The Relationship between Peripheral Refraction, Optical Correction and Myopia Progression

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Thesis Summary

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David Berkow, Doctor of Optometry, Aston University, 2021

It is clear from many sources that the prevalence of myopia is increasing at an alarming rate. Although the pathogenic mechanisms behind the development of myopia remain unclear, various factors have been associated with myopic progression, including genetics, accommodative spasm, prolonged near work, race, gender, educational level, and the amount of time spent outdoors in sunlight. Because of the personal and socio-economic burdens associated with this refractive condition, the key factors in myopia progression continue to be keenly sought.

Recent human and animal research suggests that the extent of myopia progression may be dependent on the extent of relative peripheral hyperopia, which in turn is dependent on the type of optical correction (glasses versus contact lenses) worn by an individual. This theory has been termed the hyperopic defocus theory, and the principal goal of this thesis was to assess this current (and popular) theory of myopia development. The methodology employed was a combination of retrospective data analyses and experimental measures of central and peripheral refractive status. Participants selected for inclusion in the study were all myopic, aged 6-24 years, and wore either contact lenses or spectacles.

From theoretical arguments and experimental evidence, three hypotheses were made. First, that contact lens wearers will show less myopic progression than spectacle lens wearers. Second, that higher degrees of foveal myopia (myopic progression) arise in eyes with greater amounts of relative peripheral hyperopia. And third, that the dependence of the degree of foveal myopia on relative peripheral refraction is influenced by the type of optical correction worn (contact lenses versus spectacle lenses).

In assessing the degree of myopic progression from early childhood through to late adolescence, taking into account the influence of possible covariates (i.e. initial age and initial degree of myopia), the results indicated: (a) optical correction does not have a significant influence on myopic progression; (b) there exists a significant negative correlation between foveal myopic refraction and the degree of relative peripheral hyperopia; and (c) the degree of foveal myopia on relative peripheral refraction is not influenced by the type of optical correction worn.

From these results, the first and third hypotheses cannot be supported. These non-confirmatory results of the hyperopic defocus theory, however, are balanced by the supportive finding that higher degrees of foveal myopia arise in eyes with greater amounts of relative peripheral hyperopia (i.e., Hypothesis 2). The latter has important implications for the profession of optometry because, if the theory has genuine merit, it would enable ophthalmic practitioners to not only correct myopia but also minimise the continued development of myopia in children and young adults through various treatment options, including peripheral defocus contact lenses and orthokeratology.

Key words: myopia progression, human vision, contact lenses, hyperopic defocus theory, peripheral refraction.

Acknowledgements

Firstly, I would like to thank my supervisor, Professor Stephen Anderson, for his advice and guidance throughout my Doctor of Optometry. His support and assistance has been invaluable throughout the process of gaining ethical approval, conducting the research, and in writing this thesis.

Besides my supervisor I would like to thank Dr. Mark Dunne (Aston University) for his constructive comments and his guidance with the statistical analyses of the research results.

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Thank you to my wonderful family, particularly my wife Estee for their support, never ending patience and understanding throughout the completion of the Doctor of Optometry and in writing of this thesis.

Thank you to my grandson Shir, for his assistance, at all times, with all the computer issues I could not overcome.

I do hope that this thesis will be a small contribution to the subject of Myopia Management, which is my passion, as an eye-care practitioner today.

List of Contents

Chapter Five: General Discussion and Conclusions

Appendices

List of Figures

Literature Search Strategy

PubMed and Medline were principally used to identify studies on peripheral retinal defocus and peripheral retinal refraction, as reported in articles up to and including the year 2021. The following words were used in various combinations: *prevalence, myopia progression, human vision, contact lenses, hyperopic defocus theory, peripheral refraction.* Only publications in English were used. The reference lists of relevant publications were also referred to as a potential source of information. Both human and animal studies were critically reviewed for study methodology and robustness of data, particularly with respect to peripheral retinal measurement and hyperopic defocus theories. No unpublished data were used.

List of Tables

Chapter one: Introduction

Emmetropization is often thought of as the visual regulation of eye growth, and refers to the eye development processes that yield a match between the refractive power and axial length of the eye. Without considering other factors affecting eye growth, the process of emmetropization acts to control eye growth, thus preventing refractive errors in adulthood.

In normal eye development, the eye is hyperopic at birth, moving on to become emmetropic as the child grows (Morgan and Rose, 2005). Myopia develops if the axial length of the eye is longer than that allowed for by the dioptric power of the eye.

1.1 Myopia: overview and projected prevalence

In myopia, the axial length of the eye surpasses its refractive focal length, causing blurred distance vision. In addition to the direct visual consequences of myopia, there are significant increases in the risks of vision impairment from pathologic conditions associated with high myopia (> 6D), including retinal damage, cataract and glaucoma.

By 2050, it is estimated that half the world's population will be myopic, with nearly one billion at risk of sight-threatening pathology (Holden et al., 2016). Currently, the prevalence of myopia is highest in East Asia (Pan et al., 2015). Figures 1.1 – 1.3 show the number of people that have myopia, with various projected estimates of the number that will develop the condition by 2050.

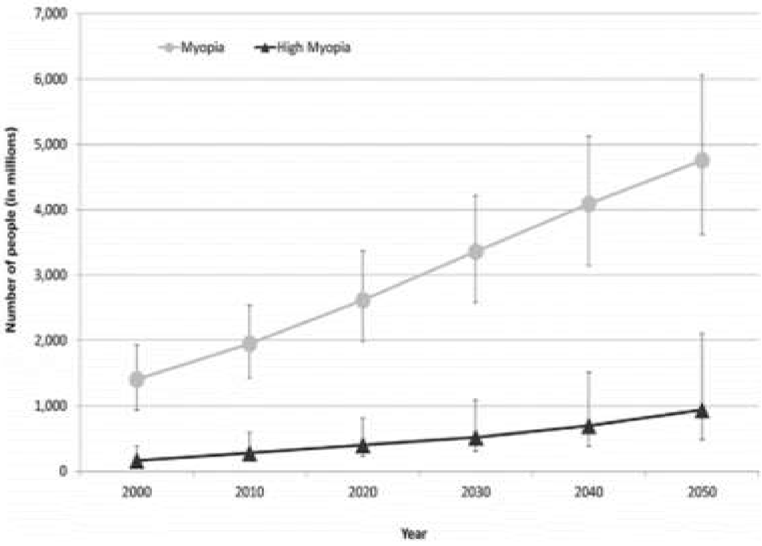


Figure 1.1: *The number people estimated to have myopia and high myopia for each decade, from the year 2000 through to 2050. Error bars represent the 95% confidence intervals (from: Holden, 2016).*

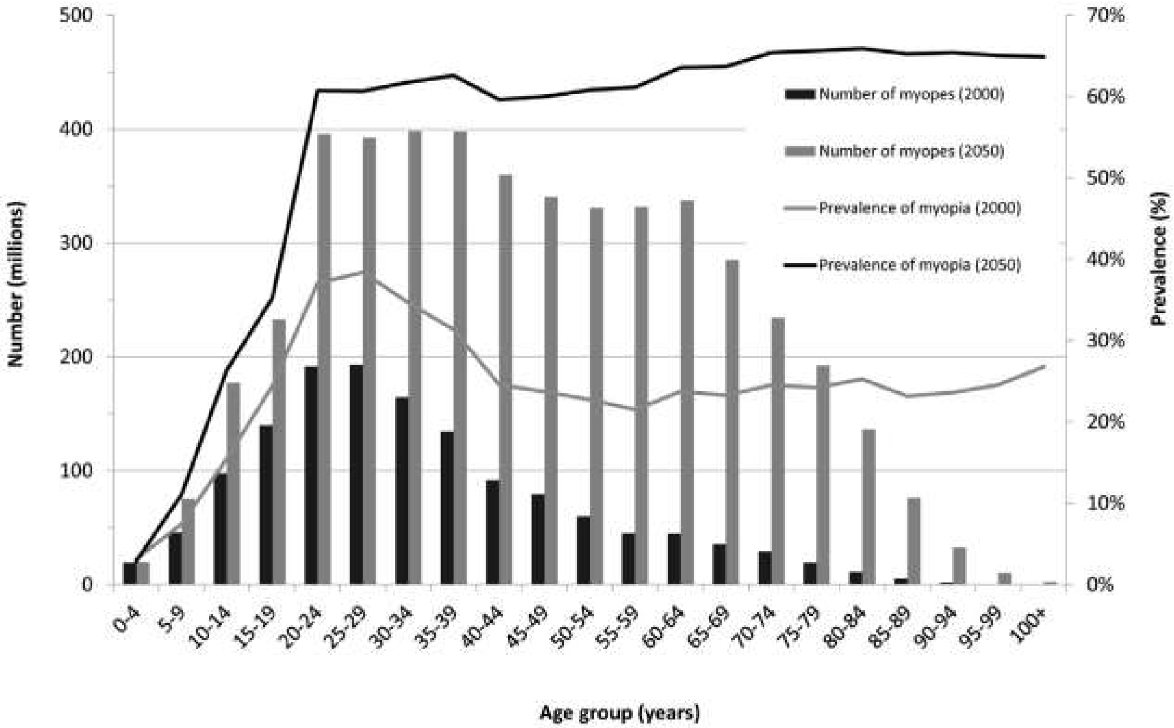


***Figure 1.2**: The distribution of people estimated to have myopia across different age groups, in the year 2000 and 2050 (from: Holden, 2016).*

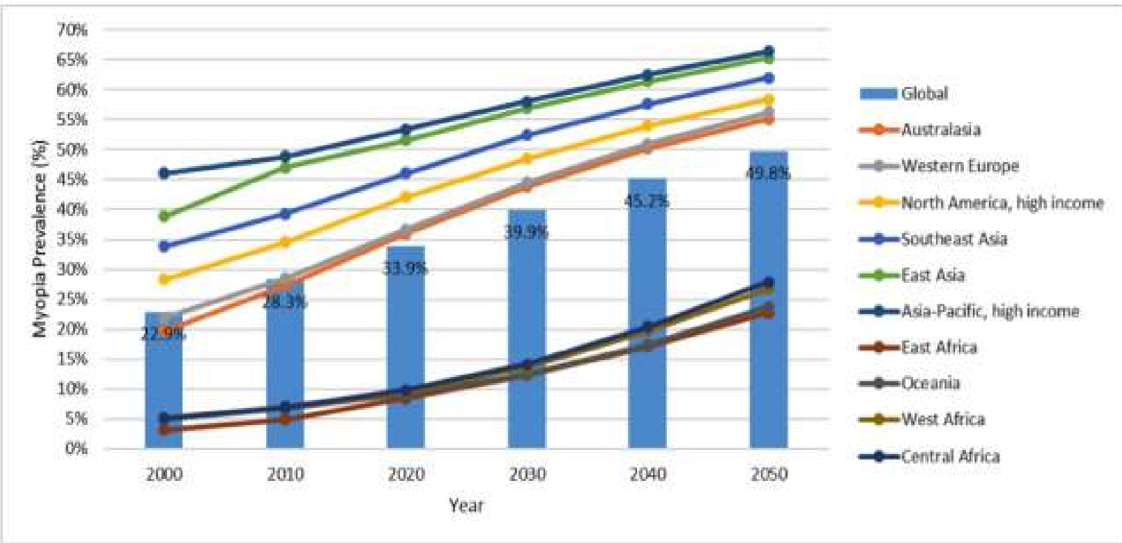


Figure 1.3: *Global Burden of Diseases (GBD) regions with estimated high (>55%) and low (<30%) myopia prevalence by 2050 (From: reviewofmm.com Rate of Myopia and High Myopia Expected to Rise, March 2019, (from: Holden et al., 2016).*

Preliminary projections and the United Nations corresponding population figures show that myopia and high myopia will affect 53% and 10%, respectively, of the world's population by 2050 (World Health Organization and Brien Holden Vision Institute Joint Report, 2015, Figure 1.4).

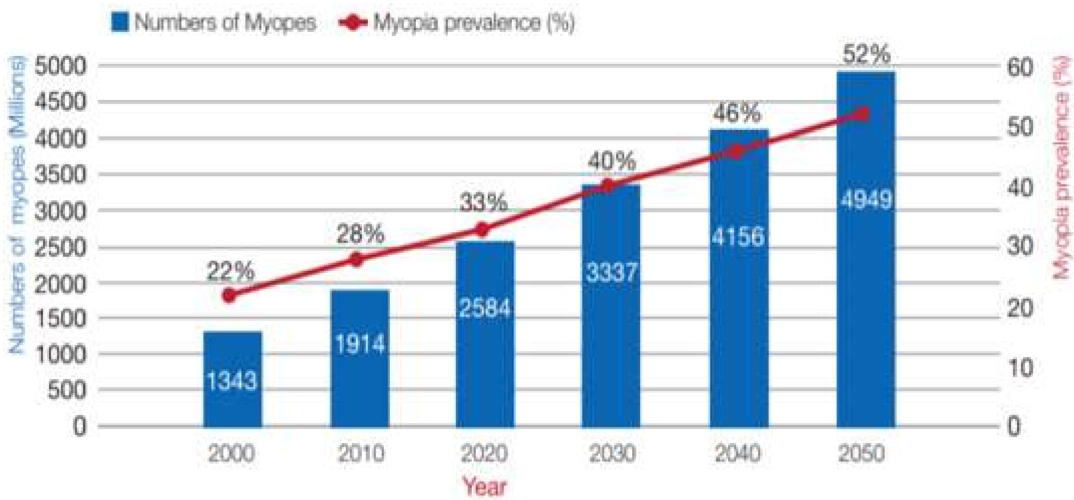


Figure 1.4: *Progression of myopia from the year 2000 to 2050 (*from *The Impact of Myopia and High Myopia, World Health Organization-Brien Holden Vision Institute Joint Meeting, 2015)*

In brief, it is clear from many sources that the prevalence of myopia, including high myopia, is increasing at an alarming rate. Myopia is currently regarded by the World Health Organisation as an epidemic. Significantly, the prevalence of myopia indicates not only an increased health problem, but also a substantial economic burden. To date, nearly $16 billion has been spent in the US alone on myopia correction (Cooper & Tkatchenko, 2018), and it is clear that myopia-related visual impairment reduces productivity and quality of life (McMonnies, 2014). Because myopia causes significant health, social and economic problems, it is vital that new methods are sought to reduce the progress of myopia in children and young adults.

1.2 Aetiology and Epidemiology of Myopia

Although the pathogenic mechanisms behind the development of myopia remain unclear (Foster & Young, 2014), various factors have been associated with myopic progression. These factors include genetics, accommodative spasm, prolonged near work, race, gender, educational level, and the amount of time spent outdoors in sunlight (e.g., Cohn, 1892; Goldschmidt, 2003; Saw et al., 2001; Schaeffer, 2016; Seang-Mei Saw, 2003).

The prevalence of myopia is known to be different amongst children of different ethnic backgrounds, different ages, and different locations. For example, in a population-based cross-sectional study of American infants, the prevalence of myopia was reported to be 1.2% in non-Hispanic whites, 3.7% in Hispanics, 3.98% in Asians and 6.6% in African Americans (Foster & Young, 2014; Wen et al., 2013). The prevalence in Australian schoolchildren was reported to be 42.7% and 59.1% in 12-year-olds and 17-year-olds of East Asian origin, respectively, while the rates for same-aged Caucasian children were 8.3% and 17.7%, respectively (French et al., 2013).

It is thought that the dramatic increase in myopia evident in East Asia may be a result of an increase in near work, the use of computers and too little exposure to sunlight (Schaeffel, 2016). The protective nature of the outdoors may relate to the release of dopamine, which is stimulated by light and may act as an inhibitor to eye growth (Morgan & Ashby, 2017; Read, 2016).

Vitale et al. (2008), He et al. (2007) and Xu et al. (2005) suggest that females are more at risk of developing high myopia than males, because estrogen may enhance choroidal neovascularization (CNV) development by increasing vascular endothelial growth factor receptor 2 (VEGF 2) gene expression (Tanemura et al., 2004).

Table 1.1: *Prevalence of blindness in pathological myopia (from: Wong et al. 2014)*

Disease stage	Parameter	Outcome
pathologic myopia	Prevalence in the general adult population	
	White	1%
	Asian	1–3%
	Estimated prevalence of vision impairment due to pathologic myopia	
	European	1–5 per 1000
	Asian	2–15 per 1000
	Annual incidence of blindness due to pathologic myopia	
	White	1–5 per 100 000
	Asian	5–10 per 100 000
Myopic choroidal neovascularization	Prevalence of choroidal neovascularization	
	General population	0.05%
	Patients with pathologic myopia	5–10%
	Incidence of choroidal neovascularization in pathologic myopia over 10 years	10%
Bilateral myopic choroidal neovascularization	Prevalence of bilateral choroidal neovascularization secondary to pathologic myopia	15–30%

Recent human and animal research studies have shown that myopia development is a result of an interaction between genetic and environmental factors. Cooper & Tkatchenko (2018) reviewed the latest concepts related to aetiology and treatment of myopia, reporting that genetic factors play a significant role in myopia development. Cooper and Tkatchenko also reported that extended periods of near work accelerated myopia development, as well as possibly less time spent outdoors. In particular, they noted that greater myopia progression occurs in winter months compared with summer months, and concluded that sheer exposure to sunlight retarded myopia progression. In general agreement with these results, Rose et al. (2008) reported that the extent of time individuals spent outside, not necessarily playing sport, was correlated with a greater hyperopic refraction (See Figure 1.5).

Outdoor Activity (Average Hours per Day)[†]	Year 1 Sample					Year 7 Sample				
				Trend					*Trend*	
	Low (0–1.7) (Mean SER)	*Moderate (1.7–2.7) (Mean SER)*	*High (2.7+) (Mean SER)*	*β Coefficient*	*P Value*	*Low (0–1.59) (Mean SER)*	*Moderate (1.6–2.8) (Mean SER)*	*High (2.8+) (Mean SER)*	*β Coefficient*	*P Value*
All children	+1.24[‡]	+1.31[‡]	+1.41	+0.05	0.009	+0.32[‡]	+0.50	+0.54	+0.07	<0.0003
Gender										
Girls	+1.37	+1.37	+1.52	+0.06	0.09	+0.14[‡]	+0.50	+0.37	+0.07	0.052
Boys	+1.10[‡]	+1.26	+1.29	+0.04	0.01	+0.54[‡]	+0.48[‡]	+0.68	+0.06	0.003
Parental myopia										
None	+1.36	+1.41	+1.44	+0.02	0.4	+0.56[‡]	+0.67	+0.79	+0.08	0.0003
Any	+1.06[‡]	+1.15[‡]	+1.40	+0.14	0.0005	−0.05	+0.18	+0.18	+0.04	0.2
Ethnicity										
European Caucasian	+1.34[‡]	+1.38[‡]	+1.49	+0.04	0.15	+0.70[‡]	+0.80	+0.89	+0.06	0.002
East Asian	+0.94	+0.87	+0.88	+0.05	0.5	−1.00	−0.63	−0.76	+0.12	0.3

*Adjusted for gender, ethnicity, parental myopia, near-work activity, maternal and paternal education, and maternal employment.
[†]Includes outdoor sports, playing out of doors, and other outdoor leisure activities. Cut points are based on population tertiles for average daily hours spent outside.
[‡]Significant ($P<0.05$) compared with the highest tertile of activity as the reference group.

Figure 1.5: *Associations between outdoor activity (Tertiles of Hours per Day) and spherical equivalent refractive error (SER) (Dioptre)** (*from: Rose et al., 2008*). *The year refers to the age of the child. Year 1 refers to a 6-year-old child and year 7 refers to a 12-year-old child.*

It has been suggested by Charman (2005) that, in the case of high levels of axial aberration or specific patterns of peripheral refraction, myopia progression can result. Figure 1.6 summarizes all the studies that compare the aberrations of myopic and emmetropic eyes.

Authors	No. of subjects	Ages	Pupil diam. (mm) used	Cycloplegia?	Type of aberrometer	Total higher-order aberration M > E?	Spherical aberration M > E?	Other comments
Applegate (1991a,b)	23	?	~7	Yes	X-cylinder (subjective)	Yes		
Collins *et al.* (1995)	21M, 16E	17–29	~4	None	X-cylinder (objective)	Possibly	No	Less fourth-order in measured myopes
He *et al.* (2002)	316	10–29	≥6.0	None	Psychophys. ray tracing	Yes	Yes	Measured at accomm. resting state
Marcos *et al.*	49M	Young	6.5	?	Laser ray tracing	Yes	No	
Porter *et al.* (2001)	109	21–65	5.0, 7.0	None	Hartmann–Shack	No	No	
Paquin *et al.* (2002)	27M, 7E	18–32	5, 9	Phenylephrine 2.5%/ tropicamide 1%	Hartmann–Shack	Yes	Yes	More coma in high myopes
Carkeet *et al.* (2002)	273	8–13	5.0	Three drops 1% cyclopentolate	Hartmann–Shack	No	No	
Cheng *et al.* (2003b)	200	26 ± 6	6.0	One drop 0.5% cyclopentolate	Hartmann–Shack	No	No	More aberration in astigmatic eyes
Radhakrishnan *et al.* (2004a,b)	8M, 8E	20–38	6.0	Two drops 1% cyclopentolate	Hartmann-Shack	No	Yes (but not sig.)	Asymmetry in blur effects on either side of focus in myopes
Llorente *et al.* (2004)	34M, 22H	23–40	6.5	One drop 1% tropicamide	Laser ray tracing			More aberration in hyperopic eyes

Figure 1.6: *Summary of studies comparing the aberrations of myopic and emmetropic eyes; M, E, and H represent myopes, emmetropes and hyperopes respectively* (*from: Charman, 2005*).

Various studies have confirmed that genetic factors are critical when assessing the likelihood of a child becoming myopic. Even before the onset of juvenile myopia, children of myopic parents have longer eyes (e.g. Zadnick et al., 1994). A systematic review conducted by Zhang et al. (2015) revealed, once again, that parents with myopia will have a significant effect on their children's chances of developing myopia (see Figure 1.7).

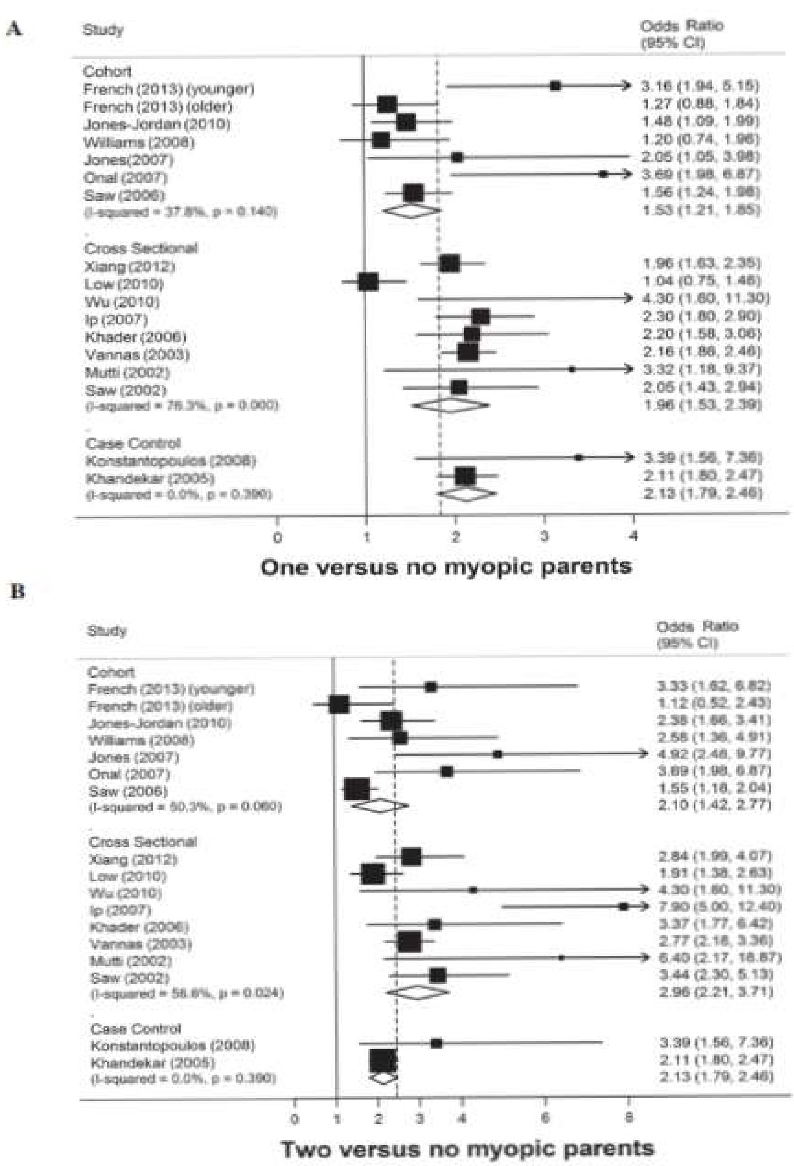


Figure 1.7: *Association between a child's risk of developing myopia when having (A) one or (B) two myopic parents (from: Zhang et al., 2015).*

The cause of myopia is clearly multifactorial, comprising both genetic and environmental factors. Because of the personal and socio-economic burdens associated with this refractive condition, the key factors in myopia progression continue to be keenly sought. This is especially so because, although it is well known that individuals with high myopia are at risk of developing vision impairment from pathologic conditions (see Table 1.1), it has recently been argued that low levels of myopia (<6 D) may also have a heightened risk of developing ocular disease (Flitcroft, 2012). For all these reasons, myopia management has become one of the highest priorities for all ophthalmic practitioners, with many placing great faith in a new and popular theory of myopia development termed the ‘hyperopic defocus theory’. Support for this theory from both animal and human research is detailed below.

1.3 Overview of Hyperopic Defocus Theory of Myopia

Peripheral refraction and its relation to myopia has been investigated for many years. Ferree, Rand & Hardy investigated the issue of peripheral retinal vision using manual objective optometers as far back as 1931 (Ferree & Hardy, 1933, Ferree, Rand & Hardy, 1931 & 1933, as cited in Atchison et al., 2003; see also Rempt et al., 1971, as cited in Atchison et al.,2015).

According to hyperopic defocus theory, if an eye has a relatively hyperopic periphery, compensating axial elongation signals may be generated without regard to the inevitable myopic defocus generated at the fovea. Wallman and Winawer (2004) suggested that the greater overall number of retinal neurons in the periphery, compared with the central retina, may allow peripheral signals to dominate eye growth. They argued that homeostatic signals to retard eye elongation generated from the myopic fovea may be overwhelmed by peripheral signals that direct greater elongation, such that, overall, the eye continues to grow and become more myopic.

Reviewing the article by Garcia et al. (2019), the theory of peripheral retinal defocus is still considered an important issue, especially when considering treatment to retard myopia progression. Garcia et al. quoted the editorial featured in *Ophthalmic and Physiological Optics* (Volume 38), where Logan and Guggenheim, following the 16th Myopia Conference held at Aston University in September 2017, commented on the discussion about treatment based on peripheral retinal defocus. If we look at other treatments available to retard myopia progression, such as MiSight, orthokeratology, and extended depth of focus contact lenses, all are based on the peripheral retinal defocus theory. It appears clear, therefore, that the hyperopic defocus theory remains a dominant theory in this field.

Figure 1.8 shows diagrammatically, peripheral hyperopic (blue function) and myopic defocus (red function). In both cases, the central light rays are focused on the fovea. As indicated in the figure, the hyperopic defocus theory posits that peripheral hyperopic defocus may act as a stimulus to increase the axial length of the eye, resulting in central myopia.

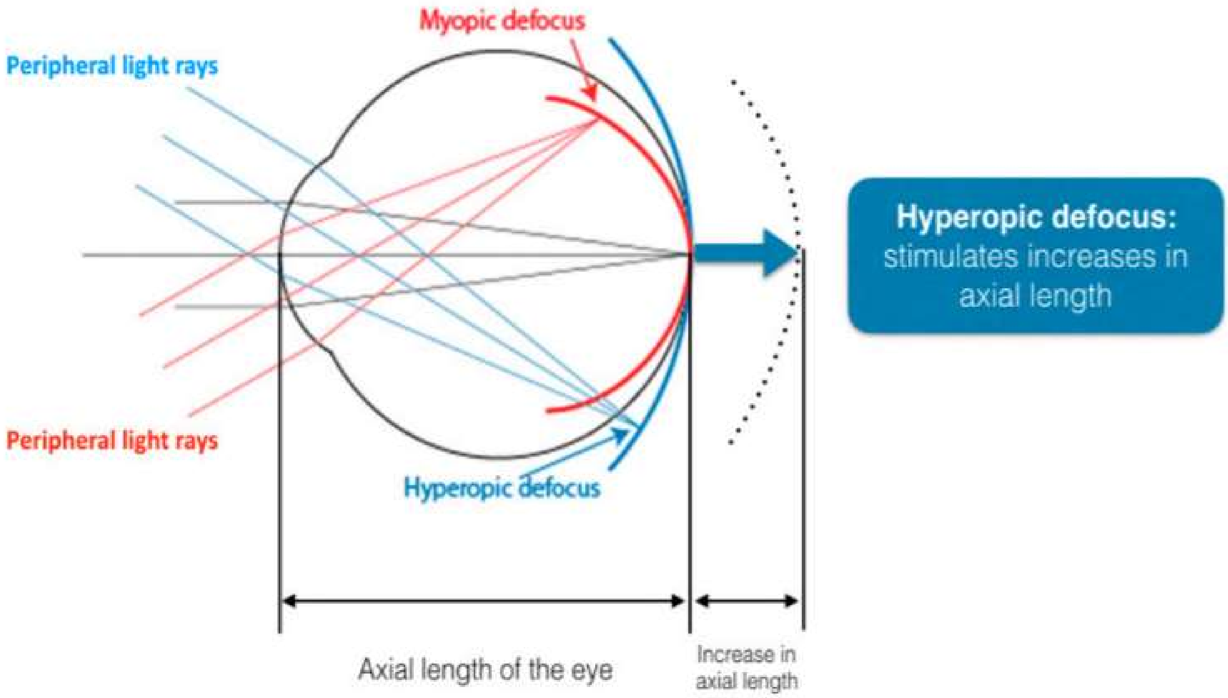


Figure 1.8: *Relative peripheral hyperopic defocus (light focused behind retina), and relative peripheral myopic defocus (light rays focused in front of the retina) (from: Menicon, 2017).*

This theory may also offer a means for treating myopia, by countering peripheral homeostatic signals that cause elongation of the eye (e.g. Kang and Swarbrick, 2015). If this is the case, it is potentially a highly significant development for the practice of optometry, for it lays open the opportunity for optometrists to not only passively correct refractive errors but also to actively alter the degree of myopic progression.

1.3.1 Retinal Shape and Consequences of Peripheral Hyperopic Defocus

It has been proposed that peripheral hyperopic defocus is a natural consequence of retinal shape, as myopes have more prolate posterior segments. According to several studies, the peripheral eye shape is dependent upon the refractive state of the eye (Atchison, 2006; Atchison et al., 2005; Logan et al., 2004; Singh et al., 2006). Mutti et al. (2000) suggest that emmetropic eyes have a spherical shape, hyperopic eyes have an oblate shape, while myopic eyes have a prolate shape. Figures 1.9 and 1.10 show diagrammatically the shapes of eyes spanning the range of refractive conditions. In Figure 1.10, the posterior eye wall is pictured as the black curve, while the white curve is the spherical image shell. Both curves coincide at the posterior pole, but not at the periphery. For myopic eyes, the eyewall is displaced posteriorly from the image shell, which results in peripheral hyperopic defocus. For hypermetropes, the opposite is true (i.e., the eyewall is displaced anterior to the image shell).

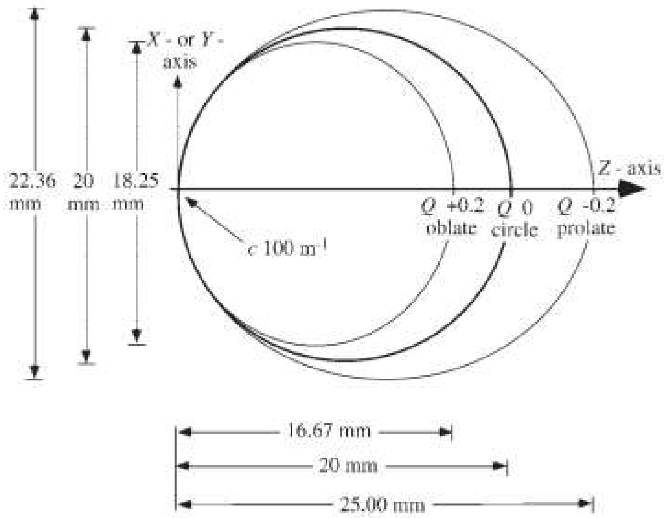


Figure 1.9: *The shape of the eye relative to eye length (from: Atchison et al., 2005).*

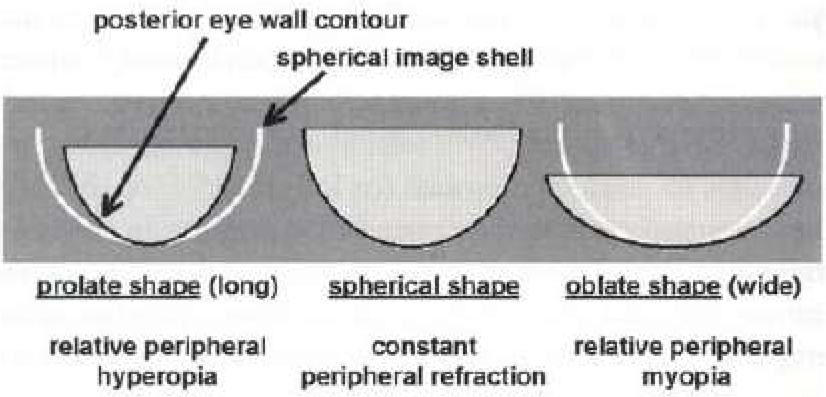


Figure 1.10: *Relative peripheral refraction and posterior eye shape (from: Stone & Flitcroft, 2004).*

1.4 Animal Studies on Peripheral Hyperopic Defocus Theory

Various animal studies have generated supporting evidence for the peripheral hyperopic defocus theory of myopia. Significant papers in this area are detailed below, divided into results obtained from either monkeys or chicks. Emphasis is placed on the data from monkeys, as it is widely accepted that results from monkeys are most applicable to humans (Smith & Hung, 1999).

1.4.1 Studies Based on Data from Monkeys

Smith et al. (2010) characterized the influence of optical defocus on ocular shape and the pattern of peripheral refraction in infant rhesus monkeys. The monkeys were reared wearing either: (i) spectacle lenses over one eye that produced relative hyperopic defocus in the nasal field but allowed unrestricted vision in the temporal field; or (ii) spectacle lenses that produced relative hyperopic defocus across the entire field of view. They observed that, with full-field hyperopic defocus, the monkeys developed relative central axial myopia, exhibiting relative peripheral hyperopia in both hemifields. In sharp contrast, monkeys with nasal-field hyperopic defocus produced relative myopia that was largely restricted to the nasal hemifield (Figures 1.11 and 1.12). They concluded that peripheral hyperopic defocus could produce alterations in ocular shape and peripheral refractive error. Importantly, the myopic refractive changes produced by full-field defocus were observed to be greatest in the central retina, decreasing with eccentricity (i.e., exhibiting relative peripheral hyperopia). These changes, they argued, must result from local mechanisms in the eye.

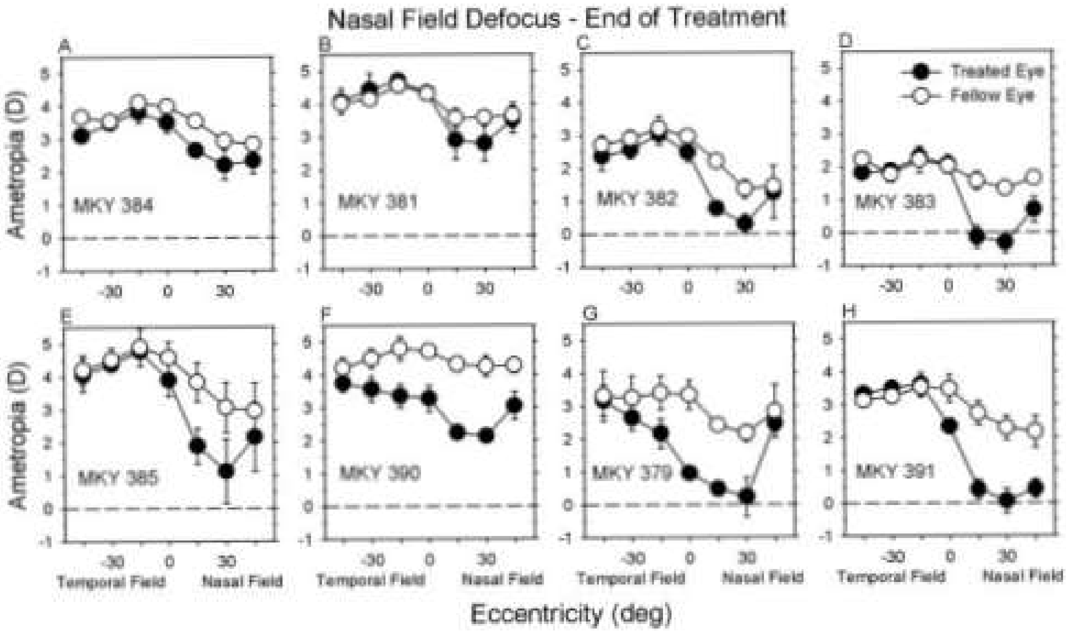


Figure 1.11: *Spherical-equivalent refractive corrections plotted as a function of horizontal eccentricity for the treated eyes (filled symbols) and fellow eyes (open symbols) of individual monkeys treated with nasal-field -3D lenses. The data points represent the mean ±SE for the final three measurement sessions of the treatment period (from: Smith et al., 2010).*

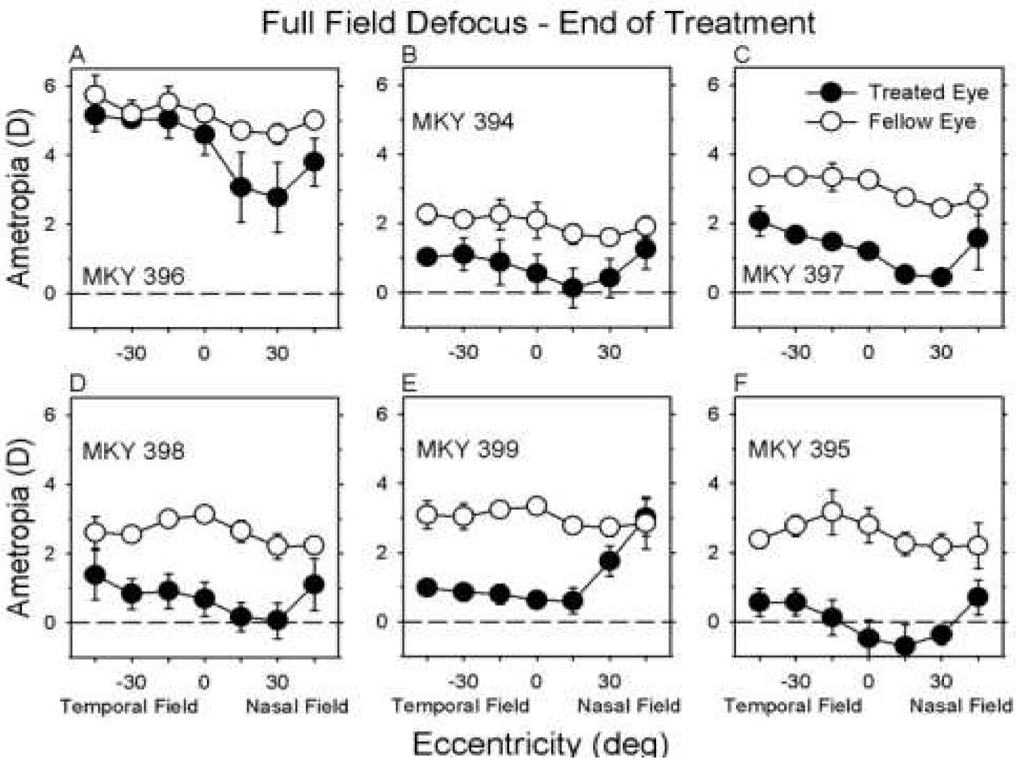


Figure 1.12: *Spherical-equivalent refractive corrections plotted as a function of horizontal eccentricity for the treated eyes (filled symbols) and fellow eyes (open symbols) of individual monkeys treated with full-field -3D lenses. The data points represent the mean ± SE for the final three measurement sessions of the treatment period (from*: *Smith et al., 2010*).

By optically imposing astigmatism to monkeys' eyes, Kee et al. (2004) also demonstrated that refractive error developed through local ocular mechanisms. They reported that most of the astigmatic eyes became more hyperopic, and that the degree of refractive error was correlated with the power of the cylindrical lenses imposed, independent of the cylinder axis. The refractive changes were mainly axial, biased toward the eye's least-hyperopic focal plane. They concluded that the mechanisms responsible for refractive development must be local, seeking out the image plane that contained the maximum effective contrast integrated across stimulus orientation.

Smith et al. (2005) examined the effect of peripheral vision of young monkeys on emmetropization. They used diffusers with 4 or 8mm apertures centred on the pupil of each eye. After using the lenses, the fovea of one eye was ablated and the refractive error was measured. They concluded that the peripheral retina could contribute to emmetropization, but unrestricted central vision was not sufficient to promise normal refractive development. This is illustrated in Figure 1.13, below.

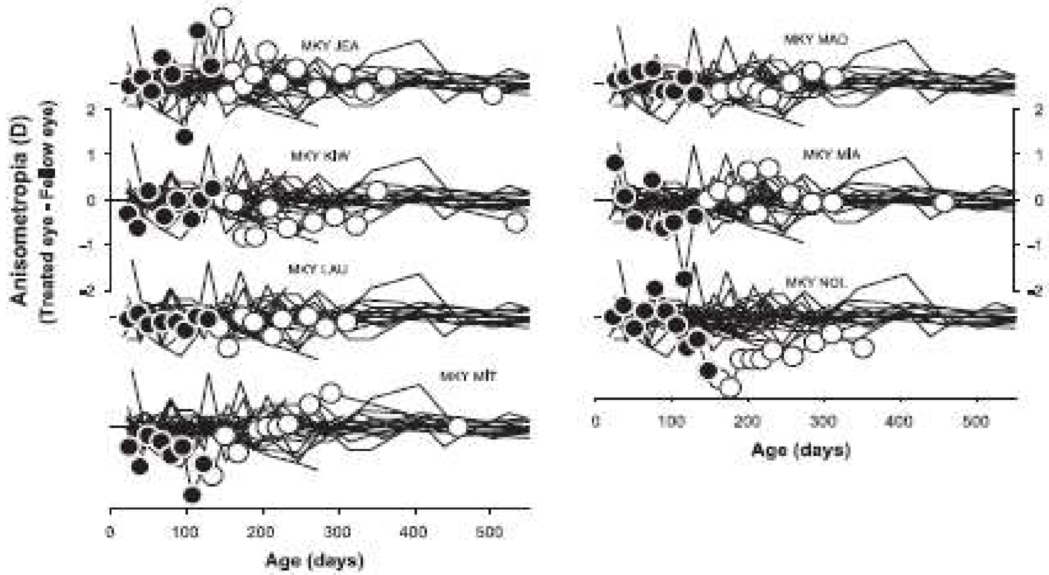


Figure 1.13: *Interocular differences in refractive error (ablated eye or right eye-fellow eye) plotted as a function of age for the seven diffuser-reared monkeys that had the fovea of one eye ablated at the end of the lens-rearing period. Data shown were obtained during (black circle) and after lens-rearing period (clear circle*) (*from: Smith et al., 2005).*

Benavente-Perez et al. (2014) found that eye growth and the refractive state in marmosets could be changed by imposing peripheral hyperopic defocus. In addition, early findings in young chicks showed that they adjusted their growth to compensate for the imposed optical defocus. With minus lenses that imposed hyperopic defocus, eyes increased in axial length, and with plus lenses that caused myopic defocus, the elongation was retarded (Liu & Wildsoet, 2011). Altering the peripheral rather than central retinal defocus had a more significant effect on axial elongation (Liu & Wildsoet, 2011). Peripheral hyperopic defocus produced axial myopia, whereas peripheral myopic defocus produced axial hyperopia (Benavente-Perez et al., 2014).

In a further study on monkeys, it was found that when there were conflicting visual signals between the fovea and peripheral retina, eye growth is determined by the peripheral retina (Smith et al., 2009). Two strategies were used to examine the effect of peripheral hyperopic defocus on the growth of the eye and the refractive development. To impose relative peripheral hyperopia on both eyes, a -3.0 D lens with 6 mm circular apertures was placed centrally over the pupil, creating an unrestricted field of view of 10.3 degrees. When objects were located at eccentricities of between 10-31 degrees, the image was diffracted by the -3D powered portion of the lens. This was true for objects 31 degrees and beyond, creating a -3D hyperopic defocus (Figure 1.14). Figure 1.14 shows that, within the multifocal zone between the dotted and dashed lines, objects are imaged at two focal planes, one determined by the eye's optics alone and a second located at a more hyperopic plane determined by the powered portion of the treatment lens.

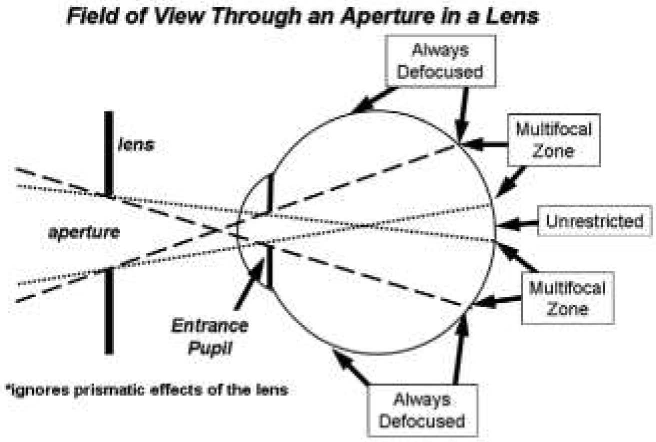


Figure 1.14: *Schematic diagram of the extent of the effects of the treatment lens aperture on retinal imagery. The dotted lines represent the projection of the eye's entrance pupil through the lens aperture and demark the object eccentricities that are imaged exclusively through the Lens aperture (i.e., the "unrestricted" portion of the field). The dashed lines delineate the object eccentricities that are imaged exclusively through the powered portion of the lens (from: Smith et al., 2009).*

Smith et al. (2009) concluded that peripheral vision can have a substantial effect on central retinal development, and that optically imposed myopic defocus that affects a large portion of the peripheral retina should be effective in slowing myopic progression.

Though it has generally been assumed that the input from the fovea affects refractive development, Smith et al. (2007) showed that foveal ablation of a monkey's eye by means of photocoagulation does not affect emmetropization (Figure 1.15). Smith et al. concluded that signals from the fovea did not have an effect on normal refractive development, and that the peripheral retina alone may be the trigger for regulating emmetropization.

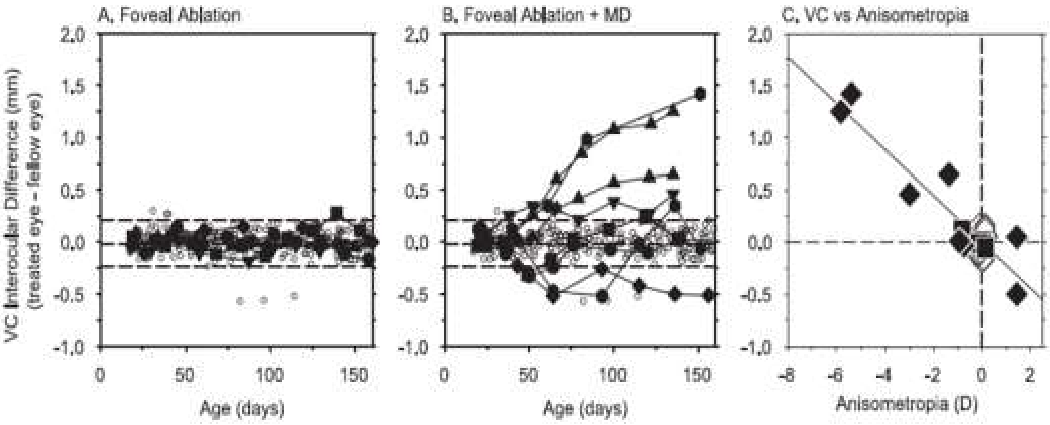


Figure 1.15: *Intraocular differences in vitreous chamber depth (right or treated eye-fellow eye) plotted as a function of age* (*from: Smith et al., 2007*). *Intraocular differences in vitreous chamber depth plotted as a function of age: Control animals (open symbols); monkeys that experienced unrestricted vision (A-filled symbols); monkeys with foveal ablation (B-filled symbols); C= vitreous chamber depth versus interocular differences in refractive error. (Control-open diamond; treated monkeys-filled squares).*

1.4.2. Studies Based on Data from Chicks

There are many research advantages in using chickens for modelling visual development: chickens have relatively large eyes (8 to 14mm), the eye grows rapidly (100 microns per day), excellent optics are possible (diffraction limit at 2 mm pupils), there is highly sensitive control of the refractive state by retinal image quality and focus, and they have active accommodation (17D) and high visual acuity. In addition, chickens are friendly, cooperative, inexpensive and easy to keep. Against this, there are some disadvantages in the chick model: chickens lack of a fovea and, in comparison with mammals, have differences in scleral composition and accommodative mechanisms. Nonetheless, studies on chicks have provided fundamental information on the mechanisms of emmetropization (e.g. Schaeffel & Feldkaemper, 2015).

Smith et al. (2014) not only conducted studies on peripheral defocus using monkeys, but also conducted studies involving chickens. They showed that the larger the area of myopic defocus imposed on the peripheral retina, the greater the success of retarding myopia progression (Figure 1.16).

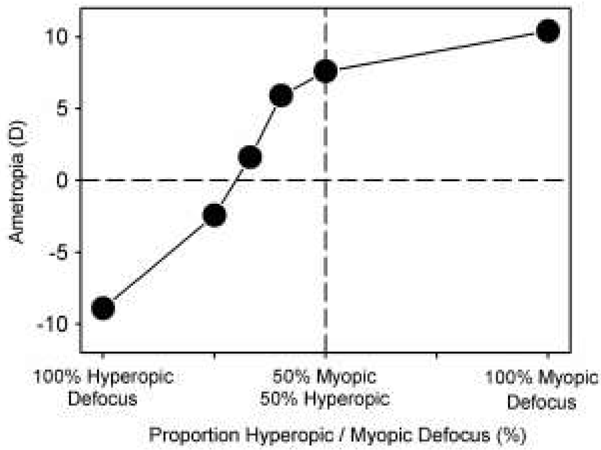


Figure 1.16: *Mean interocular differences in spherical-equivalent refractive corrections for lens-reared chickens plotted as a function of the proportion of the visual field that experienced hyperopic versus myopic defocus* (*from: Smith et al., 2014).*

Wallman et al. (2000) also conducted several experiments using lens-compensation on chickens. Refractive error and axial dimensions were measured before and after spectacle-lens wear. They noted that even short periods of imposed myopic defocus inhibited eye growth. It was therefore thought that creating myopic defocus in children might be means of inhibiting myopia progression (Wallman et al., 2000). In other words, relative myopic defocus, which has been imposed by positive lenses, may slow down axial growth (Huang et al., 2012).

Schaeffel and Howland (1988) reported similar refractive changes in chickens, following a period of time in which they were fitted with either positive or negative lenses. They noted that the induced myopia principally arose from axial eye length changes. Schaeffel and Howland also degraded the retinal image with the aid of occluders, which again produced myopia (see Figure 1.17 for details).

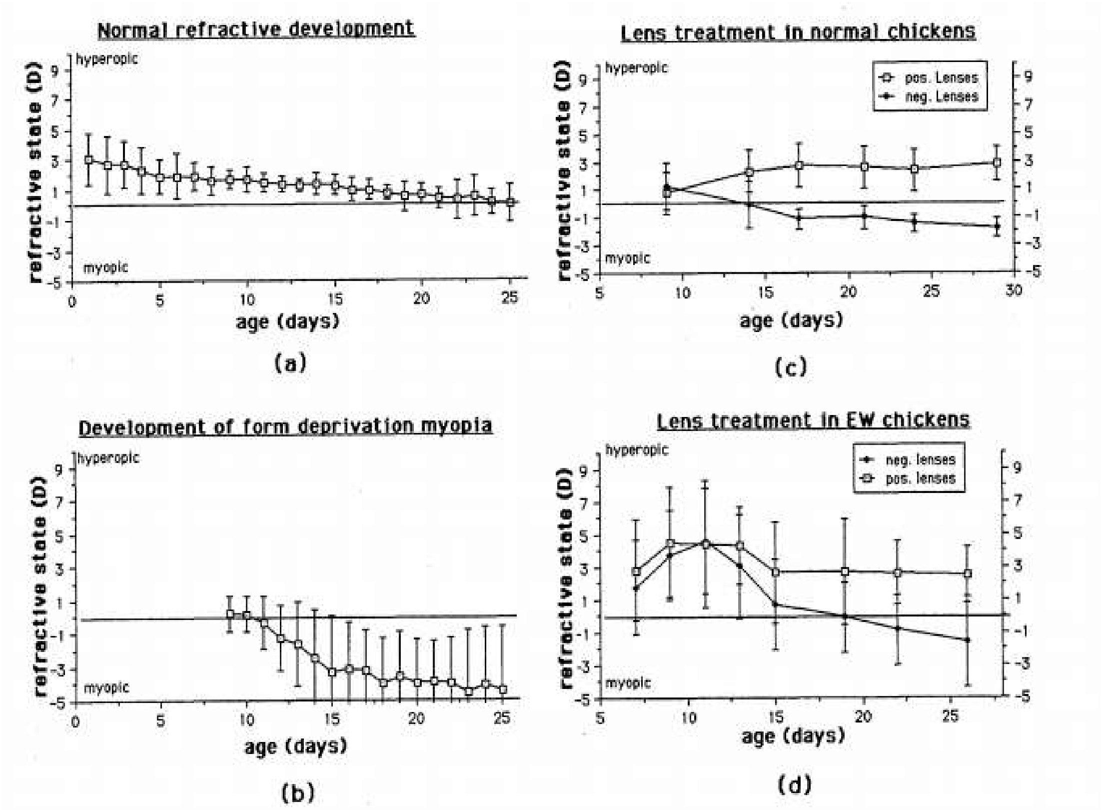


Figure 1.17: *Observations on the refractive development in chicks, new-born to age 25 days, under various treatments (from: Schaeffel & Howland, 1988).*

Other studies have shown that chicken eyes compensated for positive or negative lenses worn for short periods of time in between periods of complete darkness. Zhu et al. (2003), for example, used White Leghorn chicks and employed PMMA plastic or glass lenses of different powers (plano, +10, -6.00, and -15 dioptres). The refractive error was measured using a modified refractometer, and an A-scan ultrasonographer was used to measure internal ocular dimensions. They observed that chickens wearing a positive lens for a short period of time (12 minutes to one hour a day), experienced a compensation in the hyperopic direction even if no lens, or a negative lens, was worn the remainder of the day. In brief, the imposed myopic defocus was sufficient to nullify the effects of hyperopic defocus.

1.5 Human Studies on Peripheral Hyperopic Defocus Theory

To assess the relationship between foveal and peripheral refractive errors in humans, Seidemann & Schaeffel (2002) measured the sphero-cylindrical errors across the visual field in myopic, emmetropic and hyperopic observers. They reported that myopic eyes have more relative peripheral hyperopia than hyperopic eyes. They also noted higher amounts of oblique astigmatism, especially amongst hyperopes. This is illustrated in Figure 1.18.

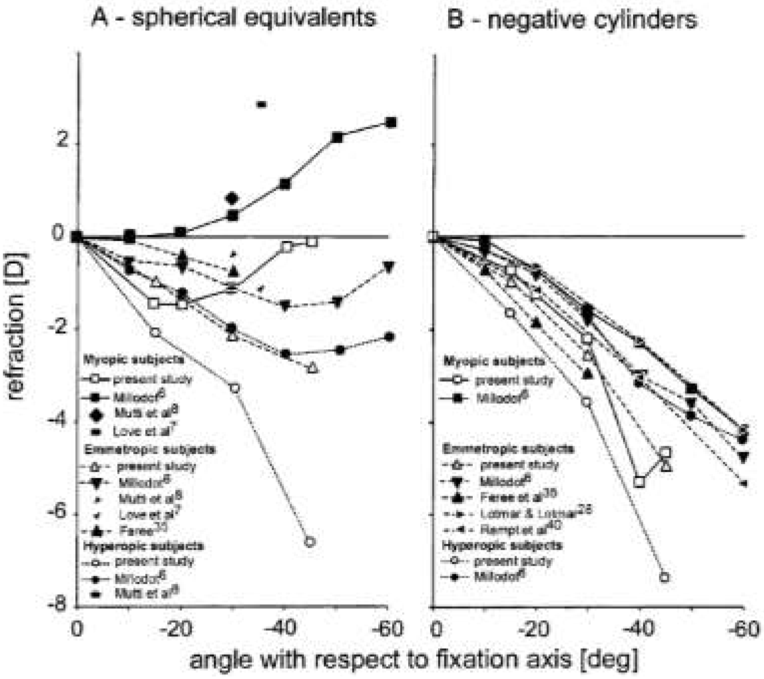
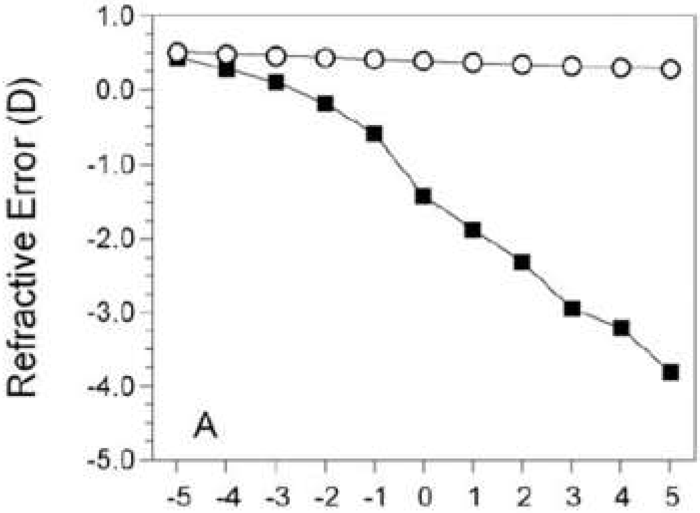


Figure 1.18: *Comparison of the spherical equivalents and negative cylindrical measures across the visual field for myopic, emmetropic and hyperopic subjects (from: Seidemann & Schaeffel, 2002).*

Mutti et al. (2007) examined the onset of myopia, refractive error, axial length and relative peripheral refractive error in a large sample of children (n = 605), aged 6 to 14 years. They reported that children who became myopic had less hyperopia and greater axial length than emmetropes, both before and after the onset of myopia (Figures 1.19 and 1.20). They found that longer eyes, more negative refractive errors, and increased relative peripheral hyperopia occurred two to four years before the onset of myopia. Longitudinal studies have shown that faster growth, fast progression and a more rapid change toward peripheral hyperopia were also predictive of the onset of myopia (Mutti et al., 2007; Troilo et al., 2019).



Visit Relative to Onset (years)

Figure 1.19: *Spherical equivalent refractive error as a function of annual visit relative to the onset of myopia (0= year of onset; -5 years = 5 years prior to onset; + 5 years= 5 years after onset) {comparing myopes (closed squares) to emmetropes (open circles)} (from: Mutti et al., 2007).*

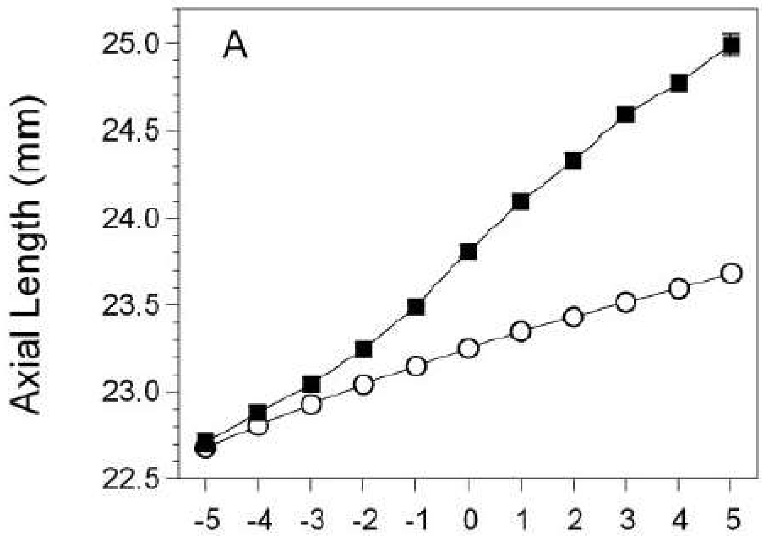


Figure 1.20: *Axial length difference between myopes (closed squares) and emmetropes (open circles) in the period five years before to five years after onset of myopia (from: Mutti et al., 2007).*

Mutti et al. (2007) provided convincing evidence the refractive status of the periphery played a significant role in the determination of central refractive status. They reported that (i) emmetropes had more relative peripheral myopia than myopes; (ii) myopes initially had relative peripheral myopia, which became more hyperopic with time: near the time of myopia onset, there was a rapid change towards relative hyperopic defocus (see figure 1.21).

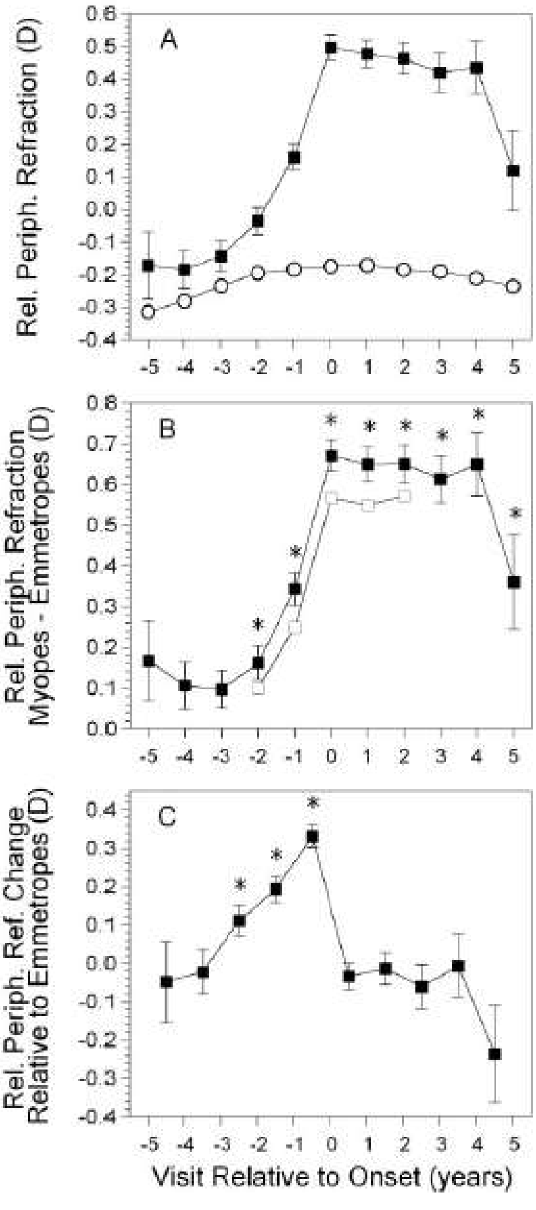


Figure 1.21: *Relative peripheral refractive error in the became-myopes (A). difference in error between myopes and emmetropes (B); and change in error between visits in the myopic group (C). Symbols: myopes (closed squares); emmetropes (open circles) (from: Mutti et al., 2007).*

Another study conducted by Mutti et al. (2000) compared the peripheral refraction to the shape of the eye in children aged between 6 and 14 years. The cycloplegic autorefraction was measured at the fovea and at 30º nasally. They also measured axial length, crystalline lens radii of curvature and corneal power. They concluded that the eyes of the myopic children were elongated into a prolate shape. Thinner crystalline lenses were associated with more relative peripheral hyperopia.

Atchison et al. (2006) measured the peripheral refraction of young adult myopes and emmetropes, out to 35º both horizontally and vertically. Their results showed that the emmetropes had steeper changes along the vertical meridian compared to the horizontal meridian. In the case of myopes, the vertical meridian myopic shifts occurred in the periphery for all refractive errors. The same did not occur in the horizontal meridian. For myopes between -2D up to -4D, there was a relative hyperopic shift in the periphery; above -4D there was little change. This is illustrated in Figure 1.22.

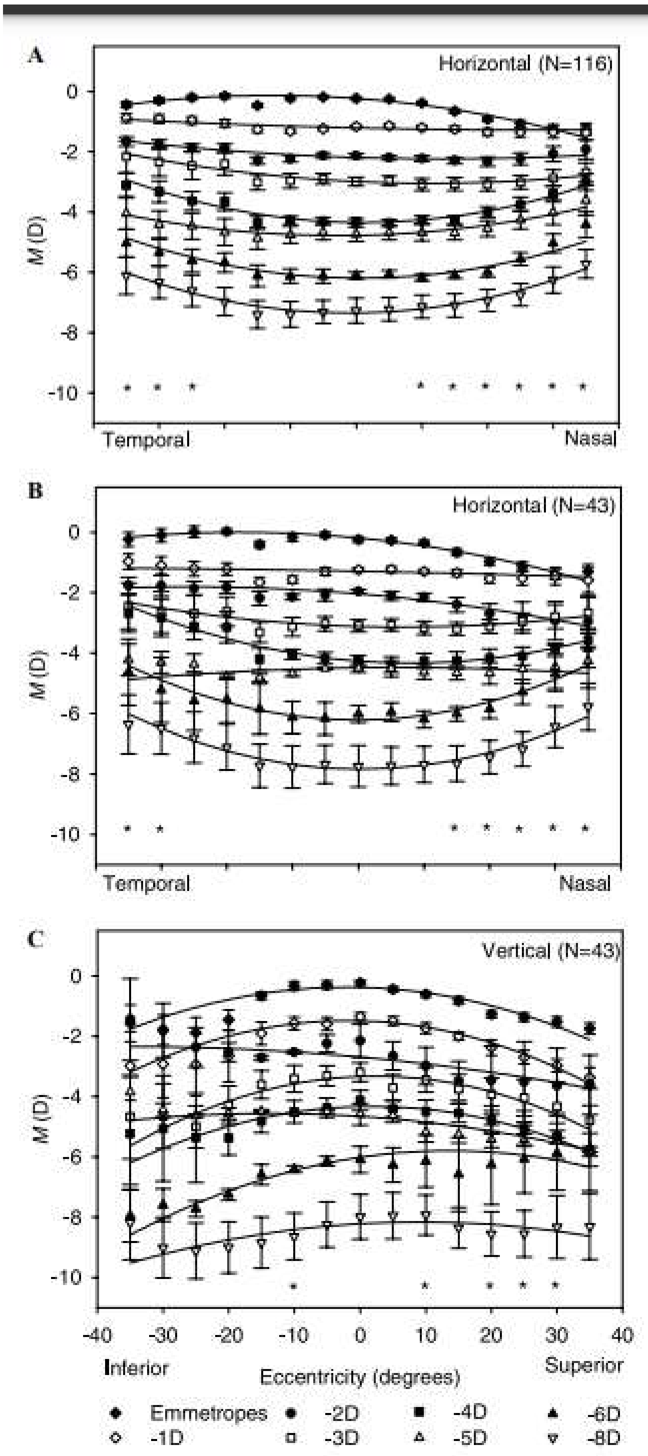


Figure 1.22: *Spherical equivalent (M) as a function of visual field angle for: (A) the horizontal visual field of all subjects (n = 116); (B) the horizontal visual field of the subset of subjects for whom also were obtained vertical visual field measurements (n = 43), and (C) the vertical visual field of the same subset of subjects (n = 43). Errors bars indicate ± SE (some error bars are smaller than the plot symbols). Visual field points marked with an*

asterisk are those for which the differences between peripheral and central M (spherical equivalent) are significantly correlated with central M ($p < 0.05$) (from: Atchison, 2006).

Using a laser Dopler interferometer, Schmid (2011) measured axial length at the fovea and at 20º temporally, nasally, inferiorly, and superiorly, at the beginning and end of one month and at the end of 24 months. He observed that baseline retinal steepness (i.e., the posterior pole shape) was correlated with the degree of relative peripheral defocus. The association between baseline relative peripheral eye length (RPEL) at the different locations, and the shift in central refraction, was determined using Structural Equation Modelling analysis. Schmid reported a correlation between the change in central spherical equivalent refraction and the change in axial length, which indicated that a myopic shift in children was due to axial elongation.

In the study by Bernsten et al. (2013) half of the children wore progressive addition lenses (PALs), the other half wore single vision lenses. Those that wore PALs and almost half of those wearing SVLs had superior relative peripheral myopic defocus with their spectacles. This meant that 74% of the children had myopic superior relative peripheral defocus (RPD) with their spectacles. Bernstern et al. (2013) observed that children with myopic relative peripheral defocus (RPD) had 0.24D less myopic progression at the fovea after one year of wearing progressive addition spectacle lenses (PAL) than children wearing single vision lenses (SVL). It should be noted that SVLs cause a hyperopic shift in the peripheral retina, whereas PALs cause a myopic shift (Figures 1.23 & 1.24). Figure 1.24A: 80% of the children experienced myopic superior retinal defocus and had much less central myopia progression compared to the children with superior retinal defocus. Figure 1.24B: 43% of the children had myopic temporal retinal defocus. This was associated with much less central myopia progression compared to children with hyperopic temporal retinal defocus.

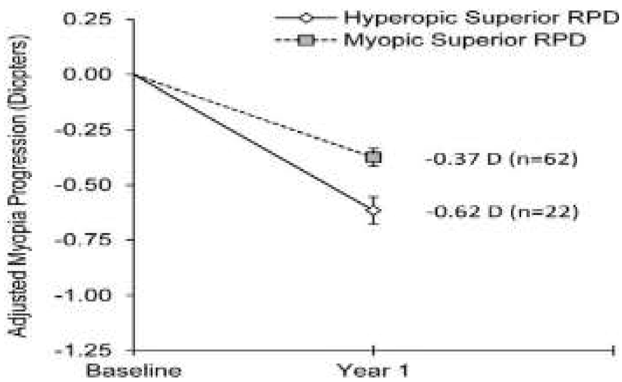


Figure 1.23: *Mean 1-year change in central spherical equivalent refractive error for children with either hyperopic RPD or myopic RPD on the superior retina. Children wore either SVLs or PALs. Annual progression was adjusted for baseline refractive error, baseline age, sex, and ethnicity. Error bars represent SE (from: Bernsten et al., 2013).*

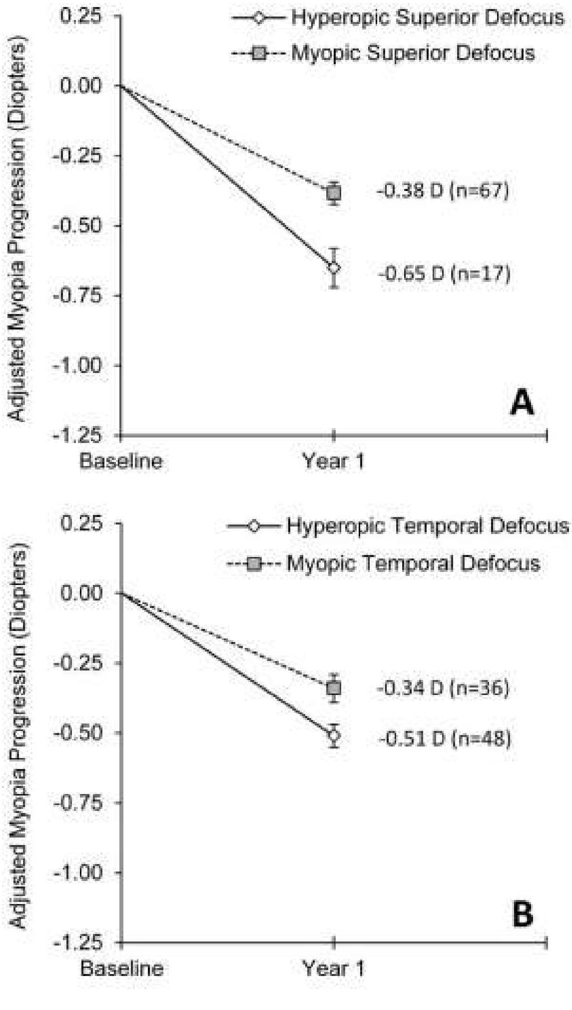


Figure 1.24: *Mean 1-year change in central spherical equivalent refractive error during the first study year (wearing either SVLs or PALs) for children with absolute peripheral*

defocus that was hyperopic versus myopic on the (A) superior retina and (B) temporal retina. Measurements were taken by the aberrometer. Annual progression is adjusted for baseline refractive error, baseline age, sex, and ethnicity. Error bars represent SE (from: Bernsten et al.,2013).

Assessing the refractive status of a total of 294 subjects, aged between 7 to 11 years, Mutti et al. (2019) reported an increase in relative peripheral hyperopia, more so in the horizontal meridian than the vertical meridian (Figure 1.25). The retinal profile was observed to be steeper as the amount of myopia increased.

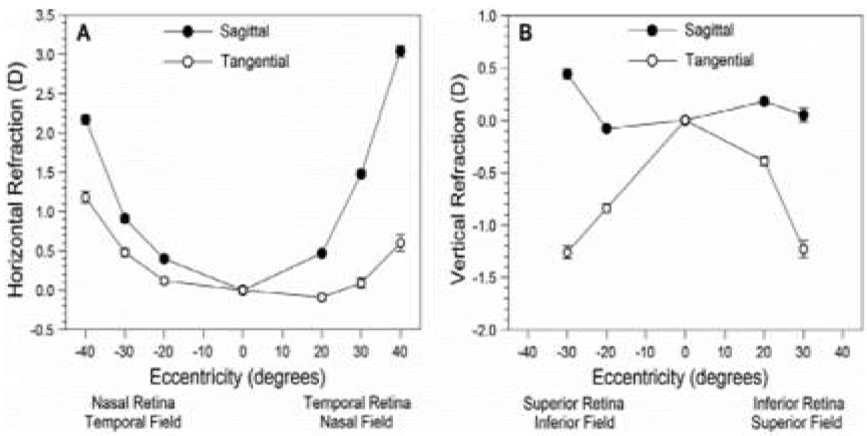


Figure 1.25: *Relative peripheral refractive error in children, in the sagittal and tangential meridians, as a function of eccentricity and meridian: horizontal (A) and vertical (B). Error bars (some obscured) represent the standard error of the mean (from: Mutti et al., 2019).*

Atchison et al. (2005) illustrated the differences in the horizontal and vertical dimensions, when comparing an emmetropic eye with a model eye for an emmetrope and -10D myope (Figure 1.26). Both the emmetropic and myopic retinas are oblate in shape, although the myopic eyes less so. In the case of the emmetropes, both the retinal-choroid and sclera were similar in thickness at the pole compared to the equator. As the myopia increased, the retinal-scleral thickness decreased both at the equator and at the pole. This data suggests that relative peripheral hyperopic shifts in the periphery are due to prolate retinal shapes.

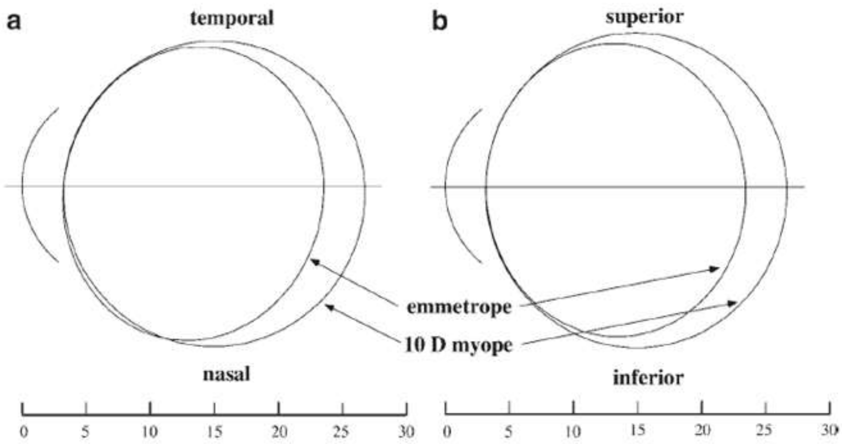


Figure 1.26: *Model of emmetrope and -10D myope in (a) horizontal and (b) vertical sections (from: Atchison et al., 2006).*

1.5.1. The Effect of Spectacle Lenses on Peripheral Defocus

Examining the effects of single vision spectacle lenses on myopic Chinese children aged 8-18 years, Lin et al. (2010) observed that such lenses caused an increase in hyperopic defocus in peripheral retina. As the refractive error and eccentricity increased, the extent of peripheral defocus also increased. All measures were conducted using a cycloplegic autorefraction, both with and without the spectacle correction in place (see Figures 1.27a and 1.27b).

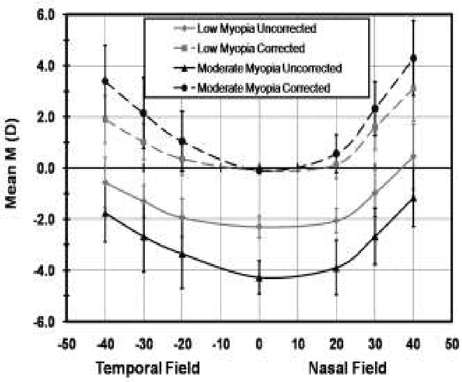


Figure 1.27a.

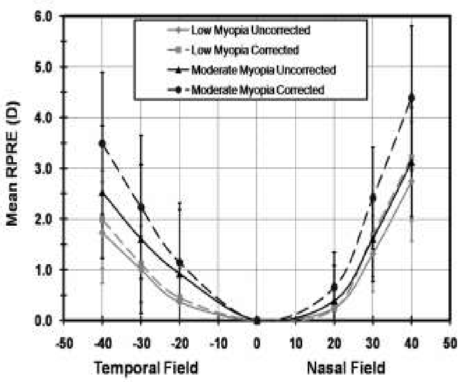


Figure 1.27b.

Figure 1.27 (a) *Spherical equivalent (M) in dioptres along the horizontal field in uncorrected and corrected Eyes with low myopia and moderate myopia. Error bars indicate ± 1 standard deviation. (b) Relative peripheral refractive error (RPRE) along the horizontal field in uncorrected and corrected eyes with low myopia and moderate myopia. Error bars indicate ± 1 standard deviation (from: Lin et al., 2010).*

Zhang et al. (2020) examined the changes in relative peripheral refraction (RPR), comparing myopic children wearing Defocus Incorporating Multiple Segments (DIMS) versus those wearing single vision (SV) spectacle lenses, with regard to myopia progression over a two-year period. This was a double-blind randomized control study on 183 children: a total of 93 subjects wore DIMS and 90 wore SV lenses. Peripheral refraction at 0º, 10º, 20º and 30º nasally and temporally was measured, under cycloplegia, every six months. Axial length also was monitored. Those wearing single vision lenses had a significant increase in hyperopic retinal peripheral refraction nasally, whereas those wearing DIMS lenses did not have a clinically significant change (See Figure 1.28). This study was the first to evidence myopia control using peripheral myopic defocus, with simultaneous central clear vision.

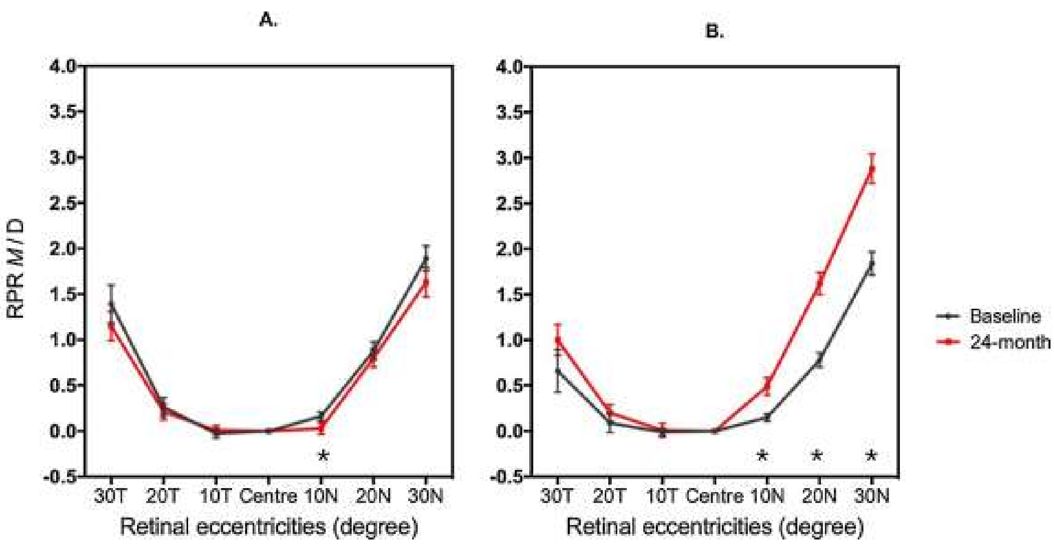


Figure 1.28*: Changes in relative peripheral refraction (RPR) in myopic children over two years, comparing defocus incorporating multiple segments (DIMS) versus single vision (SV) spectacle lenses (A) RPR changes across horizontal retina in the DIMS group. (B) RPR changes across horizontal retina in the SV group (from: Zhang et al., 2020).*

Tabernero et al. (2009) also suggested that, while conventional single vision lenses were designed to correct the foveal refractive error, they also created peripheral retinal hyperopia. Therefore, they recommended using a radial refractive gradient lens (RRG), which increased myopia in all radial directions from the centre to the periphery, in order to retard myopia progression. A total of 11 subjects (five myopes, six emmetropes) aged 25 to 30 years were refracted using a modified infrared photoretinoscope. The highest degree of peripheral hyperopia occurred with spectacle correction. The RRG lens, however, induced relative peripheral myopia (see Figure 1.29).

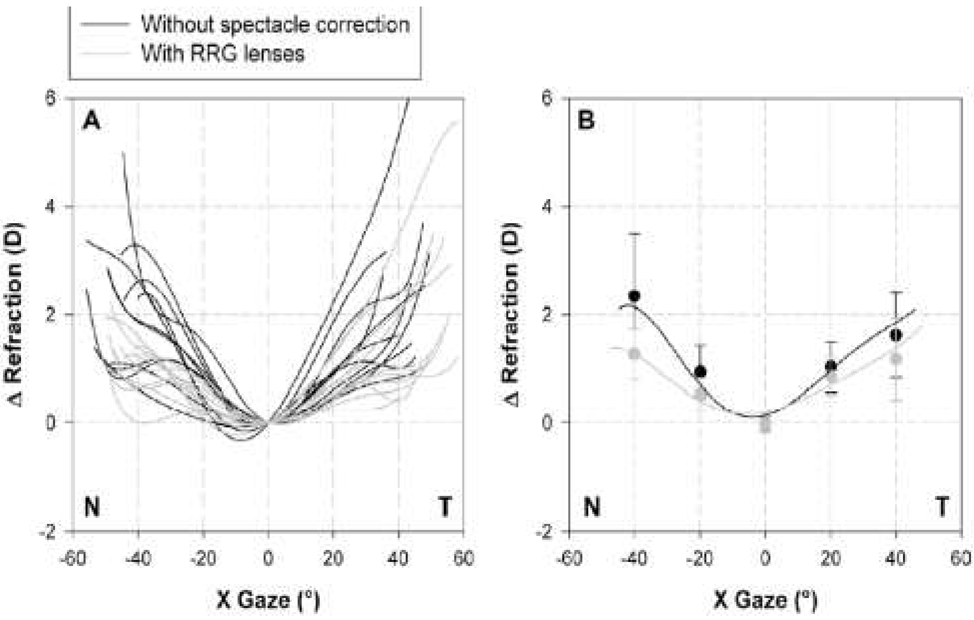


Figure 1.29: *Summary of the effects of RRG lenses on peripheral refractions. gray symbols denote refraction profiles with RRG lenses, and black without. (A) Polynomials fits to each of the refraction profiles of the individual eyes, and (B) averages of the polynomial fits from all eyes (means and standard Deviations) at five angular positions (from: Tabernero et al., 2009).*

1.5.2. The Effect of Contact Lenses on Peripheral Defocus

Several studies in children have found that various kinds of soft contact lenses caused different changes in the peripheral defocus, depending on the lens design (Moore et al., 2017; Sankaridurg et al., 2011). Lin et al. (2010) examined children (8 to 15 years), dividing them into low (-0.75 to -3.00) or moderate (-3.25 to -6.0) myope groups, depending on the strength of their single vision spectacle lenses. Hyperopic peripheral defocus was found in both groups, with the greatest defocus recorded for the moderate group. Sankaridurg et al. (2011) noted that, in comparison with spectacle lenses, children fitted with single vision contact lenses (Lotrafilcon B, CIBA Vision) had less relative peripheral hyperopia.

Lam et al. (2014) examined a novel soft contact lens (Defocus Incorporated Soft Lens {DISC}), designed to slow myopia progression. This lens was a custom-made bifocal soft lens made of concentric rings. The centre corrected the foveal refractive error, with the alternating defocusing and correction zones extending into the periphery. The defocusing zones were 2.5D relatively less negative, thus introducing myopic retinal defocus. This was a two-year, double-blind randomized controlled study: a total of 221 children, aged 8 to 13 years with refractive errors ranging from -1.00 to -5.00D were assigned to either the DISC group or the single vision lens group. The results showed that, over the two-year period, those wearing the DISC lenses had 25% less myopic progression and 31% less axial length increase than those in the single vision group (see Figure 1.30).

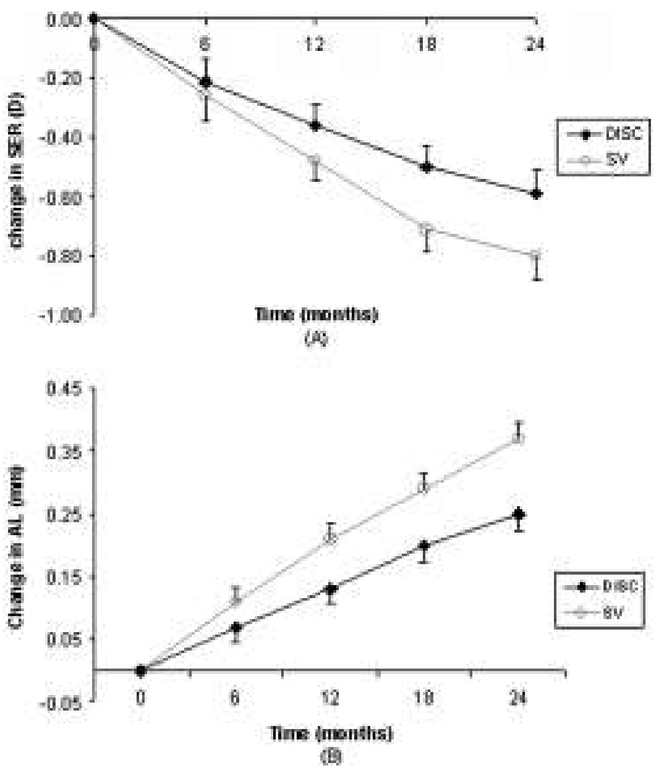


Figure 1.30*: (A) Mean and SEM of myopia progression (spherical equivalent refractions) and (B) mean and SEM of axial length elongation for the subjects who completed the study. DISC, Defocus Incorporated Soft Contact; SV, single vision* (*from: Lam et al., 2013*).

Anstice and Phillips (2011) also investigated the efficacy of a dual focus soft contact lens in reducing myopia progression. This was a prospective, randomized, paired-eye control study, with a total of 40 children aged 11-14 years. The lens design incorporated a central distance correction zone, and concentric treatment zones of 2.00D, which created myopic defocus zones during both distance and near viewing. The control was a single vision lens. Figure 1.31, below, illustrates the essential principles of the lens design.

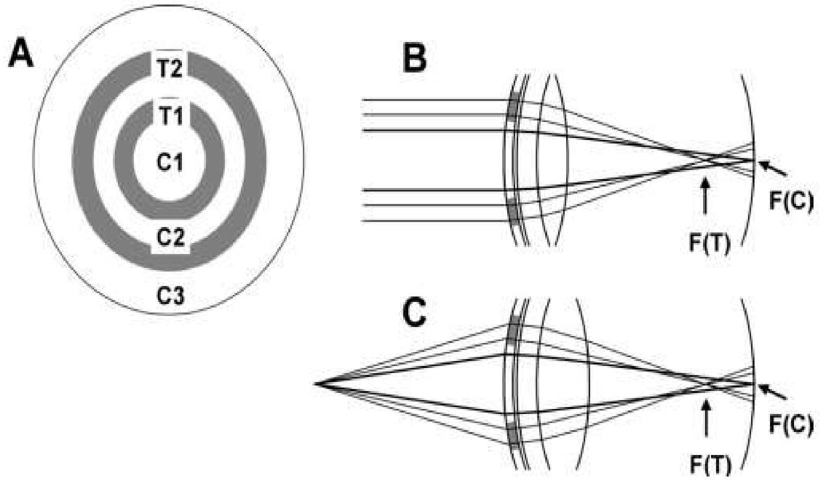


Figure 1.31: *Design of the DF contact lens. "A" depicts the correction zone. "B" shows distance viewing. "C" indicates accommodation during near viewing. During distance viewing ("B"), the focal plane F (C) of the correction zones fell on the retina, while the focal plane of the treatment zones F(T) fell anterior to the retina, thus causing myopic defocus on the retina. In diagram "C," with accommodation during near viewing, the focal plane F(C) of the correction zones was still located on (or near) the retina, while the focal plane of the treatment zones F(T) remained anterior to the retina, causing myopic defocus on the retina. DF= Dual-Focus (from: Anstice & Phillips, 2011).*

Anstice & Phillips main results are shown in Figure 1.32. Note the reduction in myopia progression and axial length increase in children that wore the dual-focus contact lens. This data suggests that sustained myopic defocus, when presented simultaneously to the retina with a central clear image, can slow myopic progression.

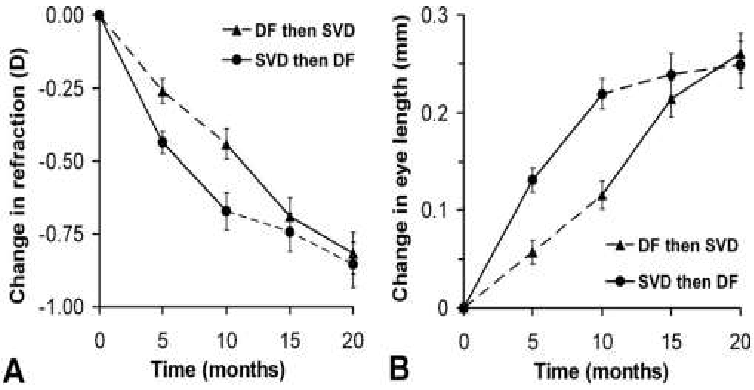


Figure 1.32: *Comparison between dual focus (DF) and single vision distance vision SVD) lens. A) Mean changes (1 standard error of the mean) in refraction over 20 months. Filled triangles show mean change in SER in dioptres in eyes that wore a DF lens in period 1 (dashed line) and an SVD lens in period 2 (solid line), i.e., filled triangles relate to the dominant eyes from participants in group 1 plus the nondominant eyes from participants in group 2. Filled circles show mean change in SER in eyes that wore an SVD lens in period 1 (solid line) and a DF lens in period 2 (dashed line), i.e., filled circles relate to the nondominant eyes from participants in group 1 plus the dominant eyes from participants in group 2. B) Mean changes (1 standard error of the mean) in eye length with time. Filled triangles show mean change in AXL (mm) in eyes that wore a DF lens in period 1 (dashed line) and an SVD lens in period 2 (solid line). Filled circles show mean change in axial length in eyes that wore an SVD lens in period 1 (solid line) and a DF lens in period 2 (dashed line). D =dioptres; DF = Dual-Focus; SVD =single vision distance (from: Anstice & Phillips, 2011).*

Sankaridurg et al. (2011) reported on a specially designed soft contact lens that was designed to reduce relative peripheral hyperopia. The central lens diameter of 1.5mm corrected the foveal refractive error. Outside the central zone, there was a progressive increase of positive power up to +2.00D at a chord length of 9 mm. A total of 45 Chinese children aged 7-14 years with myopia ranging from -0.75 D to -3.50 D were selected for the study and fitted with these contact lenses. A control group of children (n = 40) were fitted with single vision spectacle lenses. Myopia progression was monitored in both groups over a 12-month period. Here too, the novel lens showed less myopia progression compared to the spectacle lens. The authors concluded that reducing peripheral hyperopia is effective in retarding the progression of myopia (see Figure 1.33).

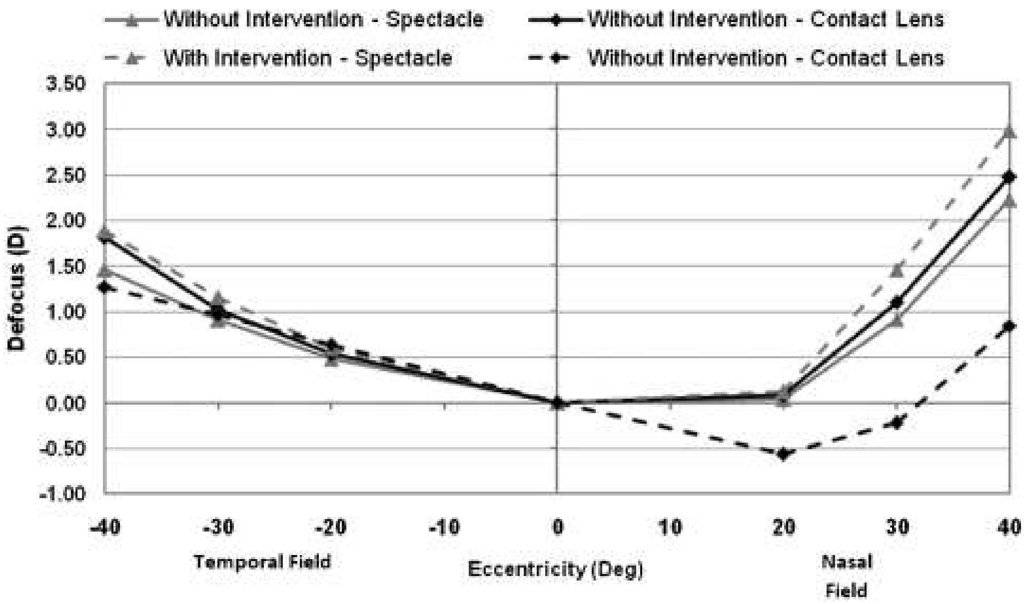


Figure 1.33*: Relative peripheral refractive error profile with and without spectacles and novel contact lenses (from: Sankaridurg et al., 2011).*

Horner and colleagues (1999) conducted a 3-year randomized clinical trial fitting adolescents with soft contact lenses, to include 175 subjects aged between 11 and 14 years and reported that there was no increase in myopia progression. The subjects were divided into two groups, those wearing spectacles and the other wearing soft contact lenses. A subjective refraction was conducted before lens dispensing and every 6 months thereafter for the duration of the 3-year study. The spectacle lens wearing group showed an increase in astigmatism over the 3-year period, whereas the contact lens group showed a minor change. They also did not find a difference in the mean spherical equivalent refractive errors when comparing spectacle wearers to contact lens wearers as can be seen in Figure 1.34 (see also, Andreo, 1990; Wildsoet et al., 2019).

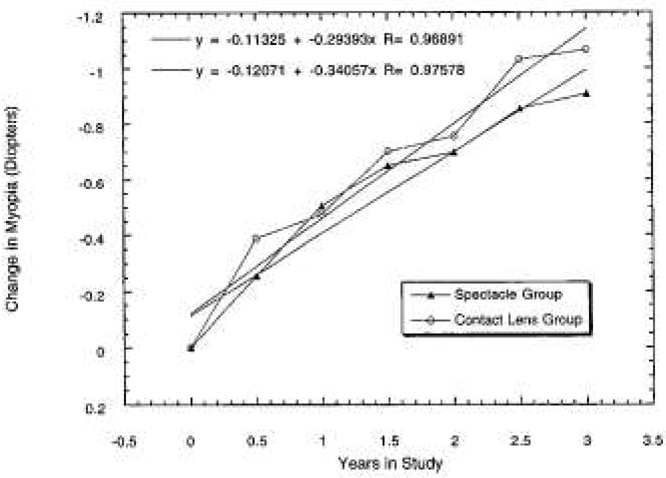


Figure 1.34: *The change in myopia (spherical equivalent, dioptres) plotted as a function of time in the study. The regression lines are shown for contact lens wearers and spectacle wearers.*

Similarly, Walline et al. (2008), in their study where they examined myopia progression over a 3-year period in 484 children aged between 8 and 11 years, also found that children who wore soft contact lenses did not have an increase in axial length, corneal curvature, or myopia, compared with spectacle lens wearers (see Figure 1.35).

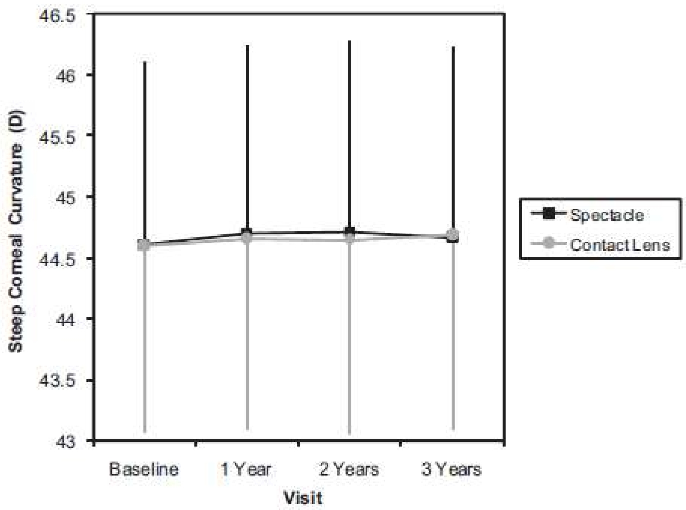


Figure 1.35: *Steep autokeratometry readings, comparing soft contact lens wearers and spectacle wearers (mean standard deviation)* (*from: Walline et al., 2008).*

The most recent F.D.A. and C.E.-approved soft contact lens for myopia control is the MiSight, manufactured by CooperVision. Chamberlain et al. (2019) completed a three-year randomized clinical trial on the MiSight lens. They examined myopic children aged between 8 to 14 years with a mean refractive error of -0.75D to -4.00D, and measured their change in cycloplegic spherical equivalent. It was a double-masked study, conducted at four different locations globally. The results of this study provided evidence that the MiSight lens was effective in slowing both myopia progression (see Figure 1.36) and axial elongation (see Figure 1.37). Note that MiSight is a dual focus lens: one focus corrects the refractive error and the other is designed to achieve constant myopic defocus on the retina. Figure 1.38 details its basic structure.

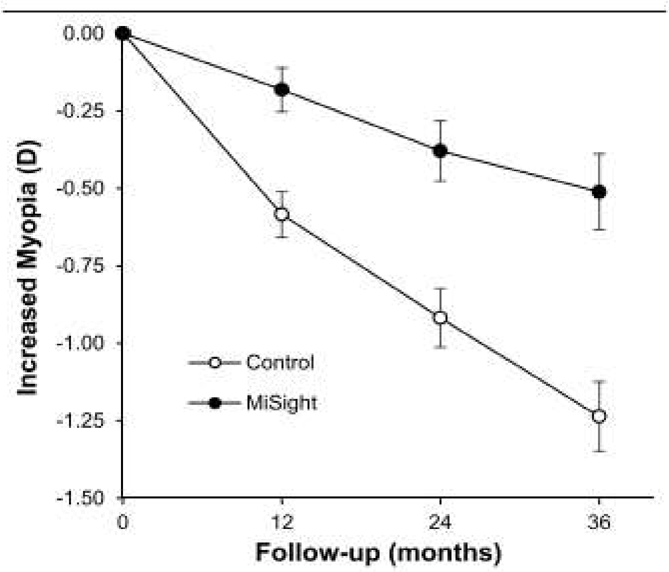


Figure 1.36: *Mean unadjusted changes in spherical equivalent refractive error (D) for the test (MiSight) and control (Proclear 1-day) study groups. The filled and open symbols represent the MiSight and control groups, respectively, for the 36-month study period. The error bars denote the 95% CI of the mean changes. The mean unadjusted differences were 0.40 D less with MiSight at 12 months, 0.54 D less at 24 months, and 0.73 D less at 36 months. CI = confidence interval.*

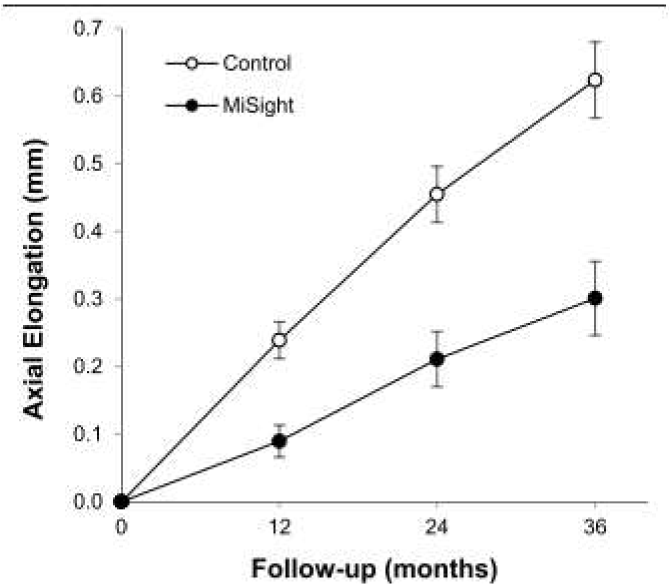


Figure 1.37: *Mean unadjusted changes in axial length (in millimetres) for the test (MiSight) and control (Proclear 1-day) study groups. The filled and open symbols represent the MiSight and control groups, respectively, for the 36-month study period. The error bars denote the 95% CI of the mean changes. The mean unadjusted differences were 0.15 mm less with MiSight at 12 months, 0.24 mm less at 24 months, and 0.32 mm less at 36 months. CI = confidence interval.*

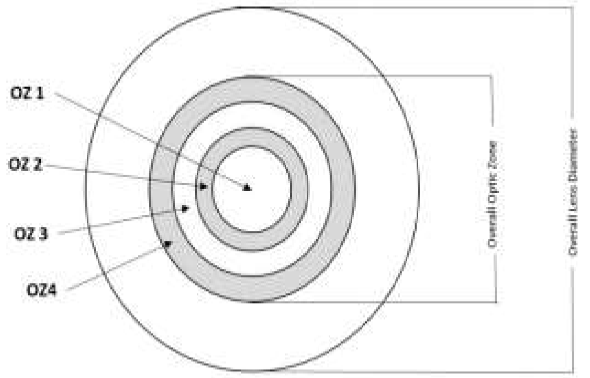


Figure 1.38: *The design of the MiSight soft lens: The optic zone design is a concentric ring design with alternating vision correction zones and treatment zones (shaded in diagram). Zones 1 and 3 are vision correction zones and the label power of the contact lens. Zones 2 and 4 are treatment zones with 2 dioptres of defocus to slow the progression of myopia (from: MiSight 1 Day Professional Fitting and Information Guide)*

Sankaridurg et al. (2011) followed Chinese children aged 7 to 14 years for one year to see whether, when wearing a novel contact lens which reduced relative peripheral hyperopia, there was a reduction in the rate of myopia progression. They reported that, compared to children wearing single vision spectacles, myopia progression was 34% less with these multifocal contact lenses at the conclusion of the study (see Figure 1.39).

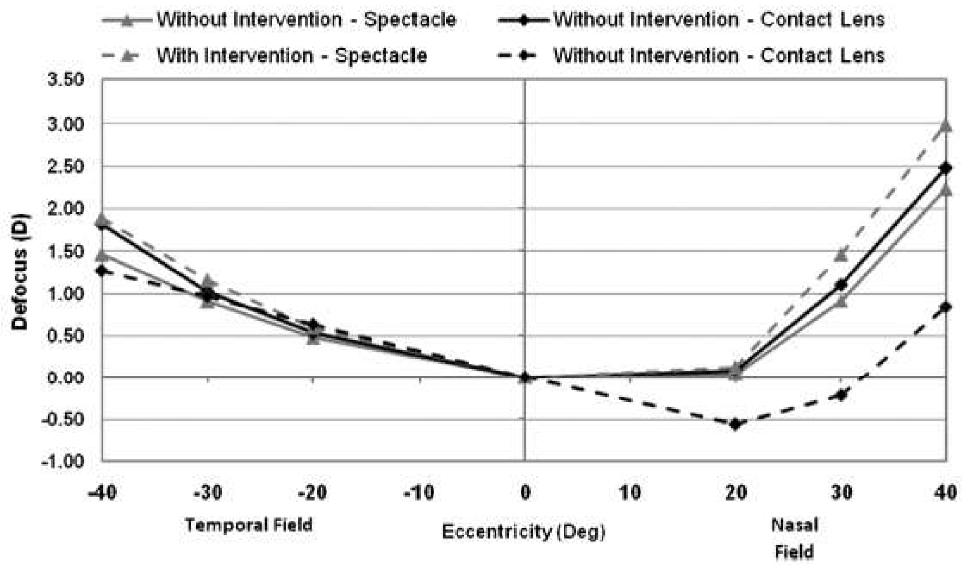


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Figure 1.39: *Relative peripheral refractive error profile with and without spectacles and contact Lenses (from: Sankaridurg et al., 2011*).

Similar results in terms of the reduction in myopic progression were reported by Anstice and Phillips (2011), who compared children wearing concentric bifocals with those wearing single vision contact lenses, monitored over a period of 20 months (Figure 1.40).

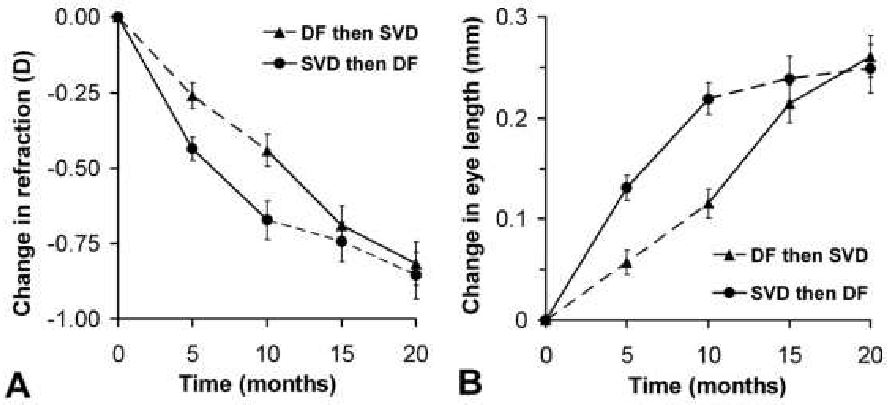
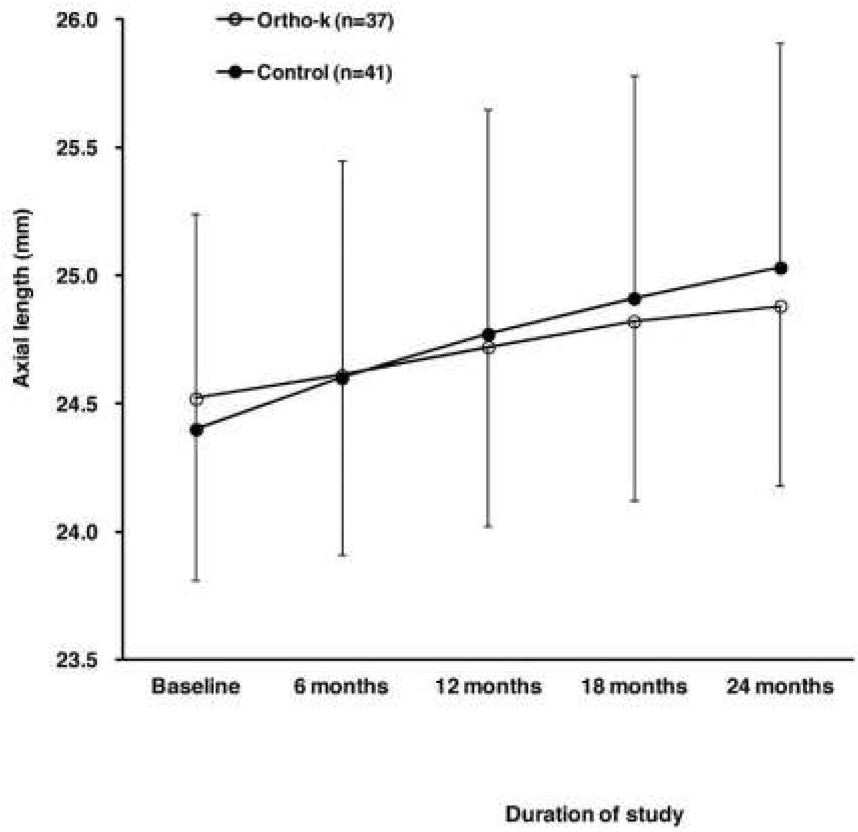


Figure 1.40: *Average changes in refraction over 20 months.* DF-Dual focus; SVD-Single vision distance. *(from: Anstice & Phillips, 2011).*

The Contact Lens and Myopia Progression (CLAMP) study found that flattening the cornea of children by using RGP contact lenses slowed down the progression of myopia (Walline et al., *2004).* Correction with corneal reshaping therapy, which reduces retinal peripheral hyperopia, reduced the rate of myopic progression by up to 43% over two years (Cho & Cheung, 2012) (Figures 1.41 and 1.42).

	Orthokeratology, *n* = 37	Control, *n* = 41	Difference	95% CI
6 months	0.09 ± 0.10	0.20 ± 0.11	0.10 ± 0.02	0.07 to 0.15
12 months	0.20 ± 0.15	0.37 ± 0.16	0.16 ± 0.04	0.09 to 0.24
18 months	0.30 ± 0.20	0.50 ± 0.21	0.20 ± 0.05	0.11 to 0.30
24 months	0.36 ± 0.24	0.63 ± 0.26	0.27 ± 0.06	0.16 to 0.38

Figure 1.41: *Changes in axial length in subjects completed the Two-year study and differences in axial elongation between the two groups at each visit. (from: Cho & Cheung, 2012).*



6-monthly increase	Ortho-k	Control	p-value #
First	0.09±0.10	0.20±0.11	<0.001
Second	0.11±0.09	0.16±0.09	0.004
Third	0.10±0.08	0.14±0.09 *	0.043
Fourth	0.06±0.08 ^	0.13±0.08 *	0.001

Figure 1.42: *Means and SD of axial length in the ortho-K and control group over two years (from: Cho & Cheung, 2012).*

1.6 Evidence against the hyperopic defocus theory of myopia progression

Balanced against the animal and human data supporting the hyperopic defocus theory of myopia, not all treatments to control myopia based on the goal of reducing relative peripheral hyperopia have been effective.

Kanda et al. (2018) did not find a therapeutic effect of the MyoVision spectacle lens, manufactured by Zeiss, on slowing myopia progression. They conducted a multicenter, prospective randomized double-blind placebo-controlled trial, enrolling 203 subjects aged between 6 to 12 years, who received either single vision lenses (SVL) or MyoVision lenses. Subjects were followed up every six months for two years. The mean adjusted change in spherical equivalent refraction was -1.43 ± 0.01 D in the MyoVision group and -

1.39 ± 0.07D in the SVL group. The axial length change was also not significantly different between the two groups: - 0.73 ± 0.04mm in the MyoVision lens group versus 0.69 ± 0.033mm in the SVL group, as illustrated in Figure 1.43, below.

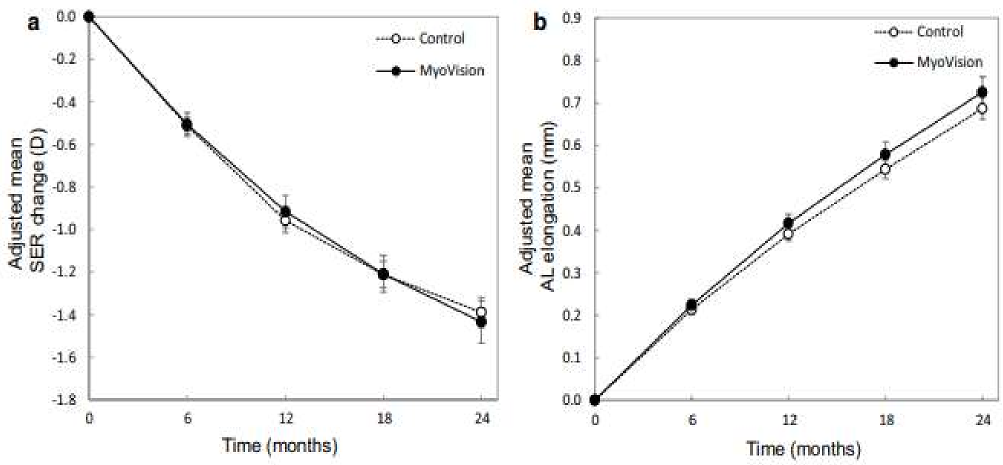


Figure 1.43: *Time courses of* ***a****) the adjusted mean SER change and* ***b****) AL elongation. solid lines, results of the MyoVision Group; dashed lines, results of the control group; error bars, standard errors* (*from: Kanda et al., 2018).*

Mutti et al. (2011) used the data accumulated from the non-myopic children participating in the CLEERE study (from 1995 to 2005). They reported that approximately 16% of the children became myopic by the eighth grade. The mean age of the children examined was 8.8 ± 0.52 years (3rd grade). They reported only a small change in myopia progression over the time monitored, and that axial elongation was not related to the average relative peripheral refractive error (see Table 1.2).

Table 1.2: *Estimates for selected Coefficients in the Regression between Myopia Progression and Relative Peripheral Refraction, Age, and Sex. Average RPR and RPR at the start of an interval were predictors in separate models. Coefficients for age and sex are from the model with average RPR. A negative sign indicates association with greater myopic progression or faster Axial elongation. AL, axial length (from Mutti et al., 2011).*

Variable	Change in Foveal Refractive Error		Change in AL	
	Coefficient	*P*	Coefficient	*P*
Average RPR	−0.024	0.020	0.0015	0.77
RPR at interval start	0.012	0.19	0.0058	0.22
Age	0.033	0.034	0.046	<0.0001
Sex	−0.090	<0.0001	−0.024	0.030

Sng and colleagues (2011) assessed whether there was a link between relative peripheral hyperopia and central myopia, examining 167 Chinese children using an autorefractor to measure the cycloplegic refraction at the fovea and at 15º and 30º peripherally, both nasally and temporally. They did not find a link between baseline peripheral refraction and the onset or progression of myopia (see Figure 1.44).

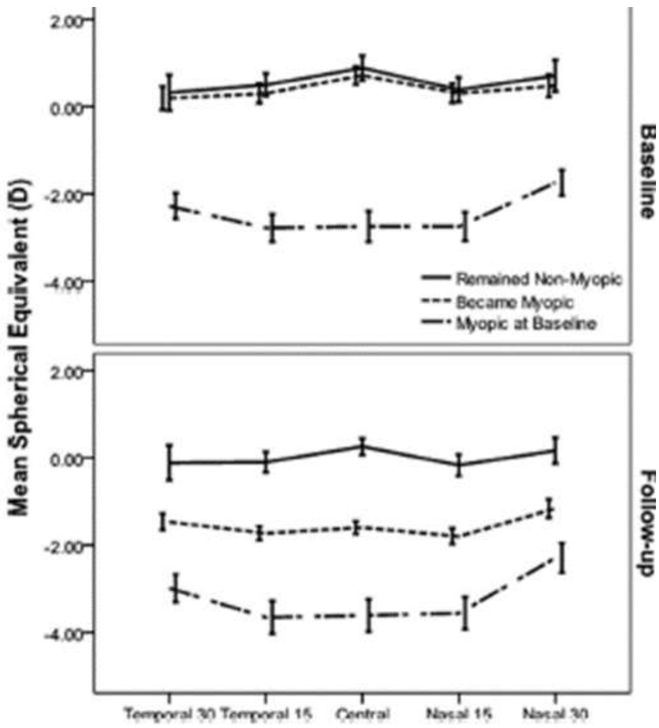


Figure 1.44: *Means of spherical equivalent (SE) as a function of visual field angle for became-myopic, remained-myopic, and remained-emmetropic children. Error bars, 95% confidence interval (CI) of mean SE (from: Sng et al., 2011).*

Another study which did not support the peripheral defocus theory was the one by Zhang et al. (2011) This study measured visual acuity, height, weight biometry and refractive error amongst 176 Xiamen children, and 1154 Chinese children in Singapore, all aged approximately 8 years. They reported that the baseline spherical equivalent refractive error was not an essential predictor of myopia. Instead, one can use simple measurements to predict myopia onset (see Table 1.3).

Table 1.3: *Characteristics of children with and without myopia at baseline in Xiamen and Singapore who did and did not go on to develop myopia by 3-year follow-up.*

	Xiamen (n = 176)			Singapore (n = 1154)		
Factor	Developed Myopia (n = 28)	Did Not Develop Myopia (n = 148)	P	Developed Myopia (n = 526)	Did Not Develop Myopia (n = 628)	P
Age, y	6.81 ± 0.65	6.88 ± 0.67	0.503	**7.69 ± 0.85**	**7.80 ± 0.81**	**0.024**
Weight, kg	24.07 ± 5.29	23.07 ± 3.68	0.102	**25.80 ± 6.03**	**26.60 ± 6.84**	**0.046**
Height, cm	123.00 ± 5.79	123.00 ± 5.24	0.995	126.00 ± 7.37	127.00 ± 6.84	0.332
Visual acuity, logMAR	**0.06 ± 0.08**	**0.03 ± 0.05**	**0.003**	**0.12 ± 0.37**	**0.09 ± 0.14**	**0.001**
Axial length, mm	22.70 ± 0.88	22.40 ± 0.80	0.059	**23.10 ± 0.71**	**22.80 ± 0.72**	**<0.001**
Anterior chamber depth, mm	3.31 ± 0.26	3.29 ± 0.27	0.577	3.58 ± 0.27	3.55 ± 0.26	0.069
Lens thickness, mm	3.52 ± 0.16	3.53 ± 0.18	0.818	3.49 ± 0.18	3.50 ± 0.18	0.386
Vitreous chamber depth, mm	15.80 ± 0.75	15.60 ± 0.75	0.058	**16.10 ± 0.69**	**15.80 ± 0.69**	**<0.001**
Corneal curvature, mm	7.75 ± 0.33	7.78 ± 0.27	0.520	7.45 ± 0.25	7.77 ± 0.25	0.075

Bold values indicate statistical significance at the $P < 0.05$ level.

The one animal study that did not support the theory of the effect of peripheral defocus on central refraction is the study on chickens by Schippert and Schaeffel (2006). The chickens wore either full field lenses (+6.9D/ -7 D), or lenses with central holes of 4, 6, or 8mm diameter, for four consecutive days (see Figure 1.45 for a diagrammatic representation of the optical set-up). They noted that peripheral refractive errors did not influence the development of the refractive error at the fovea for the hole sizes of 4, 6, or 8mm. For the tested hole sizes, the peripherally induced defocus did not influence the central refractive error (see Figure 1.46 for details).

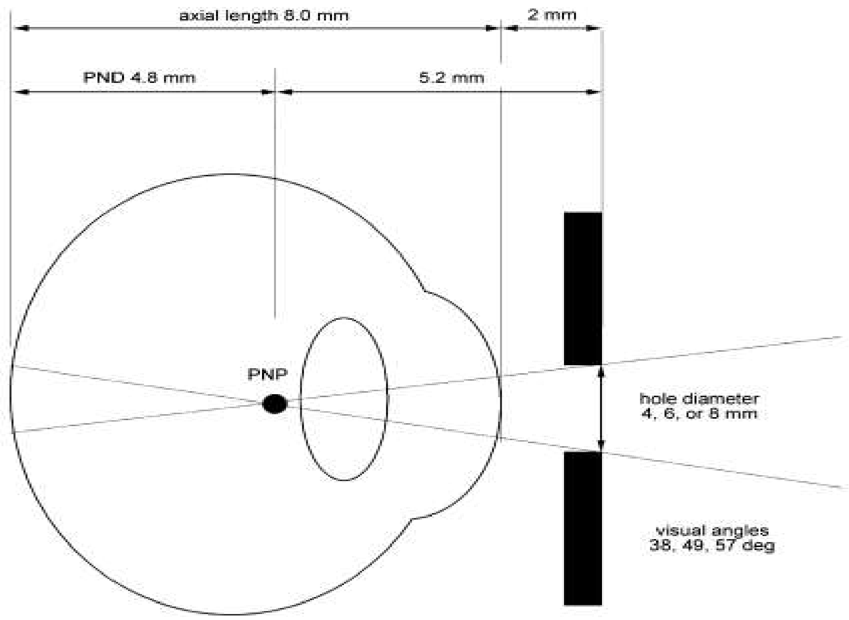


Figure 1.45: *Estimation of the visual angle of the part of the visual Weld that remained unobstructed by the spectacle lenses, due to the central holes. PND posterior nodal distance, PNP posterior nodal point. Calculations are performed for a 2 mm vertex distance.*

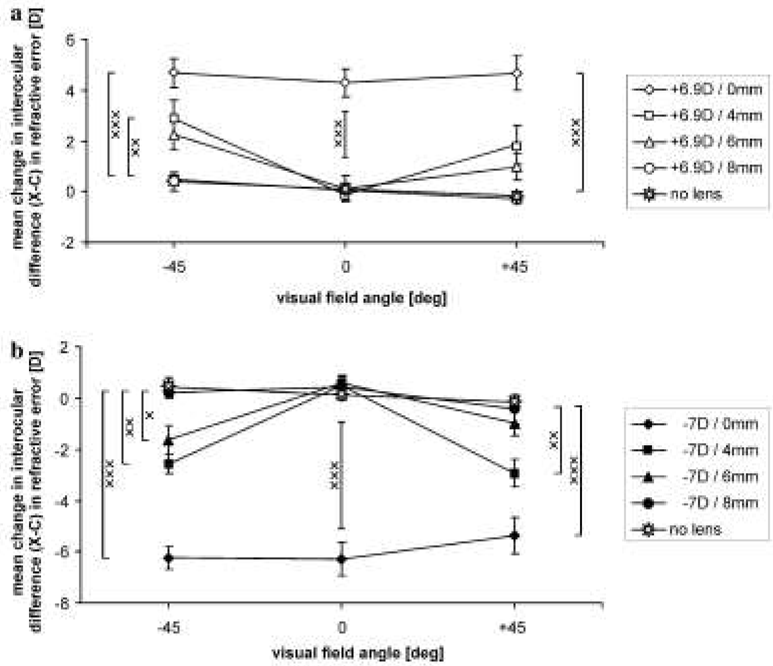


Figure 1.46: (*a) The mean changes of refractive state in interocular differences over the four days treatment period that developed after wearing positive spectacle lenses with central holes of 0 (no hole), 4, 6, and 8 mm diameter, relative to the initial value in all*

*treatment groups. Error bars denote standard errors of the means (SEM), from nD6 animals in each group. Refractions are plotted against the visual Weld angles. Asterisks denote significance levels (*p< 0.05; **p< 0.01; ***p< 0.001). Note that the refraction in the central visual Weld was not affected by the peripheral defocus, but that the defocus imposed by the lenses in the periphery was partially compensated. As expected, the smaller the central hole, the more extensive was the compensation of the peripherally imposed refractive errors. (b) The mean changes of refractive state in interocular differences over the four days treatment period that developed after wearing negative spectacle lenses with central holes of 0 (no hole), 4, 6, and 8 mm diameter, relative to the initial value in all treatment groups. Error bars denote standard errors of the means (SEM), from nD 6 animals in each group. Refractions are plotted against the visual Weld angles.*

In Appendix 8, all the known papers for and against the hyperopic defocus theory of myopia progression are listed in a table format.

1.7 Objectives

It is clear from a variety source that the prevalence of myopia, including high myopia, is increasing at an alarming rate. It is also clear that, because of the medical and socio-economic burdens associated with this refractive condition, the key factors in myopia progression have been and continue to be keenly sought. The principal goal of this thesis is to assess the recent and popular theory of myopia development, termed the hyperopic defocus theory. Following a review of both animal and human studies conducted based on this theory, four specific objectives were generated. These are:

(1) Assess whether myopia progresses more slowly for contact lens wearers than for spectacle wearers.
(2) Determine the relative importance of optical correction, initial age of correction, and initial refractive error on myopic progression.
(3) Determine the relationship between the degree of myopia and the amount of relative peripheral hyperopia.
(4) Determine the influence of optical correction on the relationship between the degree of myopia and the amount of relative peripheral hyperopia.

Following the Introduction, the thesis is organised into a General Methods chapter (ch. 2), and two experimental chapters that address myopic progression in spectacle wearers versus contact lens wearers (ch. 3) and the relationship between the degree of myopia, relative peripheral refraction and optical correction (ch. 4). The results chapters are followed by a general discussion and conclusions chapter (ch. 5). A series of appendices contain the consent and information forms (A1- A4), central and peripheral refraction details (A5 – A7), and a tabulated list of papers for and against the hyperopic defocus theory (A8).

Chapter Two: General Methods

Details relating to ethics, participant selection criteria, refractive error measurements and statistical analyses are reported here. Details of the retrospective data collection, completed to determine the degree of myopic progression with age, are reported together with the results in chapter 3.

Myopia, or near-sightedness, results in blurred distance vision. It is a refractive state whereby, when the eye is in a relaxed accommodative state, the rays of light that enter the eye along the optical axis come to focus anterior to the retina.

2.1 Research Ethics

Ethical approval was obtained from the Health and Life Sciences Research Ethics Committee at Aston University (Ethics Application number 1225 dated 15/11/2017). As data collection was conducted in Haifa, Israel, (where the author resides), ethical approval was also obtained from Rambam Hospital Ethical Committee (document number 0421-17-RMB, dated 15/10/2017). Ethics application and approval details are given in Appendix 3. The protocol and consent documents, along with all recruitment materials, are given in Appendix 3 and Appendix 4. All experimental procedures were in accordance with the tenets of the Declaration of Helsinki.

2.2 Inclusion and exclusion criteria

Table 1.1 details the specific inclusion and exclusion criteria used for the study. In brief, age-appropriate individuals were excluded from the study if they had any history of ocular or systemic disease that could affect refractive development or had discontinued wearing their refractive correction.

Table 2.1: Inclusion and exclusion criteria for selection of participants

Inclusion criteria	**Exclusion criteria**
Myopic monthly contact lens wearers	Not wearing lenses at the time of study
Myopic spectacle wearers	
Between 6 and 24 years of age	
Continuous wear of contact lenses spectacles for ≥ 3 years	Discontinued monthly contact lens wearers
Signing of Consent Form after stating he or she understood it and understood the Information Form.	Regular use of ocular medications
If participant was under consent age, signature of Consent Form by parent or guardian, after stating that he or she understood it.	History of ocular or systemic diseases that might influence refractive error
Be in good health, based on patient's and parent's/guardian's knowledge	Keratoconus, irregular cornea, amblyopia, strabismus, etc.

2.3 Participants

Participants that met the criteria for inclusion in the refractive error measurement phase of the study were identified following a retrospective clinical data collection of the author's own clinical records at his optometric practice in Haifa, Israel. All participants selected for potential inclusion were either myopic contact lens wearers or myopic spectacle wearers. The criterion used to define an individual as a contact lens wearer/spectacle wearer was at least three years of continuous wear of the said means of correction. The contact lens wearers were chosen from a cohort of patients wearing CooperVision Frequency 55 Aspheric (methafilcon A) monthly disposable soft contact lenses. Date of birth, participant number and date of examination were recorded for the experimental study. Note that the study was limited to one type of contact lens, namely CooperVision Frequency 55 Aspheric (Methafilcon A), as this was the lens most frequently prescribed in the author's practise during the 15-year period prior to commencement of the study.

The socio-economic background of the study cohort consisted of schoolchildren (< 18 yrs) and adults (18 – 26 years), principally from middle class families. As each participant's age increased, their socio-economic situation changed. Those aged between 18 and 21 years were soldiers in the Israeli Defence Force, while those aged between 22 and 26 were either university students or in full employment in a variety of office work.

Following a telephone interview in which the project was outlined, selected individuals were invited to take part in the study. For those individuals under the age of consent (18 years), either a parent or guardian was contacted. Individuals who were interested in taking part in the study were sent an information form that fully detailed the procedures involved (see Appendix 1). On the day of assessment, written consent was obtained from the participant (or their guardian) prior to any procedures being completed. The consent form is detailed in Appendix 2. The examination proceeded immediately after written consent was obtained.

The selected participants were myopic children and young adults, aged 6-24 years at the time of examination. The age range chosen for the study allowed myopia progression to be monitored in individuals wearing the same type of soft contact lenses/spectacles during their critical developmental years and into adulthood. The average age was 20.5 years. A total of 90 individuals were examined, including 35 contact lens wearers and 55 spectacle wearers. Recruitment and assessment were completed between October 2017 and December 2018. Details of the refractive status of each participant are reported together with the results in chapters 3 and 4.

The participants were divided into two groups:

1. Participants wearing spectacles continuously for at least three years prior to the study.
2. Participants wearing single vision monthly disposable contact lenses full-time for at least three years prior to the study.

2.4 Procedure for measurement of peripheral refraction

Central and eccentric refractive status of each individual was measured using an autorefractor, corroborated with traditional retinoscopy. An “open-view” autorefractor was used as it allows fixation and accommodative responses to real-world targets, thereby yielding less risk of inducing proximal accommodation (Fedtke et al., 2009). The Shin-Nippon NVision K5001 binocular open-field autorefractor, also marketed as the Grand Seiko WR-5100K, was used in this study. In comparison with subjective refraction, the Shin-Nippon K5001 is reported to yield accurate and reliable results for both central and eccentric viewing (Davies et al., 2003; Atchison, 2003; Lee and Cho, 2012, 2013).
All statistical analyses reported in the results chapters are based the autorefractor measures of central and peripheral refraction.

The Shin-Nippon open-view objective infrared autorefractor enables observation of real-world targets, avoiding proximal accommodation as no internal fixation on a near target is required. A ring target of infrared light is imaged after reflection off the retina. First, a lens is moved quickly to place the ring approximately in focus. Then the image is analysed digitally in several meridians to calculate the toroidal refractive prescription (Davies et al., 2003). Note that this instrument is reported to be highly repeatable in both adult and children, (Mallen et al., 2001), and has been widely used for research purposes (Chat & Edwards, 2001).

2.4.1 Test methods

The viewing distance with central fixation was 3 metres. One further fixation target was set along the horizontal meridian in the nasal field, corresponding to a temporal retinal eccentricity of 30º (see Figure 2.1). Both fixation targets were LEDs, and both were visible through the autorefractor. Each LED could be activated independently. All measurements were made without cycloplegia, using monocular viewing. For completion, refractive error measures were completed on both eyes. In subsequent chapters, only data for the right eye of each participant is reported. All statistical analyses reported in the results chapters (chapter 3 and 4) relate to right eye data. (See appendix 7 for autorefractor measurements @ 30º peripherally).

Figure 2.1. *A photograph of the central (white LED) and eccentric (green LED) fixation targets, as viewed in the experimental setup.*

Measurements along the horizontal were taken, as myopia is believed to have a greater effect on peripheral refractive error along the horizontal meridian than the vertical meridian (Atchison et al, 2006; Kang & Swarbrick, 2011; Kwock et al., 2012; see Introduction, section 1.3). For all individuals, central refractive errors were completed first.

For peripheral measurements, as the eye rotated to fixate on the target, the instrument-alignment targets were positioned between the corneal reflex and the centre of the pupil (Ehsaei et al., 2011). All the data were recorded by the author and entered into an Excel spreadsheet (provided by Professor James Wolffsohn, Aston University) that enabled a graphical representation of the results.

2.5 Statistical analyses

Full details of all statistical analyses are reported along with the results in chapters 3 and 4. After completing several tests of normality, the data were judged not to be normally distributed. On this basis, non-parametric statistics were employed. A summary of the analyses used is reported here for each principal objective.

For objective 1 – assessing whether myopia progresses more slowly for contact lens wearers than spectacle wearers – two separate Spearman correlation tests were applied, one for contact lens wearers and the other for spectacle wearers.

For objective 2 – determining the relative importance of optical correction, initial age of correction, and initial refractive error on myopic progression – different statistical methods were used. Logic regression was used to observe the effects of optical correction (contact lenses or spectacles) and age on the degree of myopia. A correlation Matrix was used to determine whether there is any inter-correlation between optical correction, initial age, and initial onset of myopia. Forced-binary regression analysis was completed to determine whether the optical correction could predict the likelihood of myopic progression, considering initial age and initial degree of myopia.

For objective 3 – assessing the relationship between the degree of myopia and the amount of relative peripheral hyperopia – separate Spearman correlations were used for contact lens wearers and spectacle wearers.

For objective 4 – assessing the influence of the optical correction on the relationship between the degree of myopia and the amount of relative peripheral hyperopia – binary logistic regression was used.

A full 15-year period (2003 – 2018) of the patient data base from the author's clinical records at his optometric practice in Haifa, Israel, was used to recruit all participants for both the retrospective and experimental components of this project. All participants that met the strict inclusion criteria defined above were selected to take part in the study. Although Power calculations have been completed using Gpower (Faul et al., 2009; see below), it is important to recognise that the optometric data base employed, although extensive, necessarily places a resource constraint on the amount of data that can be collected (Lakens, 2021).

Independent samples: In order to detect a medium effect size with 80% power (alpha = .05, two-tailed), GPower analysis suggests 64 participants per group are required in an independent samples t-test. For a large effect size, GPower analysis suggests 26 participants per group.

Dependent samples: In order to detect a medium effect size with 80% power (alpha = .05, two-tailed), GPower analysis suggests 34 participants are required in a paired samples t-test. For a large effect size, GPower analysis suggests 15 participants are required.

Chapter Three: Comparison of myopic progression in spectacle wearers versus contact lens wearers

Various authors have provided evidence to suggest that myopia progression may be less in contact lens wearers than spectacle wearers. Atchison (2006) reported that spherical single vision contact lenses produce a greater amount of peripheral myopic shift than spherical spectacle lenses. Accepting the hyperopic defocus theory, it was hypothesised, therefore, that contact lenses may retard myopia progression more than spectacle lenses (Wildsoet et al., 2019). Additionally, Kwok et al. (2012) reported that spherical soft contact lenses for the correction of high myopia creates a degree of myopic peripheral defocus, which may help to lesson myopia progression. Finally, Backhouse et al. (2012) reported that conventional soft contact lenses retard myopia progression more than conventional single vision spectacle lenses.

A retrospective cohort study was used, with comparison made between two cohorts. A cohort study design is widely regarded as the best method for determining the incidence and natural history of a condition – in this case, myopia (e.g. Mann, CJ. Emerg. Med J., v20, p54-60, 2003). As no intervention, treatment or exposure is administered to participants in a cohort design, no control group is defined. A limitation of such designs is that they are potentially vulnerable to the effects of confounding variables, and this could include age and refractive error. To incorporate such elements would, however, require a significantly larger patient cohort and negate the significant advantages of a cohort design. The optometric data base employed, although extensive, necessarily placed a legitimate resource constraint on the amount of data that could be collected. The experimental design and sample sizes employed were sufficient for a large effect size and provided a balance between the practical feasibilities of recruitment from a defined data base and determining significant meaningful results.

3.1 Objective

A retrospective and experimental clinical data collection was completed to determine the degree of myopic progression with age, from 6 years to 24 years. The hypothesis is that contact lens wearers will show less myopic progression than spectacle lens wearers.

3.2 Methods

A total of 51 myopic participants were recruited for this part of the study. Using a retrospective analysis of the author's record cards, the mean spherical refractive error (MSE) for foveal vision was recorded over a maximum of 15 years, in three-year intervals. Note that refractive error is usually expressed in a "Polar" form, namely sphere, cylinder, and axis. But it is also possible to express the results in a "Cartesian" form, as follows: 1) mean sphere *M (*mean spherical equivalent); 2) the cylinder component along the horizontal axis at 0º (J_0); and 3) The oblique cylindrical component along the oblique axis at 45º (J_{45}).

The three coordinates are calculated as:

- *M = Sph + Cyl / 2.*
- *J0° = Cyl * Cos (2 * Axis).*
- *J45° = Cyl * Sin (2 * Axis)*.

When described in the Cartesian form, each power vector is independent, which simplifies mathematical and statistical analyses of the refractive error (Thibos & Horner, 2000).

The current measure of central myopia in each participant was recorded on the 'study date', defined here as 'time zero' (see analyses below). Note that each participant's current refractive error (the 'time zero' dioptric value) was recorded during a single hospital visit, for eccentricities of 0º (i.e., the fovea) and 30º temporally, using the open-field autorefractor Shin-Nippon NVision-K5001. In this chapter, only the central refraction measurements were used.

Participants were divided into two groups: those wearing contact lenses and those wearing spectacles. Linear regression analysis was used to determine the degree of myopic progression with age, defined as the slope of the linear function.

The dependent variable was myopic progression. The independent variables were optical correction (contact lenses versus spectacles), initial age, and initial central refractive error.

All other methodological issues and experimental protocols are reported in General Methods (see Chapter 2).

3.3 Results

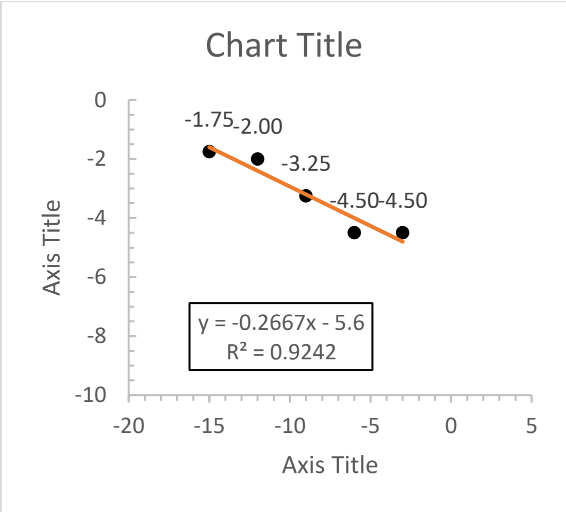
3.3.1 Mean spherical refractive error (MSE) over time in contact lens wearers and spectacle wearers

Table 3.1 shows the mean spherical refractive error (MSE), measured over a maximum of 15 years, for both contact lens (27 participants) and spectacle wearers (24 participants). The final column in Table 3.1 shows the extent of myopia progression over time. Linear regression analysis was completed on each participant's data to provide a measure of myopic progression, determined as the slope (R^2) of each fitted function. Representative regression analyses are shown in figure 3.1 for four contact lens wearers, and in figure 3.2 for four spectacle wearers.

Table 3.1: *MSE over time for contact lens wearers (n = 27) and spectacle wearers (n= 24). The age (years), type of optical correction (spectacles or contact lenses), measured central refractive error at zero to 15 years prior to study date (in 3-year intervals) are shown. The final column shows the extent of myopic progression (in Dioptres), defined as the slope of the linear regression function fitted to each participant's data set. The highlighted participant numbers in Table 3.1 show the participants' data depicted in figures 3.1 and 3.2.*

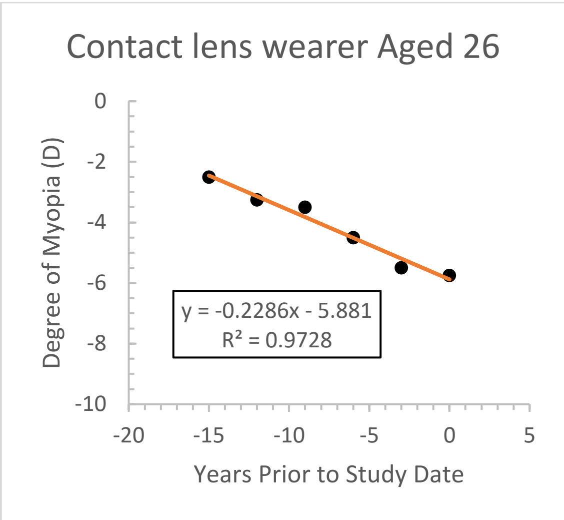
Years prior to study start date									
# Participants	Age (yrs)	optical correction	-15.00	-12.00	-9.00	-6.00	-3.00	0.00	Myopic prog. (D)
1	22	Contact lenses	-1.00	-1.25	-3.00	-5.00	-6.00	-7.00	-0.44
2	14	Spectacles				-0.50	-1.50	-2.75	-0.38
3	18	Contact lenses			-1.25	-1.50		-1.63	-0.04
4	13	Spectacles				-1.50	-4.25	-6.50	-0.83
5	14	Contact lenses				-3.75	-4.25	-4.25	-0.08
6	26	Contact lenses		-0.25	-1.25	-1.50	-2.50	-3.00	-0.23
7	21	Contact lenses			-1.50	-2.00	-2.00	-2.25	-0.08
8	15	Contact lenses				-0.75	-2.50	-3.63	-0.48
9	17	Spectacles				-0.50	-0.50	-1.00	-0.08
10	23	Contact lenses			-4.75	-5.75	-6.00	-6.50	-0.18
11	21	Spectacles				-0.25		-0.38	-0.02
12	18	Spectacles				-0.75	-1.00	-1.25	-0.08
13	18	Contact lenses		-2.00	-3.50	-4.75	-5.00	-5.75	-0.30
14	20	Contact lenses		-3.00	-3.75	-6.00		-7.75	-0.41
15	13	Spectacles				-2.00	-3.00	-3.75	-0.29
16	20	Spectacles					-4.75	-4.75	0.00
17	20	Contact lenses			-0.50	-1.13	-1.75	-2.75	-0.25
18	25	Contact lenses			-4.13	-4.38	-6.50	-6.50	-0.31
19	18	Spectacles			-1.75	-2.00	-2.75	-2.75	-0.13

20	26	Contact lenses	-0.50	-1.00	-2.00	-3.25	-3.50	-4.13	-0.26
21	22	Contact lenses		-1.75	-2.00	-3.25	-4.50	-4.50	-0.27
22	26	Contact lenses		-1.50	-2.00	-2.50		-3.00	-0.12
23	14	Spectacles				-1.25	-1.75	-3.00	-0.29
24	11	Spectacles				-2.00	-2.38	-3.25	-0.21
25	22	Spectacles	-1.25	-3.00	-5.75	-8.25	-8.50	-8.50	-0.53
26	20	Contact lenses			-1.00	-1.25	-1.50	-2.00	-0.11
27	24	Spectacles				-2.00	-2.00	-2.75	-0.13
28	21	Contact lenses			-0.50	-2.25	-2.75	-2.75	-0.24
29	20	Contact lenses		-2.75	-5.00	-6.38	-7.50	-8.38	-0.46
30	22	Contact lenses			-1.50	-3.00	-3.00	-3.00	-0.15
31	26	Contact lenses	-2.50	-3.25	-3.50	-4.50	-5.50	-5.75	-0.23
32	24	Spectacles		-1.50	-2.00	-2.00	-2.00	-2.00	-0.03
33	25	Contact lenses		-1.00	-1.75	-2.00	-2.00	-2.63	-0.12
34	26	Contact lenses			-2.00	-2.13	-3.13	-4.13	-0.25
35	26	Contact lenses	-0.25	-0.75	-1.50	-2.50	-2.75	-3.00	-0.20
36	26	Contact lenses	-1.13	-1.88	-2.63	-3.25		-4.50	-0.22
37	16	Spectacles			-2.50	-3.00	-4.00	-5.00	-0.28
38	26	Contact lenses				-4.00	-4.00	-4.00	0.00
39	25	Contact lenses	-3.50	-5.50	-6.50	-7.75		-9.38	-0.38
40	20	Spectacles			-1.00		-2.75	-3.00	-0.23
41	25	Contact lenses	-1.75	-2.25	-2.75	-3.25		-3.50	-0.12
42	26	Contact lenses	-2.00	-3.50		-3.25	-3.88	-3.88	-0.10
43	20	Spectacles			-1.88	-4.88		-5.63	-0.38
44	26	Spectacles		0.00	-1.50			-1.75	-0.12
45	26	Spectacles		-5.25		-7.50	-7.50	-7.75	-0.21
46	14	Spectacles				-1.13	-1.88	-3.75	-0.44
47	16	Spectacles			-2.00	-2.50	-4.00	-5.75	-0.43
48	20	Spectacles	-1.00	-1.75	-2.50	-3.50	-3.75	-3.75	-0.20
49	15	Spectacles	-1.00	-1.00	-1.00	-3.00	-6.00	-7.00	-0.45
50	16	Spectacles	0.00	0.00	-1.00	-1.50	-1.75	-2.25	-0.16
51	26	Spectacles	-1.25	-2.00	-2.50	-3.00	-3.00	-3.00	-0.12
								median >>	-0.22



Participant # 21

Participant # 20



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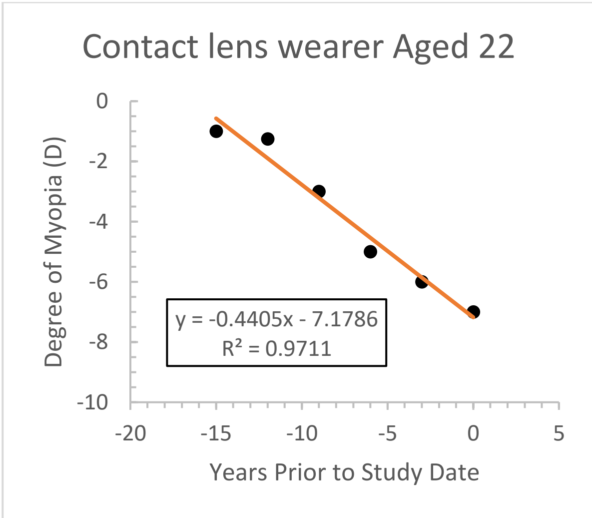
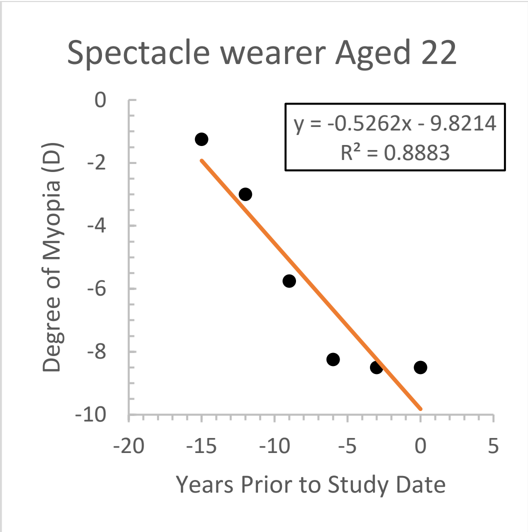
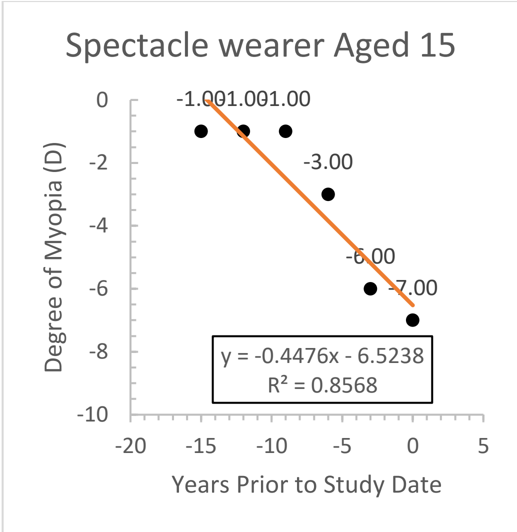


Participant #1

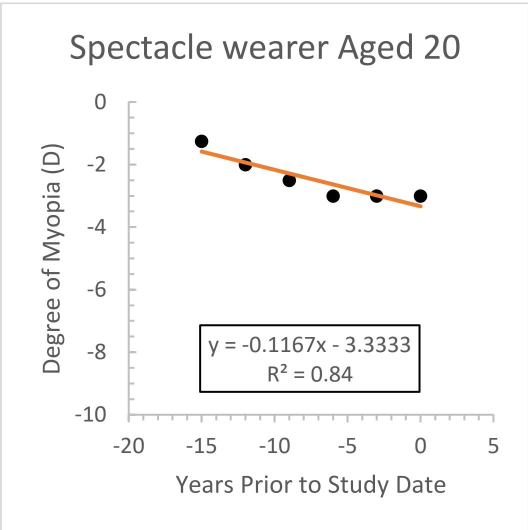
Figure 3.1 (a-c): *Each plot shows the central refractive error in a contact lens wearer on the day of the study date (zero on the X axis), and at 3 years to a maximum of 15 years prior to the study date. The solid line through each data set shows the least-squares fit of a linear regression function. The degree of myopic progression is defined as the slope of the regression function, as shown in the regression equation.*



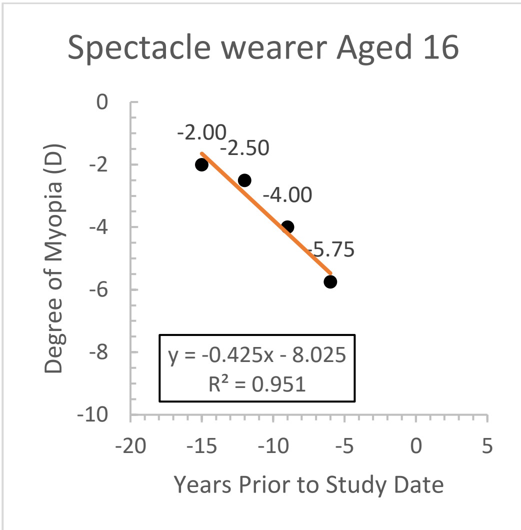
Participant # 25



Participant # 49



Participant # 51



Participant # 47

Figure 3.2 (a-c): *Each plot shows the central refractive error in a spectacle wearer on the day of the study date (zero on the X axis), and at 3 years to a maximum of 15 years prior to the study date. Other details are the same as those reported in the caption to figure 3.1.*

3.3.2 Statistical analyses

To determine whether myopic progression was normally distributed, normality was judged on several aspects of the data. Firstly, the standard error of skewness and kurtosis was measured. The results are shown in Table 3.2. Note that skewness and kurtosis fall outside the range -1 to 1: both absolute skewness and absolute kurtosis exceed twice their standard error. On this basis, the data are therefore judged not to be normally distributed.

Table 3.2: - *Data skewness and kurtosis on measures of myopic progression for all participants (N = 51) from Table 3.1*

Statistics

Myopic_Progression

N	Valid	51
	Missing	0
Skewness		-1.089
Std. Error of Skewness		.333
Kurtosis		2.093
Std. Error of Kurtosis		.656

In figure 3.3, the myopic progression data for all participants are plotted as a frequency histogram. The solid function shows a least-squares fit of a normal distribution. Note that, in agreement with the analyses reported above, the data do not fit the characteristics of a normal curve.

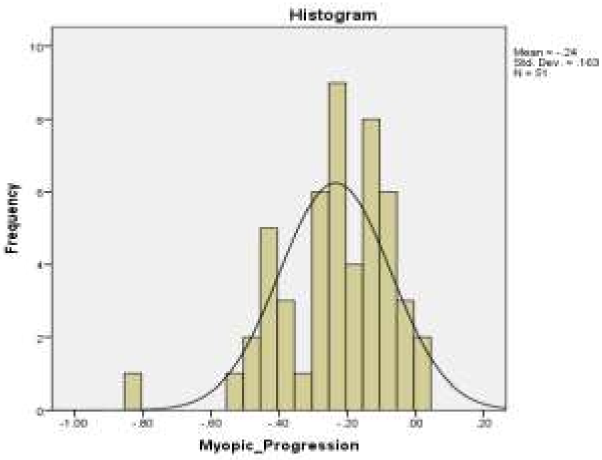


Figure 3.3. *Frequency distribution of myopic progression data for all participants (from Table 3.1)*.

Finally, data normality was assessed using the Shapiro-Wilk test. The results of this normality test are shown in Table 3.3. Note that the Shapiro-Wilk test shows a significant departure from normality.

Table 3.3: *Shapiro-Wilk test of normality of myopic progression data for all participants (from Table 3.1)*

	Shapiro-Wilk		
	Statistic	df	Sig.
Myopic Progression	.928	51	.004

Together, the assessments of normality detailed above provide evidence that the data for myopic progression are not normally distributed. Given this, the Mann-Whitney non-parametric statistical test was used to compare median myopic progression in spectacle wearers versus contact lens wearers. The results of this analysis are shown in Table 3.4. Note that the Mann-Whitney U test shows that there was no statistically significant difference (Z = -0.076, p (2-tailed) = 0.94) between the median myopic progression found in spectacle wearers (N = 24, Median = -0.21D per year, Interquartile range = -0.29D per year) versus contact lens wearers (N = 27, Median = -0.23D per year, Interquartile range = 0.18D per year).

Table 3.4: *Comparison of median progression in spectacle wearers (n = 24, optical correction 1.00) versus contact lens wearers (n = 27, optical correction 2.00), assessed using the non-parametric Mann-Whitney test.*

Mann-Whitney Test

Ranks

	Optical_Correction	N	Mean Rank	Sum of Ranks
Myopic_Progression	1.00	24	25.83	620.00
	2.00	27	26.15	706.00
	Total	51		

Test Statistics[a]

	Myopic_Progression
Mann-Whitney U	320.000
Wilcoxon W	620.000
Z	-.076
Asymp. Sig. (2-tailed)	.940

a. Grouping Variable: Optical_Correction

3.3.3 Interim summary and conclusions

Based on the analyses reported above, the hypothesis that contact lens wearers show less myopic progression than spectacle wearers is not supported.

The effect size found (r= -0.01,) was below a rating of "small", indicating that further data collection is not warranted. The effect size (r=Z/sqrt(N)) is calculated from The Mann-Whitney U test where Z=-0.076 and N=51 (Cohen,1992a; Cohen, 1992b; Cohen, 1988; Erdfelder et al., 1996).

Note that, in the analyses reported above, no attempt was made to account for the possible effects of (1) initial age and (2) initial degree of myopia. It is possible, therefore, that these factors may have obscured an effect of the optical correction used to correct myopia. These issues are examined below.

3.4 The effects of optical correction, initial age and initial degree of myopia.

Logistic regression is used here to observe the effects of optical correction, initial age, and initial myopia on myopic progression. Table 3.5 shows a re-analysis of the continuous data, with myopic progression, initial age and initial myopia divided into dichotomous data based on a median split of each data set. The independent predictor variables are optical correction (nominal), initial age (scale) and initial myopia (scale). The dependent variable is myopic progression (nominal). Binary logistic regression is chosen as the statistical test because the dependent variable, myopic progression, is dichotomous. In all instances MSE calculations were used.

Table 3.5: *Re-analysis of continuous data shown in Table 3.1, with myopic progression, initial age and initial myopia divided into dichotomous ordinal data based on a median split of each data set. Symbols used: M, Myopia; OC, optical correction; CL, contact lenses; S, spectacles; Med, median. Other details are as reported in Table 3.1.*

			Continuous data								Dichotomous ordinal data			
				Age prior to start date (years)						Initial	Initial	Myopic	Initial	Initial
#	Age	OC	Myopic prog. (D)	-15	-12	-9	-6	-3	0	Age	M	Prog.	Age	M
1	22	CL	-0.44	7	10	13	16	19	22	7	-1.00	Higher	Younger	Lower
2	14	S	-0.38				8	11	14	8	-0.50	Higher	Younger	Lower
3	18	CL	-0.04			9	12		18	9	-1.25	Lower	Younger	Lower
4	13	S	-0.83				7	10	13	7	-1.50	Higher	Younger	Higher
5	14	CL	-0.08				8	11	14	8	-3.75	Lower	Younger	Higher
6	26	CL	-0.23		14	17	20	23	26	14	-0.25	Higher	Older	Lower
7	21	CL	-0.08			12	15	18	21	12	-1.50	Lower	Older	Higher

8	15	CL	-0.48				9	12	15	9	-0.75	Higher	Younger	Lower
9	17	S	-0.08				11	14	17	11	-0.50	Lower	Older	Lower
10	23	CL	-0.18			14	17	20	23	14	-4.75	Lower	Older	Higher
11	21	S	-0.02				15		21	15	-0.25	Lower	Older	Lower
12	18	S	-0.08				12	15	18	12	-0.75	Lower	Older	Lower
13	18	CL	-0.30		6	9	12	15	18	6	-2.00	Higher	Younger	Higher
14	20	CL	-0.41		8	11	14		20	8	-3.00	Higher	Younger	Higher
15	13	S	-0.29				7	10	13	7	-2.00	Higher	Younger	Higher
16	20	S	0.00					17	20	17	-4.75	Lower	Older	Higher
17	20	CL	-0.25			11	14	17	20	11	-0.50	Higher	Older	Lower
18	25	CL	-0.31			16	19	22	25	16	-4.13	Higher	Older	Higher
19	18	S	-0.13			9	12	15	18	9	-1.75	Lower	Younger	Higher
20	26	CL	-0.26	11	14	17	20	23	26	11	-0.50	Higher	Older	Lower
21	22	CL	-0.27		10	13	16	19	22	10	-1.75	Higher	Younger	Higher
22	26	CL	-0.12		14	17	20		26	14	-1.50	Lower	Older	Higher
23	14	S	-0.29				8	11	14	8	-1.25	Higher	Younger	Lower
24	11	S	-0.21				5	8	11	5	-2.00	Lower	Younger	Higher
25	22	S	-0.53	7	10	13	16	19	22	7	-1.25	Higher	Younger	Lower
26	20	CL	-0.11			11	14	17	20	11	-1.00	Lower	Older	Lower
27	24	S	-0.13				18	21	24	18	-2.00	Lower	Older	Higher
28	21	CL	-0.24			12	15	18	21	12	-0.50	Higher	Older	Lower
29	20	CL	-0.46		8	11	14	17	20	8	-2.75	Higher	Younger	Higher
30	22	CL	-0.15			13	16	19	22	13	-1.50	Lower	Older	Higher
31	26	CL	-0.23	11	14	17	20	23	26	11	-2.50	Higher	Older	Higher
32	24	S	-0.03		12	15	18	21	24	12	-1.50	Lower	Older	Higher
33	25	CL	-0.12		13	16	19	22	25	13	-1.00	Lower	Older	Lower
34	26	CL	-0.25			17	20	23	26	17	-2.00	Higher	Older	Higher
35	26	CL	-0.20	11	14	17	20	23	26	11	-0.25	Lower	Older	Lower
36	26	CL	-0.22	11	14	17	20		26	11	-1.13	Higher	Older	Lower
37	16	S	-0.28			7	10	13	16	7	-2.50	Higher	Younger	Higher
38	26	CL	0.00				20	23	26	20	-4.00	Lower	Older	Higher
39	25	CL	-0.38	10	13	16	19		25	10	-3.50	Higher	Younger	Higher
40	20	S	-0.23			11		17	20	11	-1.00	Higher	Older	Lower
41	25	CL	-0.12	10	13	16	19		25	10	-1.75	Lower	Younger	Higher
42	26	CL	-0.10	11	14		20	23	26	11	-2.00	Lower	Older	Higher
43	20	S	-0.38			11	14		20	11	-1.88	Higher	Older	Higher
44	26	S	-0.12		14	17			26	14	0.00	Lower	Older	Lower
45	26	S	-0.21		14		20	23	26	14	-5.25	Lower	Older	Higher
46	14	S	-0.44				8	11	14	8	-1.13	Higher	Younger	Lower
47	16	S	-0.43			7	10	13	16	7	-2.00	Higher	Younger	Higher
48	20	S	-0.20	5	8	11	14	17	20	5	-1.00	Lower	Younger	Lower
49	15	S	-0.45	0	3	6	9	12	15	0	-1.00	Higher	Younger	Lower
50	16	S	-0.16	1	4	7	10	13	16	1	0.00	Lower	Younger	Lower
51	26	S	-0.12	11	14	17	20	23	26	11	-1.25	Lower	Older	Lower
		Med >>	-0.22							11.00	-1.50			

Prior to completing the binary logistic regression, it was confirmed that all cases were entered into the analysis. The 'Case Processing Summary' (see Table 3.6) confirms that all 51 cases were entered into the analysis, and the 'Categorical Variables Codings' (see Table 3.7) confirms that the analysis included 27 contact lens wearers and 24 spectacle wearers.

Table 3.6: *Case processing summary*

Case Processing Summary

Unweighted Cases[a]		N	Percent
Selected Cases	Included in Analysis	51	100.0
	Missing Cases	0	.0
	Total	51	100.0
Unselected Cases		0	.0
Total		51	100.0

a. If weight is in effect, see classification table for the total number of cases.

Table 3.7: *Categorical variables codings*

Categorical Variables Codings

		Frequency	Parameter coding (1)
Optical_Correction	Contact	27	1.000
	Spectacl	24	.000

Tables 3.8 – 3.10 show the results of the binary logistic regression analysis, conducted to determine whether optical correction (spectacles or contact lenses) predicts the likelihood of higher myopic progression when accounting for the influences of other covariates (initial age and myopia).

Table 3.8: *Regression model summary, showing both Cox & Snell and Nagelkerke estimates of 'R square'.*

Model Summary

Step	-2 Log likelihood	Cox & Snell R Square	Nagelkerke R Square
1	64.191[a]	.119	.159

a. Estimation terminated at iteration number 4 because parameter estimates changed by less than .001.

The estimates of ‘R square’ shown in Table 3.8 indicate that between 12% (Cox & Snell) and 16% (Nagelkerke) of the variance in the dependent variable is explained by the regression model.

Table 3.9: *The classification table (i.e., confusion matrix) for the logistic regression model.*

Classification Table[a]

Observed			Predicted: Myopic_Progression Higher	Predicted: Myopic_Progression Lower	Predicted: Percentage Correct
Step 1	Myopic_Progression	Higher	21	5	80.8
		Lower	10	15	60.0
	Overall Percentage				70.6

a. The cut value is .500

Table 3.9 shows that logistic regression correctly classified 70.6% of the cases overall, with 80.8% of those with higher myopic progression and 60.0% of those with lower myopic progression.

Table 3.10: *The ‘Variables in the equation’ table, showing the Wald statistic and associated degrees of freedom (df), p-value (Sig.) and 95% confidence intervals (C.I.).*

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B) Lower	95% C.I.for EXP(B) Upper
Step 1[a]	Optical_Correction(1)	-.827	.635	1.698	1	.193	.437	.126	1.518
	Initial_Age	.203	.093	4.776	1	.029	1.226	1.021	1.471
	Initial_Myopia	.009	.257	.001	1	.971	1.010	.610	1.671
	Constant	-1.699	.963	3.112	1	.078	.183		

a. Variable(s) entered on step 1: Optical_Correction, Initial_Age, Initial_Myopia.

The Wald statistic shown in Table 3.10 indicates the relative importance of each covariate, and which has a statistically significant influence on myopic progression. Note that neither optical correction (p = 0.193) nor initial degree of myopia (p = 0.971) have a significant influence on myopic progression. However, initial age does have a statistically significant effect on myopic progression (p = 0.029).

3.5 Summary and conclusions

Forced-entry binary logistic regression was carried out to determine whether optical correction (spectacles or contact lenses) predicts the likelihood of myopic progression, accounting for the influence of other covariates. The model contained three independent covariates: (1) whether spectacles or contact lenses were worn (optical correction); (2) initial age; and (3) the initial degree of myopia. Myopic progression over a 3 to 15-year period (classification as higher or lower after a median split) was treated as the dependent variable. The results of this analysis are shown in the summary table below, Table 3.11.

Table 3.11: *Binary logistic regression summary statistics for the covariates entered into the model for predicting higher or lower myopic progression, showing the log odds (B), standard error (SE), Wald statistic and its associated degrees of freedom (df), p value, and the odds ratio with 95% confidence limits for each covariate.*

							95% CL for odds	
	B	SE	Wald	df	p	odds	lower	upper
optical correction	-0.83	0.64	1.70	1	0.193	0.437	0.126	1.518
initial age	0.20	0.09	4.78	1	0.029	1.226	1.021	1.471
initial myopia	0.01	0.26	0.00	1	0.971	1.01	0.61	1.671
constant	-1.70	0.96	3.11	1	0.078	0.183		

The analyses show that, after accounting for the effects of initial age and myopia, optical correction did not have a statistically significant influence on myopic progression (p = 0.193).

In brief, the preliminary analysis failed to find that optical correction exerted a statistically significant effect on myopic progression. It was next examined whether the covariates initial age and myopia may have obscured an effect. Analysis using logistic regression indicates that this was not the case. It is concluded, therefore, that the hypothesis that contact lens wearers show less myopic progression than spectacle wearers is not supported.

Chapter Four: Relationship between degree of myopia, relative peripheral refraction & optical correction

4.1 Objectives

Central and peripheral refractive error measurements were completed to determine: (a) whether higher degrees of myopia are associated with greater amounts of relative peripheral hyperopia; and (b) the relationship between central and peripheral refraction and the type of optical correction worn. The mean spherical refractive error was calculated and implied.

Hypothesis one states that higher degrees of foveal myopia (myopic progression) arise in eyes with greater amounts of relative peripheral hyperopia. Hypothesis two states that the dependence of the degree of foveal myopia on relative peripheral refraction is influenced by the type of optical correction worn (contact lenses versus spectacle lenses).

4.2 Methods

The 90 myopic participants recruited for the study had their refractions measured at eccentricities of 0º (i.e., the fovea) and 30º temporally using the open-field autorefractor Shin-Nippon NVision 5001. Participants were divided into two groups: those wearing contact lenses and those wearing spectacles. The mean spherical refractive error (MSE) for foveal and eccentric vision was determined for each participant.

The dependent variable is the degree of foveal myopia. The independent variables include the relative peripheral refraction, the type of optical correction worn (spectacles or contact lenses) and participant age in years.

All other methodological issues and experimental protocols are reported in the General Methods (see Chapter 3).

4.3 Results

4.3.1 Mean spherical error (MSE) in central and peripheral retina.

Table 4.1 shows MSE measured at the fovea and at 30º in the temporal retina, for both contact lens wearers (35 participants) and spectacle wearers (55 participants). The relative peripheral refraction, calculated as the foveal MSE subtracted from the MSE at 30º, is shown for each participant. The final column in Table 4.1 shows dichotomized data for each individual, determined according to whether the foveal myopic error was 'higher' or 'lower' than the median foveal myopic error (N = 90; -2.94 D). Graphical representations of the data are shown in Figure 4.1 for both spectacle lens wearers (a) and contact lens wearers (b). The solid line through each data set shows the least-squares fit of a linear function. The broken line in each panel shows the 'line of equal effect' (i.e., where the foveal MSE is equal in magnitude and sign to the MSE at 30º). Note that, in each case, the fitted linear function lies above the line of equal effect, indicating that the peripheral refractive error is relatively more hyperopic than the central refractive error. Figure 4.2 shows the least-square fit of a linear function to the combined data set. Note again that the fitted function lies above the line of equal effect.

Table 4.1 *Mean Spherical Equivalent (MSE) measured at the fovea and at 30º in the temporal retina for contact lens wearers (N=35) and spectacle wearers (N=55). The relative peripheral refraction was calculated as the foveal MSE subtracted from the MSE at 30º. The final column, required for binary logistic regression analysis, shows dichotomized data for each individual, determined according to whether the foveal myopic error was 'higher' or 'lower' than the median foveal myopic error (N = 90; -2.94 D)*

#	Age (yrs)	optical correction	E = 0 (deg)	E = 30 (deg)	Relative peripheral refraction	Dichotomised data
1	22	Contact lenses	-7.50	-6.13	1.38	Higher
2	20	Contact lenses	-3.75	-3.50	0.25	Higher
3	18	Contact lenses	-1.75	-1.88	-0.13	Lower
4	14	Contact lenses	-4.25	-3.00	1.25	Higher
5	26	Contact lenses	-3.25	-1.88	1.38	Higher
6	23	Contact lenses	-4.00	-2.88	1.13	Higher
7	21	Contact lenses	-2.88	-2.00	0.88	Lower
8	15	Contact lenses	-3.13	-2.50	0.63	Higher
9	23	Contact lenses	-6.38	-5.63	0.75	Higher
10	18	Contact lenses	-1.13	-1.00	0.13	Lower
11	20	Contact lenses	-1.38	1.13	2.50	Lower
12	20	Contact lenses	-3.00	-3.38	-0.38	Higher
13	25	Contact lenses	-6.00	-4.25	1.75	Higher
14	26	Contact lenses	-3.75	-2.25	1.50	Higher

15	22	Contact lenses	-3.63	-1.50	2.13	Higher
16	26	Contact lenses	-2.75	-0.50	2.25	Lower
17	20	Contact lenses	-1.50	-2.00	-0.50	Lower
18	21	Contact lenses	-2.75	-1.13	1.63	Lower
19	20	Contact lenses	-7.13	-6.25	0.88	Higher
20	22	Contact lenses	-3.00	-2.63	0.38	Higher
21	23	Contact lenses	-7.00	-6.00	1.00	Higher
22	26	Contact lenses	-6.00	-5.88	1.50	Higher
23	25	Contact lenses	-2.00	-0.25	1.75	Lower
24	26	Contact lenses	-3.25	-0.75	2.50	Higher
25	26	Contact lenses	-2.25	-2.13	0.13	Lower
26	26	Contact lenses	-3.88	-1.13	2.75	Higher
27	22	Contact lenses	-8.88	-5.25	3.63	Higher
28	23	Contact lenses	-1.00	-0.38	0.63	Lower
29	25	Contact lenses	-2.88	-2.88	0.00	Lower
30	26	Contact lenses	-5.25	-3.38	1.88	Higher
31	26	Contact lenses	-3.38	-3.00	0.38	Higher
32	26	Contact lenses	-4.00	-7.50	-3.50	Higher
33	25	Contact lenses	-10.25	-8.75	1.50	Higher
34	25	Contact lenses	-2.25	-1.25	1.00	Lower
35	26	Contact lenses	-3.88	-4.13	-0.25	Higher
36	14	Spectacles	-3.00	-1.25	1.75	Higher
37	22	Spectacles	-2.25	-0.25	2.00	Lower
38	22	Spectacles	-0.50	0.63	1.13	Lower
39	23	Spectacles	-2.88	-3.00	-0.13	Lower
40	22	Spectacles	-1.13	0.63	1.75	Lower
41	9	Spectacles	-5.75	-4.75	1.00	Higher
42	13	Spectacles	-4.38	-1.50	2.88	Higher
43	20	Spectacles	-1.63	-0.63	1.00	Lower
44	22	Spectacles	-2.88	-1.75	1.13	Lower
45	24	Spectacles	-6.00	-5.13	0.88	Higher

46	17	Spectacles	-0.75	0.88	1.63	Lower
47	21	Spectacles	-6.13	-4.88	1.25	Higher
48	18	Spectacles	0.00	-3.38	-3.38	Lower
49	13	Spectacles	-6.50	-4.75	1.75	Higher
50	13	Spectacles	-3.25	-1.88	1.38	Higher
51	20	Spectacles	-4.38	-2.75	1.63	Higher
52	12	Spectacles	-4.75	-2.75	2.00	Higher
53	26	Spectacles	-4.13	-3.00	1.13	Higher
54	26	Spectacles	-1.88	-1.50	0.38	Lower
55	15	Spectacles	-0.63	0.88	1.50	Lower
56	12	Spectacles	-4.38	-3.63	0.75	Higher
57	18	Spectacles	-3.13	-1.50	1.63	Higher
58	21	Spectacles	-1.38	-2.50	-1.13	Lower
59	9	Spectacles	-1.63	0.13	1.75	Lower
60	19	Spectacles	-5.13	-2.38	2.75	Higher
61	26	Spectacles	-0.38	-0.63	-0.25	Lower
62	14	Spectacles	-3.00	-2.13	0.88	Higher
63	11	Spectacles	-2.75	-0.88	1.88	Lower
64	22	Spectacles	-7.25	-5.13	2.13	Higher
65	24	Spectacles	-1.38	-1.75	-0.38	Lower
66	24	Spectacles	-0.50	0.50	1.00	Lower
67	24	Spectacles	-2.25	-1.38	0.88	Lower
68	26	Spectacles	-0.63	0.63	1.25	Lower
69	26	Spectacles	-0.88	-1.13	-0.25	Lower
70	10	Spectacles	-2.00	2.00	4.00	Lower
71	26	Spectacles	-2.75	-1.38	1.38	Lower
72	24	Spectacles	-2.00	-2.13	-0.13	Lower
73	19	Spectacles	-0.50	0.00	0.50	Lower
74	26	Spectacles	-0.25	-0.38	-0.13	Lower
75	26	Spectacles	-0.75	0.75	1.50	Lower
76	26	Spectacles	-0.63	1.88	2.50	Lower
77	26	Spectacles	-3.25	-0.88	2.38	Higher
78	16	Spectacles	-4.13	-2.13	2.00	Higher
79	10	Spectacles	-1.00	-0.13	0.88	Lower
80	20	Spectacles	-3.25	-1.50	1.75	Higher
81	19	Spectacles	-4.50	-2.13	2.38	Higher
82	17	Spectacles	-0.25	0.50	0.75	Lower
83	10	Spectacles	-2.00	-0.13	1.88	Lower
84	7	Spectacles	-1.25	0.13	1.38	Lower
85	20	Spectacles	-3.25	-1.88	1.38	Higher
86	26	Spectacles	-2.00	1.50	3.50	Lower
87	8	Spectacles	-4.00	0.00	4.00	Higher
88	17	Spectacles	-2.25	0.75	3.00	Lower
89	17	Spectacles	-3.75	-2.38	1.38	Higher
90	12	Spectacles	-2.00	1.38	3.38	Lower
		median >>	**-2.94**			

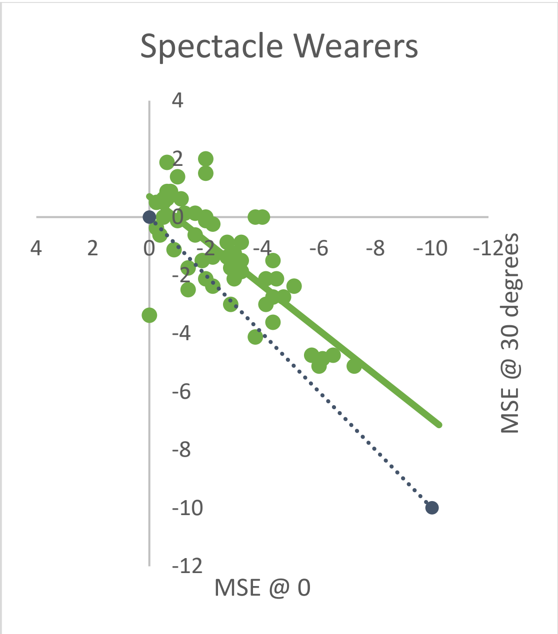


Figure 4.1 a MSE for Spectacle wearers

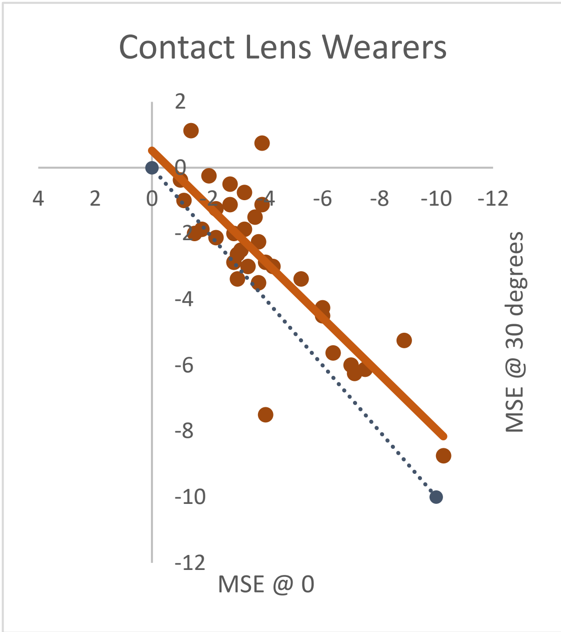


Figure 4.1 b MSE for Contact lens wearers

Figure 4.1. *Each plot illustrates graphically the mean spherical equivalent (MSE) at the fovea (x axis) and at 30 degrees in the temporal retina (y axis) for (a) spectacle lens wearers and (b) contact lens wearers. The solid line through each data set shows the least-squares fit of a linear function. The broken diagonal line in each panel shows the line of equal effect, where the foveal refractive error is equal in magnitude to the peripheral refractive error.*

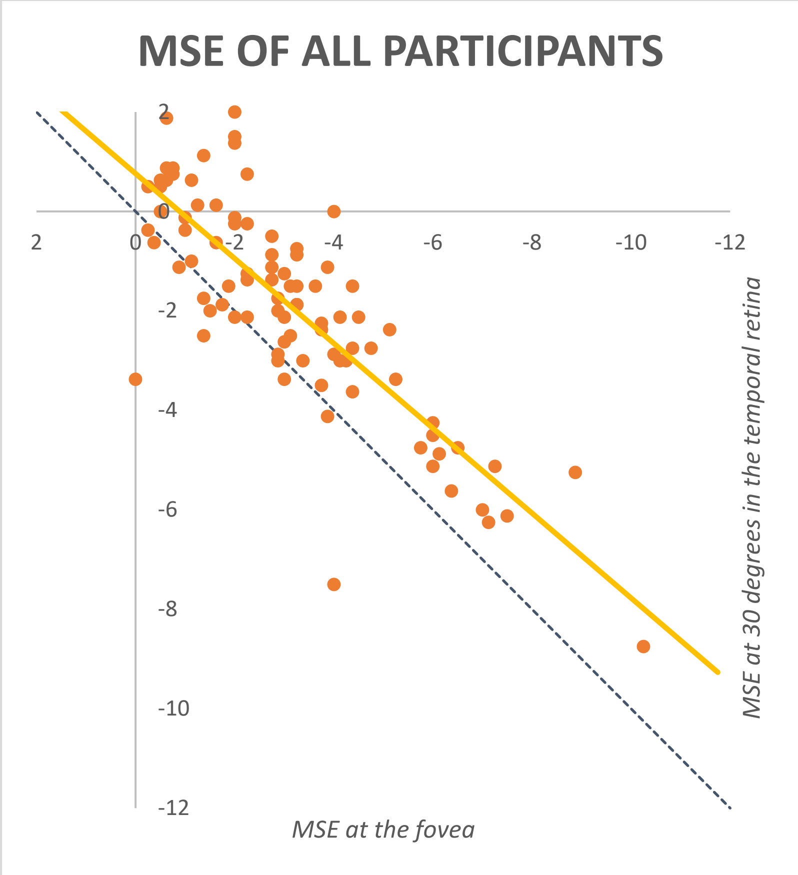


Figure 4.2. *The MSE at the fovea (x axis) and at 30 degrees in the temporal retina (y axis) for the combined data set (i.e., refractive error measures for both spectacle lens wearers and contact lens wearers). The solid line through the combined data set shows the least-squares fit of a linear function. The broken diagonal line shows the line of equal effect, where the foveal refractive error is equal in magnitude to the peripheral refractive error.*

4.3.2 Statistical analyses

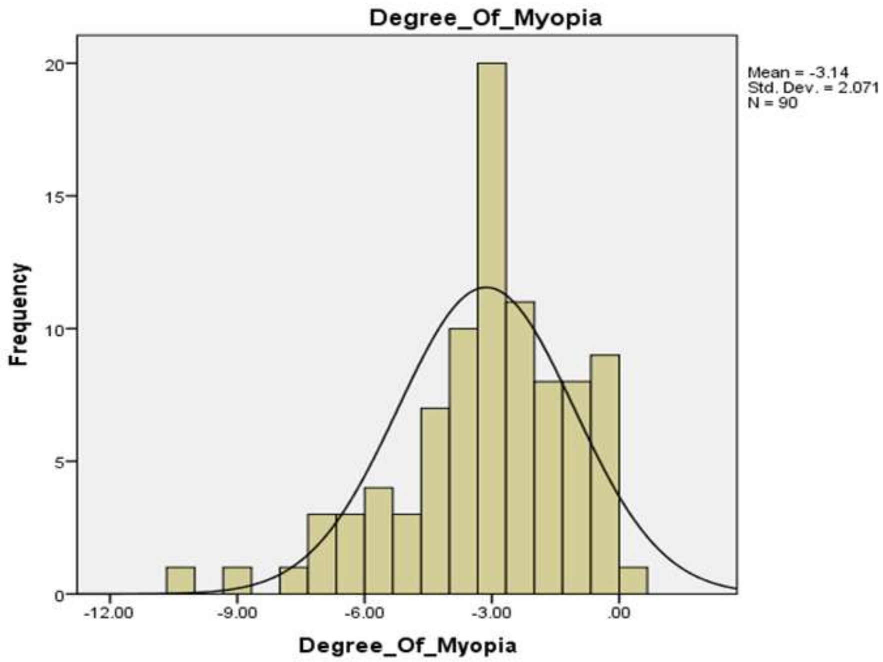
It was first determined whether the refractive error data (central and peripheral) are normally distributed. Normality was judged on several aspects of the data. Firstly, the standard error of skewness and kurtosis was measured. The results are shown in Table 4.2. Note that (a) kurtosis for relative peripheral refraction falls outside the range of -1 to 1; (b) absolute skewness exceeds twice its standard error for both variables (i.e., central and peripheral refractive error); and (c) absolute kurtosis exceeds twice its standard error for relative peripheral refraction. These results indicate that the data may not be normally distributed.

Table 4.2: *Data skewness and kurtosis on measures of degree of myopia and relative peripheral refraction for all participants (N=90, from Table 4.1).*

Statistics

		Degree_Of_Myopia	Relative_Peripheral_Refraction
N	Valid	90	90
	Missing	0	0
Skewness		-.930	-.854
Std. Error of Skewness		.254	.254
Kurtosis		.945	3.204
Std. Error of Kurtosis		.503	.503

In figure 4.3 the data the degree of myopia and relative peripheral refraction data are plotted as a frequency histogram. The solid function shows a least-squares fit of a normal distribution. Note that, in the agreement with the results reported above, the data do not fit the characteristics of a normal curve.



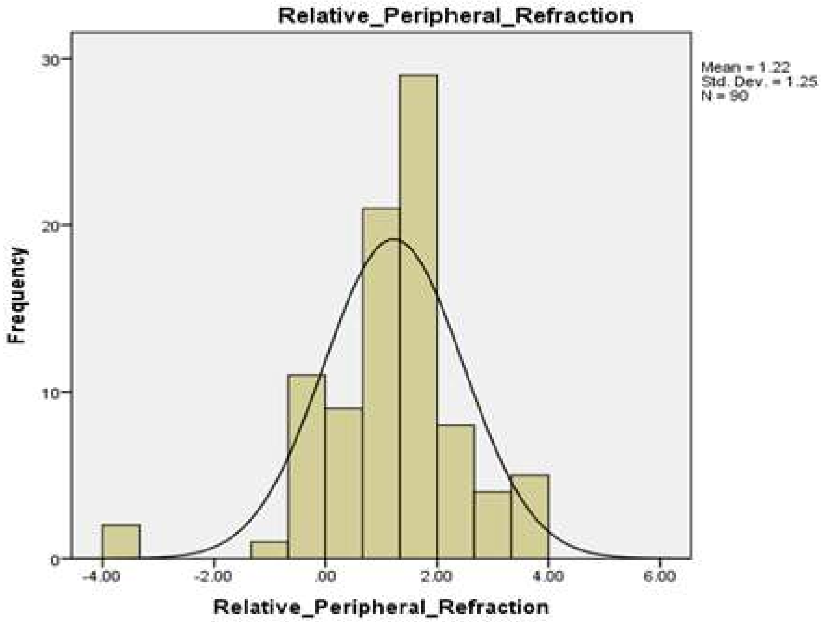


Figure 4.3: *Frequency distribution histograms for degree of myopia and relative peripheral refraction data for all participants (N = 90, from Table 4.1).*

Finally, data normality was assessed using the Shapiro-Wilk test. The results are shown in Table 4.3. Note that the Shapiro-Wilk test shows a significant departure from normality for both variables (degree of myopia, relative peripheral refraction).

Table 4.3: *Shapiro-Wilk tests of normality of degree of myopia and relative peripheral refraction data for all participants (N = 90, from Table 4.1).*

		Shapiro-Wilk	
	Statistic	df	Sig.
Degree of Myopia	.941	90	.000
Relative Peripheral Refraction	.936	90	.000

Together, the assessments of normality detailed above provide evidence that the data for the degree of myopia and relative peripheral refraction are not normally distributed. As such, nonparametric statistical analyses were employed to test the stated hypotheses. To test the first hypothesis, whether higher degrees of myopia arise in eyes with greater amounts of relative peripheral hyperopia, the Spearman correlation statistical test was used. The results of the analysis are shown in Table 4.4. Note that the Spearman correlation was statistically significant (Spearman Rho= -0.266, N= 90, p(2-tailed) = 0.011). The negative correlation indicates that higher degrees of myopia (more negative values) are associated with higher relative peripheral hyperopia (more positive values). The study hypothesis was, therefore, supported.

Table 4.4: *Spearman correlation between degree of myopia and relative peripheral hyperopia for all participants (N = 90, from Table 4.1).*

Correlations

			Degree_Of_Myopia	Relative_Peripheral_Refraction
Spearman's rho	Degree_Of_Myopia	Correlation Coefficient	1.000	-.266*
		Sig. (2-tailed)	.	.011
		N	90	90
	Relative_Peripheral_Refraction	Correlation Coefficient	-.266*	1.000
		Sig. (2-tailed)	.011	.
		N	90	90

*. Correlation is significant at the 0.05 level (2-tailed).

Note that Spearman's Rho is equivalent to Pearson's correlation coefficient, which defines the effect size of a correlation of as follows: 0.1, small; 0.3, medium; and 0.5, large. While the Spearman's Rho value of -0.266 falls just short of a medium size effect, the statistically significant finding indicates that the sample size was sufficient to provide evidence supporting the first hypothesis.

To test the second hypothesis, whether the dependence of the degree of myopia on relative peripheral hyperopia is influenced by the optical correction worn (contact lenses or spectacles), two separate Spearman correlation tests were used (i.e., one for contact lens wearers, and one for spectacle wearers). The results are shown in Table 4.5 (a – b). Note that only spectacle lens wearers showed a statistically significant effect (Spearman Rho= -0.392, N=55, p (2- tailed) = 0.003). No statistically significant effect was found for contact lens wearers (Spearman Rho= -0.272, N= 35, p(2-tailed) = 0.114).

Table 4.5. *Spearman correlation tests for contact lens wearers (top panel) and spectacle lens wearers (bottom panel).*

Correlations

			CL_Degree_of_Myopia	CL_Relative_Peripheral_Refraction
Spearman's rho	CL_Degree_of_Myopia	Correlation Coefficient	1.000	-.272
		Sig. (2-tailed)	.	.114
		N	35	35
	CL_Relative_Peripheral_Refraction	Correlation Coefficient	-.272	1.000
		Sig. (2-tailed)	.114	.
		N	35	35

Correlations

			Spx_Degree_of_Myopia	Spx_Relative_Peripheral_Refraction
Spearman's rho	Spx_Degree_of_Myopia	Correlation Coefficient	1.000	-.392**
		Sig. (2-tailed)	.	.003
		N	55	55
	Spx_Relative_Peripheral_Refraction	Correlation Coefficient	-.392**	1.000
		Sig. (2-tailed)	.003	.
		N	55	55

**. Correlation is significant at the 0.01 level (2-tailed).

The direction of the effect was the same for wearers of both forms of optical correction. However, spectacle wearers exhibited a medium size effect (>0.3), while contact lens wearers exhibited a small effect size (<0.3). These findings lend weak support to the notion that contact lenses reduce myopic progression, though it is acknowledged that the lack of a statistically significant effect for the contact lens wearers may be attributed to having too small a sample size.

4.3.3 Study limitation: the effect of age

In the calculations presented above, no attempt was made to account for the possible effect of age. The possible effect of age is assessed here. The research question can be stated as follows: Does relative peripheral refraction and optical correction (spectacles or contact lenses) predict the likelihood of higher degrees of myopia, accounting also for the variable of age?

Forced-entry, binary logistic regression was completed to determine whether relative peripheral refraction and optical correction (spectacles or contact lenses) predict the likelihood of high degrees of myopia, accounting for the influence of age. The model contained three independent variables (covariates): (a) type of optical correction; (b) relative peripheral refraction; and (c) age. The degree of myopia (a surrogate for myopia progression and classified as 'higher' or 'lower' after a median split - see final column in Table 4.1) was treated as the dependent variable. Binary logistic regression was employed because the dependent variable is dichotomous, while the independent variables are a mixture of nominal and scale variables.

Tables 4.6 and 4.7 confirm that all cases (N=90) were entered into the analyses, to include 35 contact lens participants and 55 spectacle lens wearers.

Table 4.6: *Case Processing Summary*

Case Processing Summary

Unweighted Cases[a]		N	Percent
Selected Cases	Included in Analysis	90	100.0
	Missing Cases	0	.0
	Total	90	100.0
Unselected Cases		0	.0
Total		90	100.0

a. If weight is in effect, see classification table for the total number of cases.

Table 4.7: *Categorical Variables Codings*

Categorical Variables Codings

		Frequency	Parameter coding (1)
Optical_correction	Contact	35	1.000
	Spectacl	55	.000

The Variables in the Equation Table (Table 4.8) shows the Wald statistic, which indicates which covariate has a statistically significant influence on the degree of myopia. Note that optical correction has a significant influence on the degree of myopia (Wald statistic = 7.560, df = 1, p = 0.006), but that neither relative peripheral refraction (p = 0.110) nor age (p = 0.345) have a significant effect.

Table 4.8 *Variables in the Equation table, showing Wald statistic*.

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	Optical_correction(1)	-1.397	.508	7.560	1	.006	.247	.091	.670
	Relative_peripheral_refraction	-.320	.200	2.550	1	.110	.726	.490	1.075
	Age	.043	.046	.893	1	.345	1.044	.955	1.142
	Constant	.064	.980	.004	1	.948	1.066		

a. Variable(s) entered on step 1: Optical_correction, Relative_peripheral_refraction, Age.

Table 4.9 gives information about the log odds (B), standard error (SE), Wald statistic, degrees of freedom (df), p value (p), and the odds ratio (odds) together with the 95% confidence limits for each covariate. Note that relative peripheral refraction did not have a statistically significant influence on the degree of myopia (p = 0.11), after accounting for the effects of optical correction and age.

Table 4.9: *Binary logistic regression statistics for the covariates entered into the model for predicting higher or lower degrees of myopia (myopic progression). See text for details.*

	B	SE	Wald	df	p	odds	95% CL for odds	
							lower	upper
relative peripheral refraction	-3.20	0.20	2.55	1	0.11	0.726	0.49	1.075
optical correction	-1.40	0.51	7.56	1	0.006	0.247	0.091	0.67
age	0.43	0.05	0.89	1	0.345	1.044	0.955	1.142
constant	0.06	0.98	0.00	1	0.948	1.066		

4.4 Summary and conclusions

Hypothesis one, which states that higher degrees of myopia (more negative values) are associated with higher relative peripheral hyperopia (i.e., more positive values), was supported (see Table 4.4). In assessing hypothesis two, preliminary analyses showed a statistically significant correlation between relative peripheral refraction and the degree of myopia in spectacle lens wearers but not in contact lens wearers (see Table 4.5).

Subsequent analyses, employing logistic regression, indicated that relative peripheral refraction does not influence the degree of myopia, after accounting for both the type of optical correction worn and age (see Table 4.9).

Chapter Five: General Discussion and Conclusions

Following a review of both the animal and human literature on the influence of peripheral hyperopic refractive error on the development of central myopic error, three hypotheses were made. First, that contact lens wearers will show less myopic progression than spectacle lens wearers. Second, that higher degrees of foveal myopia (myopic progression) arise in eyes with greater amounts of relative peripheral hyperopia. And third, that the dependence of the degree of foveal myopia on relative peripheral refraction is influenced by the type of optical correction worn (contact lenses versus spectacle lenses).

The principal findings from the retrospective data analyses and experimental measures of central and peripheral refractive status used to address these hypotheses are summarised below. The implications of these findings, especially about the clinical application of refractive corrections used to minimise peripheral refractive error, are then considered.

5.1 Summary of principal findings

Hypothesis 1: *Contact lens wearers show less myopic progression than spectacle wearers*

Assessing the degree of myopic progression from early childhood through to late adolescence, it was initially determined that contact lens wearers do not show less myopic progression than spectacle wearers. The analyses (Table 3.4) showed that the median myopic progression per year found in spectacle wearers (-0.21D) and contact lens wearers (-0.23D) was not significantly different ($p = 0.94$).

Further analyses of the clinical data, considering the influence of possible covariates (i.e., initial age and initial degree of myopia), was then completed. Again, these analyses indicated that optical correction does not have a significant influence on myopic progression ($p = 0.193$, Table 3.11). Given this, the hypothesis that contact lens wearers show less myopic progression than spectacle wearers cannot be supported.

Hypothesis 2: *Higher degrees of foveal myopia arise in eyes with greater amounts of relative peripheral hyperopia*

Following experimental measures of an individual's central and peripheral refractive status, it was determined that there exists a significant negative correlation (Spearman Rho= -0.266, p = 0.011) between foveal myopic refraction and the degree of relative peripheral hyperopia (see Table 4.4). In other words, the results of this analysis provides support for the hypothesis that higher degrees of foveal myopia arise in eyes with higher degrees of relative peripheral hyperopia.

Hypothesis 3: *The dependence of the degree of foveal myopia on relative peripheral refraction is influenced by the type of optical correction worn*

To determine the relationship between central and peripheral refraction and the type of optical correction worn (contact lenses or spectacles), separate Spearman correlation tests were initially used (i.e., one for contact lens wearers, and one for spectacle wearers). This preliminary analysis, shown in Table 4.5, indicated a significant correlation between relative peripheral hyperopia and the degree of myopia in spectacle lens wearers (Spearman Rho= -0.392, p = 0.003) but not in contact lens wearers (Spearman Rho = -0.272, p = 0.114). The latter provides some support for the notion that contact lenses may help to reduce myopic progression more than spectacles (Kwok et al., 2012; Moore et al., 2017; Shen et al., 2010; Walline et al., 2008). However, after accounting for both the type of optical correction worn *and* age, further analyses employing logistic regression indicated that Hypothesis 3 cannot be supported (see Table 4.9).

5.2 Mixed support for the hyperopic defocus theory

Analysis of the retrospective data and experimental measures provides evidence to reject the first and third hypotheses. Thus, it is concluded: (i) that contact lens wearers do not show less myopic progression than spectacle wearers; and (ii) the dependence of the degree of foveal myopia on relative peripheral refraction is not influenced by the type of optical correction worn.

One possible reason why Hypothesis 1 was not supported may be the fact that the number of individuals recruited for the contact lens group was too small, as GPower analysis indicated that the number recruited was not sufficient for a *medium* effect size at the 5% significance level with 80% power (see Methods, section 2.5). However, it was recognised that the optometric data base employed, although extensive, necessarily placed a legitimate resource constraint on the amount of data that could be collected

(Lakens, 2021). The sample sizes employed were sufficient for a large effect size, and provided a balance between the practical feasibilities of recruitment from a defined data base and determining significant meaningful results.

Sample size aside, though, the results reported here for hypothesis 1 are in general agreement with Marsh-Tootle et al. (2009). Although Marsh-Tootle et al. found a small statistically significant difference between contact lens wearers and spectacle wearers, they report this finding not to be clinically significant (see also, Wildsoet et al., 2019; Walline et al., 2008). Other contributing factors for the negative findings reported here include the contact lens material worn by individuals, and the age of the subjects wearing lenses. Blacker et al. (2009) showed that both factors may influence the degree of myopia progression within an individual.

In that no support was found for Hypothesis 3, at least two issues need to be taken into account. Charman and Radhakrishnan (2010) concluded that a principal factor influencing myopic progression, one that may override the type of optical correction worn, is eye shape – an eye which is more prolate in shape is most at prone to becoming more myopic. Another factor is the degree of astigmatism in the periphery of the retina, although the latter was a determination based on a study that used a chick model of vision (Vyas and Kee, 2021).

These non-confirmatory results for the hyperopic defocus theory, however, are balanced by the supportive finding that higher degrees of foveal myopia arise in eyes with greater amounts of relative peripheral hyperopia (i.e., Hypothesis 2). The principal results in support of this hypothesis are reported in Chapter 4.

5.3 Current state of research on hyperopic defocus theory

In that evidence was found both for and against the hyperopic defocus theory, the results of this thesis reflect the current state of the research findings to date. It is the case that there are several prominent animal studies (Schaeffel & Feldkaemper, 2015; Smith et al., 2005; Smith et al., 2009; Wang et al., 2015) providing convincing evidence that relative peripheral hyperopia is an important factor in the development of central myopia. In addition, there is an increasing number of human studies (Atchison et al. 2005; Atchison & Rosen, 2016; Seidemann & Schaeffel, 2002) providing confirmatory evidence in support of these animal studies.

That said, there is equally compelling evidence against accepting the hyperopic defocus theory of myopia development. Following a longitudinal study on children, Mutti et al. (2011) concluded that peripheral refractive error does not play a significant role in either the onset or progression of myopia. In particular, they state that the amount of myopia progression per year was negligible relative to the hyperopic peripheral retinal change over the same period. Further evidence against the hyperopic defocus theory is reported in the Introduction (see section 1.5.3).

5.4 Implications for the profession of optometry

The hyperopic defocus theory, as principally formulated by Earl Smith (Smith et al., 2009a; 2009b; Smith & Hung, 1999; Smith, 2013a, 2013b; Smith et al., 2005), has pioneering implications for optometry. This is so because, if the theory has genuine merit, it will enable ophthalmic practitioners to not only correct myopia but also minimise the continued development of myopia in children and young adults through various treatment options, including peripheral defocus contact lenses and spectacles and orthokeratology. The importance of reducing the level of myopia in individuals cannot be overstated, for it is well known that high levels of myopia are associated with both substantial health and economic burdens (see Introduction, section 1.1).

However, given the discord in the published literature on the hyperopic defocus theory, and the mixed results reported here, the extent to which ophthalmic practitioners should be engaged in actively trying to retard the development of myopia remains unclear. Accepting that any reduction in the degree of myopia would be advantageous to an individual, there are two questions that need to be answered before ophthalmic bodies should advocate widespread implementation of the hyperopic theory in clinical practice. First, is there sufficient evidence from ***human*** studies that implementation of the theory has led to beneficial outcomes? Second, would implementation of the theory by means of contact lenses, spectacles, or orthokeratology result in any harm to an individual, especially to a young child?

Although significant support for the hyperopic defocus theory has been garnered using both chickens and monkeys, it is not unreasonable to suggest that the best model for understanding human myopia progression is likely to be based on human studies. The human studies employed either contact lenses (e.g., Anstice and Phillips, 2011; Chamberlain et al., 2019; Lam et al., 2013; Sankaridurg et al., 2011, 2019) or spectacle lens correction (e.g., Kanda et al., 2018; Lam et al., 2020; Lin et al., 2010; Sankaridurg et al., 2010; Smith, 2013; Tabernero et al., 2009) to assess the defocus theory (see also, Introduction, section XX). Taken together, these studies provide evidence to suggest that the rate of myopic progression can be reduced by approximately 30-40%. The strongest evidence that the retinal defocus theory has positive implications in retarding myopia progression was found in those studies based on the use of orthokeratology lenses (Cho et al., 2005; Cho & Cheung, 2012; Hitaoka et al., 2012; Swarbrick et al., 2015), where the rate of myopic progression was reported to be reduced by up to 50%. Together with the results reported here (i.e., Hypothesis 2), it is concluded that there is sufficient evidence from human studies that implementation of the hyperopic defocus theory has led to beneficial outcomes.

Prescribing contact lenses to young children requires extra measures to be implemented, especially when prescribing for the express purpose of myopia management. It is the responsibility of the eye care practitioner to explain to both the parent/guardian and child what is going to happen during the examination and fitting process, contact lens after-care, monitoring the fit of the lenses, and checking for any adverse effects due to lens wear. Before proceeding to examine the child, the parent or guardian must sign a consent form (Jones et al., 2018). Accepting that these duties are the domain of all practising ophthalmic practitioners, prescribing myopia-correcting contact lenses to children aged 8 to 10 years may be accepted as a legitimate, clinical practice, assuming parental support and an understanding child (Morris, 2008; Speedwell, 2011).

A potential concern of prescribing contact lenses to children, of course, is their impact on the health of the child's eyes. However, there is ample evidence to suggest that the incidence of eye trauma in children due do contact lens wear is extremely rare (Bullimore, 2017; Cheng et al., 2020; Garcia-del Valle et al., 2020; Lee et al., 2017).

The flattening of the central cornea with orthokeratology effects a steepening of the mid-periphery of the cornea, resulting in peripheral myopic defocus (Bullimore & Johnson, 2020). The main reason for choosing orthokeratology as a treatment option for myopia control is its high effectivity compared with other treatment options (Wang et al., 2021). Some issues regarding the safety of orthokeratology lens wear have been raised, but these have generally been related to compliance (Bullimore et al., 2021) and/or contamination of the lens storage case (Wang et al., 2020), rather than overnight contact lens wear. It is possible to minimise these issues by re-educating the patient (Van Meter et al., 2008). Such factors aside, it is now generally accepted that orthokeratology is a safe option for myopic children (Bullimore et al., 2013; Bullimore, 2017; Bullimore & Johnson, 2021; Hu et al., 2021). Of particular significance, Bullimore and Johnson (2021) note that the incidence of microbial keratitis amongst children wearing overnight Ortho-K lenses was lower than that for children wearing daily disposable soft lenses.

If myopia management in children is to be instigated, contact lenses (or orthokeratology) may be preferable to spectacles for various optical and social reasons. First, peripheral defocus contact lenses are unlikely to impact childrens' normal mobility and visual behaviour. This is so because humans have poor peripheral spatial resolution (Anderson, Mullen, and Hess, 1991), and as such peripheral defocus lenses are unlikely to interfere meaningfully with peripheral vision. Second, peripheral defocus spectacles are entirely dependent on eye movements. For such lenses to succeed in reducing myopic progression, the child would, in large part, need to make head movements rather than eye movements to foveate objects, which is impractical. Third, as correcting central myopia with spectacle lenses results in greater relative peripheral hyperopic defocus than correction with contact lenses, it has been suggested that myopia progression should be slower with contact lenses than with spectacles (see Introduction, sections 1.5.1 & 1.5.2). That said, however, the results reported here do not support this hypothesis (Table 4.9; see also, Backhouse et al., 2012). Finally, it has been argued that contact lenses may allow children greater self-confidence and social acceptance than spectacles, especially children with high prescriptions (Speedwell, 2011).

5.5 Conclusion

Whether or not hyperopic defocus is a cause of myopia, there is now sufficient evidence to suggest that the rate of myopic progression can be reduced by an estimated 30-40% by decreasing hyperopic defocus through soft contact lenses, or by up to 50% when using Ortho-K rigid gas permeable contact lenses. Given the minimal risks to ocular health presented by both of these approaches, and as there are serious health and financial burdens associated with high myopia, it is concluded that clinicians should explore the use of such methods in optometric practise, especially in children with a high genetic predisposition for developing myopia. In doing so, it is hoped that the widespread use of these treatment techniques will have positive implications in reducing the myopia epidemic and its comorbidities.

In agreement with previous studies, this study found a relationship between myopia progression and relative peripheral hyperopia. If, clinically, it is possible to take peripheral retinal measurements in optometric practice, then it should be done so routinely. In this thesis, all peripheral refraction measures were completed in the nasal visual field. Moving forward, further measures may be needed in all quadrants of the retina to evaluate, based on the hyperopic defocus theory, the risk of myopia onset/progression in an at-risk child. This may be especially important in countries where optometrists are not allowed by law to conduct a cycloplegic refraction to help determine the risk of myopic progression.

Finally, given the conflicting published evidence regarding the veracity of the hyperopic defocus theory, and the conflicting evidence reported in this thesis, it is manifestly evident that further research is needed to verify the theory's credibility for global transformation of the fundamentals of myopia management in optometric practice.

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Appendix 1: Participant information form

You will be coming to my optometric practice to have the strength of your eyes measured. This will be done in two ways. The picture below shows the first way this will be done:

I will shine a light into your eyes while holding a lens in front of you. This is not painful in any way, and it will only take about 5 minutes.

The picture below shows the second way I will test your eyes, with you sitting in front of a special machine, just like this one:

This small machine measures the strength of your eyes. All you need to do is look into the machine at some coloured lights. Again, this method is not at all painful and it will only take a few minutes to complete.

Your parents or carer may stay with you the whole time. Both tests will only take about 10 minutes, and then you are free to go home. If you have any questions, just ask me, David Berkow, or your mum or dad.

Appendix 2: Ethical approval from Rambam Hospital, Helsinki

תאריך: 15 אוקטובר 2017

לכבוד:
פרופ איתן בלומנטל עיניים
מרכז רפואי רמב"ם

חוקר/ת נכבד/ה שלום רב,

בקשתך לניסוי קליני נדונה בישיבת ועדת הלסינקי המוסדית ב- 28 / ספטמבר! 2017

מצ"ב קיטוע רלוונטי מפרוטוקול הישיבה .

א. פוסי" הניסוי:

מספר הבקשה במשרד הבריאות:	מספר הבקשה בוועדת הלסינקי: ?RME5 —0421-17
נושא הניסוי הרפואי: ההשפעה של תיקון הראיה באמצעות עדשות למשקפיים חד מוקדיות לעומת תיקון באמצעות עדשות מגע חד מוקדיות ההשפעה על הרפרקציה בהיקף הרשתית	
שם נציגו בארץ וכתובתו:	שם היוזם וכתובתו: פרופ איתן בלומנטל מח' עיניים - רמב"ם הקריה הרפואית לבריאות האדם

ב. מסמכי המחקר:

תאור המסמך	תאריך	החלטת הועדה
פרוטוקול מחקר גרסה - 1.0	14/08/2017	לא מאושר
כתב הסכמה מדעת גרסה - 1.0 טופס 2 ה עברית	14/08/2017	לא מאושר
טופס 11 גרסה - 1.0 טופס 11	20/08/2017	מאושר

עיקרי הדיון הפנימי:

מטרת המחקר: לבחון את ההשפעה של תיקון הראיה באמצעות עדשות למשקפיים חד מוקדיות, לעומת תיקון באמצעות עדשות מגע חד מוקדיות וההשפעה על הרפרקציה בהיקף הרשתית. מבקשים לבדוק 206 מטופלים שמגיעים לבדיקה שיגרתית/מעקב למרפאת המחלקה.

המשתתף שמרכיב משקפיים, יעבור בדיקה שיגרתית ותוצאות הבדיקה יושוו למשתתף המרכיב עדשת מגע.
הבקשה שלא להגיש חוברת לחוקר מאושרת, כיוון שהאמ"ר מאושר בארץ.

תנאים ו/או בקשות נוספות:

- יש למנות חוקרים משניים, לא סביר שפרופ' בלומנטל יעשה את כל המחקר ללא עזרה.
- בעמוד 1 בטופס 1ב' - יש לתקן , נכתב טופס 2ה' במקום 2ב.'
- יש להגיש אישור מחודש של האמ"ר שפג תוקפו ב- .31/07/2017

פרוטוקול המחקר

1. בעמ' ,2 פרק שיטות: נכתב שייגוסן ילדים מגיל 6 עד בגירים עד גיל 24 שנים, כשבטופס 1 עמ' 4 נכתב שייגויסו אנשים מעל גיל ,18 חוסר הלימה שמחייב תיקון.
2. יש לתקן את קריטריוני ההכללה, על פי סעיף קודם.
3. יש לציין מספר הלסינקי רמב"ם.

הסכמה מדעת

Malaml Helsinki ,'51 9Oct-17-15 1 מתוך 2

RAMBAM
Health Care Campus

Prof. Eytan Blumenthal
Director

14th January 2018.

To:
Aston University
Student Ethics Application # 1225. DAVID BERKOW

To Whom it May Concern

According to the Protocol for the Rambam Helsinki Committee all research projects are listed under the Head of the Department.

The project undertaken by David Berkow Is being carried out under my supervision, at my department therefore I am listed as the Principal Investigator.

This attached letter is to confirm that DAVID BERKOW is doing the research and collecting the data under my supervision and the supervision of other doctors in my department.

He is obliged to report to me from time to time on his progress as he will report to his Supervisor at Aston University.

Yours Sincerely,

Eytan Blumenthal

Professor Eytan Blumenthal

Rambam Health Care Campus | P.O.B 9602, Haifa 3109601, Israel | State of Israel – Ministry of Health
www.rambam.org.il | E-mail: e_blumenthal@rambam.health.gov.il | T: +972 (4) 7772668 F: +972 (4) 7772142

Appendix 3: Aston University Child Consent Form

Aston University

Date 1/11/17

Child Consent Form:

Title of Project: A Retrospective Study looking at the effect of single vision spectacle lens correction versus single vision contact lens correction on peripheral retinal refraction.

Chief Researcher: David Berkow.

		Initial Box
1	I confirm that I have read /have had read to me the information sheet for the above study.	
2	I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.	
3	I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason.	

Name of participant Age Date Signature

Name of Researcher Date Signature

Appendix 4: Aston University Parent/Guardian Participant Consent Form

Aston University

Date: 11/10/2017
Parent/ Guardian Participant Consent Form:

Title of Project: A Retrospective Study looking at the effect of single vision spectacle lens correction versus single vision contact lens correction on peripheral retinal refraction.

Chief Researcher: David Berkow.

		Initial Box
1	I confirm that I have read and understand the information sheet for the above study	
2	I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.	
3	I understand that participation of my child is voluntary and that I am free to withdraw him/her from the study at any time without giving any reason, without having his/ her medical care or legal rights affected.	

Name of participant Age Date

Name of Guardian/ Parent Date Signature

Name of Researcher Date Signature

Appendix 5: Participant prescription and autorefractor measurements at 0 deg eccentricity.

Data Collection:
Spectacle Rx of Subjects' right eye and Autorefractor measurements of same eye @ 0º eccentricity. Also included is the contact lens Rx. of the relevant subjects:

A	B	C	D	E	F	G	H	I	J	K	L	M	N
Patient	age	with C/L	spec MSE	Sphere	Cyl	Axis	MSE	J0	J45	C/L Sphere	C/L Cyl	C/L Axis	C/L MSE
1	22	yes	-7	-6.75	-1.5	10	-7.5	0.70477	0.25652	-6	-1.75	180	-6.875
2	20	yes	-3.75	-3.5	-0.5	96	-3.75	-0.24454	-0.05198	-3.75			-3.75
3	14	no	-2.5	-3			-3	0	0				
4	18	yes	-1.5	-1	-1.5	94	-1.75	-0.7427	-0.10438	-1	-1.25	90	-1.625
5	22	no	-2.25	-2.25			-2.25	0	0				
6	22	no	-0.75	-0.25	-0.5	175	-0.5	0.2462	-0.04341				
7	23	no	-3.25	-2.75	-0.25	160	-2.875	0.09576	-0.08035				
8	22	no	-1.5	-1	-0.25	70	-1.125	-0.09576	0.08035				
9	9	no	-5.5	-5	-1.5	13	-5.75	0.6741	0.32878				
10	13	no	-4.5	-4	-0.75	16	-4.375	0.31802	0.19872				
11	14	yes	-4.25	-4	-0.5	80	-4.25	-0.23492	0.08551	-4			-4
12	20	no	-2.25	-1.5	-0.25	38	-1.625	0.03024	0.12129				
13	26	yes	-2.5	-2.5	-1.5	83	-3.25	-0.72772	0.18144	-2	-0.75	90	-2.375
14	23	yes	-4.25	-4			-4	0	0	-4			-4
15	22	no	-3.25	-2.5	-0.75	180	-2.875	0.375	0				
16	24	no	-6	-5.5	-1	176	-6	0.49513	-0.06959				
17	21	yes	-2.25	-2.5	-0.75	21	-2.875	0.27868	0.25092	-1.75			-1.75
18	15	yes	-3.625	-2.75	-0.75	95	-3.125	-0.3693	-0.06512	-3.5			-3.5
19	17	no	-0.75	-0.5	-0.5	121	-0.75	-0.11737	-0.22074				
20	23	yes	-7.25	-6	-0.75	144	-6.375	0.11588	-0.35665	-6			-6
21	21	no	-6	-6	-0.25	36	-6.125	0.03863	0.11888				
22	18	no	-0.375	0.25	-0.5	4	0	0.24757	0.03479				
23	18	yes	-1	-1	-0.25	138	-1.125	0.01307	-0.12432	-5.5			-5.5
24	13	no	-5.75	-5.5	-2	13	-6.5	0.89879	0.43837				
25	20	yes	-1.75	-1.25	-0.25	27	-1.375	0.07347	0.10113	-6.5			-6.5
26	13	no	-3.75	-3.25			-3.25	0	0				
27	20	no	-4.75	-4	-0.75	63	-4.375	-0.22042	0.30338				
28	12	no	-4.75	-4.75			-4.75	0	0				
29	20	yes	-2.75	-2.25	-1.5	166	-3	0.66221	-0.3521	-2.25	-0.75	150	-2.575
30	25	yes	-6.5	-6			-6	0	0	-6			-6
31	26	no	-4.5	-4	-0.25	32	-4.125	0.0548	0.11235				
32	26	no	-2	-1.75	-0.25	103	-1.875	-0.11235	-0.0548				
33	15	no	-0.75	-0.25	-0.75	115	-0.625	-0.24105	-0.28727				
34	12	no	-4.375	-3.75	-1.25	160	-4.375	0.47878	-0.40174				
35	18	no	-2.75	-2.75	-0.75	11	-3.125	0.34769	0.14048				
36	21	no	-1.875	-0.25	-2.25	7	-1.375	1.09158	0.27216				
37	26	yes	-4.125	-3.25	-1	15	-3.75	0.43301	0.25	-3.5	-1.25	180	-4.125
38	9	no	-1.25	-1.5	-0.25	164	-1.625	0.10601	-0.06624	-4.25			-4.25
39	22	yes	-3.75	-3.25	-0.75	78	-3.625	-0.34258	0.15253				
40	19	no	-5	-5	-0.25	1	-5.125	0.12492	0.00436				
41	26	yes	-3	-2.5	-0.5	90	-2.75	-0.25	0	-2.5	-0.75	90	-2.875
42	26	no	-0.625	0	-0.75	106	-0.375	-0.31802	-0.19872				
43	14	no	-3	-2.75	-0.5	90	-3	-0.25	0				
44	11	no	-3.25	-2.75			-2.75	0	0				
45	22	no	-8.5	-6.5	-1.5	5	-7.25	0.73861	0.13024				
46	20	yes	-2	-1.25	-0.5	90	-1.5	-0.25	0	-2			-2
47	24	no	-1.625	-1	-0.75	180	-1.375	0.375	0				
48	24	no	-2	-0.25	-0.5	116	-0.5	-0.15392	-0.197				
49	24	no	-2.75	-0.75	-3	180	-2.25	1.5	0				
50	26	no	-0.875	-0.25	-0.75	149	-0.625	0.17605	-0.33111				
51	21	yes	-2.75	-2.75			-2.75	0	0	-2.75			-2.75
52	26	no	-0.625	-0.5	-0.75	95	-0.875	-0.3693	-0.06512				
53	20	yes	-8.375	-6.5	-1.25	12	-7.125	0.57097	0.25421	-7	-1.75	10	-7.875
54	10	no	-2.5	-1.75	-0.5	150	-2	0.125	-0.21651				
55	22	yes	-3	-2.75	-0.5	160	-3	0.19151	-0.1607	-3			-3
56	26	no	-2.75	-2.75			-2.75	0	0				
57	23	yes	-8.75	-6.75	-0.5	20	-7	0.19151	0.1607	-7.5			-7.5
58	26	yes	-6	-6			-6	0	0	-5.75			-5.75
59	24	no	-2	-1.75	-0.5	130	-2	-0.04341	-0.2462				
60	19	no	-0.75	0	-1	110	-0.5	-0.38302	-0.32139				
61	25	yes	-2.625	-2			-2	0	0	-2.25	-0.75	70	-2.625
62	26	no	-0.75	0	-0.5	130	-0.25	-0.04341	-0.2462				

63	26	yes	-3.625	-2.5	-1.5	14	-3.25	0.66221	0.3521	-3.25	-1.75	180	-4.125
64	26	yes	-3	-2.25			-2.25	0	0	-3			-3
65	26	yes	-4.25	-3.5	-0.75	103	-3.875	-0.33705	-0.16439	-4			-4
66	26	no	-0.875	-0.5	-0.5	161	-0.75	0.197	-0.15392				
67	22	yes	-9	-8.5	-0.75	157	-8.875	0.2605	-0.26975	-8.5			-8.5
68	26	no	-1.25	-0.5	-0.25	101	-0.625	-0.1159	-0.04683				
69	23	yes	-1.5	-0.75	-0.5	105	-1	-0.21651	-0.125	-1.25			-1.25
70	25	yes	-3.5	-2.5	-0.75	17	-2.875	0.31089	0.2097	-3.5			-3.5
71	26	no	-3.375	-2.5	-1.5	100	-3.25	-0.70477	-0.25652				
72	26	yes	-6	-5.25			-5.25	0	0	-5.25			-5.25
73	26	yes	-4.25	-3	-0.75	180	-3.375	0.375	0	-4	-0.75	180	-4.375
74	16	no	-4.25	-3.75	-0.75	23	-4.125	0.2605	0.26975				
75	26	yes	-4	-3.25	-1.5	180	-4	0.75	0	-3.25	-1.25	180	-4.0625
76	25	yes	-9.375	-9	-2.5	18	-10.25	1.01127	0.73473	-8.5			-8.5
77	10	no	-1	-0.75	-0.5	14	-1	0.22074	0.11737				
78	20	no	-3	-3.25			-3.25	0	0				
79	19	no	-5.75	-4.25	-0.5	11	-4.5	0.2318	0.09365				
80	17	no	-0.75	-0.25			-0.25	0	0				
81	10	no	-2.375	-2			-2	0	0				
82	7	no	-1.5	-1	-0.5	170	-1.25	0.23492	-0.08551				
83	20	no	-3.5	-3	-0.5	10	-3.25	0.23492	0.08551				
84	26	no	-2.25	-2.25			-2	0	0				
85	25	yes	-3.5	-2.25			-2.25	0	0	-3.5			-3.5
86	8	no	-4.75	-4			-4	0	0				
87	26	no	-3.75	-3.5	-0.5	112	-3.75	-0.17983	-0.17366				
88	26	yes	-3.875	-3.5	-0.75	180	-3.875	0.375	0	-3.5	-0.75	180	-3.875
89	17	no	-2.25	-2.25			-2.25	0	0				
90	17	no	-3.75	-3.5	-0.5	150	-3.75	0.125	-0.21651				
91	13	no	-1	-1			-1	0	0				
92	12	no	-2	-1.75	-0.5	90	-2	-0.25	0				

Appendix 6: Autorefractor measurements @ 30º retinal eccentricity

Patient	age	with C/L	spec MSE	Sphere	Cyl	Axis	MSE	J0	J45	C/L Spher	C/L Cyl	C/L Axis	C/L MSE
1	22	yes	-7	-5.75	-0.75	31	-6.125	0.17605	0.33111	-6	-1.75	180	-6.875
2	20	yes	-3.75	-3.25	-0.5	160	-3.5	0.19151	-0.1607	-3.75	0	0	-3.75
3	14	no	-2.5	-0.25	-2	113	-1.25	-0.69466	-0.71934	0	0	0	0
4	18	yes	-1.5	-1.5	-0.75	72	-1.875	-0.30338	0.22042	-1	-1.25	90	-1.625
5	22	no	-2.25	0.5	-1.25	103	-0.25	-0.56175	-0.27398	0	0	0	0
6	22	no	-0.75	1.5	-1.75	95	0.625	-0.86171	-0.15194	0	0	0	0
7	23	no	-3.25	-1.75	-2.5	119	-3	-0.6624	-1.06006	0	0	0	0
8	22	no	-1.5	1	-0.75	140	0.625	0.06512	-0.3693	0	0	0	0
9	9	no	-5.5	-4.75			-4.75	0	0	0	0	0	0
10	13	no	-4.5	-0.25	-2.5	73	-1.5	-1.0363	0.69899	0	0	0	0
11	14	yes	-4.25	-2.25	-1.5	77	-3	-0.6741	0.32878	-4	0	0	-4
12	20	no	-2.25	0.25	-1.75	113	-0.625	-0.60783	-0.62942	0	0	0	0
13	26	yes	-2.5	-1	-1.75	83	-1.875	-0.84901	0.21168	-2	-0.75	90	-2.375
14	23	yes	-4.25	-1.5	-2.75	94	-2.875	-1.36162	-0.19136	-4	0	0	-4
15	22	no	-3.25	-1	-1.5	90	-1.75	-0.75	0	0	0	0	0
16	24	no	-6	-4.75	-0.75	16	-5.125	0.31802	0.19872	0	0	0	0
17	21	yes	-2.25	-1.5	-1	99	-2	-0.47553	-0.15451	-1.75	0	0	-1.75
18	15	yes	-3.625	-0.5	-4	101	-2.5	-1.85437	-0.74921	-3.5	0	0	-3.5
19	17	no	-0.75	1.5	-1.25	92	0.875	-0.62348	-0.0436	0	0	0	0
20	23	yes	-7.25	-4.75	-1.75	105	-5.625	-0.75777	-0.4375	-6	0	0	-6
21	21	no	-6	-3.75	-2.25	90	-4.875	-1.125	0	0	0	0	0
22	18	no	-0.375	-2.5	-1.75	84	-3.375	-0.85588	0.18192	0	0	0	0
23	18	yes	-1	0.75	-3.5	97	-1	-1.69802	-0.42336	-5.5	0	0	-5.5
24	13	no	-5.75	-4.25	-1	104	-4.75	-0.44147	-0.23474	0	0	0	0
25	20	yes	-1.75	1.75	-1.25	93	1.125	-0.62158	-0.06533	-6.5	0	0	-6.5
26	13	no	-3.75	-1.5	-0.75	72	-1.875	-0.30338	0.22042	0	0	0	0
27	20	no	-4.75	-2.75			-2.75	0	0	0	0	0	0
28	12	no	-4.75	-2.75			-2.75	0	0	0	0	0	0
29	20	yes	-2.75	-2	-2.75	114	-3.375	-0.92005	-1.02182	-2.25	-0.75	150	-2.575
30	25	yes	-6.5	-4.25			-4.25	0	0	-6	0	0	-6
31	26	no	-4.5	-3			-3	0	0	0	0	0	0
32	26	no	-2	0	-3	40	-1.5	0.26047	1.47721	0	0	0	0
33	15	no	-0.75	1.75	-1.75	98	0.875	-0.8411	-0.24118	0	0	0	0
34	12	no	-4.375	-3.25	-0.75	117	-3.625	-0.22042	-0.30338	0	0	0	0
35	18	no	-2.75	0.25	-3.5	97	-1.5	-1.69802	-0.42336	0	0	0	0
36	21	no	-1.875	-1.5	-2	127	-2.5	-0.27564	-0.96126	0	0	0	0
37	26	yes	-4.125	-2	-0.5	143	-2.25	0.06891	-0.24032	-3.5	-1.25	180	-4.125
38	9	no	-1.25	1	-1.75	109	0.125	-0.68951	-0.5387	-4.25	0	0	-4.25
39	22	yes	-3.75	-1	-1	83	-1.5	-0.48515	0.12096	0	0	0	0
40	19	no	-5	-1.75	-1.25	87	-2.375	-0.62158	0.06533	0	0	0	0
41	26	yes	-3	0	-1	104	-0.5	-0.44147	-0.23474	-2.5	-0.75	90	-2.875
42	26	no	-0.625	0.25	-1.75	92	-0.625	-0.87287	-0.06104	0	0	0	0
43	14	no	-3	-0.25	-3.75	114	-2.125	-1.25462	-1.3934	0	0	0	0
44	11	no	-3.25	0.5	-2.75	45	-0.875	0	1.375	0	0	0	0
45	22	no	-8.5	-4.25	-1.75	12	-5.125	0.79935	0.35589	0	0	0	0
46	20	yes	-2	-1	-2	93	-2	-0.99452	-0.10453	-2	0	0	-2
47	24	no	-1.625	0	-3.5	105	-1.75	-1.51554	-0.875	0	0	0	0
48	24	no	-2	1	-1	115	0.5	-0.32139	-0.38302	0	0	0	0
49	24	no	-2.75	-0.25	-2.25	180	-1.375	1.125	0	0	0	0	0
50	26	no	-0.875	1.5	-1.75	90	0.625	-0.875	0	0	0	0	0
51	21	yes	-2.75	0	-2.25	83	-1.125	-1.09158	0.27216	-2.75	0	0	-2.75
52	26	no	-0.625	0.5	-3.25	97	-1.125	-1.57673	-0.39312	0	0	0	0
53	20	yes	-8.375	-6	-0.5	37	-6.25	0.06891	0.24032	-7	-1.75	10	-7.875
54	10	no	-2.5	2.75	-1.5	82	2	-0.72095	0.20673	0	0	0	0
55	22	yes	-3	-1.25	-2.75	96	-2.625	-1.34495	-0.28588	-3	0	0	-3
56	26	no	-2.75	0.25	-3.25	90	-1.375	-1.625	0	0	0	0	0
57	23	yes	-8.75	-4.5	-3	83	-6	-1.45544	0.36288	-7.5	0	0	-7.5
58	26	yes	-6	-4.5			-4.5	0	0	-5.75	0	0	-5.75
59	24	no	-2	-1.25	-1.75	90	-2.125	-0.875	0	0	0	0	0
60	19	no	-0.75	2	-4	85	0	-1.96962	0.3473	0	0	0	0
61	25	yes	-2.625	0.5	-1.5	96	-0.25	-0.73361	-0.15593	-2.25	-0.75	70	-2.625
62	26	no	-0.75	0.25	-1.25	114	-0.375	-0.41821	-0.46447	0	0	0	0
63	26	yes	-3.625	-0.5	-0.5	17	-0.75	0.20726	0.1398	-3.25	-1.75	180	-4.125
64	26	yes	-3	-0.75	-2.75	90	-2.125	-1.375	0	-3	0	0	-3
65	26	yes	-4.25	-0.5	-1.25	105	-1.125	-0.54127	-0.3125	-4	0	0	-4
66	26	no	-0.875	1.5	-1.5	60	0.75	-0.375	0.64952	0	0	0	0
67	22	yes	-9	-4.25	-2	70	-5.25	-0.76604	0.64279	-8.5	0	0	-8.5
68	26	no	-1.25	2.5	-1.25	91	1.875	-0.62462	-0.02181	0	0	0	0
69	23	yes	-1.5	0.75	-2.25	97	-0.375	-1.09158	-0.27216	-1.25	0	0	-1.25
70	25	yes	-3.5	0	-5.75	163	-2.875	2.38348	-1.60768	-3.5	0	0	-3.5
71	26	no	-3.375	0.25	-2.25	85	-0.875	-1.10791	0.19535	0	0	0	0
72	26	yes	-6	-3	-0.75	180	-3.375	0.375	0	-5.25	0	0	-5.25
73	26	yes	-4.25	-2.25	-1.5	83	-3	-0.72772	0.18144	-4	-0.75	180	-4.375
74	16	no	-4.25	-1.25	-1.75	57	-2.125	-0.35589	0.79935	0	0	0	0
75	26	yes	-4	-6	-3	180	-7.5	1.5	0	-3.25	-1.25	180	-4.0625

76	25 yes	-9.375	-8	-1.5	90	-8.75	-0.75	0	-8.5	0	0	-8.5
77	10 no	-1	0.5	-1.25	90	-0.125	-0.625	0	0	0	0	0
78	20 no	-3	-0.75	-1.5	110	-1.5	-0.57453	-0.48209	0	0	0	0
79	19 no	-5.75	-1.75	-0.75	82	-2.125	-0.36047	0.10336	0	0	0	0
80	17 no	-0.75	2	-3	84	0.5	-1.46722	0.31187	0	0	0	0
81	10 no	-2.375	1	-2.25	114	-0.125	-0.75277	-0.83604	0	0	0	0
82	7 no	-1.5	0.25	-0.25	114	0.125	-0.08364	-0.09289	0	0	0	0
83	20 no	-3.5	-1.25	-1.25	73	-1.875	-0.51815	0.3495	0	0	0	0
84	26 no	-2.25	1.75	-0.5	96	1.5	-0.24454	-0.05198	0	0	0	0
85	25 yes	-3.5	0	-2.5	55	-1.25	-0.42753	1.17462	-3.5	0	0	-3.5
86	8 no	-4.75	0.5	-1	122	0	-0.21919	-0.4494	0	0	0	0
87	26 no	-3.75	-1.5	-2.75	96	-2.875	-1.36162	0.19136	0	0	0	0
88	26 yes	-3.875	-3.25	-1.75	5	-4.125	0.86171	0.15194	-3.5	-0.75	180	-3.875
89	17 no	-2.25	1.5	-1.5	98	0.75	-0.72095	-0.20673	0	0	0	0
90	17 no	-3.75	-2	-0.75	74	-2.375	-0.31802	0.19872	0	0	0	0
91	13 no	-1	0.5	-2	90	-0.5	-1	0	0	0	0	0
92	12 no	-2	1.75	-0.75	87	1.375	-0.37295	0.0392	0	0	0	0
93	14 no	-1.25	1.25	-0.5	53	1	-0.06891	0.24032	0	0	0	0

Appendix 7: Mean Spherical Equivalent (MSE) Comparison:

age	With C/L	Spec MSE	MSE @ 0	MSE @ 30
22	yes	-7.00	-7.50	-6.125
20	yes	-3.75	-3.75	-3.50
14	no	-2.5	-3	-1.25
18	yes	-1.5	-1.75	-1.875
22	no	-2.25	-2.25	-0.25
22	no	-0.75	-0.5	0.625
23	no	-3.25	-2.875	-3
22	no	-1.5	-1.125	0.625
9	no	-5.5	-5.75	-4.75
13	no	-4.5	-4.375	-1.5
14	yes	-4.25	-4.25	-3
20	no	-2.25	-1.625	-0.625
26	yes	-2.5	-3.25	-1.875
23	yes	-4.25	-4	-2.875
22	no	-3.25	-2.875	-1.75
24	no	-6	-6	-5.125
21	yes	-2.25	-2.875	-2
15	yes	-3.625	-3.125	-2.5
17	no	-0.75	-0.75	0.875
23	yes	-7.25	-6.375	-5.625
21	no	-6	-6.125	-4.875
18	no	-0.375	0	-3.375
18	yes	-1	-1.125	-1
13	no	-5.75	-6.5	-4.75
20	yes	-1.75	-1.375	1.125
13	no	-3.75	-3.25	-1.875
20	no	-4.75	-4.375	-2.75
12	no	-4.75	-4.75	-2.75
20	yes	-2.75	-3	-3.375
25	yes	-6.5	-6	-4.25
26	no	-4.5	-4.125	-3
26	no	-2	-1.875	-1.5
15	no	-0.75	-0.625	0.875
12	no	-4.375	-4.375	-3.625
18	no	-2.75	-3.125	-1.5
21	no	-1.875	-1.375	-2.5
26	yes	-4.125	-3.75	-2.25
9	no	-1.25	-1.625	0.125
22	yes	-3.75	-3.625	-1.5
19	no	-5	-5.125	-2.375
26	yes	-3	-2.75	-0.5
26	no	-0.625	-0.375	-0.625

14	no	-3	-3	-2.125
11	no	-3.25	-2.75	-0.875
22	no	-8.5	-7.25	-5.125
20	yes	-2	-1.5	-2
24	no	-1.625	-1.375	-1.75
24	no	-2	-0.5	0.5
24	no	-2.75	-2.25	-1.375
26	no	-0.875	-0.625	0.625
21	yes	-2.75	-2.75	-1.125
26	no	-0.625	-0.875	-1.125
20	yes	-8.375	-7.125	-6.25
10	no	-2.5	-2	2
22	yes	-3	-3	-2.625
26	no	-2.75	-2.75	-1.375
23	yes	-8.75	-7	-6
26	yes	-6	-6	-4.5
24	no	-2	-2	-2.125
19	no	-0.75	-0.5	0
25	yes	-2.625	-2	-0.25
26	no	-0.75	-0.25	-0.375
26	yes	-3.625	-3.25	-0.75
26	yes	-3	-2.25	-2.125
26	yes	-4.25	-3.875	-1.125
26	no	-0.875	-0.75	0.75
22	yes	-9	-8.875	-5.25
26	no	-1.25	-0.625	1.875
23	yes	-1.5	-1	-0.375
25	yes	-3.5	-2.875	-2.875
26	no	-3.375	-3.25	-0.875
26	yes	-6	-5.25	-3.375
26	yes	-4.25	-3.375	-3
16	no	-4.25	-4.125	-2.125
26	yes	-4	-4	-7.5
25	yes	-9.375	-10.25	-8.75
10	no	-1	-1	-0.125
20	no	-3	-3.25	-1.5
19	no	-5.75	-4.5	-2.125
17	no	-0.75	-0.25	0.5
10	no	-2.375	-2	-0.125
7	no	-1.5	-1.25	0.125
20	no	-3.5	-3.25	-1.875
26	no	-2.25	-2	1.5
25	yes	-3.5	-2.25	-1.25
8	no	-4.75	-4	0
26	yes	-3.875	-3.875	-4.125
17	no	-2.25	-2.25	0.75
17	no	-3.75	-3.75	-2.375

13	no	-1	-1	
12	no	-2	-2	1.375

Appendix 8: Published papers for and against the hyperopic defocus theory

Animal Studies:

For	Against
Benavente-Perez et al., 2014	Schippert & Schaeffel, 2006
Bowrey et al., 2017	
Charman & Ramamirtham, 2010	
Hung et al., 2008	
Kee et al.,2004	
Liu & Wildsoet, 2011	
Norton et al., 1995	
Schaeffel et al., 1988	
Schaeffel & Howland, 1988	
Schippert & Schaeffel, 2006	
Smith & Hung, 1988	
Smith et al., 1999,2005,2007, 2009, 2010, 2014	
Triolo et al.,2007	
Wallman et al., 2000	
Zhu et al., 2003	

Human Studies:

For	Against
Anstice & Phillips, 2011	Mutti et al., 2011
Atchison, 1987	Sng et al., 2011
Atchison et al., 2005	Zhang et al., 2011
Atchison et al., 2006	
Bernsten et al., 2013	
Chamberlain et al., 2019	
Charman, 2005	
Cho & Cheung, 2012	
Horner et al., 1999	
Kwok et al., 2012	
Kanda et al., 2018	
Lam et al., 2013	
Lin et al., 2010	
Logan et al., 2004	
Millidot, 1981	
Moore et al., 2017	
Mutti et al., 2000	
Mutti et al., 2007	
Mutti et al., 2019	
Radhakrishnan et al., 2013	
Sankaridurg et al., 2001	
Sankaridurg et al., 2011	
Sankaridurg et al., 2019	

Schen et al., 2010	
Schmid, 2004	
Seidemann & Schaeffel, 2002	
Tabernero et al., 2009	
Thibos, 1987	
Walline et al., 2008	
Zhang et al., 2020	