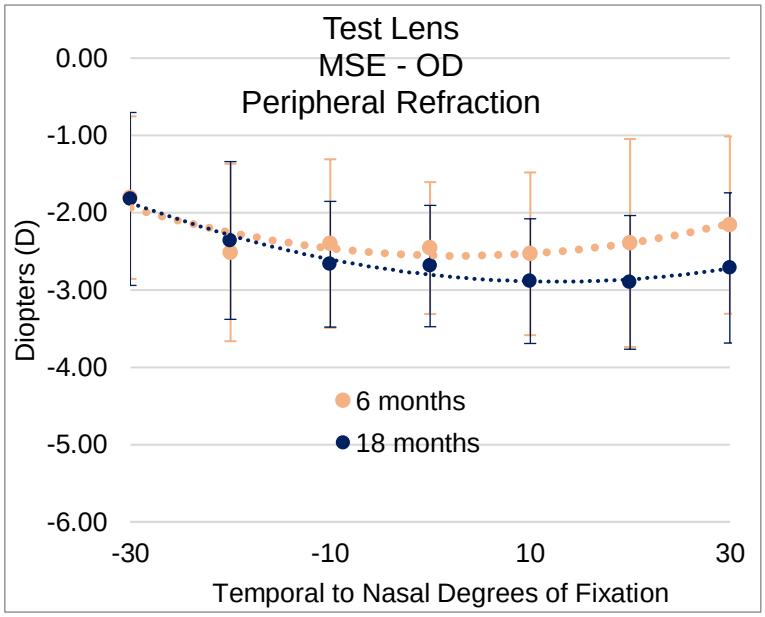


Figure 5.3 MSE central and peripheral refraction data comparing the 6 month and 18 month data for the test lens group.

Data are presented for the 30 degree peripheral refraction, in both the nasal and temporal retinal field, relative to the central refraction (see Table 5.1). The mean temporal and nasal peripheral refractions at 30 degrees are relatively hyperopic when compared with primary gaze, for both lens groups at each visit, with the exception of the nasal retina for the test group at the 18 month visit (see Table 5.1).

			Eccentricity			Peripheral Comparison	
Number of Participants	Lens Code	Visit Month	30° Temporal Retina (MSE)	Primary Gaze (MSE)	30° Nasal Retina (MSE)	30° Temporal Retina minus Primary Gaze (MSE)	30° Nasal Retina minus Primary Gaze (MSE)
n=12	**Control**	**6**	-2.52 ±1.17 D	-3.14 ±0.60 D	-2.59 ±1.97 D	0.62 ±1.06 D	0.55 ±1.73 D
n=11	**Test**	**6**	-1.8 ±1.05 D	-2.46 ±0.85 D	-2.16 ±1.15 D	0.65 ±0.76 D	0.3 ±0.53 D
n=14	**Control**	**12**	-2.72 ±1.00 D	-3.36 ±0.80 D	-2.59 ±2.16 D	0.64 ±1.06 D	0.77 ±1.58 D
n=12	**Test**	**12**	-1.74 ±1.09 D	-2.28 ±0.76 D	-2.18 ±1.13 D	0.54 ±0.81 D	0.1 ±0.97 D
n=14	**Control**	**18**	-3.25 ±1.39 D	-4.08 ±0.82 D	-3.64 ±2.31 D	0.83 ±1.07 D	0.44 ±1.98 D
n=13	**Test**	**18**	-1.82 ±1.12 D	-2.69 ±0.78 D	-2.71 ±0.97 D	0.87 ±1.05 D	**-0.02 ±0.56 D**
	Control	Mean	-2.84 ±1.20 D	-3.54 ±0.84 D	-3.08 ±2.02 D	0.7 ±1.04 D	0.46 ±1.53 D
	Test	Mean	-1.79 ±1.05 D	-2.48 ±0.79 D	-2.36 ±1.08 D	0.69 ±0.87 D	0.12 ±0.71 D

Table 5.1 Comparison of the MSE refraction data with standard deviation for primary, 30° temporal and 30° nasal refraction for the 6 month, 12 month and 18 month appointments, for both lens groups. Comparison data in the last two columns calculated the difference between primary gaze and peripheral refraction.

Research question 1: Has the nasal retina become more relatively myopic between the 6 month and the 18 month appointments?

Using the relative peripheral refraction at 30° nasal, the 6 month and 18 month data were compared. A paired t-test was performed for each lens group. The nasal retina did not show statistical progression of increasing relative myopia between the 6 month and 18 month visits for the control group (p=0.940) or the test group (p=0.178). Child 12 in the control group was deemed an outlier and was excluded from the above analysis, with Child 12 included there was also no statistical significance found (p=0.706).

5.3.2 Peripheral refraction in relation to primary gaze and myopia progression

Large variability in peripheral refraction was found between the participants in the current study. The difference between primary gaze and temporal retinal refractions at 30° ranged from -0.74 D to +3.36 D MSE and for 30° nasal retina from -0.80 to +7.06 D MSE. In contrast to the overall nasal and temporal peripheral hyperopia demonstrated in Figure 5.2 and Figure 5.3 for the combined cohort, when primary gaze was compared with 30 degrees eccentricity in the nasal and temporal retina for individuals, relative hyperopia was more consistently present, in the temporal retina (see Table 5.2).

n=23		MSE Refraction in Relation to Primary Gaze				12 Month Cycloplegic Autorefraction Progression	12 Month Axial Length Progression
Participant Number	Lens Type	6 Month		18 Month			
		Temporal Retina	Nasal Retina	Temporal Retina	Nasal Retina	(D)	(mm)
1	Control	2.70	0.40	1.86	-0.28	-1.00	0.32
2	Control	2.06	0.61	1.43	-0.12	-1.26	0.50
3	Control	0.48	0.36	1.54	0.67	-0.61	0.27
4	Control	-0.33	-0.02	1.21	-0.43	-1.25	0.38
5	Control	0.18	-0.60	0.15	-0.18	-0.52	0.20
6	Control	0.38	-0.80	0.75	0.23	-0.69	0.32
7	Control	-0.58	-0.69	0.00	-0.52	-0.74	0.27
8	Control	1.83	1.75	3.09	0.73	-0.78	0.33
9	Control	1.03	0.35	0.90	-0.46	-0.67	0.06
10	Control	0.24	-0.37	-0.43	-0.67	-0.56	0.08
11	Control	-0.08	0.04	-0.74	2.30	-0.53	0.36
12	Control	-0.46	5.59	1.84	6.63	-1.22	0.18
15	Test	1.12	1.15	0.39	1.39	-0.56	0.27
16	Test	0.58	0.58	3.36	0.47	-0.51	0.18
17	Test	0.27	-0.03	0.19	-0.75	0.10	-0.19
19	Test	0.44	1.16	-0.40	-0.49	-0.20	0.13
20	Test	0.13	-0.02	0.61	-0.18	-0.36	0.08
22	Test	0.37	0.41	0.33	0.40	-0.70	0.31
23	Test	1.30	0.25	1.34	0.24	-0.73	0.19
24	Test	0.48	0.10	1.77	-0.21	-0.93	0.26
25	Test	-0.15	-0.50	0.64	0.04	-0.42	0.15
26	Test	0.12	0.53	0.01	-0.55	-0.47	0.13
27	Test	2.53	-0.33	1.71	-0.13	-0.05	0.04

Table 5.2 Table to show MSE peripheral refraction at the 30 degree nasal and temporal retina, relative to primary gaze. The findings at the 6 month visit are compared with those for the 18 month visit. Relative myopia <0.00 D are shown in a lighter tone. 12 month cycloplegic autorefraction and axial elongation for each participant is also shown.

With the exception of 2 children (Child 16 and Child 27) with a single measurement, at a single visit, all of the children in the test lens group had maximum hyperopic peripheral refractive change, compared with primary gaze, below +2.00D (Table 5.2).

Research question 2: Was the amount of relative hyperopia correlated with myopia progression?

The 6 month MSE peripheral refraction data were assessed and the greatest hyperopic defocus present in either the nasal or temporal retina (when compared with primary gaze) was calculated for each participant. The maximum relative hyperopia was then compared with the 12 month refractive change and axial length progression to assess for correlation between myopia progression and the level of maximum hyperopic defocus in the peripheral retina.

With Child 12 included in analysis the control group (n=12) demonstrated a statistically significant strong negative correlation (r=-0.634, p=0.027) in cycloplegic refraction progression. There was no significant correlation between greater relative hyperopia at 6 months and increased axial length elongation at 12 months, (r=-0.006, p=0.985).

With Child 12 excluded from analysis, the control group (n=11) demonstrated strong negative correlation (r=-0.568, p=0.069) in cycloplegic refraction progression that was not statistically significant. There was a small positive correlation between greater relative hyperopia at 6 months and increased axial length elongation at 12 months, this was not statistically significant (r=0.469, p=0.146).

The control group maximum hyperopia ranged from 0.00 D to +2.70 D, maximum peripheral hyperopia for Child 12 was +5.59 D and was deemed an outlier in tests of normality, see box chart in Figure 5.4.

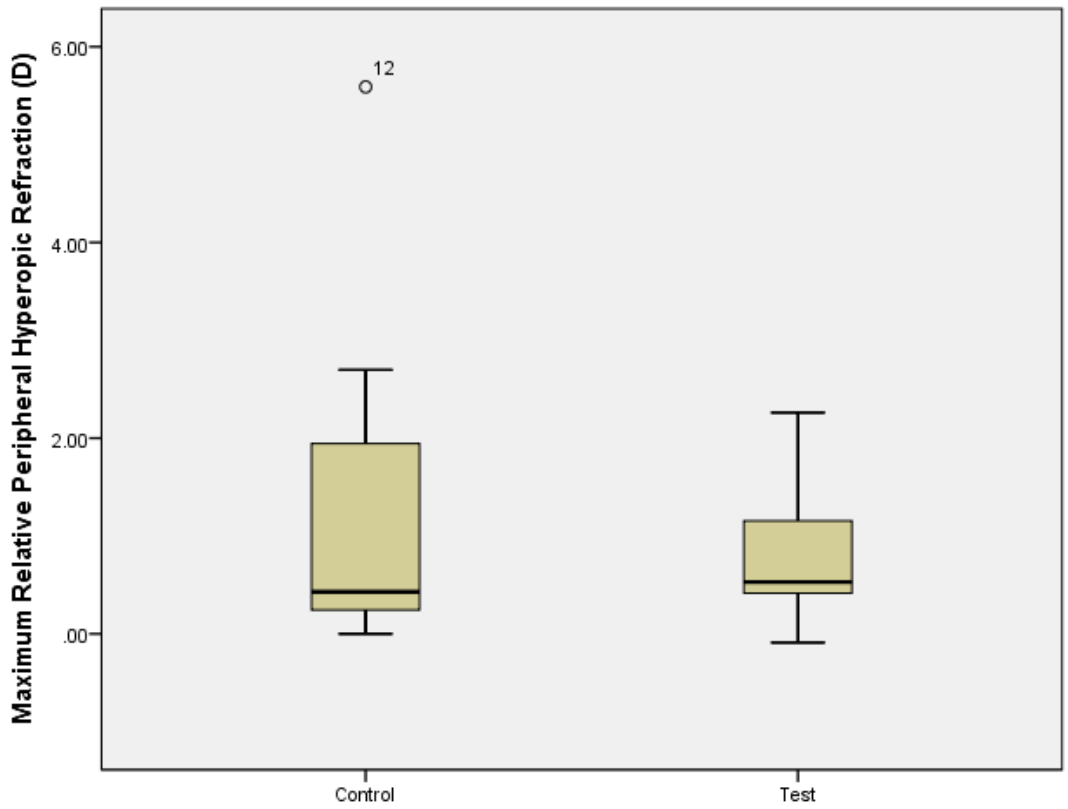


Figure 5.4 Box chart to show the 6 month maximum relative peripheral hyperopia for the control and test lens group.

There was no statistically significant correlation noted between hyperopic defocus at 6 months and either refractive myopia progression (r=+0.258, p=0.444) or axial elongation (r=-0.052, p=0.878) in the test group (n=11).

5.3.3 Peripheral refractions and traditional skiagram patterns

The participant's peripheral refractions were assessed individually and compared to traditional skiagram patterns (see section 1.1.6). Pattern types I and III, described by Ferree *et al.,* (1931) and Rempt *et al.,* (1971), are those traditionally associated with myopes. The type I skiagram pattern was evident in approximately 30% of the participants at the 6 month visit and 39% at the 18 month visit. Type III skiagram pattern was found only once, present in 1 participant overall, at the 18 month visit. An example of each pattern type can be seen next to a traditional skiagram (Figure 5.5 to Figure 5.9) using participants from the present study. Second order trend line is shown, extrapolated out to 60° periphery for comparison with traditional skiagram.

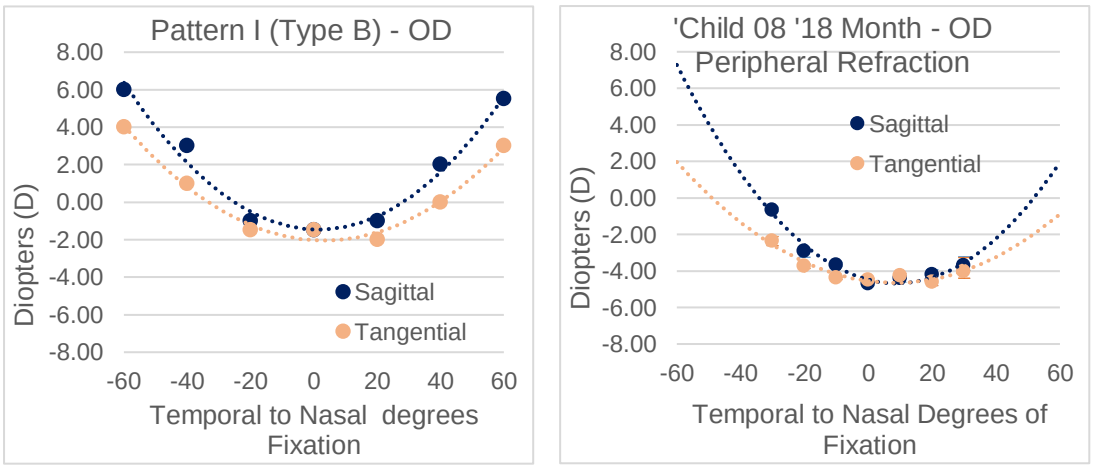


Figure 5.5 Comparison with traditional skiagram (Ferree *et al.,* 1931; Rempt *et al.,* 1971) and current study participant who exhibited pattern type I, error bars shown.

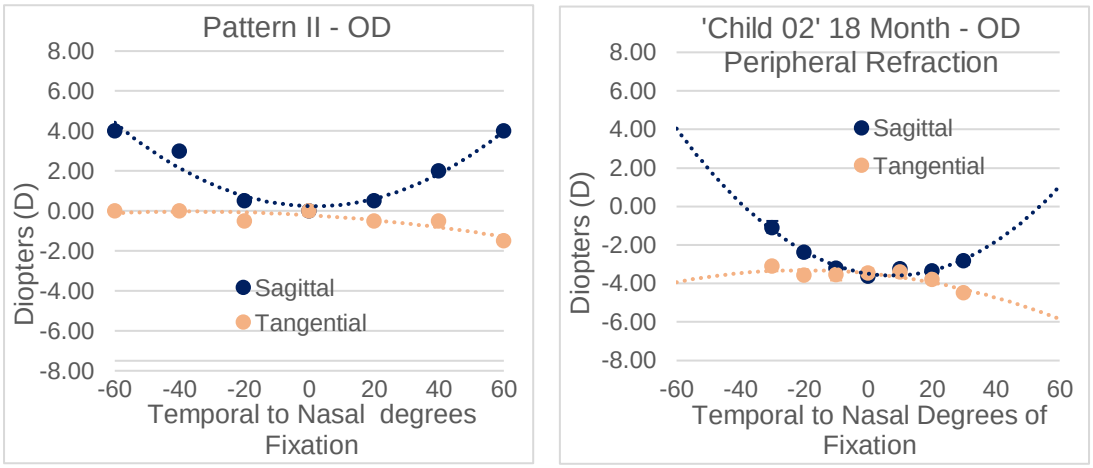


Figure 5.6 Comparison with traditional skiagram (Rempt *et al.,* 1971) and current study participant who exhibited pattern type II, error bars shown.

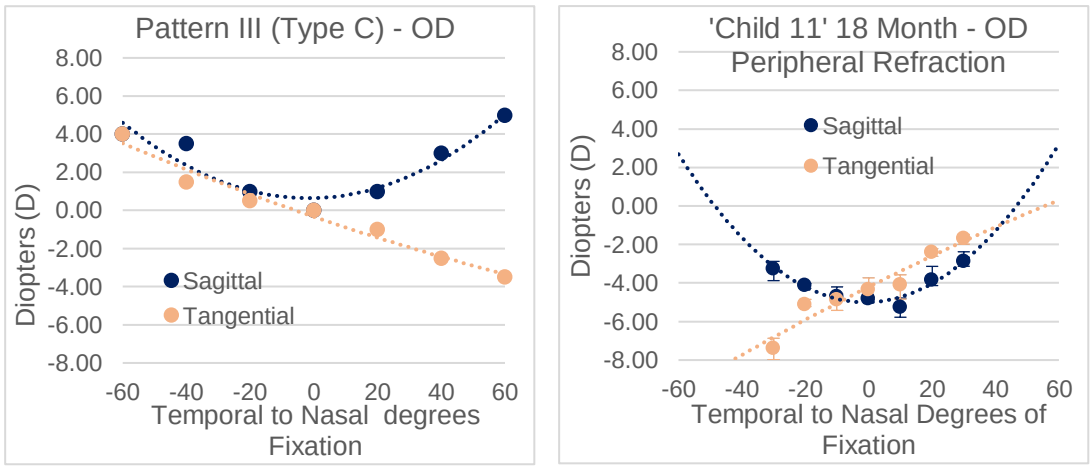


Figure 5.7 Comparison with traditional skiagram (Ferree *et al.,* 1931; Rempt *et al.,* 1971) and current study participant who exhibited pattern type III, error bars shown.

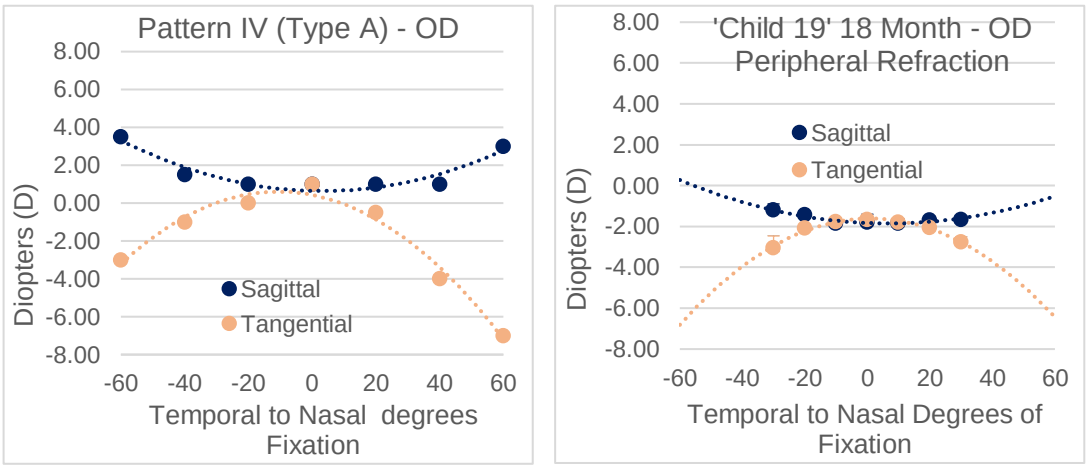


Figure 5.8 Comparison with traditional skiagram (Ferree *et al.,* 1931; Rempt *et al.,* 1971) and current study participant who exhibited pattern type IV, error bars shown.

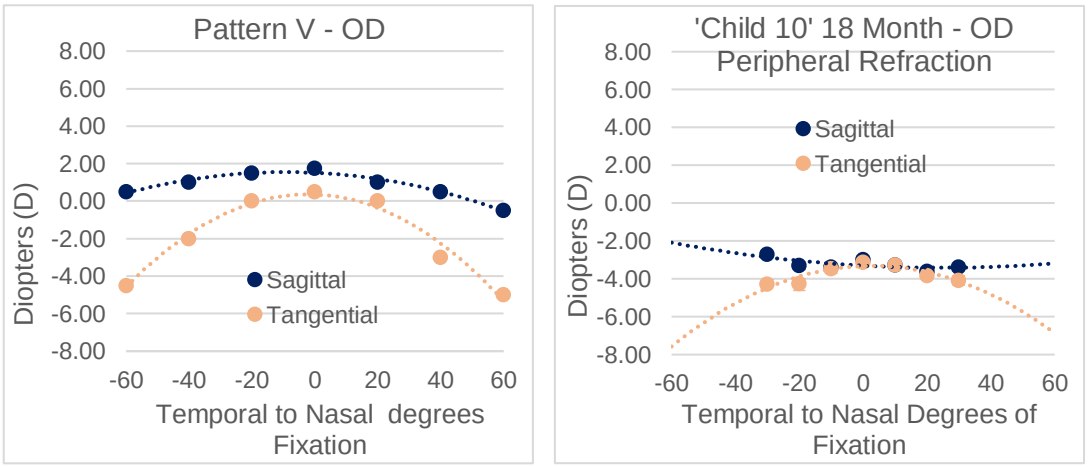


Figure 5.9 Comparison with traditional skiagram (Rempt *et al.,* 1971) and current study participant who exhibited pattern type V, error bars shown.

A one-way ANOVA was used to assess for significant differences in myopia progression between the skiagram patterns. There was no statistically significant difference between pattern type and 12 month cycloplegic refraction myopia progression or axial elongation. To summarise the skiagram patterns observed in

the current study, Table 5.3 details the percentage of children with each pattern type, at the 6 month and 18 month visits, for both the test and control group, along with the ANOVA probability results for each comparison.

n=23		Peripheral Pattern					One-way ANOVA	
Group	Visit	I	II	III	IV	V	12 Month cycloplegic progression	12 Month Axial Length progression
Control	6 month	4 33.33%	3 25.00%	0 0.00%	4 33.33%	1 8.33%	*p*=0.824	*p*=0.583
	18 month	6 50.00%	2 16.67%	1 8.33%	2 16.67%	1 8.33%	*p*=0.457	*p*=0.248
Test	6 month	3 27.27%	6 54.55%	0 0.00%	2 18.18%	0 0.00%	*p*=0.351	*p*=0.187
	18 month	4 36.36%	4 36.36%	0 0.00%	2 18.18%	1 9.09%	*p*=0.479	*p*=0.270

Table 5.3 Number of participants allocated to each peripheral pattern at the 6 month and 18 month appointments is shown, percentage of times the pattern was present in participants in brackets. One-way ANOVA significance for pattern type and 12 month cycloplegic refraction and axial length progression.

5.4 Discussion

All peripheral refraction data referred to in this chapter were obtained without optical correction and using a Shin-Nippon NVisionK 5001. The Shin-Nippon autorefractor has been widely used to assess peripheral refraction in children (Schmid, 2011; Mutti *et al.,* 2007; Lee and Cho, 2013; Kang and Swarbrick, 2011; Chen *et al.,* 2010) and has shown good agreement with comparable instruments used to obtain peripheral refraction measurements (Atchison, 2003) see section 2.2.3.

Primary gaze, nasal and temporal peripheral refractions were plotted for both lens groups (see Figure 5.2 and Figure 5.3) and generally demonstrated a trend of relative peripheral hyperopia. This could also be observed in Table 5.1 where nasal and temporal retinal refraction were additionally described in relation to primary gaze. As used by Mutti *et al.,* (2000), in order to compare relative change in the periphery, the mean spherical equivalent cycloplegic autorefraction in primary gaze was subtracted from that of the 30 degree temporal gaze (nasal retinal field). Inter-child differences were found between the peripheral refractions of the participants in the current study and this is clearly demonstrated by the length of error bars (as shown in Figure 5.2 and Figure 5.3) and the amount of standard deviation shown in Table 5.1. Despite variances between the participants, Table 5.2 demonstrates that relative hyperopia was more consistently present, in the temporal retina. Figure 5.2 shows the combined data for the control group with a fairly symmetrical, although more myopic pattern appearance during the 12 month comparison duration. The pattern of myopia progression differs for the test group, however, (see Figure 5.3) a nasal myopic shift has become apparent by 18 months, this can be observed also, and is highlighted in, Table 5.1. A relative myopic shift, suggesting a trend of change to the uncorrected peripheral retinal nasal refraction, away from hyperopia to a more myopic refraction in response to the test lens. There was, however, no statistically significant change apparent in peripheral refraction between 6 and 18 months of wearing the test lens (p=0.125).

Peripheral measurements were taken at 3 consecutive visits and the average difference between primary gaze and peripheral refraction were +0.70 (±1.04 D) temporally and +0.46 (±1.53 D) nasally for the control group and +0.69 (±0.87 D),

+0.12 (±0.71 D) respectively for the test group. The temporal retinal data in the current study were comparable to the findings reported by Mutti *et al.,* (2000) of +0.80 (±1.29 D) for myopic children, in the temporal retina (nasal visual field). No nasal retinal measurements were taken in the Mutti *et al.,* (2000) study and therefore further comparison was not possible. The mean 30° peripheral refraction for combined hemi-fields described in a New Zealand study by Backhouse *et al.,* (2012) was +0.90 (±0.14 D), however, myopia was of a higher baseline level (-5.00 D to -8.00 D) than in the current study (-0.78 to -3.95 D at baseline appointment) and the participants were older (age range 19 to 29 years) than the developing myopic children in the current study. Lin *et al.,* (2010) reported greater relative hyperopia bilaterally in a study using Chinese children (aged 8 to 15 years) with low myopia (MSE -0.75 to -3.00 D) with mean 30° peripheral refraction of +1.32 (±0.75) D nasally and +1.01 (±0.66) D temporally. Chinese children with moderate myopia were also assessed (MSE -3.25 D to -6.00 D) and found 30° peripheral refraction of +1.61 (±0.84) D nasal and +1.61 (±1.47) D temporally, suggesting a possible ethnic difference in peripheral refraction between this and the findings from the predominantly white participant studies also detailed in this section.

The maximum amount of relative peripheral hyperopia, when compared with primary gaze, for each participant, was compared for correlation with the 12 month cycloplegic myopia progression and axial elongation. The control group demonstrated a statistically significant strong negative correlation (r=-0.634, p=0.027) with 12 month cycloplegic refractive progression, suggesting that the greater the hyperopic defocus in the periphery, the more myopia progression was apparent by 12 months. Due to the presence of an outlier, data was also provided

without this participant and no statistical significance was found (p=0.069). As discussed in Chapter 3, the test group demonstrated less 12 month myopia progression in both cycloplegic refraction and axial length elongation, when compared with the control group (see section 3.3.1). There was no statistically significant correlation noted between hyperopic defocus at 6 months and either refractive myopia progression (r=+0.258, p=0.444) or axial elongation (r=-0.052, p=0.878). These measurements were taken without the contact lenses in situ and therefore the slowing of progression of myopia may be theoretically due to the dual focus lens correcting much of the unwanted hyperopic defocus when worn that may otherwise have caused greater myopia progression. The test lens group generally had maximum hyperopic peripheral refractive change, compared with primary gaze, below 2.00D. When wearing a dual focus lens which provides +2.00D addition in the periphery the test group would have experienced peripheral myopic defocus out to 30° degrees peripherally, both nasally and temporally, during lens wear (Table 5.2). All of the control group members had some level of relative hyperopic peripheral refraction within the measured eccentricities, when compared to primary gaze and would therefore be assumed to have experienced hyperopic defocus with and without their single vision contact lens correction (Table 5.2).

Patterns associated with myopia commonly demonstrate relative hyperopia in the nasal and temporal fields, when compared with primary gaze. Peripheral skiagram patterns related to myopia are generally the type I and type III shape, where both the sagittal and tangential oblique astigmatism, in either one or both horizontal semi-fields, are relatively hyperopic in comparison to primary gaze (Ferree and Rand, 1931; Hoogerheide *et al.,* 1971; Rempt *et al.,* 1971). Owing to the limited sample

size of the current study, full statistical analyses was not possible, however data are included in this chapter to allow comparison with previous published reports of peripheral refraction in children. When data were combined, for all participants, however, the type I skiagram pattern was evident in approximately 30% of the participants at the 6 month visit and 39% at the 18 month visit. Type III skiagram pattern was found only once, present in 1 participant overall, at the 18 month visit. There was no statistical difference between skiagram pattern and myopia progression for either lens group. The asymmetry described earlier in this section made the allocation of pattern type troublesome. Data were extrapolated to 60 degrees to aid comparison with traditional skiagram patterns however allocation could arguably be described as subjectively imperfect.

Studies have commonly shown good symmetry between the nasal and temporal semi-fields of the horizontal peripheral field (Rempt *et al.,* 1971; Calver *et al.,* 2007), however, many have reported asymmetry in myopes, hyperopes and emmetropes (Logan *et al.,* 2004; Ehsaei *et al.,*2013; Millodot, 1981; Seidemann *et al.,* 2002; Tabernero and Schaeffel, 2009). Logan *et al.,* (2004) reported a greater asymmetry in white eyes compared with those of Chinese participants. An inter-eye asymmetry in retinal shape has also been described by Logan *et al.,* (2004), Gilmartin *et al.,* (2013) and Nagra *et al.,* (2014).

Peripheral refraction research regularly uses one eye and a select few eccentricities, usually limited to along the horizontal meridian across approximately 60 degrees. It was a limitation of the current study to have restricted measures to one eye and also not to have measured along the vertical meridian. Additionally, the small sample group and inter-child refraction variation in the current study may have masked

peripheral refractive change in the results and would, therefore, benefit from combined data at the conclusion of the multi-centre study to allow for further assessment.

5.4.1 Summary

A nasal retina myopic shift in peripheral refraction was observed in the uncorrected test lens group that was not statistically significant in this small sample. Longitudinal changes in peripheral refraction for the broader multi-centre cohort may help to indicate if permanent peripheral retinal changes occur due to dual focus contact lens wear.

There was no significant association between the amount of maximum relative peripheral blur found in the uncorrected participants and their myopia progression. As shown in Chapter 3, there was measurably less myopia progression present in the test lens group when compared with the control group. Peripheral refraction measurements obtained without contact lenses worn may be less relevant than the refraction profile when the eyes are in their optically corrected state. Future work should include larger sample size as well as peripheral retinal measurements with dual focus contact lenses in situ, to confirm whether myopic defocus is successfully achieved across the peripheral retina. This would also highlight whether a higher peripheral plus addition is required for certain children.

The broad variation that existed between the participant's peripheral refraction data indicates that myopia intervention lenses may require modelling with individual parameters, giving maximum hyperopic refraction in order to induce widespread peripheral myopic defocus. Study of the peripheral refractive error in children may

better aid understanding of the relationship between the peripheral retina and myopia.

6. PUPIL SIZE AND RESPONSE IN MYOPIC CHILDREN AND YOUNG ADULTS

6.1 Introduction

It is well documented that pupil size decreases during accommodation, with a greater amplitude of response with greater accommodative effort (Loewenfeld, 1999; Atchison and Smith, 2000; Zinn, 1972). Pupil diameter decreases with age and also with higher levels of illumination (Winn *et al.,* 1994; Levin *et al.,* 2011; Loewenfeld, 1999; Birren *et al.,* 1950) causing much variability in size, within and between individuals. Pupil diameter in humans is thought to range from approximately 2 mm up to a maximum of 8 mm (Atchison and Smith, 2000). Hashemi *et al.,* (2015) in a study assessing ocular biometric components of 683 participants aged between 6 and 18 years, using a Lenstar optical coherence biometer, described mesopic mean pupil diameter of 4.97 (CI, 4.91–5.03) mm. Daluwatte *et al.,* (2012), using near infrared cameras, measured pupil diameters for 107 participants aged between 6 and 17 years in two lighting levels, in light adapted conditions (luminance 30 cd/m^2) 6.58 ±0.61 mm and dark adapted conditions (<0.02 cd/m^2) 7.44 ±0.77 mm.

MacLachlan and Howland (2002) measured pupil diameter for 1311 participants aged between 1 month and 19 years. The participants were placed under 300 lux ambient lighting for 5 minutes followed by 1 minute in mesopic lighting (15.9 ±0.50 lux) conditions. Using a flash powered isotropic photorefractor technique the participant's pupils were photographed from 1.5 m away. Pupil diameters were reported by age and sex. The female participants (with a mean age of 8.6 to 12.4 years) had a pupil diameter which ranged from 6.94 (±0.98) mm to 7.36 (±0.90) mm

and the male participants (with a mean age 8.5 to 12.5 years) ranged between 6.88 (±0.88) mm and 7.04 (±0.80) mm diameters.

Adult pupil responses to a near visual demand have been more widely considered than for infants and children (Bharadwaj *et al.,* 2011). Research exploring constriction in children and young adults have been described as equivocal (Gislen *et al.,* 2008) with evidence for both a reduction in young persons (<20 years old) (Wilhelm *et al.,* 1993) and the absence in children, of accommodative pupil miosis during near accommodation (Wilhelm *et al.,* 1993; Schaeffel *et al.,* 1993). Reduction in pupil size with illumination has been well documented in children as well as adults (Daluwatte *et al.,* 2012).

Knowledge of pupil size can be important for certain myopia control interventions such as dual or multi-focal contact lenses that rely on having a pupil large enough to allow access to the peripheral retina. As discussed in section 1.3.4.2 a dual focus lens has concentric treatment zones. Using the Anstice and Phillips (2011) lens as an example, in order to access and view through the smallest treatment zone, the minimum pupil size would need to be greater than 3.36 mm.

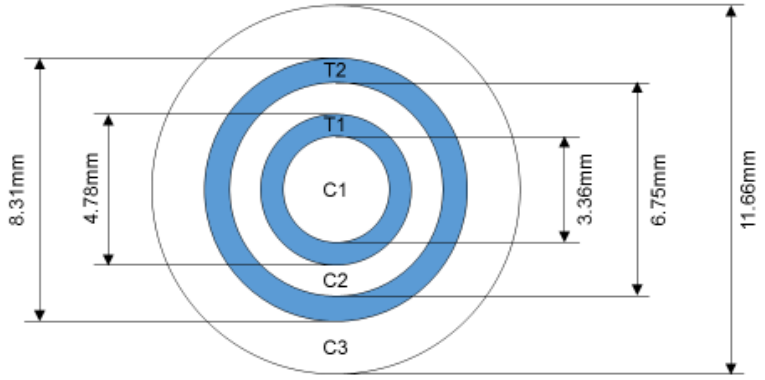


Figure 6.1 Example of a dual focus lens with treatment and correction zone diameters. Redrawn from Anstice and Phillips (2011)

The purpose of this study was to look at the normative data for this cohort and to compare pupil size in children and young adults using the same instrumentation to assess minimum and maximum pupil size and response, under photopic and mesopic conditions, at distance and near.

6.2 Methods

See section 2.1 for full details of participants. Pupil measurements were taken from 27 participants aged 8 to 12 years with myopia (≤-0.75 D MSE) and 40 young adults aged 19 to 24 years with myopia (≤-0.75 D MSE). A NeurOptics Pupillometer (NeurOptics Incorporated, Irvine, California), see section 2.2.4.2, was used to record the diameter of the pupils. The measurements were taken from the right eye only. Photopic room conditions were 447 lux and mesopic 12.5 lux as measured by Chauvin Arnoux CA810 Lux Meter (Chauvin Arnoux Group, Dewsbury, England), see Figure 2.2.

The participant was asked to fixate a +0.4 logMAR optotype on the near chart (40 cm) and +0.7 logMAR optotype on the distance chart (40 m), with their left eye. The participants were fully corrected for distance vision and wore their own spectacles or contact lenses. Target size and distance were chosen in order to relax accommodation at distance, while encouraging active accommodation of 2.50 D to the near target. Schaeffel *et al.,* (1993) demonstrated that accommodative pupillary response was absent in children at 4.00 D and unreliable at 10 D. A 23 cm (4.35 D) working distance has been shown to require a high level of accommodative and convergence response (Narayanasamy *et al.,* 2016). The greater working distance of 40 cm, a reduced demand of just 2.50 D, was chosen in the current study as a close approximation of the working distance for desk based school work and a reasonable balance between potentially unreliable data if the accommodative demand was too high and ensuring sustainable accommodation during the measurement period.

An average of 3 measurements were taken for both distances and lighting levels. The participants were asked to slowly read out the letters at near, to show they were actively accommodating whilst the measurements were taken. Data for the two groups were then compared and analysed.

6.3 Results

The mean pupil size and range, at near and distance, in both photopic and mesopic conditions are shown in Table 6.1 along with the change in pupil diameter to an accommodative target, for both children and young adults.

	Pupil diameter range and mean pupil size (mm)					
	Photopic		Mesopic		Photopic size change from distance to near	Mesopic size change from distance to near
	Distance	Near	Distance	Near		
Young Adults Range	3.30–7.20	2.80–7.20	3.60–7.30	3.20–7.50	-1.50–+0.40	-1.20–+0.80
Mean with SD	5.10 ±0.91	4.70 ±0.99	5.80 ±0.88	5.90 ±1.01	-0.40 ±0.48	+0.10 ±0.42
Children Range	4.10–6.40	3.90–6.00	4.60–7.10	5.00-7.40	-1.30–+0.20	-0.40–+1.30
Mean with SD	5.20 ±0.52	4.80 ±0.50	6.20 ±0.65	6.30 ±0.62	-0.40 ±0.38	+0.10 ±0.35

Table 6.1 Range and mean with standard deviation of pupil size, at near and distance, in both photopic and mesopic conditions, with accommodative change in pupil size, for both children and young adults

The children had larger pupils, on average, in both lighting conditions and the range of pupil size was smaller for the children than the young adults. (see Figure 6.2 and Figure 6.3). A repeated measure ANOVA was carried out and indicated an illuminance and distance interaction, however there was no statistically significant effect for age ($p = 0.150$). Data are summarised in Table 6.1.

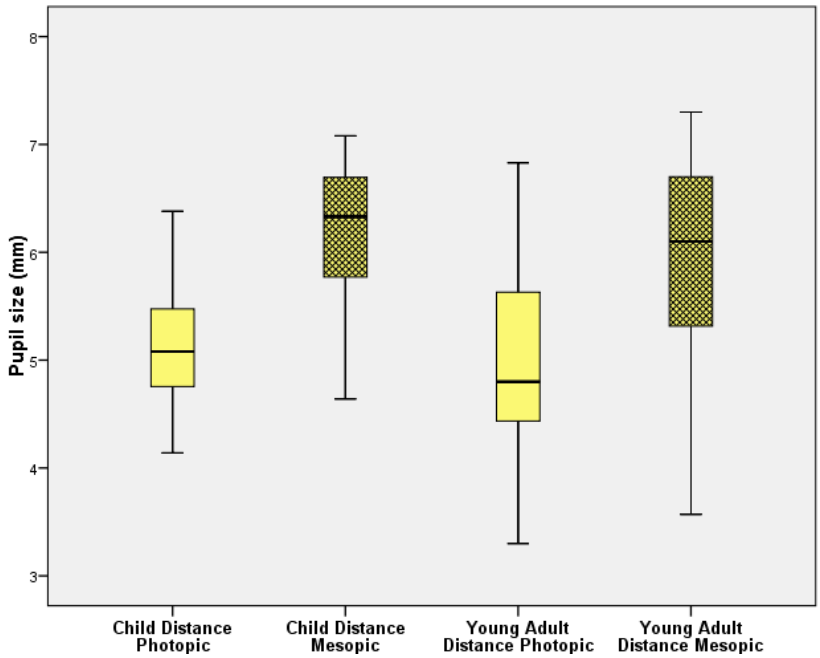


Figure 6.2 Box chart to show child and young adult pupil size at distance for both photopic and mesopic conditions.

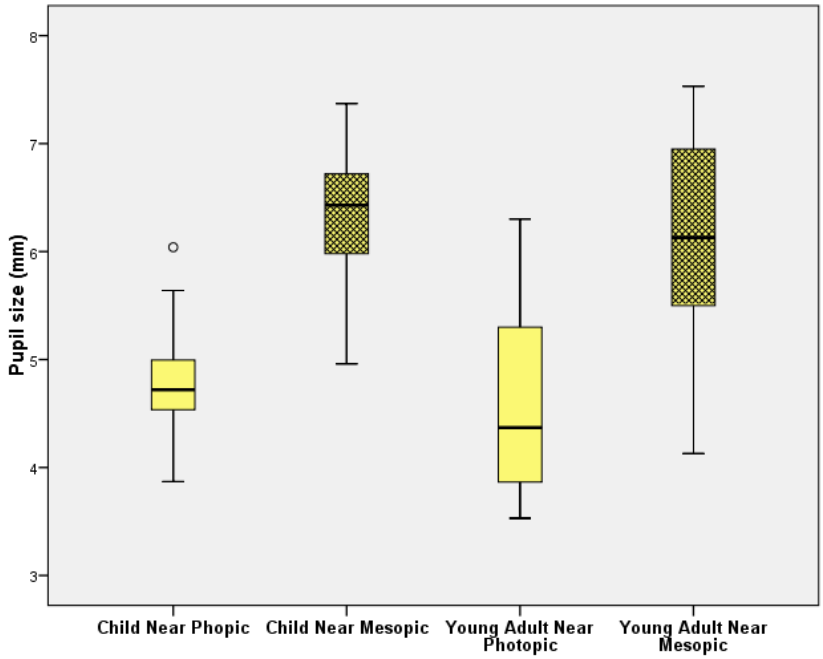


Figure 6.3 Box chart to show child and student pupil size at near for both photopic and mesopic conditions.

The mean accommodative change in pupil size was found to be similar (p=0.53), in photopic conditions for children -0.40 (±0.38) mm and young adults -0.40 (±0.48) mm. Likewise, mydriasis in mesopic conditions also corresponded (p=0.86) with +0.10 (±0.35) mm for children when compared with young adults +0.10 (±0.42) mm. See Figure 6.4.

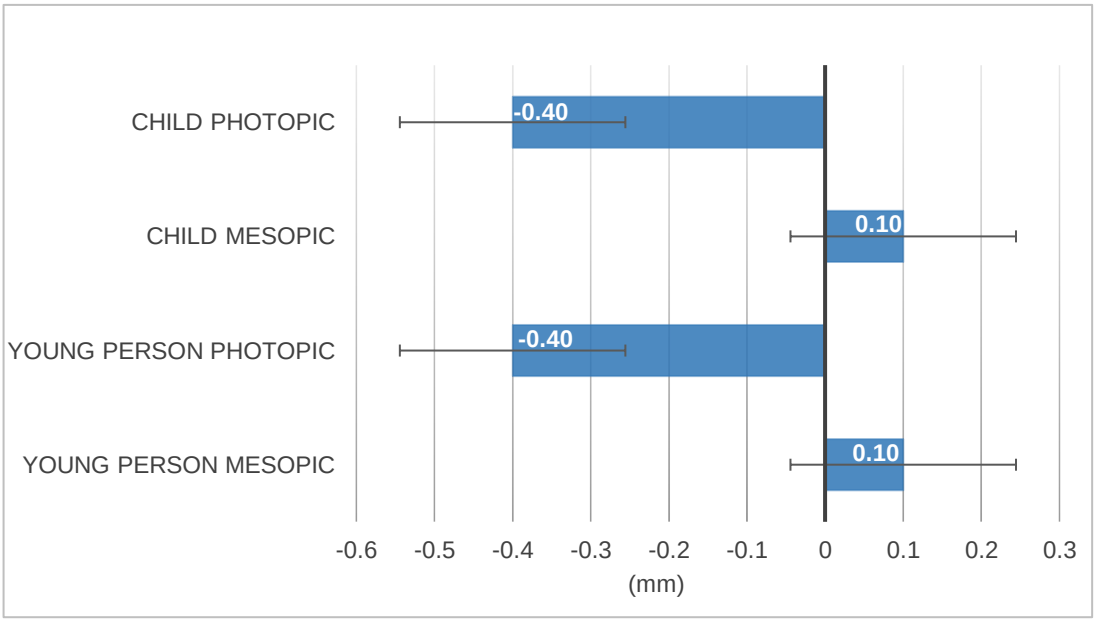


Figure 6.4 Bar chart to show average change in pupil size (mm) following accommodation to a near target in photopic and mesopic conditions for both children and young adults.

Pupil measurements were taken with the allocated study contact lenses worn. Using an independent samples t-test the average pupil size at near was compared between the participants who wore the dual focus contact lens and those who wore the single vision contact lens. There was no statistically significant difference with pupil size between the two groups for either photopic conditions (p=0.547) or mesopic conditions (p=0.577). There was, however, a statistically significant difference (p=0.031) in accommodation (see section 4.3.2) between the two groups with a

greater lag of accommodation in the control lens wearers (-0.73 ±0.59 D) than test lens wearers (0.08 ±0.82 D).

6.4 Discussion

In agreement with published data, pupil diameter was found to be smaller in photopic conditions compared to mesopic conditions for both groups and pupil size was overall slightly smaller in the older age group (Winn *et al.,* 1994; Levin *et al.,* 2011; Loewenfeld, 1999; Birren *et al.,* 1950; MacLachlan and Howland, 2002).

There is a paucity of research into pupil size and response in children for different lighting levels and working distances. As can be seen in Table 6.2 studies of pupil size have used a variety of techniques, age groups as well as lighting levels and descriptions making comparison challenging.

	Technique	Number of Participants	Age Range	Pupil Diameter	Description of Lighting Level
Hashemi *et al.,* 2015	Lensstar Optical Coherance Biometer	683	6 - 18 years	4.97 mm (CI, 4.91–5.03) mm	'mesopic'
Daluwatte *et al.,* 2012	Infrared Cameras	107	6 - 17 years	6.58 (±0.61) mm 7.44 (±0.77) mm	30 cd/m^2 <0.02 cd/m^2
MacLachlan and Howland, 2002	Flash Powered Photorefractor	1311	1 month - 19 years	5.77 - 7.53 mm	15.9 (±0.5) lux

Table 6.2 Studies of pupil size in children and young people in varying lighting levels

For children in the current study pupil size at near ranged from 3.90 to 6.00 mm (mean 4.80 ±0.50 mm) in photopic conditions and from 5.00 to 7.40 mm (mean 6.33 ±0.62 mm) in mesopic conditions. MacLachlan and Howard (2002) measured child pupil diameter in 1311 participants, aged from 1 month to 19 years, in 15.9 lux illumination. They found that for the 10.5 year age range, mean pupil diameter at distance was 7.06 (±0.89) mm for girls and 7.22 (±0.91) mm for boys. The children in the current study had a mean age of 10 years and had a mean distance mesopic pupil size of 6.20 (±0.70) mm girls and 6.20 (±0.60) mm for boys.

As discussed in section 1.4, the data by Winn *et al.,* (1994) were used as a pupil size guide for the development of the dual focus contact lens by Anstice and Phillips (2011). This lens was then trialled on children aged 11 to 14 years. The age range used in the Winn *et al.,* (1994) pupil study was 17 to 83 years, broader and older than used in the current study or in the Anstice and Phillips (2011) study. Additionally, Winn *et al.,* (1994), used a Badal lens, at near, however, there could still have been an element of proximal accommodation that may have induced pupil constriction.

At low illumination, the mesopic distance pupil size difference, found in this study, was 0.40 mm between the age groups. Winn *et al.,* (1994) calculated a 0.043 mm reduction in pupil size per year as people age. The median age of the child group, in the current study, was 10 years and the young adults 21.5 years. Therefore, if the calculation from Winn *et al.,* (1994) is applied to the current study (11.5 years difference x 0.043 = 0.49 mm), a close agreement between the two studies is found.

The children and young adults in the current study show comparable size in pupil diameter to other pupil studies (Winn *et al.,* 1994; Levin *et al.,* 2011; Loewenfeld,

1999; Birren *et al.,* 1950; MacLachlan and Howland, 2002, Chen *et al.,* 2012). While accepting the anatomical separation between cornea and pupil, it is thought that the children trialling the dual focus contact lens discussed in Chapter 3 would successfully access the treatment zones in the current lens design (presumed to be approximately 3.36 mm), as all participants had minimum pupil diameters of ≥3.90 mm. Minimum and maximum pupil size found in the current study are shown in relation to concentric zones in Figure 6.5 and Figure 6.6. Of the participants within the young adults group, four out of forty (10%) fell below a 3.36 mm minimum pupil size in either photopic conditions or for mesopic conditions at a near working distance. Children and young adults with progressing myopia, who may otherwise be suitable to use this contact lens, would need a pupil size in excess of 3.36 mm in both photopic and mesopic conditions or they would not visually access the first treatment zone and would therefore use the distance segment only, making it effectively a single vision contact lens.

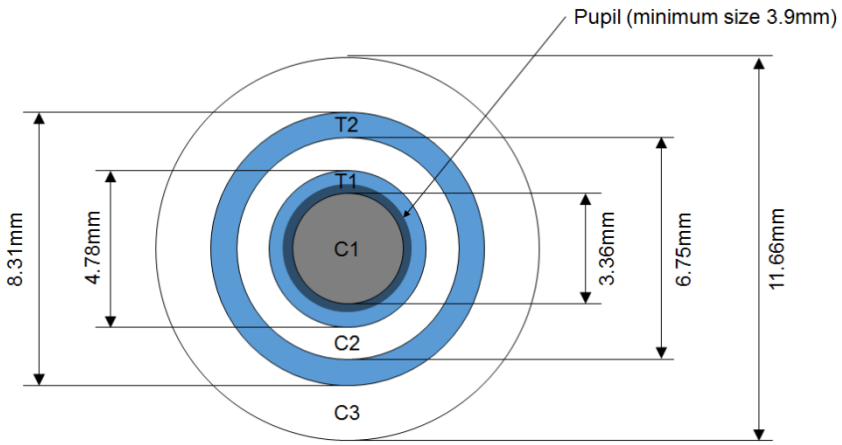


Figure 6.5 Example of a dual focus lens with mean minimum pupil size from the current study. Redrawn from Anstice and Phillips (2011)

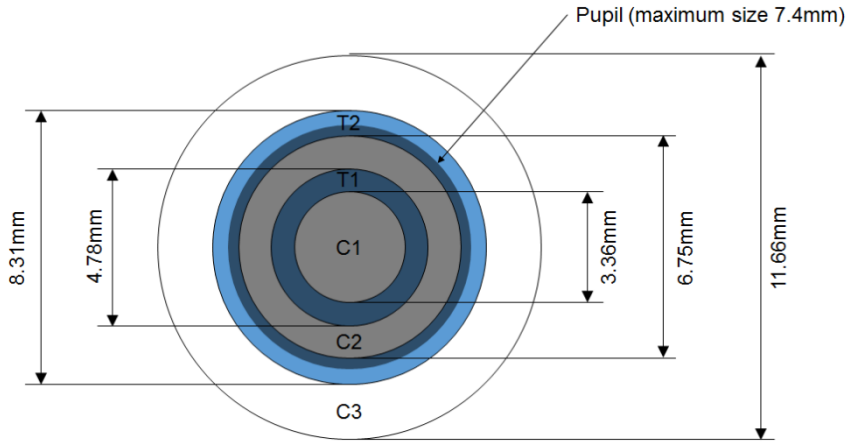


Figure 6.6 Example of a dual focus lens with mean maximum pupil size from the current study. Redrawn from Anstice and Phillips (2011)

Adults display pupil constriction when viewing a near target as part of the accommodative near pupil response (Atchison and Smith, 2000; Levin *et al*., 2011; Zinn, 1972). A number of studies have found a reduction or complete lack of accommodative pupil miosis during near accommodation with children and infants (Bharadwaj *et al*., 2011; Gislen *et al*., 2008; Schaeffel *et al*., 1993). The increase in pupil size for both groups, to a near target in mesopic conditions, was an unexpected finding in the current study. Prior to myopia onset, the crystalline lens is thought to become thinner and flatter (Mutti *et al.,* 2012). The previously associated compensating action between the crystalline lens and axial growth appear to become interrupted at the onset of myopia (Mutti *et al.,* 2012). A myopic crystalline lens, being of thinner structure, would be expected to have fewer aberrations. Aberrations have been shown to increase with greater pupil size (Paquin *et al.,* 2002; Wang *et al.,* 2003). Therefore, if aberrations were already minimal in the young adults and children in the present study, it could be theorised that the stimulus to constrict, to reduce aberrations, would not be present. Additionally, it has been shown that pupil

constriction improves depth of focus and reduces the required accommodative effort (Levin *et al.,* 2011). The higher levels of accommodation found in younger people may account for a reduced requirement for pupil constriction in both of these age groups.

Wilhelm *et al.,* (1993), Schaeffel *et al.,* (1993) and MacLachlan and Howard (2002) used binocular devices, whereas a monocular device was used in this study. The removal of binocular cues may have an effect on the normal responses to converge and accommodate and therefore, affect the pupillary response. Binocular measurement may better resemble normal conditions for participants and it would have been of interest to have additionally used a binocular measurement for comparison purposes. Mean pupil diameter, accommodation and vergence responses have been found to be greater under binocular viewing conditions compared with monocular, for infants, children and adults showing that without binocular cues the overall responses in the near triad (accommodation, convergence and pupil response) may be reduced (Bharadwaj *et al.,* 2011).

The accommodation accuracy to a near target was found to be better in children wearing dual focus contact lenses compared to single vision contact lenses (see section 4.3.2). As accommodation and pupil reactions are both part of the near vision triad it is therefore plausible that the pupil response could be expected to be altered in children wearing the dual focus lenses compared to the control group. No differences in pupil size were found for the two groups of children in either lighting condition. Similar findings have been reported by Sreenivasan *et al.,* (2011) when assessing the effects of near adds on the variability of accommodative response in myopic children. Pupil response was compared in children aged 7 to 14 years

wearing distance correction and fixating a target at 33cm and subsequently with +2.00 D and -2.00 D adds. Small reductions in pupil diameter were only found for the -2.00 D add condition and not for the +2.00 D add or distance vision correction conditions.

6.5 Summary

Pupil size in this child cohort is large enough to allow peripheral myopic defocus to be imposed with dual focus contact lenses in both lighting levels and when viewing both distance and near targets. The pupil size in the young adults was also of a sufficient size to suggest that most of the group (90%) would have experienced imposed peripheral myopic defocus had they worn dual focus contact lenses, in both lighting levels and at both distance and near targets.

Further studies measuring older adults, participants with varying ametropia and additional target distances would be beneficial. Whether similar findings would also occur under binocular viewing conditions is unknown, future work should consider this.

7. SELF-REPORTED TIME SPENT OUTDOORS AND MYOPIA PROGRESSION

7.1 Introduction

Recent studies have shown that increased time spent outdoors may be protective against myopia development (He *et al*., 2015; Rose, Morgan, Ip *et al.,* 2008; Rose, Morgan, Smith *et al.,* 2008; Jones *et al.,* 2007). Progression (Jones-Jordan *et al.,* 2012) and stabilisation (Scheiman *et al.,* 2014) of myopia may be less associated with outdoor time. The exact mechanism to explain why time outdoors may lower the risk of, and protect against, myopia remains unclear (Pan *et al.,* 2012; Flitcroft, 2012; Smith *et al.,* 2012; Wu *et al.,* 2013). Rose, Morgan, Ip *et al.,* (2008) proposed that an increased intensity of light found outdoors may provide protection, due to the stimulation of an increase in the retinal transmitter dopamine, which inhibits eye growth. This theory is supported by animal studies (Ashby *et al.,* 2009; Smith *et al.,* 2012).

Smith *et al.,* (2012) observed an 87% reduction in myopic anisometropia in monocular, form deprived infant monkeys who were exposed to an additional 6 hours per day of 25,000 lux illuminance in addition to normal laboratory illuminance (15 to 630 lux). Ashby and Schaeffel (2010) found that chicks exposed to high illuminance of 15,000 lux, 5 hours per day, had a significantly slower compensation to negative lenses when compared to those reared in normal laboratory illuminance of 500 lux. When the chicks were injected daily with Spiperone, a dopamine receptor antagonist, the protective effect was eliminated. Quartz-halogen lights were used in this study, which do not emit ultraviolet (UV) waves and thereby indicating that UV light is

unlikely to be a factor in the protective quality of light in animal studies (Ashby *et al.,* 2009).

An alternative theory suggested by Flitcroft (2012) considers the outdoor environment and its effect on defocus on the retina. Flitcroft (2012) suggests that the greater distance experienced outdoors compared with indoors may cause a dioptric flattening which impacts how the eye responds to defocus. Pupil size will be smaller when outdoors due to the higher levels of illumination, creating an increased depth of focus and a reduction in image blur (Ashby *et al*., 2009).

Associations have been made with myopia and Vitamin D receptor polymorphism (Mutti, Cooper *et al.,* 2011) additionally, there is some indication that myopes may have a lower average blood content of vitamin D than non-myopes (Mutti and Marks, 2011).

Guggenheim *et al.,* (2014) analysed data for children participating in the Avon Longitudinal Study of Parents and Children (ALSPAC). They hypothesised that vitamin D mediated the protective effects of time outdoors against myopia. Vitamin D was found to be a biomarker for time spent outdoors although there was no statistically significant data to suggest an association between the participant serum level and later myopia.

It could be hypothesised that children would spend more time outdoors in summer and thus the rate of myopia progression may vary with season. Fulk *et al*., (2002) evaluated myopia progression for seasonal variations over a 30 month period in 71 myopic children (mean age 10.7 ±1.34 years) and noted that their myopia progression was reduced in the 6 month periods that included summer holidays.

There was no associated change in axial length. Gwiazda *et al.,* (2014) carried out a similar analysis on 358 myopic participants, aged between 6 and 11 years, over the 3 year COMET study duration. Mean progression in winter was greater, -0.35 (±0.34) D than that measured in summer -0.14 (±0.32) D.

Data to establish length of time spent outdoors are commonly collected using questionnaires. The subjective responses rely on estimation and have the potential for memory bias (Alvarez and Wildsoet, 2013). In order to investigate any such inconsistencies, Alvarez and Wildsoet (2013) gave 27 young adults, in California, a light sensor to wear continuously for a 2 week period. The participants were additionally asked to complete a questionnaire on visual activity including an estimation of the amount of time spent indoors/outdoors. Subjective over-estimation caused poor agreement between light sensor data and questionnaire results.

This chapter aims of to explore subjective data from a group of myopic children to assess for any relationship between time spent outdoors and the progression of myopia. Myopia progression will be considered in terms of both refractive error change and axial length progression.

7.2 Methods

See section 2.1 for full details of participants. The 27 children, aged between 8 and 12 years, had been randomly allocated to wear either a novel dual focus soft contact lens or a single vision soft contact lens, 10 to 15 hours per day, 6 to 7 days per week for 3 years. Time outdoors was assessed by direct interview. The child participant, with their parent present to support estimation, was asked how much time they spent outdoors. They were asked this question at their 1 week, 1 month, 6 month, 12 month

and 18 month visits range, to gain a mean figure and to allow for seasonal changes in behaviour. The children were asked to estimate how many minutes they spent firstly on a standard weekday and secondly on a weekend day. Weekday and weekend minutes were averaged and a daily average was calculated using the same technique as Guo *et al.,* (2013) detailed as follows:

((average weekday x 5) + (average weekend x 2)) / 7

The Shin-Nippon NVision-K 5001 was used to measure the participant's distant refractive error. A logMAR chart was situated 4 m from the participant and they were asked to fixate the middle letter from a line above their best vision while 10 measurements were taken from each eye and averaged. Measurements of refractive error under cycloplegia were taken annually. A drop of 1% Tropicamide was instilled into each eye a minute after 1 drop of 0.5% Proxymetacaine Hydrochloride, had been instilled. If the child had dark irides then a further drop of Tropicamide was instilled into each eye. After 25 minutes, when the Tropicamide was at maximum effectiveness (Eperjesi and Jones, 2005), the autorefraction measurements were taken.

7.3 Results

7.3.1 Overall cohort average time spent outdoors

A paired sample t-test was used to compare average weekday and weekend minutes. The participants spent significantly longer (p=0.0005) outdoors at weekends by 61.22 (±77.11) minutes on average (see Table 7.1).

	Average Outdoor minutes						
	1 Week Visit	1 Month Visit	6 Month Visit	12 Month Visit	18 Month Visit	Weekday Average Time Outdoors	Weekend Average Time Outdoors
Mean (minutes)	151.11	183.17	160.32	157.70	123.49	137.67	198.89
Standard Deviation	±92.40	±124.34	±81.22	±79.00	±49.50	±54.27	±102.23

Table 7.1 Average minutes spent outdoors for all children, per visit, with weekend and weekday minutes.

Daily average reported minutes spent outdoors changed between children and between visits (see Table 7.2).

	Average Daily Outdoor minutes					
Patient Number	1 Week	1 Month	6 Month	12 Months	18 Months	Average Daily Minutes Outdoors
1	120.00	120.00	145.71	81.43	141.43	121.71
2	385.71	257.14	111.43	120.00	171.43	209.14
3	274.29	385.71	308.57	308.57	180.00	291.43
4	222.86	480.00	214.29	257.14	214.29	277.71
5	90.00	90.00	60.00	60.00	60.00	72.00
6	154.29	184.29	102.86	377.14	115.71	186.86
7	120.00	304.29	154.29	180.00	150.00	181.71
8	300.00	480.00	64.29	214.29	77.14	227.14
9	90.00	77.14	30.00	30.00	90.00	63.43
10	60.00	60.00	240.00	102.86	51.43	102.86
11	47.14	128.57	137.14	120.00	77.14	102.00
12	137.14	137.14	154.29	137.14	167.14	146.57
13	81.43	90.00	107.14	137.14	120.00	107.14
14	81.43	115.71	205.71	201.43	214.29	163.71
15	94.29	94.29	240.00	102.86	60.00	118.29
16	137.14	120.00	197.14	205.71	158.57	163.71
17	154.29	231.43	171.43	126.43	132.86	163.29
18	167.14	167.14	77.14	154.29	120.00	137.14
19	377.14	377.14	197.14	120.00	214.29	257.14
20	210.00	210.00	162.86	218.57	64.29	173.14
21	64.29	102.86	214.29	137.14	98.57	123.43
22	120.00	120.00	120.00	107.14	120.00	117.43
23	60.00	171.43	38.57	175.71	77.14	104.57
24	94.29	60.00	334.29	197.14	120.00	161.14
25	94.29	64.29	137.14	77.14	94.29	93.43
26	214.29	240.00	308.57	240.00	162.86	233.14
27	128.57	77.14	94.29	68.57	81.43	90.00
Mean	151.1111	183.1746	160.3175	157.6984	123.4921	155.15873

Table 7.2 Average daily outdoor minutes for each participant, per visit. Reported minutes greater than participant average are shown in a lighter tone.

7.3.2 Average time spent outdoors and lens type worn

An independent samples t-test found no statistically significant difference for minutes spent outdoors between children wearing the test lens and those children in the control lens group (p=0.623).

No correlation was found between time spent outdoors and myopia progression. The participants who wore the test lens showed a positive Pearson 2-tailed correlation of r=+0.319 for axial length change and a negative r=-0.356 for cycloplegic autorefraction change compared with time spent outdoors, neither were significant (p=0.558 and p=0.212 respectively). The Pearson 2-tailed test for the control lens wearers was a negative correlation of r=-0.179 for axial length change and a positive r=+0.155 for cycloplegic autorefraction change when compared with time spent outdoors. Again neither were significant (p=0.558 and p=0.612 respectively). See Figure 7.1 and Figure 7.2 for scatter charts.

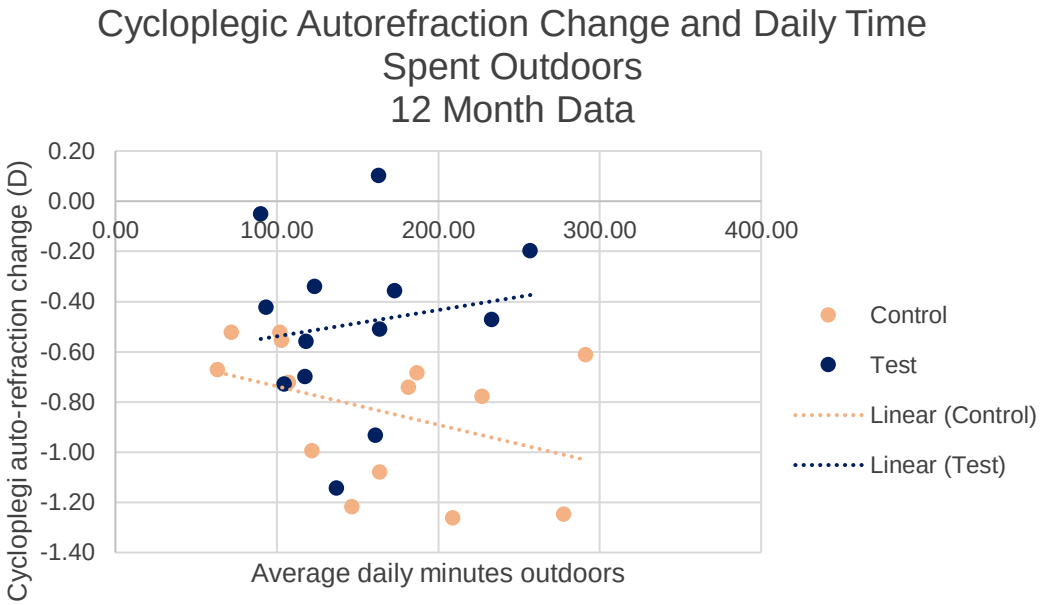


Figure 7.1 Scatter Chart to show no significant correlation between the 12 month change in cycloplegic autorefraction between participants who wore the test lens, when compared with participants who wore the control lens, when each are plotted against average daily minutes spent outdoors.

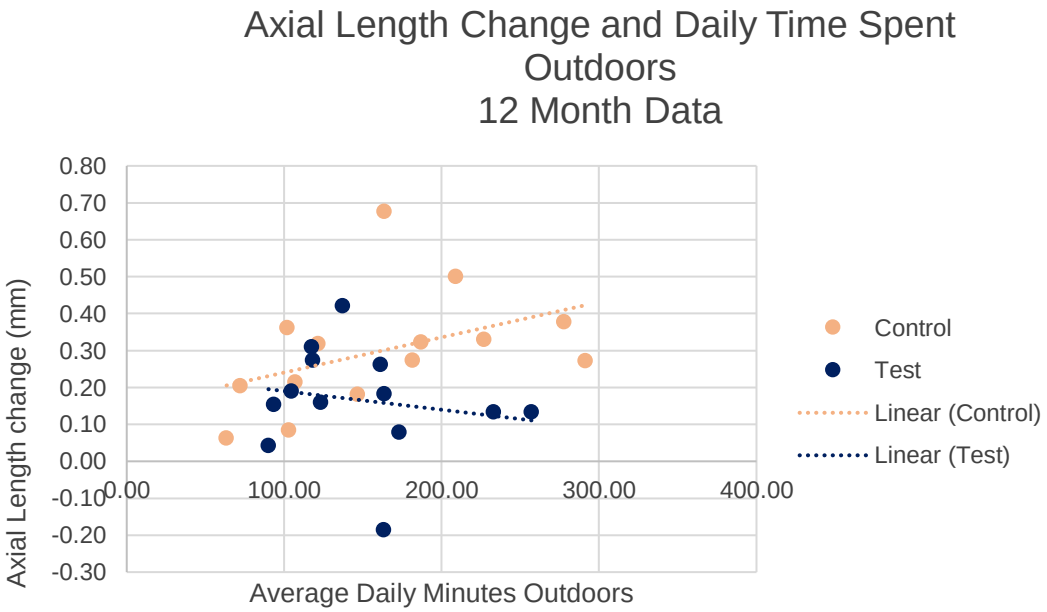


Figure 7.2 Scatter Chart to show no significant correlation between the 12 month change in axial length between participants who wore the test lens compared with participants who wore the control lens, when each are plotted against average daily minutes spent outdoors.

7.3.3 Average time spent outdoors factorial ANOVA

There was a statistically significant factorial ANOVA interaction between axial length, lens type and time spent outdoors p=0.006. There was no significant interaction when cycloplegic autorefraction was substituted with axial length change.

Lens Type: Test or Control	+	Cycloplegic Autorefraction	+	Time Outdoors	p=0.168
		Axial Length		Time Outdoors	***p*=0.006**

Table 7.3 Myopia progression factorial ANOVA data for lens type with time outdoors relationship.

The 12 month axial length elongation as a percentage increase from baseline was additionally calculated and this also showed statistical significance p=0.005.

Lens Group: Control or Test Lens	Time Spent Outdoors	Axial Length Progression (mm)	Percentage Change (%)
Test	≥150 minutes	0.10 (±0.15) mm	0.41%
Control	<150 minutes	0.20 (±0.11) mm	0.82%
Test	<150 minutes	0.22 (±0.12) mm	0.92%
Control	≥150 minutes	0.39 (±0.14) mm	1.62%

Table 7.4 Axial length elongation by lens group and time spent outdoors (minutes).

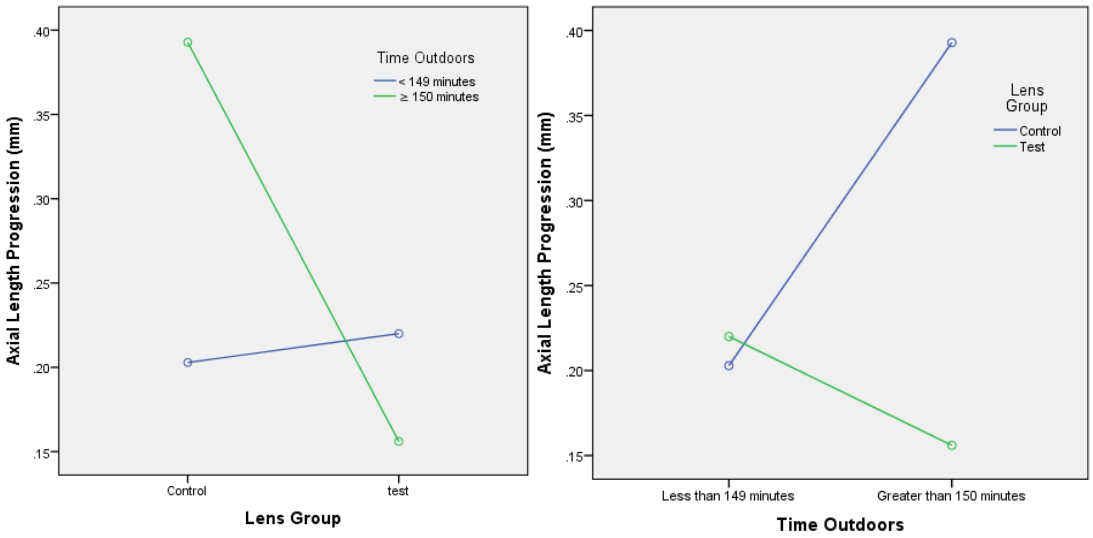


Figure 7.3 Factorial ANOVA of 12 month axial length change, lens type and time spent outdoors, plotted using both lens group and time outdoors.

7.3.4 Average time spent outdoors and age group

	Outdoor minutes					
	1 Week	1 Month	6 Month	12 Months	18 Months	Average Daily Minutes
Age 8 - 10 years (n=16)	143.84	160.18	161.25	157.23	109.29	146.36
Standard Deviation	±91.88	±115.12	±87.86	±88.41	±48.76	±55.05
Age 11 - 12 years (n=11)	161.69	216.62	158.96	158.38	144.16	167.96
Standard Deviation	±96.58	±135.05	±74.64	±67.10	±44.84	±71.46

Table 7.5 Average Daily minutes spent outdoors, arranged by age group.

When the data were averaged, the children aged 8 to 10 years reported they had spent, approximately 2.5 hours outdoors per day, 12.86% less than the 11 to 12 year

olds estimate of 21.6 minutes more per day. The older participants experienced slightly more cycloplegic autorefraction myopia progression, -0.96 (±0.29) D compared with the younger participants, -0.76 (±0.26) D and slightly less axial elongation +0.27 (±0.08) mm when compared with the younger participants 0.31 (±0.19) mm. There was no statistically significant difference between the 12 month myopia progression between the two age groups for cycloplegic autorefraction (p=0.20) or axial elongation (p=0.695).

7.4 Discussion

The subjective data for time spent outdoors averaged at 155.16 (±61.88) minutes per day. A slightly higher figure than the participants of the Sydney Myopia Study, who reported approximately 140 mins per day for children aged 6 and 12 years (Rose, Morgan, Ip *et al.,* 2008).

Daily average minutes spent outdoors changed between children and between visits (see Table 7.2) possibly indicating seasonal variation. Myopia progression has been shown to slow in warmer months and is thought to be related to increased time spent outdoors when conditions are improved (Gwiazda *et al.,* 2014). No significant correlation was found between the amount of time spent outdoors and a reduction in progression of myopia for either group. The participants were all myopic at the start of the study and while time spent outdoors has been shown to offer protection from myopia (He *et al.,* 2015; Rose, Morgan, Ip *et al.,* 2008; Rose, Morgan, Smith *et al.,* 2008; Jones *et al.,* 2007), there is a weaker association between increased time outdoors and a reduction in the progression of existing myopia (Bullimore, 2014; Jones-Jordan *et al.*, 2012; Scheiman *et al.,* 2014; Wu *et al.,* 2013). It has been

suggested, however, that less time spent outdoors may increase the chance of existing myopia to progress. (Rose, Morgan, Smith *et al.,* 2008).

Jones *et al.,* (2007) used survey data from the Californian Orinda Longitudinal Study of Myopia for 514 school–age children, of whom 111 became myopic. Less sports and outdoor activities combined with having myopic parents were found to be the best predictors of having myopia in the future. Rose, Morgan, Ip *et al.,* (2008) assessed the correlation in Sydney, between outdoor activity and myopia prevalence for 1765 children of 6 years of age and 2367 children of 12 years of age. The group of children with the highest levels of outdoor activity had the lowest odds ratio for myopia, whereas no association was found between indoor sport and myopia.

Wu *et al.,* (2013) investigated whether outdoor activity during school break-time impacted myopic changes in 7 to 11 year old students from two schools in Taiwan. Children from the first school (n=333) were encouraged to spend their break-time outdoors, a total time of 80 minutes per day. The 238 children from the second school did not have any intervention to change behaviour. Twelve months after implementing these changes there was less myopia onset and a slightly reduced myopic shift in the outdoor intervention school, with 8.41% and -0.25 D/year versus 17.65% and -0.38 D/year at the control school. Jones-Jordan *et al.,* (2012) investigated the association between the progression of myopia and time spent outdoors for the 835 myopic participants of the CLEERE study in the USA, using a parental questionnaire. No correlation between outdoor/sport activity and annual progression of myopia was found. Scheiman *et al.,* (2014) evaluated the relationship between time spent outdoors on myopia stabilisation by age 15 years for the participants of the Correction of Myopia Evaluation Trial (COMET). The 469 myopic

6 to 11 year old children were enrolled on the trial with each randomised to wear either single vision or progressive addition spectacle lenses for a 5 year duration. The participants and/or parents completed a diary detailing near work and outdoor activity. No association was found between time spent outdoors and myopia stabilisation by age 15.

At the 1 week visit, the subject of time spent outdoors was first introduced to the participants and their parents in the current study. The subject was met with interest and it raised enquiries which often led to a discussion about current research. On average there was approximately a 30 minute increase in reported time spent outdoors between the 1 week and 1 month visit, with subsequent visits showing a steady decline in reported time outdoors (see Table 7.2). The week 1 visit was 1 week after contact lenses were first dispensed and the children were then seen 3 weeks later, 1 month after dispense. It is not known if this increase in reported minutes was a random finding, an exaggerated estimate following the discussion on current research, or if it simply demonstrated a reflection of improved efforts to spend time outdoors.

The substantial visit schedule range (see Appendix 6) made accurate comparison of seasonal variations challenging as the spacing between visits varied. Additionally, a few of the children spent parts of their school holidays in other countries and this was likely only included in their estimates if they were recently home from a trip.

Table 7.5 presented the time outdoors data for the cohort divided into two age groups. These figures are based on their age at the baseline visit and therefore the children were 10 to 14 years of age by their 18 month visit. Average daily minutes by age

group suggested the older children spent more time outdoors. This was due, possibly to more relaxed supervision with age. The two age groups were assessed for difference in 12 month cycloplegic refractive error and axial elongation change, to assess if the small difference in time spent outdoors had any effect on myopia progression. The control group were used since they had received no other myopia intervention. When the data were averaged the children aged 8 to 10 years reported they had spent, approximately 2.5 hours outdoors per day, 12.86% less than the 11 to 12 year olds estimate of 21.6 minutes more per day. There was no statistically significant difference between 12 month myopia progression between the two age groups for cycloplegic autorefraction (p=0.20) or axial elongation (p=0.695).

There was a statistically significant factorial ANOVA interaction between axial length, lens type and time spent outdoors p=0.006. There was no significant interaction when cycloplegic autorefraction was substituted with axial length change. Further analysis using the percentage change from baseline to the 12 month visit gave a comparable statistical significance (p=0.005) indicating that the baseline differences in axial length had not confounded the data results. The least axial elongation in the cohort (+0.10 ±0.15 mm) was present in the test group who spent ≥150 minutes outdoors. The test lens wearers who spent <150 minutes outdoors were found to have +0.22 (±0.12) mm axial elongation. To explore the theory that time outdoors may slow myopia progression in an existing myope, the 2 sub-groups (≥150 minutes outdoors and <150 minutes) in the test group were compared using an independent t-test, however, there was no statistical significance (p=0.142). The highest axial elongation was present in the control group who spent ≥150 minutes outdoors. This was an unexpected finding. Further analysis revealed that the highest and lowest

axial elongation groups also had corresponding highest and lowest cycloplegic refractive 12 month progression of -0.4 (±0.34) D for the least axial growth and -0.92 (±0.27) D for the highest axial growth. The high probability level indicates a robust finding, however, greater time spent outdoors is evident in both extremes suggesting relevant factors that were not controlled for or perhaps questionable subjective data was utilised.

The use of questionnaires or a direct interview relies on recall from the participants. Studies have expressed concerns over the precision and reliability (French, Ashby *et al.,* 2013; Jones *et al.,* 2007) of questionnaires, as a way to measure outdoor exposure. Conversely, Guggenheim *et al.,* (2012) reported finding questionnaires highly predictive for incident myopia. Light sensors are a more objective way to measure time spent out doors and physical activity monitors would also indicate if a person is simply outdoors or partaking in activity.

The Raine Eye Health Study (REHS) in Western Australia explored the association between conjunctival ultraviolet autofluorescence (UVAF) and myopia in 1344 participants aged between 19 and 22 years of age. They observed sun damage on the conjunctiva to fluoresce under ultraviolet light and then measured this area in mm^2 for each participant. The prevalence of myopia was observed to be more than doubled in the lower quartile (33.0%), when compared with the higher quartile (15.6%) of UVAF mm^2. There was a strong correlation present between conjunctival UVAF and self-reported outdoor time measured by questionnaire (McKnight *et al.,* 2014). However, the protective association of higher levels of UVAF against myopia was found to be more robust than that of increased levels of time spent outdoors as measured by their questionnaire (McKnight *et al.,* 2014). UVAF can also be used as

a biomarker for outdoor exposure from light. Studies have shown lower levels of UVAF in myopes when compared to non-myopes (Sherwin *et al*., 2012; McKnight *et al*., 2014).

7.5 Summary

Spending time outdoors has been shown to be protective for myopia development in children. The research regarding whether spending more time outdoors has an impact on myopia progression is equivocal. The equivocal results in the current study may result from the use of subjective recall to assess time outdoors. The participants in the current study were seen at different points in time and therefore a questionnaire was viewed as a suitable technique. Future research would benefit from assessing the accuracy of participant recall by using both a subjective and an objective technique. The UK may not benefit from the required levels of daylight duration and light strength when compared to countries such as Australia, USA and China, who have had good effects from increased time spent outdoors.

8. DISCUSSION

8.1 Summary

Myopia can be considered a lifelong condition characterised by high prevalence and significant social and financial burden. Having myopia increases the risk factors for associated pathology with no true safe level of myopia identified (Flitcroft, 2012).

Single vision spectacles and contact lenses, strategies widely utilised to correct myopic refractive error, effectively correct central retinal blur. Although these traditional forms of correction reduce foveal blur, they do not necessarily correct off-axis retinal blur. In many cases, it is thought they may induce hyperopic defocus in the peripheral retina, which is believed to stimulate further elongation of the eye (Schaeffel *et al.,* 1988; Smith & Hung, 1999; Flitcroft, 2012; Smith, Hung, Huang *et al.,* 2013; Berntsen and Kramer, 2013).

Therefore, while myopia can be corrected with spectacles and standard contact lenses, neither will prevent the eye from continued growth nor further progression of myopia. Refractive error of the eye at birth can be significant, as the eye grows the refractive error commonly reduces in magnitude and the process is termed 'emmetropisation' (Smith, 1998). Considerable evidence exists to suggest that emmetropisation is an active process which relies on a normal visual experience otherwise a refractive error will occur (Wallman and Adams, 1987; Schaeffel *et al.,* 1988; Wallman and Winawer, 2004). Research from animal models has shown the periphery of the retina also plays a role in the emmetropisation process. Modification of the peripheral focus has been found to influence myopia progression. (Schaeffel *et al.,* 1988; Smith and Hung, 1999; Flitcroft, 2012; Smith, Hung, Huang *et al.,* 2013).

Recent research by Anstice and Phillips (2011) using a Dual-Focus contact lens, which provided clear central vision and simultaneous peripheral myopic retinal defocus, showed a reduction in axial myopic progression in children aged 11 to 14 years.

This thesis aimed to describe the rationale, study set up and results of a parallel-group, double blind, and randomised controlled trial of a dual focus contact lens as a possible intervention to limit the progression of myopia. Biometric data were compared for 27 myopic child participants who were aged between 8 and 12 years at baseline visit. The children who wore the test lens had 40.96% less progression of myopia as measured by cycloplegic refraction and 44.54% less axial elongation after 12 months of lens wear. The overall 2 year findings, for the partial cohort who had reached the 2nd year of lens wear, were 29.75% less myopia progression in the test lens group and 46.73% less axial elongation. This indicates that a dual focus contact lens is an effective intervention to limit the progression of myopia in this cohort of myopic children. It is currently unknown whether the same effect, in terms of myopia progression, will be found for each further year of the study. If will be of interest to assess whether the greatest treatment effect will have been in the 1st year, as found in other myopia control studies (Gwiazda *et al.,* 2003; Chua *et al*., 2006). Non-cycloplegic autorefraction data, over an 18 month period, indicated that the children who wore the test lens had a fairly consistent reduction in progression of myopia when compared to the control group (Table 3.3).

Tropicamide (1%) was shown to be an effective cycloplegic drug, in agreement with previous findings (Manny *et al.,* 2001). Due to the shorter duration of action, the child

could attend school afterwards without a noticeable and prolonged accommodative deficit, advantageous to maintain a low dropout rate in a longitudinal study.

One of the theories related to myopia control concerns lag of accommodation. Lag of accommodation was assessed to explore an association between the effectiveness of the lens and increased lag of accommodation to a near target, to show whether myopic patients with this particular deficit would be better suited to this type of intervention. The findings of this study to date do not support the hypothesis of a link between higher accommodative lag (measured with single vision correction) and myopia progression. However, there was a relationship detected between lower lag of accommodation and improved treatment effect of the dual focus lens. The impact of dual focus contact lenses on the accommodative status in children is of interest. The theoretical reduced retinal blur present in the children wearing the dual focus contact lenses may have improved the accommodation accuracy.

Relative peripheral hyperopia has been associated with myopia progression. There was no significant association found between relative hyperopic peripheral refraction change and the prediction or development of myopia progression. The reduction in myopia progression present in the participants who wore the dual focus lens group supports the theory that the peripheral retina is key to myopia progression and perhaps the peripheral refraction without intervention may be less relevant than how the refraction measures in an optically corrected state.

Knowledge of pupil size can be important for certain myopia interventions such as dual or multi-focal contact lenses. As discussed in section 1.3.4.2 a dual focus lens can have concentric treatment zones. Using the Anstice and Phillips (2011) lens as

an example, in order to access and view through the smallest treatment zone, the wearer would need to have an adequately suitable minimum pupil size. The pupil size in mesopic and photopic conditions and at two working distances were explored to compare dimensions with a dual focus lens of known lens zone diameters. Pupil size of the participants was shown to be of suitable size to correctly access the treatment zones in both lighting conditions and at both working conditions trialled. Additionally, the pupil size of a group of myopic young adults were assessed and the majority of the cohort were found to have been suitable for a dual focus lens.

There are large disparities in myopia prevalence between geographical locations and ethnicities (Pan *et al.,* 2012; Smith, 2013; Lin *et al.,* 1999). Research has demonstrated that children who spend more time in outdoor activities have a lower risk of future myopia (Guggenheim *et al*., 2012; Jones *et al.,* 2007; Rose, Morgan, Ip *et al.,* 2008; Rose, Morgan, Smith *et al.,* 2008; Wu *et al.,* 2013). The amount of time spent outdoors each day was assessed and compared with annual myopia progression to assess the effectiveness of this possible intervention in this cohort. No correlation was found between time spent outdoors and cycloplegic refractive change or axial elongation. The limitations of subjective responses to time spent outdoors was discussed.

8.2 Future research

Larger sample sizes would have been preferred in all aspects of the current study. Recruitment was challenging for a number of reasons. As with all areas of healthcare in the UK, there is no database or central area for a researcher to access and locate potential participants. It makes poor commercial sense for optometry practices to

assist with recruitment and therefore only community optometrists with links to the University successfully recommended patients to the current study. Radio advertisement was an effective route for recruitment. Parents of the participants later reported that their initial scepticism about research on children was normalised to some extent by hearing about the study on their usual radio station. The entry age range of 8 to 12 years worked well and there were no particular difficulties with teaching safe lens management that were associated with young age. The younger participants commonly reported that they had initially developed myopia up to 2 years prior to commencing the study. Future studies may consider children from an earlier age, prior to higher myopia levels being reached. Strict entry requirements can make recruitment challenging. As discussed in section 2.1.1.1 over 100 children were screened for suitability for inclusion into the study and 29 children were enrolled. The children were required to be aged between 8 and 12 years, have -0.75 to -4.00 D of myopia, -0.75 D or less of astigmatism and 1.00 D or less of anisometropia. All responses were from parents with a child, or children, within the specified age range, however the spectacle prescription was largely unknown. Despite the radio advert describing myopia in terms of 'short-sightedness', there were 33 responses from parents with a hyperopic child. Further advert wording refinement was felt difficult as parents were unaware of the details and relevance of their child's prescription. While this made the process time consuming it was felt the scope of the advert increased the database of children across a broader variety of specialist areas for the Vision Sciences department. Many of the respondents who were unsuitable fell very clearly outside of the inclusion/exclusion criteria, notably however, had the astigmatism criteria been widened to -1.00 D or less, 2 additional children would have been suitable and a further 2 more children had the criteria been -1.25 D or less of

astigmatism. Over the course of the study several of the children developed similar levels of astigmatism on autorefraction measurement which they did not tolerate when presented in spectacle lens form during subjective refraction. These children continued to show best corrected vision of +0.1 logMAR or better, in both eyes, in their spherical contact lenses. Future study recruitment may benefit from an astigmatism criteria level that relates more to the spectacle prescription rather than the autorefraction finding. Astigmatism often occurs in conjunction with myopia development. The current study was interested in spherical myopia and thus limited the amount of astigmatic error. How astigmatic blur affects the progression of myopia is unknown and would also need to be considered in future work.

A rebound in the treatment effect of interventions to limit myopia progression have been reported in child studies using ortho-k (Lee and Cho, 2010) and high concentrations of atropine (Tong *et al.,* 2009; Chia *et al.,* 2014). The consequences of rebound have yet to be fully explored. Studies that have reassessed patients after the treatment has ceased have reported that myopia in the test group progresses towards the levels achieved in the control group, however, some residual treatment effect appears to remain. These findings of rebound must now become a consideration for all myopia progression interventions. It is not known if a sudden increase in axial elongation over a short length of time post myopia control intervention would cause a greater negative effect on the structure of the eye, further increasing the likelihood of related myopic pathology in later years. Ortho-k and particularly low dose atropine have proven effective interventions to slow myopia progression and therefore it is likely further research will incorporate the phenomenon of rebound occurrence in their design structure. Anstice and Phillips (2011), in their

cross over design study, reported that after the 2nd phase the eye that had worn the dual focus contact lens in the 1st phase (and wore the single vision contact lens in the 2nd phase) had a similar rate of progression of myopia and axial elongation that the eye wearing the single vision lens had in the 1st phase. Suggesting there was no apparent accelerated growth found after dual focus contact lens wear was ceased.

The duration of use of an intervention to limit or halt the progression of myopia has yet to be determined, it could be reasoned to last anywhere from a brief use, to the duration of childhood into early adulthood, when physical growth is complete, up to lifelong treatment. The ethical and legal implications of an optometrist prescribing an intervention that may cause a potentially harmful rebound effect in the future, would need to be considered in detail. The alternative of continuing to prescribe optical corrections that aggravate myopia progression is a poor alternative to intervening, however.

Recent studies have suggested that certain commercially available contact lenses may cause more hyperopic defocus than others and therefore exacerbate myopia progression (Wagner *et al.,* 2015; de la Jara *et al.,* 2014). This may encourage greater debate on the subject of current myopia prescribing in the UK, in readiness to commence change in clinical practice.

Future work considering peripheral refraction would benefit from the inclusion of data from both eyes, the addition of vertical measurements and assessment of the peripheral retinal shape along with objective analysis of peripheral plots using second order polynomials. The children tired very quickly in the early visits, learning all of the new procedures required. We were unable to take peripheral data from some of

the children at the 6 month visit due to fatigue and therefore earlier peripheral refraction data collection would likely only be possible in a study with less additional procedures. The broad variation that existed between the participant peripheral refraction data indicates that myopia intervention lenses may require modelling with individual parameters, treating the maximum hyperopic refraction in order to induce widespread peripheral myopic defocus. The nasal peripheral retina myopic shift in refraction over a one year period was not statistically significant in this small sample. Longitudinal changes in peripheral refraction for the broader multi-centre cohort may help to indicate if permanent peripheral retinal changes occur due to dual focus contact lens wear. Future work should also assess peripheral retina measurements while dual focus contact lenses were worn, to confirm if myopic defocus was achieved or whether a higher peripheral plus addition is required for certain children. There are a number of additional measurements that would have been of interest to have also obtained such as anterior chamber depth and dynamic lag measurements. Participants grew tired due to the duration of the examination and further assessments would have been valuable but data may have been less reliable.

Recent animal studies have demonstrated a protective effect of light (McCarthy *et al.,* 2006; Ashby *et al.,* 2009; Ashby and Schaeffel, 2010; Smith *et al.,* 2012) on myopia development and progression. Further research is required to reveal whether high illuminance could have an effect on myopia development in children. Outdoor activities are hugely popular in countries that enjoy clement weather conditions. For children in those countries who experience the more extreme weather patterns and fewer daylight hours, the introduction of an indoor lighting solution would probably be beneficial. Individual ultra-violet sensors have proven effective to measure time

spent outdoors and can highlight deficits in subjective estimations (Alvarez and Wildsoet, 2013). Children on the current study, when further questioned, included time spent reading under a gazebo in the garden, as outdoor activity. The current lack of understanding on the mechanism of light limits the restrictions we can place on the reported 'outdoor' time. The statistically significant factorial ANOVA interaction between axial length, lens type and time spent outdoors (p=0.005) indicated that the least axial elongation was present in the test group who spent ≥150 minutes outdoors (+0.10 ±0.15 mm). This finding may support the theory that time outdoors may positively affect myopia progression in an existing myope. The greatest axial elongation was present in the control group who spent ≥150 minutes outdoors. This was an unexpected finding. The high probability level indicates a robust finding however greater time spent outdoors is evident in both extremes suggesting questionable subjective data was utilised. Animal studies have indicated that ultra-violet light is not thought to be a factor in current theories of time outdoors (see 1.2.4), the assessment for evidence of ultra-violet damage in the eyes, however, or an ultra-violet sensor worn by a participant would give a clearer indication of outdoor exposure level. Future work assessing the effect of time spent outdoors to limit the progression of myopia would likely benefit from a more objective approach. Much of the research investigating myopia and time spent outdoors indicates a preventative element, reducing the likelihood of a child developing myopia (Jones *et al.,* 2007; Rose, Morgan, Ip *et al.,* 2008; Rose, Morgan, Smith *et al.,* 2008). This may indicate a greater benefit from collecting time spent outdoors data from non-myopes at an early age and follow up some years later to assess for myopia in relation to retrospective outdoor duration.

A factorial ANOVA analysis suggested a significant relationship between axial length change, lens type and sex (p=0.026). Axial length change was lowest in male participants who wore the test lens and highest in male participants who wore the control lens. There was no statistically significant difference between axial elongation in boys when compared to girls. There was no statistical difference reported between time outdoors between boys and girls and no other research differences were noted. Future work over a longer duration with more detailed behavioural data may offer more insight into this finding.

Factors which increase the likelihood of myopia lie in family history, ethnicity, near work, time spent outdoors and from early (pre myopic) ocular changes in the eye such as increased axial length, peripheral refraction and central refraction at age 6 years (Zadnik *et al.,* 2015). While individually many of the current techniques to limit progression of myopia have shown encouraging success, it is likely that a combination of current thinking or further evolution of theories will ultimately become commonplace treatments for myopia, and perhaps solutions to prevent the initial onset of myopia. However, not all the techniques would partner well. Flitcroft (2012) has suggested the future modification of our environments may prove beneficial, such as ergonomic design considerations.

This thesis has demonstrated that a dual focus contact lens is effective at slowing the progression of myopia in children over an 18 month period and that interventions to limit the progression of myopia may need to be tailored to individual child characteristics. A lower lag of accommodation was associated with an improved treatment effect of a dual focus lens. Pupil size for a group of myopic children and myopic young adults were shown to be largely suitable to access treatment areas of

a dual focus contact lenses. This thesis has also questioned the precision of subjective estimates of time outdoors as a methodology and has shown no associated reduction in myopia progression in a small sample size of children in the UK.

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